

Numéro d'ordre : H 551

MÉMOIRE

Présenté à

L'Université des Sciences et Technologies de Lille

par

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en vue d'obtenir

L'Habilitation à Diriger des Recherches en Sciences Physiques

Étude des mécanismes de la transition vitreuse et de l'action bioprotectrice des sucres

Soutenue le 8 Décembre 2006 devant la commission d'examen :

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Préambule

Ce mémoire résume mes activités de recherche au Laboratoire de Dynamique et Structure des Matériaux Moléculaires (LDSMM) - UMR CNRS 8024 depuis 1996. Celles-ci ont été menées dans le cadre d'un séjour postdoctoral (ATER) de 1996 à 1998 et en tant que chargé de recherche CNRS par la suite.

Il est organisé en deux grandes parties correspondant à mes deux thématiques de recherche principales abordées par simulation numérique (Monté-Carlo et Dynamique Moléculaire) et diffusion neutronique (Spin-Echo) :

- la problématique de la transition vitreuse de cristaux moléculaires organiques présentant un désordre orientationnel – les cristaux vitreux – et de liquides atomiques modèles formateurs de verre.
- la problématique de l'action bioprotectrice des sucres et en particulier le tréhalose.

Les publications associées à ces deux thèmes sont jointes dans le présent document. Par manque de place et par cohérence avec le reste du mémoire ne figurent pas certains résultats de collaboration sur des modélisations aidant à la résolution de structures cristallines par diffraction X sur poudres, sur la dénaturation des protéines par diffusion Raman ou sur des études par diffusion neutronique de la dynamique de liquides moléculaires vitrifiables présentant un pre-pic du facteur de structure statique.

En annexe, mes principales collaborations scientifiques, mes responsabilités d'encadrement, ma participation à des contrats de recherche et à l'organisation de colloques ainsi que mes activités d'enseignement sont aussi indiquées.

Pour conclure ce préambule, je remercie les membres du laboratoire qui ont contribué à mes activités de recherche pendant ces 10 dernières années et en particulier Marc Descamps qui est associé à l'ensemble de ce travail.

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Contexte et principaux résultats

On sait depuis longtemps que de nombreux matériaux très différents comme la silice, les liquides de faible poids moléculaire (sucres, alcools,...), les polymères ou même certains types de cristaux moléculaires désordonnés présentent une très intrigante propriété commune appelée *transition vitreuse*. Lors d'un refroidissement rapide (trempe), leur cristallisation peut être évitée et ils sont alors dans un état appelé sous-refroidi où leur mobilité subit un extraordinaire ralentissement : plus de dix ordres de grandeur en temps pour une variation de température d'un simple facteur deux sans changement structural significatif. Ce ralentissement est si important qu'on observe un gel des degrés de liberté translationnels et/ou orientationnels sur l'échelle de temps de l'expérience. Ce gel intervient à une température communément notée T_g qui peut être repérée, par exemple, par un saut de chaleur spécifique. La compréhension des mécanismes conduisant à la transition vitreuse a été le sujet d'importants travaux expérimentaux, théoriques et numériques mais aucun modèle unanimement accepté n'a été proposé jusqu'à présent.

Ces dernières années, des progrès significatifs ont cependant été réalisés dans la description des liquides sous-refroidis. Une question fondamentale concerne la nature des mécanismes précurseurs de la transition vitreuse qui se développent dans le régime dynamique pico-nanoseconde (ps-ns) où apparaissent les effets de « cage » et de découplage des dynamiques. D'importants travaux portent sur les idées introduites par la théorie de couplage de modes (MCT) [1]. Cette théorie initialement développée pour les liquides atomiques simples prédit l'existence d'une instabilité dynamique à une température critique T_c , qui est généralement décrite comme une brisure de l'ergodicité du système. Expérimentalement, cette transition vitreuse *idéale* n'est pas observée car les relaxations lentes (appelées α) ne gèlent qu'à la température de transition vitreuse calorimétrique $T_g < T_c$. Certains processus encore mal compris, appelés « processus de sauts thermiquement activés », sont supposés restaurer l'ergodicité du système au dessous de T_c . D'autres concepts proposés dans l'esprit des travaux pionniers de Goldstein [2] et de Stillinger [3] montrent que dans ce régime (ps-ns), la dynamique et la thermodynamique d'un système commencent aussi à être totalement contrôlées par la topologie de son *paysage énergétique* : l'énergie potentielle de ce système lorsqu'elle est tracée dans l'espace des $3N$ coordonnées de configuration. En dessous d'une température, généralement notée T_A et proche de la température critique T_c prédite par MCT, la dynamique d'un liquide sous-refroidi pourrait être décrite par deux échelles de temps différentes : au temps court, des mouvements de faibles amplitudes associés à des minima locaux de l'énergie (vibrations), et au temps longs par des transitions

entre différents puits du paysage énergétique. Au dessus de T_A , le système disposerait d'une énergie thermique $k_B T$ suffisante pour vaincre toutes les barrières d'énergie entre les différents minima et la dynamique serait de nature diffusive.

La première partie de mes activités de recherche s'inscrit directement dans la problématique de la transition vitreuse. Celle-ci a d'abord été abordée sur des modèles de cristaux vitreux (voir section 1.1), une famille de composés qui offre d'intéressantes alternatives aux verres de liquides conventionnels et permet à priori d'affiner la compréhension du mécanisme de vitrification car seuls les degrés de liberté associés aux rotations moléculaires sont susceptibles d'être gelés. En effet, de nombreux cristaux moléculaires présentent une phase haute température dite *plastique* où l'orientation des molécules est dynamiquement désordonnée alors que les centres de masse forment en moyenne un réseau cristallin. Certains, appelés *cristaux vitreux* [4], tels que le cyanoadamantane [5], l'éthanol [6; 7], le cyclooctanol [8] ou les fullerènes [9], peuvent être sous-refroidis et possèdent alors de nombreuses propriétés caractéristiques des verres de liquides conventionnels : saut de la chaleur spécifique à la transition vitreuse ou des évolutions non-Arrhéniennes des temps de relaxation. Ils constituent des systèmes modèles pour l'étude de la problématique des verres car la présence d'un réseau cristallin support permet l'utilisation des méthodes générales d'investigation des cristaux (RX, neutrons). Il est à noter que ces systèmes ne possèdent pas de désordre positionnel susceptible d'entraîner une frustration intrinsèque comme c'est le cas par exemple avec les verres orientationnels de type $K(CN)_x Br_{1-x}$ [10].

Par simulation Monté-Carlo, j'ai pu étudier les conditions de transformation des phases désordonnées ainsi que leurs stabilités relatives. Ces investigations ont permis d'aider à l'interprétation d'expériences de diffraction X réalisés au laboratoire sur le cyanoadamantane et de confirmer l'existence d'une phase métastable transitoire dans le domaine profondément sous-refroidi et préciser son rôle dans le processus de vitrification. Par simulation de dynamique moléculaire, j'ai pu mettre en évidence l'existence d'un « effet de cage orientationnelle » dans les cristaux plastiques et montrer que certaines prédictions de la version idéale de MCT étaient valides. Celles-ci décrivent bien la dynamique rotationnelle de plusieurs cristaux à désordre d'orientation. En jouant sur la taille des modèles de molécules étudiés (adamantanes avec des substituants différents, molécule planaire ou globulaire), j'ai pu sonder des domaines dynamiques différents et prédire l'existence d'un régime dynamique « intermédiaire » $[T_A - T_c]$ où T_A et T_c sont les deux températures décrites précédemment. Ces travaux ont permis de clarifier les similarités et les différences entre les dynamiques lentes des cristaux plastiques et des liquides moléculaires formateurs de verres et de discuter notamment le rôle des corrélations statiques $S(Q)$. Ces résultats ont engendré un nouvel intérêt général pour les cristaux vitreux – le sujet historique du laboratoire – et ont motivé de nouvelles investigations expérimentales : RMN, diffusion Raman, diffraction X et diffusion neutronique qui ont permis de confirmer avec succès les résultats numériques.

Une autre partie de ce travail sur la transition vitreuse (voir section 1.2) a été consacrée à une propriété commune à l'ensemble des liquides formateurs de verre qui est l'apparition dans le domaine ps-ns de nombreux phénomènes supposés être précurseurs de la vitrification : décroissance non-exponentielle ($\exp[-(t/\tau)^\beta]$) des fonctions de corrélation dépen-

dantes du temps, relaxation super-Arrhénienne, violation de la relation de Stokes-Einstein (S-E),... Ces phénomènes ont fait l'objet de nombreuses études expérimentales [11; 12; 13; 14] et numériques [15; 16] mais leur origine reste encore mal comprise. Des investigations de liquides formateurs de verre modèles [17; 18; 19] ont cependant révélé qu'ils apparaissaient dans le régime $[T_A - T_c]$ décrit précédemment à partir duquel la topologie du paysage énergétique joue un rôle prépondérant. Par des simulations MD de liquides atomiques modèles formateurs de verre, j'ai pu montrer que l'anharmonicité du potentiel d'interaction inter-particule jouait un rôle particulièrement important sur la fragilité du verre, la topologie du paysage énergétique et son exploration, sur plusieurs paramètres comme la décroissance non-exponentielle et sur des corrélations surprenantes observées expérimentalement entre les propriétés vibrationnelles du verre sous T_g et sa fragilité. Ces investigations m'ont aussi permis d'utiliser la relation de Stokes-Einstein – et en particulier sa violation dans les formateurs de verre – comme une sonde de la taille des fluctuations des particules et de relier la température à partir de laquelle on observe cette violation avec la température T_A .

La deuxième partie de mes activités a été consacrée à un sujet émergeant depuis plusieurs années au laboratoire, à l'interface avec la biologie, qui porte sur l'action bioprotectrice des sucres pour lequel j'avais bénéficié d'un soutien ACI « jeunes chercheurs » en 2001. Ce thème de recherche a été abordé « en physicien » dans la continuité de l'étude des mécanismes de la transition vitreuse à l'aide des mêmes concepts, modèles et outils comme le prouve la description donnée ci-dessous.

L'amélioration de la stabilité des matériels biologiques sur de très longues périodes est actuellement l'un des objectifs des industries pharmaceutiques et biotechnologiques. Les techniques de refroidissement-séchage (lyophilisation), qui sont des méthodes courantes de stabilisation, peuvent conduire dans certains cas à des pertes irréversibles de la fonctionnalité des biomolécules. Pour éviter cette dénaturation, l'addition de certains sucres spécifiques s'est avérée être un excellent moyen de protéger les biomatériaux au cours des procédés de conservation et d'augmenter leur durée de vie après traitement. Le tréhalose apparaît comme l'un des meilleurs bioprotecteurs dans des conditions défavorables extrêmes. L'origine moléculaire de l'efficacité du tréhalose par rapport à d'autres carbohydrates et de façon encore plus générale la bioprotection elle-même demeure mal comprise. Plusieurs modèles ont été proposés mais aucun n'est unanimement accepté :

- l'hypothèse de Green et Angell [20] porte sur la vitrification du solvant (protectant et eau) dans lequel sont placés les biomatériaux. Une image simple est celle de l'ambre emprisonnant les insectes. L'efficacité du tréhalose serait due à sa température de transition vitreuse particulièrement élevée ($T_g \sim 120$ °C). Des matrices avec un T_g plus faible (mélange glycerol-trehalose) forment cependant de meilleurs protecteurs et d'autres avec un T_g plus haut (polysaccharides) sont moins efficaces. Des interactions spécifiques (liaisons OH), encore mal identifiées, entre le bioprotecteur et la biomolécule semblent donc nécessaires.
- l'hypothèse de remplacement d'eau proposée par Crowe [21] suggère que les molécules de sucres se substitueraient lors de la déshydratation aux molécules d'eau autour de la

molécule biologique afin de préserver un réseau de liaisons hydrogènes avec la biomolécule pour stabiliser sa structure tridimensionnelle. Cependant, on ne comprend pas dans ce modèle comment certaines molécules d'eau situées dans la structure interne de certaines protéines (myoglobine) pourraient être remplacées. Pour d'autres modèles comme celui de Timasheff [22], les protéines demeurent principalement hydratées et les sucres sont préférentiellement exclus de leur surface.

- l'hypothèse de S. Magazu [23] porte sur la déstructuration du réseau tétraédrique de l'eau par les sucres. La présence des sucres perturberait le réseau tétraédrique des liaisons hydrogènes de l'eau, empêchant ainsi la formation de glace au profit d'une structure amorphe d'un liquide sous-refroidi. Ce modèle ne fournit cependant qu'une explication partielle car il ne considère que les situations où la concentration en eau est importante.

Cette problématique a été abordée par des simulations MD de l'action de trois disaccharides homologues : le tréhalose, le sucrose et le maltose à différentes concentrations et températures ainsi que leur interaction avec une protéine modèle le lysozyme. Une approche stratégique en deux étapes fut adoptée :

La première étape a porté sur l'étude des mélanges binaires sucre/eau afin de bien comprendre les propriétés du bioprotectant seul. Il ressort clairement de la littérature que les propriétés physiques spécifiques des sucres en solution dans leurs états vitreux ou sous-refroidis jouent un rôle important dans les mécanismes de biopréservation [24] indépendamment de la molécule biologique où celle-ci peut être considérée comme « esclave » des propriétés du solvant. Un objectif était de réaliser une étude comparative complète des trois sucres à différentes températures et concentrations utilisant le même champ de force Ha *et al.* [25] et incluant plusieurs tests de l'influence du modèle de l'eau considéré (TIP3P ou SPC/E) générant un réseau de liaisons hydrogènes plus ou moins rigide.

Dans une seconde étape, une étude des mélanges ternaires lysozyme/sucre/eau a été réalisée afin d'obtenir une identification fine des interactions protéine/solvant (sites privilégiés - types de résidus affectés) liées à la bioprotection, discuter les différentes hypothèses proposées et de comprendre leurs liens.

Ces investigations révèlent que la capacité des différents sucres à interagir avec les autres sucres ou avec l'eau apparaît primordiale pour « l'homogénéité » des solutions. L'étude de la structure des mélanges binaires sucre/eau suggère notamment que le tréhalose serait capable de former des matrices plus « homogènes » que le sucrose ou le maltose. Le tréhalose pourrait former des agrégats de grandes tailles tout en maintenant un nombre d'hydratation supérieur aux autres sucres. De cette manière un nombre faible de molécules d'eau resterait inaffecté par la présence de ce sucre : la probabilité de formation de glace et les contraintes engendrées par la perte d'eau pendant la déshydratation seraient réduites. Ces résultats ont été confirmés sur les mélanges ternaires et semblent aussi cohérents avec des travaux de spectrométrie IR et de modélisation réalisés par Cordone *et al.* [26] sur la myoglobine dans des matrices de sucres très concentrées.

Les conclusions de notre étude sur la manière dont les sucres interagissent avec les biomolécules montrent que les sucres peuvent former un certain nombre de liaisons hydrogènes avec la protéine mais que celui-ci est faible par rapport à une estimation théorique.

Ce résultat indique que les sucres ne parviennent pas à remplacer totalement les liaisons hydrogènes manquantes dues à la perte d'eau. Le lysozyme apparaît préférentiellement hydraté contrairement à l'hypothèse de Crowe [21] et le tréhalose préférentiellement exclu de la surface de la protéine comme proposé par Timasheff [22]. Par une analyse de densité vibrationnelle de l'eau dans les solutions ternaires, on observe, de plus, un renforcement du réseau de liaisons hydrogènes de l'eau en bon accord avec les études Raman réalisées au laboratoire [27] qui suggèrent que le principal effet des sucres bioprotecteurs est de stabiliser la structure tertiaire de la protéine, via ce renforcement.

Chapitre 1

Transition vitreuse

1.1 Cristaux moléculaires à désordre d'orientation

1.1.1 Rôle des états métastables dans le processus de vitrification

Certaines investigations expérimentales révèlent pour de nombreux liquides vitrifiables des processus complexes de recristallisation sous des trempes profondes. Ces études suggèrent un lien direct mais encore très mal compris entre ces phénomènes et la transformation vitreuse proprement dite. On observe notamment dans les liquides métalliques sous-refroidis [28] une tendance à la formation d'un ordre local icosahédrique qui apparaît comme une source de frustration pour la recristallisation et qui favorise la formation du verre. De plus, il a été montré que la structure de liquides sous-refroidis était réminiscente de celle d'états métastables cristallins. La transformation de certains systèmes sous trempes profondes vers une phase différente de l'état ultimement stable a aussi été observée. L'influence de ces états métastables sur le processus de vitrification est d'ailleurs renforcée par la découverte récente de polyamorphisme dans certains matériaux moléculaires [14; 29].

Des investigations de calorimétrie révèlent un lien possible entre la structure et la transformation vitreuse. Le saut de chaleur spécifique à la température de transition vitreuse T_g , très élevé dans les liquides fragiles, indique une évolution rapide de l'entropie en fonction de la température et par conséquent des changements configurationnels importants dans le liquide sous-refroidi. Si de telles transformations structurales apparaissent, un problème fondamental est de déterminer quel est l'état considéré stable pour le liquide sous-refroidi et si celui-ci peut être une source de frustration et contribuer au gel du système.

Le composé pur cyanoadamantane $C_{10}H_{15}CN$ (CNa) et son mélange avec le chloroadamantane (Cla), noté $(CNa)_{1-x}(Cla)_x$, sont les cristaux vitreux qui jusqu'à présent se sont le mieux prêtés à une investigation expérimentale au laboratoire [30; 31; 32; 5]. Ceux-ci possèdent un faible désordre orientationnel (voir figure 1.1) et des monocristaux de très bonne qualité peuvent être obtenus. Il est en effet difficile de tirer complètement avantage de la structure cristalline des cristaux plastiques dans une investigation de diffraction X car le désordre orientationnel réduit considérablement le nombre de pics de Bragg observables.

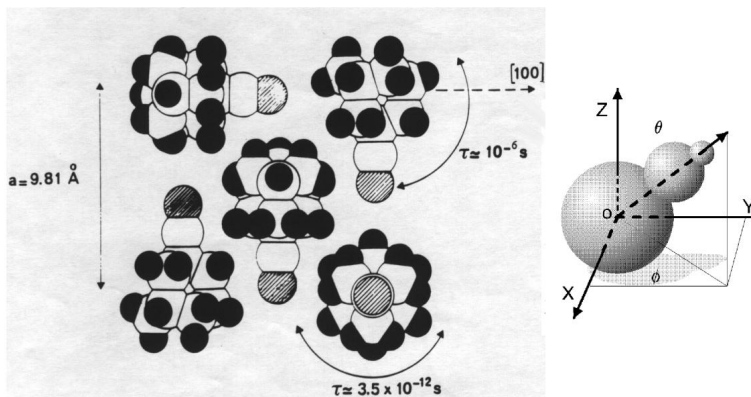


FIG. 1.1 – *Gauche : Molécules de cyanoadamantane en phase plastique. Droite : Modélisation du cyanoadamantane pour les simulations MC et MD.*

Le mélange $(\text{CNa})_{1-x}(\text{Cla})_x$ pour $x = .25$ offre, de plus, des conditions cinétiques favorables à une investigation de diffraction X résolue en temps sur un domaine étendu de la phase à désordre d'orientation sous-refroidie. Des investigations expérimentales ont montré l'existence d'une phase pseudo-tétragonale métastable et transitoire, notée (t), après une trempe profonde de ce mélange. Des signatures d'un ordre local possédant la même symétrie que la phase (t) sont observées en diffraction X pour le composé pur ($x = 0$) mais seulement en dessous de T_g . A plus hautes températures, les transformations trop rapides de ce dernier interdisent une investigation détaillée.

Afin de confirmer l'existence d'une phase intermédiaire et de préciser sa symétrie, j'ai effectué, en collaboration avec B. Kuchta, une étude par simulation numérique Monté-Carlo du cyanoadamantane dans différentes phases cristallines stables et métastables [33; 34]. Nous avons développé un modèle générique de simulation des adamantanes substitués (CNa, Cla,...) où le groupe adamantane de la molécule ($\text{C}_{10}\text{H}_{15}$) est remplacé par un super-atome (voir figure 1.1). Tout le problème était de modéliser suffisamment pour atteindre la fenêtre temporelle de la dizaine de nanosecondes, un temps long pour la simulation de dynamique moléculaire, tout en gardant les spécificités physiques des phases étudiées (paramètre de maille, orientations préférentielles,...). Un potentiel de type Lennard-Jones est utilisé pour représenter les interactions entre molécules. Celles-ci possèdent un moment dipolaire, expérimentalement connu, relativement important. L'utilisation de méthodes de sommation d'Ewald a donc été nécessaire pour rendre compte des interactions électrostatiques. L'ensemble statistique optimal pour la simulation de solides est NPT où le nombre de molécules N , la pression P et la température T sont contrôlés. Il a été employé dans nos calculs avec une boîte de simulation déformable et des conditions aux limites périodiques.

En utilisant le modèle décrit précédemment, nous avons notamment montré par simulation MC que la phase plastique cfc du cyanoadamantane était parfaitement reproduite. Nous avons observé que les molécules possédaient six orientations préférentielles le long des directions [100] du cube et une amplitude de libration d'environ 3 degrés en bon ac-

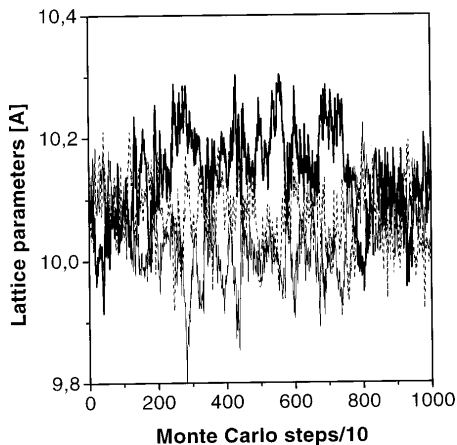


FIG. 1.2 – *Fluctuation pendant un run MC du paramètre de maille de la phase plastique cfc du CNa dans les directions x , y et z de la maille cubique.*

cord avec les observations expérimentales [35] (voir figure 1.1). La figure 1.2 représente les fluctuations du paramètre de maille de la structure cfc suivant les directions cristallographiques [100], [010] et [001] observées pendant un run MC. On observe clairement sur cette figure des déformations de la maille cubique vers une forme tétragonale. On peut montrer que celles-ci sont induites par les fluctuations des orientations moléculaires en raison d'un couplage translation-rotation très fort.

A la suite de cette investigation, nous avons réalisé une étude de la phase métastable (t). La configuration initiale MC fut déterminée à partir des données de diffraction X concernant la microstructure où des pics situés au point X du réseau réciproque sont observés. Les configurations initiales et finales obtenues par simulation MC sont représentées sur la figure 1.3. Le résultat le plus frappant est la distorsion de l'état initial parfaitement tétragonal avec un ordre antiferroélectrique en une structure orthorhombique où les dipôles sont inclinés par rapport à la direction z . On constate aussi que la périodicité de la maille est doublée le long de cet axe et qu'il y a 4 molécules par maille. Il faut noter que ce doublement de la maille a permis de déterminer l'origine de pics additionnels localisés entre les points X du réseau réciproque qui étaient non-expliqués. La distorsion de la configuration initiale est une conséquence immédiate des fortes interactions dipôle-dipôle dans les plans xy qui forcent l'association des groupes CN en paires. Celles-ci sont formées par deux molécules appartenant à deux plans successifs dans le réseau cubique.

Afin de déterminer la stabilité relative des phases cubique et orthorhombique (tétragonale déformée) nous avons estimé l'entropie rotationnelle de la phase plastique de CNa. En négligeant les corrélations intermoléculaires qui sont cependant certainement présentes, l'entropie configurationnelle peut s'écrire $S \simeq \sum_{i=1}^N \int_{\Omega} d\Omega P_i(\Omega) \ln P_i(\Omega)$ où $P_i(\Omega)$ est la probabilité orientationnelle de la molécule i . La figure 1.3 représente la différence d'énergie libre entre ces deux phases. Elle montre clairement que la phase cubique plastique devient

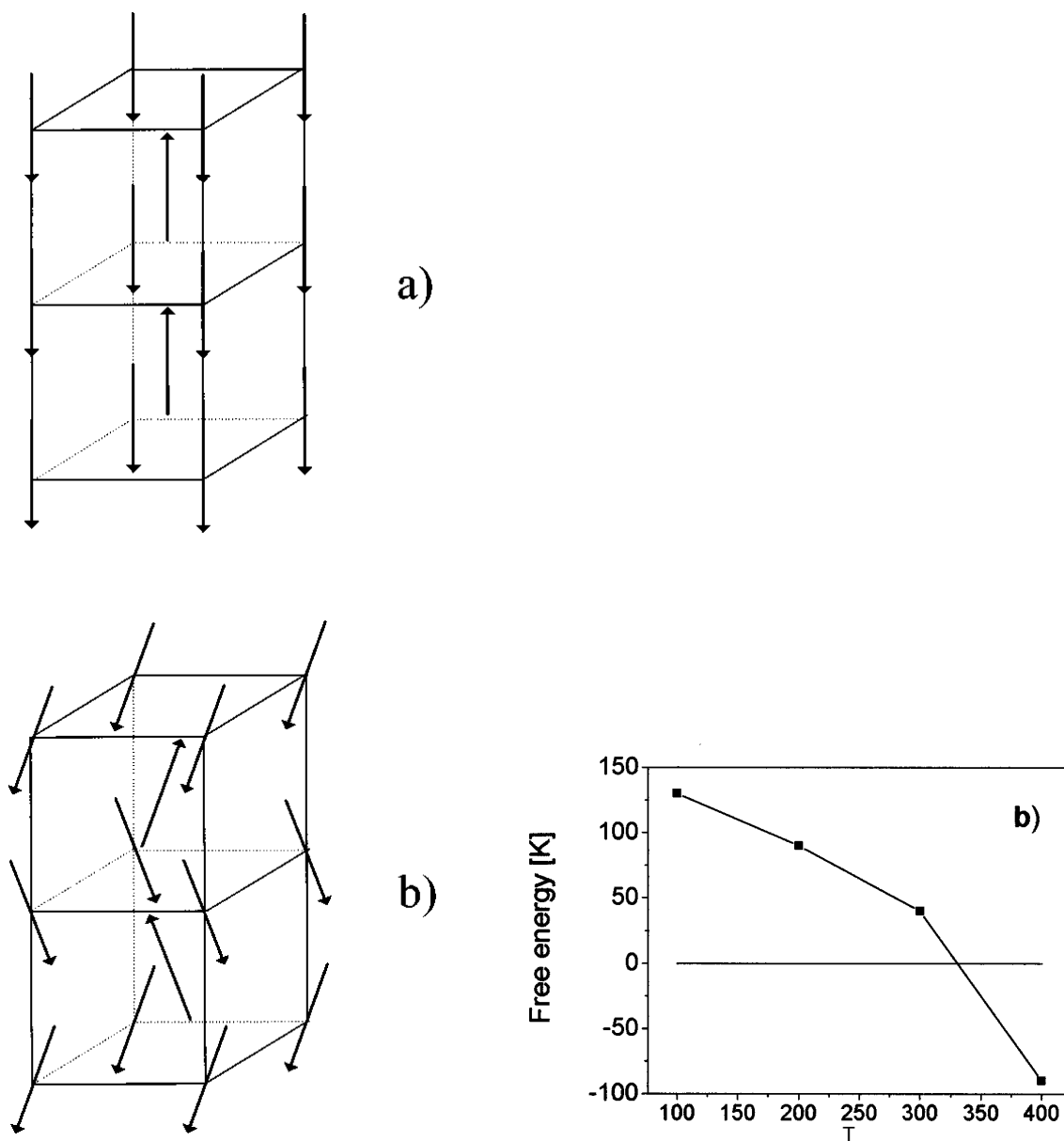


FIG. 1.3 – Gauche : Configuration initiale tétragonale antiferroélectrique (a) et finale orthorhombique inclinée (b) de CNa obtenues par simulation MC. Droite : Différence d'énergie libre $\Delta F(T) = F_{ortho}(T) - F_{plast}(T)$ en fonction de la température T entre la phase orthorhombique et la phase plastique obtenue par simulation MC.

plus stable que la phase orthorhombique seulement à haute température. Cette condition n'apparaît que lorsque le terme entropique dû au désordre orientationnel parvient à compenser la différence d'énergie potentielle favorable à la phase orthorhombique.

1.1.2 Transition dynamique

Une multitude d'investigations expérimentales (temps de vol [36], diffusion Raman [37], relaxation diélectrique [38], effet Kerr optique [39], spin echo [40]) et simulations numériques de dynamique moléculaire [41; 42; 43; 44; 45; 46] ont été réalisées dans le but de valider la théorie MCT. Il a notamment été montré numériquement que MCT donnait une excellente description de la dynamique de systèmes simples comme les mélanges Lennard-Jones binaires ou les sphères dures. La majorité des composés vitreux sont cependant des liquides moléculaires où les degrés de liberté translationnels, orientationnels et vibrationnels sont inextricablement mêlés. Ils rendent la caractérisation de la topographie du paysage énergétique ou la validation de la théorie de couplage de modes extrêmement difficile. De plus, pour ces systèmes, l'accord entre les prédictions de MCT et les données expérimentales ou numériques semble seulement qualitatif.

Une possibilité d'affiner la compréhension de ces problèmes est particulièrement offerte par l'étude de systèmes modèles comme les cristaux à désordre d'orientation qui possèdent un désordre intrinsèque partiel et dont la dynamique est essentiellement contrôlée par les rotations.

1.1.2.1 Mise en évidence d'un changement dynamique

Le chloroadamantane $C_{10}H_{15}Cl$ (Cla) possède une phase à désordre d'orientation étendue [244 – 442] K (voir Fig. 1.4) et une structure isomorphe à celle du cyanoadamantane. Compte tenu de la plus petite taille de son substituant, Cla présente cependant une dynamique plus rapide, susceptible de changer en nature comme il est suggéré par des expériences de diffusion incohérente quasi-élastique de neutrons [48]. De plus, une investigation expérimentale de calorimétrie adiabatique de Cla a été réalisée par Oguni *et al.* [47] et a montré une anomalie très nette et d'origine inconnue de la chaleur spécifique C_p (voir figure 1.4).

A partir du modèle générique des adamantanes substitués (voir figure 1.1), j'ai réalisé un ensemble de simulations de dynamique moléculaire de Cla dans sa phase à désordre d'orientation entre 220 K et 500 K. La nature des changements dynamiques et de l'anisotropie des mouvements moléculaires peuvent être décrits en calculant les fonctions de corrélations orientationnelles suivantes :

$$C_l(t) = \frac{1}{N} \sum_{i=1, N} \langle P_l(\vec{\mu}_i(t) \cdot \vec{\mu}_i(0)) \rangle \quad (1.1)$$

où P_l est le polynôme de Legendre d'ordre l et $\vec{\mu}_i$ le moment dipolaire de la molécule i .

La figure 1.5 montre clairement que les fonctions de corrélation $C_2(t)$ présentent à partir d'une certaine température notée T_A par la suite, un processus de relaxation en deux temps

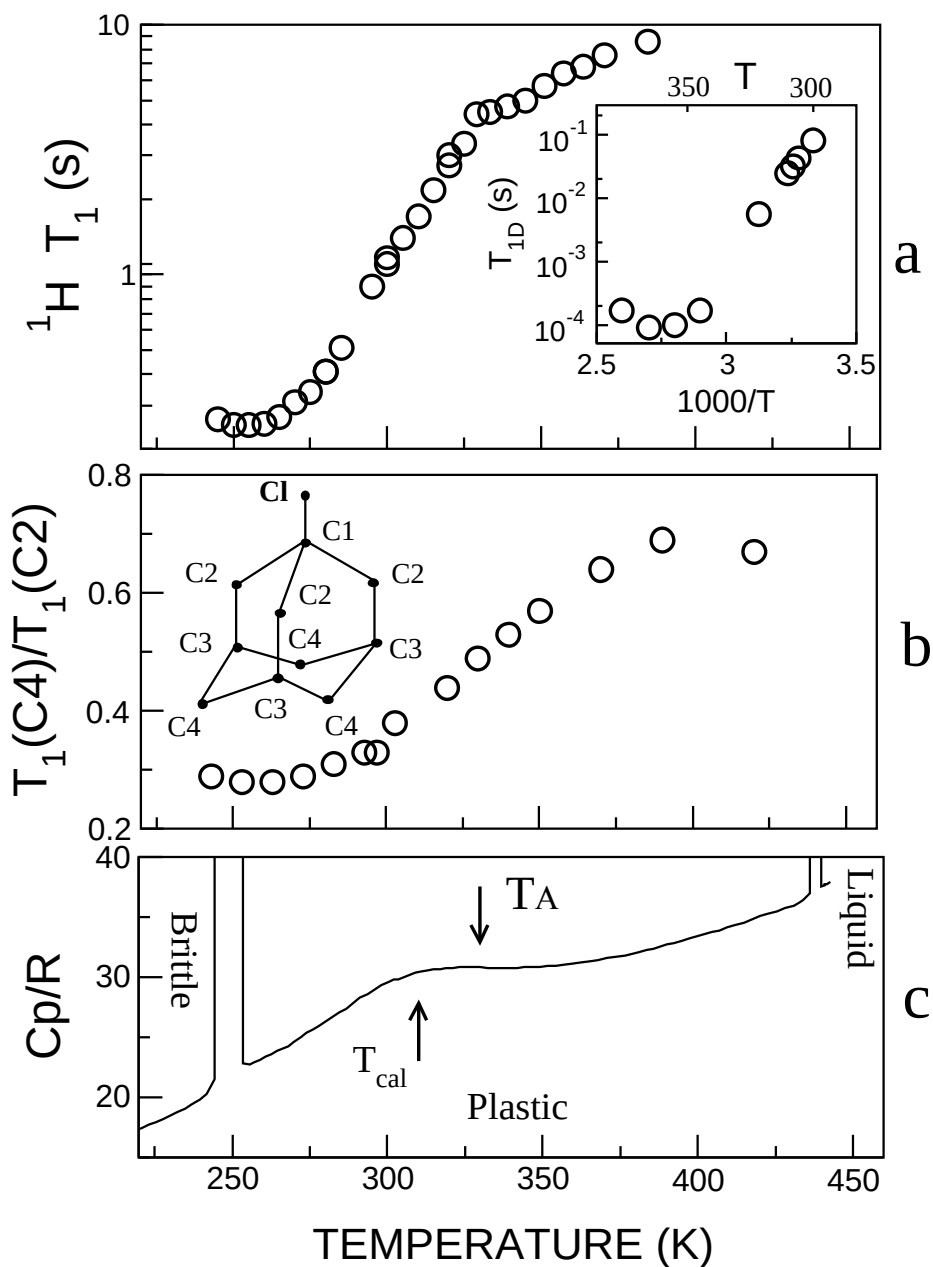


FIG. 1.4 – Résultats expérimentaux de Cla en fonction de la température. **a**, temps de relaxation T_1 en RMN du proton et ordre dipolaire T_{1D} . **b**, la molécule de chloroadamantane avec ses différents carbones est représentée en inset. Rapport $T_1(\text{C4})/T_1(\text{C2})$ des temps de relaxations de différents carbones. **c**, chaleur spécifique extraite de Oguni et al. (Ref [47]). La température de l'anomalie calorimétrique ($T_{\text{cal}} \simeq 310$ K) et celle du changement dynamique RMN ($T_A \simeq 330$ K) sont aussi indiquées.

(α et β) observé classiquement dans les verres de liquides conventionnels et prédit par la théorie MCT. On constate le même comportement pour la fonction $C_1(t)$ non représenté ici. Aux temps courts, on observe une décroissance rapide qui correspond au régime des vibrations.

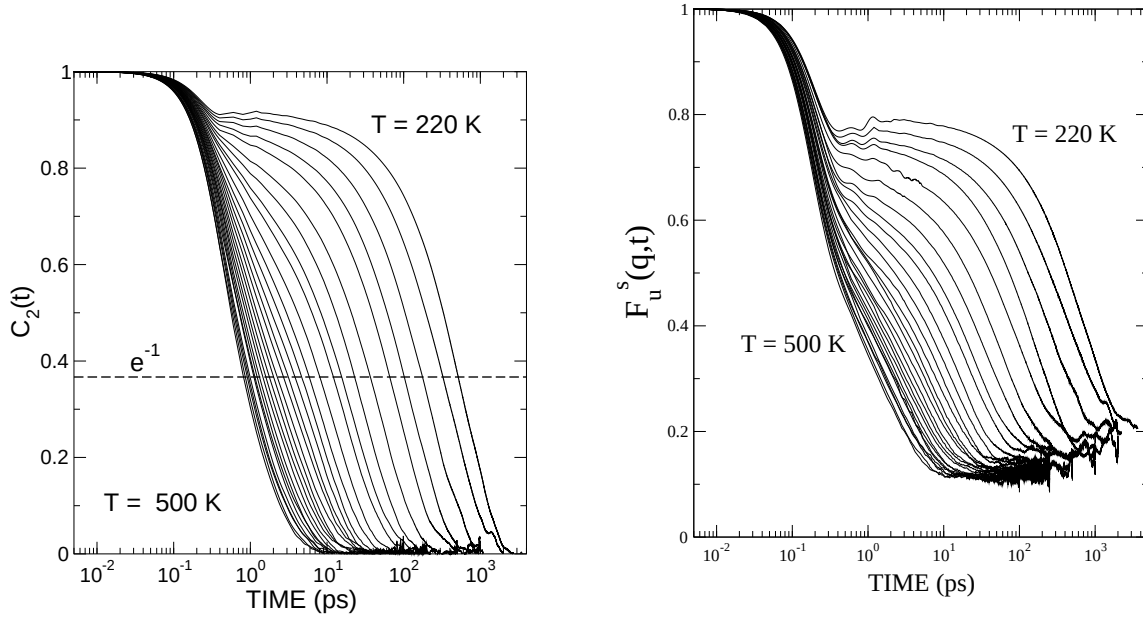


FIG. 1.5 – *Fonction de corrélation orientationnelle $C_2(t)$ et $F_u^s(\vec{q}, t)$ pour $q = 3.06 \text{ \AA}^{-1}$ en fonction du temps à différentes températures de 220 à 500 K.*

Ce dernier est suivi d'un plateau (relaxation β) qui prouve la présence de cages orientationnelles : la rotation d'une molécule est interdite en raison de l'encombrement stérique de ces voisines. Ce phénomène est l'analogue orientationnel de « l'effet de cage » translationnel observé dans les liquides. Les fonctions décroissent finalement jusqu'à zéro par un processus de relaxation lente (α) correspondant pour notre système à des mouvements de réorientations de large amplitude entre orientations les plus probables du cristal plastique. Ces dernières sont clairement mises en évidence sur la figure 1.6 où l'on constate, de plus, l'apparition d'effets coopératifs correspondant au relâchement des cages orientationnelles.

On peut définir le temps caractéristique τ_l de relaxation de la fonction $C_l(t)$ comme le temps nécessaire à cette fonction pour décroître de 1 à $1/e$. Les temps τ_1 et τ_2 sont représentés sur la figure 1.6. Près de la température $T_A \simeq 350 \text{ K}$, on observe clairement que ces temps de relaxation divergent nettement du comportement Arrhénien haute température. Une investigation expérimentale RMN a permis de confirmer l'existence d'un changement de la nature de la dynamique caractérisé par la présence d'une cassure dans l'évolution du temps de relaxation T_1 (voir figure 1.4). Les énergies d'activation apparentes obtenues par simulation, aux hautes et basses températures, sont de plus en bon accord avec les données

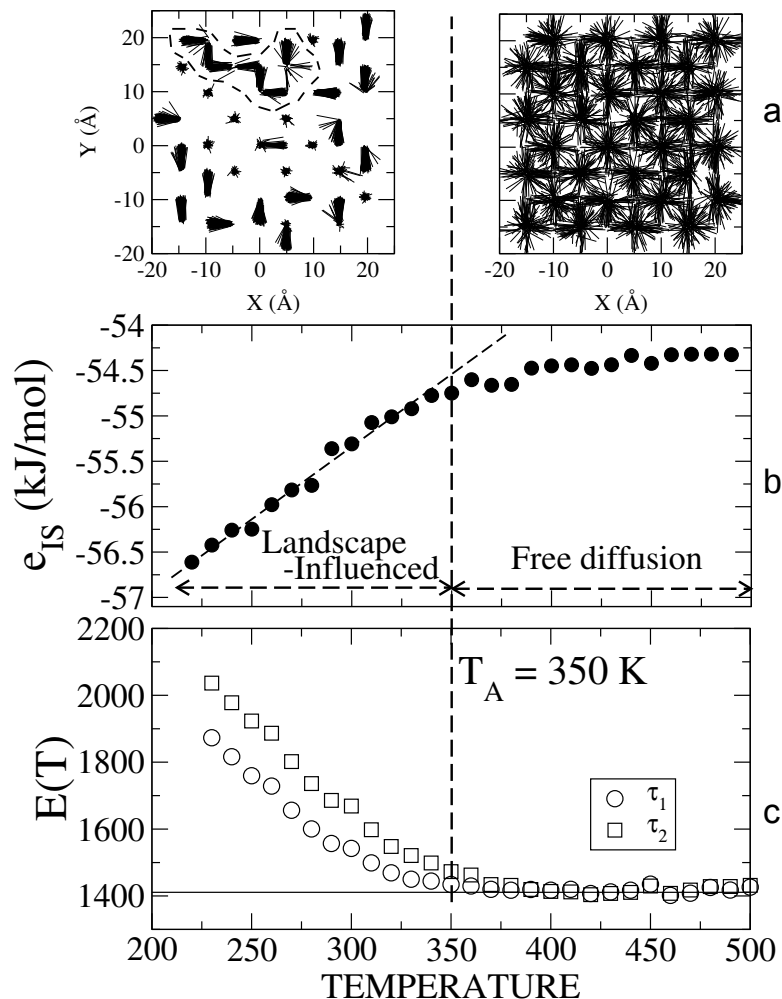


FIG. 1.6 – **a**, Trajectoire des moments dipolaires $\vec{\mu}$ projetés sur un plan cristallographique xy à différents instants d'un run de simulation de 250 ps à $T = 400$ K. Des réorientations collectives sont visibles dans le domaine indiqué par les traits pointillés (droite) et à $T = 220$ K (gauche). A $T = 220$ K, certaines orientations ne sont pas occupées car le système n'est pas complètement à l'équilibre sur cet intervalle de temps. **b**, Énergie potentielle moyenne des minima locaux (inherent structures). **c**, Énergie d'activation $E(T) = T \ln(\tau_{1,2}/\tau_\infty)$ où le temps τ_∞ est obtenu par fit d'une loi d'Arrhénius $\tau_{1,2} \simeq \tau_\infty \exp(E_\infty/T)$ pour $T = [400-500]$ K.

RMN [49]. Le rapport τ_1/τ_2 des temps de relaxation permet de déterminer la nature des mouvements orientationnels au dessus et en dessous de T_A . En effet, à haute température, on obtient un rapport $\tau_1/\tau_2 \simeq 3$ qui correspond à une dynamique de rotation diffusionnelle quasi-libre par petits pas (small-step rotational diffusion). À plus basse température, ce rapport décroît vers 1 indiquant clairement des mouvements de sauts thermiquement activés de larges amplitudes [50; 51] (voir aussi figure 1.6). Ce résultat démontre clairement, pour la première fois dans un cristal à désordre d'orientation, l'existence d'une *transition dynamique*. Celle-ci peut aussi s'interpréter comme le véritable analogue rotationnel de la température de changement dynamique suggérée par Goldstein dans les liquides [2]. Des résultats préliminaires concernant l'exploration du paysage énergétique (voir section 1.2.3) ont été obtenus pour le modèle de Cla (voir figure 1.6). Nous avons notamment observé que l'énergie potentielle moyenne des minima locaux (inherent structures) ne change pas de façon significative au dessus de T_A alors qu'elle décroît de manière sensible en $1/T$ en dessous de cette température en bon accord avec certains travaux numériques réalisés sur des liquides formateurs de verre modèles [17; 52]. Ce changement correspond à l'existence d'un régime dynamique appelé « influenced-landscape » dans le domaine $[T_c - T_A]$. En dessous de T_A , la dynamique du système peut notamment être décrite comme des « processus de sauts thermiquement activés » entre minima de ce paysage comme l'illustre la figure 1.6.

Suite à l'étude numérique MD, de nombreuses investigations expérimentales ont été effectuées au laboratoire. Une étude de diffraction X de Cla a été menée et a confirmé l'existence d'une signature structurale de l'accident dynamique. Ces résultats expérimentaux en accord avec la dynamique moléculaire établissent la très forte anharmonicité du champ cristallin. De plus, une investigation récente réalisée par diffusion Raman [53] révèle un changement fort du mode de bending de la molécule de Cla à la transition dynamique T_A indiquant une mise en ordre claire de l'ordre local dipolaire du système comme suggéré par le calcul numérique.

1.1.2.2 Validité des prédictions MCT

Un problème très actuel en physique des verres est de déterminer l'importance relative des translations et des rotations au cours du ralentissement visqueux. La possibilité de suivre principalement l'évolution dynamique des degrés de liberté rotationnelle est offerte par les cristaux plastiques. Pour ces systèmes de nombreuses investigations ont été menées dans le domaine profondément sous-refroidi [30; 6; 7; 54]. Cependant, très peu d'études ont été réalisées loin de T_g , dans le domaine des prédictions MCT et du changement de nature des dynamiques proposé par Goldstein. Stimulé par le manque d'information en ce domaine, j'ai réalisé, pour la première fois pour des cristaux plastiques, un test complet des prédictions MCT.

Une question fondamentale était de déterminer si ces théories s'appliquaient à des composés où la dynamique est essentiellement contrôlée par les rotations.

La figure 1.5 montre l'évolution de la fonction de corrélation temporelle [55] :

$$F_u^s(\vec{q}, t) = \sum_{j=1}^N \sum_{a=1}^{N_a} \langle \exp[i\vec{q} \cdot (\vec{u}_{j,a}(t) - \vec{u}_{j,a}(0))] \rangle \quad (1.2)$$

où $\vec{u}_{j,a} = \vec{R}_{j,a} - \vec{R}_j^{c.m}$ et $\vec{R}_j^{c.m}$ est la position du centre de masse de la molécule j et $\vec{R}_{j,a}$ la position du site a de la molécule j ($N = 256$ et $N_a = 2$ dans cette étude).

On observe clairement sur cette figure l'existence de processus de relaxation α - β confirmant les résultats obtenus sur les fonctions de corrélation dipolaires $C_{l=1,2}$. Aux temps longs, les fonctions $F_u^s(\vec{q}, t)$ tendent vers une valeur non nulle appelée facteur de structure élastique incohérent (EISF) et notée $A_0(q) = \lim_{t \rightarrow \infty} F_u^s(q, t)$. Cette valeur se superpose aux contributions quasi-élastiques [56] et fournit une information sur les géométries moyennes des mouvements de réorientations moléculaires.

MCT dans sa version dite « idéale » décrit un scénario de relaxation en deux temps (α - β) pour toutes les fonctions de corrélation dépendantes du temps ($F_u^s(q, t)$, $C_l(t)$, ...) [1]. A temps court, MCT prédit que celles-ci décroissent vers une valeur plateau appelée paramètre de non-ergodicité et noté f_q^c . Le régime dynamique associé à cette région est appelé β . Il est centré autour d'un temps $t_\sigma = t_0|\sigma|^{-1/2a}$ où t_0 est un temps caractéristique macroscopique et σ une mesure de l'écart à la température critique $\sigma \sim |T - T_c|$. Au dessus de T_c , la fin du régime β (ou le début du régime α qui lui succède) associée au départ du plateau, est décrite par la loi suivante :

$$\phi(q, t) = f_q^c - h_q^{(1)} \cdot (t/\tau)^b + h_q^{(2)} \cdot (t/\tau)^{2b} \quad (1.3)$$

où les deux premiers termes correspondent à la classique loi de Von Schweidler, le dernier terme est une correction de second ordre et $\tau = t_0|\sigma|^{-\gamma}$ avec $\gamma = 1/2a + 1/2b$. Les paramètres a et b sont liés par la relation $\Gamma^2(1-a)/\Gamma(1-2a) = \Gamma^2(1+b)/\Gamma(1+2b)$ où $\Gamma(x)$ est la fonction spéciale gamma. A temps long, MCT prédit que la relaxation β précédente est suivie par un régime plus lent, appelé α , caractérisé par le temps de relaxation τ .

Dans le but de tester la validité des relations décrites ci-dessus, j'ai d'abord cherché à fixer l'exposant b en utilisant le théorème de factorisation (séparation des dépendances en q et T) où les processus de « sauts » sont supposés ne pas être trop importants. Le rapport $R_\phi(t) = (\phi(t) - \phi(t_1))/(\phi(t_2) - \phi(t_1))$ où (t_1, t_2) sont deux temps arbitraires différents dans le régime β a été calculé à différentes températures et pour différentes fonctions de corrélations : $F_u^s(q, t)$ pour les vecteurs d'onde $q = 3.06, 2.45, 1.22, 0.62$ et $0.30 \text{ \AA}^{-1}$ et $C_l(t)$ pour $l = 1, 2$. Les résultats obtenus sont représentés sur la figure 1.7. On constate clairement sur cette figure qu'il existe un domaine temporel où toutes les fonctions de corrélation se superposent sur une courbe maîtresse. On peut montrer que celle-ci ne dépend que du paramètre b . Des affinements des différentes fonctions de corrélation ont été réalisés pour plusieurs températures. Les meilleurs résultats sont obtenus pour $b = 0.79$ impliquant $a = 0.36$ et $\gamma = 2.02$.

En fixant la valeur de l'exposant $b = 0.79$, j'ai réalisé un ensemble d'affinements des fonctions de corrélations à partir de l'équation 1.3 avec les paramètres libres f_q^c ,

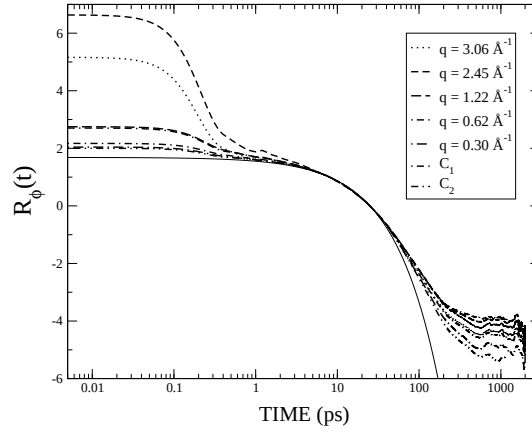


FIG. 1.7 – Rapport $R_\phi(t) = (\phi(t) - \phi(t_1))/(\phi(t_2) - \phi(t_1))$ à $T = 260$ K où (t_1, t_2) sont deux temps arbitraires dans le régime β . La courbe maîtresse (trait plein) est obtenue à partir de la loi de Von Schweidler avec un exposant $b = 0.79$.

$\tilde{h}^{(1)} = h^{(1)}(q) \cdot \tau^{-b}$ et $\tilde{h}^{(2)} = h^{(2)}(q) \cdot \tau^{-2b}$. Le pré-facteur total $\tilde{h}^{(1)}$ est tracé sur la figure 1.8 (le pré-facteur $\tilde{h}^{(2)}$ présente le même comportement). $\tilde{h}^{(1)}$ montre clairement la dépendance en température prédite par MCT. En extrapolant l'évolution des différentes fonctions on obtient une valeur unique pour la température critique $T_c \simeq 225 \pm 8$ K. Pour des températures proches de T_c , on observe une déviation des prédictions MCT qui peut être attribuée aux processus de sauts.

Dans le régime α , on peut définir un temps caractéristique τ_q pour les différentes fonctions de corrélation $F_u^s(q, t)$ défini comme le temps de décroissance de 1 à $1/e$. On supposera que tous les temps caractéristiques ont la même dépendance en température $\tau_q(T) \sim \tau(T)$. De plus, ces fonctions ont été normalisées par l'EISF $[F_u^s(t) - A_0(q)]/[1 - A_0(q)]$ afin de décroître de 1 à 0. MCT prédit que les différents temps $\tau_q^{-1/\gamma}(T)$ doivent suivre une loi linéaire qui intersecte l'axe des abscisses à T_c . La figure 1.8 montre clairement que ces prédictions sont correctes et conduisent à une température critique identique à celle obtenue dans le régime β . On observe aussi sur cette figure un désaccord avec les prédictions vers les basses températures dû aux processus activés. L'existence du changement dynamique à haute température est aussi clairement confirmé sur la figure 1.8 où l'on constate une déviation nette au comportement MCT. Il s'agit de la température $T_A \simeq 350$ K mise en évidence précédemment au dessus de laquelle les temps caractéristiques peuvent être décrits par une simple loi d'Arrhénius $\tau = \tau_0 \exp(E/T)$. Nous obtenons donc, pour la première fois dans un cristal à désordre d'orientation, une preuve claire d'un régime intermédiaire $[T_c - T_A]$ où MCT pourrait s'appliquer.

Notre étude montre pour la première fois qu'un système dont la dynamique est principalement contrôlée par les rotations partage des caractéristiques dynamiques communes avec les verres de liquides canoniques. Celles-ci peuvent être décrites relativement bien par la version idéale de MCT certainement en raison de la structure mathématique simi-

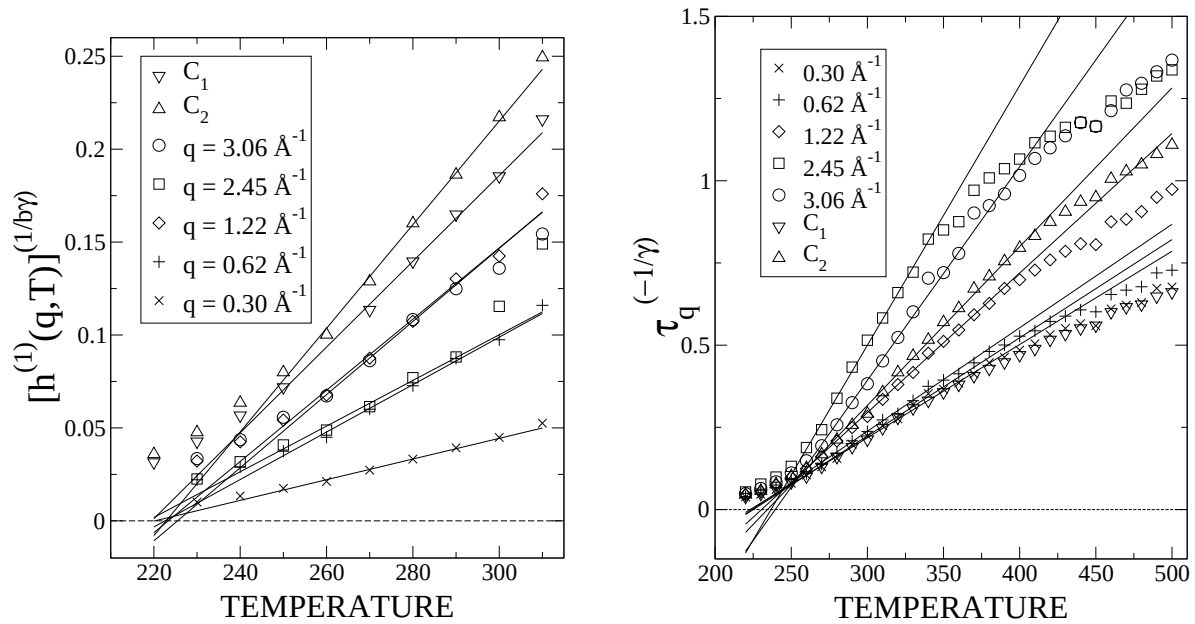


FIG. 1.8 – Gauche : Pré-facteur total $[\tilde{h}^{(1)}]^{1/b\gamma}$ en fonction de la température pour les différentes fonctions de corrélation étudiées. Un affinement linéaire (traits pleins) de la dépendance en température conduit à une température critique identique pour toutes les fonctions $T_c \simeq 225 \pm 8$ K. Droite : Temps de relaxation $\tau_q^{-1/\gamma}$ du régime α en fonction de la température pour les différentes fonctions de corrélations étudiées. L'exposant $\gamma = 2.02$ est obtenu à partir de l'analyse MCT du régime β . Les différentes droites (traits pleins) représentent les prédictions MCT $\tau_q^{-1/\gamma} \sim (T - T_c)$. Une forte déviation à celles-ci est observée à $T > T_A \simeq 350$ K où l'évolution de $\tau_q(T)$ peut être décrite par une simple loi d'Arrhénius.

laire des équations MCT pour les cristaux plastiques et les liquides [57]. L'extraction de la même température critique $T_c \simeq 225$ K dans les deux régimes α et β renforce encore plus cette description. Nos travaux confirment l'existence d'une température de changement de nature de la dynamique T_A observée expérimentalement (RMN, Raman, Diffraction X, calorimétrie) qui permet de fixer clairement le domaine de validité $[T_c - T_A]$ de MCT.

1.1.2.3 MCT pour les cristaux moléculaires à désordre d'orientation

Les investigations menées sur Cla suggèrent clairement la possibilité de développer une théorie de couplage de modes pour les cristaux vitreux de manière analogue à celle réalisée sur les verres de liquides moléculaires (Molecular MCT) [58; 59; 60]. Des travaux récents réalisés par R. Schilling *et al.* [61; 62] ont permis d'étendre MCT aux cristaux moléculaires à désordre d'orientation. Les auteurs ont pu notamment étudier le gel orientationnel d'un système constitué d'ellipsoïdes uniaxiaux « durs » sur réseau en utilisant le facteur de structure statique extrait de la théorie de Percus-Yevick [61]. Ils ont démontré que l'origine de cette transition n'est pas pilotée par un effet de cage orientationnelle analogue aux liquides mais par l'extension d'un ordre orientationnel. Celui-ci se manifeste par une augmentation des fonctions de corrélation orientationnelles statiques et du « memory kernel » de MCT. Ce gel orientationnel apparaît avant que la longueur de corrélation orientationnelle ne diverge à la transition vers la structure ordonnée et non dans le régime sous-refroidis.

Afin d'éclaircir la nature précise de la transition vitreuse dans les cristaux plastiques, j'ai entrepris en collaboration avec R. Schilling une étude du gel orientationnel du Cla dans le cadre de MCT. Nous avons utilisé le modèle décrit précédemment dans lequel l'orientation de la molécule de Cla n peut être caractérisée par les angles polaires $\Omega_n(t) = (\Theta_n(t), \phi_n(t))$. Le développement sur une base d'harmoniques sphériques $Y_\lambda(\theta, \phi)$, $\lambda = (\ell, m)$ conduit à l'expression de la densité dans l'espace réciproque :

$$\rho_\lambda(\vec{q}, t) = i^\ell \sum_{n=1}^N Y_\lambda(\Omega_n(t)) e^{i\vec{q} \cdot \vec{R}_n} \quad (1.4)$$

où $\vec{R}_n$ est la position du site n du réseau cristallin et $\vec{q}$ un vecteur de la première zone de Brillouin. Les fonctions de corrélations dépendantes du temps peuvent s'écrire alors :

$$S_{\lambda\lambda'}(\vec{q}, t) = \frac{4\pi}{N} \langle \delta\rho_\lambda^*(\vec{q}, t) \delta\rho_{\lambda'}(\vec{q}, 0) \rangle \quad (1.5)$$

Celles-ci sont similaires à celles étudiées précédemment (voir équations 1.1 et 1.2) et présentent les mêmes types de comportement bien décrits par MCT. MCT fournit une équation du mouvement pour $S_{\lambda\lambda'}(\vec{q}, t)$. En raison de l'anisotropie du cristal, ces fonctions dépendent de $\vec{q}$ et sont plus complexes que pour les liquides. Nous nous sommes donc limités à la détermination de la température critique T_c^{MCT} et des facteurs de non-ergodicité critiques $f_{\lambda\lambda'}^c(\vec{q})$. Ceux-ci peuvent être obtenus par la résolution d'un ensemble d'équations algébriques non-linéaires couplées dépendant uniquement des fonctions de corrélation statique

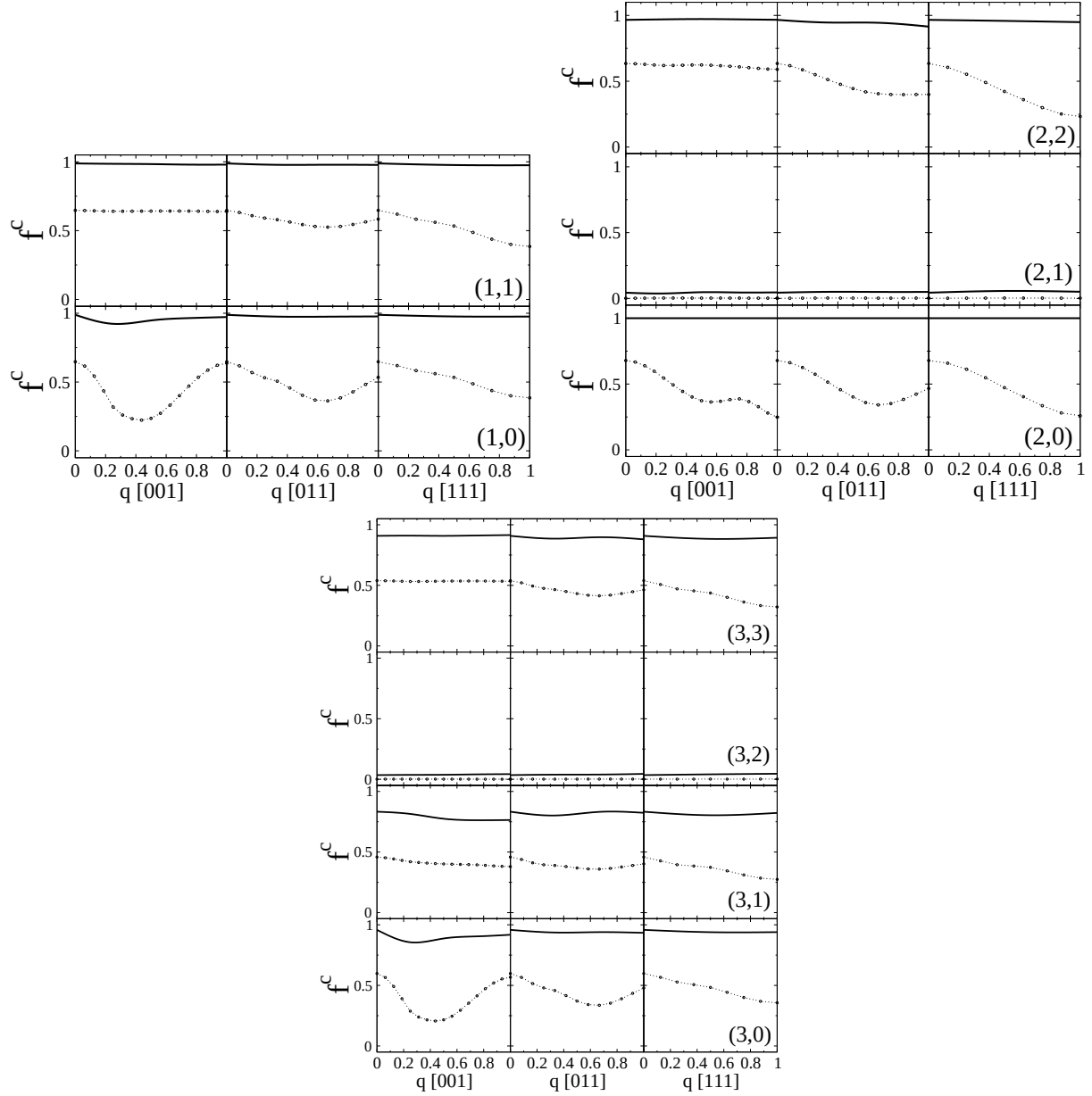


FIG. 1.9 – Dépendance en $\vec{q}$ des facteurs de non-ergodicité critique $f_{\lambda\lambda'}^c(\vec{q})$ le long des directions de haute symétrie $[001]$, $[011]$ et $[111]$ pour $\lambda = \lambda' = (1,0)$, $(1,1)$, $\lambda = \lambda' = (2,0)$, $(2,1)$, $(2,2)$ et $\lambda = \lambda' = (3,0)$, $(3,1)$, $(3,2)$, $(3,3)$. Les résultats de simulation MD sont indiqués avec des traits pleins et les prédictions MCT avec des traits pointillés.

$S_{\lambda\lambda'}(\vec{q}, t = 0)$ qui peuvent être déterminées par simulation MD. Les résultats obtenus sont résumés sur la figure 1.9.

De manière générale, des différences apparaissent entre les résultats MD et les prédictions MCT. On peut cependant noter trois points communs significatifs entre les résultats de simulation MD et le calcul MCT :

- l'existence d'un minimum pour $f_{10,10}^c$ et $f_{30,30}^c$ dans la direction [001]
- les valeurs quasi-nulles de $f_{21,21}^c \simeq 0$ et $f_{32,32}^c \simeq 0$
- La hiérarchie $f_{21,21}^c < f_{22,22}^c < f_{20,20}^c$ et $f_{32,32}^c < f_{31,31}^c < f_{33,33}^c < f_{30,30}^c$ bien respectée

La température à laquelle les facteurs de non-ergodicité $f_{\lambda\lambda'}(\vec{q})$ deviennent non-nuls permet de plus de déterminer la température critique $T_c^{MCT} \simeq 267$ K. Celle-ci est supérieure à la température déterminée par simulation MD T_c (voir section 1.1.2.2) mais l'écart de 20 % est similaire avec les résultats obtenus sur les liquides formateurs de verre [60; 59; 63].

Une explication des différences observées entre la simulation MD les prédictions MCT pourrait provenir du champ cristallin propre aux cristaux à désordre d'orientation qui n'est pas pris en compte par MCT. En effet, l'énergie potentielle V d'un cristal plastique composé de molécules d'orientations $(\Omega_1, \dots, \Omega_N)$ peut s'écrire de manière simplifiée comme :

$$V(\Omega_1, \dots, \Omega_N) \simeq V_0 + \sum_n V_1(\Omega_n) + \frac{1}{2} \sum_{n \neq m} V_2(\Omega_n, \Omega_m) \quad (1.6)$$

où V_0 est une énergie de référence (isotrope), V_1 est le champ cristallin dû à l'anisotropie cristalline qui est composé d'un nombre fini de minima locaux et V_2 représente les interactions entre molécules différentes. Dans le cas $V_2 = 0$, les molécules effectueraient seulement des mouvements de réorientations par sauts thermiquement activés comme illustrés dans la figure 1.6. Ce type particulier d'effet de cage généré par un potentiel à une particule n'est pas décrit par MCT qui considère des effets de cage à plusieurs particules.

1.1.3 Structure et dynamique rotationnelle collective

Une étude conjointe de simulation MD, de diffusion neutronique par échos de spins (NSE) réalisée à l'ILL (Grenoble) et de diffraction X a été menée sur le difluorotétrachloroethane (DFTCE) à différentes températures entre 130 et 260 K (collaboration E. Cochin). Ce système est un cristal vitreux composé de petites molécules $\text{CFCl}_2 - \text{CFCl}_2$ proches des molécules diatomiques modèles utilisées comme prototypes des verres moléculaires dans les simulations numériques [42]. DFTCE présente une transition vitreuse de la dynamique rotationnelle à $T_g = 86$ K. Nous nous sommes intéressés à ce système car des changements de sa dynamique – passage d'une dynamique de rotations moléculaires individuelles à des rotations corrélées entre molécules – avaient été observés par RMN et relaxation diélectrique [64; 65].

1.1.3.1 Structure

Compte-tenu du désordre orientationnel, les cristaux plastiques présentent seulement quelques pics de Bragg mais une intense et très structurée diffusion diffuse qui peut fournir

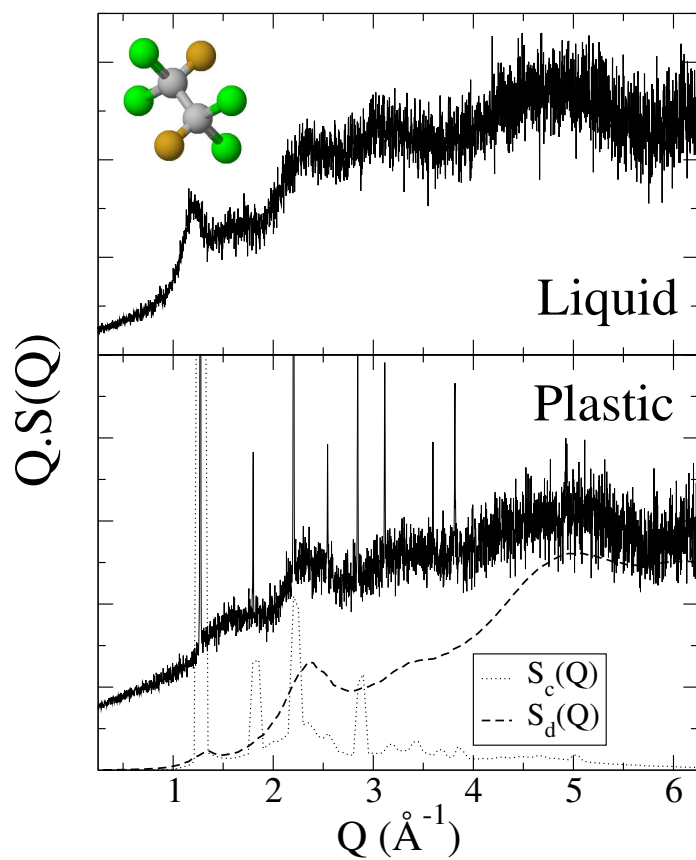


FIG. 1.10 – Facteur de structure expérimental $S(Q)$ de DFTCE en phase liquide à $T = 305\text{ K}$ et en phase plastique à 140 K . Les fonctions de diffusion élastique $S_e(Q)$ et diffusive $S_d(Q)$ obtenues par simulation sont aussi représentées pour comparaison. La molécule de DFTCE est représentée en inset.

des informations afin de caractériser les réorientations moléculaires. La figure 1.10 montre le facteur de structure statique $S(Q)$ de DFTCE obtenu expérimentalement par diffraction X dans la région $[0.4 - 6.5] \text{ \AA}^{-1}$. Huit pics de Bragg sont clairement identifiés et peuvent être indexés par une structure cc avec un paramètre de maille de $6.985 \text{ \AA}$. Ce résultat confirme l'étude préliminaire réalisée par Kishimoto *et al.* [66]. Par simulation MD, nous avons calculé les fonctions de diffusion élastique $S_c(Q)$ et diffuse $S_d(Q)$ en bon accord avec les résultats expérimentaux (voir figure 1.10). Les maxima de $S_c(Q)$ coïncident notamment avec les positions des pics de Bragg et les maxima de $S_d(Q)$ avec les contributions de la diffusion diffuse. De plus, une forte similarité entre l'allure du diagramme de la phase plastique et du liquide est observée. Le premier pic le plus intense du liquide correspond au premier pic de Bragg du cristal. Les maxima de la diffusion diffuse sont presque identiques entre les deux phases. Les deux diagrammes sont similaires pour les grandes valeurs de Q qui sondent essentiellement la structure interne de la molécule. Ce résultat suggère une forte analogie entre le comportement du liquide et du cristal plastique qui sera discutée dans la section 1.1.4.

La distribution orientationnelle des molécules de DFTCE peut être décrite à partir de la fonction de probabilité $f(\vec{u})$ où $\vec{u}$ est un vecteur unitaire situé le long de l'axe carbone-carbone de la molécule de DFTCE (voir figure 1.10). A l'aide d'un développement de $f(\vec{u})$ sur une base d'harmonique cubique compte tenu du groupe de symétrie du cristal Oh, nous avons montré que les molécules s'alignaient préférentiellement le long de la direction [111] de ce cristal cubique. Nous avons aussi observé un accroissement de la probabilité orientationnelle suivant cette direction contrairement aux directions [100] ou [110] qui suggère une localisation de l'orientation des molécules similaire à celle des adamantanes substitués.

1.1.3.2 Dynamique rotationnelle collective

Les dynamiques collectives de DFTCE ont été analysées à partir des fonctions de corrélation $S(Q, t)$ obtenues par simulation MD et mesurées par NSE à l'ILL (Grenoble). $S(Q, t)$ est représenté sur la figure 1.11 à différentes températures pour le vecteur d'onde arbitraire $Q = 1.54 \text{ \AA}^{-1}$. Un bon accord entre les données expérimentales et numériques est clairement mis en évidence. Lorsque la température diminue, on observe l'apparition d'un découplage α et β des dynamiques et d'un plateau correspondant aux localisations des molécules suivant les orientations préférentielles. Il s'agit d'un effet de cage orientationnelle mentionné précédemment. La figure 1.12 représente le temps caractéristique $\tau_{1/e}$ extrait des fonctions $S(Q, t)$ obtenues par simulation et par diffusion neutronique et comparé aux données expérimentales de la littérature. Nos résultats sont parfaitement consistants avec les résultats de RMN et de relaxation diélectrique extrapolés dans le régime pico-nanoseconde. Un ajustement par une loi de Vogel-Fulcher-Tammann (VFT) :

$$\tau_{VFT} = \tau_0 \exp \left(\frac{1}{K_{VFT}(T/T_{VFT} - 1)} \right) \quad (1.7)$$

où K_{VFT} mesure l'indice de fragilité du système et T_{VFT} est la température de divergence apparente, donne : $K_{VFT} = 0.20$ et $T_{VFT} = 86.9 \text{ K}$. $K_{VFT} = 0.13$ et $T_{VFT} = 70 \text{ K}$ sont obte-

nues à partir des données de relaxation diélectrique obtenues à l'approche de la transition vitreuse.

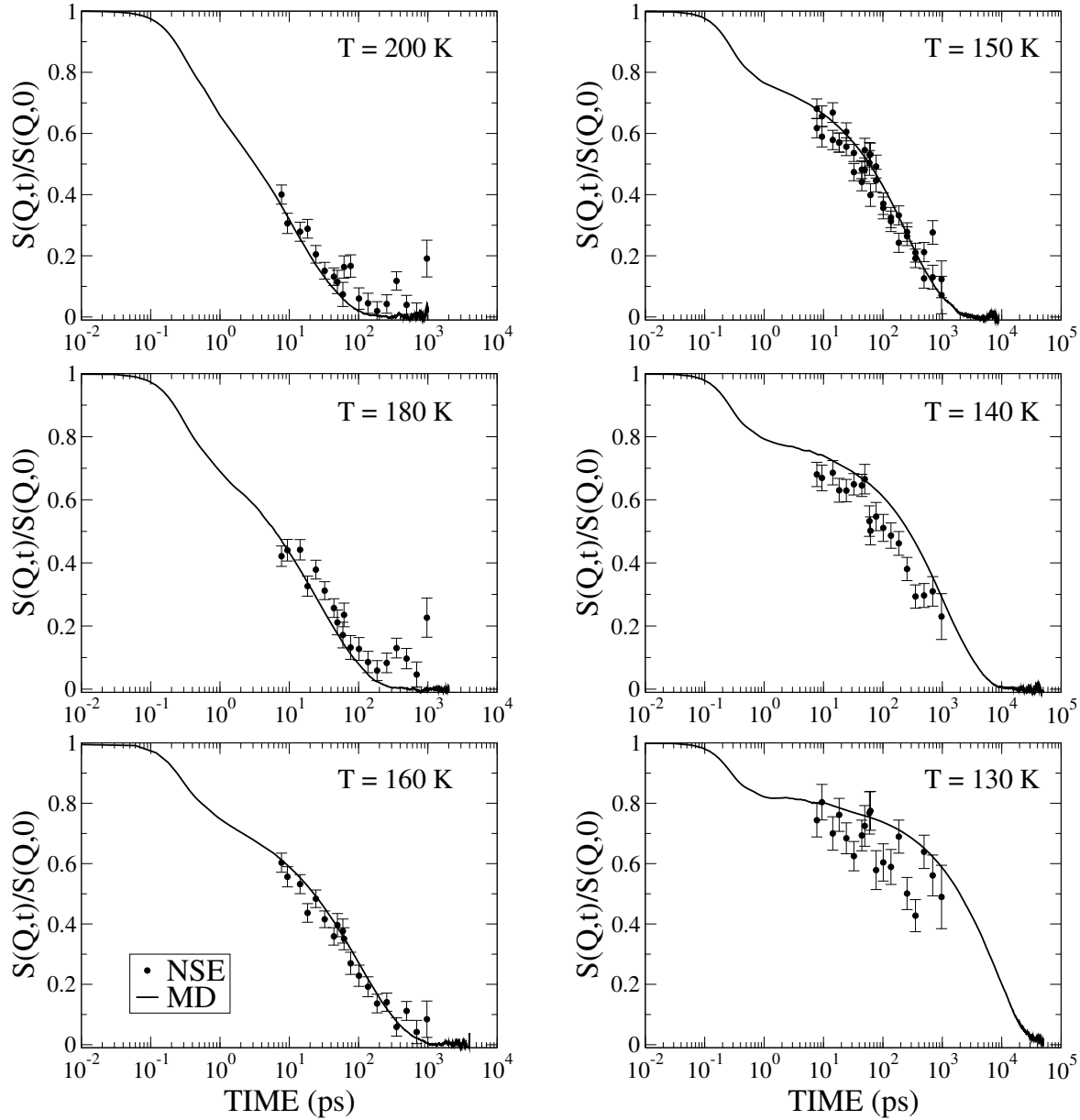


FIG. 1.11 – Fonctions de corrélation des dynamiques collectives $S(Q,t)/S(Q,t=0)$ à $Q = 1.54 \text{ \AA}^{-1}$ obtenues par NSE et par simulation MD à différentes températures.

Dans les précédents calculs MD sur Cla, nous avons montré que de nombreuses prédictions de MCT étaient vérifiées. Afin de confirmer ces résultats sur le DFTCE, on a représenté sur la figure 1.13 les fonctions $S(Q,t)$ tracées en fonction de $t/\tau_{1/e}$. On observe

clairement que les différentes fonctions expérimentales et numériques se superposent sur une courbe maîtresse qui valide le principe de superposition, une des prédictions principales de MCT. Pour la plus basse température $T = 130$ K, $S(Q, t)$ dévie de la courbe maîtresse et révèle que cette prédiction de MCT cesse d'être valide. Ce résultat est confirmé par les trajectoires de molécules cibles qui montrent qu'à basses températures la dynamique est associée à de larges rotations entre orientations préférentielles similaires à celles observées pour Cla (voir figure 1.6). Celles-ci sont les équivalents des processus de sauts thermiquement activés suggérés dans les liquides formateurs de verre qui ne sont pas pris en compte dans la théorie MCT. Cette déviation est classiquement observée près de la température critique T_c prédite par MCT et nous permet donc de l'estimer grossièrement à 130 K.

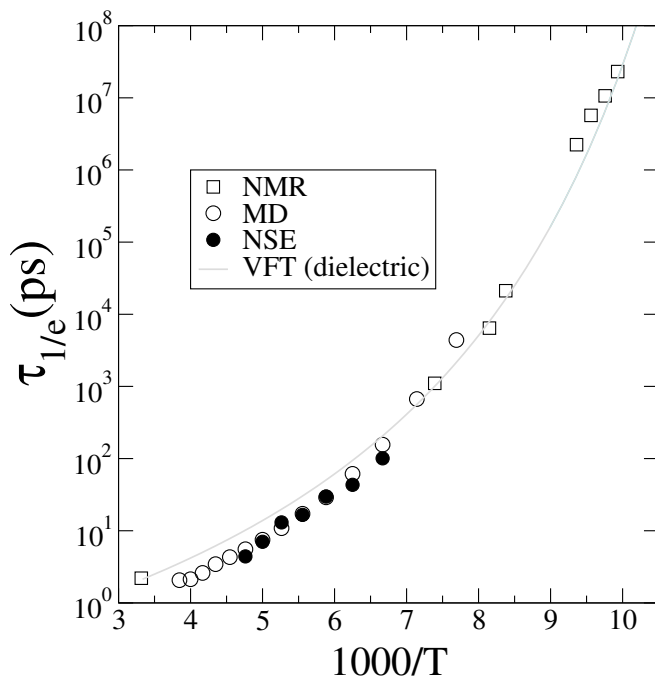


FIG. 1.12 – Temps caractéristiques des dynamiques lentes $\tau_{1/e}$ obtenus par NSE et simulation MD et comparés aux données RMN et diélectriques.

Une des prédictions fondamentales de MCT porte sur le contrôle des fonctions dépendantes du temps par le facteur de structure statique $S(Q)$. Cette prédiction a été testée avec succès pour de nombreux formateurs de verres : mélange d'atomes Lennard-Jones et liquides moléculaires comme l'orthoterphényle. Encouragé par le bon accord entre la structure expérimentale et simulée de DFTCE (voir figure 1.10), nous avons étudié la dépendance en Q du temps de relaxation τ_Q , du facteur de non-ergodicité f_Q et des préfacteurs $h_1(Q, T)$ et $h_2(Q, T)$ obtenus à partir d'ajustement de $S(Q, t)$ à l'aide de l'équation 1.3. Les résultats montrent que τ_Q et f_Q oscillent en phase avec $S_d(Q)$ et $S_c(Q)$ tandis que $h_1(Q, T)$ et $h_2(Q, T)$ sont en phase avec $S_d(Q)$ et en antiphase avec $S_c(Q)$ en très bon accord avec

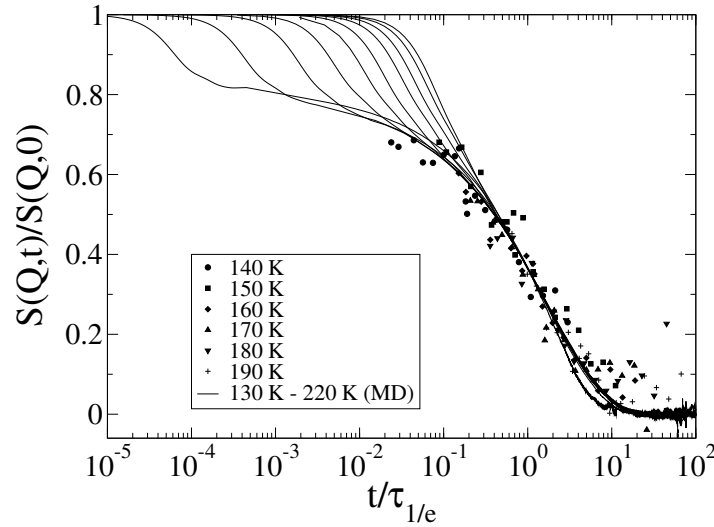


FIG. 1.13 – *Fonctions de corrélation des dynamiques collectives $S(Q,t)$ à $Q = 1.54 \text{ \AA}^{-1}$ obtenues par NSE et par simulation MD à différentes températures en fonction de $t/\tau_{1/e}$.*

la théorie MCT (voir figure 1.14).

1.1.4 Analogie entre cristal plastique et liquide moléculaire formateur de verre

Une petite classe de composés moléculaires comme l'éthanol présente l'extraordinaire propriété de former un verre à la fois à partir du liquide et de la phase plastique. Une investigation de ces matériaux est particulièrement intéressante pour comprendre le rôle précis des rotations ainsi que le couplage translation/rotation à l'approche de la transition vitreuse. Nous avons réalisé une étude comparative des dynamiques lentes du DFTCE en phase plastique et liquide. La phase liquide de DFTCE peut être sous-refroidie compte tenu des vitesses de trempe extrêmement rapides utilisées en simulation MD. La figure 1.14 représente les fonctions de corrélation dynamique collectives $S_d(Q,t)$ de DFTCE à différentes températures et une très forte similitude est observée entre ces deux phases bien que des degrés de liberté différents soient mis en jeu. Des tests de la théorie MCT ont pu être effectués avec succès pour la phase liquide de la même manière que pour la phase plastique. Une comparaison des dépendances en Q du temps caractéristique τ_Q et du facteur de non-ergodicité f_Q des deux phases est représentée sur la figure 1.14. Celle-ci souligne particulièrement bien les similitudes des comportements dynamiques entre liquide et cristal plastique.

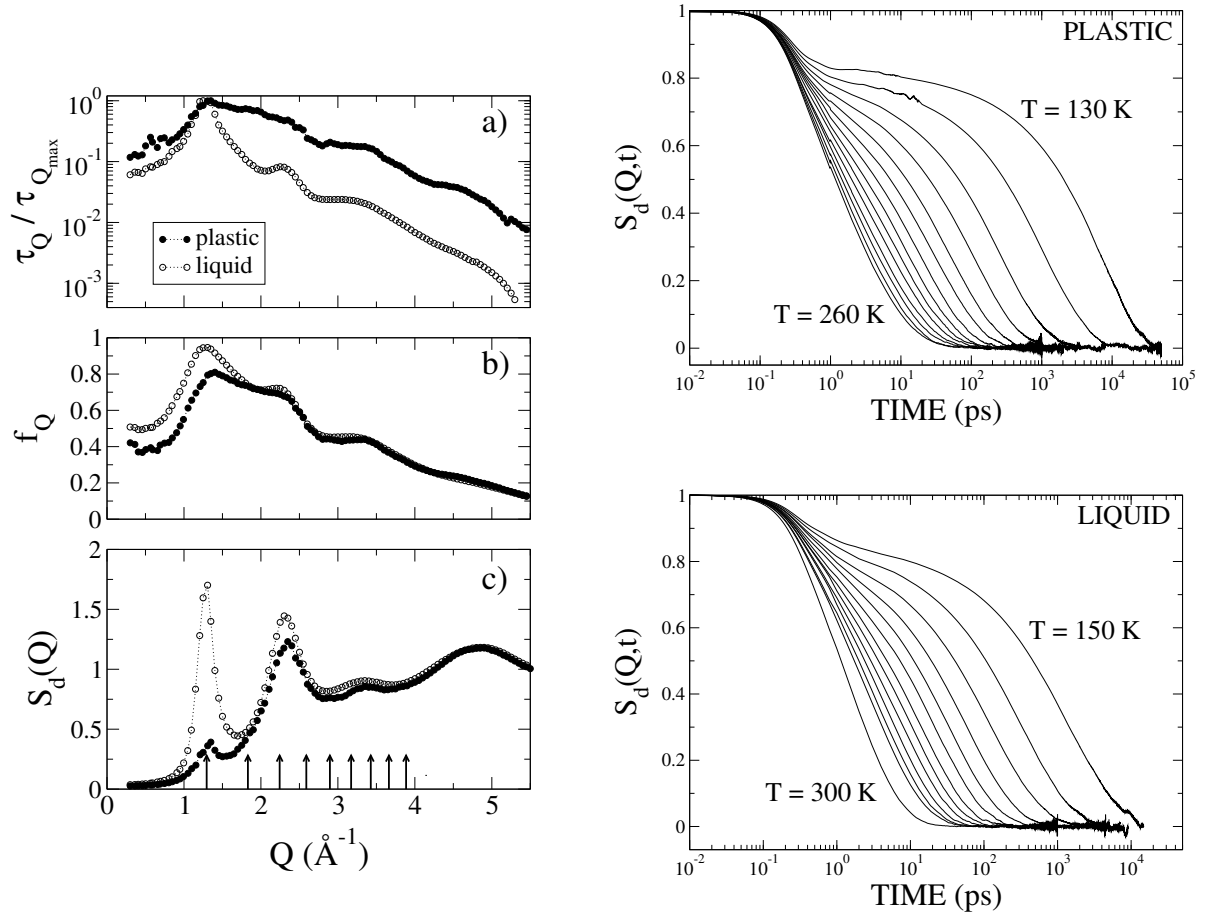


FIG. 1.14 – Gauche : Dépendance en Q de différents paramètres de la phase plastique et liquide de DFTCE à la température $T = 160$ K : a) temps de relaxation $\tau_Q / \tau_{Q_{\max}}$ où $Q_{\max}$ est la position du maximum du facteur de structure statique $S(Q)$; b) facteur de non-ergodicité f_Q et c) Diffusion diffuse $S_d(Q)$. La position des pics de Bragg ($S_c(Q)$) est représentée par des flèches. Droite : Fonctions de corrélation des dynamiques collectives $S_d(Q, t)$ à $Q = 1.54 \text{ \AA}^{-1}$ obtenues par simulation MD pour la phase plastique et liquide de DFTCE.

A Monte Carlo study of metastable structures of the cyanoadamantane crystal

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(Received 26 March 1998; accepted 21 July 1998)

We report results of the Monte Carlo simulations of stable and metastable phases of cyanoadamantane crystal, which is a model of an orientational glass forming system. The structures which have been found stable within the Monte Carlo runs include the plastic cubic phase, two different monoclinic phases, and an orthorhombic phase. The calculations have shown that all those structures remain metastable in the whole studied range of temperatures between 100 and 400 K. The orthorhombic arrangement is energetically the most favorable but the cubic phase is the most stable phase at high temperature because of the disorder and large entropy term in the free energy. The transient orthorhombic phase is playing an important role in the transformations from quenched cubic phase into stable low temperature structure. A possibility of a disorder in the orthorhombic phase is discussed and pointed out as a factor which may affect the mechanism and kinetics of the transformation between quenched cubic structure and the low temperature ordered phase. The present model is not able to stabilize thermodynamically the monoclinic structure at low temperature, and the simplified representation of the intermolecular interaction seems to be the cause. © 1998 American Institute of Physics. [S0021-9606(98)50240-1]

I. INTRODUCTION

Many molecular crystals form plastic or, so-called, rotator phases. They are equilibrium structures which exist below melting and are characterized by a dynamic orientational disorder of molecules and a translational order of positions of molecular centers of mass. Upon decreasing the temperature they undergo a transition into a phase where also orientations of molecules become ordered. This transition is generally of the first-order character, so, often some undercooling is possible. In some cases, the transition can be bypassed by a rapid temperature quench. As a result, one may find the system in a metastable orientationally disordered state which transforms at still lower temperature into a state with frozen molecular orientations. Such crystals were called “glassy crystals.”¹

A glassy crystal has numerous similarities with conventional glassy state. It exhibits a thermodynamic glass transition marked by a heat capacity jump,² Vogel–Fulcher behavior of the relaxation,³ and low temperature anomalies.⁴ However, the main difference is that the freezing primarily involves the rotational movement of molecules. Their centers of mass remain to form an average lattice of the initial crystal matrix.⁵ There is also an important distinction between glassy crystals and the orientational glasses such as $(\text{KCN})_{1-x}(\text{KBr})_x$, where the transition toward an ordered state is suppressed by dilution effect.^{6,7} For glassy crystals, before the glassy state is reached, the plastic phase becomes metastable with respect to the low temperature ordered crys-

talline phase. The fundamental importance of underlying equilibrium states, both stable and metastable, is important if one wants to understand the glass forming conditions and the glass transition itself. The fact that all involved states are crystalline is an advantage. We may follow the evolution of lattice parameters or fluctuations and their symmetry to get more information about the microscopic states. In particular, they offer an interesting opportunity to describe a short- and a medium-range order in the three-dimensional frame of the underlying crystal lattice. Also, progress can be expected in the understanding of the role that competition between different phases could play to generate structural frustration.⁸

The ability of systems to form metastable states has never been studied extensively in molecular crystals. However, such states can often be detected in the far-from-equilibrium situations, especially, in the glass forming systems or rotationally disordered crystals.⁹ The structural experiments on the deeply quenched cyanoadamantane (CNa) crystal^{10–13} have also revealed the existence of metastable phases, the lifetimes of which are long enough to be detected experimentally. Metastability properties have been found to depend on the temperature of quenching and the aging time of the quenched sample. Because CNa is less disordered than the majority of glassy crystals, cyclohexanol,² for example, it offers larger experimental possibilities that are easier to interpret.

The main goal of the Monte Carlo simulations presented in this paper is to explore the metastable phases of solid CNa in the wide range of temperatures, from the melting tempera-

ture down below the temperature of the transformation into glassy state. Here, we do not attempt to simulate the glass transition itself. Instead, we study various structural aspects of stable and metastable states which may play a role in the mechanism of generation of the structural frustration in the glassy crystals. This frustration must be intrinsically self-generated by the system, but its origin is not fully understood. Ultimately we hope to understand which structural changes generate the frustration, what the role of metastable states is, and how they affect the mechanism of freezing. A second role of the calculations presented in this paper is a test of several intermolecular interaction potentials for the CNa molecules in order to obtain a model as realistic as possible.

II. THE SOLID PHASES OF CYANOADAMANTANE

Among glassy crystals, cyanoadamantane (CNa), and also a mixed compound with chloroadamantane (Cla), seem to be particularly interesting examples of systems that are suitable for exploration of the phase diagram and the vitrification mechanism. An experimental advantage of this system is the fact that the single crystal of the rotator (*R*) phase can be grown and safely quenched to the glassy state. There are two equilibrium phases of the cyanoadamantane crystal reported experimentally. Below the melting temperature ($T_m = 465$ K) it forms a plastic phase (*R*) with cubic $Fm\bar{3}m$ space group symmetry.¹⁴ The orientational disorder of the molecules can be characterized by both structural and dynamic features. There is a random distribution of molecular axis (the molecular dipoles) along $\langle 100 \rangle$, $\langle 010 \rangle$, and $\langle 001 \rangle$ directions and the molecules librate ($\langle \theta^2 \rangle^{1/2} \approx 3.2^\circ$) about each direction. The residence time τ of a molecule in a given orientation at room temperature is very long ($\tau \approx 10^{-6}$ s) compared to the libration frequency because the activation barrier for molecular flip is high.^{15,16} However, there is a second type of orientational motion which is much less constraining. This is the rotation of each molecule around its molecular (dipole) axis ($\tau \approx 10^{-11}$ s).^{16,17} The second, orientationally ordered phase (*m*) (monoclinic $C2/m$) is stable below 283 K. Its structure is built with parallel planes of anti-ferroelectrically ordered molecules.¹⁸ However, a supercooled disordered phase I_g can be obtained by quenching the cubic phase at a sufficiently rapid rate to a temperature below 180 K.^{18,19} An experimental study of cyanoadamantane structural changes as a function of temperature is difficult in practice since the single crystal is destroyed by the transformation into phase (*m*). Apparently, the process of ordering of the molecules produces strong stresses which have their origin in a strong deformation of the cubic unit cell into the monoclinic one. The deformation is strongly coupled to the rotational motion because all molecules must fit into an approximate anti-ferroelectric order along one of the cube diagonal's directions.

The ability to form rotator phases is common for the mixed compounds of CNa and Cla $[(CNa)_{1-x}(Cla)_x]$, $0 \leq x \leq 1$. All these disordered phases are iso-structural. However, their rotational dynamics depends on the concentration parameter x . At the same time, the mixed character does not suppress the ordering transition as it happens in the orienta-

tional glasses.²⁰ So, the concentration is one more parameter, in addition to temperature and aging time, which may affect the mechanism of the formation of metastable structures. The glassy crystal states have been found in the structures for $0 \leq x \leq 0.5$. The low temperature ordered phases, which are all monoclinic, possess different space group symmetries ($C2/m$ for $x=0$, $P2_1/c$ for $x=0.25$). In the $C2/m$ structure (low values of x), the molecular dipoles are ordered anti-ferroelectrically along the pseudo-threefold axis of the initial cubic cell. In the $P2_1/c$ structure (larger values of x) they form a planar ordered herringbone-type structure which is iso-structural with the low temperature phase of pure Cla.

All the quenched rotator states, upon deep undercooling down close to the thermodynamic glass transition temperature (T_g), give a rich manifestation of nonequilibrium states whose structural and calorimetric signatures are difficult to interpret. The x-ray diffraction experiments performed on the cubic CNa single crystal quenched below T_g revealed a slow and sluggish growth of superstructure peaks located at the forbidden points of the reciprocal lattice of the face-centered-cubic (fcc) lattice (X boundary point of the Brillouin). They indicated a slow ordering process of the molecules in a way that was different than expected for the monoclinic phase (*m*) stable at that temperature. The distribution of the corresponding scattering data was shown to be compatible with a local tetragonal structure with molecules anti-ferroelectrically ordered along one of the fourfold cubic axis.^{21,22} Also, the calorimetric experiments performed on annealed samples (at different temperatures and aged differently) revealed that the stability of this intermediate phase is strongly dependent on the conditions of the annealing.²³ In particular, the temperature of the endothermic, monotropic transition observed on reheating depends on the annealing conditions. This result suggested that the free energy of each sample must have been different as a consequence of the strongly nonequilibrium situation in which the phase was prepared. The structural origin of such dependence of the stability of structures on the annealing conditions is not yet fully understood.

III. THE MONTE CARLO METHOD AND THE POTENTIAL MODEL

Simulations were performed on a set of 256 CNa molecules in a Monte Carlo (MC) box with periodic boundary conditions within a constant pressure, constant temperature (NPT) ensemble. The Metropolis Monte Carlo method was used to generate the microscopic states of the crystal. At each temperature, the system was first equilibrated. Following the equilibration, main runs were performed during which the configurations were saved for the later analysis. The simulations were carried out at four temperatures: 400, 300, 200, and 100 K. Depending on temperature, the trajectories of all particles were followed over 25 000–100 000 MC steps, after an initial 5000–10 000 steps which equilibrated the system. We used the deformable boundary conditions which allowed the MC box to change its shape and volume during the runs. At each MC step, the degrees of freedom of the box were randomly changed and then followed by translational and orientational moves of each molecule.

TABLE I. The intermolecular potential model parameters (models I and II).

Site	x	y	z [Å]	ϵ [K]	σ [Å]	q [e]	
						Model I	Model II
N	0.0	0.0	3.5575	85.41	3.250	-0.712	-0.491
C	0.0	0.0	2.4175	35.15	3.550	0.712	0.325
X	0.0	0.0	0.1947	...	...	...	0.166
adm	0.0	0.0	-0.5838	1000.00	6.300	...	...

In order to be able to afford runs as long as possible in the metastable regime, a simple model of a CNa molecule was defined. The molecule was represented by a rigid three-site model which is build from two atomic sites (C and N atom of the cyano group) and one site playing the role of the entire adamantane atoms (adm) group (super-atom approximation). Molecules interact with one another by virtue of the site-site potentials. The site-site interactions are approximated by the Lennard-Jones form, $v(r) = 4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6]$, where the values of (na, nr) vary depending on the type of the site-site contact and the potential model (see Tables I and II).

There are two different potential models used in our calculations (see Table I) which we developed in a process of searching for the best representation of molecular interaction. The parameters of the C-C, N-N, and H-H potentials in models I²⁴ and II were taken from the paper which reported values for different organic functional groups, including cyano groups.²⁵ The parameters for *adm-adm* interactions have been determined²⁴ from the atom-atom interactions between atomic sites of the adamantane part of the molecules. First, the averaged energies over all molecular orientations were calculated for different distances of centers of mass of the adamantane part of molecules. Then, they were fitted into the Lennard-Jones form. The parameters for interactions between dissimilar sites have been determined by the combining rules: $\epsilon_{AB} = (\epsilon_{AA}\epsilon_{BB})^{1/2}$ and $\sigma_{AB} = (\sigma_{AA} + \sigma_{BB})/2$. The 6-12 Lennard-Jones functions were applied for all dissimilar interactions (see Table II).

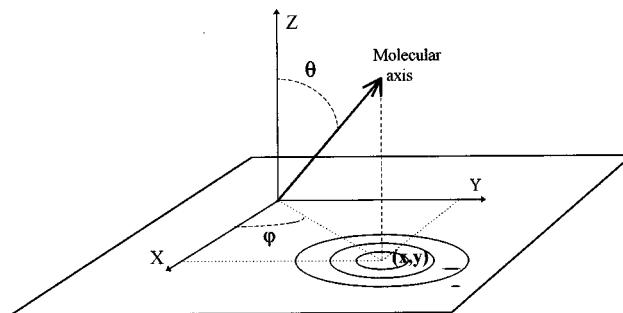
Apart from the van der Waals and repulsive interaction, there is also electrostatic interaction between CNa molecules. The CNa molecule possesses a relatively large dipole moment [experimental value: $d = 3.92$ D (Ref. 26)]. The electrostatic interaction was introduced by defining point charges distributed along the molecular axis. We have used two different models of the charge distribution: two charges (model I) and three charges (model II). In the two-charges model, two point charges of opposite sign (see Table I) were located on the cyano group atoms. However, such a representation overestimates the dipole moment of this group. Therefore, we have carried out *ab initio* calculations of the charge distribution on the CNa isolated molecule. The three-charges model has been constructed using the calculated two charges on the cyano group atom and a third one, the value of which has been chosen to make the total molecular charge equal to zero and its position to reproduce the total dipole moment [theoretical *ab initio* value: $d = 4.46$ D (Ref. 27)]. Obviously, the difference between model I and II is only because of the different charge distributions.

TABLE II. The (na, nr) parameters of the generalized Lennard-Jones potential $v(r) = 4\epsilon[(\sigma/r)^{nr} - (\sigma/r)^{na}]$ and values of the dipole moments [in Debye].

Site-site contact	(na, nr)	
	Model I	Model II
N-N	(6,12)	(6,12)
C-C	(6,12)	(6,12)
N-C	(6,12)	(6,12)
adm-adm	(10,16)	(10,16)
adm-N	(6,12)	(6,12)
adm-C	(6,12)	(6,12)
Dipole	3.92	4.46

The effective linear form of the molecules allows us to represent their orientations by two polar angles, θ and ϕ , as defined in Fig. 1. Figure 1 also defines the way in which we represent orientational distribution maps in this paper. The orientation of a molecule is represented on the xy plane as a point which is a projection of the end of the unit vector parallel to the molecular axis. In other words, the orientational distributions are functions of Cartesian variables $x = \cos(\phi)\sin(\theta)$ and $y = \sin(\phi)\sin(\theta)$.

The ultimate conclusions concerning a stability of phases must be based on the free energy calculations.²⁸ However, we do not attempt to calculate the free energies of all phases found in the cyanoadamantane. As will be discussed in the next chapter, some conclusions about the unconditional stability of the phases may be formulated without free energy calculations, which are known to be computationally very time consuming.²⁹ The other reason which makes such calculations difficult in the case of cyanoadamantane is the nonergodic behavior of the system within the accessible simulation time. Such behavior is always expected in disordered systems, where the disordering dynamics time scale is much longer than typical lattice vibrations. In such a situation the simulations are usually too short to allow the system to probe the configuration space properly. So, two types of averages have to be performed: first, the thermal average in the presence of a quenched disorder, and second, over the randomness, that is, over different quenched configurations (see Appendix).

FIG. 1. A representation of the orientational distribution maps on the xy planes. Molecules are represented by a unit vector (parallel to the molecular dipole), the orientation of which is defined by polar angles φ and θ .

IV. RESULTS OF THE SIMULATIONS

A. Plastic phase

The calculations were started from the simulation of the cubic phase. The initial configuration of molecules was constructed by placing their centers of mass on the cubic fcc lattice and their orientations randomly distributed among six ($\langle 001 \rangle$, $\langle 010 \rangle$, $\langle 001 \rangle$) equivalent directions of the cubic symmetry in accordance with the experimental structure.^{14,16,17} It is important to remember that the orientation of a molecule on a crystal site is not totally random because there is a correlation between orientations of the neighbors.³⁰ The shape and size of the CNa molecule, as well as orientations of neighbors, impose some space limitations on packing of molecules in a nonoverlapping way and put constraints on possible orientations of a molecule on the site. In the box of

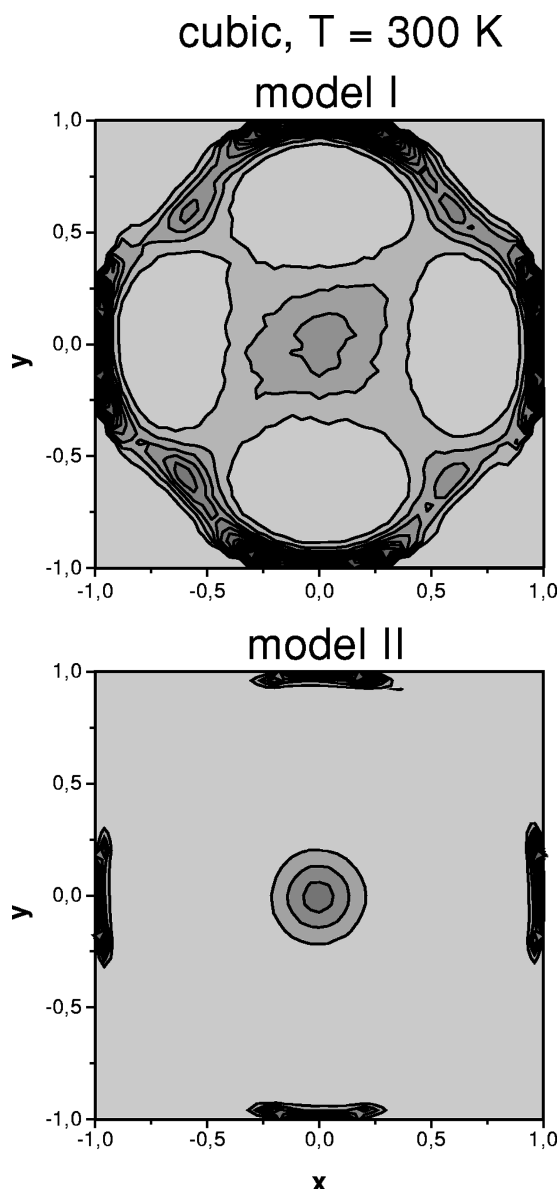


FIG. 2. The orientational distribution xy maps for the cubic phase, at the temperature $T=300$ K. The maps show two orientational probability distributions calculated from simulations performed for two different potential models.

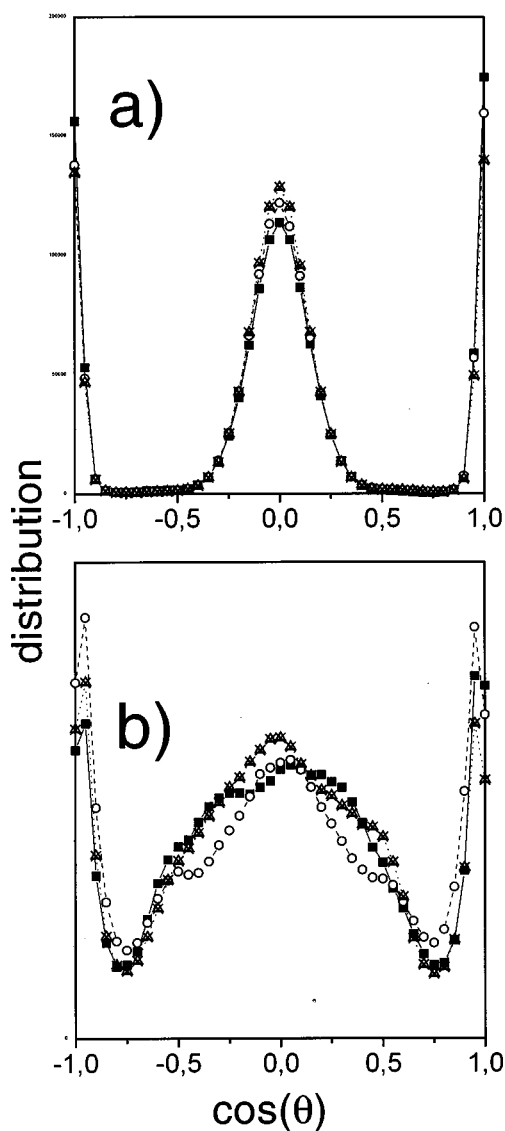


FIG. 3. $\cos(\theta)$ distribution function for cubic phase at 300 K calculated from the simulations using (a) model II, (b) model I. Each graph shows three plots corresponding to different choices of the z axis of the coordinate system (as defined in Fig. 1) along $\langle 001 \rangle$, $\langle 010 \rangle$, and $\langle 100 \rangle$ cubic axes, respectively.

256 molecules we found two sites where the molecules did not fit into any of the six $\langle 001 \rangle$ directions, and initially were put in some intermediate orientation. However, this was a consequence of the finite size of the MC box and periodic boundary conditions which imposed additional constraints on the molecular orientations in the MC box.

The simulations, performed for temperatures in the range from 100 to 400 K, showed that the cubic phase behaved as if it were stable in the whole range of studied temperatures, that is, we observed that the cubic structure does not transform into any other structure in very long Monte Carlo runs, independently on the used potential model. As a consequence, it can easily form metastable states. This numerical result is consistent with the experimental situation where the cubic phase can be easily quenched to low temperature. In the course of simulations it was observed that the system often produced thermal fluctuations which distorted the cubic unit cell dynamically. However, any static distortion hap-

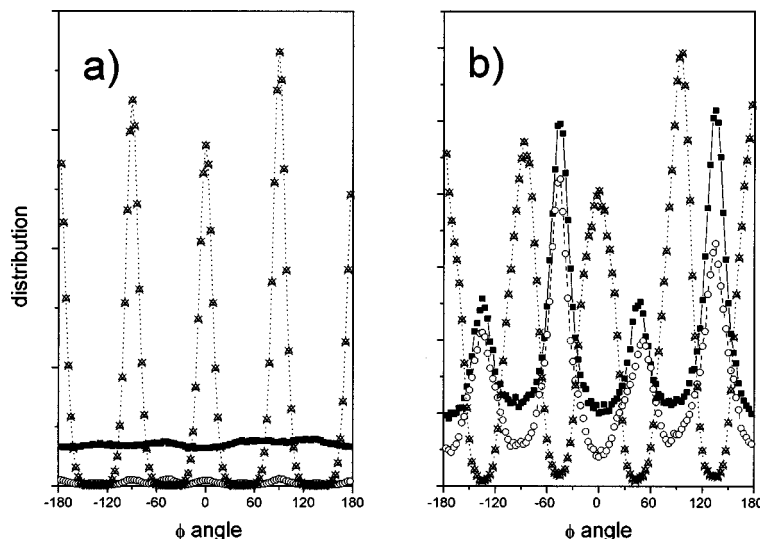


FIG. 4. φ angle distribution function for cubic phase at 300 K calculated from the simulations using (a) model II, (b) model I. Different graphs show the distribution corresponding to different ranges of $\cos(\theta)$: $|\cos(\theta)| < 1/3$ (full squares), $1/3 < |\cos(\theta)| < 2/3$ (open circles), $2/3 < |\cos(\theta)|$ (crossed triangles).

pened very rarely and was possible only if the system overcame an energy barrier and jumped off from the minimum corresponding to the cubic structure.

An analysis of the influence of the potential model on the calculated structure showed that the orientational distribution of molecules was very sensitive to the charge distribution on the CNa molecule. We compared results calculated from Monte Carlo simulation using models I and II. As it has been mentioned in the previous chapter, the difference between them is only because of the modified charge distribution. The calculations performed with our interaction model I (two-charges model) gave a large dynamic orientational disorder.²⁴ At room temperature, we observed large amplitude molecular movements, and distributions of molecular orientations were not limited to the $\langle 100 \rangle$, $\langle 010 \rangle$, $\langle 001 \rangle$ directions (Fig. 2). This was not the case for model II, which gave the distributions very well localized. Such a picture agrees with the experimental data, which give six possible orientations of the molecules which librate with an amplitude of approximately 3.2° .

Figures 3 and 4 present some details of the orientational probabilities, showing $\cos(\theta)$ and φ distributions, respectively. It is obvious that model II allows the molecules to orient only along the $\langle 001 \rangle$, $\langle 010 \rangle$, $\langle 001 \rangle$ directions. Model I, on the other hand, does not constrain molecules and allows them to have much more orientational freedom. The θ distribution is much wider and gives nonzero probability for any angle. Also, the φ distribution exhibits many peaks which correspond to orientations different from the $\langle 001 \rangle$, $\langle 010 \rangle$, $\langle 001 \rangle$ directions. The difference between the results obtained with models I and II tells us that the electrostatic part of the interaction plays a key role in determining the structural and dynamical properties of the cyanoadamantane crystal. The electrostatic part of the crystal energy of the cubic phase, as well as the total crystal energy, is presented in Fig. 5. Its role in determining the stability of the phase will be discussed after the presentation of the simulation results of other phases.

On the other hand, the volume depends mostly on the Lennard-Jones part of the interactions. This aspect is shown

in Table III, where one can see that models I and II do not differ much in their ability to reproduce the experimental volume of the crystal. However, we use model II because it represents the molecular distribution in accordance with the experimental data.

B. The orthorhombic phase

Figure 6 presents an example of the fluctuation observed in the Monte Carlo runs within the cubic phase at high temperatures (300 K and higher). Such fluctuations deform the cubic unit cell toward a tetragonal shape. They are indirectly induced by fluctuations of molecular orientations which prefer, because of dipole–dipole interactions, more uniaxial local order (see discussion below). So, it is a strong translational–rotational coupling which is the direct cause of the fluctuations. They show a tendency of the system to order itself at lower temperature, where the entropy contribution decreases and the cubic disordered structure becomes stable.

Therefore, as a next step we performed Monte Carlo simulations, the initial configurations of which were constructed as a perfect tetragonal arrangement with antiferroelectric order of molecular dipoles [Fig. 7(a)]. The choice of the initial structure was based on the experimental x-ray data analysis of the microstructure, connected with an appearance of peaks situated at the X point of the reciprocal lattice, measured in the experiment performed on the quenched crystal.²² This experiment could be best interpreted in terms of a local tetragonal structure. It is worth noticing that the corresponding molecular arrangement has a lot in common with the cubic structure, and molecules maintain one of the orientations of the cubic phase but arrange themselves in an antiparallel order along one of the fourfold axes. Therefore, the only change is that the molecules stop all their reorientational jumps of large amplitude. The structural results of the simulations at 200 K are presented in the Fig. 8. The most striking feature is the distortion of the initial tetragonal geometry into an orthorhombic one because the molecules are tilted with respect to the z axis. Also, the pe-

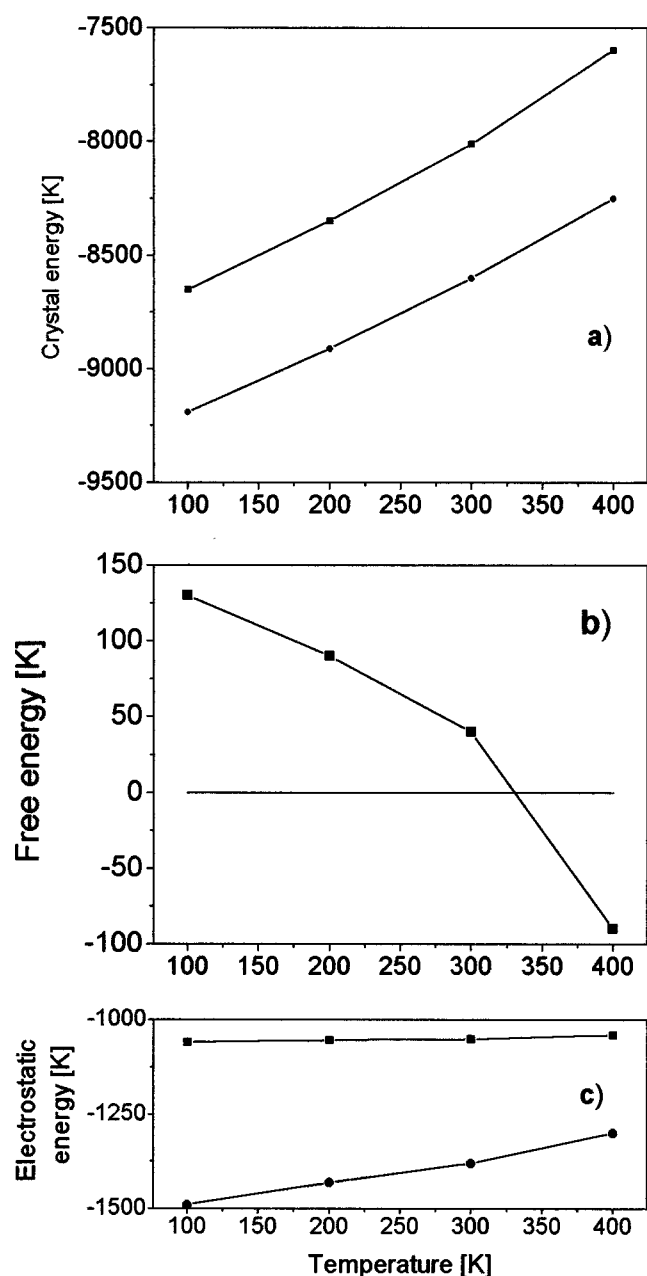


FIG. 5. Lattice energy of two phases: cubic (squares, solid line) and orthorhombic (circles, dashed line). (a) total energy, (b) difference of free energy, (c) electrostatic energy. The lines are the guides for eyes only.

riod of the unit cell has been doubled along the z direction, so there are four molecules in the unit cell [see Fig. 7(b)]. The distortion of the tetragonal arrangement is a consequence of strong dipole-dipole interaction within xy planes

TABLE III. Cubic unit cell lattice parameters [in Å] calculated in simulations using different potential models as a function of temperature.

	Model I	Model II	Exp
$T=100$ K	9.84	9.82	9.63
$T=200$ K	9.90	9.88	9.72
$T=300$ K	9.98	9.95	9.81
$T=400$ K	10.06	10.04	9.92

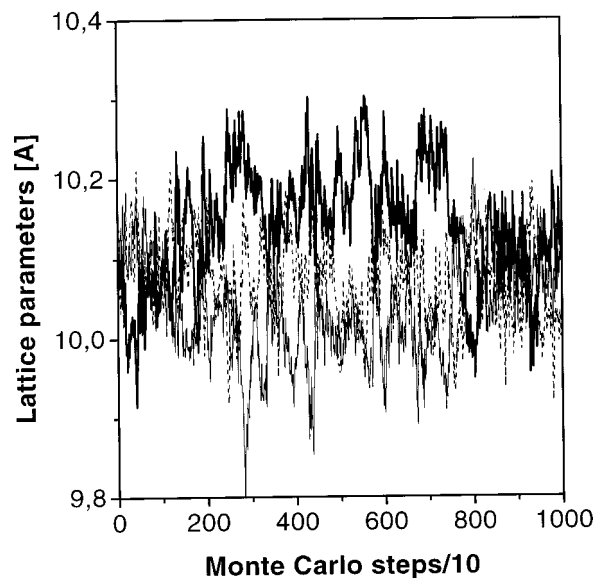


FIG. 6. Fluctuations of the cubic cell parameter showing a volume fluctuation of tetragonal shape.

which forces the CN groups to associate in pairs. It is seen that such pairs are formed from two molecules which belonged to two successive planes in the fcc lattice (Fig. 8). The interaction between the planes formed by molecular pairs is much weaker than within each plane. The calculated structure is consistent with new x-ray scattering data which show additional small peaks in between some specific X points of the reciprocal lattice³¹ in the quenched cubic state. The appearance of the additional peaks indicates a doubling

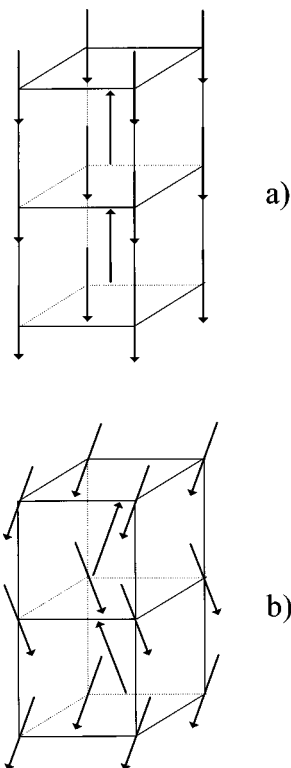


FIG. 7. The anti-ferroelectric orders of molecular axis: (a) antiparallel, tetragonal symmetry, (b) tilted, orthorhombic symmetry.

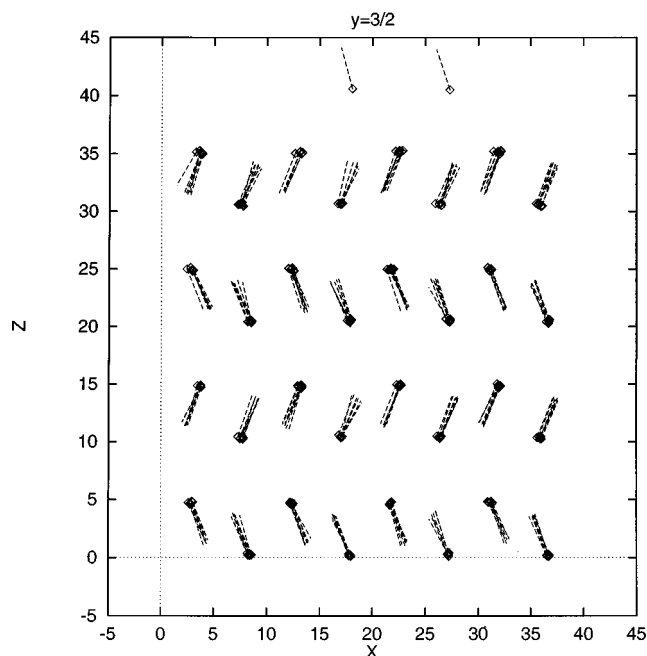


FIG. 8. Few snapshots from the Monte Carlo runs for orthorhombic phase ($T = 200$ K).

of the unit cell caused by the out-of-phase tilting of the molecules along the pseudotetragonal axis. The stability of this orthorhombic phase will be discussed in Sec. IV.

Another interesting behavior observed in the course of the simulations of the orthorhombic phase is a possibility of a disorder between planes, where each plane is formed from molecules associated into pairs (xy planes in Fig. 8). This tendency is dependent on the temperature and, obviously, the disorder is more easily formed at higher temperature, where the disordering fluctuations are produced with higher probability. The differences between the orientational distributions of the ordered orthorhombic and disordered (on average tetragonal) structures are presented in Figs. 9, 10, and 11. Figure 9 presents orientational distributions calculated at 200 (ordered) and 300 K (disordered). The xy map at 300 K shows four orientational maximums corresponding to the average tetragonal symmetry. Such distribution is a result of the orientational disorder along the z axis. Figures 10 and 11 present the details of the $\cos(\theta)$ and φ distributions, respectively, calculated for molecules which form one plane perpendicular to the z axis. Apparently, the molecules stay perfectly ordered within each plane and the distribution looks qualitatively the same for all planes perpendicular to the z axis (only the position of the peak changes its position in different planes). The inserts in Figs. 10 and 11 show the total $\cos(\theta)$ and φ distributions calculated from the orientations of all molecules in the Monte Carlo box. There are four equivalent peaks in the φ distribution which indicate an existence of the disorder in the system. It means that the correlation between planes is weaker than within the planes and, therefore, the disorder can be formed by rotation of all molecules in each plane in the way schematically presented in Fig. 12. Each plane may choose randomly one of the four possible orientations of molecules in the plane.

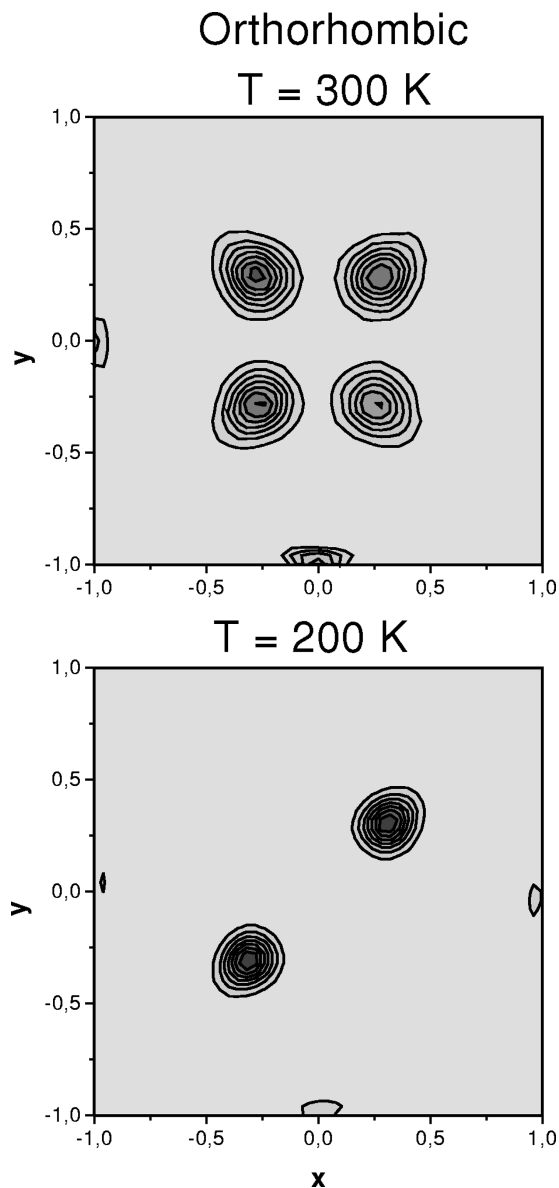


FIG. 9. The orientational distribution xy maps for the tetragonal-orthorhombic phase.

The possibility of formation of the orthorhombic structures with various degrees of orientational disorder may be related to the experimentally observed peculiar mechanism of the transformation between the low temperature ordered phase and the rotator phase. Experimentally, it has been observed that the transition temperature strongly depends on the aging conditions, and the reasons for such dependence are not yet understood.²³

C. The monoclinic phase

The monoclinic phase (m), experimentally observed below 283 K was simulated starting from initial configuration prepared according to the experimental structural information.¹⁸ The ordered structure, with $C2/m$ space group symmetry, was found stable in the MC runs at all studied temperatures. However, there are some discrepancies between the calculated and experimental structures. The analysis of the structure showed that the molecules in which ex-

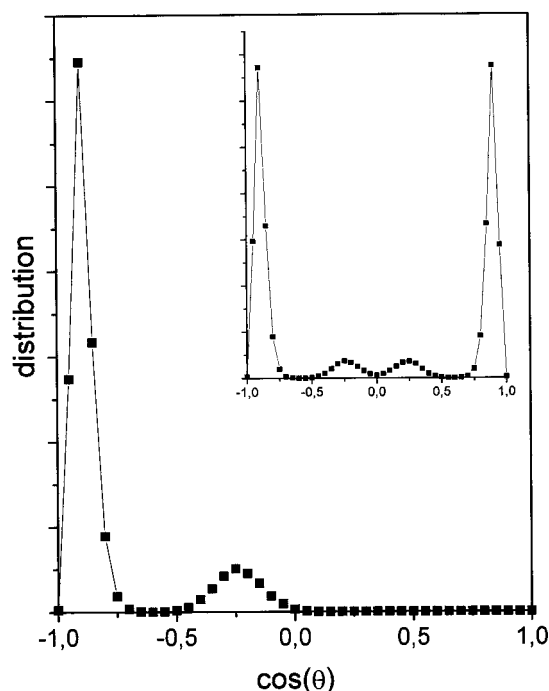


FIG. 10. $\cos(\theta)$ distribution function calculated for one orthorhombic plane at 300 K. The insert shows the total distribution for all planes. The small second peak represents molecules which form some imperfections in the lattice.

perimental fractional coordinates of the center of mass were initially close to the position $(1/4, 0, 1/4)$ in the monoclinic unit cell have been displaced in the course of the simulations close to the position $(1/4 + 1/8, 0, 1/4)$. Simultaneously, the

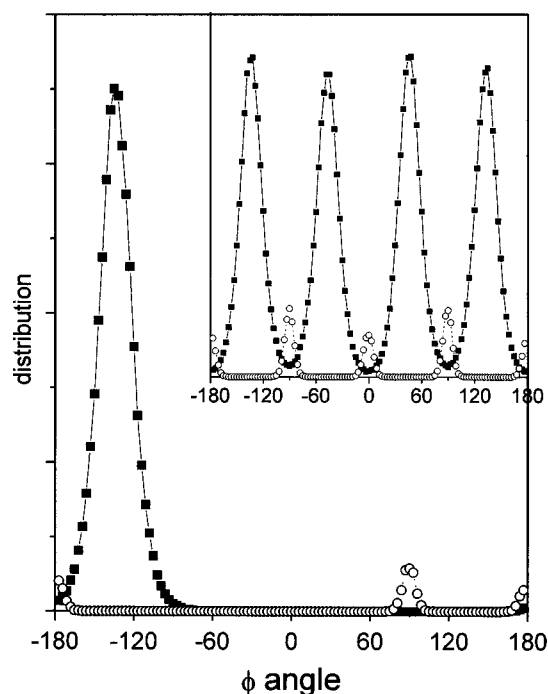


FIG. 11. ϕ angle distribution function calculated for one orthorhombic plane at 300 K. The insert shows the total distribution for all planes. Different graphs show the distribution corresponding to different ranges of $\cos(\theta)$: $|\cos(\theta)| < 1/3$ (full squares), $1/3 < |\cos(\theta)| < 2/3$ (open circles). The small peaks represent molecules which form imperfections in the lattice.

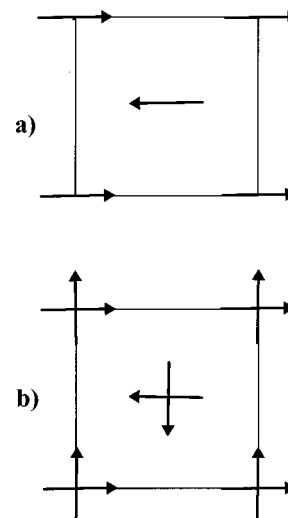


FIG. 12. Projections of the orthorhombic arrangements of the molecular axes: (a) ordered structure, (b) a disordered structure.

unit cell has been contracted along the b axis (Table IV). The crystal energy of the monoclinic phase is higher than the cubic one in the whole range of studied temperatures. So, the cubic phase is definitely more stable, as it is disordered and the entropy term will lower its free energy more than the energy of the monoclinic ordered structure.

It seems that the CNa system can easily form various metastable structures in the wide range of temperatures. We observed such tendency in our calculations for the monoclinic phase as well as for the cubic and orthorhombic phases discussed above. To test more this capability of the system to sustain many metastable states, we carried out an additional calculation for a structure which is not stable experimentally for cyanoadamantane crystal but is known to form a stable

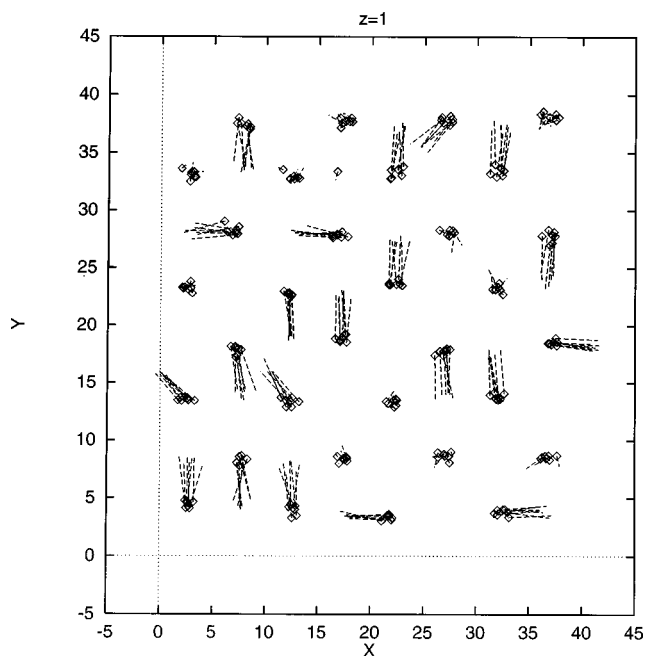


FIG. 13. Few snapshots from the Monte Carlo runs for cubic phase ($T = 300$ K).

TABLE IV. Monoclinic unit cell parameters [in Å] (model II).

Parameters	T = 138 K		T = 240 K	
	Theor.	Exper.	Theor.	Exper.
A	11.73	11.041	11.83	11.278
B	6.83	6.923	6.88	6.874
C	12.00	11.851	12.03	12.092
β	97.10	98.44	96.8	101.37

phase of a system which belongs to the same family, namely chloroadamantane. It forms a monoclinic ordered phase with $P2_1/c$ space group symmetry.³² This structure is also formed by the $(\text{CNa})_{1-x}(\text{Cla})_x$ ($x=0.25$) mixed crystal, so, it is important to compare its stability for pure CNa. It turned out that also this structure stays metastable within even very long MC runs (up to 5×10^5 steps) at all studied temperatures.

D. Relative stability of phases and interaction models

Figure 5(a) shows crystal energies of simulated cubic and orthorhombic phases as functions of the temperature. The energies of monoclinic phases, not shown there, are higher than cubic ones. This allows us to state that both monoclinic phases are metastable. Such a conclusion can be formulated without any calculations of the entropy because both monoclinic phases and orthorhombic structure are very well ordered. In such a case, the entropy difference is relatively small and the entropy term in the free energy cannot compensate for the large difference in the potential energy. The cubic phase, on the other hand, will lower its free energy due to the large orientational disorder (Fig. 13) and, in principle, may become more stable than the orthorhombic one. We have estimated an effect of the rotational entropy on the stability of the cubic (see Appendix). The calculated free energy differences between the plastic cubic phase and orthorhombic one, for temperatures 100, 200, 300, and 400 K, are shown in Fig. 5(b). This result shows that the cubic phase becomes more stable than the orthorhombic phase at high temperature above approximately 300 K. The exact value of this temperature is not very important in view of the mean field approximation applied to calculate the orientational distribution as described in the Appendix. The main importance of this result is the fact that the disorder existing in the cubic phase may stabilize the cubic phase with respect to the orthorhombic one, in spite of the large potential energy difference which favors the latter structure.

This study arises some questions about the representation of the potential and its ability to model crystal properties. The dominating feature of our model, where the molecules are effectively linear, seems to be the dipole–dipole interaction which leads to the association of the molecules in pairs in the ordered phases. The orthorhombic arrangement [Fig. 7(b)], instead of the tetragonal structure [Fig. 7(a)] of the transient state, is a consequence of strong dipole–dipole interaction which forces the CN groups to associate in pairs and the nearest neighbor molecules [on the sites (0,0,0) and (0.5, 0.5, 0.5) of the unit cell] tilt toward each other (Fig. 8). The pairs of the molecules form dimers bonded by dipole–

dipole interaction in a similar way as observed for organic nitriles.³³ A tendency of molecules to associate in pairs was also seen when we simulated the monoclinic phase. However, it did not help the phase to become thermodynamically stable. On the contrary, the monoclinic phase isomorphous with the chloroadamantane seems to be more stable. At the same time, both monoclinic phases stay metastable with respect to both cubic and tetragonal phases in the whole range of studied temperatures.

The representation of the electronic state of molecules (charge distribution) seems to be an extremely important factor affecting the stability of the phases. As we have shown above, the orientational distribution in the cubic phase is very sensitive to the charge distribution. This sensitivity is not a surprise and there are other similar examples, such as the fullerene C_{60} molecule, where the low temperature ordered phase was stabilized only by modeling details of the molecular electronic structure^{34,35} or potassium perchlorate, where changes of a charge on the oxygen shifted the transition temperature from a few degrees up to several hundred.³⁶ Figure 5(c) shows that the low crystal energy of the orthorhombic phase is mainly determined by the electrostatic interaction. In general, a comparison between the total crystal energies [Fig. 5(a)] and the electrostatic part of the energy [Fig. 5(c)] shows that differences between energies are mostly determined by the electrostatic interactions. The problem of the proper representation of the charge distribution is also related to the representation of the molecules as a linear set of force centers and linear point charges distribution. This problem will be discussed separately in a forthcoming paper.²⁷

The calculated volume depends mostly on the Lennard-Jones part of the interactions. However, both models I and II are not able to reproduce the experimental dependence of the molecular volume on temperature (see Tables III and IV). Also, the calculations presented in this paper are not able to simulate the monoclinic stable phase of the cyanoadamantane crystal. The lack of the thermodynamic stabilization of the monoclinic structure is definitely a consequence of the simplified model of the CNa molecule as a linear object. At low temperature the crystal structure is much more sensitive to the detailed shape (packing) of molecules and to fine details of the electronic structure. In fact, our calculations performed for two-charge models have shown how it is sensitive to electrostatic interaction. Still, even as a metastable structure, the monoclinic volume and lattice parameters are reproduced with surprising accuracy (better than 5%).

V. DISCUSSION

The simulations have given strong evidence that the rotator phase transforms most easily into a state where dipoles are anti-ferroelectrically ordered along one of the fourfold axes of the parent cubic lattice. The real system under deep quench also prefers first to go to such an intermediate state instead of transforming directly into the phase which is ultimately stable at low temperature. The simulations allowed us to reveal the details of such anti-ferroelectric order of dipoles. It has been shown that the dipoles do not form perfect antiparallel structure. Instead, the molecules prefer to tilt

(about 15–20°) with respect to the fourfold axis, forming orthorhombic structure, with alternate orientations along the z axis (Figs. 7 and 8) which double the unit cell parameter of the parent cubic lattice. Molecules associate themselves into dimers which form ordered planes perpendicular to the fourfold axis direction. Thus, the simulations have provided new structural information, the details of which cannot be obtained easily in diffraction experiments. This is due to the short coherence length of the superstructure periodicity in the real space. However, a careful reexamination of the x-ray spectrum revealed that such super-lattice periodicity manifests itself through small broad peaks³¹ which support the theoretical prediction.

The simulations have provided additional information about the temperature evolution of the order within the orthorhombic frame. When temperature is increased, the structure shows a tendency to be disordered. The molecules preserve the ordered structure of dimers in each plane but the correlation between the orientations in different planes is progressively destroyed. Such decorrelation effects should be taken into account when interpreting the very unusual influence of the aging time and temperature on the stability of the low temperature order phase and its transition to the rotator phase. As observed experimentally,²³ the occurrence of this transition strongly depends on the aging conditions.

There is no doubt that the most stable phase at high temperature is the cubic rotator structure. The large orientational entropy stabilizes this disordered phase, as we have discussed in the previous Section. Still, at high temperature we observe fluctuations which deform the cubic symmetry into the tetragonal one. Such a sign of possible inversions of stability is a consequence of quasiergodic effects and finite size of the Monte Carlo cell. It is because of the slow orientational dynamics which does not allow the system to achieve perfect ergodicity within the time window available in the simulations. Also, the periodic boundary conditions introduce an artificial long range correlation which makes the local fluctuations look more stable than they are in a real system.

Contrary to the spin or quadrupolar glasses,³⁷ there are no extrinsically introduced sources of frustration in the glassy crystal. The structural frustration must be produced intrinsically. Since there is obvious experimental evidence that seeds of the metastable orthorhombic structure appear always near the glass transition,^{10,23} the frustrating role of this structure may be important in the mechanism of freezing. Therefore, any computer simulations of the vitrification process will require much larger Monte Carlo systems which can reproduce the main experimental features of the morphology. It has been observed that the glassy crystals upon annealing³⁸ show: (i) orthorhombic zones of various degeneracy grow in perfect coherency with the underlying cubic phase whose average symmetry is preserved; (ii) the size of those ordered zones is extremely small (≈ 20 – 30 Å from x-ray analysis); (iii) the time dependence of the zone size is very weak.

Other interesting information has been obtained concerning the choice of the potential to be used for future investigations. Obviously, to reproduce the stable low temperature

monoclinic structure one certainly needs to take into account more details of the molecular shape. However, we have shown that the structural features related to the plastic phase and to the local ordering in the quenched plastic phase are perfectly reproduced by the simulation. As a consequence, the use of linear molecules is probably sufficient in a first attempt to study the frustration effects and the glass transition itself. The short-range Lennard-Jones representation of the potential should, however, be improved in order to approach more closely the experimental cubic unit cell parameters. This is an important feature of the potential because of the possible role of rotational–translational coupling effects. We are investigating this aspect in the course of molecular dynamics numerical simulations of CNa.

ACKNOWLEDGMENTS

One of us (B.K.) wants to thank Region de Nord Pas de Calais for the support which made his visit in the L.D.S.M. of the University of Lille 1 possible and allowed him to conduct the research presented in this paper. The project was partially supported by a grant from Wroclaw University of Technology for 1997.

APPENDIX

We define the orientational probability function as a distribution averaged over all molecules and different runs to get the mean orientational distribution representing all possible orientations of a molecule. The distribution is to be used to calculate the rotational entropy and to estimate the free energy difference between phases. We define the orientational distribution function for a molecule on a site α ,

$$P_{\alpha} = p_{\alpha}(\theta, \varphi) = \left\langle \frac{1}{N} \sum_{k=1}^N \delta(\theta - \theta_k) \delta(\varphi - \varphi_k) \right\rangle.$$

Because $p_{\alpha}(\theta, \varphi)$ represents a mean distribution of all molecules in the crystal, and its shape is the same for each crystal site, we may skip the index α below. Total distribution is $P = \prod P_{\alpha}$. However, it is important to remember that this is an approximation because it neglects correlation between the molecules. Numerically we define a finite uniform grid of a size $\Delta\Omega_i = \Delta\theta_i \Delta\varphi_i$. The value of the distribution function $p(\theta, \varphi)$ is approximated to be constant within each segment of the grid (indexed by i),

$$p(\Delta\Omega_i) = \int_{\Delta\Omega_i} p(\theta_i, \varphi_i) \sin \theta_i d\Omega_i$$

and

$$\sum_i^M p(\Delta\Omega_i) = 1.$$

So, we may estimate the entropy $S = -\sum S_{\alpha}$ and calculate the configurational entropy per molecule as (N —number of molecules in the crystal)

$$S/N = -\sum_i^M p(\Delta\Omega_i) \ln p(\Delta\Omega_i). \quad (\text{A1})$$

The entropy, as defined by (A1), depends on the number M of the segments $\Delta\Omega_i$. However, our numerical tests showed that the difference of two entropies $\Delta S = S_2 - S_1$, both calculated on the same grid, is not sensitive to the number of segments of the grid, for big numbers of M . Such behavior can be understood when one realizes that dividing the grid uniformly into n smaller segments changes (A1) by a constant which has no contribution in the entropy difference. An estimation of the entropy using the formula (A1) takes into account only orientational states, so, it will give reasonable results only if other contributions to the entropy are much smaller. Therefore, we apply Eq. (A1) in the case of the orientational order-disorder transitions where we expect that the major entropy change at the transition temperature results mainly from the orientational ordering mechanism.

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Two-step rotational relaxation in glassy crystal cyanoadamantane

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(Received 2 April 1998)

Results of molecular-dynamics numerical simulations are presented for a simple model of glass forming orientationally disordered crystal. In this system, glass formation is not induced by quenched diluted disorder, but it occurs similarly to conventional glasses. Simulations show that the relaxational dynamics of this orientational glass involves a multiple-step mechanism. The simplicity of the system and the existence of an underlying average lattice allows us to visualize clearly the molecular motions involved in the different relaxational processes. The role of translation-rotation coupling is stressed. The results obtained with this model are used to discuss the validity and occurrence of the mode coupling theory in the experimental system. [S0163-1829(99)50614-0]

An important part of the recent active studies on the glassy state and glass transition¹ have been formed on the ideas introduced by the mode coupling theory (MCT).² This theory, which initially described simple van der Waals atomic liquids, predicts in its first version the following main features. A dynamical instability, which is described as an ergodic to nonergodic transition, should exist at a critical temperature $T_c > T_g$, where T_g is the experimental calorimetric glass transition. MCT also predicts the appearance, close to T_c , of a two-step relaxation process called α and β . The slower α regime should exist only above T_c and diverges when approaching this temperature, while the faster β process should be present on both sides. Experimentally, this *ideal* glass transition is not observed. Later revisions of this idealized version of the MCT argued that thermally activated hopping processes restore ergodicity below T_c , thus relaxations can continue. The dynamical properties of glass forming systems is currently a field of intense investigation both from theoretical and experimental points of view. In the past, several computer simulations have been performed on simple atomic systems.³ Since most of the experimentally investigatable glasses are molecular liquids, the role of the orientational degrees of freedom (ODOF) in addition to translational motions has recently been investigated. However, owing to the very long molecular dynamics (MD) runs which are required to catch, for example, the α relaxation features, only a few simulation studies were performed to investigate dynamical properties and check the MCT in those complex systems. Briefly, we just mention the studies on the prototypical network glassformer SiO_2 ,⁴ water,⁵ model diatomic molecules,⁶ orthoterphenyl,⁷ and methanol⁸ which have shown that, to some extent, MCT was also applicable to molecular liquids. The absence of long-range order makes conventional glass forming systems hard to investigate by the experimental methods used for crystals. However, the simulation of a strictly periodic array model of colliding hard needles has recently shown that a dynamic glass transition can occur in a purely orientational system.⁹

The phenomenology of conventional glass transition has been shown experimentally to be also displayed by some orientationally disordered crystals, i.e., glassy crystals.^{10,11}

At high temperature, in those systems, the average molecular centers of mass are ordered in a lattice while the orientations are dynamically disordered. Upon cooling, rotational motions are frozen and glassy crystals present many properties characteristic of conventional molecular liquid glasses both in the way the glass occurs (undercooling) and the thermodynamics signatures. In opposition to the so-called “orientational glasses,”¹² for example $(\text{KCN})_x(\text{KBr})_{1-x}$, glassy crystals are not frustrated by quenched disorder externally imposed by a dilution. The main motivation of the present paper is to study, using a MD simulation technique, a glassy crystal which is the very analog of liquid glasses and to offer an excellent opportunity to focus on the role of the ODOF and translation rotation (TR) coupling in a system where the center of mass of the molecules are caged in a perfect average crystalline translational order. Our goal is to check if the two-step relaxation process predicted by MCT emerges in this type of glassy system. It is also to identify which molecular motions are associated with the different types of relaxation since it is always a matter of debate for glass forming liquids at present.

Our MD simulation is a simple model of glassy crystal cyanoadamantane $\text{C}_{10}\text{H}_{15}-\text{C}\equiv\text{N}$, which is an excellent experimental compound.¹³ A complete description of the model is given in Ref. 14 where the phase diagram, compared to the real system behavior, is presented; and a study of the dynamics near the melting point is shown in Ref. 15, so we give here only the essential details. The simulated system is composed of rigid linear molecules with three atoms: one nitrogen (N), one carbon (C), and one super atom that models the adamantane group $\text{C}_{10}\text{H}_{15}$. Molecular dynamics calculations were performed on a system of $N=256$ ($4\times 4\times 4$ fcc crystalline cells) modeled cyanoadamantane molecules interacting through a short-range site-site Lennard-Jones potential. This model has been constructed to keep the main experimental features but also to speed up simulations—since it is less sterically compact than the real compound—in order to reach the nanosecond regime. The cyanoadamantane molecule possesses a relatively large dipolar moment $\vec{\mu}$ (3.92 debyes) which is parallel to the $-\text{C}\equiv\text{N}$ axis. The electrostatic interactions were handled by the Ewald method with a

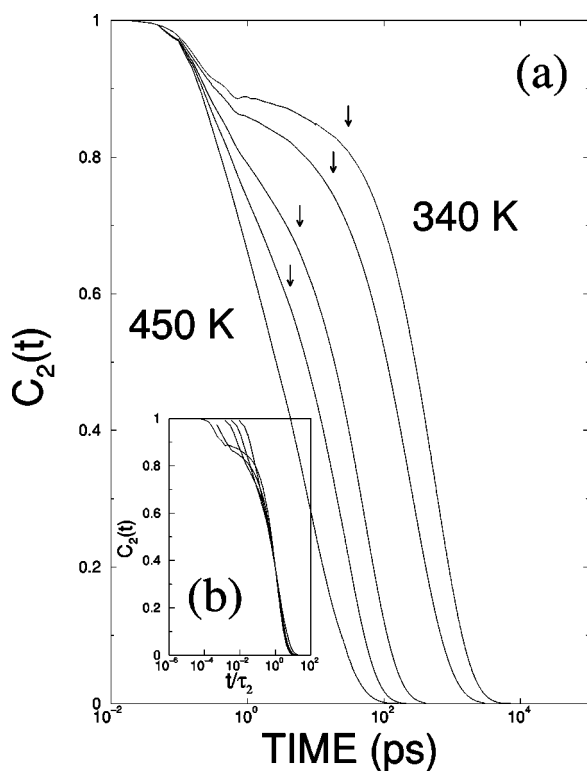


FIG. 1. Orientational time correlation function C_2 as function of time t (a) and rescaled time t/τ_2 (b) at $T=340, 360, 400, 420$, and 450 K. The dipolar residence time along the fourfold crystallographic axes is also indicated ($\downarrow$).

three-site charge distribution computed from *ab initio* calculations of an isolated molecule. Newton's equations of motion were solved with a time step of $\Delta t = 5$ fs. We worked in the N - P - T statistical ensemble with periodic boundary conditions.

MD simulations were done at 16 different temperatures from $T=340$ to 465 K for a sample corresponding to the crystalline fcc rotator phase. During the time of the simulation, the sample remains in an undercooled metastable state compared to the ultimately ordered crystalline phase. Owing to the very long MD runs, we succeeded in investigating truly equilibrated states of the system down to 340 K. Above this temperature the system shows the dynamically rotational disorder observed typically in plastic crystal as demonstrated in Fig. 2. For rotational degrees of freedom, if we focus our attention on the motion of the dipole vector $\vec{\mu}$, convenient functions are the first two self-angular correlation functions ($l=1,2$) (Ref. 6)

$$C_l(t) = \frac{1}{N} \sum_{i=1,N} \langle P_l(\vec{\mu}_i(t) \cdot \vec{\mu}_i(0)) \rangle, \quad (1)$$

where P_l is the l -order Legendre polynomial. Experimentally, $C_1(t)$ can be measured in dielectric relaxation and $C_2(t)$ in Raman scattering.¹⁶ Figure 1 shows those $C_2(t)$ time correlation functions for all investigated temperatures above 340 K. First of all, we see that $C_2(t)$ functions are going to zero which is an indication that we have investigated the equilibrium dynamics of the system. Clearly, at least for the lowest temperatures, a two-step relaxation

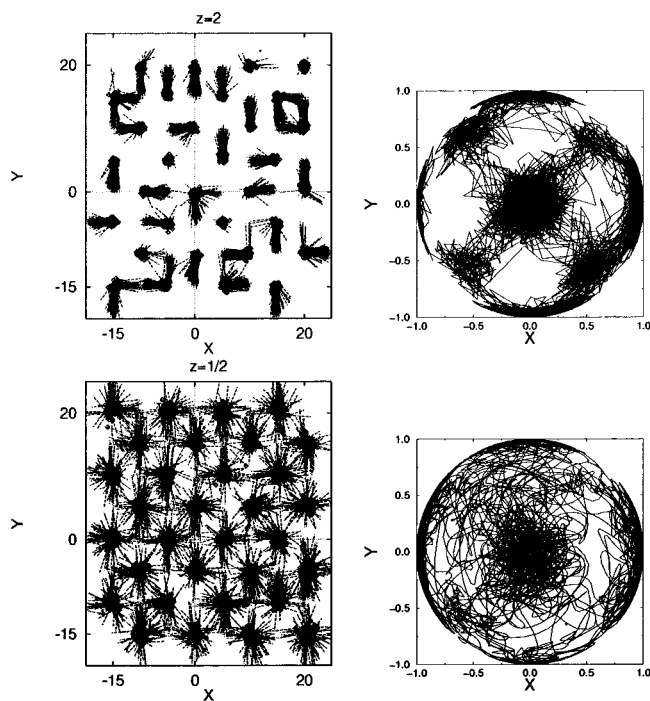


FIG. 2. Snapshots of the $\vec{\mu}$ dipolar moments, in the rotator phase, projected on one xy plane at different instants in a run of 400 ps. Over this duration, at $T=340$ K (top), some orientations are not populated. The system is therefore in a nonergodic situation while it is ergodic at $T=450$ K (bottom). Collective orientational motions of neighboring molecules are detected in the snapshot which correspond to the breaking of the cages. Beside each snapshot, at the same temperatures, the trajectory of the dipole moment $\vec{\mu}$ of a selected molecule projected on the xy plane is given.

behavior—as predicted by MCT and already observed in supercooled molecular liquids^{5–7}—is shown in our simulation.

At very short times, we observe a fast decay corresponding to a microscopic regime which is modulated by vibrolibrational motions. This latter is followed by a plateaulike region, which becomes more pronounced at the lowest temperatures. This feature is identified with the β regime. Finally, the last step is a decay to zero corresponding to the α process. $C_1(t)$ time correlation functions, not displayed in the present paper, show a very similar behavior to the $C_2(t)$ functions. However, as already found for molecular liquids,^{5,6} the height of the plateaulike region which is a measure of the nonergodicity parameter is lower for $C_2(t)$ than for $C_1(t)$. The nature of the two different relaxation processes can be extracted from snapshots and trajectories of the dipolar moment $\vec{\mu}$. Snapshots of the dipolar moments, at different instants over the same duration (400 ps) projected on one xy crystallographic plane, are displayed in Fig. 2 at two different temperatures. Over this duration, at $T=340$ K the system is in a nonergodic situation whereas it is ergodic at 450 K. Similar pictures are obtained for all crystallographic planes. The most probable orientations of the dipolar axis are localized along the fourfold crystallographic axes of the cubic cell which is in good agreement with experiment.¹⁷

Molecules show at least three kinds of perfectly identified rotational dipolar motions in completely different ranges of time:

(i) At very short time, fast librational motions are per-

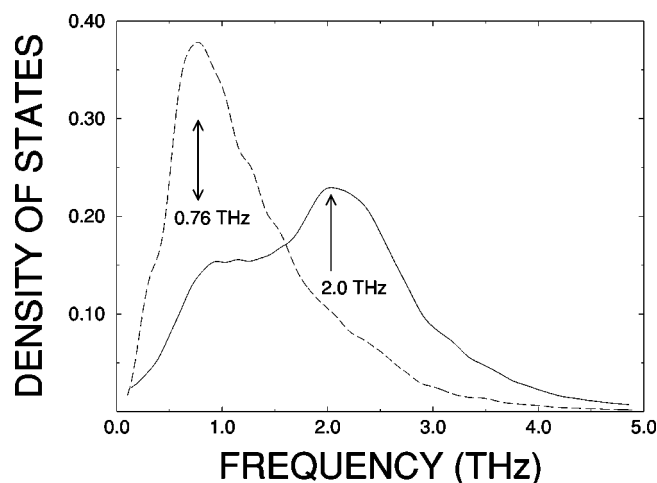


FIG. 3. Rotational (solid line) and translational (dashed line) normalized density of states as a function of the frequency in THz at $T = 340$ K.

fectly seen at 340 K in Fig. 2, where the large amplitude tumbling motions are rare. Details about these fast microscopic motions are shown in the high-frequency part of the density of states in Fig. 3. The rotational density of states shows a peak corresponding to the librational frequency $\nu \approx 2$ THz. A second peak which is localized at the same frequency as vibrations is also detected ($\nu \approx 0.76$ THz). This result proves the presence, at short time, of a TR coupling expected for orientationally disordered crystals.

(ii) At long time, tumbling reorientations of the dipole axis between $[100]$ directions of the cubic cell with rather long residence times are also detected. This long process requires collective orientational motion of neighboring molecules and corresponds to the breaking of the cages as displayed in Fig. 2. This dipolar motion is certainly strongly involved in the α process. Indeed, the beginning of the α process decay observed for $C_1(t)$ and $C_2(t)$ time correlation functions corresponds approximately to the dipolar residence time along the fourfold crystallographic axes.

(iii) At intermediate time, between vibrolibrational and tumbling motions, the trajectory of one target dipole displayed in Fig. 2 revealed hindered rotations between fourfold axes and threefold axes. Actually, those latter correspond to aborted tumbling rotations (described previously) performed by dipoles in cages formed by their neighbors. Those motions are expected to be involved in the β regime.

The time-temperature superposition principle of the α process predicted by MCT has been checked. If τ_2 is defined as the time it takes for the time correlation function $C_2(t)$ to decay e^{-1} of its initial value, then we observe in Fig. 1 that $C_2(t/\tau_2)$ functions fall reasonably well onto a master curve in the α regime. The same behavior is also observed for $C_1(t/\tau_1)$ functions. The τ_1 and τ_2 relaxation times are displayed in Fig. 4 in an Arrhenius plot. Clearly, τ_1 and τ_2 relaxation times deviate from the Arrhenius law when temperature increases. At high temperature a fit with a power law $1/(T-T_c)^\gamma$, as predicted by the MCT, has been computed and works well. The critical temperature was determined to be $T_c \approx 370$ K for τ_1 and τ_2 . The critical exponent γ is about 1.63 for τ_1 and 2.13 for τ_2 , close to the values found for liquids.^{5,6}

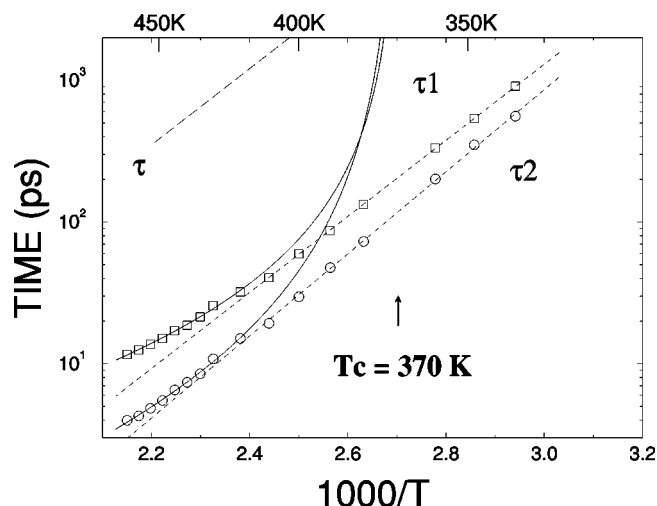


FIG. 4. α -relaxation time τ_1 ($\square$) and τ_2 ($\circ$) obtained by simulation as a function of the temperature T . Data are fitted with a power law (solid line) $1/(T-T_c)^\gamma$ at high temperature and an Arrhenius law (dashed line) at low temperature. The α -relaxation time τ (long-dashed line), observed experimentally in dielectric experiments, is also given and follows an Arrhenius law in this domain of temperature.

In order to probe TR coupling at long time, which is an important aspect of plastic crystal dynamics,¹⁶ we have studied local volume fluctuations using the autocorrelation function $\phi_V(t)$ of the Voronoi polyhedron (Wigner-Seitz cells). The autocorrelation functions $\phi_V(t)$ are displayed in Fig. 5. Clearly, a two-step relaxation behavior is also seen for translational motions, which become more and more pronounced as the temperature decreases. It shows also that the TR coupling effects already detected for librations persist at long times in the α regime.

In summary, we have investigated structure and dynamics of a simple model of glass forming orientationally disordered crystal. A two-step rotational relaxation (α , β) as predicted by MCT is detected. A clear visualization of the different

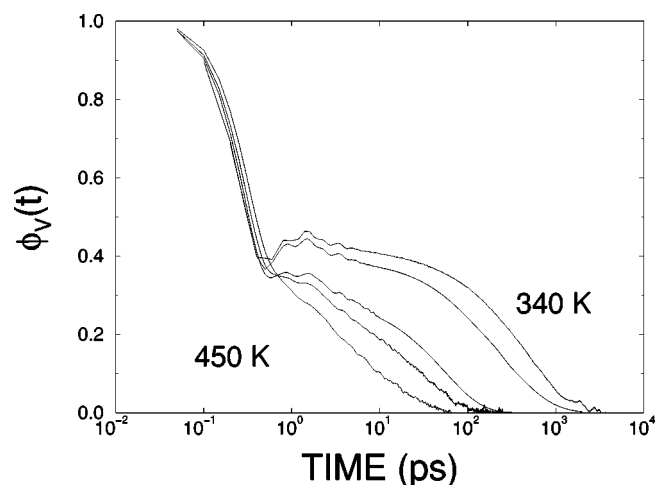


FIG. 5. Cubic cell volume fluctuations autocorrelation function $\phi_V(t) = 1/N \sum_{i=1,N} [\langle V_i(t) \cdot V_i(0) \rangle - \langle V_i \rangle^2] / (\langle V_i^2 \rangle - \langle V_i \rangle^2)$ where $V_i(t)$ is the Voronoi volume of the molecule i at the instant t , as a function of time at $T = 340, 360, 400, 420$, and 450 K.

dipolar motions has revealed that slow tumblings between fourfold axes are associated with the α process. Faster rotational motions, corresponding to aborted tumblings, are expected to be at the origin of the β regime. Our simulation also provides strong evidence for Goldstein's view,¹⁸ that the system evolves critically from free small-step rotational diffusion to jumplike motion as shown in Fig. 2. This feature is confirmed by the ratio τ_1/τ_2 which is close to the value of 3 when associated with free diffusion at high temperature and decreases to 1 when associated with activated jumplike motion¹⁹ at low temperature. A comparison of the relaxation times in the activated regime—found experimentally and by simulation (see Fig. 4)—allows us to predict this dynamical

transition for the real compound very close to the melting point ($T_m \approx 465$ K) and, therefore, far above the experimental calorimetric glass transition temperature of $T_g \approx 175$ K. Experiments should be performed to detect these phenomena. The slowing down of the α process leading to the experimental T_g has to be attributed certainly to further correlations involving motions of molecules yet rotationally caged at T_c .

The authors wish to acknowledge the use of the facilities of the IDRIS, Bâtiment 506, Faculté des Sciences d'Orsay, F-91403 Orsay, where some of the simulations were carried out.

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Experimental and numerical signatures of dynamical crossover in orientationally disordered crystals

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(received 25 October 2000; accepted 22 December 2000)

PACS. 64.70.Pf – Glass transitions.

PACS. 76.60.-k – Nuclear magnetic resonance and relaxation.

PACS. 61.43.-j – Disordered solids.

Abstract. – By means of NMR experiment and MD computer simulation we investigate the dynamical properties of a chloroadamantane orientationally disordered crystal. We find a plastic-plastic dynamical transition at $T_x \simeq 330$ K in the pico-nanosecond regime. It is interpreted as the rotational analogue of the Goldstein crossing temperature between quasi-free diffusion and activated regime predicted in liquids. Below T_x , NMR experimental data are well described by a Frenkel model corresponding to a strongly anisotropic motion. At higher temperatures, a drastic deviation is observed toward quasi-isotropic rotational diffusion. We show also that two-step relaxations emerge close to T_x which probably does not correspond to the T_c of the Mode Coupling Theory. An interpretation which is based on the present study of a specific heat anomaly detected by a recent calorimetric experiment is proposed.

The elusive nature of the glass formation relates to the sharp rise of the transport coefficients (viscosity or relaxation times) in a narrow temperature range above the calorimetric transition temperature T_g [1]. Some of the recent active investigations focus on the existence of a dynamical crossover which could occur above T_g in glass-forming liquids. The idealized version of the Mode Coupling Theory (MCT) [2] predicts that a dynamical decoupling occurs at a critical temperature $T_c > T_g$ [3]. It is however suspected that T_c is close to the temperature T_x at which the system also starts being sensitive to the energy landscape in its exploration of the configurational hyperspace [4–6]. Motions in liquids would thus be dominated at low temperature by activated processes between potential energy minima while free diffusion occurs at high temperatures. Such dynamical crossover was already argued by Goldstein thirty years ago [7]. In the last few years a significant effort has been undertaken to investigate experimentally and numerically the properties of glass-forming liquids in order to detect such dynamical changeover. However, most of the good glass-formers which allow easy investigations of the supercooled metastable state such as o-terphenyl [8] are molecular liquids where contributions due to translational, orientational and internal degrees of freedom (TDOF, ODOF) are inextricably mixed. It makes the properties of the energy landscape topography, MCT predictions or detection of dynamical transitions extremely hard to investigate. A clear visualization of the different processes at the molecular level of simple model

compounds is needed. The discovery that some orientationally disordered crystals exhibit the phenomenology of conventional glasses is therefore an exciting opportunity.

Indeed, some molecular crystals present a *plastic phase* in which the molecular centers of mass show a perfect average crystalline translational order while the orientations are dynamically disordered [9]. Some plastic crystals, *i.e.* glassy crystals [10,11], can be undercooled and present many properties characteristic of conventional molecular-liquid glasses, both in the way the glass occurs (undercooling) and the thermodynamic signatures. Glassy crystals which are the very rotational analogue of liquid glass-formers offer an excellent opportunity to focus on the role of the ODOF. Substituted adamantanes plastic crystals such as the cyanoadamantane [12], denoted CNa in the following, are good experimental candidates and some of them exhibit a glass transition signature. In [13], MD numerical simulations of a simple model inspired from the CNa molecular geometry allowed us to investigate both TDOF and ODOF properties. In this work a dynamical decoupling and two-step relaxations were found to be possible in a rotator phase. We note that such features have been also observed by Renner *et al.* in [14] for a colliding hard needle model on a rigid lattice.

In the present letter, we address the possibility of finding such a behaviour in a real system. We have found chloroadamantane $C_{10}H_{15}Cl$ (Cla) to be a very favorable and relevant system for this investigation. It shows a plastic phase over a wide interval of temperature [244–442] K (see fig. 1c) and a structure isomorphous to CNa [15]. The Cla molecule possesses a smaller substitute than CNa does. This gives rise to faster dynamics in the plastic phase where rotational motions are also suspected to change in nature, as is reported from earlier incoherent quasielastic neutron scattering experiments [16]. Our results show for the first time, for a rotator phase, using experimental NMR and numerical MD simulations, the evidence of a dynamical crossover between quasi-free rotational diffusion and activated motion occurring in the pico-nanosecond regime. It is also shown that this accident can explain the existence of a calorimetric anomaly (see fig. 1c) recently detected in Cla by Oguni *et al.* [17].

NMR experiments were performed on chloroadamantane on Bruker spectrometers ASX100 and ASX400. ^1H and ^{13}C linewidths and relaxation times were measured. The experiments were carried out on powder samples sealed in glass tubes for ^1H experiments or packed into zirconium rotors for ^{13}C MAS experiments. The spinning speed of the sample was 4 kHz. The sample temperature was regulated to within ± 0.5 K by a Bruker BVT 2000 temperature controller. The spin lattice relaxation times were measured using the inversion recovery pulse sequence, the recovery of the magnetization was always found to be exponential within experimental accuracy. The ^1H spin lattice T_1 *vs.* temperature is reported in fig. 1a. The main feature of this curve is the occurrence of an abrupt change of the activation energy, from 1400 K to 3400 K, at a temperature close to $T_x \simeq 330$ K which is far from both the melting temperature and the brittle-to-plastic transition. Slow diffusive motions of the molecules are generally observed in plastic phases. In the present study, their contribution to the spin-lattice relaxation time T_1 was found to be negligible in the temperature range investigated. This fact was particularly evidenced by measurements of the dipolar order T_{1D} (see fig. 1a). The diffusional correlation time ($\tau_{diff} \simeq 30000$ s at room temperature) was found to be strongly temperature dependent with a very high activation energy $\simeq 14000$ K. Self-diffusion has thus to be discarded as the origin of the break observed in T_1 . Previous neutron studies [16] have suggested that two types of motion occur in the rotator phase of Cla: tumbling of the molecular C_3 axis among six fourfold crystallographic axes along the [100] directions, and fast uniaxial rotation about the threefold axis. It was shown that the motion around the molecular axes is very fast ($\simeq 10^{-12}$ s at room temperature) with an activation energy of about 1240 K. Therefore, it takes place outside the time window where the dynamical crossover is detected at T_x . Dipolar tumbling motions are thus mainly involved in the evolution of the spin-lattice

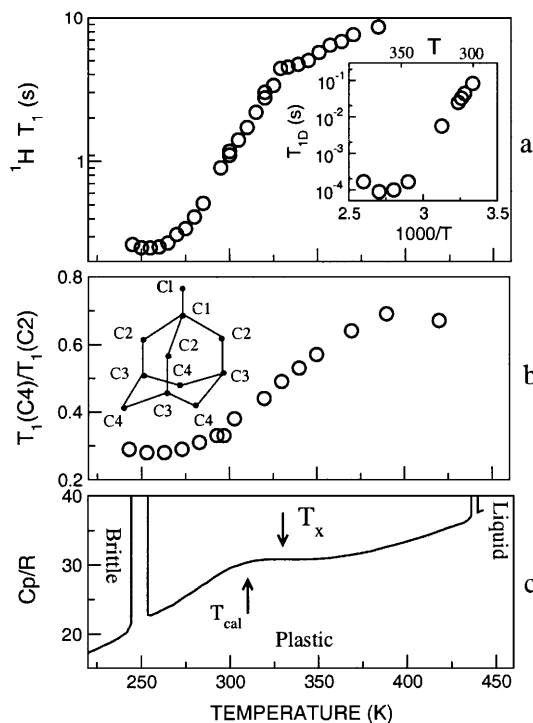


Fig. 1 – Experimental data as a function of temperature in Cla. All data are plotted as a function of the temperature for a direct comparison with fig. 4. (a) The experimental proton relaxation time T_1 and the dipolar order T_{1D} . (b) The ratio $T_1(C4)/T_1(C2)$ of the methylene relaxation times. The chloradamantane molecule with the different carbons is displayed in the inset. (c) Experimental heat capacity where data have been extracted from Oguni *et al.* (ref. [17]). The temperature where the calorimetric hump is determined by Oguni *et al.* ($T_{cal} \simeq 310$ K) and the temperature of the NMR dynamical crossover ($T_x \simeq 330$ K) are also indicated in the same figure.

relaxation. Two separate temperature domains are clearly identified: below T_x , both NMR experimental proton and carbon data are well described by a Frenkel model assuming an Arrhenian behavior of tumbling and uniaxial rotations. Above T_x , it was not possible to describe the evolution of T_1 using the previous model. Hence, we expect that some hypotheses of this model, in particular the finite number of equilibrium positions, become irrelevant at high temperatures.

Anisotropy in the rotational motion can be precisely seen from the spin-lattice relaxation times of the three different protonated carbons. Effectively, the main relaxation process of the methylene and methine carbons is the dipole-dipole interaction between the ^{13}C nuclei and their attached protons (see fig. 1b). Relaxation times for carbon were measured as a function of temperature in the rotator phase. The ratio $T_1(C4)/T_1(C2)$ of the relaxational times for methylene (C2, C4) is displayed in fig. 1b. A strongly anisotropic motion is found below T_x where the ratio of the carbon relaxational times is about 0.25. This latter value can be well reproduced by the previous Frenkel model. A drastic deviation from the anisotropic behaviour occurs at high temperatures where a ratio value of 0.7 is reached. Since free isotropic rotational diffusion processes would correspond to identical relaxational times for the methylene, this result reveals the influence of the residual crystalline field on the rotational dynamics. The

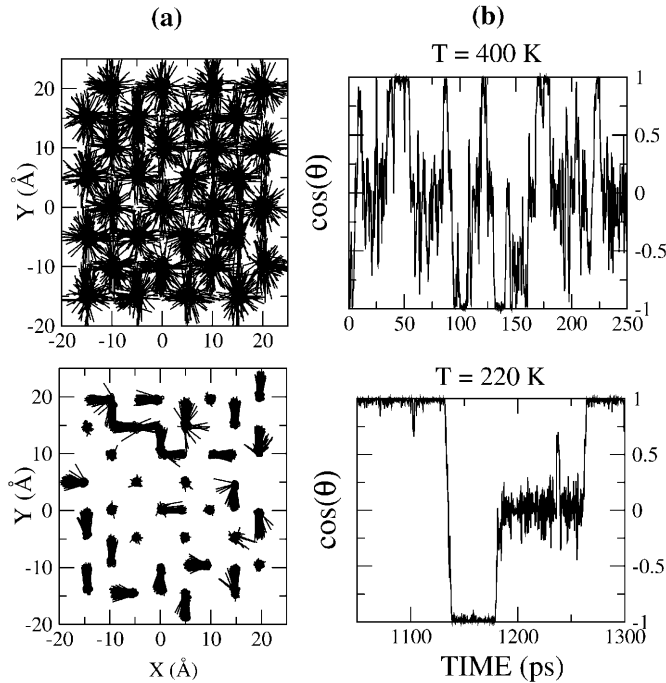


Fig. 2 – (a) Snapshots of the μ dipolar moments are projected on one xy -plane at different instants in a run of 250 ps above (400 K) and below (220 K) $T_x \simeq 360$ K. At $T = 220$ K, some orientations are not populated since the system is not completely equilibrated *over this duration*. (b) Trajectory of the dipolar cosine angle θ of a target molecule at the same temperatures.

experimental heat capacity obtained by Oguni *et al.* [17] in the Cla plastic phase is reported in fig. 1c. The evolution of C_p shows an anomalous hump which was reported to resemble somewhat a Schottky anomaly. Owing to the nature of the Cla molecule which is mainly rigid, conformational changes have to be discarded for the origin of the Schottky anomaly. Clearly, the hump covers the entire temperature range where the dynamical crossover is seen in our NMR investigation. Its origin will be discussed in the light of the MD simulation results.

MD simulations have been performed at 29 different temperatures from $T = 220$ to 500 K for a sample corresponding to the crystalline fcc rotator phase on a simple model of Cla (see fig. 2). A complete description of the model is given in [18,19], so we give here only the essential details. The simulated molecules are composed of two sites: one chlorine (Cl) and one super atom that models the adamantane group $C_{10}H_{15}$. Molecular dynamics calculations were performed on a system of $N = 256$ ($4 \times 4 \times 4$ fcc crystalline cells) modeled Cla molecules interacting through a short-range site-site Lennard-Jones potential. Size effects have been checked and no significant structural or dynamical change has been found for a larger system made of 2048 molecules. The electrostatic interactions were handled by the Ewald method. Two partial charges ($q = \pm 0.151$ e) are localized on both sites in order to reproduce the dipolar moment μ (2.39 Debyes). A time step of $\Delta t = 5$ fs was used. We worked in the NPT statistical ensemble with periodic boundary conditions. Owing to the very long MD runs, we succeeded in investigating truly equilibrated states of the system down to 220 K. The

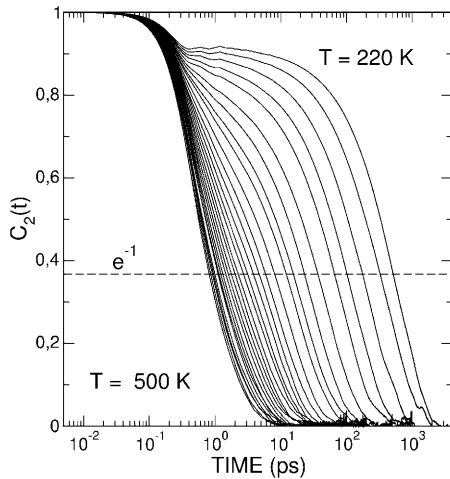


Fig. 3

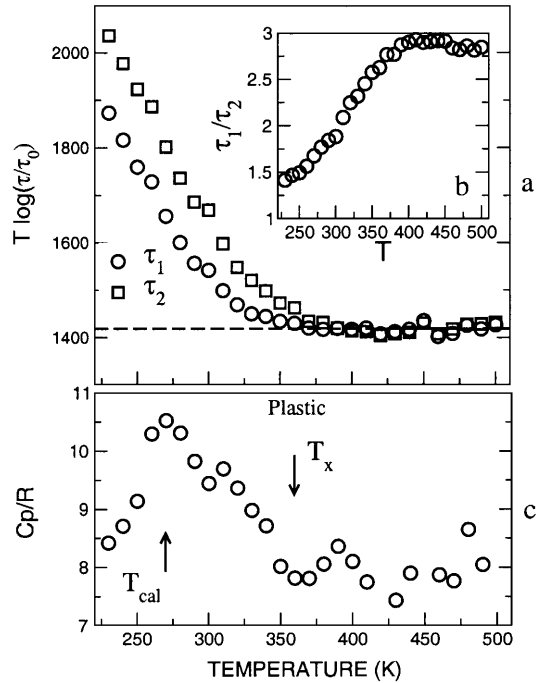


Fig. 4

Fig. 3 – Orientational correlation function C_2 as a function of time t at different temperatures from 220 to 500 K.

Fig. 4 – Numerical data as a function of temperature in the Cla plastic phase. (a) Orientational α -relaxation time τ_1 (circle) and τ_2 (square). The quantity plotted is $T \ln(\tau_{1,2}/\tau_0)$, where the time τ_0 is obtained by fitting the relaxation times values for $T = [400-500]$ K to an Arrhenius form. Deviation from the constant high-temperature value $\simeq 1418$ K (dashed line) is observed around $T_x \simeq 360$ K. The low-temperature *apparent* activation energy (taking only into account the four lowest temperatures) is about 3109 K for τ_1 and 3325 K for τ_2 (solid line), in good agreement with NMR experimental data. (b) The ratio of the relaxational times τ_1/τ_2 . (c) Calculated heat capacity. The position of the maximum of the hump ($T_{\text{cal}} \simeq 270$ K) and the temperature where the dynamical crossover is observed in the MD simulation ($T_x \simeq 360$ K) are also indicated.

reorientational motions can be described by a set of correlation functions which are defined as

$$C_l(t) = \frac{1}{N} \sum_{i=1,N} \langle P_l(\boldsymbol{\mu}_i(t) \cdot \boldsymbol{\mu}_i(0)) \rangle ,$$

where P_l is the l -order Legendre polynomial and $\boldsymbol{\mu}_i$ is the individual dipolar moment of the molecule i . The nature of dynamical changes and anisotropy can be checked by computing $C_{l=1,2}$ functions which can also be related to the information obtained from NMR relaxation measurements. Figure 3 shows the $C_2(t)$ time correlation function for all investigated temperatures above 220 K. Clearly, a two-step relaxational behaviour classically seen in supercooled molecular liquids [8, 20] is shown in our simulations. When lowering the temperature, an intermediate plateau region emerges which proves the presence of an orientational caging between neighboring molecules. This is the rotational analogue of the translational *cage effect*

observed in liquids. This transient regime is followed by a slow α process which can be associated in our system, as checked for CNa [13], with large tumbling motion between fourfold crystallographic directions where dipoles are preferably localized (see fig. 2). A consequence is that the tumbling of one molecule is allowed only if an orientational rearrangement of its local neighbors occurs. This *cooperative motion* is clearly displayed using projections of the individual dipolar moments on one crystallographic plane in fig. 2.

The τ_1 and τ_2 relaxational times are defined as the time it takes for their respective time correlation functions to decay e^{-1} of their initial values. They are displayed in fig. 4a. Clearly, close to $T_x \simeq 360$ K, both τ_1 and τ_2 relaxational times start diverging simultaneously from the Arrhenian high-temperature behaviour. Both high- and low-temperature *apparent* activation energies are found to be in good agreement with NMR experimental results. The high-temperature apparent activation energies are determined from a fit of all the relaxational times above 360 K with an Arrhenius law. Only the four lowest temperature points were used for the computation of the low-temperature apparent activation energies. The nature of the rotational motions involved in this dynamical change is given by the ratio τ_1/τ_2 in fig. 4b. This latter evolves from a value equal to 3 corresponding to free small-step rotational diffusion to a value of 1 classically associated to activated jump-like motion (see also fig. 2) [21, 22]. These results prove for the first time the existence of a plastic-plastic transition which can be interpreted as the rotational analogue of the Goldstein crossing temperature in liquids. It could also be associated with a different process of exploring the energy landscape topography above and below T_x . As has been recently proposed [4–6], the dynamics of the system can be viewed as hopping processes between separated inherent structures at sufficiently low temperatures. However, there are some hints that the present dynamical crossover temperature T_x does not probably correspond to the MCT critical temperature T_c . Indeed, a preliminary check of the asymptotic predictions of MCT (ideal version) in the α and β regimes reveals that the superposition principles and the scaling laws hold reasonably well [23]. In our system, the ideal glass transition temperature T_c should be close to 220 K. Furthermore, our system is still ergodic at the lowest temperature which is much below T_x , while it is usually observed that ergodicity is not granted below T_c [8].

Specific heats have been directly extracted from the calculated enthalpy ($C_p = dH/dT$) and are shown in fig. 4c. Clearly, a pronounced hump is seen which extends over the low-temperature part of the rotator phase below 360 K. It proves that our MD simulation captures the main features which are responsible for the anomaly found in calorimetric experiments by Oguni *et al.* [17]. A good agreement with the experimental results is found for the area under the C_p hump and its temperature extension, while for the position of the maximum it is only fair. Obviously, the underlying absolute value of the specific heat is not reproduced in this computation owing to the simplicity of our model, where the internal vibrational contributions of the Cla molecule and the fast uniaxial rotations have not been taken into account. Thermodynamically, the anomalous hump requires an abrupt decrease and a sharp change in curvature of the entropy *vs.* temperature evolution. Figure 4c shows that as the temperature is lowered the C_p hump begins to develop when the dynamics change in nature. The strong localization of the dipole along the [100] directions (see fig. 2) which develops below T_x is thus the prime suspect for the drastic change of the configurational entropy.

In conclusion, convincing experimental and numerical evidence for a dynamical crossover (T_x) in the rotator phase of chloroadamantane has been obtained, very much in keeping with recent views on structural glass-formers. It is seen as a transition from quasi-free rotational diffusion of the molecular dipoles to activated geared tumblings at low temperatures. This rotational localization is shown numerically to give rise to a specific heat hump as was recently measured [17]. The possible existence of such a calorimetric signature of a dynamical accident

in liquids is highly debated and was unsuccessfully searched until now [24,25]. Certainly, the underlying lattice and specificity of the orientational disorder contribute to make dynamical changes in the system much sharper than in liquids. We now feel confident that orientationally disordered crystals provide a valuable analog and alternative to the conventional liquid glass-formers. Results of the present study offer particularly new interesting possibilities of testing the Molecular Mode Coupling Theory (MMCT) approaches of the ideal glass formation as recently proposed for supercooled liquids [26–28].

* * *

The authors are indebted to Prof. K. NGAI for stimulating discussions. This work was supported by the INTERREG II program (Nord Pas de Calais/Kent). The authors wish to acknowledge the use of the facilities of the IDRIS where some of the simulations were carried out.

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Is There Something of Mode Coupling Theory in Orientationally Disordered Crystals?

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(Received 20 December 2000; published 28 June 2001)

Molecular dynamics simulations have been performed on the orientationally disordered crystal chloroadamantane. We stress that universal behavior, relatively well described by the mode coupling theory, is shared by systems whose dynamics are almost completely controlled by translations or rotations. This investigation also shows the existence of a second remarkable dynamical crossover at the temperature $T_x > T_c$, consistent with a previous NMR and molecular dynamics study [F. Affouard *et al.*, *Europhys. Lett.* **53**, 611 (2001)]. This allows us to support clearly the existence of a “landscape-influenced” regime as recently proposed [S. Sastry *et al.*, *Nature* **393**, 554 (1998)].

DOI: 10.1103/PhysRevLett.87.035501

PACS numbers: 61.43.-j, 64.70.Pf

In recent years, a great deal of work has been done to obtain a fundamental understanding of the glassy state and the glass formation but no well-accepted theory has emerged so far [1]. At present, the only theory which gives precise predictions of the supercooled liquids' dynamics is the mode coupling theory (MCT) [2]. It particularly predicts an ergodic-to-nonergodic transition at the critical temperature T_c usually found above the calorimetric glass formation temperature T_g . T_c is now commonly considered as the crossover temperature to an activated dynamical regime recently called “landscape dominated” by Sastry *et al.* [3] since it is suspected that dynamics can be described by hopping processes between the different inherent structures of the potential energy landscape [4]. It must be noted that MCT does not intrinsically take into account these ergodicity-restoring processes, and deviations from the prediction of this theory are clearly observed below T_c . The existence of a second remarkable crossing temperature, denoted by T_x in this Letter, was recently shown from computer simulations [3–5]. The precise nature of this temperature found above T_c remains unclear but should correspond to the onset of nonexponential relaxation and non-Arrhenius temperature dependence of the relaxation times.

During the past ten years, a variety of experiments and molecular dynamics (MD) computer simulations have provided considerable insight into the nature of supercooled liquids [6]. Significant advances were particularly obtained concerning the role of the translational degrees of freedom, for which MCT gives detailed predictions, in the underlying mechanism of slow dynamics. Most glass formers also possess orientational degrees of freedom (ODOF) which are certainly involved in the glass formation. However, their relative importance during the dynamical slowing down remains unclear and have been the subject of very few thorough investigations. It should be noted that MCT was extended recently to liquids of non-spherical molecules [6,7]. One class of compounds offers attractive possibilities to focus mainly on the role of the

partially overlooked ODOF and provides a valuable alternative to the molecular liquid glass formers. Indeed, some molecular crystals show a high temperature *plastic* phase in which the average positions of the centers of mass are ordered on a lattice while the orientations are dynamically disordered [8]. Some of them, called *glassy crystals* [9], such as cyanoadamantane [10], ethanol [11,12], carboranes [13], or cyclooctanol [14], can be deeply supercooled and present many properties characteristic of the conventional glass formers.

In this Letter, we discuss precisely, by means of a case study of chloroadamantane, if dynamical universal behavior is shared by orientationally disordered crystals and molecular liquids. Indeed, since both systems possess the same striking features of glass and glass formation, one can expect that some common microscopic mechanism is involved. One particularly has to mention numerical works made on very simple models of plastic crystal which exhibit typical dynamical features of supercooled liquids: Brownian planar rotors based on a uniformly frustrated XY model on a square lattice [15] and colliding hard needles distributed on a lattice [16]. Stimulated by these previous studies and by the various predictions of MCT, we have chosen to study the chloroadamantane $C_{10}H_5Cl$ (noted Cla in the following) plastic crystal. This compound belongs to the substituted adamantane family which presents excellent experimental candidates [10]. Very recently, by means of a NMR experiment and MD computer simulation, we have shown that this system exhibits a dynamical crossover transition at $T_x \approx 350$ K in the pico-nanosecond regime [17]. It was interpreted as the first indication of a change in the energy landscape topography, as was recently proposed [3]. A two-step (α - β) relaxation was also observed to emerge but there were some indications that the T_x probably did not correspond to the T_c of the MCT, as developed for structural glass formers.

MD simulation of orientationally disordered molecular crystal Cla was performed at different temperatures from $T = 220$ to 500 K. Despite the very long MD runs,

equilibrium of the system could not be obtained below $T \approx 220$ K. A simple model was used which is described in detail in [17], so only the essential details are given in [18].

Figure 1 shows the orientational self-intermediate scattering function $F_u^s(q, t)$, for the arbitrary wave vector $q = 3.06 \text{ \AA}^{-1}$, as defined by Lewis and Wahnström in [19], where only the ODOF are taken into account. Clearly, by lowering the temperature, as already observed for the orientational correlation functions $C_l(t) = \langle P_l[\vec{\mu}(t) \cdot \vec{\mu}(0)] \rangle$ in [17], the rotator phase of Cla exhibits a two-step relaxation. At intermediate times, $F_u^s(q, t)$ shows a plateau-like region which reveals the existence of an *orientational cage effect*, i.e., the rotational analog of the translational cage effect observed in liquids. This transient regime is followed by a slow decay to a nonzero value called the elastic incoherent structure factor (EISF) and denoted by $A_0(q) = \lim_{t \rightarrow \infty} F_u^s(q, t)$ [8] which gives information on the time-averaged orientational geometry of the molecular motions. $A_0(q)$ is displayed in Fig. 2 for different wave vectors and exhibits an unusual temperature dependence which confirms, as already seen in [17], the existence of a change of the rotational dynamics. Indeed, at high temperature, an isotropic diffusion rotation model gives a good description of the dynamics. By lowering the temperature, discrepancies of this model are clearly seen in Fig. 2 and a jumplike motion between preferred orientations may be assumed.

In the following, we try to describe our data in the MCT framework. The idealized version [2] of this theory pre-

dicts a two-step relaxation scenario (fast β , slow α) of all the time dependent correlators $\phi(q, t)$. MCT particularly states the following points: At short time, $\phi(q, t)$ decays to a plateau value, the so-called nonergodicity parameter classically noted f_q^c . The dynamical regime associated with this plateau is called β . It is centered around the rescaling time t_σ which is given by $t_\sigma = t_0 |\sigma|^{-1/2a}$, where t_0 is a characteristic microscopic time and σ is proportional to $|T - T_c|$. Above T_c , the late β regime or the early α relaxation is described by the following power law (going beyond first order):

$$\phi(q, t) = f_q^c - h_q^{(1)} \cdot (t/\tau)^b + h_q^{(2)} \cdot (t/\tau)^{2b}, \quad (1)$$

where the first two terms correspond to the classical von Schweidler law, the last term is a second-order correction, and $\tau = t_0 |\sigma|^{-\gamma}$ with $\gamma = 1/2a + 1/2b$. At long time, MCT also predicts that the previous fast regime is followed by a slow relaxation, called α , with the characteristic time τ . Furthermore, parameters a and b are temperature and q independent and related via $\Gamma^2(1 - a)/\Gamma(1 - 2a) = \Gamma^2(1 + b)/\Gamma(1 + 2b)$, where $\Gamma(x)$ is the gamma function.

In order to verify the validity of those scaling laws, we first tried to fix the exponent b by using the factorization theorem in the β regime, where hopping processes are not supposed to be dominant. The ratio $R_\phi(t) = [\phi(t) - \phi(t_1)]/[\phi(t_2) - \phi(t_1)]$, where (t_1, t_2) are two different arbitrary times in the β regime, has been calculated at different temperatures and for different correlators ϕ [$F_u^s(q, t)$ for several wave vectors and $C_l(t)$ for $l = 1, 2$ as defined in [17]]. The results are displayed in Fig. 3. Clearly, there exists a time domain where the different correlation functions collapse onto a master curve in the β regime, as predicted by MCT. Assuming

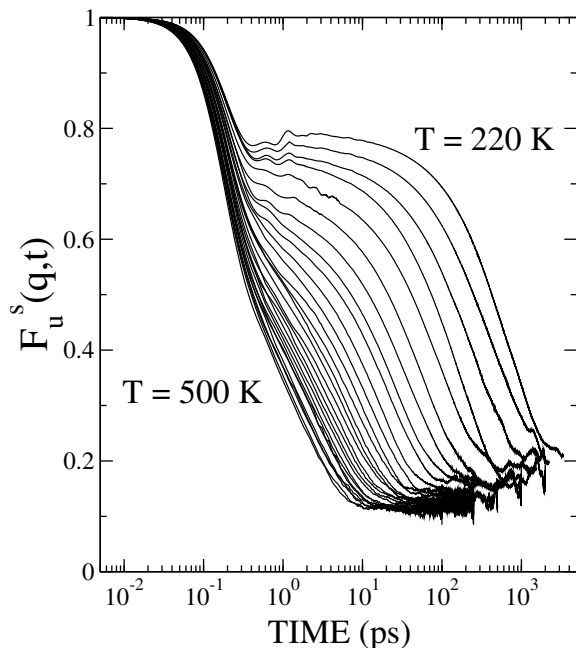


FIG. 1. Orientational self-intermediate scattering function $F_u^s(\vec{q}, t)$ as a function of time t for wave vector $q = 3.06 \text{ \AA}^{-1}$. $F_u^s(\vec{q}, t)$ is defined as $\sum_{i=1}^N \sum_{a=1}^{N_a} \langle \exp[i\vec{q} \cdot (\vec{u}_{i,a}(t) - \vec{u}_{i,a}(0))] \rangle$, where $\vec{u}_{i,a} = \vec{R}_{i,a} - \vec{R}_i^{\text{c.m.}}$. $\vec{R}_i^{\text{c.m.}}$ is the center of mass of molecule i and $\vec{R}_{i,a}$ denotes the position of site a in each molecule ($N_a = 2$ in this paper).

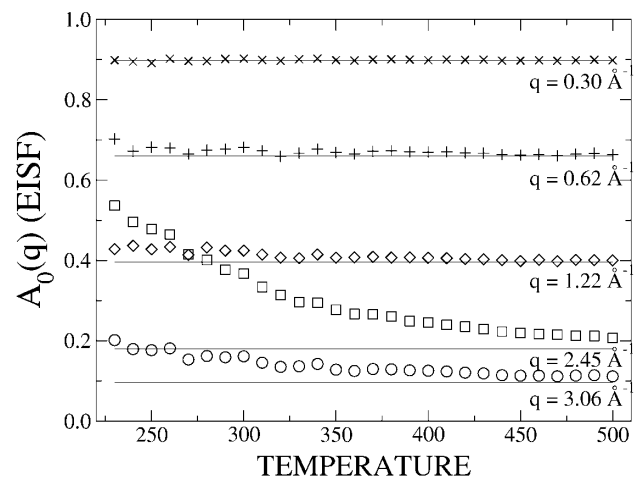


FIG. 2. Elastic incoherent structure factor as a function of temperature for the arbitrary wave vectors $q = 3.06, 2.45, 1.22, 0.62$, and $0.30 \text{ \AA}^{-1}$. For a rotational diffusion model (solid lines), the EISF for one scattering atom moving on a sphere of radius a can be written as $A_0(q) \sim j_0(q \cdot a)$, where j_0 is the zero-order spherical Bessel function [8].

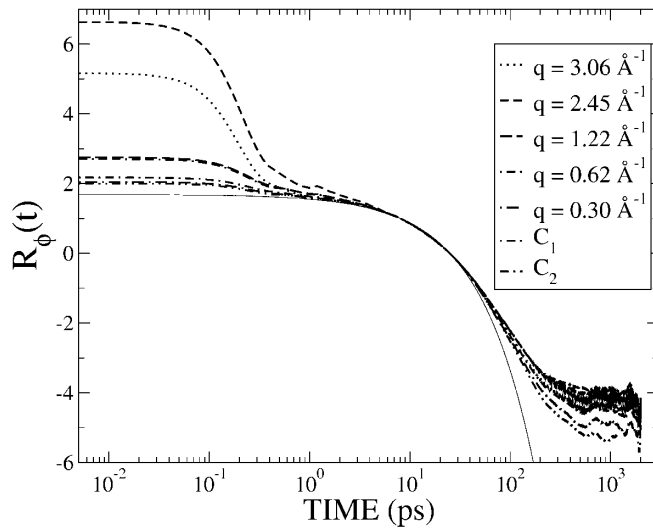


FIG. 3. Ratio $R_\phi(t) = [\phi(t) - \phi(t_1)]/[\phi(t_2) - \phi(t_1)]$, where (t_1, t_2) are two different arbitrary times in the β regime at $T = 260$ K. The following correlation functions have been used: $\phi(t) = F_u^s(q, t)$, for wave vectors $q = 3.06, 2.45, 1.22, 0.62$, and $0.30 \text{ \AA}^{-1}$, and $\phi(t) = C_l(t)$, for $l = 1, 2$ angular correlation functions (see [17]). The master curve (solid line), obtained by the von Schweidler law with the exponent $b = 0.79$, is also displayed.

the correlator function ϕ departs from the plateau with a von Schweidler law, it is possible to show that the master curve depends only on the exponent b . Using a fitting procedure performed at several different temperatures for all correlators mentioned previously, we obtained the best results for $b = 0.79$ which corresponds to $a = 0.36$ and $\gamma = 2.02$. Then, fixing these values, we performed individual fits of the different correlators in the late β regime using Eq. (1) with free parameters f_q^c , $\tilde{h}^{(1)} = h^{(1)}(q) \cdot \tau^{-b}$, and $\tilde{h}^{(2)} = h^{(2)}(q) \cdot \tau^{-2b}$. Only the temperatures below 330 K, where the plateau region is clearly defined, were considered. The total prefactor $\tilde{h}^{(1)}$ is displayed in Fig. 4. $\tilde{h}^{(2)}$ is not shown in this Letter but it exhibits the same temperature dependence. A temperature dependence is clearly found which extrapolates to zero at the critical temperature $T_c \approx 225 \pm 8$ K for the different correlators. A deviation to the linear evolution is observed close to T_c which could be attributed to the occurrence of hopping processes. The nonergodicity parameter f_q^c shows a relatively smooth temperature evolution but we have no clear evidence of a cusp at T_c due to the lack of data at low temperature.

In the α regime, we defined the relaxation time τ_q as the time it takes for the different correlators to decay from 1 to $1/e$. It is assumed that any characteristic times belonging to the α regime show asymptotically the same temperature dependence $\tau_q \sim \tau$. The τ_1 and τ_2 relaxation times are defined similarly for the orientational correlation functions $C_{l=1,2}$. For a direct comparison, orientational self-intermediate scattering functions were rescaled with the EISF as $[F_u^s(t) - A_0(q)]/[1 - A_0(q)]$ in order to decay

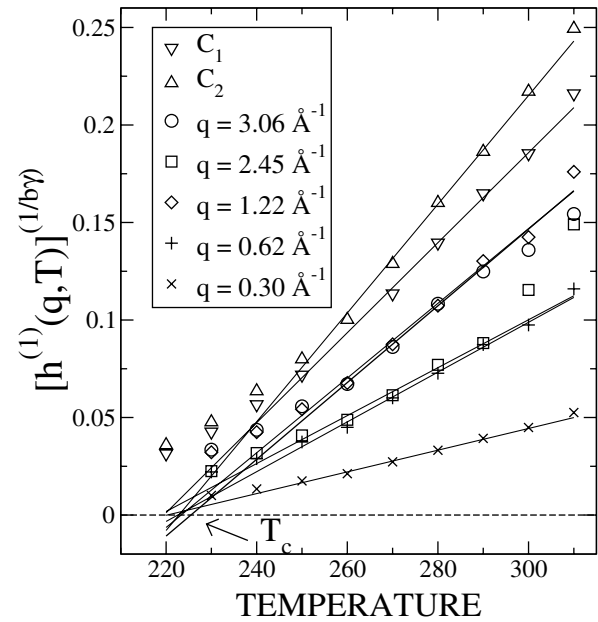


FIG. 4. Total prefactor $[\tilde{h}^{(1)}]^{1/b\gamma}$ as a function of temperature for all investigated correlators (see Fig. 3). The fitting procedure reveals a linear dependence (solid lines) of the total prefactor which extrapolates to zero at the critical temperature $T_c \approx 225 \pm 8$ K for all correlators.

with time from 1 to 0. According to MCT, the α relaxation times, $\tau_q^{-1/\gamma}(T)$, should yield straight lines intersecting the abscissa at $T = T_c$. Figure 5 shows that for all investigated correlators this prediction holds well over a relatively large temperature range. Extrapolation of the temperature dependence gives a critical temperature of $T_c \approx 225 \pm 8$ K, consistent with the β -regime analysis. About 40 K above T_c , discrepancies with the MCT power law prediction are seen, as already shown in the fast regime, and are certainly due to the hopping processes. Furthermore, the time-temperature superposition principle was also checked and we found that all correlators fall onto a master curve in the α time domain when plotted as a function of the rescaled time t/τ_q (not display in this Letter). However, at high temperatures, close to the dynamical crossover previously observed at T_x in [17], a clear deviation of the α relaxation from the MCT prediction is found. At $T > T_x \approx 350$ K, we have calculated that our data can be very well reproduced by a simple Arrhenius law. The T_x crossing temperature alters slightly for the different correlators. At present, we have no clear interpretation of this feature.

Very recently, we obtained promising results concerning the energy landscape description of this model. Since further investigations are necessary, they are not included in this Letter. It was particularly observed that the average energy of the inherent structures does not change significantly above T_x while it decreases progressively below this temperature. As has been clearly demonstrated for a binary Lennard-Jones MD simulation in [3–5], we obtained in this paper a strong indication of the existence of a

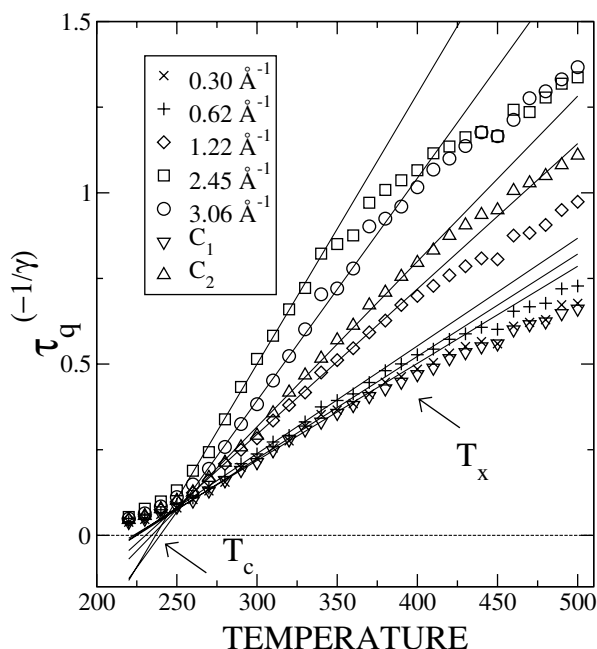


FIG. 5. α relaxation time $\tau_q^{-1/\gamma}$ as a function of temperature for all investigated correlators (see Fig. 3). The exponent $\gamma = 2.02$ has been extracted from the MCT analysis in the β regime. The solid lines indicate MCT fit using the linear law $\tau_q^{-1/\gamma} \sim (T - T_c)$. Deviation from the MCT prediction is found at $T > T_x \approx 350$ K, where τ_q can be fitted with a simple Arrhenius law.

landscape-influenced regime occurring in the temperature range $[T_c - T_x]$.

In conclusion, this study reveals that systems whose dynamics are almost completely controlled by ODOF share some common dynamical features with liquid glass formers, relatively well described by the idealized version of the MCT. It was recently shown that the asymptotic predictions of this theory which initially described simple van der Waals atomic liquids still hold for molecular systems [6,7]. Nevertheless, an extension of the MCT to systems, which possess ODOF only, has not been developed so far. Our work suggests such a possibility. Furthermore, this investigation confirms the existence of a second remarkable dynamical crossover at the temperature $T_x > T_c$, consistent with previous calorimetric [20], NMR, and MD studies [17]. This allows us to determine precisely the temperature range $[T_x - T_c]$ of the landscape-influenced regime in this system as defined recently by Sastry *et al.* [3] for a model glass forming liquid. Our results obtained for Cla call for new investigations: (i) It would be of great interest to study the q dependence of the different parameters f_q^c , $h_q^{(1)}$, or τ_q which was not performed in this Letter for Cla due to the limited number of investigated wave vectors. (ii) Experimental and numerical extensions of this Letter to other well-documented orientationally disordered crystals such as cyclooctanol, carboranes, or ethanol are

needed to fully validate the MCT picture. (iii) Theoretical studies are highly desirable in order to clarify the precise nature of the dynamical crossover occurring at T_x which remains unclear at present.

The authors acknowledge the use of the facilities of the IDRIS, F-91403 Orsay, where some of the simulations were carried out. This work was supported by the INTERREG II program (Nord Pas de Calais/Kent).

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- [18] Molecules are composed of two sites: one chlorine and one superatom that models the adamantane group $C_{10}H_{15}$. Calculations were performed on a system of $N = 256$ ($4 \times 4 \times 4$ fcc crystalline cells) molecules interacting through a short range site-site Lennard-Jones potential. Size effects were checked and no significant change was found for a larger system made of $N = 2048$ molecules. The electrostatic interactions were handled by the Ewald method with two partial charges ($q = \pm 0.151e$) localized on both sites which reproduce the experimental dipolar moment $|\mu| \approx 2.39$ D. A time step of $\Delta t = 5$ fs was used to integrate Newton's equations of motion. We worked in the NPT statistical ensemble with periodic boundary conditions.
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Journal of Non-Crystalline Solids 307–310 (2002) 9–15

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NON-CRYSTALLINE SOLIDS

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Orientationally disordered crystals: from the onset of slow dynamics to the glass transition

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Abstract

Calorimetric and X-ray experiments and molecular dynamics (MD) simulations have been performed on adamantane substituted plastic crystals. We show that orientationally disordered crystals provide a valuable alternative to the molecular liquid glass formers since they offer attractive possibilities to investigate the fundamental mechanism of the glass transition both in the dynamical decoupling regime (high temperature) and in the deep undercooled situation. This investigation confirms the existence of a second remarkable dynamical crossover at the temperature T_x found higher than the mode coupling theory critical T_c and consistent with previous NMR, Raman and MD studies. This allows us to confirm clearly the existence of a 'landscape-influenced' regime occurring in the temperature range $[T_c - T_x]$ as recently proposed. Furthermore, a clear signature of cooperatively rearranging regions which develop on approaching T_g is found. Instead of well defined independent domains as proposed by Adam and Gibbs, the cooperative regions can rather be identified here to short range order fluctuations whose spatial extent can be characterized by the associated correlation length.

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1. Introduction

The discovery that *plastic crystals*, in which the average position of the centers of mass are ordered on a lattice while the orientations are dynamically disordered, exhibit the phenomenology of conventional liquid glass formers is an exciting opportunity. Indeed, some of them, called *glassy crystals* [1], such as cyanoadamantane (CNa) [2],

ethanol [3,4], cyclooctanol [5] or difluorotetrachloroethane [6] can be deeply super-cooled and present many properties characteristic of the conventional molecular liquid glasses. They offer a valuable alternative to the canonical glass formers and an excellent opportunity to focus on the role of the orientational degrees of freedom (ODOF) whose importance during the glass formation remains a matter of debate at present. It has to be noticed that glassy crystals in opposition to the so called 'orientational glasses' like mixed crystals $\text{Ar}_{1-x}(\text{N}_2)_x$ or $(\text{KCN})_x(\text{KBr})_{1-x}$ are not frustrated by any quenched disorder externally imposed by a dilution [7]. Orientationally disordered crystals had led recently to a new interest [8,9] since they have

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been found relevant to investigate the pico-nano-second regime where the mode coupling theory (MCT) [10] predicts a dynamical decoupling. In addition to the critical temperature T_c predicted by MCT, much attention has been recently devoted to the existence of a second remarkable crossover temperature noted T_x in the following [11]. This latter has been identified in simple liquids above T_c and associated with the onset of slow dynamics influenced by the energy landscape topography [12,13]. Very recently, by means of NMR and Raman experiments and MD computer simulation [14,15], we have also shown that plastic crystal chloroadamantane (Cla) exhibits this second dynamical crossover between quasi-free rotational diffusion and activated motion. Our previous results obtained for Cla call for new investigations to clarify the precise nature of the dynamical crossover occurring at T_x which remains unclear at present and are presented in Section 3.

An other fundamental question of the physics of glasses concerns the microscopic description of the cooperative mechanisms which are recognized to develop in the undercooled liquid between T_x and T_g [16–18]. The dynamical signature of this cooperativity is a more or less strong increase of the activation energy on approaching T_g , which divides fragile liquids from strong liquids [19]. This dynamical behavior is directly connected to the thermodynamic properties of the system since the most fragile liquids are also those for which the configurational entropy shows the steepest decrease on approaching T_g . A most important point which remains open is to determine if this cooperativity is associated to the development of some structural order [20]. Such a structural evolution is absolutely not predicted by the actual theories for the glass transition like MCT [10] or the Adam and Gibbs theory [16]. It has never either been detected experimentally in glass forming liquids for which any detailed structural information is deeply buried into the halo X-ray diffraction pattern characteristic of non-crystalline solids. The radial distribution function is, in particular, not sensitive to changes in short range order (SRO). From that point of view, glassy crystals [1,21] provide better conditions to search for structural evolutions accompanying the vitrification mechanism. Com-

pared to glass forming liquids, the frozen disorder is more simple to characterize since it involves only the ODOF. Moreover, this orientational freezing occurs on an underlying crystalline lattice which gives access to detailed structural information through X-ray diffraction experiments. CNa is another adamantane substituted which is known to be a prototype glassy crystal [2]. It has the advantage over other glassy crystals to provide single crystals of very high quality which can be quenched easily and without any damage [21]. The orientational disorder mainly comes from the tumbling motion of the molecular dipoles along the [100] direction of the fcc structure of the plastic phase [22]. This very limited disorder can be mapped onto a 6-states Potts model and lead to an extended X-ray diffraction pattern which provides rich structural information. We have taken advantage of the specific properties of CNa to follow the structural and thermodynamic evolution of its plastic phase into an orientational glassy state. This could be done by calorimetric measurements and single crystal X-ray diffraction during the undercooling of the plastic phase. The results are shown in Section 4 and reveal a clear structural signature of the cooperativity which develops on approaching T_g .

2. Experiments and details of the simulation

The MDSC experiments presented in this paper were performed between 150 and 300 K using the MDSC 2920 micro-calorimeter of TA Instruments. During all measurements, the calorimeter head was flushed with highly pure helium gas. The temperature and enthalpy readings were calibrated using pure adamantane [23] which exhibits an order-disorder transition at $T_t = 208.6$ K ($\Delta H = 3.38$ kJ/mol). The sample consists of commercial CNa purchased from Aldrich and purified by sublimation in order to get a purity better than 99.9%. It was sealed in an aluminum capsule of 50 μ l. A small amount (9.6 mg) of a very fine CNa powder was used to improve the thermal equilibration of the sample and to avoid crystallization effects upon cooling.

The X-ray diffraction experiments were performed with an automatic diffractometer (Philips PW 1100) using a conventional Mo X-ray source equipped with a pyrolytic graphite monochromator ($\lambda_{\text{Mo K}\alpha} = 0.711 \text{ \AA}$). The single crystal of CNa was grown by slow evaporation at room temperature (RT) of a slightly undersaturated solution of the compound in methanol. Low temperatures were achieved by placing the sample into a gaseous nitrogen flow at the required temperature. Using this procedure, the sample is quenched within a few seconds, and its temperature can be controlled within 0.5 K between 110 and 300 K.

The MD simulations of orientationally disordered molecular crystal Cla have been performed on a system of $4 \times 4 \times 4$ fcc crystalline cells i.e. $N = 256$ molecules interacting through a short range site–site Lennard-Jones potential. The model has been used previously to simulate both Cla and CNa and it is completely described in [14, 24, 25], so only the essential details are given here. Modeled molecules are composed of two sites: one chlorine and one super atom that models the adamantane group $\text{C}_{10}\text{H}_{15}$. The electrostatic interactions were handled by the Ewald method with two partial charges ($q = \pm 0.151e$) localized on both sites which reproduce the experimental dipolar moment $|\vec{\mu}| \simeq 2.39$ Debyes [26]. A time step of $\Delta t = 5$ fs was used to integrate the Newton's equations of motion. We worked in the NPT statistical ensemble with periodic boundary conditions. Plastic Cla has been investigated at 29 different temperatures from $T = 220$ to 500 K. Owing to the very long MD runs, equilibrium of the system could not be obtained below $T \simeq 220$ K.

3. Onset of slow dynamics in Cla

Rotational dynamics can be probed by calculating the orientational self intermediate scattering function $F_u^s(q, t)$, for different arbitrary wave vectors q as defined by Lewis et al. in [27] where only the ODOF are taken into account (Fig. 1). With lowering the temperature below T_x , all $F_u^s(q, t)$ correlators, as already observed for the dipolar orientational correlation functions $C_{l=1,2}(t)$, ex-

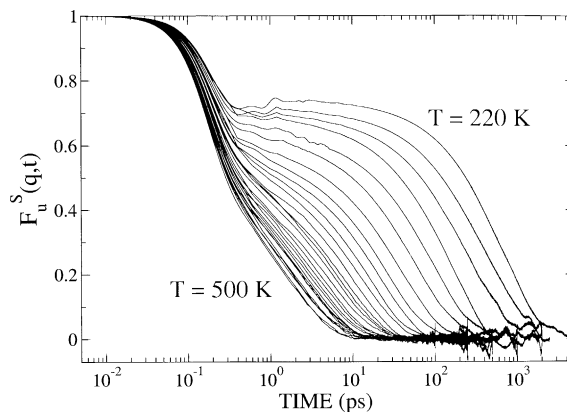


Fig. 1. Orientational self intermediate scattering function $F_u^s(\vec{q}, t)$ as function of time t for wave vector $q = 3.06 \text{ \AA}^{-1}$. $F_u^s(\vec{q}, t)$ have been rescaled with the elastic incoherent structure factor A_0 as $[F_u^s(t) - A_0(q)]/[1 - A_0(q)]$ in order to decay with time from 1 to zero. $F_u^s(\vec{q}, t)$ is defined as $\sum_{i=1}^N \sum_{a=1}^{N_a} \langle \exp \times [\vec{q} \cdot (\vec{u}_{i,a}(t) - \vec{u}_{i,a}(0))] \rangle$ where $\vec{u}_{i,a} = \vec{R}_{i,a} - \vec{R}_i^{\text{cm}}$. $\vec{R}_i^{\text{cm}}$ is the center of mass of molecule i and $\vec{R}_{i,a}$ denotes the position of site a in each molecule ($N_a = 2$ in the present study).

hibit a two-step (α – β) relaxation [8, 14]. At intermediate times, $F_u^s(q, t)$ shows a plateau-like region which reveals the existence of an *orientational cage effect* i.e. the rotational analogue of the translational cage effect observed in liquids (see Fig. 2(c)). This transient plateau like is followed by a slow α process which can be associated in our system, as checked for CNa [28], with large tumbling motion between fourfold crystallographic directions where dipoles are preferably localized (see Fig. 2(c)). A consequence is that the tumbling of one molecule is allowed only if an orientational rearrangement of its local neighbors occurs. This *cooperative motion* is clearly displayed using projections of the individual dipolar moments on one crystallographic plane. The structural signature of this cooperativity could be identified by X-ray diffraction on single crystals and will be presented in the next section.

α relaxation times $\tau(T)$ are obtained, as a function of the temperature, as the time it takes for the different correlators $F_u^s(q, t)$ to decay from 1 to $1/e$. At high temperature, for all correlators, $\tau(T)$ can be well fitted with an Arrhenius law $\tau(T) = \tau_0 \exp(E_0/T)$ where the parameters (τ_0, E_0) allow us to calculate the temperature dependent activation

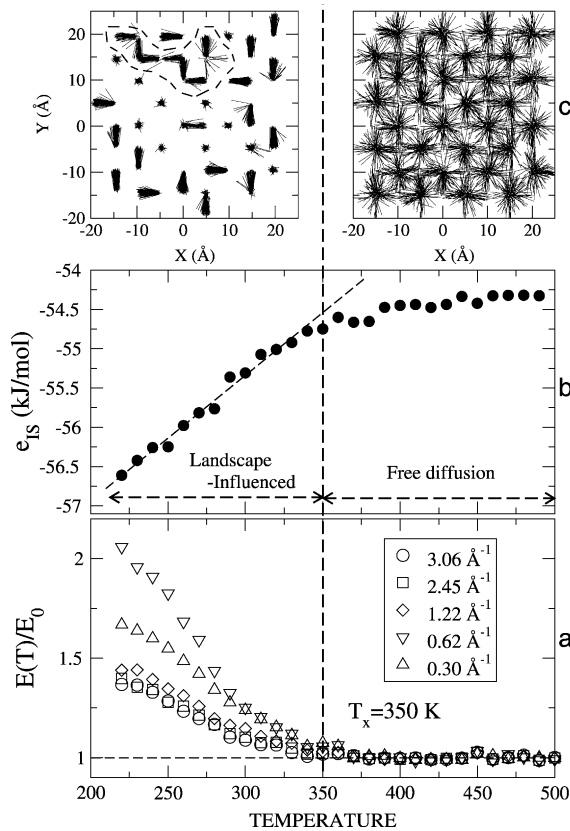


Fig. 2. (a) Temperature dependent activation energy $E(T) = T : \ln(\tau_q/\tau_0)$ normalized to the high temperature value E_0 . We defined the relaxation time τ_q as the time it takes for the different orientational self intermediate scattering functions $F_u^s(\vec{q}, t)$ to decay from 1 to $1/e$ [8], (b) mean inherent structure energy per molecule as a function of the temperature of the equilibrated system from which the inherent structures were generated by energy minimization, (c) snapshots of the dipolar moments are projected on one xy plane at different instants in a run of 250 ps at $T = 220 \text{ K}$ (left) and $T = 400 \text{ K}$ (right). At $T = 220 \text{ K}$, some orientations are not populated since the system is not completely equilibrated over this duration. A cooperative region is encircled with dashed line in the same figure.

energy $E(T) = T \log(\tau/\tau_0)$. Fig. 2(a) displays $E(T)/E_0$ as function of the temperature. Clearly, close to $T_x \simeq 350 \text{ K}$, all activation energies start diverging simultaneously from unity corresponding to the Arrhenian high temperature behaviour.

The average inherent structure energy per molecule $e_{IS}(T)$ as a function of the temperature has been calculated by energy minimization and is displayed in Fig. 2(b). Clearly, the average energy

of the inherent structures does not change significantly above T_x while it decreases progressively below this temperature very much in keeping with recent MD investigations concerning binary Lennard-Jones [11–13,29]. We obtain in the present study a strong indication of the existence of a crossover from a free diffusion regime to a *landscape influenced* regime occurring at T_x corresponding to a transition from quasi-free rotational diffusion of the molecular dipoles to activated geared tumblings as seen in Fig. 2(c).

4. Thermodynamic and structural evolution in CNa on approaching T_g

Fig. 3 shows the heat capacities of the stable, metastable and glassy plastic phase measured by the MDSC technique. In order to investigate the whole domain of non-equilibrium the experiment was performed upon cooling with the following sweeping rate and modulation parameters:

$q = -5 \text{ K/min}$ (average sweeping rate)

$\omega/2\pi = 80 \text{ s}$ (period of modulation)

$A = 0.5 \text{ K}$ (amplitude of modulation).

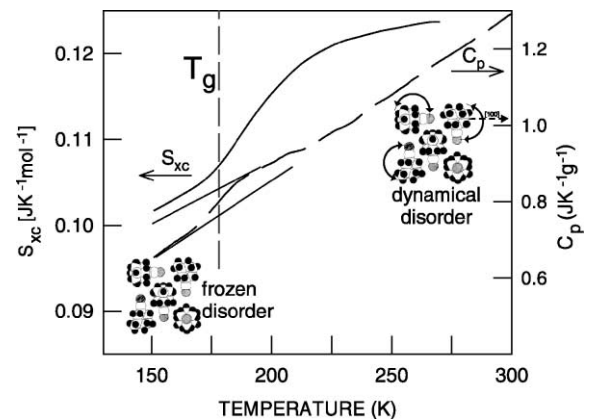


Fig. 3. Heat capacity and entropy evolutions of CNa measured by MDSC upon cooling (-5 K/min) the plastic phase through its stable, metastable and glassy domain. The insets show possible instantaneous configurations of the CNa molecular dipoles in the plastic phase (where the orientational disorder is dynamic) and in the glassy phase (where the orientational disorder is frozen).

Using these parameters, no exothermic peak corresponding to a transformation towards a more ordered phase is observed in the $C_p(T)$ curve. This indicates that the plastic phase can be easily undercooled. Below 250 K, the $C_p(T)$ curve shows a slight upward curvature which get arrested at about 180 K. Below this temperature the C_p begins to decrease by about 20% over a range of 10 K giving rise to a rounded, but well defined, discontinuity similar to that of a conventional glass transition. At 180 K, dielectric relaxation experiments [30,31] which probe the dipolar tumbling motions, have revealed relaxation times comparable to the temperature modulation period (80 s). The C_p anomaly shown in Fig. 3 can thus be attributed to the freezing of the tumbling motions of the molecular dipoles.

Fig. 3 also shows the evolution of the excess entropy (S_{xc}) of the undercooled plastic phase with respect to the ordered monoclinic phase [32] which is stable at low temperature. It reveals a decrease of S_{xc} which get more and more pronounced with the undercooling. The glass transition is marked by an inflection point which indicates a slowing down of the entropy decrease in the glassy domain. The decrease of the excess entropy in the undercooled plastic phase reflects the loss of some accessible microscopic configurations and, thus, the decrease of the configurational entropy.

Such a behavior is a usual feature of glass forming liquids [33]. However, up to now, the structural modifications which are expected to be responsible for the loss of configurational entropy could never be extracted from the spatially average structure factor $S(|\vec{Q}|)$ of liquids. Better conditions are expected to be found in CNa glassy crystal for which detailed structural information about the orientational freezing can be obtained through XRD diffraction experiments on single crystal. We have taken advantage of this possibility to probe the structure factor $S(\vec{Q})$ in the plastic phase at RT and around the glass transition. In the intermediate temperature range, it must be noted that the life time of the undercooled plastic phase has been found too short to be investigated by the same technique.

The comparison of the main Bragg peaks at RT and just after a quench near T_g (at 170 K) indicates

that the quenched state remains cubic [34]. X-ray diffuse scattering pattern have revealed broad diffuse scattering spots at the X-points of the Brillouin zone which are forbidden reflections of the fcc lattice. As shown in Fig. 4, these peaks are weak but clear at RT in the stable plastic phase, but develop considerably and sharpen in the quenched state. This indicates that antiferroelectric correlations of short range nature set up in the system during the cooling stage. In the hypothesis of Ornstein Zernicke fluctuations a correlation length characterizing the antiferroelectric SRO can be derived from the full width at half maximum of the diffuse scattering peaks. The data of Fig. 4 indicate that such a correlation length increases from 12 to 18 Å during the undercooling of the plastic phase toward its glassy crystal state.

This characterization of the thermodynamic and structural evolution of CNa plastic crystal in its route toward a glassy crystal state indicates

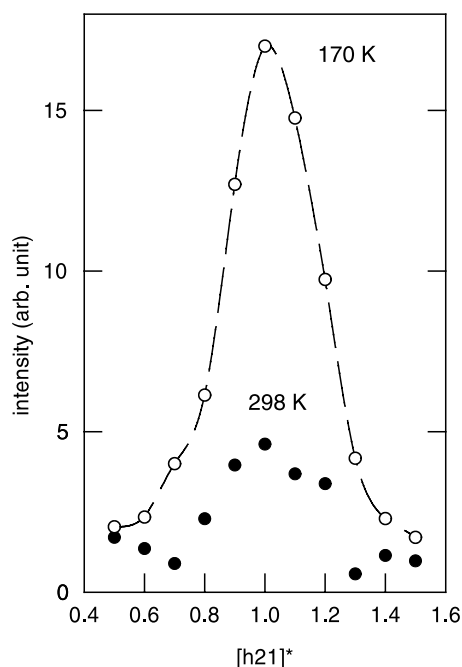


Fig. 4. Diffuse scattering measured along the $[h21]^*$ direction by X-ray diffraction using a single crystal of CNa. The measurements have been performed in the plastic phase, at 298 K and just after a quench at 170 K. The dashed line is a guide for eye.

that, while the freezing only concerns the orientational degrees of freedom, the thermodynamic properties are fully similar to those of glass forming liquids. In particular, the glass transition is characterized by a C_p jump, and its approach induces a strong decrease of the configurational entropy. Moreover, taken advantage of the underlying lattice which supports the orientational freezing, it was possible to detect a structural signature of the entropy decrease. Up to now, such a signature could never be observed in glass forming liquids. In CNa this signature corresponds clearly to the development of an antiferroelectric SRO which develops homogeneously and reversibly during the quenching process.

5. Conclusion

The present numerical simulation investigation confirms the existence of a second remarkable dynamical crossover in Cla at the temperature T_x consistent with previous NMR [14], Raman [15], calorimetric [35] experiments and MD studies [14,28]. This allows us to confirm clearly the existence of a ‘landscape-influenced’ regime occurring in the temperature range $[T_c - T_x]$ as recently proposed [11–13] where T_c is the critical temperature predicted by MCT which was determined in [8]. In this latter investigation, our work revealed that plastic crystals whose the dynamics are almost completely controlled by rotation shares some common dynamical features with liquid glass formers relatively well described by the idealized version of the MCT where the same critical temperature $T_c \simeq 225$ K was particularly extracted both in the α and β regime. However, no MCT for plastic crystals has been proposed yet. It has been recently shown that the asymptotic predictions of this theory which initially described simple van der Waals atomic liquids still hold for molecular liquid systems [36,37]. It should be also noted that one theory which predicts an ergodic to non-ergodic transition has been developed for diluted orientational glasses by Michel [38]. It was proposed on the basis of a specific mode coupling approach which does not consider frustration as an essential feature. A key point of this theory mainly involves

the interplay of rotational–translational and rotational-strains coupling [38] where strains result from the substitutional disorder (the Br atoms in $(\text{KCN})_x(\text{KBr})_{1-x}$). It is reasonable to assume that an alternate MCT for glassy crystals should be developed. Essential factors to include could be the rotational–translational coupling, the crystal symmetry and the crystal field [39].

The relaxation of glass forming systems is widely recognized to be governed by co-operative mechanisms. Such a view makes for instance the framework of the Adam and Gibbs theory [16] which assumes the existence of ‘cooperatively rearranging regions’ (CRR) whose size is expected to be inversely proportional to the configurational entropy of the system. From their ‘ad hoc’ definition the CRR are expected to be both well defined and independent from one another. However, up to now these assumptions could not be confirmed by any direct experimental observation of cooperative processes. The recent finding of heterogeneous dynamics [40–42] in some under-cooled liquids and glasses is the only experimental fact which infers the existence of cooperative molecular motions.

The image of the CRR which emerges from our results in CNa glassy crystal is quite different from that proposed by Adam and Gibbs. Instead of well defined independent zones, the CRR can rather be identified in CNa to SRO fluctuations whose spatial extent can be characterized by the associated correlation length.

Acknowledgements

The authors wish to acknowledge the use of the facilities of the IDRIS, F-91403 Orsay, where some of the simulations were carried out. This work was supported by the INTERREG II program (Nord Pas de Calais/Kent).

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Analogy of the slow dynamics between the supercooled liquid and supercooled plastic crystal states of difluorotetrachloroethane

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(Received 20 January 2005; published 29 July 2005)

Slow dynamics of difluorotetrachloroethane in both supercooled plastic crystal and supercooled liquid states have been investigated with molecular dynamics simulations. The temperature and wave-vector dependence of collective dynamics in both states are probed using coherent dynamical scattering functions $S(Q, t)$. Our results confirm the strong analogy between molecular liquids and plastic crystals for which α -relaxation times and nonergodicity parameters are controlled by the nontrivial static correlations $S(Q)$, as predicted by the mode coupling theory.

DOI: [10.1103/PhysRevE.72.012501](https://doi.org/10.1103/PhysRevE.72.012501)

PACS number(s): 64.70.Pf, 61.12.Ex, 61.43.-j

It is well known that very different materials, such as silica, low-molecular-weight liquids (carbohydrates, alcohols), polymers, and even proteins are able to exhibit a very intriguing feature called *glass transition* [1]. This latter is characterized by an extraordinary decrease of several orders of magnitude of the mobility in a narrow temperature range. Translational (TDOF), orientational (ODOF), or even internal degrees of freedom can be at the origin of the mobility of a specific substance and approaching the glass transition temperature T_g , all of them are inextricably coupled. Most of the investigations performed on glassy materials considered molecular liquids and focused on TDOF so far. The precise role of the ODOF remains particularly unclear, as demonstrated by the so-called low-temperature translation-rotation paradox [2]. Plastic crystals, i.e., molecular crystals composed of orientationally disordered molecules, offer an interesting solution in order to investigate mainly ODOF during the freezing process. Indeed, some of the plastic crystals called *glassy crystals* [3], such as cyanoadamantane [4], ethanol [5], or orthocarborane [6], can be considered as true rotational analogs of canonical liquid glass formers since they show a step of the specific heat at T_g or a non-Arrhenius behavior of the rotational relaxation times. Only a few substances show the extraordinary property to exhibit a glass transition from both the plastic and the liquid phase: ethanol [5,7], cyclohexene [8], PMS [9] or 2-bromothiophene [10]. An investigation of such materials is particularly interesting to understand the fundamental microscopic mechanisms of the glass transition and the precise interplay between the different degrees of freedom.

In the high temperature pico to nanosecond regime, a fundamental question concerns the onset of the precursor cooperative mechanisms that lead to the glass transition at T_g . In the last two decades, much attention has been devoted to mode coupling theory (MCT) [11]. So far, it is the only theory that provides a microscopic description of supercooled atomic liquids. The intrinsic basis of MCT states that the behavior of any time-dependent correlators describing the dynamics of the system is only controlled by its static

density correlator, i.e., $S(Q)$ and predicts the existence of a critical temperature T_c . Scaling properties predicted by MCT approaching T_c have been validated in numerous experiments and molecular dynamics (MD) simulations [12] of systems whose dynamics are controlled by TDOF. Some of the most important tests of the theory originating from experiments on colloidal systems [13]. Recently, some extensions of MCT called molecular mode coupling theory (MMCT) [12] have been proposed to take ODOF into account: one diatomic probe molecule in an atomic liquid, liquids made of linear molecules, or water, to cite only a few. The authors have shown in particular that some of the basic predictions of MCT still hold, due to TDOF/ODOF coupling. As revealed by a recent MD investigations [14] performed on orthoterphenyl (OTP), coupling of the rotational dynamics to the center-of-mass motion can be very complex. No microscopic theory has been developed for plastic crystals so far. However, in [4,15], we have shown from NMR and Raman experiments, and MD computer simulations that some predictions of the idealized version of the MCT (critical temperature T_c and time scaling laws) were able to describe relatively well rotational dynamics of different plastic crystals. This intriguing previous result call for new investigations to clarify the similarity between slow dynamics behavior of plastic crystals and molecular liquids.

In this article, we present results of a molecular dynamics comparative numerical study of the supercooled plastic and the supercooled liquid phases of difluorotetrachloroethane (DFTCE). It should be noted that the supercooled state of liquid DFTCE is obtained owing the hyperquenching rate of the MD simulation. This compound is composed of simple molecules $\text{CFCl}_2\text{—CCl}_2$ close to dumbbells extensively used in MD calculations as prototype of molecular glass-former liquids [16]. DFTCE plastic crystal has been experimentally widely studied and exhibits a glass transition of the overall rotation of the molecules at $T_g=86\text{ K}$ [17]. Changes concerning the nature of dynamics in this system have been reported from NMR experiments, and Brillouin and dielectric spectroscopy, where it was suggested that the freezing process could be described on the basis of MCT [17].

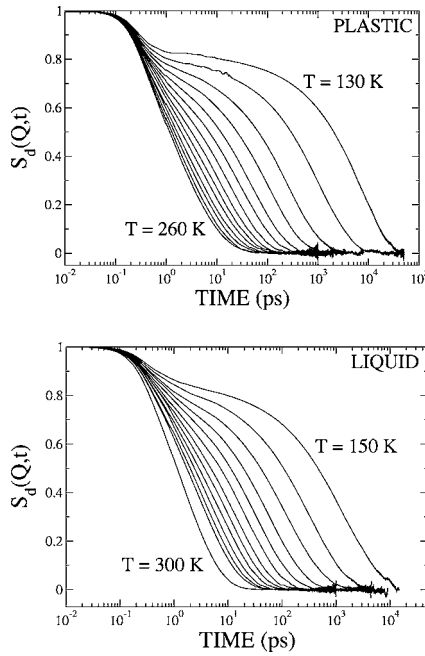


FIG. 1. Coherent intermediate scattering function $S_d(Q, t)$ at $Q = 1.54 \text{ \AA}^{-1}$ obtained for the plastic phase from $T = 130$ to 260 K and the liquid phase from $T = 150$ to 300 K . Scattering functions are normalized by their respective $S_d(Q, t=0)$ values.

MD simulations were performed for an orientationally disordered crystal sample of DFTCE at 14 different temperatures from $T = 130$ to 260 K in steps of 10 K and a supercooled liquid sample at 13 different temperatures from $T = 150$ to the melting temperature $T_m \approx 300 \text{ K}$ in steps of 10 K . The same model was used for both phases and it is completely described in [18,19].

The intermediate scattering function as it can be classically obtained from coherent neutron scattering experiments will be mainly considered: $S(\vec{Q}, t) = \langle \rho_{\vec{Q}}(t) \rho_{\vec{Q}}^*(0) \rangle$, where $\rho_{\vec{Q}}(t)$ is the time-dependent density correlator; $\rho_{\vec{Q}}(t) = \sum_{\alpha} b_{\alpha} \exp[i\vec{Q} \cdot \vec{r}_{\alpha}(t)]$, where the sum is over all the atoms α of the system. b_{α} and $\vec{r}_{\alpha}$ are the coherent scattering length and the position of the α atom, respectively. An average over isotropically distributed Q -vectors having the same modulus Q is performed in order to obtain $S(Q, t)$ for a polycrystalline sample. In general, $S(Q, t)$ can be expressed as [20]: $S(Q, t) = S_c(Q) + S_d(Q, t)$, where $S_c(Q) = \langle |\rho_{\vec{Q}}|^2 \rangle$ is the coherent elastic scattering and $S_d(Q, t) = \langle \delta \rho_{\vec{Q}}(t) \delta \rho_{\vec{Q}}^*(0) \rangle$, where $\delta \rho_{\vec{Q}}(t) = \rho_{\vec{Q}}(t) - \langle \rho_{\vec{Q}} \rangle$ is the fluctuation of the time-dependent density operator. For plastic crystals, $S(Q, t)$ is identical to $S_d(Q, t)$ except for Q -vectors corresponding to Bragg peaks for which the long time limit of $S(Q, t)$ reaches the nonzero value $S_c(Q)$. This behavior is found at all temperatures and it is associated with the crystalline order of the TDOF and not the freezing process of the ODOF. Therefore, in the following, $S_d(Q, t)$ will be preferred to $S(Q, t)$ in order to be able to compare directly molecular liquids and plastic crystal behaviors.

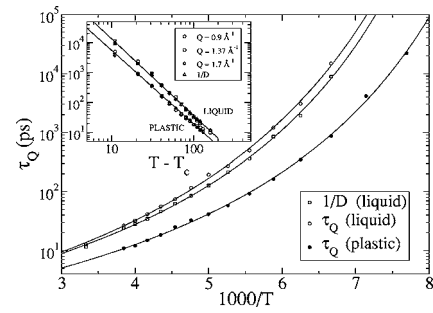


FIG. 2. Temperature dependence of the relaxation τ_Q at $Q = Q_{\max} \approx 1.27 \text{ \AA}^{-1}$ for both the plastic and the liquid phases. Inverse of the diffusion constant D is also indicated. Solid lines show VFT fits (see text). Relaxation times τ_Q at $Q = 0.9, 1.37$, and $1.7 \text{ \AA}^{-1}$ and diffusion constant D ($10^{-9} \text{ m}^2 \text{ s}^{-1}$) as function of the rescaled temperature $T - T_c$ are displayed in the inset. Solid lines show fits using power law dependence $(T - T_c)^{-\gamma}$. ($T_c^l \approx 139 \text{ K}$, $\gamma^l \approx 2.55$) and ($T_c^p \approx 129 \text{ K}$, $\gamma^p \approx 2.45$) are found for the supercooled liquid and the supercooled plastic crystal, respectively. Relaxation times are shifted in order to demonstrate the overlap and the generic power law dependence.

Upon cooling, as shown in Fig. 1, both plastic and liquid $S_d(Q, t)$ display a two-step decay, as classically observed in supercooled systems [16]. For the plastic crystal phase of DFTCE, it is evident that ODOF dominates in $S_d(Q, t)$. For the liquid phase, the answer is not so clear. Inspired by the work of Lewis and Wahnström [21] on OTP, several partial intermediate scattering functions controlled by only ODOF or TDOF have been calculated. This preliminary investigation (not shown here) reveal that both degree of freedom are coupled as observed in [21] and that both TDOF and ODOF qualitatively behave in a similar way. The long time α -relaxation of both plastic and liquid $S_d(Q, t)$ is separated from short time regime (β) by a plateau-like region. This latter can be associated to the so-called cage effect corresponding to the trapping of molecules. The nature of this cage is of translational origin for liquids and of rotational origin (steric hindrance) for plastic crystals [4]. The height of this plateau is usually called the nonergodicity parameter and will be noted f_Q in the following. In order to probe the long time regime, we also defined the characteristic α -relaxation time τ_Q of the rotational dynamics as the time it takes for $S_d(Q, t)$ to decay from 1 to 0.1. In Fig. 2, we plot the relaxation time τ_Q at $Q = Q_{\max}$ corresponding the first diffraction peak [see Fig. 3(c)]. In addition, for liquid DFTCE, the translational diffusion constant D has also been calculated from the mean square displacement $\langle r^2(t) \rangle$. τ_Q characteristic times and D are found to exhibit a very similar non-Arrhenius behavior. In order to quantify this similarity, we used a Vogel-Fulcher-Tammann (VFT) law, written as $\tau = \tau_{\infty} \exp[1/K_{\text{VFT}}(T/T_{\text{VFT}} - 1)]$, where T_{VFT} is the temperature of apparent divergence of τ and K_{VFT} measures the kinetic fragility. We obtained $K_{\text{VFT}} \approx 0.18, 0.16$, and 0.20 and $T_{\text{VFT}} \approx 92.5, 90.4$, and 86.9 K from the inverse of the diffusion coefficient τ_Q of the liquid and τ_Q of the plastic crystal, respectively. Results obtained from MD calculations are in fair

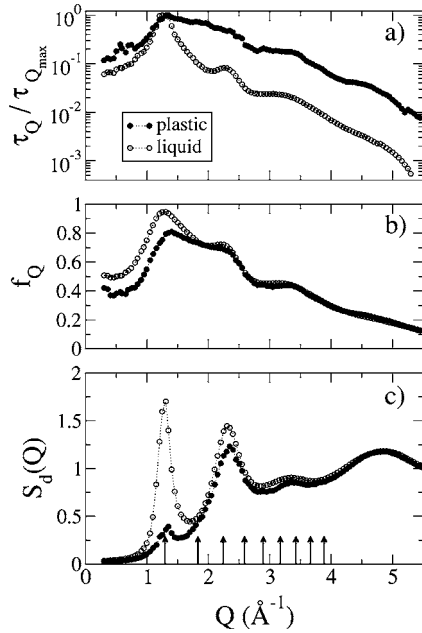


FIG. 3. Q -dependence of different parameters for the plastic (full circles) and the supercooled liquid (circles) phase at the temperature $T=160$ K. (a) The α -relaxation times $\tau_Q/\tau_{Q_{\max}}$, where $\tau_{Q_{\max}}$ is about 345 ps in the plastic phase and 4122 ps in the liquid phase at this temperature. (b) The nonergodicity parameter f_Q obtained from a fitting procedure using a von Schweidler law as derived from MCT including second-order corrections. (c) The diffuse scattering $S_d(Q)$. First Bragg peaks are also indicated with vertical arrows.

agreement with the parameters $K_{\text{VFT}}=0.13$ and $T_{\text{VFT}}=70$ K found from dielectric experiments of plastic DFTCE [17]. We have no clear explanation as to why the relaxation time for the liquid state is slower than for the plastic state. In order to fully compare both systems, a plot of both plastic and liquid relaxation times as function of a rescale temperature T_{ref}/T where T_{ref} is the temperature at which the relaxation times reach 10 ns has been performed (not shown here). It reveals a very similar behavior for both physical states. It should be noted that characteristic times, mostly τ_2 extracted from Raman or NMR experiments, exhibit no discontinuity at the liquid-plastic crystal transition (see many examples reported in [22]). Moreover, O'Dell and Berne [23] showed for a rough sphere fluid that rotational motion could be less hindered in the plastic phase just below the melting point. Both points seem consistent with our results.

In [15], we suggested that some common microscopic mechanisms, relatively well described by MCT, are involved in both orientationally disordered crystals and molecular liquids. Therefore, in the following, we discuss in the MCT framework the wave-vector and temperature dependence of dynamics for both plastic and liquid DFTCE. MCT predictions on the scaling features $\tau_Q(T)=A(Q)(T-T_c)^{-\gamma}$ in the long time decay have been carefully checked using a procedure completely described in [15], and results are displayed in Fig. 2. For plastic crystal DFTCE, it was possible to extract the critical temperature $T_c^p \approx 129$ K and scaling exponent $\gamma^p \approx 2.45$ from an independent fitting analysis per-

formed in the α regime at different Q . Using the same method, $T_c^l \approx 139$ K and $\gamma^l \approx 2.55$ were found for the supercooled liquid DFTCE. Some deviations from MCT predictions are observed at high temperatures. As reported in other papers [4,15], those could be attributed to the crossover from the mean-field regime to a landscape-influenced regime. Nevertheless, the good agreement with the T -dependent MCT predictions is also confirmed by other tests in the β regime wherein data were analyzed using a von Schweidler law including the second-order correction, which will be described elsewhere. Q -dependent MCT predictions are presented in the following.

A fundamental property of MCT or MMCT stresses that dynamics are driven by the static density correlator $S(Q)$. This has been confirmed in several numerical and experimental studies for simple [24] or molecular liquids [25]. In order to check this behavior in plastic crystals, we calculated the static density correlator $S(Q)=S(Q, t=0)$ at different temperatures and wave vectors, as well as the nonergodicity parameter f_Q , the total prefactors $h^1(Q)$ and $h^2(Q)$, and the relaxation time τ_Q . A fitting procedure using a von Schweidler law as derived from MCT including second-order correction was employed [15]. Similarly to the intermediate scattering function, the static correlator can be decomposed into two components: $S(Q)=S_c(Q)+S_d(Q)$, where $S_d(Q)=\langle |\delta \rho_Q|^2 \rangle = \langle |\rho_Q|^2 \rangle - |\langle \rho_Q \rangle|^2$ is the diffuse scattering. Owing to the high rotational disorder, plastic crystals yield only a few diffraction peaks, but exhibit intense and highly structured diffusive scattering, which provide useful information to characterize rotational motions and most probable orientations [20]. Moreover, remarkable similarities of the structure factor between plastic and liquid phases of different systems have been observed [20,26]. Both $S_c(Q)$ and $S_d(Q)$ are displayed in Fig. 3(c) as function of the wave vector Q . At the largest Q -vectors, both plastic and liquid $S_d(Q)$ merge since the intramolecular structure is probed by the wave vector Q . τ_Q and f_Q are also shown in Figs. 3(a) and 3(b), respectively. Both plastic and liquid DFTCE Q -dependence clearly exhibit very similar features. In the investigated Q -range $[0.3-5.5] \text{ \AA}^{-1}$, $S_c(Q)$ shows a few Bragg peaks expected for a bcc crystalline structure with a cell parameter $a=6.82 \text{ \AA}^{-1}$ (experimentally, $a=6.98 \text{ \AA}^{-1}$). For $S_d(Q)$, four broad bumps are localized at 1.27, 2.30, 3.34, and $4.85 \text{ \AA}^{-1}$ both in the supercooled plastic and liquid phases. The first sharp diffraction peak of the liquid particularly corresponds to the first and most intense Bragg peak of the plastic phase. Clearly, we see that f_Q and τ_Q obtained for plastic or liquid phases are mainly correlated with $S_d(Q)$ as predicted by MCT. The total prefactors not displayed in Fig. 3 exhibit the same behavior. The nonergodicity parameter or the total prefactor obtained from $S(Q)$ of the plastic phase also shows a modulation with Bragg peaks of the elastic scattering $S_c(Q)$ (not shown here). It should be mentioned that colliding infinitely thin needles distributed on a lattice are often considered as prototype of glassy crystals [27,28]. Two-step relaxation processes are observed, and an ideal glass transition can be obtained when the length of the rods (the analog of the temperature for these systems) reaches a critical value. If the thickness of the rods are chosen infinitely thin, all static

correlations vanish, and thus, following MCT predictions, no glass transition is expected [27,28]. The present work seems to illustrate some differences between real plastic crystals and the colliding needles on the origin of their respective ideal glass transitions.

The authors wish to acknowledge the use of the facilities of the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France) where calculations were carried out. This work was supported by the INTERREG III (FEDER) program (Nord Pas de Calais/Kent).

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Onset of slow dynamics in difluorotetrachloroethane glassy crystal

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(Received 17 February 2005; accepted 8 June 2005; published online 26 August 2005)

Complementary neutron spin-echo and x-ray experiments and molecular-dynamics simulations have been performed on difluorotetrachloroethane ($\text{CFCl}_2\text{--CFCl}_2$) glassy crystal. Static, single-molecule reorientational dynamics and collective dynamics properties are investigated. Our results confirm the strong analogy between molecular liquids and plastic crystals. The orientational disorder is characterized at different temperatures and a change in the nature of rotational dynamics is observed. A careful check of the rotational diffusion model is performed using self-angular correlation functions C_l with high l values and compared to results obtained on molecular liquids composed of A-B dumbbells. Below the crossover temperature at which slow dynamics emerge, we show that some scaling predictions of the mode coupling theory hold and that α -relaxation times and nonergodicity parameters are controlled by the nontrivial static correlations. © 2005 American Institute of Physics. [DOI: 10.1063/1.1990111]

I. INTRODUCTION

Understanding of the mechanisms leading to the glass transition has been a subject of intense research in recent years and it is still a matter of numerous theoretical and experimental studies.¹ A fundamental question particularly concerns the microscopic description of the precursor cooperative mechanisms which develop in the high-temperatures picosecond-nanosecond regime far above the glass transition temperature T_g . It is now commonly suspected, mainly from theoretical and numerical results, that dynamical behaviors of glass-forming systems could be described by involving two characteristic temperatures:² (i) T_A (T_S or T_x are also seen) corresponding to the onset of slow dynamics where nonexponential relaxation and non-Arrhenius behavior emerge.² The first appearance of rotational heterogeneity is also reported.³ The role of T_A in the vitrication process is still not completely understood but it is often considered as the temperature below which dynamics are influenced by the potential-energy landscape.² (ii) T_c , the critical temperature predicted by the mode coupling theory (MCT).⁴ In the last two decades, enormous work has been devoted to this theory and it is so far the only one which provides a microscopic description of simple liquids. The intrinsic basis of MCT states that the behavior of any time-dependent correlators describing the dynamics of the system is only controlled by its static density correlation, i.e., $S(Q)$ and predicts the existence of a critical temperature T_c indicating a bifurcation from ergodic to nonergodic dynamics. The role of $S(Q)$ and the scaling properties predicted by MCT approaching T_c have been successfully validated in numerous experiments and molecular-dynamics (MD) simulations.⁵ However, no

sharp transition is observed at T_c itself owing some activated processes not included in the theory which restores ergodicity. Thus, T_c is also associated with a dynamical crossover to a “landscape-dominated” regime in which diffusion processes can be described in terms of thermally activated jumps.

Most of the glassformers are molecular liquids and accordingly possess both translational and rotational degrees of freedom (TDOF and RDOF). Approaching the glass transition, the coupling between TDOF and RDOF is far from being understood and the precise role of the RDOF remains unclear, as demonstrated by the so-called low-temperature translation-rotation paradox.^{6,7} MCT has been initially developed to provide a microscopic understanding of simple atomic liquids. However, general predictions have also been successfully validated for molecular compounds. Recently, some extensions of MCT called molecular mode coupling theory⁵ (MMCT) have been proposed to take RDOF into account: one diatomic probe molecule in an atomic liquid,⁸ liquids made of linear molecules⁹ or water¹⁰ to cite only a few. The authors have particularly shown that some of the basic predictions of MCT still hold owing TDOF/RDOF coupling. As revealed by recent MD investigations^{11,12} performed on orthoterphenyl (OTP), coupling of the rotational dynamics to the center-of-mass motion can be complex.

An alternative to the glassforming molecular liquids is offered by at least two partially disordered systems which provide an interesting solution in order to investigate only RDOF during the freezing process:

- (i) The so-called *orientational glasses* such as $\text{Ar}_{1-x}(\text{N}_2)_x$ or $(\text{KCN})_x(\text{KBr})_{1-x}$ mixed crystal where rotational motions are frustrated by a quenched disorder externally imposed by a dilution.¹³ Michel¹⁴ developed a

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MCT for these systems which involved the interplay or rotational-translational and rotational-strains couplings where strains result from the substitutional disorder.

- (ii) *Glassy crystals*¹⁵ such as cyanoadamantane¹⁶ ethanol^{17,18} orthocarborane,¹⁹ or cyclooctanol²⁰ which are true rotational analogs of canonical liquid glass-formers. These systems are generally composed of globular molecules and exhibit a partially disordered phase, called plastic, which possesses a crystalline translational order and a dynamical orientational disorder. They can be rapidly cooled from the plastic phase and exhibit a step of the specific heat at the calorimetric temperature T_g or a non-Arrhenius behavior of the rotational relaxation times.

No microscopic theory has been developed for plastic crystals so far. However, in Refs. 21–23, we have particularly shown from NMR and Raman experiments, and MD computer simulations that some predictions of the idealized version of the MCT (critical temperature T_c and time scaling laws) were able to describe relatively well rotational dynamics of different plastic crystals. It should be noted that the other remarkable temperature T_A was also identified. These intriguing previous results call for new investigations to clarify the similarity between slow dynamics behavior of plastic crystals and molecular liquids and, in particular, to discuss the role of the static correlations $S(Q)$. In this paper, we present for the first time results of neutron spin-echo (NSE) and x-ray experiments and MD simulations of the glassy crystal difluorotetrachloroethane (DFTCE). This compound is composed of simple molecules $\text{CFCl}_2\text{--CFCl}_2$ close to A-B dumbbells extensively used in MD calculations as prototype of molecular glass-formers liquids.^{24–26} DFTCE has been experimentally widely studied and presented a rich variety of unusual properties. DFTCE exhibits a glass transition of the overall rotation of the molecules at $T_g=86$ K.²⁷ Two additional heat anomalies are found at 60 and 130 K and associated, respectively, with a sub- T_g β process and the freezing of the transformation between *trans*- and *gauche*-conformation of the molecule. Changes concerning the nature of dynamics in this system have been reported from NMR experiments.²⁸ Brillouin and dielectric spectroscopies.²⁹ In this latter investigation, a crossover from individual to correlated rotational motions was particularly suggested.

II. EXPERIMENTS AND DETAILS OF THE SIMULATION

The samples used in both x-ray and NSE experiments consist of commercial 1,2-difluorotetrachloroethane purchased from Sigma-Aldrich and purified by melting zone.

The x-ray-diffraction experiment was performed on a laboratory diffractometer equipped with an INEL curved sensitive detector CPS 120 made up of 4096 channels and allowing us to record simultaneously the x-ray diffraction on a 2θ range of about 120 deg. The incident beam was monochromatized with a bent of quartz crystal which selects the $K\alpha_1$ wavelength of a Cu x-ray tube ($\lambda=1.540\,56$ Å). Powder DFTCE was introduced in Lindemann glass capillary of

0.5 mm in diameter. It was mounted on the axis of the diffractometer and rotated during the experiment in order to reduce the effect of preferential orientation. The correspondence between the channel number and the 2θ angle was determined by a preliminary x-ray experiment of cubic $\text{Na}_2\text{Ca}_2\text{Al}_2\text{F}_{14}$ (NAC) (Ref. 30) with a cubic spline interpolation between the Bragg peaks of NAC. Low temperatures were achieved by placing the sample into a gaseous nitrogen flow at the required temperature. Using this procedure, the sample is quenched within a few seconds, and its temperature can be controlled within 0.5 K between 110 and 300 K. In the present experiment, the x-ray pattern was recorded at 140 K during 3600 s for a sample quenched at 2 K/min.

The NSE experiments were performed on the IN11 spectrometer at the Institut Laue-Langevin (ILL), Grenoble, France. We used the multidetector version of IN11 which allows simultaneous measurements at different scattering angles. A setup with an incident wavelength of $\lambda=5.5$ Å ($\Delta\lambda/\lambda \approx 16\%$) gave access to wave numbers approximately between 1.28 and 1.72 Å⁻¹ and we covered the time range of 8 ps–1 ns. We made measurements of the coherent signal of polycrystalline systems filled into a flat Al container from $T=130$ to 220 K in steps of 10 K. For normalization, a resolution scan of the elastic scattering was realized at $T=5$ K in the glassy phase and all data were divided by the polarization at this temperature. Two samples of different mass identified as A ($m \approx 0.33$ g) and B ($m \approx 2$ g) were investigated. Although preliminary measurements showed that transmission of sample A was better, 93% to be compared to 77% obtained for sample B, this latter was preferred for most of the measurements since its scattering signal was more intense. Unfortunately, only data obtained from sample A are available at $T=130$ and 140 K.

MD calculations were performed on a system of $N=686$ ($7 \times 7 \times 7$ bcc crystalline cells) molecules. Each DFTCE molecule $\text{CFCl}_2\text{--CFCl}_2$ is described by its eight atoms and considered as a rigid unit. Molecular geometries have been taken from Ref. 28. The system is made of a constant 50% ratio of both *trans* and *gauche* conformers randomly distributed over the bcc crystalline structure. The slow *trans*-*gauche* transformation has been neglected in our simulation. Indeed, using the energy barrier calculated of about 40 kJ/mol given in Ref. 27, this process has been estimated to be several order of magnitudes slower than the characteristic correlation times found in the investigated temperature range. It should be mentioned that the freezing of this transformation is suspected to be at the origin of the calorimetric anomaly observed at $T \approx 130$ K.²⁷

Molecules interact through a Buckingham short-range atom-atom potential (see parameters in Table I) and the electrostatic contributions have been neglected since the DFTCE molecule possesses a weak dipolar moment. No structural or dynamical change has been found for a system where electrostatic interactions are taken into account. It should be noted that both structure and dynamics were found in good agreement with experimental results (see Figs. 1 and 4). Newton's equations of motion were solved with a time step of $\Delta t=5$ fs. We worked in the *NPT* statistical ensemble with periodic boundaries conditions where the simulation box is

TABLE I. Simulation coefficients taken from literature for Buckingham potential $\phi(r) = A \exp(-\rho \cdot r) - C/r^6$.

Site-site	A (kJ mol $^{-1}$)	ρ (Å $^{-1}$)	C (kJ mol $^{-1}$ Å ^{6})
C-C	226 307	0.288	2420
C-F	196 747	0.260	1168
C-Cl	390 940	0.284	3864
F-F	171 038	0.237	565
F-Cl	320 883	0.258	1808
Cl-Cl	586 389	0.284	5798

allowed to change in size and shape. MD simulations were done for a sample corresponding to the DFTCE orientationally disordered phase at 14 different temperatures from $T = 130$ to 260 K in steps of 10 K. This very simple DFTCE model allowed us to perform very long MD runs of about 50 ns.

In this paper, single-molecule reorientational dynamics of DFTCE will be obtained from the self-angular correlation functions C_l (Ref. 24) defined as

$$C_l(t) = \frac{1}{N} \sum_{i=1, N} \langle P_l(\mathbf{u}_i(t) \cdot \mathbf{u}_i(0)) \rangle \quad (1)$$

where P_l is the l -order Legendre polynomial and $\mathbf{u}_i$ is a unit vector directed along the C_3 -symmetry carbon-carbon molecular axis of the DFTCE molecule i (see Fig. 1). From C_l , we can obtain clarification on the nature of dynamical changes and anisotropy of the molecular motions. Experimentally, $C_1(t)$ can be directly measured in dielectric relaxation and $C_2(t)$ in Raman scattering.³¹ Both functions can also be related to the informations obtained from NMR relaxation measurements.²¹

In order to investigate collective dynamics, the intermediate scattering function as it can be classically obtained from coherent neutron-scattering experiments will be mainly considered:

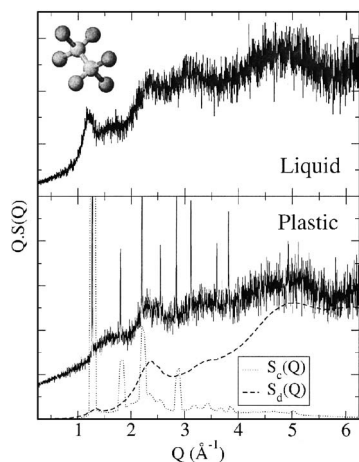


FIG. 1. Experimental x-ray powder diffraction pattern in the liquid phase at $T=305$ K (top) and the plastic phase at $T=140$ K (bottom) as function of the wave-vector Q . The calculated coherent elastic scattering $S_c(Q)$ (dotted line) and the calculated diffuse scattering $S_d(Q)$ (dashed line) in the plastic phase are also indicated for comparison. The DFTCE molecule is displayed in inset.

$$S(\mathbf{Q}, t) = \langle \rho_{\mathbf{Q}}(t) \rho_{\mathbf{Q}}(0) \rangle, \quad (2)$$

where $\rho_{\mathbf{Q}}(t)$ is the time-dependent density correlator:

$$\rho_{\mathbf{Q}}(t) = \sum_{\alpha} b_{\alpha} \exp[i\mathbf{Q} \cdot \mathbf{r}_{\alpha}(t)], \quad (3)$$

where the sum is over all the atoms α of the system. b_{α} and $\mathbf{r}_{\alpha}$ are the coherent scattering length and the position of the α atom, respectively. An average over isotropically distributed Q vectors having the same modulus Q is performed in order to obtain $S(Q, t)$ for a polycrystalline sample. In general, $S(Q, t)$ can be expressed as³²

$$S(Q, t) = S_c(Q) + S_d(Q, t), \quad (4)$$

where $S_c(Q) = |\langle \rho_{\mathbf{Q}} \rangle|^2$ is the coherent elastic scattering and

$$S_d(Q, t) = \langle \delta \rho_{\mathbf{Q}}(t) \delta \rho_{\mathbf{Q}}(0) \rangle, \quad (5)$$

where $\delta \rho_{\mathbf{Q}}(t) = \rho_{\mathbf{Q}}(t) - \langle \rho_{\mathbf{Q}} \rangle$ is the fluctuation of the time-dependent density operator. For plastic crystals, $S(Q, t)$ is identical to $S_d(Q, t)$ except for Q vectors corresponding to Bragg peaks for which the long-time limit of $S(Q, t)$ reaches the nonzero value $S_c(Q)$. This behavior is found at all temperatures and it is associated with the crystalline order of the TDOF and not the freezing process of the RDOF. Similarly to the intermediate scattering function, the static correlator can be decomposed into two components, $S(Q) = S_c(Q) + S_d(Q)$ where $S_d(Q)$ is the diffuse scattering:

$$S_d(Q) = \langle |\delta \rho_{\mathbf{Q}}|^2 \rangle = \langle |\rho_{\mathbf{Q}}|^2 \rangle - |\langle \rho_{\mathbf{Q}} \rangle|^2. \quad (6)$$

III. RESULTS AND DISCUSSION

A. Static

Owing the high rotational disorder, plastics crystals yield only a few diffraction peaks but exhibit intense and highly structured diffusive scattering which provides useful information to characterize rotational motions and most probable orientations.³² Figure 1 shows both numerical and experimental static structure factors obtained in the Q range of 0.3–6.5 Å $^{-1}$. The diffraction pattern of the plastic phase presents eight Bragg peaks localized at 1.272, 1.799, 2.203, 2.543, 2.844, 3.114, 3.596, and 3.816 Å $^{-1}$ which are well indexed as a bcc structure having a cell parameter of 6.985 Å $^{-1}$. The cell parameter is found 2% smaller from MD simulation. This result confirms the preliminary x-ray-diffraction investigation of this crystal performed by Kishimoto *et al.*²⁷ The elastic and the diffuse scattering have been extracted from the MD study and are found in good agreement with the x-ray experiment: maxima of $S_c(Q)$ coincide with the position of the experimental Bragg peaks and maxima of $S_d(Q)$ with the broad bumps of the diffuse scattering at $Q \approx 1.3, 2.34, 3.36$, and 4.8 Å $^{-1}$. It should be mentioned that an additional diffuse scattering bump is observed experimentally close to $Q \approx 1.6$ Å $^{-1}$. This feature which is also present in the pattern of the liquid phase (see Fig. 1) mainly derives from the scattering contribution of the glass capillary sample holder. Moreover, a strong similarity of the x-ray pattern is observed between the liquid and plastic phases. Such remarkable feature has been already reported

TABLE II. Orientational order parameters $\langle K_4 \rangle$, $\langle K_6 \rangle$, and $\langle K_8 \rangle$ at different temperatures. Values for pure [111], [110], and [100] ordering are also indicated.

Temperature	$\langle K_4 \rangle$	$\langle K_6 \rangle$	$\langle K_8 \rangle$
140	-0.647	0.465	0.211
160	-0.638	0.409	0.191
180	-0.623	0.368	0.173
200	-0.596	0.319	0.151
220	-0.577	0.291	0.134
240	-0.549	0.257	0.120
260	-0.515	0.223	0.105
[111]	-1.528	2.266	0.877
[110]	-0.573	-2.071	1.665
[100]	2.291	1.275	2.961

for ethanol³³ or CBr₄.³² The first sharp diffraction peak of the liquid particularly corresponds to the first and most intense Bragg peak of the plastic phase. Broad bumps of the diffuse scattering are found almost identical in both phases and merge at the largest Q vectors since the same intramolecular structure is probed. This result could suggest a strong analogy between the supercooled liquid and the supercooled plastic crystal of the same compound in the framework of the MCT which predicts that dynamics are controlled by non-trivial static correlations. This question will be addressed in another paper.

The orientational distribution of the DFTCE molecules can be described with the probability distribution function $f(\mathbf{u})$ where $\mathbf{u}=(x,y,z)$ is a unit vector along the carbon-carbon molecular axis of DFTCE (see Fig. 1). Since the site symmetry of the crystal is O_h , $f(\mathbf{u})$ may be expanded as a series of cubic harmonics K_i :³⁴

$$f(\mathbf{u}) = \frac{1}{4\pi} \left(1 + \sum_{i=4,6,8,\dots} \langle K_i \rangle K_i \right), \quad (7)$$

where $K_4=(21/16)^{1/2}(5Q-3)$, $K_6=(13/128)^{1/2}(462R+21Q-17)$, and $K_8=(561/1024)^{1/2}(65Q^2-208R-94Q+33)$ with $Q=x^4+y^4+z^4$ and $R=x^2y^2z^2$. The $\langle K_i \rangle$ coefficients are the averages of the corresponding K_i . K_4 , K_6 , and K_8 have been calculated from MD simulations at different temperatures and are reported in Table II. This table clearly shows no strong ordering of the DFTCE molecules along the preferred [111], [110], or [100] directions of the cubic lattice consistent with the high rotational disorder of plastic phases. However, a slight preference for [111] directions is observed. Upon lowering the temperature, we also found an increase of the orientational probability along [111] unlikely to [110] or [100]. These results are also illustrated from different snapshots of individual molecule trajectories as displayed in Fig. 3.

B. Single-molecule reorientational dynamics

Single-molecule reorientational dynamics have been investigated from the self-angular correlation functions C_l defined in Eq. (1). Figure 2(a) shows $C_2(t)$ functions for all investigated temperatures from 130 to 260 K. $C_l(t)$ for other l values exhibits a similar behavior to the $C_2(t)$ function (not

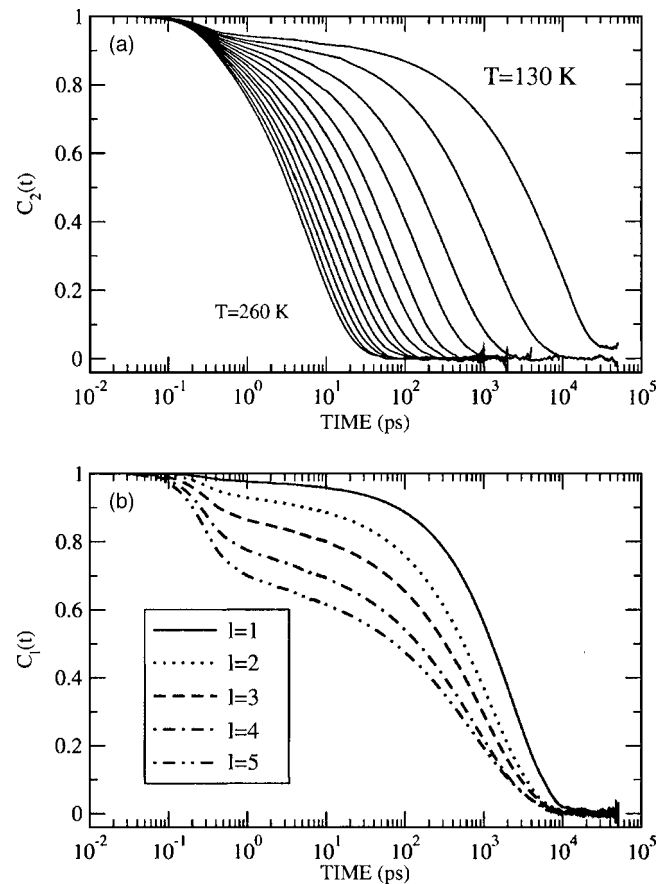


FIG. 2. (a) The angular time-correlation function $C_2(t)$ at different temperatures from 130 to 260 K. (b) The angular time-correlation function $C_l(t)$ at 140 K for $l=1, 2, 3, 4$, and 5 .

displayed in the present paper). At high temperatures, $C_2(t)$ rapidly decays to zero and can be described by a simple exponential shape. When lowering the temperature, dynamics slow down and the long-time decay can only be well fitted with a stretched exponential. A two-step process is seen as already observed in chloroadamantane plastic crystals^{21,23} and in supercooled liquids.²⁴ This process is often interpreted in terms of α - β relaxations which will be carefully analyzed in Sec. III C for collective dynamics in the framework of MCT. One of the most striking properties of the $C_l(t)$ functions at low temperatures is the existence of a plateau region originating from the orientational trapping of molecules. $C_l(t)$ correlators are displayed at 140 K for different l values in Fig. 2(b). A strong similarity between plastic crystal and molecular liquids is found. The height of the plateau regime particularly decreases when l increases, as observed in the investigations performed on liquids made of A-B dumbbells.^{24,25} This behavior is associated with the greater sensibility to the cage effect of C_l functions with high l values. It should be mentioned that this cage mainly arises from TDOF for liquids and RDOF for plastic crystals. However, unlikely to A-B dumbbells studies, C_l of plastic crystal DFTCE do not exhibit a crossing between C_1 and C_2 or between C_3 and C_4 correlators which are usually attributed to frequent 180° reorientations of dumbbells at low temperatures. Indeed, the C_l correlators with even values of l being not influenced by this type of motions possess a slower de-

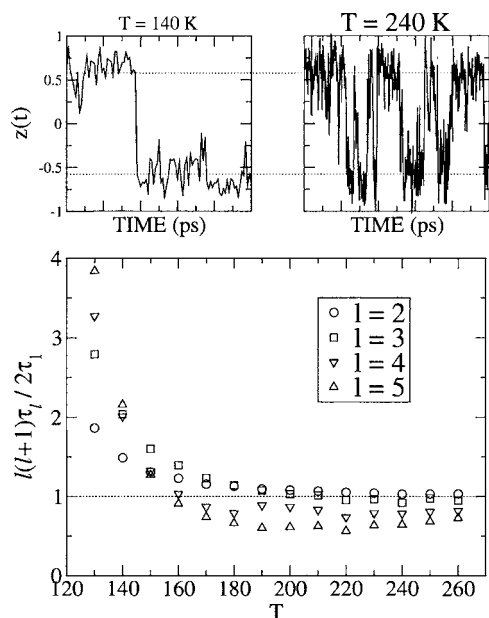


FIG. 3. Trajectories (top) of the unit vector $\mathbf{u}(t) = (x(t), y(t), z(t))$ of one target molecule over a 1-ns run at 140 K (left) and 240 K (right). Horizontal lines indicate preferred orientation of $\mathbf{u}$ along cubic $[111]$ directions. Ratio (bottom) of reorientation correlation times $l(l+1)\tau_l / 2\tau_1$ obtained from MD simulation as function of temperature from 130 to 260 K.

cay. In the present investigation, low-temperature rotational dynamics can be mainly described by tumblings between preferred orientations along $[111]$ directions of the cubic cell which are detected by all C_l correlators. This type of motion is illustrated from snapshots of single-molecule trajectories in Fig. 3.

Reorientation times τ_l have been extracted from the time it takes for their respective self-angular correlation functions C_l to decay e^{-1} of their initial values. For uncorrelated small angular steps motion (rotational diffusion), it can be shown that $C_l(t)$ functions follow an exponential decay $\exp[-t/\tau_l]$ where $1/\tau_l = l(l+1)D_r$ and D_r is the rotational diffusion coefficient. In the literature, the ratio τ_l/τ_2 is generally used as a probe of the orientational dynamics.^{24,35–37} Inspired by the work of De Michele and Leporini²⁵ and in order to characterize more precisely the nature of dynamics and check more drastically the validity of different models, we calculated the ratio $l(l+1)\tau_l / 2\tau_1$ for $l = 1, 2, 3, 4$, and 5 . All quantities are expected to be equal to 1 in the rotational diffusion model. The results are displayed in Fig. 3 and seen qualitatively similar to the work performed by De Michele and Leporini²⁵ on A-B dumbbells. At high temperatures, $l = 2$ and 3 ratios are found rather close to unity and thus in good agreement with a simple diffusion model while this agreement is only fair for $l = 4$ and 5 . It also seems surprisingly better for DFTCE than A-B dumbbells. Indeed, DFTCE is a plastic crystal and even at high temperatures some preferred molecular orientations are expected. Those are not compatible with a purely isotropic diffusion model in which on a time average a molecule has no preferred orientations in space.³¹ The high-temperature deviation from the rotational diffusion model found for A-B dumbbells is not observed for DFTCE for $l = 2$ and 3 owing to the melting of the plastically crystal-line phase. It should be noted that the same analysis has been

performed on a simplified model²³ of chloroadamantane plastic crystal made of linear molecules which exhibits a plastic phase over a wider interval of temperature, 244–442 K. This investigation shows very similar results with the study realized on A-B dumbbells by De Michele and Leporini and consistent with the present investigation.

Upon lowering the temperature, all quantities clearly deviate from their high-temperature behavior and suggest another kind of rotational dynamics where τ_l does not depend on the l value, i.e., the so-called jump-rotation model.³⁸ This situation classically corresponds to collective large-angle tumbling motions between preferred orientation as shown in Ref. 39 for plastic crystal chloroadamantane. Additional MD simulations of DFTCE at temperature below 130 K are needed to fully confirm this trend. This deviation from the high-temperature diffusive regime also reveals the existence of a remarkable temperature $T_A \approx 180$ K corresponding to a crossover from simple dynamics to slow dynamics, i.e., from the mean-field regime to a landscape-influenced regime as reported in other papers.^{16,23} It should be mentioned that analogous features have been recently shown from MD simulations of supercooled liquid CS_2 .³⁵

C. Collective dynamics

The coherent intermediate scattering function $S(Q, t)$ has been calculated from MD at different temperatures and different Q wave vectors and it is compared with the NSE data in Fig. 4 at the arbitrary wave-vector $Q = 1.54 \text{ \AA}^{-1}$. A good agreement between experimental and numerical $S(Q, t)$ is found. The setup of the NSE experiment gave access to wave numbers approximately between 1.28 and $1.72 \text{ \AA}^{-1}$ which roughly correspond to two Bragg peak positions (see Fig. 1). In this limited Q range, all NSE $S(Q, t)$ functions exhibit similar behavior except those close to the Bragg peaks for which the NSE signal is mainly elastic. However, some discrepancies are particularly observed at high temperatures at the longest Fourier times for which the NSE $S(Q, t)$ does not decay completely to zero (see Fig. 4). Since no elastic contribution is expected outside the Bragg Peaks, this feature is most likely due to uncertainties in the background subtraction. At low temperatures, at $T = 130$ and 140 K, differences between experiment and simulation are also seen. Those are also the data which show the largest error bars. One explanation could be the use of a different sample (see experimental details) providing a less intense scattering signal. Since the deviation between the simulation and the experiment seems systematic in character, this may also reveal that the DFTCE force field is not able to perfectly reproduce rotational dynamics. The activation energy of the rotational motion probed from the characteristic time $\tau_{1/e}$ (see below) seems higher for the simulation than the experiment as shown in Fig. 6.

Upon cooling, $S(Q, t)$ displays a decay classically observed in MD simulations¹² and in the NSE experiments of glass-forming molecular liquids such as glycerol⁴⁰ or CKN.⁴¹ For a DFTCE glassy crystal, the long-time relaxation corresponding to the overall rotations of molecules is separated from the short time regime by a plateaulike region. This

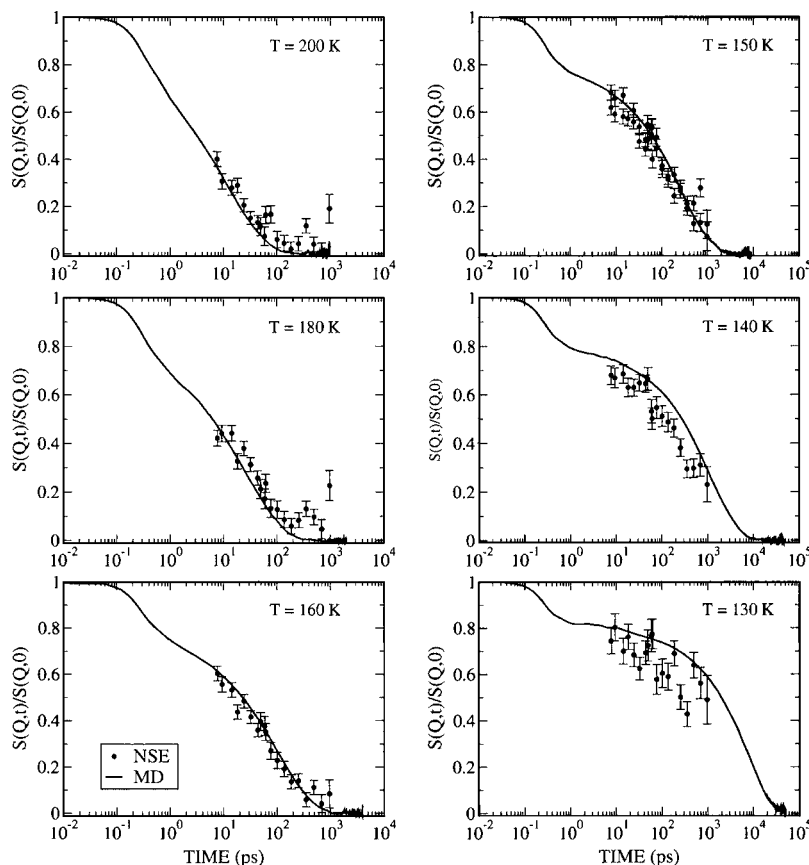


FIG. 4. Coherent intermediate scattering function $S(Q,t)$ at $Q=1.54 \text{ \AA}^{-1}$ obtained from neutron spin echo experiments (full circle) and MD computer simulations (solid line) at $T=130, 140, 150, 160, 180$, and 200 K .

latter can be associated with the orientational trapping of molecules, the analog of the cage effect in liquids⁴² as already demonstrated in Ref. 39 for other plastic crystals. In the long-time relaxation regime, we defined the characteristic time $\tau_{1/e}$ of the rotational dynamics as the time it takes for $S(Q,t)$ to decay from 1 to $1/e$ at the wave-vector $Q = 1.54 \text{ \AA}^{-1}$. This arbitrary definition is chosen in order to fully compare both the NSE and MD data. Owing the limited Q and time domain investigated in the present NSE experiment, other definitions such as fits with stretched exponential of Kohlrausch or time measured to decay from 1 to 0.1 cannot be employed. An alternative definition will be particularly used in the following section concerning the MCT analysis of the MD data.

$\tau_{1/e}$ obtained experimentally and numerically are displayed in Fig. 5. We found that both NSE and MD characteristic times $\tau_{1/e}$ are consistent with previous NMR (Ref. 28) and dielectric investigations²⁹ and allows us to extend DFTCE data at high temperatures over 3–4 decades. It confirms the non-Arrhenius behavior of the rotational dynamics. For comparison, we also plotted in Fig. 6 the Vogel-Fulcher-Tammann (VFT) law $\tau_{\text{VFT}} = \tau_{\infty} \exp[1/K_{\text{VFT}}(T/T_{\text{VFT}} - 1)]$ where T_{VFT} is the temperature of apparent divergence of τ_{VFT} and K_{VFT} measures the kinetic fragility. Parameters $K_{\text{VFT}} = 0.13$ and $T_{\text{VFT}} = 70 \text{ K}$ were determined from dielectric experiments of plastic DFTCE (Ref. 29) in the temperature range $[95-120] \text{ K}$. From MD simulation, we obtained $K_{\text{VFT}} \approx 0.20$ and $T_{\text{VFT}} \approx 86.9 \text{ K}$ for $\tau_{1/e}$ in fair agreement with the dielectric experiment. A perfect agreement cannot

be expected owing the Q dependence of the neutron-scattering technique and the different temperature domains investigated.

In Refs. 23 and 39, we suggested that some common microscopic mechanisms, relatively well described by MCT, are involved in both orientationally disordered crystals and molecular liquids. Therefore, in the following, we analyze our data in the MCT framework. In Fig. 7, $S(Q,t)$ is plotted against the rescaled time $\tau_{1/e}$ previously determined. We find

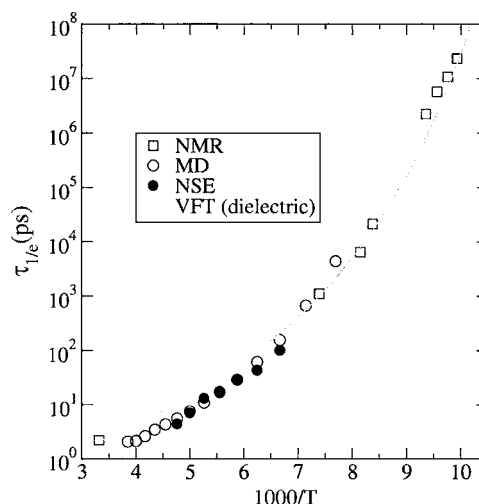


FIG. 5. Characteristic time $\tau_{1/e}$ obtained from NSE experiment (full circle) and MD simulation (open circle) at $Q=1.54 \text{ \AA}^{-1}$ as function of the temperature. Data extracted from NMR (square) (Ref. 28) and dielectric experiment using a VFT fit (gray line) (Ref. 29) are also indicated.

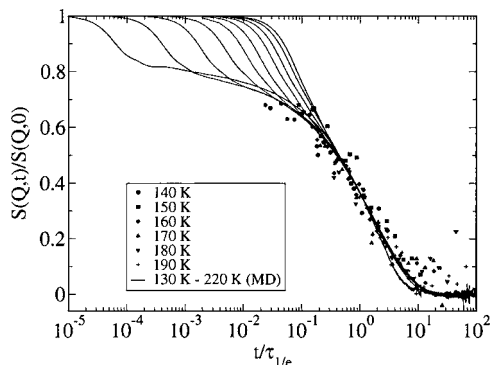


FIG. 6. $S(Q, t)$ obtained from NSE experiment at $Q = 1.54 \text{ \AA}^{-1}$ plotted against the scaled time $t/\tau_{1/e}$ at different temperatures from $T = 140$ to 190 K . $S(Q, t)$ calculated from MD simulation at same Q wave vectors is displayed at different temperatures from 130 to 220 K .

that one of the main predictions of MCT, i.e., the time-temperature superposition principle (TTSP) holds relatively well both for NSE and MD data. We show that the curves overlap for the large time part and collapse gradually onto a master curve upon cooling. This feature is made particularly clear since we have developed a realistic MD model of DFTCE which allows us to access data in the plateau region of $S(Q, t)$ which was not possible in the present NSE experiment. At $T = 130 \text{ K}$, $S(Q, t/\tau_{1/e})$ obtained from MD deviates from the master curve. This indicates that MCT ceases to be valid at that temperature. Snapshots and trajectories of target molecules nicely illustrate this result. As already observed for other plastic crystals in Refs. 16 and 39, the lowest-temperature rotational motions correspond to activated tumblings of the overall molecules between preferred molecular orientations, i.e., the so-called hopping processes not taken into account in the ideal version of MCT (see Sec. III A). Moreover, this deviation also allows us to roughly estimate the critical temperature T_c .

Above T_c , MCT predicts that the late β regime or the early α relaxation is described by the following power law (going beyond first order):

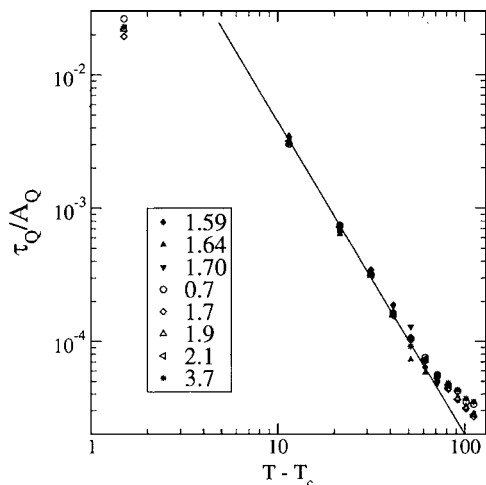


FIG. 7. Relaxation times τ_Q calculated from NSE experiment (full circle) and MD simulation (open circle) $S(Q, t)$ as function of the rescaled temperature $T - T_c$. Data are shown at different wave-vectors Q ranging from 0.7 to $3.9 \text{ \AA}^{-1}$. $T_c = 128 \text{ K}$ was used and the data have been rescaled by A_Q (see text) in order to demonstrate the power law dependence. A power law of exponent $\gamma = 2.35$ is also displayed as a straight line.

$$\phi(Q, t) = f_Q^c - h_Q^{(1)} \cdot (t/\tau)^b + h_Q^{(2)} \cdot (t/\tau)^{2b}, \quad (8)$$

where f_Q^c is the so-called nonergodicity parameter associated with the plateau height and $\tau = t_0(T - T_c)^{-\gamma}$ with $\gamma = 1/2a + 1/2b$. The parameters t_0 , γ , and b are temperature and q independent and related via $\gamma = 1/2a + 1/2b$ and $\Gamma^2(1 - a)/\Gamma(1 - 2a) = \Gamma^2(1 + b)/\Gamma(1 + 2b)$ where $\Gamma(x)$ is the gamma function. The first two terms of Eq. (8) correspond to the classical von Schweidler law and the last term is a second-order correction. First, we determined the exponent b by performing individual fits of the different correlators $S(Q, t)$ in the late β regime using Eq. (8) at $T = 140 \text{ K}$ expected to be the lowest temperature where MCT predictions are valid (see Fig. 6). We used the following free parameters: b , f_Q^c , $\tilde{h}^{(1)} = h^{(1)}(Q) \cdot \tau^{-b}$ and $\tilde{h}^{(2)} = h^{(2)}(Q) \cdot \tau^{-2b}$. Best results are obtained for $b = 0.59$ which corresponds to $a = 0.31$ and $\gamma = 2.45$.

Then, scaling properties of the α relaxation regime have been investigated and compared to the results obtained in the β regime. $\tau_Q(T)$ is chosen as a characteristic time of the α relaxation and it is defined as the time it takes for $S(Q, t)/S(Q, t = 2 \text{ ps})$ to decay from 1 to $1/e$. This alternative definition eliminates the short-time dynamics and ensures that the β relaxation does not perturb the α -relaxation time, i.e., $\tau_Q(T)$ is not influenced by other parameters f_Q , $h^{(1)}(Q)$, or b . This definition also avoids a tedious fitting procedure with stretched exponential of Kohlrausch. It is assumed that any characteristic times belonging to the α regime show asymptotically the same temperature dependence $\tau_Q \sim \tau$ defined in Eq. (8). MCT predictions on the scaling features $\tau_Q(T) = A(Q) \cdot (T - T_c)^{-\gamma}$ in the long-time decay have been carefully checked using a fitting procedure with three adjustable parameters $A(Q)$, T_c , and γ . The temperature-dependent correlators $\tau_Q(T)$ extracted from the MD simulation are displayed in Fig. 7 for different Q vectors. A similar behavior to molecular liquids is clearly seen.⁴³ This figure particularly reveals that it exits a temperature range of about one decade where all relaxation times $\tau_Q(T)$ obey the same $(T - T_c)^{-\gamma}$ law where $T_c \approx 128 \text{ K}$ and $\gamma \approx 2.35$ in agreement with the values found in the β regime. Contrary to MCT predictions, this investigation also reveals a weak Q dependence of about 3 K for T_c and 0.1 for γ . However, these results seem significant owing the wide Q range investigated and allow us to be confident on the values of the exponent γ and the critical temperature T_c . It should be mentioned that the time $\tau_Q(T)$ at the lowest investigated temperature $T = 130 \text{ K}$ can never be adjusted in the different fits which confirms that the system has already reached the sub- T_c regime at this temperature.

Moreover, a deviation from MCT predictions is observed at high temperatures close to 180 K in Fig. 7 for all correlators. It confirms the existence of the dynamical crossover observed for single-molecule correlation functions. As observed in previous MD of molecular glass-forming liquids,²⁴ polymer melts,⁴⁴ or plastic crystals,²³ this temperature seems dependent on the chosen correlator $S(Q, t)$, i.e., on the space range probed at the wave-vector Q . In order to compare numerical and experiment data, the same work was also performed on the NSE data and results are displayed in Fig. 7. τ_Q is unfortunately not accessible in our present experimental data and $\tau_{1/e}$ times which can be influenced by the β regime

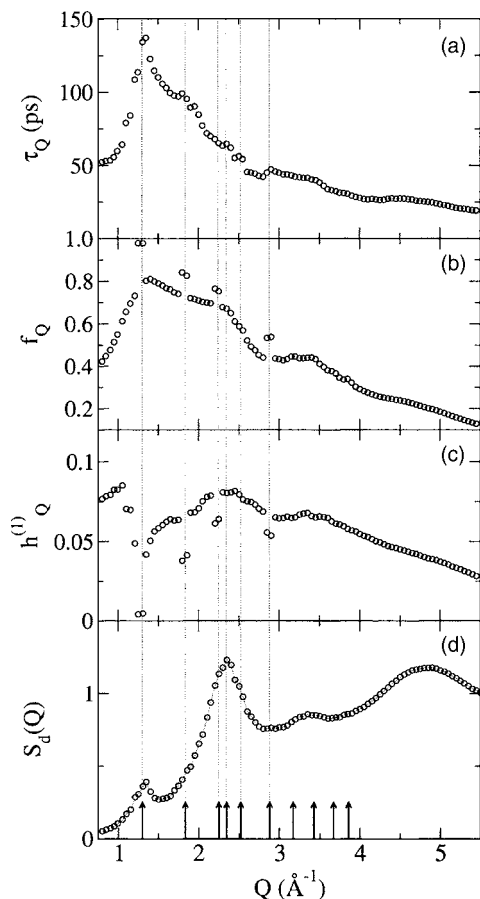


FIG. 8. Q dependence of different parameters at the temperature $T = 160$ K. (a) The α -relaxation times τ_Q extracted from the $S_d(Q, t)$ correlators. (b) and (c) The nonergodicity parameter f_Q and the total prefactor $\tilde{h}^{(1)}_Q(Q)$ obtained from a fitting procedure of $S(Q, t)$ using a von Schweidler law as derived from MCT including second order corrections [see Eq. (8)]. $\tilde{h}^{(2)}_Q(Q)$ is not shown but exhibits the same Q dependence as $\tilde{h}^{(1)}_Q(Q)$. (d) The diffuse scattering $S_d(Q)$. First Bragg peaks positions clearly identified from MD are also indicated with vertical lines.

were used. Despite this drawback, reasonable results are obtained for the narrow Q range investigated in the NSE experiment in fair agreement with the MD data and clearly motivate measurement at shorter times using time-of-flight experiment to describe the plateau regime.

A fundamental property of MCT or MMCT stresses that dynamics are driven by the static density correlator $S(Q)$. This has been confirmed in several numerical and experimental studies for simple⁴⁵ or molecular^{12,43} glass-forming liquids. Since a good agreement between experiment and simulation was found for the elastic and the diffuse structure factors (see Fig. 1), we checked the Q dependence of the α -relaxation time τ_Q , the nonergodicity parameter f_Q , and the total prefactors $\tilde{h}^{(1)}_Q(Q)$ and $\tilde{h}^{(2)}_Q(Q)$ at $T=160$ K. Results are shown in Fig. 8. Clearly, we found that τ_Q and f_Q oscillate in phase with $S_d(Q)$ and $S_c(Q)$ while the amplitudes $\tilde{h}^{(1)}_Q(Q)$ and $\tilde{h}^{(2)}_Q(Q)$ oscillate in phase with $S_d(Q)$ and out of phase with $S_c(Q)$. It should be noted that the Q modulation of the nonergodicity parameter and the total prefactor strongly resembles to the results obtained by Franosch *et al.* for a hard-sphere colloidal suspension model.⁴⁶ It should be also mentioned that this modulation seems to illustrate some dif-

ferences on the origin of their respective ideal glass transition between real plastic crystals and colliding infinitely thin needles distributed on a lattice often considered as a prototype of glassy crystals.^{47,48} Indeed, for needles systems, two-step relaxation processes are observed and an ideal glass transition can be obtained when the length of the rods (the analog of the temperature for these systems) reaches a critical value. If the thickness of the rods are chosen infinitely thin, all static correlations vanish and thus, following MCT predictions, no glass transition is expected.^{47,48}

IV. CONCLUSION

In this paper, we have investigated the static and dynamical properties of difluorotetrachloroethane glassy crystal using complementary x-ray and NSE experiments and MD simulations performed for a realistic molecular model. This study clearly confirms that supercooled molecular liquids and supercooled orientationally disordered crystal share many properties in the picosecond-nanosecond regime where some precursor features (nonexponentiality or non-Arrhenius behavior) of the glass transition emerge. We particularly found that some MCT equations developed for atomic liquids provide a good description of rotational dynamics: some MCT predictions such as the superposition principle or the power law $(T-T_c)^{-\gamma}$ dependence of the α -relaxation time characterizing collective dynamics hold well. We also demonstrated that the α -relaxation time τ_Q , the nonergodicity parameter f_Q , and the amplitudes $\tilde{h}_1(Q)$ were modulated by the static correlation consistent with the MCT predictions. In addition, the other remarkable temperature T_A was detected at about 180 K for both self- and collective dynamics. A careful check of the rotational diffusion model was performed using self-angular correlation functions C_l with l values ranging from 1 to 5. The results were found compatible with the works on molecular liquids composed of A-B dumbbells but a better agreement is shown. Additional experimental investigations are clearly needed in order to fully validate the MD results. It will be particularly of great interest (i) to complete the present NSE study over a wider Q range and for longer Fourier times in order to reach the estimated T_c and (ii) to make measurement at shorter times using time-of-flight experiment to describe the plateau region.

ACKNOWLEDGMENTS

The authors wish to acknowledge the use of the facilities of the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France) where calculations were carried out. This work was supported by the INTERREG III (FEDER) program (Nord Pas de Calais/Kent).

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Glassy behavior of molecular crystals: A comparison between results from MD-simulation and mode coupling theory

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Abstract

We have investigated the glassy behavior of a molecular crystal built up with chloroadamantane molecules. For a simple model of this molecule and a rigid fcc lattice a MD-simulation was performed from which we obtained the dynamical orientational correlators $S_{\lambda\lambda'}(\mathbf{q}, t)$ and the ‘self’ correlators $S_{\lambda\lambda'}^{(s)}(t)$, with $\lambda = (\ell, m)$, $\lambda' = (\ell', m')$. Our investigations are for the diagonal correlators $\lambda = \lambda'$. Since the lattice constant decreases with decreasing temperature which leads to an increase of the steric hindrance of the molecules, we find a strong slowing down of the relaxation. It has a high sensitivity on λ, λ' . For most (ℓ, m) , there is a two-step relaxation process, but practically not for $(\ell, m) = (2, 1), (3, 2), (4, 1)$ and $(4, 3)$. Our results are consistent with the α -relaxation scaling laws predicted by mode coupling theory from which we deduce the glass transition temperature $T_c^{\text{MD}} \cong 217$ K. From a first-principle solution of the mode coupling equations we find $T_c^{\text{MCT}} \cong 267$ K. Furthermore mode coupling theory reproduces the absence of a two-step relaxation process for $(\ell, m) = (2, 1), (3, 2), (4, 1)$ and $(4, 3)$, but underestimates the critical nonergodicity parameters by about 50 per cent for all other (ℓ, m) . It is suggested that this underestimation originates from the anisotropic crystal field which is not accounted for by mode coupling theory. Our results also imply that phonons have no essential influence on the long time relaxation.

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PACS: 64.70.Pf; 61.43.–j

Keywords: Glass transition

1. Introduction

The mode coupling theory (MCT) [1] is the most successful *microscopic* approach to describe glassy dynamics of supercooled liquids on a qualitative, and partly even on a quantitative level [2–4]. Particularly, *first-principle* comparisons between the solutions of MCT equations and results from experiments and simulations for various systems like the binary Lennard–Jones liquid [5], liquids of diatomic molecules [6,7], water [8,9], silica melt [10] and a model for orthoterphenyl [11] have confirmed the quality of MCT. These comparisons were restricted to

the glass order parameters, the nonergodicity parameters. Going beyond that, even time-dependent quantities, like the intermediate scattering function, have been compared with each other for the binary Lennard–Jones liquid [12], binary mixtures of hard spheres [13,14] and the polydisperse quasi-hard-sphere system [15], again demonstrating consistency with MCT.

Glassy dynamics of systems with self-generated disorder is not restricted to liquids. Molecular crystals in their plastic phase exhibit glassy behavior as well. This has been found experimentally three decades ago [16]. Recently two of the present authors have extended MCT to molecular crystals [17]. Using the static structure factors from Percus–Yevick theory [18] the orientational glass transition of uniaxial hard ellipsoids on a simple cubic lattice has been

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investigated [17]. There it has been found that this transition is not driven by an orientational cage effect, analogous to supercooled liquids, but by the growth of orientational order. This growth manifests itself in an increase of the *static* orientational correlators at the Brillouin center or edge, which in turn leads to an increase of the memory kernel. However, before the corresponding orientational correlation length diverges at the corresponding equilibrium phase transition line, the nonlinear feedback mechanism of MCT results in an orientational glass transition. The same mechanism has been identified for a liquid of uniaxial hard ellipsoids [19]. Accordingly, the MCT glass transition line is located within the orientationally disordered ergodic phase [17,19] and not in the supercooled regime.

One may ask whether there also exists a cage-effect-driven glass transition for molecular crystals. Good candidates are plastic crystals which undergo a first order equilibrium phase transition to an orientationally ordered phase. Several such systems exist such as cyanoadamantane, ethanol, cyclooctanol, difluorotetrachloroethane or C₆₀ [20]. Another one is chloroadamantane, which exhibits an equilibrium phase transition at $T_{\text{eq}}^{\text{exp}} \cong 244 \text{ K}$ [21]. A simple model for chloroadamantane (see next section) has been studied by MD-simulations [22,23]. A MCT analysis for the critical amplitudes and the α -relaxation time have demonstrated consistency with MCT predictions [23]. These predictions can really be extended from liquids to plastic crystals because the MCT equations for the latter have the same mathematical structure than for multi-component simple liquids [17].

It is the main goal of the present paper to perform a first-principle comparison between the results for chloroadamantane from a MD-simulation and MCT. The outline of our contribution is as follows. In Section 2 we will describe the model, introduce the orientational correlation functions, give some details of the simulational procedure and shortly describe the relevant MCT equations. Results are presented and discussed in Section 3 and Section 4 contains a summary and some conclusions.

2. Model and technical details

Chloroadamantane C₁₀H₁₅Cl is a rather huge molecule which belongs to the substituted adamantane family. It shows a plastic phase structure isomorphous to cyanoadamantane, but the chloroadamantane molecule possesses a smaller substitute and a faster dynamics well adapted for MD-simulation investigations. Chloroadamantane undergoes at $T_{\text{eq}}^{\text{exp}} \cong 244 \text{ K}$ a first order transition from an ordered monoclinic structure to a rotator phase with face-centered-cubic (fcc) symmetry [21]. The plastic–liquid transition occurs at $T_{\text{m}} \cong 442 \text{ K}$ [21].

The simulated system is composed of rigid linear molecules with two sites: one chlorine atom (noted Cl) and one super atom (noted Adm) that models the adamantane part C₁₀H₁₅. The distance of both pointlike atoms is 3.3 Å and the molecule's moment of inertia is 302.733 amu Å².

Molecular dynamics calculations were performed on a system of $N = 256$ molecules ($4 \times 4 \times 4$ fcc crystalline cells) interacting through a Lennard–Jones short range site–site potential of the form

$$v(r) = 4\epsilon((\sigma/r)^p - (\sigma/r)^q),$$

where r is the distance between two different sites. The parameters ϵ , σ , p and q are specified in Table 1.

The chloroadamantane molecule possesses a relatively large dipolar moment $\bar{\mu}$ (2.39 D) which is parallel to the molecular axis. The electrostatic interactions were handled by the Ewald method with two partial charges ($q = \pm 0.151e$) localized on both sites. Newton's equations of motion were solved with a time step of $\Delta t = 5 \text{ fs}$. We worked in the NPT (constant number of molecules, temperature and pressure) and NVT (constant number of molecules, temperature and volume) statistical ensembles with periodic boundaries conditions. The sample was first equilibrated in the NPT ensemble. Then, MD runs at constant volume using the average volume determined from the NPT simulations were performed.

Since our molecule-model has one rotational symmetry axis we can use the angles $\Omega_n(t) = (\Theta_n(t), \phi_n(t))$ to characterize the orientation of the n th molecule at site n and time t . The microscopic local orientational density is given by

$$\rho_n(\Omega, t) = \delta(\Omega | \Omega_n(t)) \quad (1)$$

with $\delta(\Omega | \Omega') = (\sin \Theta)^{-1} \delta(\Theta - \Theta') \delta(\phi - \phi')$. Expansion with respect to spherical harmonics $Y_\lambda(\theta, \phi)$, $\lambda = (\ell, m)$ and performing a lattice Fourier transform leads to the tensorial orientational density modes:

$$\rho_\lambda(\mathbf{q}, t) = i^\ell \sum_{n=1}^N Y_\lambda(\Omega_n(t)) e^{i\mathbf{q} \cdot \mathbf{R}_n}, \quad (2)$$

where N is the number of lattice sites and $\mathbf{R}_n$ the lattice vector of the n th lattice site. The reader should note that we assume a *rigid* lattice and that $\mathbf{q}$ is restricted to the 1. Brillouin zone. Introducing the fluctuations $\delta\rho_\lambda(\mathbf{q}, t) = \rho_\lambda(\mathbf{q}, t) - \langle \rho_\lambda(\mathbf{q}, t) \rangle$ we can define the time dependent, tensorial orientational correlators:

$$S_{\lambda\lambda'}(\mathbf{q}, t) = \frac{4\pi}{N} \langle \delta\rho_\lambda^*(\mathbf{q}, t) \delta\rho_{\lambda'}(\mathbf{q}, 0) \rangle, \quad (3)$$

where $\langle \dots \rangle$ denotes the canonical average over the initial conditions. Note that the absence of a head–tail symmetry leads to nontrivial correlators for all $\ell \geq 1$, while the absence of phonons leads to $S_{\lambda\lambda'}(\mathbf{q}, t) = 0$ for $\lambda = (0, 0)$ and/or $\lambda' = (0, 0)$ within the 1. Brillouin zone.

Table 1
Parameters for the two-site chloroadamantane model

Site–Site	p	q	ϵ (kJ/mol)	σ (Å)
Cl–Cl	12	6	1.441	3.350
Cl–Adm	14	8	3.087	4.786
Adm–Adm	16	11	12.47	6.200

These correlators have been investigated by a MD-simulation. In contrast to earlier work [22,23] the present simulation has been done for each temperature T for a rigid lattice with lattice constant $a(T)$ determined from the average size of the system obtained from NPT simulations. It is represented in Fig. 1, which also contains the experimental result [21]. It is the shrinking of the lattice constant (cf. Fig. 1) which leads to an increase of the steric hindrance with decreasing temperature and in turn to a slowing down of the orientational dynamics. The increase of steric hindrance manifests itself in an increase of the static structure factors for most $\mathbf{q}$ in the 1. Brillouin zone. An example is shown in Fig. 2. Decreasing the temperature from 400 K to 270 K, which is close to the MCT-transition temperature (see below), $S_{20,20}(\mathbf{q})$ increases for about 80% of $\mathbf{q}$ -values along [001]-direction. In contrast to hard ellipsoids, $S_{20,20}(\mathbf{q})$ and all the other calculated static correlators for $\ell = \ell' \leq 4$ do not give any hint for a divergency at the Brillouin zone center and/or edge. This rules out a glass transi-

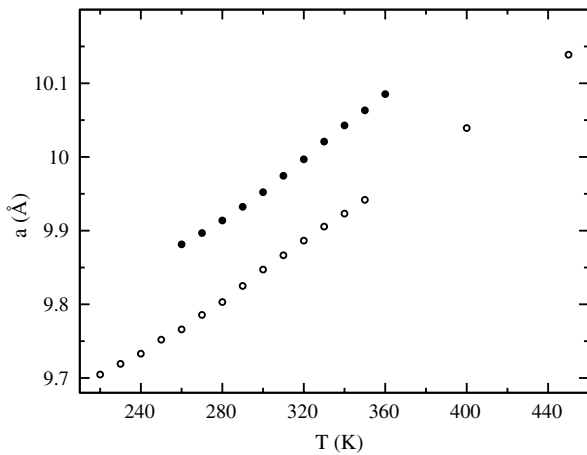


Fig. 1. Temperature dependence of the lattice constant obtained from experiments (●) and MD-simulation (○).

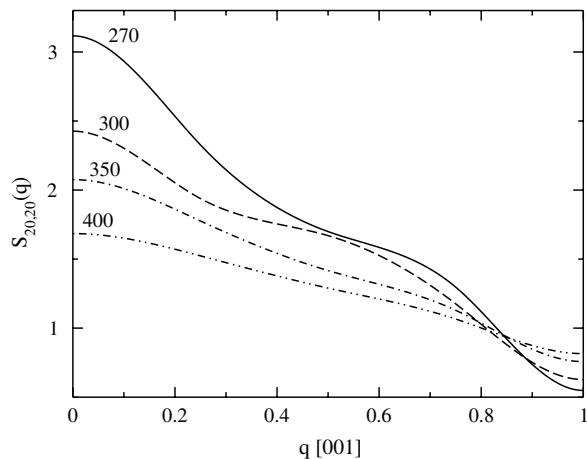


Fig. 2. Temperature dependence of $S_{20,20}(\mathbf{q})$ along [001]-direction for $T = 270, 300, 350$ and 400 K.

tion driven by a precursor of long range orientational order for the present molecular crystal.

On the other hand, MCT provides an equation of motion for $S_{\lambda\lambda'}(\mathbf{q}, t)$ which requires the static correlators $S_{\lambda\lambda'}(\mathbf{q}, 0)$ as an input. Because of the crystal's anisotropy, these correlators also depend on the direction of $\mathbf{q}$. Therefore the numerical solution of the t -dependent MCT equations is rather involved such that we will restrict ourselves to the determination of the MCT glass transition temperature T_c and the normalized nonergodicity parameters

$$f_{\lambda\lambda'}(\mathbf{q}) = \lim_{t \rightarrow \infty} \phi_{\lambda\lambda'}(\mathbf{q}, t), \quad (4)$$

$$\phi_{\lambda\lambda'}(\mathbf{q}, t) = S_{\lambda\lambda'}(\mathbf{q}, t) / [S_{\lambda\lambda}(\mathbf{q}, 0) S_{\lambda'\lambda'}(\mathbf{q}, 0)]^{1/2}$$

taken at $T = T_c$. They are solutions of an infinite set of nonlinear coupled algebraic equations [17]:

$$f_{\lambda\lambda'}(\mathbf{q}) = \mathcal{T}_{\lambda\lambda'}(\mathbf{q}, \{f_{\lambda\lambda'}(\mathbf{q})\}). \quad (5)$$

The mode coupling polynomial $\mathcal{T}_{\lambda\lambda'}$ is related to the memory kernel and depends on temperature through the static correlators. The static correlators have been taken from the MD-simulation. The numerical solution of Eq. (5) requires a truncation at $\ell_{\max}$, for which we have chosen $\ell_{\max} = 4$.

3. Results

As mentioned above the collective correlators (Eq. (3)) are nontrivial for $\ell \geq 1, \ell' \geq 1$. Besides these, one can also determine the 'self' correlators:

$$S_{\lambda\lambda'}^{(s)}(t) = \frac{4\pi}{N} \sum_{n=1}^N \langle \delta \rho_{n,\lambda}^*(t) \delta \rho_{n,\lambda'}(0) \rangle = \frac{1}{N} \sum_{\mathbf{q} \in 1.BZ} S_{\lambda\lambda'}(\mathbf{q}, t). \quad (6)$$

$\delta \rho_{n,\lambda}(t)$ is the expansion coefficient of $\delta \rho_n(\Omega, t)$ with respect to $Y_\lambda(\Omega)$. Fig. 3 shows the normalized collective correlator at $\mathbf{q} = 0$ and the 'self' correlator for $\lambda = \lambda' = (1, 0)$ and $T = 220$ K and 280 K. First of all we observe a slowing down of the α -relaxation by a factor of about twenty by changing the temperature from 280 K to

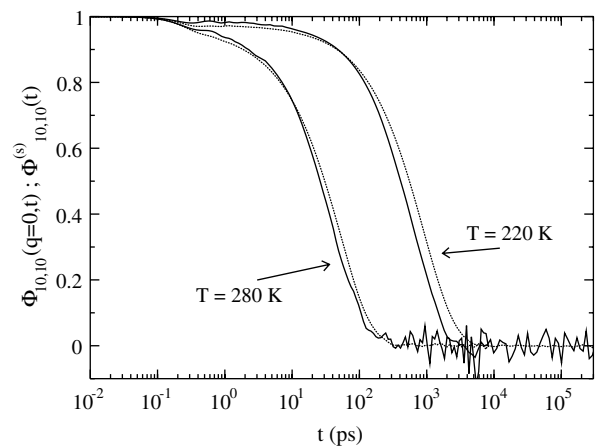


Fig. 3. Time-dependence of the collective correlator ($\mathbf{q} = 0$) (solid line) and 'self' correlator (dotted line) for $\lambda = \lambda' = (1, 0)$ and $T = 220, 280$ K.

220 K, i.e. by about one fifth. Second, no significant difference occurs between the collective and the ‘self’ correlator. The former possesses some oscillations on the microscopic time scale below 10 ps, in contrast to the self correlator. At the lowest temperature 220 K both reveal a two-step relaxation process, however, with a plateau height very close to one. Since the system size of 256 sites is not very huge, we have also performed a simulation at $T = 300$ K with 2048 sites. The result for $\lambda = \lambda' = (1,0)$ is presented in Fig. 4(a) (collective) and (b) (‘self’) and shows no significant finite size effects. Whether this holds also at the lowest temperature $T = 220$ K has not been possible to study because of very long equilibration times.

One of the predictions of MCT is the validity of the $t - T$ superposition principle, i.e. scaling of t by the α -relaxation time $\tau_{\lambda\lambda'}(\mathbf{q}, T)$ should yield a data collapse for all T and t large enough. Taking $\tau_{\lambda\lambda'}(\mathbf{q}, T)$ as the time at which $\phi_{\lambda\lambda'}(\mathbf{q}, t)$ has decayed to $1/e$ the rescaled data are given in Fig. 5(a) and (b) for the collective ($\mathbf{q} = 0$) and ‘self’ correlator, respectively, for $\lambda = \lambda' = (1,0)$. A satisfactory collapse is found over a rather huge temperature range. As can be seen from Fig. 6 this is not true for $\phi_{30,30}^{(s)}(t)$. Restriction to $220 \text{ K} \leq T \leq 260 \text{ K}$ leads to a satisfactory result for $t/\tau > 1$, which, however, excludes the von Schweidler regime (see inset of Fig. 6). One of the highly nontrivial predictions of MCT is the validity of the power law dependence of τ on $(T - T_c)$:

$$\tau(T) \sim (T - T_c)^{-\gamma}, \quad T \geq T_c. \quad (7)$$

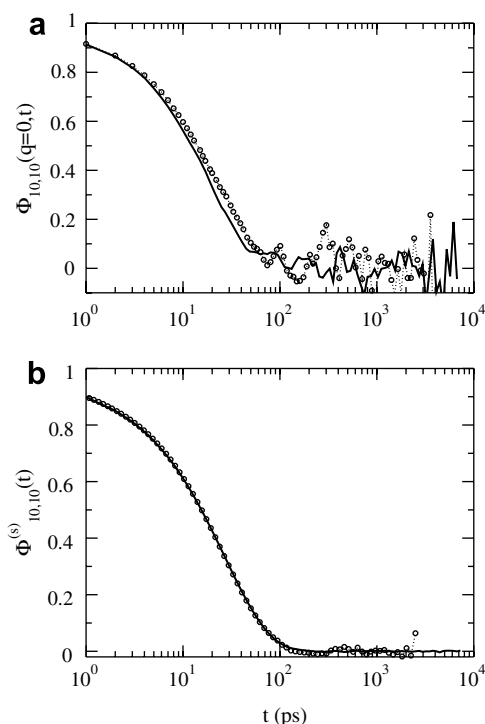


Fig. 4. Time-dependence of (a) the collective correlator ($\mathbf{q} = 0$) and (b) ‘self’ correlator for $\lambda = \lambda' = (1,0)$ at $T = 300$ K for $N = 256$ particles ($\circ$) and $N = 2048$ particles (—), respectively.

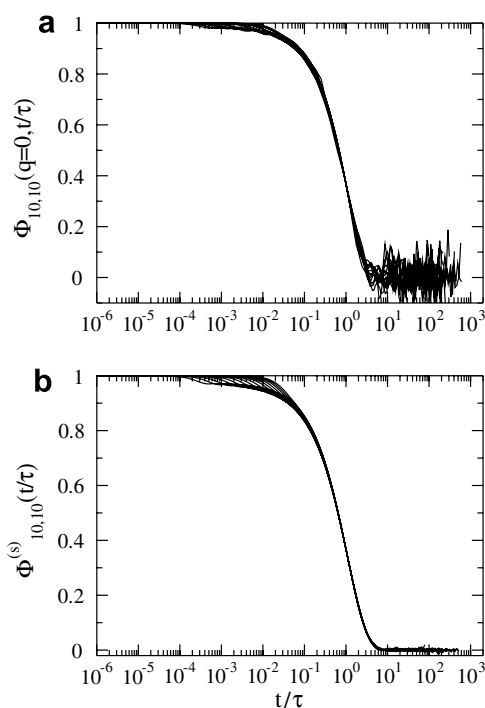


Fig. 5. (a) Collective correlator ($\mathbf{q} = 0$) and (b) ‘self’ correlator for $\lambda = \lambda' = (1,0)$ versus the rescaled time t/τ . τ has been determined as the time at which the correlators have decayed to $1/e$. Correlators are shown for $T = 220$ – 350 K in 10 K steps.

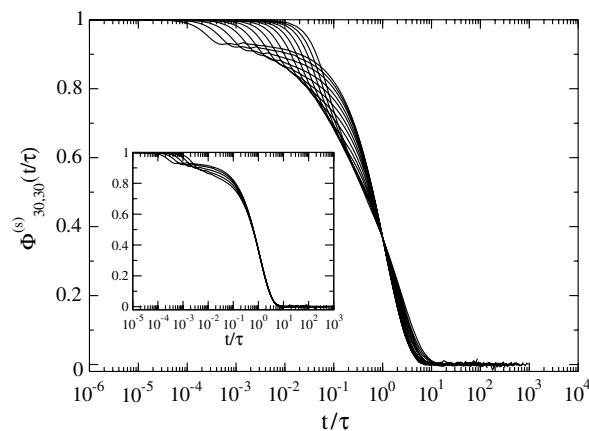


Fig. 6. Same as Fig. 4(b), but for $\lambda = \lambda' = (3,0)$. The inset shows the lowest five temperatures, only.

Fig. 7(b) shows $\tau^{-1/\gamma}$ versus T for the ‘self’ correlators for different $\lambda = \lambda'$ and Fig. 7(a) the corresponding result for the collective one at $\mathbf{q} = 0$ and $\lambda = \lambda' = (1,0)$. There is a linear behavior for $250 \text{ K} < T < 350 \text{ K}$. Its extrapolation to zero yields

$$T_c^{\text{MD}} \cong 217 \pm 5 \text{ K}.$$

For the exponent we find $\gamma_{\lambda\lambda'} \cong 2.0 \pm 0.2$ depending on $\lambda = \lambda'$.

An interesting behavior has been found for the collective correlators with $\lambda = \lambda'$ and $\ell = 2, 3$. The corresponding

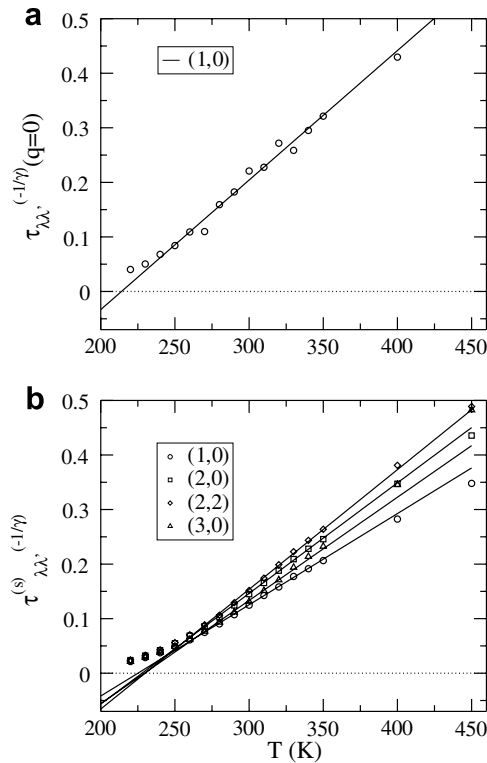


Fig. 7. $\tau^{-1/\gamma}$ versus T for (a) the collective correlator for $\lambda = \lambda' = (1,0)$ at $q = 0$ and (b) the 'self' correlator for $\lambda = \lambda' = (1,0), (2,0), (2,2)$ and $(3,0)$.

results at the *Brillouin center* are presented in Fig. 8(a) and (b) for the lowest temperature $T = 220$ K. Both correlators

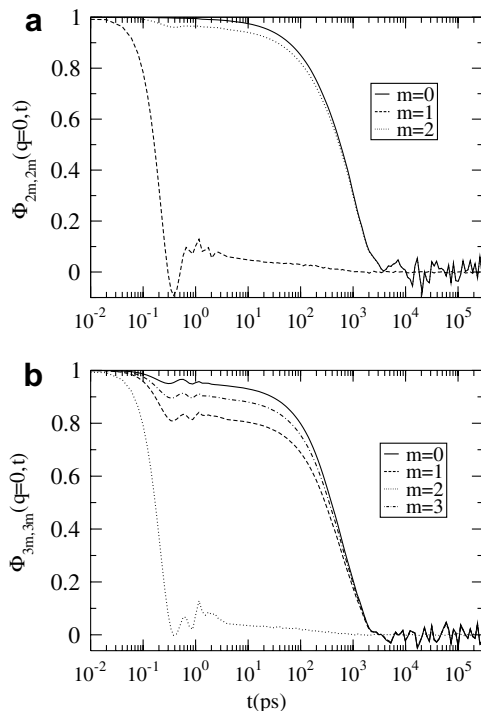


Fig. 8. Time- and m -dependence of the collective correlator at $q = 0$ and $T = 220$ K for (a) $\ell = \ell' = 2$ and (b) $\ell = \ell' = 3$.

exhibit a high sensitivity on the m -index. For $\ell = 2$ and $\ell = 3$ there is a two-step relaxation for $m = 0, 2$ and $m = 0, 1, 3$, respectively, with rather high plateau values, particularly for $\ell = 2$. But for $\ell = 2, m = 1$ and $\ell = 3, m = 2$ there is a rather unusual t -dependence showing no typical two-step relaxation with a convex 'short' and a concave 'long' time part joining at an inflection point (the β -relaxation regime of MCT). The 'long' time relaxation for $t > 4$ ps has a convex curvature on the logarithmic time scale starting at a height of about 0.05 for both cases. If this height is interpreted as a plateau height, it has an unusual small value. Surprisingly, it is observed that the correlators without two-step relaxation decay faster as the temperature is lowered.

For $(\ell, m) = (4, 0), (4, 2)$ and $(4, 4)$ we also have a two-step relaxation, while for $(\ell, m) = (4, 1)$ and $(4, 3)$ it is missing, as for $(2, 1), (3, 2)$. The results for $\ell = 4$ yield no new physical insight and are not shown in this work.

In a final step we have investigated how far these plateau values (which are roughly equal to the critical nonergodicity parameters) are reproduced by MCT for plastic crystals. First, we have fitted the MD-results by the von Schweidler law in order to determine the critical nonergodicity parameters $f_{\lambda\lambda'}(q)$ from the correlators at the lowest simulated temperature $T = 220$ K, which is close to T_c^{MD} . On the other hand we have used the static correlators from the simulation to solve Eq. (5) by iterations. This allows to locate the MCT-temperature T_c^{MCT} , at which the trivial solution $f_{\lambda\lambda'}(q) \equiv 0$ changes discontinuously to $f_{\lambda\lambda'}(q) \neq 0$.

As a result we have found

$$T_c^{MCT} \cong 267 \text{ K.}$$

The corresponding critical nonergodicity parameters from MCT are given together with those from the simulation in Figs. 9–11. The q -dependence is shown along three highly symmetric reciprocal directions. Let us discuss first $\ell = \ell' = 1$ (Fig. 9). The numerical result is very close to one for all q . For $m = m' = 0$, there is a shallow minimum along $[001]$ direction. This minimum also appears in the

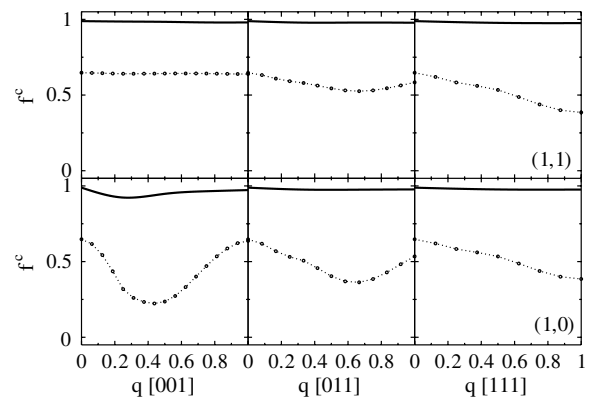
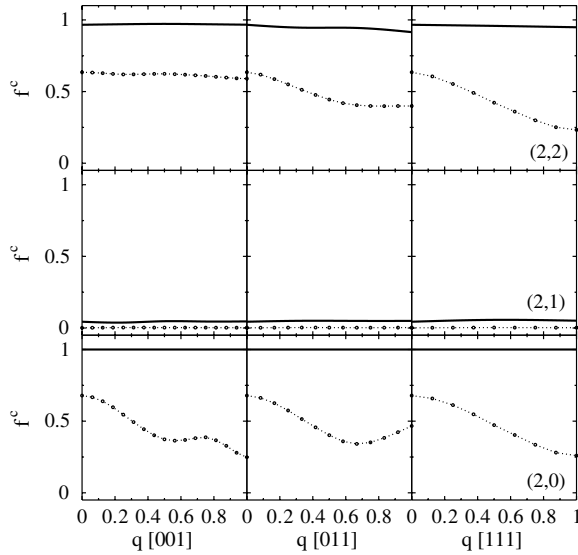
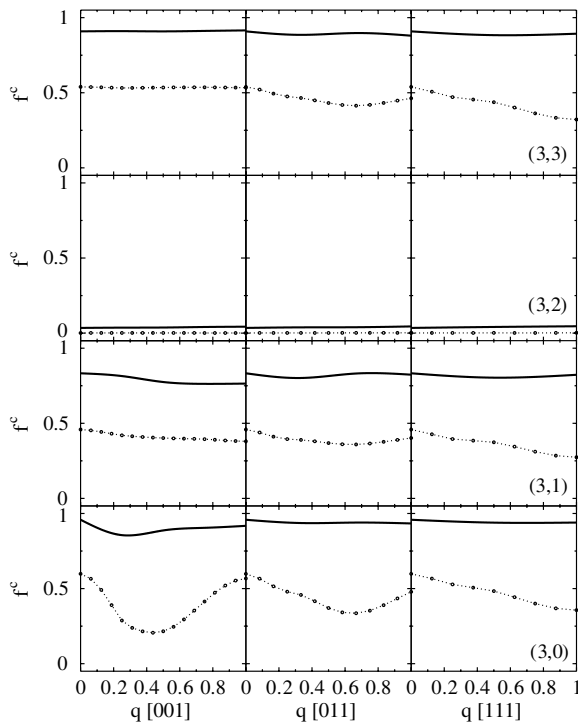


Fig. 9. q -dependence of the critical nonergodicity parameters along the $[001]$, $[011]$ and $[111]$ directions for $\lambda = \lambda' = (1,0), (1,1)$. The result from the MD-simulation is given by the solid line and from MCT by the dots (the lines connecting the dots are a guide for the eye).

Fig. 10. Same as Fig. 8, but for $\lambda = \lambda' = (2,0), (2,1), (2,2)$.Fig. 11. Same as Fig. 8, but for $\lambda = \lambda' = (3,0), (3,1), (3,2), (3,3)$.

corresponding MCT-result. However, $f_{10,10}^c(\mathbf{q})$ from MCT is *not* close to one and deviates from the MD-result by about 50%. Furthermore, the former exhibits a much stronger q -dependence, whereas the MD-results are practically q -independent with exception for $m = m' = 0$ along the [001] direction. Similar conclusions can be drawn for $\ell = \ell' = 2$ (Fig. 10) and $\ell = \ell' = 3$ (Fig. 11). There are two features which are reproduced by MCT. *First*, we observe that the MCT-result for $f_{21,21}^c(0)$ (Fig. 10) and $f_{32,32}^c(0)$ (Fig. 11) is practically zero, in semi-quantitative

agreement with the corresponding MD-result. This is even true for all $\mathbf{q}$. *Second*, the hierarchy $f_{21,21}^c(0) < f_{22,22}^c(0) < f_{20,20}^c(0)$ and $f_{32,32}^c(0) < f_{31,31}^c(0) < f_{33,33}^c(0) < f_{30,30}^c(0)$ is valid for both MCT and MD.

4. Summary and conclusions

The main motivation of the present paper has been the test of the validity of the MCT predictions for the glassy behavior of molecular crystals. MCT has been recently extended from liquids to molecular crystals [17]. Since the corresponding equations of motion have the same structure as for multi-component simple liquids, the MCT predictions for the liquid systems also hold for molecular crystals.

In order to check the validity of these predictions we have performed a MD-simulation for a simple model of chloroadamantane. In contrast to earlier simulations [22,23], we have used a *rigid* fcc-lattice, however, with an appropriately chosen temperature-dependent lattice constant $a(T)$. The decrease of $a(T)$ with decreasing temperature enhances the steric hindrance, which is responsible for the glassy dynamics. Fig. 3 clearly demonstrates the validity of this physical picture.

There are two kinds of tests. On the one hand one can check the validity of the two scaling laws predicted by MCT [2–4]. Without attempting to calculate the corresponding exponents from first principles this represents an important qualitative test. On the other hand a first-principle comparison can be made between the MD- and MCT-results, as has been done in Refs. [5–15]. Concerning the test of the scaling laws we have restricted ourselves to the second scaling law which holds for the α -relaxation regime. In this regime, MCT for liquids and molecular crystals predicts the $t - T$ superposition principle which implies a data-collapse under rescaling time by the α -relaxation time τ . Fig. 5 clearly demonstrates the validity of the second scaling law over a large temperature range, e.g. the collective and ‘self’ correlators with $\lambda = \lambda' = (1,0)$. Increasing ℓ and ℓ' leads to a shrinking of that temperature range and also of the interval of validity for t/τ (see Fig. 6). The T -dependence of τ is shown in Fig. 7. As predicted by MCT a power law dependence is found with a glass transition temperature $T_c^{\text{MD}} \cong 217$ K. Close to T_c^{MD} deviations from the power law exist, due to ergodicity restoring processes. The value T_c^{MD} is about 20% below T_c^{MCT} , consistent with what has been found for liquids [5–11].

The MD-results have shown a very high sensitivity of the relaxational behavior on m . For instance the collective correlators for $\ell = \ell' = 2$ and $m = m' = 0, 2$ exhibit a two-step relaxation process with a plateau very close to one, but a very peculiar behavior for $m = m' = 1$ (see Fig. 8(a)). For the latter there is practically no plateau. The same holds for $\ell = \ell' = 3$, $m = m' = 2$ (see Fig. 8(b)) and for $\ell = \ell' = 4$, $m = m' = 1, 3$ (not shown here). A first-principle comparison between the MD- and MCT-results (see Figs. 9–11) reproduces this unusual m -dependence. We stress that this unusually low plateau value is

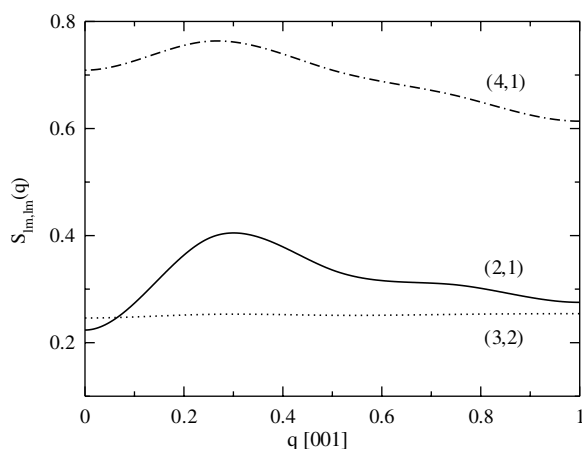


Fig. 12. Static correlators at $T = 270$ K for $(\ell, m) = (\ell', m') = (2, 1)$, $(3, 2)$ and $(4, 1)$.

not related to a small corresponding static correlator as can be observed from Fig. 12. Whereas these correlators vary between ≈ 0.25 and ≈ 0.75 , the corresponding nonergodicity parameters are $\approx 10^{-3}$ – 10^{-4} , i.e. at least two orders in magnitude smaller than the corresponding static correlators. The fact that some of the nonergodicity parameters from MCT can practically be zero, although the corresponding static correlators are about of order one has already been found for hard ellipsoids [17] and seems to be not a spurious effect. However, the critical nonergodicity parameters for $\ell = \ell' = 2$, $m = m' = 0, 2$ and for $\ell = \ell' = 3$, $m = m' = 0, 1, 3$ from MCT deviate by about 50% from the numerical ones. This strong discrepancy can have several reasons. First, the potential energy of the rigid molecular crystal can be written as follows:

$$V(\Omega_1, \dots, \Omega_N) = V_0 + \sum_n V_1(\Omega_n) + \frac{1}{2} \sum_{n \neq m} V_2(\Omega_n, \Omega_m) \quad (8)$$

in case of two body interactions. The isotropic part V_0 is not essential. Besides the pair interactions given by V_2 there is a one-particle term V_1 , which is a kind of crystal field, due to the crystal's anisotropy. $V_1(\Omega)$ will have a finite number of local minima. If the pair interaction V_2 would be zero, the molecules at finite temperatures would perform thermally activated jumps between these local minima, as can be really seen in Fig. 2 of Ref. [22]. Starting in one of the local minima it is obvious that the long time limit of, e.g. the 'self' correlators, will be positive. This happens for all initial conditions with energy below the corresponding energy barrier, and has already been investigated for a ϕ^4 -model [24]. This type of cage effect generated by an anisotropic one-particle potential is not accounted for by MCT which describes a two-, three-, etc., particle-cage-effect in a self consistent way. Second, the truncation at $\ell_{\max} = 4$ may lead to an underestimation of the critical nonergodicity parameters. However, as observed for a li-

quid of rigid diatomic molecules the variation of $\ell_{\max}$ has led to a noticeable change of T_c , but only to a small variation of the nonergodicity parameters [7]. Therefore, we believe that the large numerical values for the critical nonergodicity parameters are *mainly* due to such a one-particle-cage-effect.

Let us finally comment on the role of phonons, which are absent in the present MD-simulation, and also in MCT for molecular crystals [17]. A comparison of, e.g. T_c^{MD} and γ from the present simulation with earlier ones for the same model for chloroadamantane but on a non-rigid lattice shows that phonons do not have a noticeable influence on these quantities and on the long time dynamics.

Acknowledgments

Two of the authors (F.A. and M.D.) wish to acknowledge the use of the facilities of the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France) where calculations were carried out. This work was supported by the INTERREG III (FEDER) program (Nord-Pas de Calais/Kent).

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1.2 Liquides atomiques modèles formateurs de verre

1.2.1 Violation de la relation de Stokes-Einstein

Dans cette étude menée pendant le séjour postdoctoral de P. Bordat, nous nous sommes plus particulièrement intéressés à la relation de Stokes-Einstein qui relie le coefficient de diffusion D et la viscosité de cisaillement η :

$$d = \frac{k_b T}{3\pi D \eta} \quad (1.8)$$

où T est la température et d un paramètre avec la dimension d'une longueur. Dans le cas d'un liquide simple, d est une constante et correspond au rayon hydrodynamique des molécules. Pour un liquide visqueux, d varie avec la température à l'approche de T_g .

Les coefficients de transport comme la viscosité η jouent un rôle très important dans la caractérisation des liquides formateurs de verre. Il est donc très important de les déterminer par une méthode numérique rapide et fiable. De nombreuses méthodes ont été développées et peuvent être classées en deux catégories [67] :

- les méthodes à l'équilibre qui reposent sur les fluctuations du système en utilisant le formalisme d'Einstein ou de Green-Kubo. Ces techniques présentent le désavantage de converger lentement.
- les méthodes hors équilibre qui reproduisent un schéma expérimental en appliquant une force ou un champ externe (la cause) sur le système à étudier et en mesurant le flux résultant (la conséquence). Ces méthodes sont très rapides mais perturbent le système qu'il faut coupler à un bain.

Nous avons utilisé une méthode originale de dynamique moléculaire hors équilibre appelée R-NEMD (Reverse Non-Equilibrium Molecular Dynamics) [68; 69]. Dans la méthode R-NEMD, nous allons imposer le flux (la conséquence) et mesurer le champ résultant (la cause) : elle est donc « renversée » par rapport aux méthodes classiques. R-NEMD est très rapide et permet de contrôler facilement le régime linéaire et de travailler dans divers ensembles statistiques. L'atout majeur de cette nouvelle méthode est de minimiser les perturbations que subit le système car aucune information n'est ajoutée ni supprimée (l'énergie totale et la quantité de mouvement totale sont conservées). R-NEMD a été validée sur des liquides modèles atomiques et moléculaires très différents. Elle a aussi été utilisée sur des solutions de polymères dans le but de vérifier les prédictions de plusieurs théories (Rouse, Zimm, reptation).

Nous avons entrepris une étude par simulation R-NEMD de la relation de S-E sur le liquide binaire de Lennard-Jones (LJ) développé par Kob et Andersen (K-A) [41] et considéré comme un excellent formateur de verre. Il s'agit d'un système modèle constitué de deux types de particules (80% du type 1 et 20% du type 2) de même masse interagissant par un potentiel 12-6 de Lennard-Jones (LJ) de la forme :

$$V_{\alpha\beta}(r) = 4\epsilon_{\alpha\beta} \left[\left(\frac{\sigma_{\alpha\beta}}{r} \right)^{12} - \left(\frac{\sigma_{\alpha\beta}}{r} \right)^6 \right] \quad (1.9)$$

où les paramètres de LJ $\epsilon_{\alpha\beta}$ et $\sigma_{\alpha\beta}$ ($\alpha, \beta \in \{1, 2\}$) représentent respectivement l'énergie minimum et la portée du potentiel d'interaction entre particules. Un choix ad hoc des paramètres $\epsilon_{\alpha\beta}$ et $\sigma_{\alpha\beta}$ permet d'empêcher la cristallisation.

Le diamètre d obtenu par la relation de S-E est représenté sur la figure 1.15 en fonction de la température. A haute température, la longueur mesurée par la relation de S-E correspond bien au diamètre hydrodynamique des particules : σ la portée du potentiel d'interaction. En dessous de $T \simeq 1$ (en unités réduites), on observe une déviation aussi observée expérimentalement dans les systèmes réels vers un plus petit diamètre.

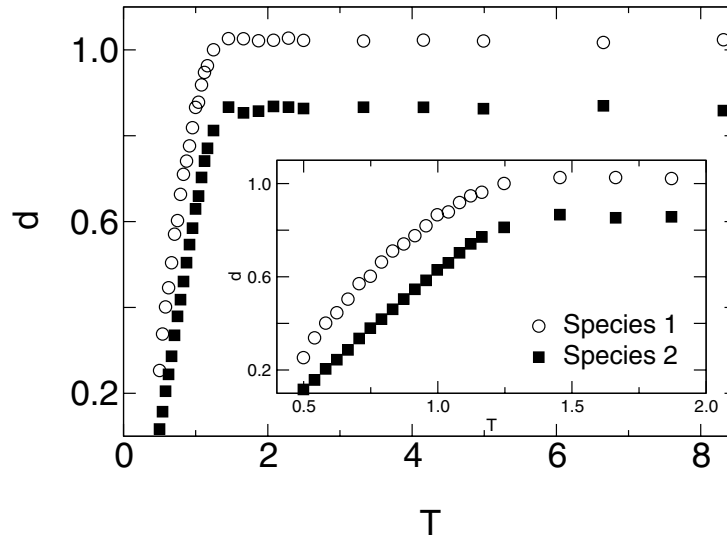


FIG. 1.15 – Distance $d = \frac{k_b T}{3\pi D \eta}$ extraite de la relation de S-E en fonction de la température en unité réduite. Pour les plus hautes températures $d_1 = 1.02$ et $d_2 = 0.85$ sont obtenues pour les particules de types 1 et 2 respectivement. Ces résultats sont en bon accord avec les portées du potentiel d'interaction $\sigma_1 = 1.0$ et $\sigma_2 = 0.88$.

La déviation observée à $T \simeq 1$ de la relation SE offre un renseignement important car elle coïncide avec la température identifiée par S. Sastry, généralement notée T_A , en dessous de laquelle le système est influencé par le paysage énergétique (voir partie précédente sur les cristaux à désordre orientationnel). Pour $T < T_A$, les particules ne diffusent plus librement mais obéissent à un processus de diffusion par sauts dû à la formation d'une cage formée par

leur proche environnement : « l'effet de cage ». Un exemple de trajectoire d'une particule cible, présentée sur la figure 1.16, nous permet de distinguer les fluctuations des particules au sein de la cage et les sauts. Ces deux comportements peuvent être également distingués à l'aide du déplacement carré moyen en fonction du temps (voir figure 1.16). En dessous de $T \simeq 1$ il apparaît entre le régime balistique (temps très courts) et le régime diffusif (temps très longs) un régime intermédiaire assimilé à un plateau caractéristique de l'effet de cage mentionné précédemment. Une information sur la taille de la cage est directement donnée par la hauteur du plateau λ .

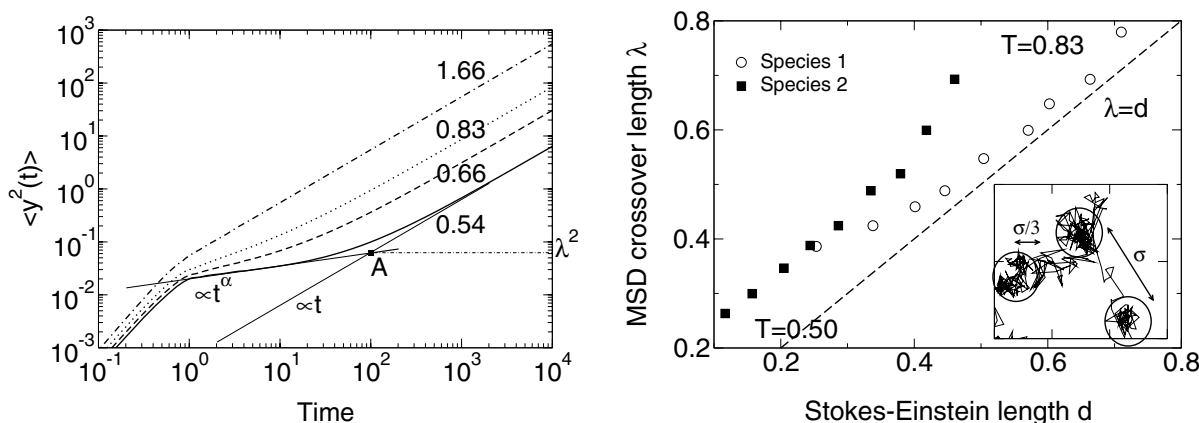


FIG. 1.16 – Gauche : Déplacement carré moyen des particules au cours du temps. Extraction de la hauteur du plateau λ à partir de l'intersection du régime intermédiaire $\simeq t^\alpha$ et diffusif $\simeq t$. Droite : Trajectoire d'une particule cible où σ est la portée du potentiel de LJ.

Dans cette étude, nous avons pu montrer que la distance mesurée par la relation de S-E d et la taille des fluctuations des particules λ étaient corrélées. Cette corrélation suggère l'utilisation de la relation de S-E comme d'une mesure de la taille des fluctuations des particules qui peuvent atteindre le diamètre hydrodynamique à haute température.

1.2.2 Fragilité vs Anharmonicité

Un paramètre fondamental caractérisant les liquides formateurs de verres est appelé la fragilité m et il est généralement défini par la relation :

$$m = \lim_{T \rightarrow T_g^+} \frac{d \log(\tau)}{d(T_g/T)} \quad (1.10)$$

m mesure la sensibilité du temps de relaxation structurale d'un liquide τ à un changement de température T_g/T . L'indice m peut varier énormément d'un liquide à un autre : $m \simeq 17$ pour des verres dits « forts » comme la silice présentant un comportement quasi-Arrhénien de τ ; $m \simeq 100$ pour des verres dits « fragiles » comme certains liquides de faible poids moléculaire (tréhalose, glycérol, orthoterphényle). De nombreux travaux ont été réalisés afin de comprendre les mécanismes microscopiques à l'origine des différences

observées pour m . Des corrélations entre ce paramètre et d'autres quantités dynamiques ou thermodynamiques ont notamment été recherchées dans l'espoir de trouver le facteur qui déterminerait m . On peut citer par exemple les corrélations entre m et : i) $n = 1 - \beta$ où β est l'exposant de la fonction de Kohlrausch $\exp[-(t/\tau)^\beta]$ décrivant les fonctions de corrélations dépendantes du temps [70] ; ii) le déplacement carré moyen $\langle u^2 \rangle$ obtenu à partir du facteur de Debye-Waller [71] ou iii) la statistique des minima du paysage énergétique [72]. Récemment, une corrélation surprenante entre m - un paramètre intrinsèquement déterminé au dessus de T_g - et les propriétés vibrationnelles du verre en dessous de T_g a été découverte par Scopigno *et al.* par des mesures de diffusion inélastique par rayon X dans de nombreux liquides formateurs de verre forts et fragiles [73]. Cette équipe a pu montrer que le paramètre de non-ergodicité $f(Q \rightarrow 0, T)$, contrôlé uniquement par les vibrations sous T_g , pouvait être bien décrit par la relation $[1 + \alpha.(T/T_g)]$ où α était directement proportionnel à m .

Il est clair que le potentiel d'interaction $V(r)$ entre les constituants d'un système physique détermine toutes ses propriétés dynamiques, thermodynamiques et vibrationnelles au dessus ou en dessous de T_g . Les différences observées pour m , $n = 1 - \beta$, $\langle u^2 \rangle$ et α entre différents verres trouvent donc certainement leur origine dans un changement des interactions entre les constituants de ces systèmes. Nous avons entrepris une investigation afin de déterminer l'influence d'un paramètre microscopique - l'anharmonicité du potentiel d'interaction - sur la fragilité m . Nous avons réalisé des simulations de dynamique moléculaire de variantes du mélange binaire de K-A (voir équation 1.9), constitué de deux types de particules 1 et 2, pour lesquelles le potentiel d'interaction $V_{11}(r)$ entre les particules de type 1 suit la relation :

$$V_{11}(r) = \frac{\epsilon_{11}}{q-p} \left[p \left(\frac{r_0}{r} \right)^q - q \left(\frac{r_0}{r} \right)^p \right] \quad (1.11)$$

où $r_0 = 2^{1/6}\sigma_{11}$ représente la position du minimum du potentiel. Les interactions V_{12} et V_{22} restent identiques au potentiel de K-A. Nous avons étudié trois liquides binaires, notés I, II et III, ayant les mêmes valeurs pour ϵ_{11} et r_0 mais pour lesquelles les exposants (p, q) sont différents (voir figure 1.17). Le minimum du potentiel d'interaction est donc le même pour les trois systèmes mais leur courbure assimilée à l'anharmonicité diffère près du minimum. Le potentiel I est plus harmonique que le potentiel II, lui-même plus harmonique que III. Le potentiel II ($q = 12, p = 6$) correspond au modèle K-A original et au potentiel de LJ classiquement utilisé dans la littérature.

Il faut cependant souligner que l'anharmonicité est déterminée par la définition ci-dessus « loin » du minimum du potentiel. Une autre définition plus rigoureuse peut être obtenue à l'aide d'un développement de V_{11} près du minimum :

$$V_{11}/\epsilon_{11} \simeq -1 + \frac{pq(r-r_0)^2}{2r_0^2} + \frac{pq(p+q+3)(r-r_0)^3}{6r_0^3} + \dots \quad (1.12)$$

Dans ce cas, l'anharmonicité peut être définie comme le rapport du terme d'ordre trois par le terme d'ordre deux. Ce rapport croît en $n + p + 3$ et l'ordre de l'anharmonicité

entre les trois potentiels est alors inversé. Cette différente définition de l'anharmonicité sera discutée dans la section 1.2.3 portant sur le paysage énergétique des trois modèles.

1.2.2.1 Analyse structurale

La figure 1.17 montre la fonction de distribution radiale $g(r)$ des particules 1 obtenue pour les trois modèles à la température $T = T_{ref}$ dont la définition est donnée dans la figure 1.18. Elle révèle que les trois liquides I, II et III présentent globalement une structure similaire. Aucun phénomène de cristallisation n'est observé à basse température pour les modèles I et III ce qui confirme leur nature de bons formateurs de verre comme reporté dans la littérature pour le modèle II [41].

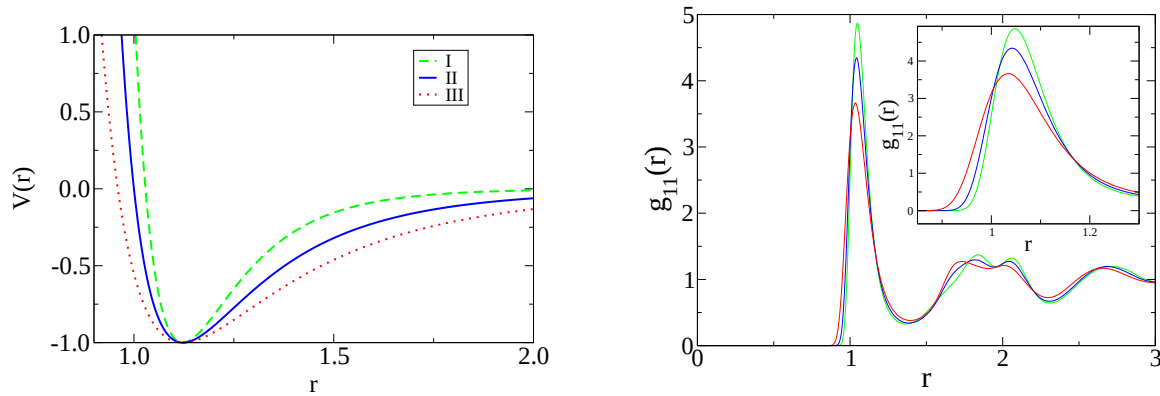


FIG. 1.17 – *Gauche : Potentiels d'interaction I, II et III étudiés par simulation MD. Droite : Comparaison des distributions radiales des trois modèles étudiés à T_{ref} .*

Une analyse plus détaillée (voir inset de la figure 1.17) nous permet cependant de mettre en évidence de petites différences sur la position et la largeur du pic principal caractéristique de l'organisation du liquide à courte portée. On obtient par exemple pour la position du premier pic les valeurs : 1.05, 1.04, 1.03 pour les modèles I, II et III respectivement. Celles-ci sont cohérentes avec la forme des potentiels d'interaction des trois modèles (voir figure 1.17) pour lesquelles les interactions - attractives - aux grandes distances augmentent du modèle I au modèle III compte-tenu de leurs différentes anharmonicités. Selon le modèle proposé par K. Ngai [74], ce résultat peut s'interpréter comme une augmentation du « couplage » entre particules qui va croissant avec l'anharmonicité des interactions.

1.2.2.2 Fragilité

La dynamique des trois modèles a été étudiée à partir des fonctions de corrélations dynamiques individuelles $F_S(Q, t)$ et collectives $F(Q, t)$ des particules de type 1 à $Q = Q_0 = 2\pi/r_0$ près du premier pic du facteur de structure statique. A haute température, $F_S(Q, t)$ présente un comportement exponentiel. Lorsque la température décroît, on observe

un découplage des dynamiques avec l'apparition de relaxations en deux temps qui peuvent être bien décrites par la théorie MCT (voir partie précédente sur les cristaux à désordre d'orientation).

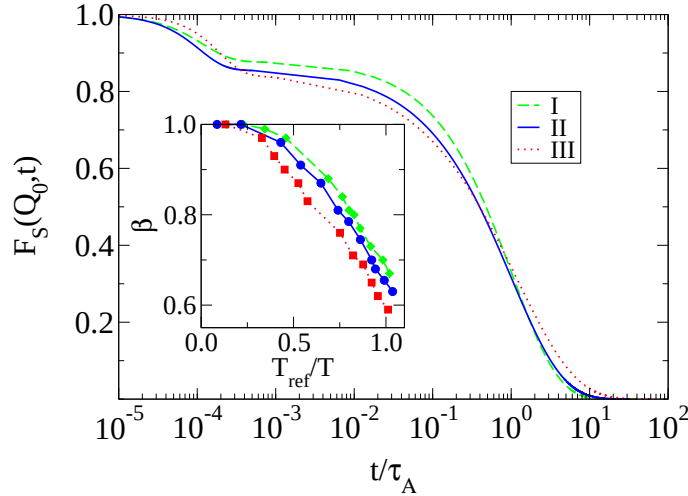


FIG. 1.18 – *Fonction de corrélation individuelle $F_S(Q, t)$ à $T = T_{ref}$ et $Q = Q_0 = 2\pi/r_0$ (voir texte) en fonction de t/τ_A où $\tau_A = 46435.8$ à T_{ref} pour les trois modèles. $T_{ref} = 0.688$, 0.431 et 0.263 pour les modèles I, II et III respectivement. En inset : l'exposant β obtenu à partir d'un ajustement $A.exp[-(t/\tau)^\beta]$ de $F_S(Q, t)$ est représenté en fonction de T_{ref}/T .*

Les fonctions de corrélation individuelles $F_S(Q, t)$ sont représentées sur la figure 1.18 en fonction de t/τ_A où τ_A est le temps de relaxation du liquide obtenu à partir d'un ajustement à l'aide de fonctions $A.exp[-(t/\tau_A)^\beta]$. La figure montre aussi en inset le comportement de β en fonction de la température. On observe clairement que β est systématiquement plus élevé pour le modèle I (le plus harmonique) et plus faible pour le modèle III (le plus anharmonique). Dans le cadre du « coupling model » développé par K. Ngai, $n = 1 - \beta$ fournit une mesure du couplage inter-particule. Celui-ci serait donc plus important pour un potentiel plus anharmonique. Ce résultat est confirmé par la figure 1.17 qui montre simplement à partir de la forme du potentiel que les interactions aux grandes distances augmentent du modèle I au modèle III.

Le temps de relaxation τ_A est tracé sur la figure 1.19 en fonction de T/T_{ref} de manière analogue au diagramme dit d'Angell où T_{ref} a été utilisé à la place de T_g . Il apparaît que τ_A présente un comportement non-Arrhénien et ne peut être ajusté par une simple droite dans ce diagramme. Le modèle III, le plus anharmonique, montre la déviation la plus importante. Afin de quantifier cette déviation, l'indice de fragilité des trois modèles a été calculé de deux manières utilisées : i) à partir de la pente de τ_A à $T/T_{ref} = 1$ (voir équation 1.10) et ii) à partir d'un ajustement par une loi VFT (voir équation 1.7). Les résultats obtenus sont indiqués dans le tableau 1.1. Il apparaît clairement que la fragilité augmente lorsqu'on passe du modèle I au modèle III pour les deux définitions utilisées : la

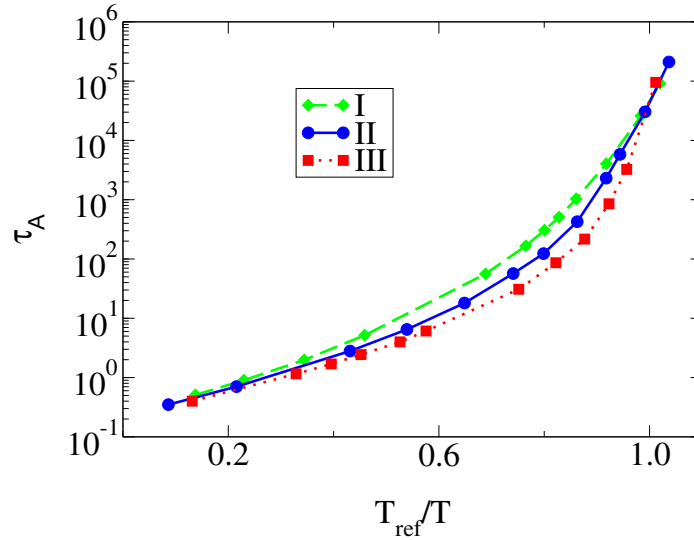


FIG. 1.19 – Temps de relaxation τ_A des modèles I, II et III en fonction de T_{ref}/T .

fragilité augmente donc lorsque l'anharmonicité augmente.

Modèle	I	II	III
(q,p)	(12,11)	(12,6)	(8,5)
m	15.07	18.57	26.58
K(VFT)	0.195	0.241	0.405

TAB. 1.1 – Indices de fragilité déterminés à partir de deux méthodes différentes (voir texte).

1.2.2.3 Propriétés vibrationnelles

Motivés par les résultats de Scopigno *et al.*, nous nous sommes aussi intéressés aux propriétés vibrationnelles des trois modèles en dessous de T_{ref} en trempant le liquide et en permettant aux seuls degrés de liberté vibrationnels de relaxer. Aux très basses températures, le facteur de non-ergodicité $f(Q, T)$ a été évalué à partir des fonctions de corrélation collectives $F(Q, t)$ contrôlées totalement par les vibrations du système. La figure 1.20 montre le comportement de $f(Q, T)$ en fonction de la température lorsque Q tend vers zéro. Pour les trois modèles, $f(Q \rightarrow 0, T)^{-1}$ peut être ajusté par une simple droite $[1 + \alpha(T/T_{ref})]$ de manière équivalente aux résultats expérimentaux de Scopigno *et al.* La pente α de ces droites augmente avec l'anharmonicité du potentiel. L'inset de la figure 1.20 montre une relation de proportionnalité entre les paramètres m et α en bon accord avec Scopigno *et al.* [73].

Cette étude démontre que les différentes corrélations entre les paramètres $n = 1 - \beta$,

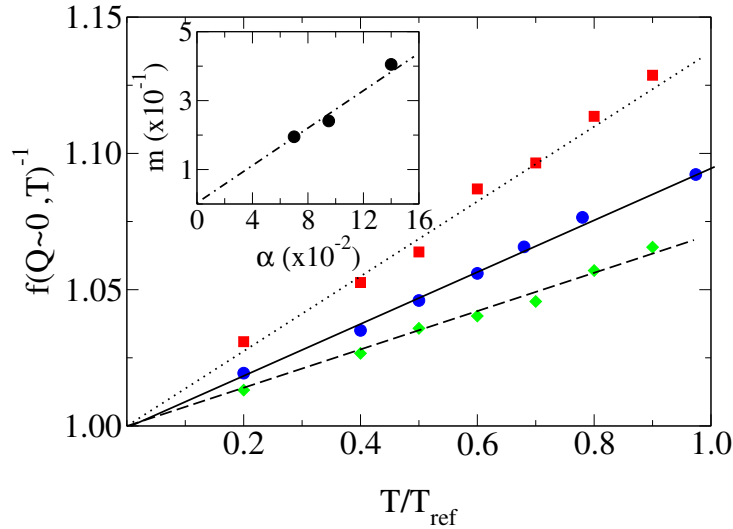


FIG. 1.20 – Facteur de non-ergodicité $f(Q \rightarrow 0, T)^{-1}$ en fonction de la température pour les trois modèles étudiés. En inset, l'indice de fragilité est représenté en fonction du coefficient α .

α et m observées expérimentalement sont bien reproduites par simulation en modifiant le potentiel d'interaction. Plus spécifiquement, l'anharmonicité du potentiel et le couplage inter-particule apparaissent comme des facteurs particulièrement pertinents. Ces travaux suggèrent un comportement analogue pour les formateurs de verre réels.

1.2.3 Influence de l'anharmonicité d'interaction sur le paysage énergétique

Dans ce travail réalisé pendant le stage de MASTER2 de F. Vasconcelos, nous avons entrepris une investigation numérique par dynamique moléculaire afin de déterminer l'influence de l'anharmonicité du potentiel d'interaction $V(r)$ sur la topologie du paysage énergétique et la manière d'explorer ce paysage pour les différents modèles décrits préalablement en utilisant le formalisme de Stillinger-Weber [75].

L'énergie potentielle totale Φ d'un système de N atomes identiques de masse m en interaction dépend simultanément des coordonnées $\vec{r}_i$ de toutes les particules i . La fonction $\Phi(\vec{r}_1 \cdots \vec{r}_N) \equiv \Phi(\vec{r}^N)$ décrit alors une surface dans un espace à $3N + 1$ dimensions, communément appelée *paysage énergétique* (PE). Il est important de remarquer que la topologie du paysage énergétique, est dans ce cas simple, indépendante de la température, la température n'intervient que sur la manière dont le système explore la surface d'énergie potentielle Φ et ceci avec une probabilité proportionnelle au facteur de Boltzmann $\exp(-\Phi/k_B T)$.

Une figure schématique du paysage énergétique, directement inspirée des travaux de Goldstein [2] et Stillinger [3] et confirmée par de nombreuses investigations numériques

réalisées jusqu'à présent [17; 18; 19] est donnée en figure 1.21. Dans cette représentation, le paysage énergétique est constitué : i) de nombreux minima de haute énergie séparés par de faibles barrières et ii) par un nombre de plus en plus faible de minima de basse énergie séparés par des barrières de plus en plus hautes. On peut imaginer qu'aux hautes températures le système disposera d'une énergie $k_B T$ suffisante pour vaincre toutes les barrières d'énergie entre les différents minima : la topologie du paysage énergétique influencera donc très peu la dynamique du système. On peut aussi supposer qu'il existe une température (T_A) en dessous de laquelle, la « rugosité » du paysage énergétique contrôlera totalement sa dynamique constituée de « sauts » entre les différents puits de la surface d'énergie potentielle. Dans cette approche, la dynamique d'un liquide sous-refroidi pourrait être décrite par deux échelles de temps différentes : aux temps courts, des mouvements de faibles amplitudes associés à des minima locaux de l'énergie (vibrations), et aux temps longs par des transitions entre différents puits du paysage énergétique.

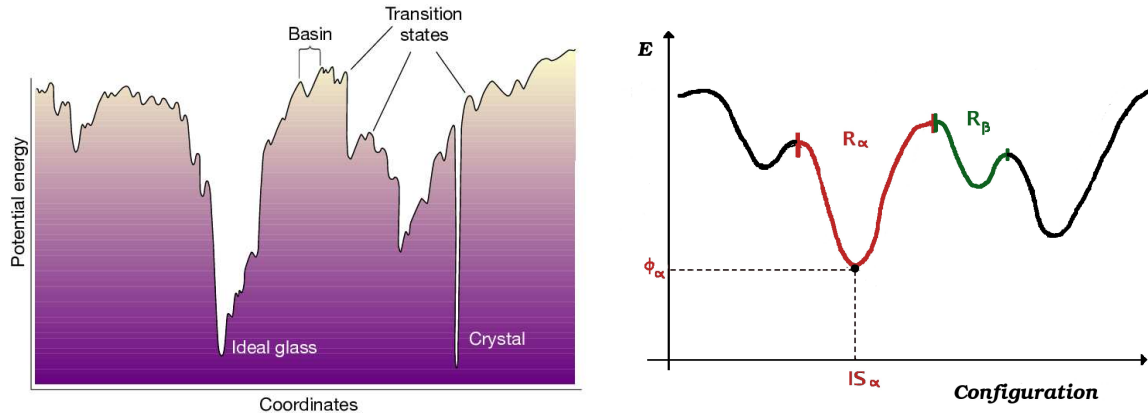


FIG. 1.21 – *Gauche* : Représentation schématique du paysage énergétique d'un système formateur de verre. L'axe des abscisses représente les coordonnées de configurations $\{r^N\}$, et l'axe des ordonnées l'énergie potentielle (d'après [3]). *Droite* : Représentation schématique des configurations IS ($\alpha, \beta, \dots$) et de différents bassins d'attraction ($R_\alpha, R_\beta, \dots$) qui leur sont associés. Les bassins d'énergie représentent l'ensemble des configurations ayant le même minimum après une trempe.

1.2.3.1 Formalisme de Stillinger-Weber

La fonction de partition Z d'un système composé de N particules en contact avec un thermostat à la température T , dans un volume V , et après intégration des variables dynamiques, s'écrit :

$$Z = \frac{1}{\Lambda^{3N} N!} Q \quad (1.13)$$

avec

$$Q = \int d\vec{r}^N e^{-\beta \Phi(\vec{r}^N)} \quad (1.14)$$

où $\Lambda = \sqrt{h^2\beta/2\pi}$, $\beta = 1/k_B T$ et Φ est la fonction d'énergie potentielle. Pour la suite, on prend également comme hypothèse que nous avons à faire à un système qui ne cristallise jamais. Concrètement, les configurations des états cristallins ne seront pas dénombrées dans la fonction de partition totale.

On définit les « Inherent Structures » (IS) comme les configurations correspondant aux minima locaux du paysage énergétique (figure 1.21). Ces configurations sont mécaniquement stables et décrivent l'ensemble des structures à $T = 0$. Un bassin d'énergie correspond à l'ensemble des points dans l'espace des configurations qui tendent vers un même minimum (IS) au cours d'une trempe. Numériquement, on modélisera une trempe par une minimisation de l'énergie potentielle. Pour chaque configuration IS α , d'énergie e_{IS}^α , nous associons un bassin d'énergie de surface R_α (figure 1.21). En remarquant que l'ensemble des surfaces $\{R_\alpha\}$ couvre entièrement la surface du paysage énergétique, on constate que la fonction de partition peut alors se décomposer en une somme de fonctions de partition individuelles pour chaque IS α :

$$Z = \frac{1}{\Lambda^{3N}} \sum_{\alpha} Q_{\alpha} \quad (1.15)$$

avec

$$Q_{\alpha} = e^{-\beta e_{IS}^\alpha} \int_{R_\alpha} d\vec{r}^N e^{-\beta(\Phi - e_{IS}^\alpha)} \quad (1.16)$$

À la limite thermodynamique, on peut donc réécrire la fonction de partition en terme de densité d'état $\Omega(e_{IS})$ avec $\Omega(e_{IS})de_{IS}$ le nombre d'IS d'énergie e_{IS} sur l'intervalle $[e_{IS}; e_{IS} + de_{IS}]$:

$$Z = \int de_{IS} \Omega(e_{IS}) \exp[-\beta(e_{IS} + F_{vib}(e_{IS}, T))] \quad (1.17)$$

F_{vib} étant l'énergie libre de vibration du bassin de minimum e_{IS} obtenue par la sommation sur un bassin d'une fonction de partition restreinte $\int_{R_\alpha} \exp[-\beta(e_{IS} - e_{IS}^\alpha)] d\vec{r}^N$ [72].

En introduisant la densité d'entropie configurationnelle $\mathbf{S}_c \equiv k_B \ln \Omega$ dans la fonction de partition, on obtient finalement :

$$Z = \int de_{IS} \exp[-\beta(e_{IS} + F_{vib}(e_{IS}, T) - T\mathbf{S}_c(e_{IS}))] \quad (1.18)$$

À la limite thermodynamique, l'énergie libre totale $F(T)$ du système est donnée par la relation :

$$F(T) = \langle e_{IS}(T) \rangle + F_{vib}(\langle e_{IS} \rangle, T) - T\mathbf{S}_c(\langle e_{IS} \rangle) \quad (1.19)$$

où $\langle e_{IS}(T) \rangle$ représente la valeur moyenne des énergies IS échantillonnée à une température T .

La relation 1.19 est fondamentale car elle relie l'énergie libre totale du système avec les caractéristiques du paysage énergétique : les minima d'énergies (IS), l'énergie libre de vibration et l'entropie configurationnelle.

1.2.3.2 Évolution des paramètres du paysage énergétique au cours d'une trempe

Des minimisations d'énergie ont été effectuées sur les trois modèles I, II, III décrits précédemment à partir de trajectoires MD réalisées à différentes températures. La figure 1.22 représente les valeurs moyennes des minima $\langle e_{IS}(T) \rangle$ ainsi que les distributions d'énergie $P(e_{IS}, T)$ associées pour différentes températures T . Au cours du refroidissement, nous constatons que le système échantillonne des configurations de plus en plus basse en énergie et que les distributions se resserrent en bon accord avec le modèle schématique de paysage énergétique présenté auparavant.

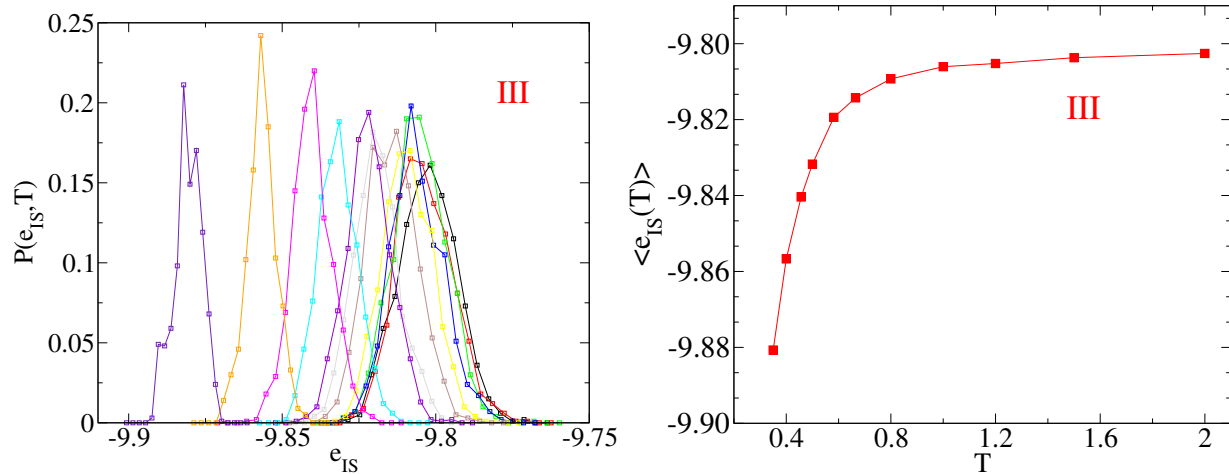


FIG. 1.22 – Gauche : Comportement du modèle III lors d'une diminution de la température. Distributions d'énergie $P(e_{IS}, T)$ pour toutes les températures du modèle III. Droite : Évolution de $\langle e_{IS} \rangle$ en fonction de la température T . Les mêmes types de comportements sont observés pour les modèles I et II.

1.2.3.3 Entropie configurationnelle et vibrationnelle

Dans le cadre du formalisme de Stillinger et Weber, il est possible de décomposer l'entropie totale du système $S(T, V)$ en une partie configurationnelle $S_c(T, V)$ et une partie vibrationnelle $S_{vib}(T, V)$:

$$S(T, V) = S_c(T, V) + S_{vib}(T, V) \quad (1.20)$$

Pour renverser cette relation et estimer la dépendance en température de l'entropie configurationnelle $S_c(T, V)$, l'entropie totale du système a été estimée par une intégration thermodynamique [19]. Cette méthode consiste à simuler le système dans un état similaire

au gaz parfait (basse densité et haute température), puis à suivre une isotherme jusqu'au volume souhaité V . Ensuite, le système est simulé à différentes températures le long d'une isochore jusqu'à la température de travail T . L'entropie du gaz parfait étant connue théoriquement, on peut ainsi obtenir une estimation de l'entropie totale du système $S(T, V)$.

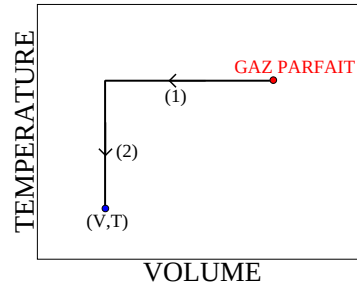


FIG. 1.23 – *Intégration thermodynamique.* L'équation $P = -(\partial F/\partial V)_T$ est intégrée le long de l'isotherme (1) et $C_v = -T(\partial S/\partial V)_V$ le long le l'isochore (2).

L'énergie potentielle autour d'une IS d'énergie e_{IS} peut toujours être approximée par une forme quadratique. La diagonalisation de la matrice Hessienne nous donne une base propre de $3N$ directions indépendantes. Dans cette base, la dynamique du système est décrite par la somme de $3N$ oscillateurs harmoniques indépendants de fréquence ω_i . L'entropie de vibration $S_{vib}(T, V)$ peut alors s'écrire :

$$S_{vib}(T, V) = \left\langle \sum_{j=1}^{3N} 1 - \ln(\beta \hbar \omega_j) \right\rangle \quad (1.21)$$

où $\langle \rangle$ indique une moyenne sur plusieurs IS. Par le calcul des modes de vibration et l'intégration thermodynamique nous avons calculé l'entropie de configuration $S_c(T)$ qui est représentée sur la figure 1.24. On constate que celle-ci peut être clairement ajustée par une loi linéaire $T.S_c(T) = K_{AG}(T/T_{AG} - 1)$. La notation AG est utilisée par analogie avec le modèle d'Adam-Gibbs. Nous avons pu déterminer les températures T_{AG} pour lesquelles l'entropie s'annule et les fragilités K_{AG} . Ces valeurs sont reportées dans le tableau 1.2.

On observe que la fragilité K_{AG} déterminée par cette méthode diminue avec l'anharmonicité du potentiel d'interaction contrairement au comportement obtenu précédemment pour K_{VFT} (voir tableau 1.1). Une estimation du paramètre de Grüneisen obtenue en étudiant la variation des modes de vibration avec un changement de volume (voir tableau 1.2) confirme que le potentiel III serait en fait le plus harmonique. Ces résultats pourraient suggérer que la fragilité K_{AG} obéit à la seconde définition de l'anharmonicité donnée par l'équation 1.12 *i.e.* K_{AG} n'est pas influencée par la même partie du potentiel d'interaction que K_{VFT} . Une autre possibilité serait une inversion de fragilité de K_{VFT} entre les trois modèles à plus basse température.

La figure 1.25 montre le temps caractéristique τ_A de la mobilité obtenu à partir des fonctions intermédiaires de diffusion retracées en fonction de $(TS_c(T))^{-1}$. Il apparaît clai-

rement que la prédiction d'Adam-Gibbs pour laquelle $\tau_A \sim \exp[A/(T.S_c)]$ s'applique bien pour les trois modèles.

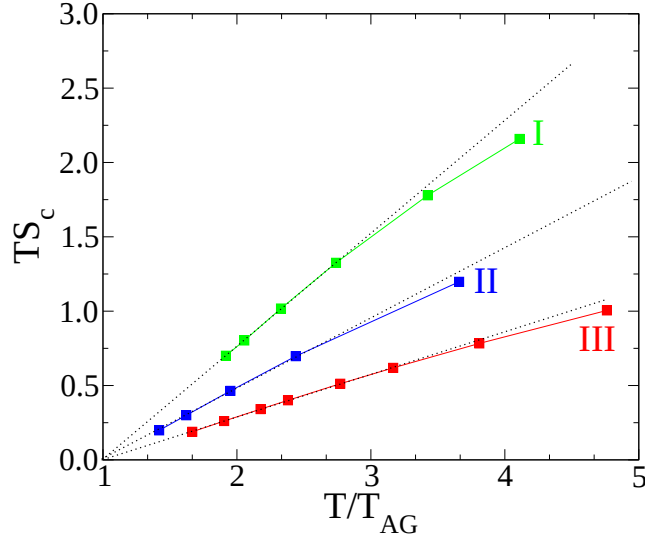


FIG. 1.24 – Représentation de l'évolution de l'entropie configurationnelle $TS_c(T)$ en fonction de la température T/T_{AG} où T_{AG} est la température pour laquelle $S_c(T)$ s'annule pour les modèles I, II et III.

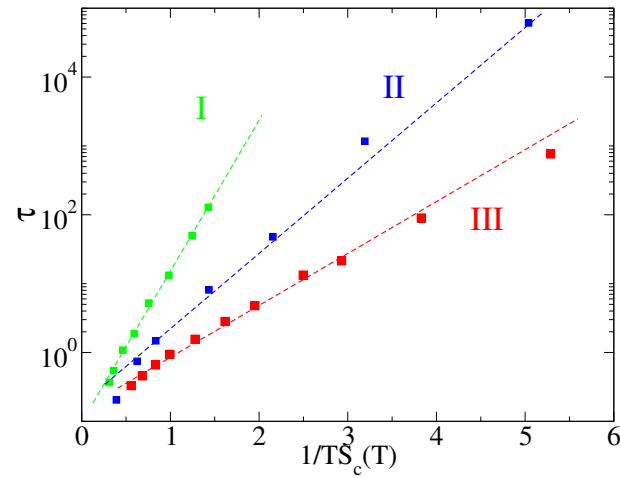


FIG. 1.25 – Représentation de l'évolution du temps de relaxation τ en fonction de $1/TS_c$, pour les trois modèles. Les traits pointillés sont des guides pour l'oeil.

Nous avons représenté sur la figure 1.26, les densités d'états des structures IS pour toutes les températures étudiées pour les trois modèles. On constate que les fréquences moyennes de vibration (maximum de $g(\omega)$) sont cohérentes avec la forme du potentiel V_{11} des trois modèles : le potentiel le plus ouvert (III) possédant des fréquences de vibration plus basses.

La largeur des distributions apparaît cependant très différente entre les trois modèles et plus étroite pour le modèle III. Ces deux résultats - en bon accord avec les valeurs de la fragilité K_{AG} - laisse donc supposer des barrières d'énergie plus basses pour le modèle III mais des fonds de puits plus semblables, au contraire du modèle I qui posséderait des barrières plus hautes mais des IS très différentes. Le modèle II serait un cas intermédiaire. Une représentation « naïve » du paysage énergétique des trois modèles est tracée sur la figure 1.26. On constate également que la fréquence des modes change peu en fonction de la température. Ce résultat indiquerait une forte similarité des formes des puits explorées à haute et basse énergie. Une analyse plus fine de $g(\omega)$ révèle aussi la présence de points isobestiques qu'il serait nécessaire d'étudier plus précisément.

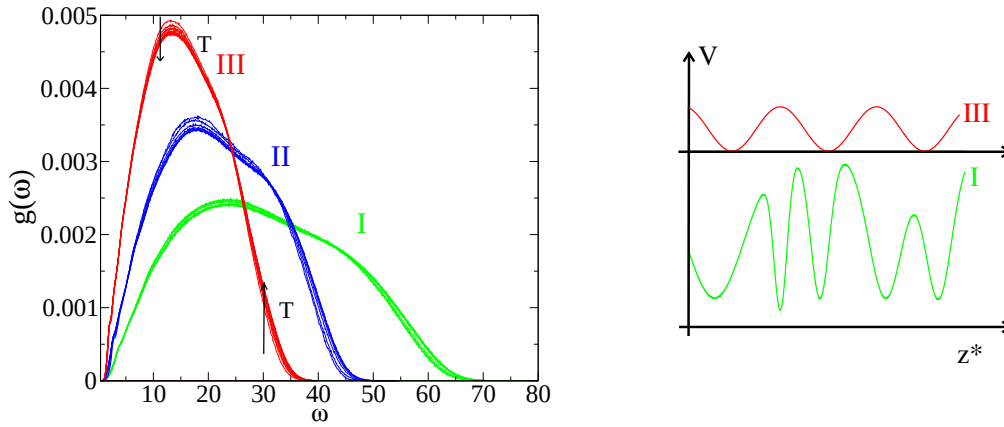


FIG. 1.26 – *Gauche : Densités d'états des modes de vibrations $g(\omega)$ des configurations IS pour toutes les températures des trois modèles étudiés. Droite : Représentation schématique du paysage énergétique pour le modèle I et III.*

1.2.3.4 Approximation gaussienne

Il a été observé [72; 18] que la distribution $\Omega(e_{IS})$ était bien décrite par une loi gaussienne. Dans cette hypothèse, le nombre de minimum, compris entre e_{IS} et $e_{IS} + de_{IS}$, est donné par :

$$\Omega(e_{IS})de_{IS} = \frac{e^{aN} e^{-N(e_{IS}-e_0)^2/(\sigma^2)}}{(2\pi\sigma^2)^{1/2}}$$

Le terme aN exprime l'effet de taille sur le nombre d'IS [75], le paramètre a détermine le nombre total de configurations, e_0 joue le rôle d'origine d'énergie et σ^2 mesure la largeur de la distribution. À partir de cette hypothèse, on peut faire une prédiction sur l'énergie moyenne $\langle e_{IS}(T) \rangle$:

$$\langle e_{IS} \rangle (T) = e_0^{eff} - \frac{\sigma^2}{2Nk_B T} \quad (1.22)$$

où e_0^{eff} est une constante indépendante de la température qui ne dépend que des paramètres de l'approximation gaussienne et de la variation de l'entropie vibrationnelle en fonction de e_{IS} . Sur la figure 1.27, nous avons retracé les évolutions de $\langle e_{IS}(T) \rangle - e^{eff}$ réduites à partir des paramètres de l'approximation gaussienne. Dans cette représentation l'approximation gaussienne est donnée par la droite d'équation $y = -x$. On constate pour les trois modèles une bonne concordance de l'approximation gaussienne en dessous d'une température que l'on identifie à T_A . Au dessus de cette température le système ne sent pas l'influence de la « rugosité » du paysage énergétique, la dynamique n'est alors pas encore découplée entre les deux échelles de temps : temps courts pour les déplacements locaux et temps longs pour les transitions entre bassins.

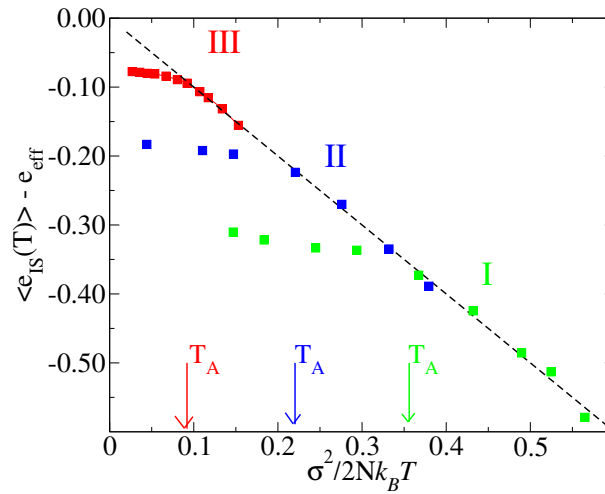


FIG. 1.27 – Évolution de $\langle e_{IS}(T) \rangle - e^{eff}$ en fonction de $\sigma^2/2Nk_B T$ pour les trois modèles. A partir d'une certaine température T_A , on constate que la description en terme de paysage énergétique n'est plus possible.

	Modèle I	Modèle II	Modèle III
(q, p)	(12, 11)	(12, 6)	(8, 5)
ρ_S	1.05	1.11	1.19
T_A	2.3	1.2	0.7
T_{AG}	0.73	0.38	0.21
K_{AG}	0.76	0.49	0.28
$\gamma_{Gruneisen}$	8.73	7.35	6.96

TAB. 1.2 – Paramètres extraits de l'analyse du paysage énergétique pour les trois modèles étudiés (voir texte).

The breakdown of the Stokes–Einstein relation in supercooled binary liquids

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Received 30 April 2003, in final form 16 June 2003

Published 1 August 2003

Online at stacks.iop.org/JPhysCM/15/5397

Abstract

Using reverse non-equilibrium molecular dynamics simulations, we report the calculation of the shear viscosity and the tracer diffusion coefficient of a binary Lennard-Jones mixture that is known as a model glass-former. Several remarkable temperatures are well reproduced in our calculations, i.e. T_S (the onset of slow dynamics), T_c (the critical temperature predicted by the mode-coupling theory) and T_K (the Kauzmann temperature). A breakdown of the Stokes–Einstein relation is found at temperature T_S . We propose that, at low temperatures below T_S , the size of single-particle positional fluctuations between particle-hopping events corresponds to the length measured by the Stokes–Einstein relation, which is equated to the hydrodynamic radius of particles at high temperatures.

1. Introduction

The elusive nature of glassy systems relates to the sharp rise in the transport coefficients (viscosity or relaxation times) in a narrow temperature range above the calorimetric transition temperature, T_g . Despite great interest in glassy systems over the past 40 years, as revealed by the development of several models and theories [1–5], a complete understanding of the glassy state and glass formation has not yet emerged. Some of the most recent investigations focus on the picosecond–nanosecond timescale, where it is suspected that the onset of features of the glass transition phenomena occur. Some paradigms and precise theories have been developed especially to explain the behaviour of supercooled liquids [5] in this domain and from the point of view of the potential energy landscape. Dynamic processes could be described in this fast regime over a temperature range $T_c < T < T_S$ that involves two characteristic temperatures:

- (i) The critical temperature, T_c , predicted by the mode-coupling theory (MCT) [6, 7]. T_c corresponds to an ergodic-to-nonergodic transition in the ideal version of this theory.

It is now commonly considered to be a crossover temperature to a ‘landscape-dominated’ regime in which diffusion processes can be described in terms of thermally activated jumps.

- (ii) A second remarkable temperature, denoted T_S (although T_A or T_x are also seen), whose nature is still unclear at present. T_S is detected above T_c , where non-exponential relaxation and non-Arrhenius behaviour are first observed. This marks the crossover from a normal liquid to slow dynamic behaviour. Both temperatures T_c and T_S have been identified in liquid glass-formers from computer simulations and experiments [8–10], and have also been encountered in many molecular systems [11], in polymers [12] and more recently in protein folding [13].

Diffusion coefficients or shear viscosity are useful parameters for following the evolution of the transport properties of glass-formers from high temperatures (picoseconds–nanoseconds, 10^{-2} Poise) to low temperatures close to T_g (seconds, 10^{12} Poise). Several experimental studies [14–21] have determined the diffusion coefficients and the shear viscosity of systems that have the ability to form a glass, and these works have pointed out the deviation from the Stokes–Einstein relation in the $[T_c, T_S]$ crossover temperature range, below a temperature of about 1.2 times the glass transition temperature. This phenomenon is still not understood and some hypotheses have been suggested, such as the *cage effect* of particles or the existence of dynamic heterogeneities [20–22].

In this work we have performed molecular dynamics simulations of a binary Lennard-Jones mixture in order to clarify the mechanisms responsible for the breakdown of the Stokes–Einstein relation. We have calculated the translational diffusion coefficient and the shear viscosity using a recent technique called reverse non-equilibrium molecular dynamics (RNEMD) [23, 24] which provides faster convergence than the usual numerical methods [25]: i.e. shear flow (non-equilibrium MD) or fluctuations of the stress tensor (equilibrium MD). This RNEMD method is based on the phenomenological relation:

$$J_z(p_x) = -\eta \left(\frac{\partial v_x}{\partial z} \right), \quad (1)$$

where $(\frac{\partial v_x}{\partial z})$ is the shear, $J_z(p_x)$ is the transverse momentum flux, and η is the shear viscosity. This method differs from the usual techniques because $J_z(p_x)$ is *imposed* and the shear is *measured*. In the z direction, the simulation box is divided into N_{slab} slabs. Two slabs, spaced by half the simulation box, move oppositely in the x direction to mimic the shear. This motion is achieved by suitably selecting two particles (one particle in each of these two slabs) and exchanging x components of their velocities. This exchange corresponds to an unphysical momentum transfer. As momentum is conserved, the system responds with a physical flux in the opposite direction. The physical flux leads to a velocity profile. After the two fluxes reach the same magnitude and the system converges towards a steady state, we can calculate the shear viscosity. For details of the RNEMD method, which can be used without an external thermostat, see [24]. This method has also been applied to the calculation of the thermal conductivity [26] and the thermal diffusion coefficient [27, 28] (the Ludwig–Soret effect).

2. Computational details

All simulations were performed with the molecular dynamics package YASP [29], in which the RNEMD method was implemented [24]. We use a binary Lennard-Jones system composed of 1500 particles (1200 of species 1 and 300 of species 2), which has been studied extensively as a model glass-former [30–32]. The particles interact via non-additive Lennard-Jones potentials

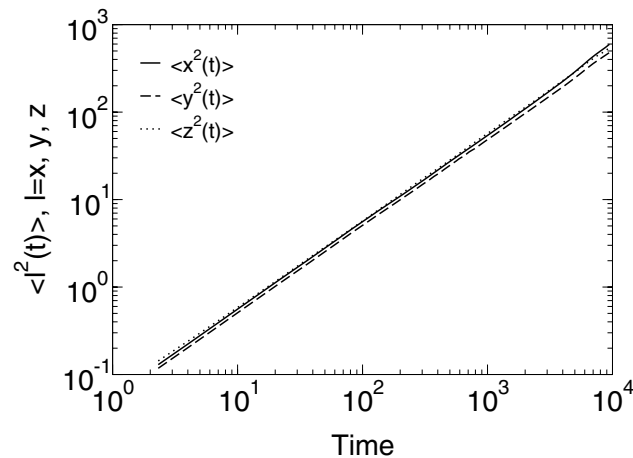


Figure 1. Mean square displacements (MSDs) in the x (solid line), y (dashed line) and z (dotted line) directions of species 1 versus time from a non-equilibrium simulation at $T = 1.66$ with an exchange period of 300 time steps.

Table 1. The parameters of the Lennard-Jones potentials that describe the three types of interactions in the binary mixture.

Interaction	1–1	2–2	1–2
ε	1.0	0.50	1.5
σ	1.0	0.88	0.8

with the parameters collected in table 1, and they are not charged. We use the Lennard-Jones reduced units [33] with σ_1 , ε_1 and m_1 as the reference length, energy and mass. A cut-off of 2.9369 is applied. In previous work, Lennard-Jones potentials have been truncated at $r_{\alpha\beta} = 2.5\sigma_{\alpha\beta}$ (with $\alpha, \beta = 1, 2$) and shifted for more efficient molecular dynamics simulations. It can be shown that these truncation details have only a minor influence on the dynamics and the structure of the system. The neighbour list cut-off is 3.23055, and it is updated every 15 time steps. The time step is 2.3218×10^{-3} . The simulations are performed in the NVT (constant number of particles, constant volume and constant temperature) ensemble using a Berendsen thermostat with a coupling time of 0.23218. The temperature ranges from 0.49887 to 8.3145 and we have performed from 2×10^6 to 8×10^6 time steps, depending on the temperature, in order to get a sufficiently long steady state. Below $T = 0.49887$, the shear viscosity becomes very large ($\eta \approx 10^4$ at $T \approx 0.443$) and the steady state cannot be reached in a reasonable computational time. Non-equilibrium simulations in the NVE (constant number of particles, constant volume and constant energy) ensemble as well as NVT and NVE equilibrium simulations have been performed at different temperatures to check the consistency of the diffusion coefficient and of the shear viscosity. The simulation box is orthorhombic and of size $L \times L \times 3L$, where $L = 7.469$ is chosen to yield a density ρ of 1.2. The simulation box is divided into 20 slabs in the z direction, and the period between velocity (v_x) exchanges is 300 time steps, so the system remains in the linear regime for all temperatures investigated. To get good statistics for the velocity gradient and for the momentum flux, the mean flow velocity within each slab, $\langle v_x(z) \rangle$, and the exchanged momentum are output every 10 time steps. The velocity gradient ($\frac{\partial v_x}{\partial z}$) is obtained by a linear least-squares fit to the velocity profile (excluding the exchange slab).

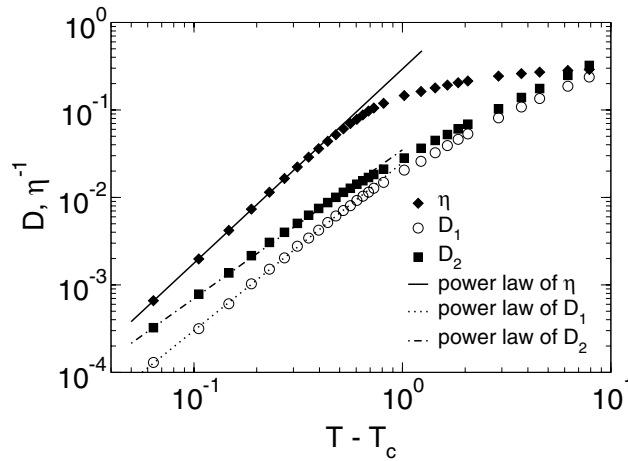


Figure 2. The diffusion coefficient of species 1 (empty circles) and 2 (filled squares), and the inverse shear viscosity (filled diamonds) as a function of the temperature $T - T_c$, where T_c is the critical temperature predicted by the MCT and is fixed at $T_c = 0.435$, according to previous calculations [35]. The lines are power laws of temperature, with exponents of 1.9 (dotted line) and 1.7 (dot-dashed line) for the diffusion coefficients and 2.2 (solid line) for the inverse shear viscosity.

Figure 1 shows the mean square displacements (MSDs) of the x , y and z components obtained from non-equilibrium simulations at $T = 1.66$ with an exchange period of 300 time steps. In this figure, the MSD of the x component is the raw MSD from which a quadratic correction term has been subtracted, which accounts for the part of the displacement in x caused by shearing. This is $V_{x,\text{num}}^2 t^2$, where $V_{x,\text{num}}^2 = (1/N_{\text{slab}})(\sum_{i=1}^{N_{\text{slab}}} \langle v_{x,i} \rangle^2)$. The quantity $\langle v_{x,i} \rangle$ is an average of the x components of the velocities of all particles within slab i among the N_{slab} slabs and over the time of the simulation once steady state has been reached. Theoretically, the correction could also be obtained from the average velocity in the exchange slab $V_{x,\text{theor}}^2 = (2/3L) \int_0^{3L/2} \langle v_x(z) \rangle^2 dz = \frac{1}{3} \langle v_{x,1} \rangle^2$ with $\langle v_x(z) \rangle = \langle v_{x,1} \rangle - (4\langle v_{x,1} \rangle/3L)z$. The notations $v_{x,1}$ and $v_x(z)$ refer to the mean velocity of slab 1 (the exchange slab) and the mean velocity at the z coordinate, respectively, due to the shear. The symbol $\langle \dots \rangle$ represents an average of the simulation over time after steady state has been reached. $V_{x,\text{num}}^2$ and $V_{x,\text{theor}}^2$ are very close; the small difference can be explained by the numerical errors in the velocity profile that make it not rigorously linear. In figure 1, the MSD curves are almost superposed with a slope of 1. This means that the diffusion coefficient in the x , y and z directions are equal, within the error bars. The system is isotropic in diffusion, even though the three directions are not equivalent symmetrically. We have also checked the behaviour of the MSDs in the x , y and z directions for two other exchange periods (100 and 600 time steps) and we have found the same diffusion coefficients. Moreover, we have obtained the same diffusion coefficients, within error bars, by using equilibrium simulations. Thus we conclude that the shear does not affect the single-particle diffusion of the system significantly. The diffusion dynamics are found to be in good agreement with previous studies [34, 35] under equilibrium conditions.

3. Results and discussion

3.1. Determination of outstanding temperatures

Figure 2 shows the diffusion coefficients of both species and the inverse shear viscosity as a function of the temperature $T - T_c$, where $T_c = 0.435$ is the critical temperature predicted

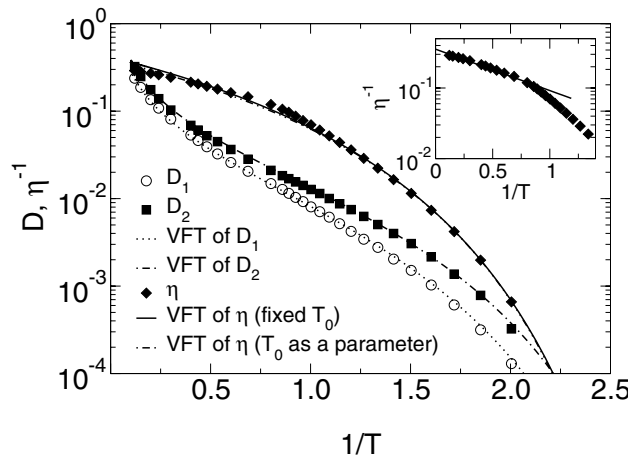


Figure 3. The diffusion coefficient of species 1 (open circles) and 2 (filled squares) and the inverse shear viscosity (filled diamonds) as a function of inverse temperature. The curves for the diffusion coefficients (dotted and dot-dashed curves for species 1 and 2, respectively) correspond to least-squares fits with a modified VFT function (see equation (3)). For the shear viscosity, the curves correspond to VFT functions (see equation (2)), where the limiting temperature T_0 is a parameter (dot-dot-dashed curve) or is fixed to the Kauzmann temperature T_K (solid curve). The inset shows the inverse shear viscosity as a function of inverse temperature and its corresponding Arrhenius fit as a solid curve.

by MCT and previously determined in [35]. The diffusion coefficients exhibit a power-law dependence $(T - T_c)^\gamma$ in a small temperature range above T_c , as predicted by MCT. The exponents— $\gamma \simeq 1.9$ and 1.7 for species 1 and 2, respectively—are found to be in good agreement with previous MD simulations [34, 35]. Above $T = T_S \simeq 1$, the evolution of the diffusion coefficients clearly deviates from the MCT behaviour. It should be noted that Sastry *et al* [9] have associated this change with the onset of slow dynamics, where the system is ‘landscape-influenced’. Figure 2 also demonstrates that the shear viscosity follows a power law with an exponent of $\gamma \simeq -2.2$ in the same temperature range as that of the diffusion coefficients. This exponent is found to be in fair agreement with the values of $\gamma \simeq -2.6$ and -2.45 obtained by Kob and Andersen [35] and Berthier and Barrat [36], respectively. The origin of the difference could be due to the better power-law fits for Kob and Andersen [35] and Berthier and Barrat [36], as they investigated lower temperatures closer to T_c .

To identify the different dynamic regimes, the diffusion coefficients of both species and the shear viscosity are displayed in an Arrhenius plot in figure 3. At high temperatures, the shear viscosity follows an Arrhenius law with an activation energy of $T_{\text{act}} = 1.31$, as shown in the inset of figure 3. At low temperatures ($T < T_S \simeq 1$), the evolution of the shear viscosity deviates from this Arrhenius behaviour. To fit the numerical values of the shear viscosity over the whole temperature range that was investigated, we have used a Vogel–Fulcher–Tammann (VFT) expression:

$$\eta = \eta_\infty \exp\left(\frac{AT_0}{T - T_0}\right). \quad (2)$$

This function characterizes the increase of the shear viscosity as the temperature decreases towards a limit that is denoted by T_0 . The parameter A often refers to the fragility of the system and η_∞ is the shear viscosity of the liquid at infinite temperature. The product AT_0 is analogous to the activation energy in the Arrhenius law at high temperatures. For the diffusion coefficients,

Table 2. Parameters of the least mean square fits, using a modified VFT function (see equation (3)) for the diffusion coefficients and a VFT function (see equation (2)) for the shear viscosity.

Diffusion coefficients			
Parameter	ξ	A	T_0
Species 1	31.4	3.30	0.292
Species 2	23.5	2.80	0.295
Shear viscosity			
Parameter	η_∞	A	T_0
Fit 1	2.41	4.49	0.293
Fit 2	2.59	4.30	$T_K = 0.2976$ (fixed)

a VFT function—similar to the one used for the shear viscosity—fits the data well. However, we have used a modified VFT function to fit the numerical values over the largest possible temperature range. This modified VFT function is

$$D = \frac{T}{\xi} \exp\left(\frac{-AT_0}{T - T_0}\right), \quad (3)$$

where ξ is a friction parameter.

The fitted parameters are summarized in table 2. Clearly, all data can be described well by the modified VFT law for the diffusion coefficient of both species and a VFT law for the shear viscosity. Reasonable reliability is expected in this fitting process, since the temperature $T_0 \simeq 0.294$ is almost the same for both transport coefficients. Moreover, $T_0 \simeq T_K$ emerges from our calculations, where $T_K = 0.2976$ is the Kauzmann temperature that was determined in previous MD simulations for the same system [5, 37]. Therefore, T_0 can be considered to be a good estimation of the Kauzmann temperature in our calculations, even if it is known that the VFT fits do not work properly at low temperatures. The correct way of determining T_K should be the calculation of the configurational entropy, as shown in [5, 37] and recently proposed by Coluzzi *et al* [38, 39].

3.2. Breakdown of the Stokes–Einstein relation

Two important dynamic quantities—the diffusion coefficient and the shear viscosity—are accessible in our simulations. Consequently, it is possible to check the validity and the breakdown of the Stokes–Einstein relation as temperature changes. The Stokes–Einstein relation is given by

$$d = \frac{k_B T}{3\pi D \eta} = \text{constant} \quad (4)$$

for stick boundary conditions. Figure 4 shows the evolution of the quantity $d = \frac{k_B T}{3\pi D \eta}$ as a function of temperature. Two curves have been plotted that correspond to d_1 and d_2 obtained from the diffusion coefficient of species 1 and 2, respectively. According to the Stokes–Einstein approximation, the constant d is a length that is defined as the hydrodynamic diameter of the particles. For the case of Lennard-Jones particles, the hydrodynamic diameter corresponds to the diameter of the particles defined by σ . Indeed, at high temperatures (for $T > T_S$), $d_1 = 1.02$ and $d_2 = 0.85$ are found, which are in good agreement with the diameters $\sigma_1 = 1$ and $\sigma_2 = 0.88$ for species 1 and 2, respectively (see figure 4). However, the Stokes–Einstein relation does not hold below T_S , since the apparent length d decreases for both species.

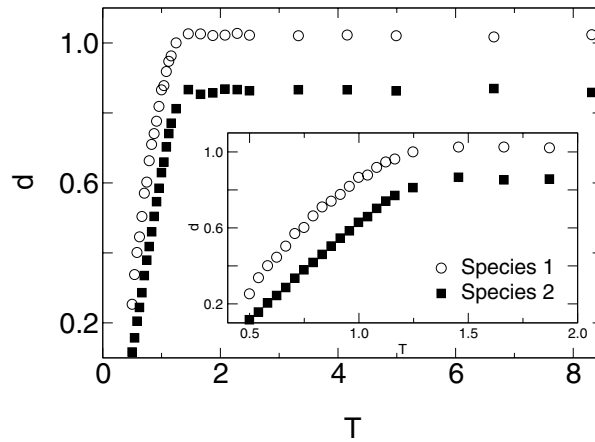


Figure 4. The length d , determined from the Stokes–Einstein relation (see equation (4)) as a function of temperature. Open circles and filled squares are for species 1 and 2, respectively. At high temperatures the length is constant and corresponds to the hydrodynamic diameter of particles. The inset shows length d in the temperature range [0.5–2].

For example, at $T = 0.54$ we find $d_1 = \sigma_1/3.0$ and $d_2 = \sigma_2/5.6$. As the lengths d measured by the Stokes–Einstein relation decrease as temperature decreases, d cannot be associated with a domain size that is expected to grow, lowering the temperature. It should be noted that this behaviour has already been observed in highly viscous silica melt by Horbach and Kob [40] using the appropriate Green–Kubo formula and also by Barrat *et al* [41] for the same model at different pressures and by Yamamoto and Onuki [42] for a binary hard sphere mixture.

Several works have proved that, in the temperature range $[T_c, T_S]$, the continuous diffusion process is replaced by a single-particle hopping process [8, 43–45]. These investigations have shown in particular that particles are confined on sites where they oscillate within a small space for a long time and then hop to another place where they are again localized. This jump corresponds approximately to a particle exchange with near neighbours separated by about σ . This single-particle hopping process has been correlated to the shape of the self-part of the van Hove function [8, 43, 46] and to its non-Gaussian nature [44, 45]. This suggests the existence of clusters of mobile particles. These clusters or groups of particles move faster than the majority of the particles in the system and are therefore called dynamic heterogeneities. In the inset of figure 5 we have plotted the trajectory of a single particle projected on the (y, z) plane at $T = 0.54$. The hopping process can clearly be seen: the trajectory of the particle is localized at three different sites that are highlighted by circles and separated by jumps. The size of the jumps is about σ and the radius of the circles is about $\frac{\sigma}{3}$.

This single-particle hopping process is also revealed in figure 6 by the existence of a subdiffusive regime, i.e. a plateau-like domain in the MSD curves. At low temperatures in the plateau regime the MSD curves can be fitted with the von Schweidler law, which depends on an exponent b in relation to the exponent γ , as predicted in MCT and used in figure 2. We found $b \approx 0.45$, which is in good agreement with the previous estimations of 0.48–0.52 according to Kob and Andersen [47, 48]. The plateau regime is defined between two inflexion points: the first one marks the end of the ballistic regime and the second indicates the start of the diffusive regime. The time dependence of the diffusive regime has been fitted by using a linear law t , whereas a power law t^α ($\alpha < 1$)—inspired by the von Schweidler law—has been used for the subdiffusive regime. A characteristic length, λ , can be derived from the intersection of subdiffusive and diffusive regimes, identified as point A in figure 6. The length λ corresponds

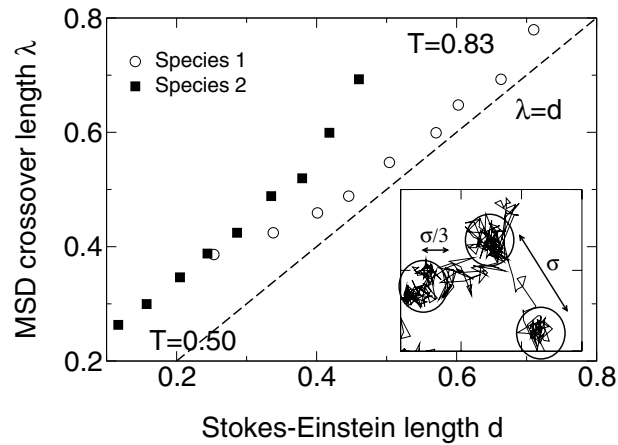


Figure 5. The length λ of the subdiffusive-to-diffusive crossover, determined from the MSD curves, versus the apparent hydrodynamic diameter d from the Stokes–Einstein relation (see equation (4)) for species 1 (open circles) and 2 (filled squares) at different temperatures ($T = 0.5, 0.54, 0.58, 0.62, 0.66, 0.71, 0.75, 0.79, 0.83$). The length λ has been multiplied by $\sqrt{3}$ to take into account the x , y and z directions. The inset shows the trajectory of a single particle projected on the (y, z) plane at $T = 0.54$. Its motion is dominated by hopping due to the cage effect. It is the origin of the plateau or the subdiffusive regime observed in the MSD curves at intermediate times.

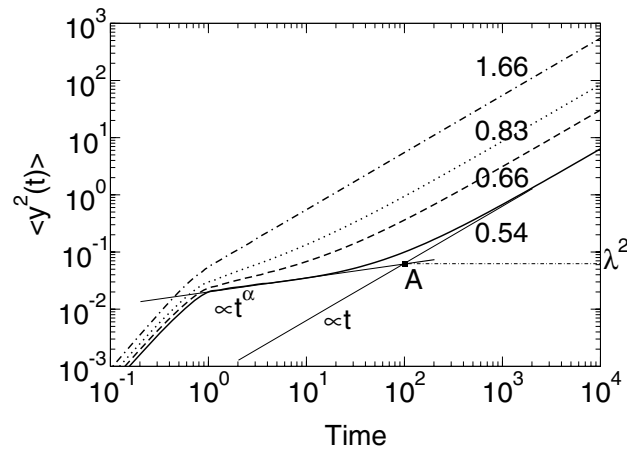


Figure 6. MSD (thick curves) of species 1 along the y coordinate versus time for four different temperatures: $T = 0.54$ (solid), 0.66 (dashed), 0.83 (dotted) and 1.66 (dot-dashed). λ is defined as the ordinate of point A. This point corresponds to the intersection of two fitted lines based on the diffusive regime at long times and on the subdiffusive regime at intermediate times of the MSD. The fitted lines are represented by solid thin lines. This length cannot be defined for $T = 1.66$.

to the distance covered by a particle until the particle succeeds in escaping from the cage formed by its neighbourhood. Therefore, λ provides a measure of the size of the confined regions (cage) explored by the particles. This length (called ‘MSD crossover length’ in the following) can only be determined if the plateau-like regime is clearly defined. We found $T \simeq T_S$ —the highest temperature for which this determination is possible. This confirms the existence of the onset of slow dynamics, as already highlighted by the diffusion coefficient and the shear viscosity. According to the Kob–Andersen model [35], it should be noted

that λ does not converge to zero but to a finite value equal to $r_c\sqrt{6} \approx 0.17$, where r_c is the Lindemann localization length. Below T_S , $1/\lambda$ can be considered to be a coupling term between the particle and its neighbours. Indeed, at high temperatures (above T_S) the particles normally diffuse, because they are controlled mainly by their kinetic energy rather than their potential energy. Nevertheless, at low temperatures (below T_S) the intermolecular potential is large compared to the kinetic energy. Thus, the dynamics of the particle are slowed down by the cage effect. This picture is analogous to the ‘landscape-influenced’ regime proposed by Sastry [9].

In figure 5 we have plotted the MSD crossover length λ versus the apparent hydrodynamic diameter d from the Stokes–Einstein relation at different temperatures between $T = 0.50$ and 0.83 . For species 1 we show that $\lambda \approx d$ holds well, which means that the Stokes–Einstein relation is sensitive to the confined fluctuations of the particles. Then the length d extracted from the Stokes–Einstein relation does not correspond to the hydrodynamic diameter σ in the $[0.5; 0.83]$ temperature range. At high temperatures the motion of the particles is governed by the diffusion process. Then the particles move freely to the location of their nearest neighbours, so the positional fluctuations are equal to the hydrodynamic diameter. In this case, jumps and fluctuations become indistinguishable. Yet, at lower temperatures the spatial fluctuations and the jumps (or the hydrodynamic diameter) become uncorrelated. As the Stokes–Einstein relation measures the positional fluctuations and not the jumps, the length d measured by the Stokes–Einstein relation must decrease with temperature. At this stage, this new look at the length d measured by the Stokes–Einstein relation is not incompatible with the hydrodynamic diameter; it is a generalization. As for species 2, λ is described well by a linear function of d , but $\lambda = d$ is not granted. One explanation could be the following. As the system is composed of 1200 particles of species 1 and 300 particles of species 2, one particle of species 2 is more likely to be surrounded by particles of species 1. Therefore, the size of the fluctuations of one particle of species 2 results from the interaction between species 1 and 2 rather than between species 2 and itself. Moreover, as the strength of the potential (ε) of species 2 is only 0.5 compared with 1.0 for species 1 and 1.5 for mixed interactions, the particles of species 1 can overlap the particles of species 2 more: the particles of species 2 can be seen as spheres that are less hard than the particles of species 1. These two observations lead to the diameter d being too small, as measured by the Stokes–Einstein relation. Another point is that the species 2 particles are more mobile than the species 1 particles, so there is greater uncertainty in the fit of the plateau of species 2 and the λ of species 2 is less accurate. It should also be mentioned that, at low temperatures approaching T_c , it is difficult to estimate accurately the diffusion coefficients and the shear viscosity due to the very long relaxation time of the system. Consequently, a relatively large error can be suspected for d .

4. Conclusion

In this paper, we have shown that the RNEMD is a well adapted method for investigating the transport properties of glass-forming systems. RNEMD is a recent technique that provides faster convergence than the usual numerical non-equilibrium or equilibrium methods. A binary Lennard-Jones mixture has been studied that is well documented in the literature and is known as a model glass-former. Despite the very slow dynamics occurring at low temperature, the shear viscosity has been calculated and its temperature dependence has been analysed with other transport coefficients as the diffusion coefficients. Using different fitting laws, we were able to reproduce—with good precision—some outstanding temperatures: i.e. the Kauzmann temperature $T_K \simeq 0.29$ [31], the critical temperature $T_c \simeq 0.435$ [35], predicted by MCT; and the crossover temperature $T_S \simeq 1$ [9], showing the onset of slow dynamics.

From the shear viscosity and the diffusion coefficients of both species, we have calculated the apparent hydrodynamic diameter d from the Stokes–Einstein relation. A temperature-independent constant with an Arrhenius behaviour is found at high temperatures in the normal liquid state, as expected according to hydrodynamics theory. Below T_S , the Stokes–Einstein relation breaks down, as observed in some experiments on glass-former systems. We have shown that the motion of the particles is not described by continuous diffusion but by hoppings between sites where particles are localized. We have correlated the length d , extracted from the Stokes–Einstein relation, with the length λ corresponding to the size of the positional fluctuations of particles on sites where they are localized. This interpretation of the Stokes–Einstein relation is an extension to the original concept and could be useful in understanding the mechanisms of the formation of the glassy state. The breakdown of the Stokes–Einstein relation appears to be a sensitive probe of the jump process when the system starts being ‘landscape-influenced’. As the diffusion process also involves the motion of particles over a distance approximately equal to the hydrodynamic diameter at low temperatures, the breakdown of the Stokes–Einstein relation means that the momentum transport described by the viscosity is characterized by another length, which appears in this work as the size of the single-particle positional fluctuations between particle hopping events. This suggestion will be studied in future work.

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Does the Interaction Potential Determine Both the Fragility of a Liquid and the Vibrational Properties of Its Glassy State?

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(Received 8 January 2004; published 2 September 2004)

By performing molecular dynamics simulations of binary Lennard-Jones systems with three different potentials, we show that the increase of anharmonicity and capacity for intermolecular coupling of the potential is the cause of (i) the increase of kinetic fragility and nonexponentiality in the liquid state, and (ii) the T_g -scaled temperature dependence of the nonergodicity parameter determined by the vibrations at low temperatures in the glassy state. Naturally, these parameters correlate with each other, as observed experimentally by T. Scopigno *et al.* [Science **302**, 849 (2003)].

DOI: 10.1103/PhysRevLett.93.105502

PACS numbers: 61.20.Ja, 64.60.Ht, 64.70.Pf

The structural relaxation time, τ , of all glass-forming liquids increases on cooling. It becomes so long at some temperature T_g that equilibrium cannot be maintained and the liquid is transformed into a glass. T_g is defined as the temperature at which τ reaches some arbitrarily chosen long time, say, 10^2 s. Although this behavior is shared by glass formers of diverse chemical and physical structures, the scaled temperature dependence of τ in the liquid state can differ greatly from one liquid to another in the degree of departure from the Arrhenius scaled temperature dependence [1,2]. The departure can be characterized by the rapidity of the change of $\log(\tau)$ with T_g/T at $T_g/T = 1$, which is given by the steepness index or the fragility m defined by [3]

$$m = \left. \frac{d \log(\tau)}{d(T_g/T)} \right|_{T_g/T=1}. \quad (1)$$

The values of m of glass formers of all kinds vary over a large range, from the least value of about 17 for strong glass formers (such as silica) having nearly Arrhenius scaled temperature dependence of τ , to values as high as about 200 found for some glass formers called fragile. Naturally, such large variations observed in m beg the question of its microscopic origin. Several attempts have been made in the past to correlate m with other dynamic or thermodynamic properties, with the hope that the correlations will lead to the factor or factors that determine m . Examples include (i) the correlation of m with $n \equiv (1 - \beta)$ at $T = T_g$, where β is the stretched exponent in the Kohlrausch function, $\exp[-(t/\tau)^\beta]$, used to fit the time dependence of the correlation functions such as the intermediate scattering functions; (ii) the correlation of m or $(1 - \beta)$ with the mean-square displacement $\langle u^2 \rangle$ obtained [4] from quasielastic neutron scattering measurement of the Debye-Waller factor $\exp[-\langle u^2 \rangle Q^2/3]$ [glass former with larger m or $(1 - \beta)$ has a larger $\langle u^2 \rangle$ at the

same value of T/T_g and rises more rapidly as a function of T/T_g , below T_g as well as near and across T_g in the liquid states [4]]; (iii) the correlation between m and the slope of the change of the configurational entropy, S_c , with T/T_g at T_g [5]; (iv) the correlation of m with the statistics of potential energy minima of the energy landscape [6,7]; and (v) the correlation of m with the temperature dependence of the shear modulus of the liquid [8]. Perhaps the most intriguing of all correlations is (vi) between m and the vibrational properties of the glass at temperatures well below T_g found recently by Scopigno *et al.* [9]. The nonergodicity parameter, $f(Q, T)$ at $T \ll T_g$, is determined by vibrations. From inelastic x-ray scattering data, the temperature dependence of $f(Q \rightarrow 0, T)$ is well described by $[1 + \alpha(T/T_g)]^{-1}$. Scopigno showed that m and α are proportional for many glass formers. Apparently, this last correlation (vi) seems to be related to (ii) for $\langle u^2(T/T_g) \rangle$ from neutron scattering at temperatures well below T_g .

In any glass former, it is the interaction potential, $V(r)$, that determines ultimately all dynamic, thermodynamic, and vibrational properties at all temperatures both below and above T_g . Changes in any of the quantities, m , n , $\langle u^2(T/T_g) \rangle$, α , S_c , free volume v [10], and the degree of dynamic heterogeneity, from one glass former to another, originate from the change in $V(r)$. Thus, correlations found between these quantities are clues for finding out which aspects of $V(r)$ determine them and give rise to the correlations between them. One would like to examine the interaction potentials in real glass formers. However, in such materials, the different kinds of chemical bonding and the different sizes of the basic structural unit make the comparisons ambiguous. For this reason we consider the binary Lennard-Jones (LJ) particles with different choices of interaction potentials $V(r)$ between the particles, and perform molecular dynamics (MD) simulations on them to obtain m , n , α , and $\langle u^2(T/T_g) \rangle$. Correlations

are found between all these quantities, thus reproducing the empirical findings from real glass formers. Since the number of particles as well as their density ($\rho = 1.2$) are the same, the changes of these quantities are predominantly due to the change in $V(r)$. The latter is well controlled, and therefore we identify anharmonicity and the capacity of intermolecular coupling of $V(r)$ to be responsible for enhancement of m , n , α , and $\langle u^2(T/T_g) \rangle$, and hence their correlations.

MD simulations were performed on binary LJ particles systems with three different interaction potentials by the MD package *DLPOLY* [11]. Technical details of the MD simulations are given in [12]. We have performed from 10^5 to 6×10^7 time steps, depending on temperature. We have investigated 12 temperatures in the range of [0.675–5], [0.416–5], and [0.26–2] for models I, II, and III, respectively. All models are composed of 1500 uncharged particles (1200 species *A* and 300 species *B*). The generalized (q, p) LJ potentials have the form $V(r) = \frac{E_0}{(q-p)} \times [p(\frac{r_0}{r})^q - q(\frac{r_0}{r})^p]$. The parameters r_0 and E_0 represent the position of the minimum of the well and its depth, respectively. The reduced LJ units [13] are used. The choice of $q = 12$ and $p = 6$ corresponds to the standard LJ potential used by Kob and Andersen (KA) [14] and by others for extensive studies by simulation. For the purpose of investigating the change of dynamics with controlled change of $V(r)$, we developed two other models by changing only the exponents, q and p , of the LJ potential for the *A-A* interactions. They are $(q = 8, p = 5)$ and $(q = 12, p = 11)$ and are shown together with the (12,6) LJ potential in Fig. 1. The well depth and the position of the minimum of $V(r)$ are unchanged, and we have kept the standard (12,6) LJ potentials of the KA model for the *A-B* and *B-B* interactions in order to retain as much as possible the remarkable ability of the KA model to form a glass upon cooling. The (12,11) LJ potential is more harmonic than the classical (12,6) LJ potential, while the (8,5) LJ

potential is a flat well and exceedingly anharmonic. Whenceforth the (12,11), (12,6), and (8,5) potentials are referred to as models I, II, and III, respectively, reminding us that anharmonicity is increasing in this order. The $V(r)$ potentials are not truncated and shifted according to [14]. This modification does not alter the behavior of the models.

The structure has been briefly studied by the radial *A-A* distribution functions $g(r)$ of the (12,11) and (8,5) models, which have been calculated and found very similar to that of the (12,6) model in the temperature ranges investigated (see inset of Fig. 1). Respectively for models I, II, and III at $T = 0.700, 0.440$, and 0.268 , the position of the first peak of $g(r)$ is at 1.072, 1.066, and 1.057 and its width at half the maximum is 0.129, 0.147, and 0.191. The $g(r)$ of the three models in the supercooled state is similar to that in the liquid regime, ensuring that the structures have disorder in the middle and long range.

Dynamics have been investigated by computing the self- $F_S(Q, t)$ and the total- $F(Q, t)$ intermediate scattering functions of particles *A* at $Q_0 = 2\pi/r_0$, close to the maximum of the collective static structure factor $S(Q)$, for the three models. At high temperatures, $F_S(Q_0, t)$ decays linear exponentially to zero with a characteristic time of about 0.45 close to crossover time $t_c \approx 1$ to 2 ps used as a fundamental time in the coupling model [15,16]. When temperature is lowered, the dynamics slows down dramatically and a two-step process appears. This behavior is well described by the mode coupling theory [17]. For the three models, it is indeed possible to draw a master curve with $F_S(Q_0, t)$ at each of these lower temperatures in the reduced unit t/τ_A , where τ_A is the relaxation time. From the master curves, we find an independent temperature β , the stretched exponent, equal to 0.84, 0.81, and 0.76 with error bars of 0.1 for models I, II, and III, respectively. Because of the relatively large error bars, we have determined the nonergodicity parameter (height of

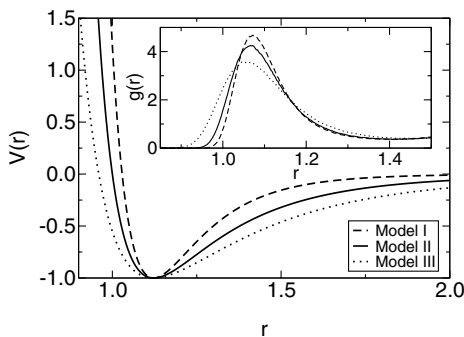


FIG. 1. Potential $V(r)$ governing the *A-A* interaction. The dashed curve is the (12,11) LJ potential for model I, the solid curve is the (12,6) LJ potential for model II, and the dotted curve is the (8,5) LJ potential for model III. Inset: radial distribution function $g(r)$ of species *A* at $T = 1.02T_{\text{ref}}$ for the three models (see below for the definition of T_{ref}).

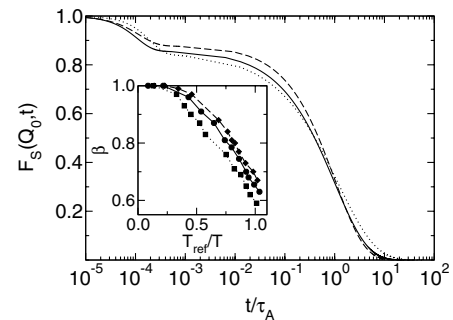


FIG. 2. Self-intermediate scattering function $F_S(Q_0, t)$ vs scaled time t/τ_A . Dashed, solid, and dotted lines are for models I, II, and III, respectively. For all three models, $\tau_A(T_{\text{ref}}) = 46435.8$. The inset shows the stretched exponent $\beta = (1 - n)$ as a function of the scaled reciprocal temperature T_{ref}/T for the three models: (◆) model I, (●) model II, and (■) model III. For definitions of τ_A and β , see text.

the plateau), $f_S(Q_0, T)$, the relaxation time, τ_A , and the stretched exponent, β , from the fit to the second step decay of individual $F_S(Q_0, t)$ (rather than the master curves) by $f_S(Q_0, T) \exp[-(t/\tau_A)^\beta]$. Shown in Fig. 2 are $F_S(Q_0, t)$ vs t/τ_A of all three models at the reference temperature T_{ref} defined by $\tau_A(T_{\text{ref}}) = 46435.8$, a very long time in our simulations. The values of T_{ref} are 0.688, 0.431, and 0.263 for models I, II, and III, respectively.

Shown in Fig. 2 (inset) are β of the three models as a function of T_{ref}/T . At any T_{ref}/T , $(1 - \beta)$ is least for model I and largest for model III. At $T = T_{\text{ref}}$, $\beta = 0.69, 0.65$, and 0.60 , respectively, for models I, II, and III. Thus $(1 - \beta)$, which provides a measure of the intermolecular coupling according to [15], increases with anharmonicity. In Fig. 3, $\log(\tau_A)$ is plotted against T_{ref}/T and the data of the three models show systematic change. It can be seen that the slope, fragility index $m(\tau_A) \equiv [d \log(\tau_A)]/[d(T_{\text{ref}}/T)]$ as $(T_{\text{ref}}/T) \rightarrow 1$, increases monotonically in the order of models I, II, and III. The values of $m(\tau_A)$ determined from this latter relation are 15.07, 18.57, and 26.58 for models I, II, and III. Alternatively, the estimated values of $m(\tau_A)$ based on the Sastry method [7] are 0.195, 0.241, and 0.405 for models I, II, and III, respectively. Hence, $m(\tau_A)$ increases with anharmonicity. The fragility index found in the present study for model II is in good agreement with the value determined in an earlier work on the same model [7]. The diffusion coefficient, D_A , of particles A was calculated from the mean-square displacement $\langle u^2(t) \rangle$ at long times when $\langle u^2(t) \rangle$ assumes the linear t dependence. The evolution of $1/D_A$ is comparable to τ_A , leading to another definition of the steepness or fragility index, $m(D_A) \equiv [d \log(1/D_A)]/[d(T_{\text{ref}}/T)]$ as $(T_{\text{ref}}/T) \rightarrow 1$. Again, $m(D_A)$ increases monotonically in the order of models I, II, and III, or with anharmonicity.

So far we are concerned for dynamic quantities and their correlations for $T > T_{\text{ref}}$, as analogues of them in the

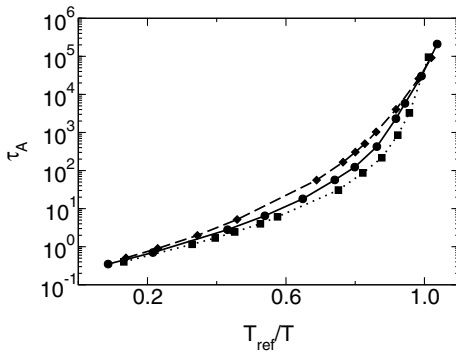


FIG. 3. The relaxation times τ_A obtained from $F_S(Q_0, t)$ for the three models as a function of T_{ref}/T , where T_{ref} is defined as the temperature at which τ_A reaches 46 435.8: (◆) model I, (●) model II, and (■) model III. T_{ref} is the analogue of T_g for simulations when the dynamics of the system slows down to more than 10 ns.

liquid state of real glass formers. Next we examine the vibrational properties of the three models at temperatures lower and much lower than T_{ref} by first quenching the liquid and then allowing vibrational degrees of freedom to relax. At low temperatures, relaxation of any kind is absent in the simulation time window, and the nonergodicity parameter $f(Q, T)$ determined from $F(Q, t)$ is contributed entirely from vibrations. As performed in [9], we have followed the behavior of $f(Q \rightarrow 0, T) \equiv f_0(T)$, which has been obtained by a Q -quadratic extrapolation of $f(Q, T)$ for the lowest temperatures. The results of the three models are shown by a plot of $f_0(T)^{-1}$ vs T/T_{ref} in Fig. 4.

In all three cases, the dependence of $f_0(T)^{-1}$ on T/T_{ref} is approximately linear, and $f_0(T)^{-1}$ has the extrapolated value of unity at the origin. The dependence of $f_0(T)$ from simulation on T/T_{ref} is governed by the parameter, α , through the expression

$$f_0(T)^{-1} = 1 + \alpha \frac{T}{T_{\text{ref}}}, \quad (2)$$

just like a similar expression used to represent the dependence of $f_0(T)$ on T/T_g of real glass formers obtained by inelastic x-ray scattering [9]. We see from Fig. 4 that the increase of $f_0(T)^{-1}$ with T/T_{ref} is fastest for model III and slowest for model I. Equivalently stated, the slope α is largest for model III and smallest for model I. α increases with anharmonicity of the potential, such as $m(\tau_A)$ or $m(D_A)$, and $(1 - \beta)$, as seen before (Figs. 1–3). Hence the interacting potential is the origin of the correlation of α with $m(\tau_A)$ or $m(D_A)$, and $(1 - \beta)$ in our simulation, suggesting the same holds for real glass formers. Moreover, in the inset of Fig. 4, we observe that $m(\tau_A)$ and α are proportional together, as shown in [9].

Presumably there is no disagreement that the interaction potential is pivotal in determining all dynamic, thermodynamic, and vibrational properties of glass formers at all temperatures. With all these experimentally

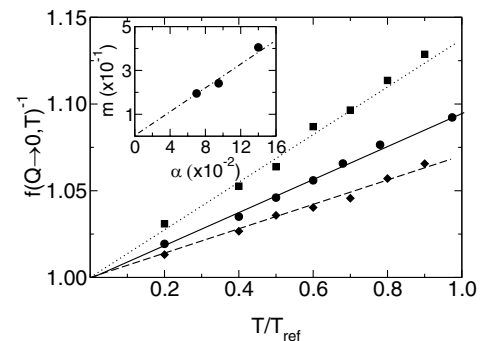


FIG. 4. $f(Q \rightarrow 0, T)^{-1} \equiv f_0(T)^{-1}$ vs T/T_{ref} for the three models: (◆) model I, (●) model II, and (■) model III. $f_0(T)^{-1}$ is almost linear relative to T/T_{ref} with a slope noted α . The inset shows the correlation of the fragility m with α from the results of the three models.

accessible properties originating from the interaction potential, it is not surprising to find correlations or anticorrelations between them. Making this point is one of the motivations of the work in demonstrating that the various correlations between α , m , $(1 - \beta)$, and $\langle u^2(T/T_g) \rangle$ observed in real glass formers are reproduced by simulations as the analogues of correlations between α , $m(\tau_A)$, $m(D_A)$, and $(1 - \beta)$ by varying the interaction potential $V(r)$. The results confer a bonus in identifying which feature of the interaction potential is responsible for enhancement of α , $m(\tau_A)$, $m(D_A)$, and $(1 - \beta)$. Certainly the anharmonicity of $V(r)$ increases when going from model I to models II and III, but one also can observe from Fig. 1 that the long range interaction becomes more pronounced. The latter trend means that neighboring LJ particles are more coupled in their motions. The increase in interparticle coupling from model I to model III is consistent with the position of the first peak of radial distribution functions $g(r)$ (1.072, 1.066, and 1.057 for models I, II, and III, respectively) and with its width at half the maximum (0.129, 0.147, and 0.191 for models I, II, and III). This insight from simulation, when transferred to real glass formers, suggests that the capacity for intermolecular coupling and the anharmonicity of the interaction potential determine the dynamic, thermodynamic, and vibrational properties of glass formers above as well as below T_g . Although the thermodynamic variables, configurational entropy S_c , and free volume ν are determined by $V(r)$, they reenter into the dynamics by their influence on molecular mobility. Thus two factors govern dynamics, the capacity for intermolecular coupling directly from $V(r)$, and S_c and ν that come indirectly through $V(r)$. On supercooling a liquid, S_c and ν change, and since the kinetic fragility m is the slope of T_g -scaled temperature variation of τ , it is not surprising that m is correlated with the slope of the corresponding change of S_c , i.e., the thermodynamic fragility. The capacity for intermolecular coupling of $V(r)$ is solely responsible for the shape of the dispersion or the nonexponentiality parameter $(1 - \beta)$, and it also determines τ in conjunction with S_c and ν . The results of our simulation with the three potentials support this view. Increasing the density of the particles of the binary LJ system with the fixed (12,6) potential effectively forces the particles to be closer to each other and thereby increases intermolecular coupling. The simulation performed in this manner [7] showing that m increases with density can be reinterpreted as due to the increase of intermolecular coupling. Intermolecular coupling manifests itself in the dynamic properties in various ways, such as the $Q^{-2/\beta}$ dependence of τ [4]. All these provide evidence for intermolecular coupling that must be taken into consideration in conjunction with S_c and ν for explaining all observed experimental facts in the liquid state. At low temperatures and deep in the glassy state, S_c

and ν having constant values cannot influence the temperature dependence of the vibrational properties characterized by α . Hence, α is controlled by the anharmonicity of $V(r)$, as demonstrated by the simulations.

In summary, we demonstrate by using three different interparticle potentials of binary LJ systems that the capacity for intermolecular coupling and the anharmonicity of the potential are responsible for the correlations between various dynamic, thermodynamic, and vibrational properties of glass formers. The increase of the capacity for intermolecular coupling and anharmonicity has the effects of increasing the kinetic fragility, m , and the nonexponentiality parameter, $(1 - \beta)$, in the liquid state, and of increasing in the glassy state the parameter α that characterizes the T_g -scaled temperature dependence of the nonergodicity parameter determined by vibrations at low temperatures. The correlations between m , $(1 - \beta)$, α , and other quantities follow as consequences, and their observations by experiments have now been explained.

The authors wish to thank the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France) for the use of the computational facilities. This work was supported by the INTERREG III (FEDER) program (Nord-Pas de Calais/Kent). Work at NRL was supported by the Office of Naval Research.

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Molecular dynamics investigations of glassforming binary Lennard-Jones systems with different anharmonicities

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Abstract

Dynamical properties of three glassforming binary Lennard-Jones systems with different anharmonicities of the interaction potential have been studied by molecular dynamics simulations. The onset temperature of slow dynamics T_A , the Mode Coupling theory critical temperature T_C and the Vogel–Fulcher–Tamman temperature T_{VFT} have been determined for the three models. A good agreement is found with most of the predictions of the Mode Coupling Theory. However, a detailed analysis of the master curve obtained from the superposition of the intermediate scattering functions reveals a significative temperature dependence of the stretched exponent β over a wide temperature range from the liquid state to the glass transition. It is shown that both fragility and stretched exponent β unambiguously correlate with anharmonicity of the interaction potential.

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PACS: 61.20.Ja; 64.60.Ht; 64.70.Pf

Keywords: Glass transition; Molecular dynamics; Fragility; Structural relaxation

1. Introduction

Understanding of the mechanisms leading to the glass transition has been a subject of intense research in the last decades and it is still a matter of numerous theoretical and experimental studies [1]. Much attention has been recently devoted to the microscopic origin of the very large variations of the fragility m observed between very different glassforming systems: molecular liquids, polymers, ionic materials or orientationally disordered crystals. Indeed, the fragility m offers a useful measure of the temperature dependence of the mobility which is the intrinsic parameter of glass formation phenomena. m can be usually calculated from the slope of the viscosity η or a characteristic relaxation time τ at the glass transition T_g [2–4].

$$m = \left. \frac{d \log(\eta)}{d(T_g/T)} \right|_{T_g/T=1} \quad \text{or} \quad m = \left. \frac{d \log(\tau)}{d(T_g/T)} \right|_{T_g/T=1}. \quad (1)$$

Where T_g is classically defined as the temperature for which $\tau = 10^2$ s or $\eta = 10^{13}$ P. It should be pointed out that while T_g is unambiguously defined by the value of the relaxation time, the corresponding viscosity depends on the shear modulus through the Maxwell relation, which can be quite different for polymers and molecular liquids, for instance. The fragility m spreads from 17 for strong glass-formers (having nearly Arrhenius scaled temperature dependence of η or τ) such as silica up to 200 for fragile ones such as polymers or low weight molecular liquids. m has been already correlated with thermodynamical or dynamical properties [5–7], or even recently with the vibrational properties of the glass well below T_g by Scopigno et al. [8].

In a previous study [9], we investigate some properties of binary Lennard-Jones glassforming systems similar to the

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well-documented and classical Kob–Andersen model known for its remarkable ability to form a glass upon cooling [10,11]. We considered some alternative potentials with different shapes, i.e., with different anharmonicities of the interaction potential $V(r)$. This class of glassforming systems was preferred to others for the simplicity of the interaction potential: basic structural units are simple neutral particles interacting via Lennard-Jones potentials. Indeed, other interaction potentials used in computer simulations are often very difficult to compare: the potentials for silica used in the simulations of Horbach et al. [12] are fundamentally different from those used for ortho-terphenyl (OTP) by Lewis and Wahnstrom [13]. In Ref. [9], we particularly demonstrated that m and the vibrational properties or the long and short time dynamics are controlled by the anharmonicity and the intermolecular coupling of the potentials. In the present study, we focus on the dynamical properties of the alternative models to the K–A model developed previously [9] and we compare the capabilities of the mode coupling theory (MCT) [14] to describe dynamics of the different models.

2. Computational details

Molecular dynamics simulations were performed on binary Lennard-Jones (LJ) particles systems with three different interaction potentials by the MD package DLPOLY [15]. Technical details of the MD simulations are given in [16]. We have performed from 10^5 to 6×10^7 time steps, depending on temperature. We have investigated 12 temperatures in the range of [0.675–5], [0.416–5] and [0.26–2] for Model I, II and III, respectively, which are defined in the following. All models are composed of 1500 uncharged particles (1200 species A and 300 species B). The generalized (q, p) LJ potentials have the form

$$V(r) = \frac{E_0}{(q-p)} \left(p \left(\frac{r_0}{r} \right)^q - q \left(\frac{r_0}{r} \right)^p \right). \quad (2)$$

The parameters r_0 and E_0 represent the position of the minimum of the well and its depth, respectively. The reduced LJ units [17] are used. The choice of $q = 12$ and $p = 6$ corresponds to the standard LJ potential used by Kob and Andersen (K–A) [10,11]. The parameters of the K–A model are collected in Table 1.

For the purpose of investigating the change of dynamics with controlled change of $V(r)$, we developed two other models by changing only the exponents, q and p , of the LJ potential for the A–A interactions. They are ($q = 8$,

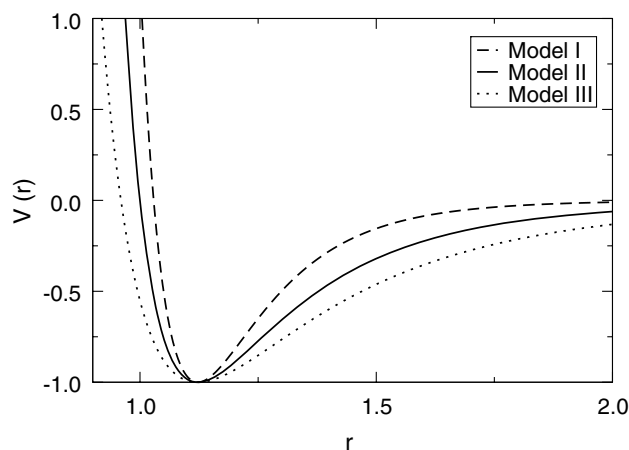


Fig. 1. Potential $V(r)$ governing the A–A interaction. The dashed curve is the (12,11) LJ potential for model I, the solid curve is the (12,6) LJ potential for model II and the dotted curve is the (8,5) LJ potential for model III.

$p = 5$) and ($q = 12$, $p = 11$) and shown together with the (12,6) LJ potential in Fig. 1.

The well depth and the position of the minimum of $V(r)$ are unchanged, and we have kept the standard (12,6) LJ potentials of the K–A model for the A–B and B–B interactions, in order to retain as much as possible the remarkable ability of the K–A model to form a glass upon cooling. The (12,11) LJ potential is more harmonic than the classical (12,6) LJ potential, while the (8,5) LJ potential is a flat well and exceedingly anharmonic. Anharmonicity is not defined using the usual prefactor of the cubic term of a Taylor expansion of the potential close to its minimum. We define anharmonicity as the width of the well at $V(r) = -0.5$ in order to take into account the shape of the potential, i.e., the long range interaction of the potential. Whenceforth the (12,11), (12,6) and (8,5) potentials are referred to as Model I, II and III, respectively, reminding us that anharmonicity is increasing in this order.

3. Checks of some MCT predictions

Model II is the well-documented and classical K–A model known for forming a glass when cooled down [10,11]. Since no data were available for Models I and III, we have determined some basic properties of both models aiming to show they were able to exhibit the classical features of supercooled liquids as displayed by model II. From the results at various temperatures for the three models, we have estimated T_A , the onset temperature of non-exponential time dependence and non-Arrhenius relaxations [18], and T_C , the critical temperature of the mode-coupling theory (MCT) [14]. We have also determined the limiting temperature T_{VFT} of the Vogel–Fulcher–Tamman (VFT) fit of τ_A , the α relaxation time of species A.

In the pico-nanosecond regime, two remarkable temperatures have been pointed out by molecular dynamics simu-

Table 1
Parameters of the Lennard-Jones potentials that describe the three types of interactions in the Kob–Andersen model [10,11]

Interaction	A–A	A–B	B–B
$\varepsilon = \frac{E_0}{6}$	1.0	0.50	1.5
$\sigma = \frac{r_0}{2^{1/6}}$	1.0	0.88	0.8

lations [18,19] on glass-forming liquids: (i) T_C , the critical temperature predicted by MCT where a dynamical decoupling is expected. T_C also marks the crossover to the ‘landscape-dominated’ regime and (ii) T_A , the temperature associated with the onset of non-exponential and non-Arrhenius relaxations [18] where the dynamics of the system has been identified as ‘landscape-influenced’. In the $[T_C - T_A]$ temperature range, correlation functions exhibit a long and almost flat plateau-like region which reveals the existence of a cage effect associated to fluctuations of particles around their equilibrium position separated by jumps [16]. We have checked the slowing down of the dynamics of the three models according to the predictions of MCT [14]. We have calculated the self-intermediate scattering function $F_S(Q_0, t)$ at $Q_0 = 2\pi/r_0$ where r_0 is the position of the maximum of the first peak of the radial distribution function. Then, we have determined a long relaxation time τ corresponding to the α process, when the correlator $F_S(Q_0, t)$ has decayed by a factor of e^{-1} from the plateau-like region. At high temperatures, the α relaxation time can be well fitted with an Arrhenius law $\tau(T) = \tau_0 \exp(T_0/T)$ where the parameters (τ_0, T_0) allow us to calculate the temperature dependent activation energy $E(T) = T/T_0 \log(\tau/\tau_0)$. From the evolution of $E(T)$ relative to T , we can extract the crossover temperature T_A defined previously, when the activation energy diverges from one (Fig. 2).

In the MCT framework, a two-step relaxation scenario (fast β , slow α) of all the time dependent correlators is predicted. At short times especially, MCT predicts that all correlators decay to a plateau value, the so-called non-ergodicity parameter $f_S(Q_0, T)$. Above T_C , the late β regime or the early α relaxation can be described by the classical von Schweidler law $F_S(Q, t) = f_S(Q, T) - h(Q)^{(1)} (t/\tau)^b$ where $\tau \propto (T - T_C)^{-\gamma}$. The parameters γ and b are temperature and Q independent and are linked to each other by the relations $\gamma = 1/2a + 1/2b$ and $\Gamma^2(1 - a)/\Gamma(1 - 2a) = \Gamma^2(1 - b)/\Gamma(1 - 2b)$ where $\Gamma(x)$ is the gamma function. In order to check the validity of those scaling

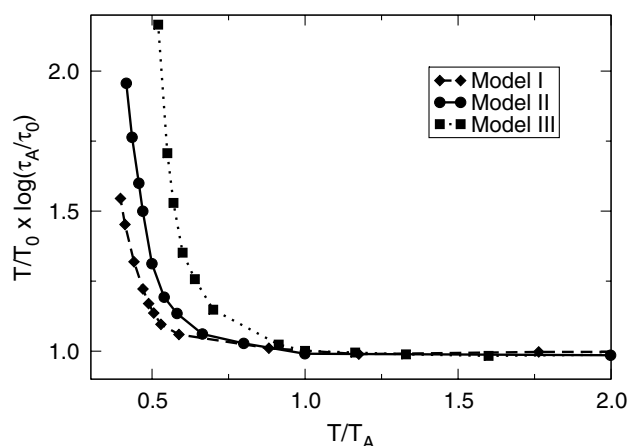


Fig. 2. Temperature dependent activation energy $E_A(T)$ of species A as a function of T/T_A for Model I (♦), Model II (●) and Model III (■).

laws, we have first determined the exponent b from the master-curve of $F_S(Q_0, t)$. Another method would consist in using the factorization theorem in the β regime as described in [20]. Knowing b , we have deduced a , leading to a value for the exponent γ . Once γ is known, we have fitted the α relaxation times $\tau(T)^{-1/\gamma}$ by a linear law of the form $(T - T_C)$ in order to get the critical temperature T_C of MCT. This linear behavior, only valid close to T_C , is shown in Fig. 3 for the three studied systems.

Data collected from the analysis of the three studied models are given in Table 2. Since the different characteristic temperatures cannot be directly compared, we calculated the temperature ratio T_A/T_C and T_{VFT}/T_C for the different models.

$T_A/T_C = 2.44, 2.3$ and 1.9 are found for Model I, II and III, respectively. Thus, this ratio decreases as anharmonicity increases and it reveals that the onset of collective slow dynamics require a higher temperature for the more harmonic system. Indeed, Model I has a very harmonic intermolecular potential constraining the particles to move locally around their positions so that it is very difficult to

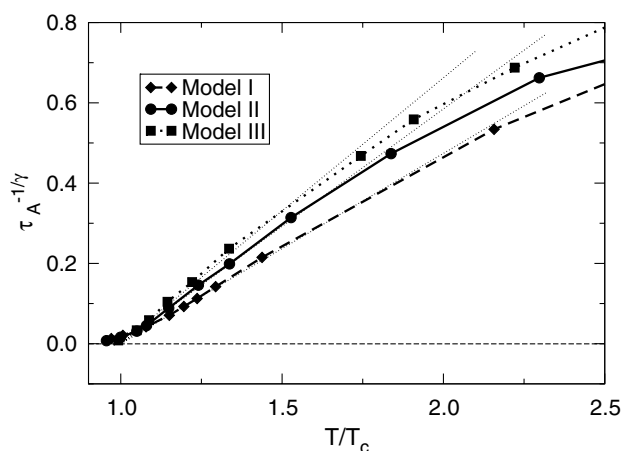


Fig. 3. α relaxation time $\tau^{-1/\gamma}$ of species A versus T/T_C . Data can be fitted with a straight line $\sim(T/T_C - 1)$ for Model I (♦), Model II (●) and Model III (■).

Table 2

Data obtained for the three studied models (I, II and III)

	Model I	Model II	Model III
(q, p)	12-11	12-6	8-5
(τ_0, T_0)	(0.127, 5.890)	(0.169, 2.982)	(0.167, 1.591)
γ from τ_A	2.62	2.51	2.38
γ from D_A	2.12	1.91	1.65
T_A	1.7	1.0	0.5
T_C	0.695	0.435	0.262
T_{VFT}	0.446	0.311	0.215

(τ_0, T_0) taken for the Arrhenius laws, the onset temperature of slow dynamics T_A , the MCT critical temperature T_C , the limiting temperature T_{VFT} in a Vogel–Fulcher–Tamman (VFT) fit of the α relaxation time of species A, and the exponent γ used in a power law fit of either the α relaxation time of species A or the diffusion coefficient of species A. We can notice that these two γ exponents are not equal, which is a consequence of the breakdown of the Stokes–Einstein relation [16].

relax the system in a collective way. On the contrary, Model III characterized by an extremely flat (anharmonic) potential favors intermolecular coupling and relaxations so that even at low temperatures, the system can still relax and exhibits a dynamical behavior of a supercooled liquid. The glass transition of Model III is only reachable at very low temperatures. Model II is the intermediate case. The ratio T_{VFT}/T_C can be used as an estimation of the fragility, inspired by Refs. [21–23]. In the present study, we obtained 0.642, 0.715 and 0.821 from Model I to Model III, respectively. Therefore, it indicates that fragility increases as anharmonicity increases. This behavior is consistent with our previous findings [9] on the behavior of the fragility directly determined from the slope of τ at T_{ref} or based on Sastry's method [7].

Moreover, it is clear that γ obtained either from τ_A or D_A decreases from Model I to Model III, i.e., γ decreases as anharmonicity increases. Moreover, γ exponents extracted from the α relaxation time or the diffusion coefficient are found different. This result is a direct consequence of the breakdown of the Stokes–Einstein relation [16] at $T = T_A$.

4. Temperature dependence of the non-exponential relaxation

From the self-intermediate scattering functions $F_S(Q_0, t)$ and τ_A at different temperatures for the three models, we can plot a master-curve obtained from the superposition of $F_S(Q_0, t/\tau_A)$ in the long time regime. The master-curve of Model III is displayed in Fig. 4.

Upon lowering the temperature from the normal liquid state, we observe that the self-intermediate scattering functions progressively collapse onto an apparent master curve. However, a detailed view of this thick curve reveals that the different functions do not strictly superpose. Therefore, it is only approximatively possible to extract a temperature independent stretched exponent β using a Kohlrausch–Wil-

liams–Watt (KWW) fit of the master curve in a restricted temperature range.

The same also stands for Models I and II. We have obtained $\beta = 0.84$, 0.81 and 0.76 for Models I, II and III, respectively. The error bar is about 0.1 due to the thickness of the master-curve.

Since a strict superposition of $F_S(Q_0, t/\tau_A)$ functions does not hold, it is interesting to consider a temperature dependent stretched exponent β which is displayed in Fig. 5. β is observed to continuously decrease from one at high temperatures to 0.69, 0.65 and 0.60 at very low temperatures below T_C for Models I, II and III, respectively. Moreover, β obtained from Model I is always found higher than β of Model II, itself higher than β of Model III. Therefore, the stretched exponent β decreases as anharmonicity increases. This behavior indicates that the anharmonicity of the intermolecular potential significantly controls the long range interactions between particles and therefore their collective relaxations. This result strongly supports the idea developed in the coupling model [5] that the intermolecular coupling measured by the parameter $n = 1 - \beta$ controls relaxations in liquids. We can stress this latter point with Fig. 6, which shows the value of the fragility m estimated from different definitions for the three models identified by the intermolecular coupling parameter $n = 1 - \beta$.

Whatever the definition used to calculate the fragility m , Fig. 6 shows that m of Model I is smaller than m of Model II, itself smaller than m of Model III, and that the increase of m is in relation with the increase of n . Moreover, before concluding, we observe the same trend for the fragility m determined from method (3). It is then important to note that the parameter n , which is a measure of the intermolecular coupling due to the anharmonicity of the interaction potentials also controls the short time dynamics observed via the non-ergodicity parameter f below T_{ref} . This point

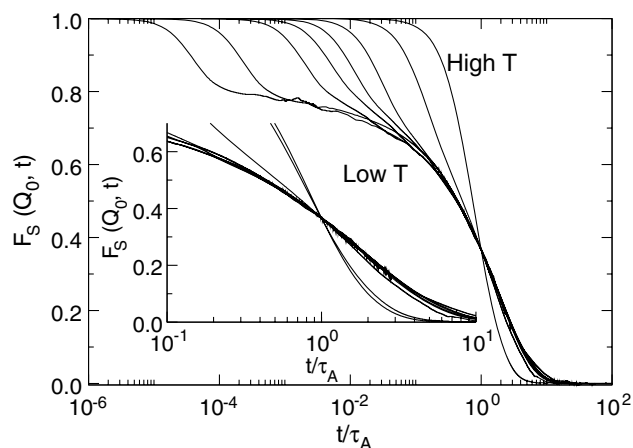


Fig. 4. Check of the superposition principle of the self-intermediate scattering functions $F_S(Q_0, t/\tau_A)$ for Model III. A detailed view is given in the inset.

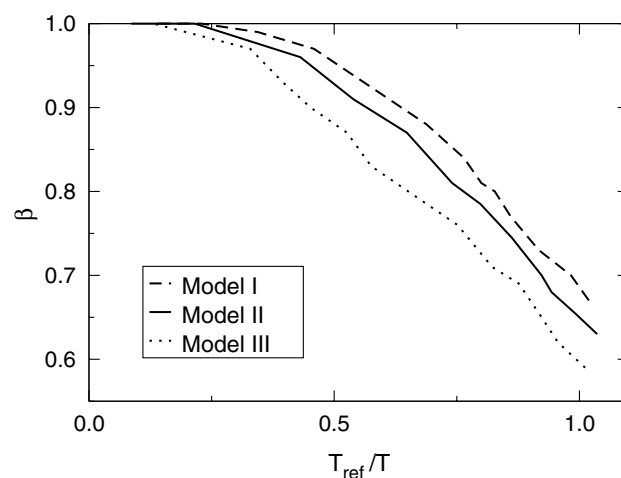


Fig. 5. Temperature dependent stretched exponent β as a function of T_{ref}/T for Model I (dashed line), Model II (solid line) and Model III (dotted line). T_{ref} is an arbitrary temperature defined as the temperature for which $\tau_A = 46435.8$.

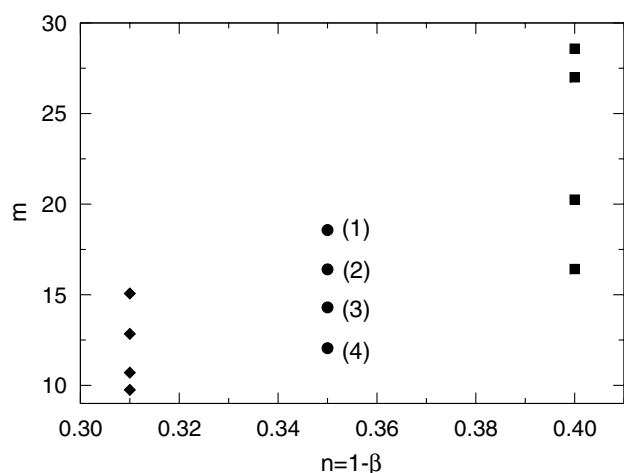


Fig. 6. Fragilities calculated by different methods for Model I (♦), Model II (•) and Model III (■). (1) is obtained from Eq. (1) in the text; (2) corresponds to the ratio $(T_{VFT}/T_C) \times 50$; (3) is the result of $\frac{d \log f}{dT} \big|_{T=T_g}$ multiplied by 100, where f is the temperature dependant non-ergodicity parameter determined at different temperatures below T_{ref} in the non-equilibrium state identified as a numerical glassy state and (4) is obtained from Sastry's method [7] and multiplied by 20.

is detailed in Ref. [9]. So, the shape of the interaction potential and particularly its anharmonicity is the key parameter to understand the long time relaxations in super-cooled liquids, the vibrations in glasses and to link them together.

5. Conclusion

We have demonstrated that three Lennard-Jones systems differing only in the anharmonicity of the interaction potential exhibit dynamical properties which can be interpreted and predicted by MCT. Indeed, we have identified a critical temperature T_C , an onset temperature T_A . We have also shown that the α relaxation time and the diffusion coefficient follow a power law in the vicinity of T_C in agreement with MCT. All these characteristics have been confirmed for the three models. However, we can notice some deviations to MCT, particularly in the temperature behavior of the stretched exponent β . While MCT predicts

a temperature independent β , we have pointed out that a more complete description of the dynamical slowing down has to consider a temperature dependent β .

Acknowledgments

The authors wish to thank for the use of the computational facilities of the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France). This work was supported by the INTERREG III (FEDER) program (Nord-Pas de Calais/Kent). Work at NRL was supported by the Office of Naval Research.

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Chapitre 2

Action bioprotectrice des sucres

2.1 Contexte

L'amélioration de la stabilité des matériaux biologiques est l'un des principaux objectifs des industries pharmaceutiques et biotechnologiques [76; 77]. Les peptides et protéines d'intérêt thérapeutique constituent maintenant plus de 20% du Top 200 des meilleures ventes de médicaments mondiales (40 milliards de \$ en 2004). La découverte de nouvelles biomolécules thérapeutiques ne débouche cependant pas, le plus souvent, sur des applications cliniques car celles-ci sont particulièrement labiles. L'activité biologique de la plupart de ces matériaux, qui se présentent généralement en solution aqueuse, décroît en effet très rapidement au cours du temps ce qui limite leur temps de vie et leur utilité pratique dans les applications thérapeutiques ainsi que dans leur manipulation.

La lyophilisation est un procédé coûteux mais courant de conservation à l'état solide des matériaux biologiques complexes et fragiles. Elle est généralement décrite en plusieurs étapes de refroidissement et de séchage au cours desquelles la biomolécule peut être dégradée : dénaturation froide, forte variation de pH, perte de l'eau d'hydratation, formation de cristaux de glace. Des additifs protecteurs (disaccharides, polyols, polymères) dont les mécanismes d'action demeurent encore peu clairs sont utilisés afin de palier aux contraintes rencontrées.

La mise en oeuvre du procédé de lyophilisation nécessite en fait un parcours complexe dans le diagramme de phase impliquant l'eau, les biomolécules, et des additifs bioprotecteurs. L'optimisation de l'ensemble des processus mis en jeu et la conservation du lyophilisat sur de longues périodes sont des problèmes majeurs de l'élaboration des protocoles de lyophilisation. C'est aussi un concentré de problématiques physiques riches à l'interface de la biologie et la chimie : transformation d'états, comportement hors équilibre (vitrification), polyAmorphisme, confinement. Les changements de comportement de la biomolécule sont par exemple analogues aux problèmes de transformation d'états (transition vitreuse, transition dynamique, transition polyamorphique liquide-liquide) qui sont des thèmes de recherche très actifs de la physique des systèmes hors-équilibre (voir chapitre précédent).

Afin de palier aux contraintes rencontrées pendant et après la lyophilisation, on utilise,

de manière encore empirique, deux types d'additifs : les cryoprotecteurs et lyoprotecteurs qui sont principalement des matériaux moléculaires formateurs de verre. Les seuls matériaux reconnus comme étant efficace pour protéger les biomatériaux contre ces deux sources de contraintes sont les disaccharides, dont le tréhalose est souvent désigné comme étant le plus efficace sous des conditions extrêmes de déshydratation et de refroidissement [78; 79]. Il faut noter que ces agents protecteurs - en particulier le tréhalose ou le sucrose - sont aussi présents en grande quantité dans le milieu cellulaire de certains organismes (spores, plantes, insectes, grenouilles,...) capables de survivre dans des milieux où les conditions de sécheresse et de température sont particulièrement défavorables. La nature précise de leurs mécanismes d'action demeure mal comprise et en particulier l'origine moléculaire de l'efficacité du tréhalose par rapport aux autres mono- et polysaccharides.

Plusieurs « modèles » ont été proposés afin d'expliquer au niveau microscopique ces mécanismes de bioprotection mais aucun n'est unanimement accepté car ils ne décrivent en général qu'un domaine limité de température et d'hydratation.

Pour de forts taux d'hydratation, il a été proposé que les protéines peuvent être stabilisées par « l'exclusion préférentielle » des protectants de leur surface [22] qui défavorise thermodynamiquement l'augmentation de la surface accessible au solvant (SASA) à la dénaturation. Cette exclusion pourrait provenir d'effets de volume exclu et d'augmentation de la tension de surface de l'eau induite par les protectants. S. Magazu [23] a suggéré d'autre part une déstructuration du réseau tétraédrique de l'eau par les protectants et en particulier les sucres. La présence de ces sucres perturberait le réseau tétraédrique des liaisons hydrogènes de l'eau, empêchant ainsi la formation de la glace au cours d'un refroidissement au profit d'une structure amorphe d'un liquide sous-refroidi. Le tréhalose possède un nombre d'hydratation (voir section 2.2.1) plus important que d'autres disaccharides comme le sucrose ou le maltose et serait donc plus exclu de la surface de la protéine et plus efficace à perturber le réseau tétraédrique de l'eau. Ces deux modèles ne fournissent cependant qu'une explication partielle car ils ne considèrent que les situations où la concentration en eau est importante.

Pour des concentrations en eau plus faibles selon l'hypothèse par Green et Angell [20], le solvant (sucre et eau résiduelle) dans lequel sont placés les biomatériaux pourrait vitrifier : on aurait alors une situation analogue à l'image de l'ambre qui emprisonne les insectes. L'efficacité du tréhalose serait due à sa température de transition vitreuse particulièrement élevée ($T_g \sim 120^\circ \text{C}$) proche de celle des tétrasaccharides. Des matrices avec un T_g plus faible (mélange glycerol-trehalose) [80] forment cependant de meilleurs protecteurs et d'autres avec un T_g plus haut (Dextran, PVP) sont moins efficaces. Des interactions spécifiques (liaisons OH), encore mal identifiées, entre le bioprotecteur et la bio-molécule ou via l'eau d'hydratation semblent donc nécessaires. Un modèle proposé par J. Crowe [81] suggère que les molécules de sucres se substitueraient lors de la déshydratation aux molécules d'eau autour de la molécule biologique afin de préserver le réseau de liaisons hydrogènes nécessaire avec la biomolécule pour stabiliser sa structure tridimensionnelle. Cependant, on ne comprend pas dans ce modèle comment certaines molécules d'eau situées dans la structure interne de certaines protéines (myoglobine) pourraient être remplacées.

En accord avec l'hypothèse d'hydratation préférentielle [22], Belton et Gil [82] ont aussi

avancé que l'interaction directe entre la matrice formée principalement de protectant et la biomolécule serait très limitée et qu'il subsisterait une couche d'eau non-cristallisée autour de la protéine. Lins *et al.* [83] ont confirmé ce point de vue et observé par simulation MD que les molécules de tréhalose s'agrégeaient et piégeaient une fine couche d'eau dans un état confiné dans le voisinage de la protéine. Une autre hypothèse émise par A. Cesàro *et al.* [84] évoque le rôle possible de la formation du cristal de tréhalose dihydrate et de sa transformation réversible en un état anhydre (phase α) lors de la déshydratation. Celle-ci n'induirait pas de changement important de volume ou de pression dans les cellules comme observé pour la glace.

Il est vraisemblable que les diverses hypothèses évoquées ci-dessus soient partiellement vérifiées dans une certaine gamme de température et/ou de degré d'hydratation lors d'un processus de refroidissement-déshydratation et que plusieurs de ces hypothèses restent partiellement valables une fois le processus terminé. D'ailleurs, des résultats récents de diffusion neutronique [80] laissent penser que ces deux grandes catégories d'hypothèses ne sont pas mutuellement exclusives. En effet, ils montrent qu'une matrice de tréhalose pur n'assure pas nécessairement un meilleur degré de protection des biomolécules que certains mélanges glycérol-tréhalose dont la température de transition vitreuse T_g est inférieure. Ceci prouve l'importance des interactions spécifiques dans le phénomène de bioprotection.

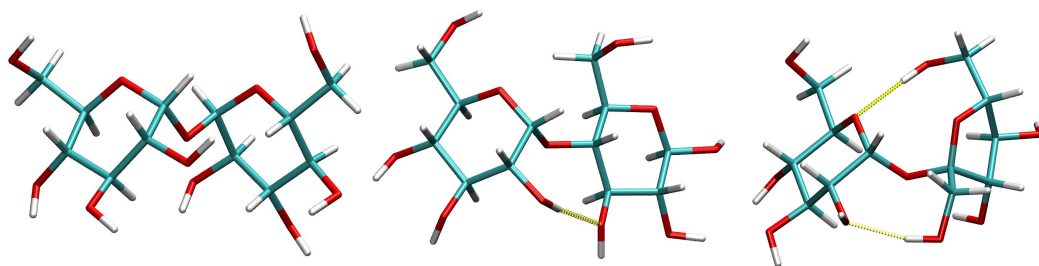


FIG. 2.1 – Molécule de tréhalose, maltose et sucrose (de gauche à droite). Les liaisons hydrogènes intramoléculaires sont aussi indiquées par des traits jaunes.

Afin de clarifier les mécanismes physiques de la bioprotection, nous avons réalisé pendant la thèse d'A. Lerbret et les séjours postdoctoraux de P. Bordat et F. Migliardo une investigation par modélisation moléculaire et diffusion neutronique de l'action de trois disaccharides homologues tréhalose, sucrose et maltose (voir figure 2.1) à différentes concentrations et températures ainsi que leur interaction avec une protéine modèle le lysozyme. Ces travaux furent couplés à des investigations Raman réalisées en parallèle au laboratoire (collaboration A. Hédoux).

Les bioprotecteurs étudiés sont des composés de la famille des disaccharides et il est généralement reconnu que le tréhalose est l'un des plus efficaces. L'étude de composés de la même famille comme le sucrose ou le maltose (d'efficacité différente) de même formule chimique $C_{12}H_{22}O_{11}$ mais de conformation différente, permet apporter des informations importantes sur les mécanismes de bioprotection et les propriétés physiques de ces matériaux directement impliquées dans ces mécanismes. Le choix du lysozyme comme protéine

modèle a été motivé par sa petite taille accessible à la simulation MD, sa structure expérimentalement connue et de sa très grande stabilité car elle est majoritairement composée d'hélices alpha. De plus, sa fluorescence raisonnable dont la contribution au spectre de vibration peut être facilement extraite permettait aussi des investigations en diffusion Raman.

2.2 Mélanges binaires sucre/eau

Nous avons mené une étude comparative des disaccharides tréhalose, sucrose et maltose en solution aqueuse par dynamique moléculaire et diffusion neutronique. Nous nous sommes intéressés à la structure et la dynamique des solutions eau/sucre : interactions sucre-eau et sucre-sucrose. Notre but était de mettre en évidence des paramètres pertinents capables de différencier les effets du tréhalose de ceux de ses homologues dans le but de comprendre les mécanismes moléculaires à l'origine de la bioprotection.

2.2.1 Interactions sucre/eau

La figure 2.2 montre une comparaison des facteurs de structure statique $S_{XX}(Q)$ des solutions sucre/eau à 49% et de l'eau pure obtenus expérimentalement et par simulation MD. On observe un assez bon accord entre l'expérience et la simulation MD qui confirme que les calculs réalisés fournissent une idée globalement réaliste de la structure des mélanges. Une analyse précise de la perturbation du réseau de liaisons hydrogènes de l'eau en présence des sucres est difficile. Il apparaît cependant assez clairement une contribution à $Q \simeq 0.6^{-1}$ pour les solutions sucre/eau où la contribution de l'eau est faible qui peut être associée aux distances intermoléculaires entre sucres. Cette contribution aux petits vecteurs d'onde suggère des associations sucre-sucrose (agrégats) dans les différents mélanges qui seront confirmées par la suite dans la section sur l'homogénéité des solutions.

Les molécules de tréhalose, maltose et sucrose possèdent la même formule chimique $C_{12}H_{22}O_{11}$ et le même nombre de groupes hydroxyles : 8. Le nombre moyen de molécules d'eau liées par liaison hydrogène à chaque sucre - appelé nombre d'hydratation n_H par la suite - fournit un paramètre intéressant pour quantifier les interactions sucre/eau. Ce paramètre est représenté sur la figure 2.3. On observe que n_H décroît nettement avec la concentration en sucre. Pour les forts taux d'hydratation, chaque molécule de sucre est entourée de plusieurs couches d'hydratation et leur structure est principalement influencée par leur interaction avec l'eau. Lorsque la concentration en sucre augmente, les disaccharides commencent à partager les mêmes molécules d'eau et forment des liaisons hydrogènes entre eux. Ce dernier point sera discuté dans la section suivante. A partir des résultats de la figure 2.3, on constate clairement que le tréhalose est plus hydraté que le sucrose ou le maltose à toutes les concentrations étudiées. Il se lie donc à plus de molécules d'eau que les autres sucres et perturbe la structure native de l'eau de manière plus importante. La différence observée entre les différents sucres est faible mais significative. En effet, cette tendance pour le tréhalose est confirmée sur deux modèles d'eau différents SPC/E et TIP3P (ce

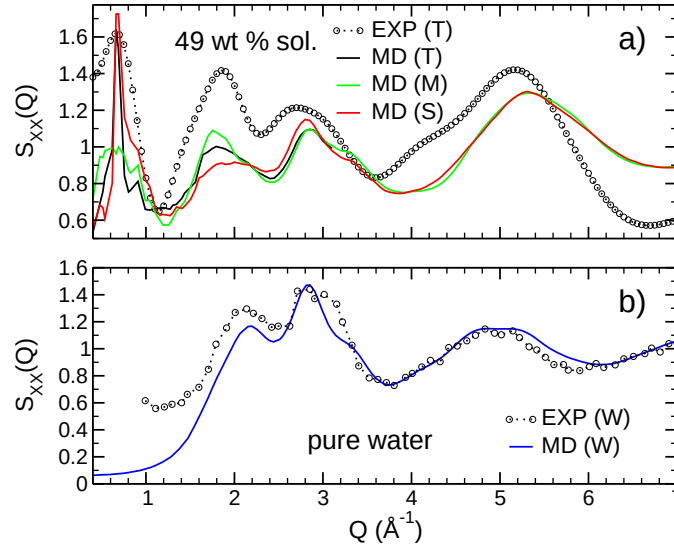


FIG. 2.2 – *Facteur de structure partiel $S_{xx}(Q)$ excluant les atomes d'hydrogène pour les solutions sucre/eau (concentration 49%) à la température $T = 293$ K obtenu par simulation MD et par diffraction neutronique [85; 86] (a). Les résultats pour l'eau pure sont aussi indiqués pour comparaison [87] (b).*

dernier formant des liaisons hydrogènes plus faibles que SPC/E) ainsi que par les valeurs numériques et expérimentales trouvées dans la littérature (voir tableau 2.1).

Une explication des différences observées pourrait provenir du nombre de liaisons hydrogènes intramoléculaires possibles pour chaque sucre : deux pour le sucrose, une pour le maltose et aucune pour le tréhalose sont observées dans leur structure cristalline respective. Le tableau 2.1 présente une statistique des liaisons hydrogènes intramoléculaires moyennes pour chaque sucre et confirme ce résultat.

Le réseau de liaisons hydrogènes de l'eau peut être décrit par la fraction de molécules d'eau f_j liée par 1,2,..., j liaisons hydrogènes avec les molécules d'eau voisines. En assumant que la probabilité de former une liaison hydrogène est non coopérative et que le nombre de coordination de l'eau est 4, Stanley et Teixeira [88] ont montré que la fraction f_j pouvait s'écrire :

$$f_j = \binom{4}{j} \cdot p_{HB}^j \cdot (1 - p_{HB})^{4-j} \quad (2.1)$$

où p_{HB} est la probabilité de former une liaison hydrogène. La figure 2.4a représente p_{HB} en fonction de la concentration en disaccharides. La décroissance observée provient principalement de la substitution des liaisons hydrogènes eau-eau par les liaisons eau-sucre. Une conséquence directe est que l'évolution de p_{HB} est contrôlée par le nombre d'hydratation n_H de chaque sucre : p_{HB} diminue plus en présence de tréhalose qu'en présence des autres sucres. Ce résultat est clairement confirmé sur la figure 2.4b lorsqu'on exclut les molécules d'eau de la première couche d'hydratation. Dans ce cas, la variation de p_{HB} en fonction de

la concentration en sucre est beaucoup plus faible et l'on ne peut presque plus distinguer des différences entre les trois sucres.

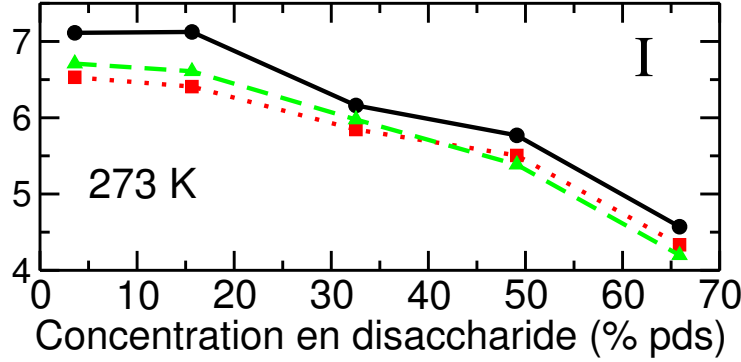


FIG. 2.3 – Nombre d'hydratation n_H du tréhalose (trait noir), maltose (trait vert) et sucrose (trait rouge) en fonction de leur concentration à $T = 293$ K. On suppose que deux molécules sont liées par liaison hydrogène si la distance entre deux atomes d'oxygène est inférieure à 3.4 Å et que l'angle $O-H \cdots O$ est plus grand que 160 deg.

n_H	SPC/E	TIP3P	Autres MDs	Expérience
Tréhalose	6.5 (I) 16.4 (II)	6.1 (I) 16.8 (II)	7.8[89],13.4[90],18.9[91] 22.5[94],27.5[89]	7.95[92],10.9[93],12.1[23] 15.2[23],15.3[95]
Maltose	6.5 (I) 16.1 (II)	5.7 (I) 16.1 (II)	10-11[96], 22.6[97]	6.50[92],9.5[93],11.7[23] 14.2[23],14.5[95]
Sucrose	6.2 (I) 14.8 (II)	5.6 (I) 15.1 (II)	7.0[98], 11.7[99], 24.7[98]	6.33[92], 8.5[93], 11.2[23] 13.8[23], 13.9[95]

TAB. 2.1 – Nombre d'hydratation n_H du tréhalose, maltose et sucrose calculé à partir des modèles SPC/E et TIP3P de l'eau à $T = 293$ K. Les valeurs de n_H obtenues à partir d'autres simulations MD et de mesures expérimentales (acoustiques [95; 23], viscosité [23] et calorimétriques [92; 93]) sont aussi indiquées pour comparaison.

Le paramètre d'ordre q proposé par Debenedetti *et al.* [100] dans le cadre de l'eau pure quantifie la déviation de l'arrangement d'une molécule d'eau donnée et ses quatre plus proches voisins au réseau tétraédrique parfait. Il est défini par la relation :

$$q = 1 - \frac{3}{8} \sum_{j=1}^3 \sum_{k=j+1}^4 \left(\cos(\Psi_{j,k}) + \frac{1}{3} \right)^2, \quad (2.2)$$

où $\Psi_{j,k}$ correspond à l'angle formé par les lignes joignant l'atome d'oxygène d'une molécule donnée à ceux des j^{eme} et k^{eme} plus proches voisins. Pour un réseau tétraédrique parfait, $q = 1$. Pour un arrangement aléatoire avec des distributions angulaires uniformes non

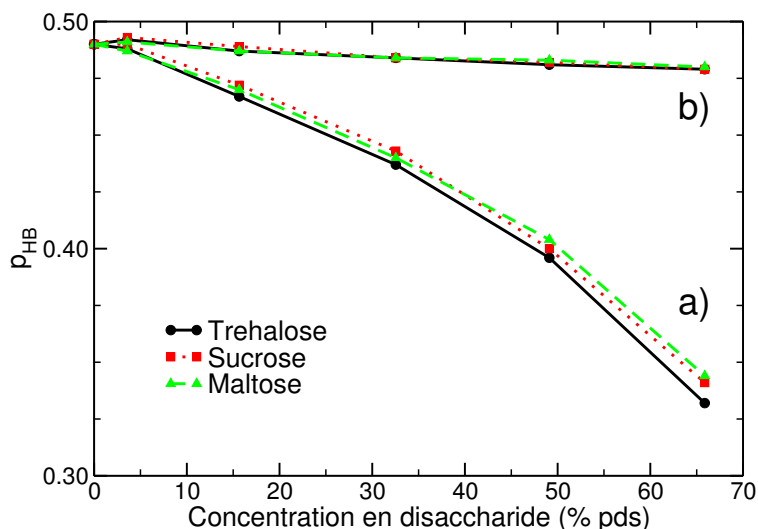


FIG. 2.4 – Probabilité p_{HB} de former une liaison hydrogène entre molécules d'eau en fonction de la concentration en sucre : a) toutes les molécules d'eau sont prises en comptes, b) les molécules d'eau de la première couche d'hydratation sont exclues.

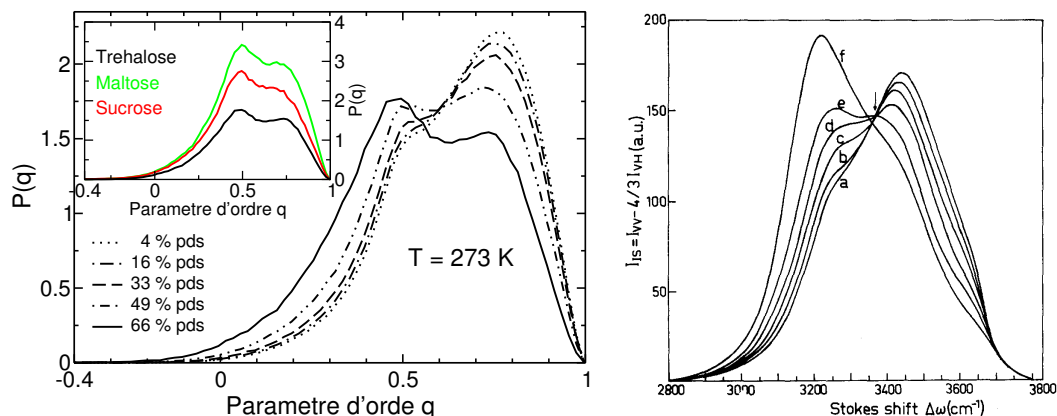


FIG. 2.5 – Gauche : Distributions du paramètre d'ordre q [100] des molécules d'eau non liées par liaisons hydrogènes au tréhalose pour différentes concentrations massiques (%) à $T = 273$ K. L'inset représente les distributions des trois solutions de disaccharides pour une concentration de 66 % à $T = 273$ K. Les courbes du sucrose et maltose ne sont pas normalisées dans le but de montrer l'influence des nombres d'hydratation. Droite : Le spectre Raman de la bande O-H à différentes températures 368 K (a), 353 K (b), 333 K (c), 313 K (d), 293 K (e) et 259 K (f) extrait de [101] est aussi indiqué pour comparaison.

corrélées, $q = 0$. Dans le cas de solutions mixtes, les molécules d'eau dans le proche voisinage des sucres ne peuvent pas adopter un arrangement tétraédrique régulier - surtout aux hautes concentrations - pour des raisons stériques évidentes. Ces molécules d'eau n'ont donc pas été prises en compte dans l'analyse du paramètre q . La distribution du paramètre q des solutions tréhalose/eau pour différentes concentrations à $T = 273$ K est tracée sur la figure 2.5. A basse concentration, la distribution de q présente deux pics, similaires à ceux de l'eau pure à basse température. Le pic au grand q correspond aux molécules d'eau structurées (semblables à de la glace), tandis que le pic à faible q repère l'eau déstructurée. Lorsque la concentration augmente, le pic au grand q décroît en faveur du pic à faible q . Cette tendance devient significative pour des concentrations supérieures à $\phi_A \simeq 40$ %. Cette tendance est analogue à celle observée pour l'eau pure lors d'une augmentation de température [100].

La figure 2.5 rappelle naturellement le spectre Raman de bande O-H obtenu en fonction de la température où la présence d'un point isobestique fut mis en évidence [101]. De ce résultat, plusieurs auteurs ont proposé une décomposition des molécules en deux classes : « open » et « closed ». Les premières associent les molécules d'eau présentant une structure tétraédrique tandis que les autres représentent les molécules d'eau libres ou avec des géométries déformées.

Les résultats obtenus sur le paramètre q sont en bon accord avec les travaux Raman réalisés par Magazù *et al.* [102] qui ont montré que l'ajout de sucres augmentait les contributions « closed » au profit des contributions « open ». Contrairement à ces travaux [102], la comparaison de la distribution de q pour les trois disaccharides (voir l'inset de la figure 2.5) ne révèle cependant pas de différence nette entre les trois sucres, suggérant que, en moyenne, les molécules d'eau adoptent des configurations semblables dans les trois solutions. Pourtant, le nombre de molécules d'eau formant une liaison hydrogène avec le tréhalose (proportionnel à l'aire totale de la courbe) est clairement réduit par rapport à celui avec le sucrose et le maltose. On peut alors dire que le tréhalose est plus apte à perturber le réseau tétraédrique de liaisons hydrogènes que le sucrose et le maltose en raison de son hydratation supérieur en bon accord avec le modèle proposé par S. Magazù [23].

2.2.2 Interactions sucre/sucre - Homogénéité des solutions

Pour les hautes concentrations en sucre, le nombre de liaisons hydrogènes intermoléculaires sucre-sucre augmente considérablement comme indiqué dans le tableau 2.2. Des différences significatives apparaissent entre les sucres. Le sucrose forme le moins de liaisons intermoléculaires alors que le maltose en forme le plus. Le tréhalose présente un comportement intermédiaire. Cette tendance suggère la formation d'agrégats de molécules de sucres de tailles différentes pour les trois sucres. Afin de mettre en évidence ce comportement, nous avons défini un agrégat comme un certain nombre de molécules de sucres n_S liées entre elles par au moins une liaison hydrogène. La figure 2.6 représente la taille moyenne de ces agrégats en fonction de la concentration en sucre. Pour les faibles concentrations (20-30%), $\langle n_S \rangle / N_S$ reste constant et indique que de petits agrégats peuvent apparaître dont la taille est directement proportionnelle au nombre de sucres. A plus haute concen-

tration, la taille des agrégats $\langle n_S \rangle / N_S$ augmente fortement jusqu'à la valeur de 1 où tous les sucres appartiennent au même agrégat et où il y a percolation du réseau hydrogène des sucres. Des différences de comportement entre les sucres sont clairement visibles (figure 2.6). La taille des agrégats de molécules de sucrose est plus petite que les deux autres sucres. Une explication pourrait être sa capacité à former des liaisons intramoléculaires : un plus grand nombre de molécules de sucrose par rapport au maltose ou au tréhalose est nécessaire pour atteindre une certaine taille d'agrégat. La situation est opposée pour le maltose qui forme des agrégats de grandes tailles. La figure 2.6 indique un comportement intermédiaire pour le tréhalose qui pourrait provenir de sa capacité à former des liaisons hydrogènes préférentiellement avec l'eau.

La capacité des différents sucres à interagir avec les autres sucres ou avec l'eau apparaît primordiale pour « l'homogénéité » des solutions. Le dessin schématique de la figure 2.7 résume notre étude sur la structure des mélanges binaires sucre/eau. Elle suggère que le tréhalose serait capable de former des matrices plus « homogènes » que le sucrose ou le maltose. Le tréhalose pourrait former des agrégats de grandes tailles tout en maintenant un nombre d'hydratation supérieur aux autres sucres. De cette manière un nombre faible de molécules d'eau resterait in affecté par la présence de ce sucre : la probabilité de formation de glace et les contraintes engendrées par la perte d'eau pendant la déshydratation seraient réduites. Les autres solutions (sucrose/eau et maltose/eau) apparaissent plus inhomogènes. Pour le sucrose, sa forte probabilité de former des liaisons intramoléculaires, réduit sa capacité à interagir avec l'eau ou les autres molécules de sucres. Le maltose possède une forte tendance à interagir préférentiellement avec les autres molécules de maltose et à former des agrégats de grandes tailles qui l'empêche d'interagir aussi efficacement que le tréhalose avec l'eau. Des calculs MD réalisés sur les systèmes ternaires myoglobine/sucre/eau par Cottone *et al.* à forte concentration en sucre semblent confirmer cette hypothèse sur l'homogénéité des matrices sucre/eau. Cette investigation MD motive clairement une étude expérimentale de la nanostructure de ces solutions pendant une cinétique de déshydratation afin de valider les résultats.

ϕ (pds %)	$\langle n_{HB} \rangle_{inter} / N_S$			$\langle n_{HB} \rangle_{intra} / N_S$		
	T	M	S	T	M	S
4	0.000	0.000	0.000	0.304	0.739	2.490
16	0.153	0.361	0.266	0.146	0.455	1.962
33	0.767	0.853	0.435	0.141	0.373	2.058
49	1.322	1.942	0.738	0.451	0.346	2.210
66	2.689	2.985	2.293	0.175	0.400	1.979

TAB. 2.2 – Nombre de liaisons hydrogènes inter- $\langle n_{HB} \rangle_{inter} / N_S$ et intramoléculaire $\langle n_{HB} \rangle_{intra} / N_S$ pour les différentes solutions eau/sucre (Tréhalose, Maltose et Sucrose) à $T = 293$ K. ($\langle \rangle$ indique une moyenne sur le temps et N_S le nombre de molécules de sucre).

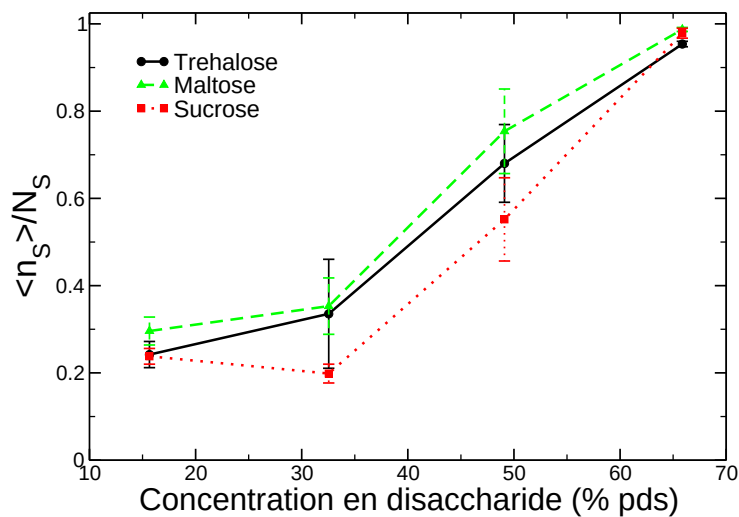


FIG. 2.6 – Dépendance en fonction de la concentration de la taille moyenne des agrégats de sucre $\langle n_s \rangle / N_s$. Un agrégat consiste en un certain nombre de molécules de sucre liées entre elles par au moins une liaison hydrogène.

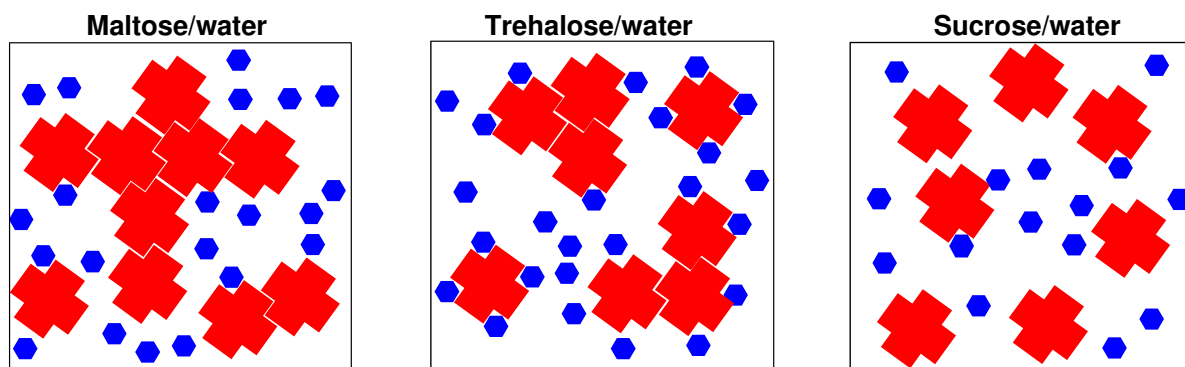


FIG. 2.7 – Représentation schématique de la structure microscopique des solutions sucre/eau. Les molécules de sucre sont représentées par les formes de grande taille et l'eau par celles de petite taille.

2.2.3 Dynamique

Le comportement dynamique des solutions à une concentration massique de 49% a été étudié au moyen du facteur de structure dynamique $F_S(Q, t)$ défini par la relation suivante :

$$F_S(Q, t) = \frac{1}{N} \left\langle \sum_i b_i^2 e^{i \cdot \mathbf{Q} \cdot [\mathbf{r}(t) - \mathbf{r}(0)]} \right\rangle, \quad (2.3)$$

où N correspond au nombre d'atomes, b_i est la longueur de diffusion de l'atome i , $\mathbf{Q}$ le vecteur d'onde et $\mathbf{r}_i(t)$ le vecteur position de l'atome i à l'instant t . Les symboles $\langle \cdot \cdot \cdot \rangle$ signifie que la moyenne est effectuée sur toutes les origines de temps. Les fonctions $F_S(Q, t)$ calculées par simulation MD et mesurées par diffusion neutronique sont représentées sur la figure 2.8 pour quelques valeurs de Q et quelques températures. Un accord satisfaisant est obtenu qui prouve le réalisme des simulations par rapport aux données structurales. La figure 2.9 montre $F_S(Q, t)$ pour la dynamique de l'eau uniquement. Aux très courts temps (inférieurs à 0.1 ps), une première décroissance est observée pour toutes les solutions et toutes les températures. Elle correspond à la dynamique vibrationnelle qui ne change pratiquement pas en fonction de la concentration en sucre. Par contre, pour des temps supérieurs à 0.1 ps, on observe des changements importants. En effet, aux hautes températures, $F_S(Q, t)$ décroît mono-exponentiellement à zéro. Lorsque la température diminue, la dynamique ralentit considérablement et on voit l'apparition d'un processus à deux temps avec l'émergence d'un plateau. Ceci est semblable aux comportements connus des liquides sous-refroidis (voir chapitre précédent) [41]. Ce comportement est couramment interprété comme un découplage des dynamiques $\alpha - \beta$ décrit par la théorie des modes couplés (MCT) [103] (voir chapitre précédent sur la transition vitreuse). La relaxation aux temps longs (α) ajustée par une exponentielle étirée ou de type Kohlrausch-Williams-Watts, est séparée du régime aux temps courts par un plateau qui est associé à un effet de cage [104]. A partir du $F_S(Q, t)$, nous pouvons estimer une température de changement dynamique notée T_A qui correspond au démarrage de la dynamique lente lorsque les relaxations non-Arrhéniennes et non-exponentielles apparaissent. T_A a été identifiée sur des liquides binaires de Lennard-Jones [17] au-dessus de la température critique T_c prédite par MCT et interprétée comme la température à laquelle le système commence à être influencé par le paysage de l'énergie potentielle. Nous avons identifié T_A comme la température à laquelle le plateau de $F_S(Q, t)$ apparaît. Au-dessus de T_A , le système possède les propriétés d'un liquide simple. Pour la solution tréhalose/eau à 49 pds %, $T_A \simeq 320$ K alors que pour les solutions sucrose/eau et maltose/eau, $T_A \simeq 300$ K. Cela signifie que l'eau en présence de tréhalose peut être maintenue dans une situation de dynamique lente à plus haute température que lorsque l'eau est en présence de sucrose ou maltose. Sur la figure 2.9, on peut constater que les temps de relaxation (α) de l'eau en présence de tréhalose extraits de la décroissance des fonctions $F_S(Q, t)$ sont plus longs que ceux de l'eau mélangée en même quantité avec du sucrose ou du maltose. De plus, ces temps sont de 1.2 fois à 10 fois plus longs que ceux de l'eau pure selon la température.

Ces résultats montrent nettement que le tréhalose ralentit de manière plus importante la dynamique de l'eau en bon accord avec les résultats obtenus sur la structure des solutions.

Ils mettent en évidence des différences significatives dans le régime dynamique $[T_A - T_c]$ des trois solutions étudiées alors que celles-ci possèdent une température de transition vitreuse semblable par une extrapolation Gordon-Taylor. Des investigations supplémentaires sont cependant nécessaires afin de vérifier si ces comportements pourraient avoir une importance sur l'effet bioprotecteur notamment dans le cadre du modèle de Green et Angell [20].

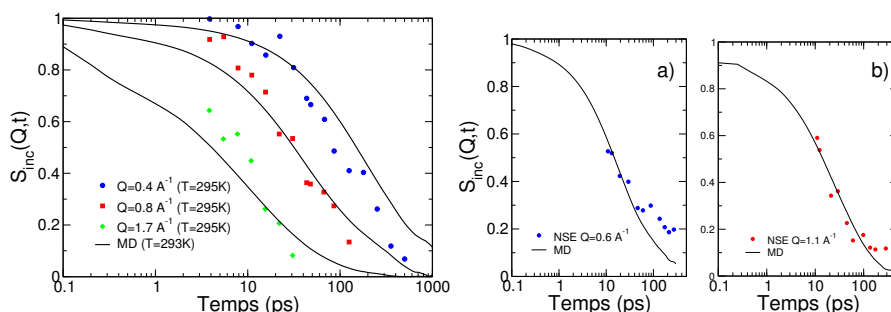


FIG. 2.8 – Comparaison des fonctions de corrélation dynamique obtenues par diffusion neutronique et simulation MD à différents Q . Gauche : Solution tréhalose/eau à température ambiante [105]. Droite : Solution tréhalose/eau à 353 K (a) [106] et sucrose/eau à température ambiante (b) [106].

2.3 Mélanges ternaires protéine/sucre/eau

Afin d'éclaircir les mécanismes bioprotecteurs des sucres et plus particulièrement de caractériser les interactions de ces sucres avec une molécule biologique, nous avons réalisé une série de calculs de dynamique moléculaire d'une protéine dans une solution sucre/eau (tréhalose, maltose et sucrose) à l'aide du programme CHARMM. La protéine considérée est le lysozyme de blanc d'oeuf.

Motivés par les résultats obtenus sur les solutions binaires, nous nous sommes plus particulièrement intéressés à l'influence de la structure du solvant sur différentes propriétés structurales, dynamiques et vibrationnelles de la protéine en nous plaçant dans le cadre de diverses hypothèses proposées pour expliquer l'effet bioprotecteur des sucres : i) exclusion préférentielle des sucres de la surface de la protéine, ii) « remplacement d'eau » par les protectants à la surface de la protéine, iii) effet destructurant des sucres sur le réseau tétraédrique de l'eau défavorisant la formation de la glace et iv) biomolécules « esclaves » de propriétés de vitrifications spécifiques du solvant.

2.3.1 Structure

L'influence des sucres sur la conformation du lysozyme (voir figure 2.10) a été caractérisée à partir de différents paramètres : la déviation de la structure de la protéine par rapport à la structure cristalline (RMSD), le rayon de giration R_g (voir figure 2.11) et la surface

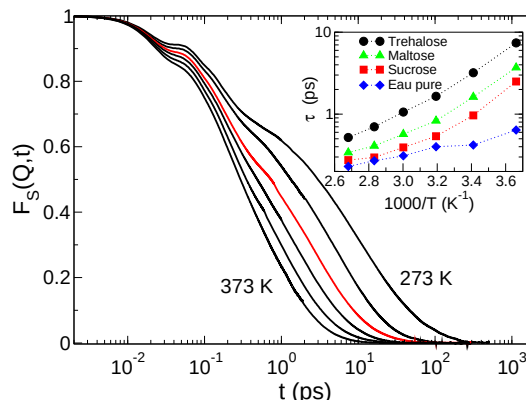


FIG. 2.9 – Fonction de corrélation dynamique $F_S(Q, t)$ individuelle de l'eau en présence de tréhalose pour une concentration de 49 % à différentes températures de 273 à 373 K par pas de 10 K. Les solutions de sucrose et maltose présentent le même comportement. La courbe rouge est obtenue à une température proche de T_A . La valeur $Q = 2.29 \text{ \AA}^{-1}$ correspond au maximum du premier pic du facteur de structure. En inset, le temps de corrélation caractéristique de la dynamique de l'eau est représenté en fonction de la température pour les différentes solutions sucre/eau et pour l'eau pure.

de la protéine accessible au solvant (SASA). Ils confirment que la structure de la protéine en présence des sucres est similaire à celle observée dans l'eau. Les changements conformationnels sont cependant réduits mais on ne constate pas de différences significatives sur l'action des différents sucres.

La manière dont les sucres interagissent avec les biomolécules reste encore mal compris et a fait l'objet de nombreux travaux [107; 108; 26]. D'après le modèle de « remplacement d'eau » proposé par Crowe [21], les sucres formeraient des liaisons hydrogènes directes avec la molécule biologique pendant la déshydratation se substituant ainsi aux molécules d'eau. Pour d'autres modèles comme celui de Timasheff [22], les protéines demeurent principalement hydratées et les sucres sont préférentiellement exclus de leur surface. Le tableau 2.3 résume une étude statistique du nombre moyen de liaisons hydrogènes entre la protéine et l'eau et les différents disaccharides à différentes concentrations. On constate que les sucres peuvent former un certain nombre de liaisons hydrogènes avec la protéine et que ce nombre augmente logiquement avec la concentration en sucre. Cependant, celui-ci représente seulement environ 10 à 20 % du nombre total de liaisons hydrogènes protéine-solvant. Un nombre faible par rapport au nombre théorique qu'ils pourraient former en supposant que l'eau et les sucres puissent former des liaisons hydrogènes avec la même probabilité. De plus, le nombre total de liaisons hydrogènes protéine-solvant tend à diminuer lorsque la concentration des sucres augmente. Ce résultat indique que les sucres ne parviennent pas à remplacer totalement les liaisons hydrogènes manquantes dues à la perte d'eau. On n'observe pas de différences majeures entre les différents sucres et en particulier le tréhalose ne forme pas plus de liaisons avec la protéine que les autres sucres contrairement à l'hypothèse de Crowe [21]. Les résultats obtenus semblent même suggérer l'effet inverse et

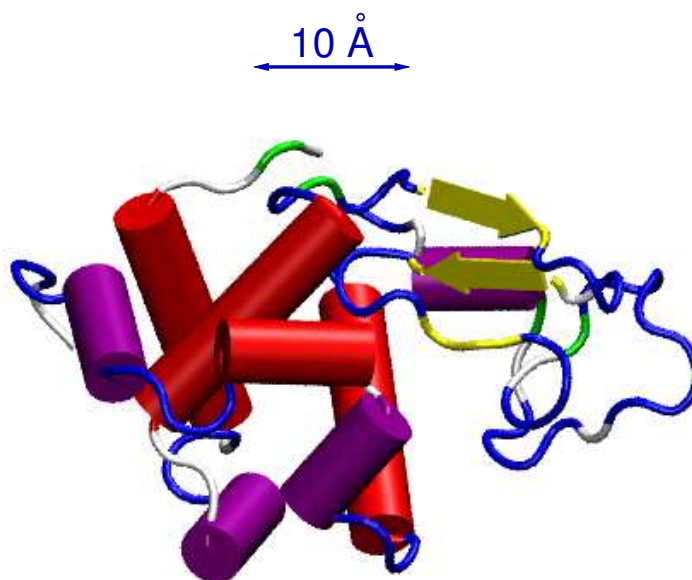


FIG. 2.10 – Représentation du lysozyme en feuillets, hélices et boucles.

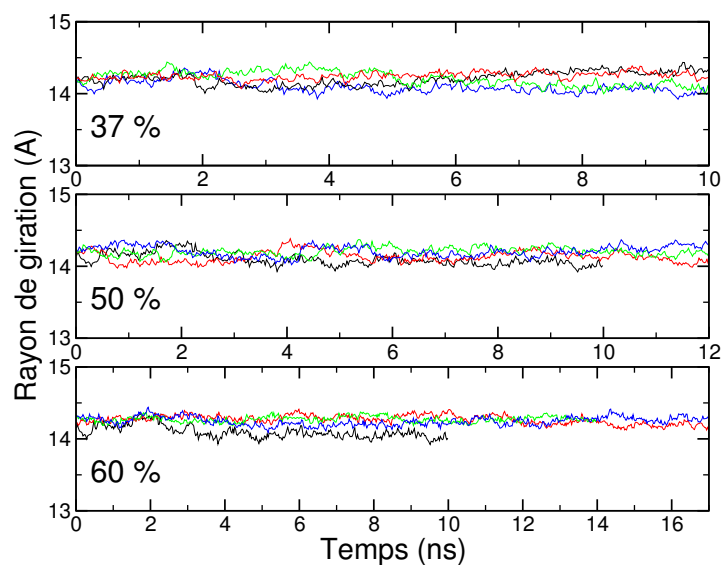


FIG. 2.11 – Rayon de giration R_g du lysozyme dans l'eau pure (bleu) et en présence des sucres (tréhalose : noire, maltose : vert et sucrose : rouge) en fonction du temps pendant la simulation.

ϕ (% pds)		$n_{HB}(\text{Eau-Lysozyme})$	$n_{HB}(\text{Sucre-Lysozyme})$
0		329.0	-
37	T	290.0	33.9
	M	285.7	45.4
	S	277.1	35.5
50	T	261.4	50.9
	M	265.1	54.9
	S	281.5	34.1
60	T	259.7	57.0
	M	247.2	62.1
	S	243.6	64.0

TAB. 2.3 – Nombre moyen de liaisons hydrogènes entre le lysozyme et l'eau et les différents disaccharides tréhalose (T), maltose (M) et sucrose (S) à différentes concentrations massiques ϕ .

une investigation de la structure du solvant confirme cette tendance (voir ci-dessous).

Le nombre de liaisons hydrogènes entre protéine et solvant ne décrit pas complètement les interactions protéine-solvant car les molécules du solvant ne forment pas de liaisons hydrogènes avec les groupes non-polaires des protéines. De manière similaire à Cottone *et al.* [108], nous avons calculé le rapport $g_{N,Ow}$ défini par la relation :

$$g_{N,Ow} = n_{OW}/(n_{OW} + n_{OS})(r)/(N_{OW}/(N_{OW} + N_{OS})) \quad (2.4)$$

où n_{OW} et n_{OS} sont les nombres d'atomes d'oxygène des molécules d'eau et de sucres situés à la plus petite distance r d'un atome lourd de la protéine. N_{OW} et N_{OS} représentent respectivement le nombre total d'atomes d'oxygène de l'eau et des sucres dans le système. Le rapport $g_{N,Ow}$ est supérieur à 1 si la protéine est principalement hydratée (les sucres sont exclus) et inférieur à 1 si les sucres interagissent préférentiellement avec la protéine (l'eau est exclue). $g_{N,Ow}$ est représenté sur la figure 2.12 en fonction de la concentration en sucre. Le lysozyme apparaît préférentiellement hydraté. Cette hydratation augmente de plus quand la concentration en sucre augmente. A des distances supérieures à 5 Å, on observe une diminution de $g_{N,Ow}$ sous la valeur 1 qui caractérise la présence des sucres. L'hydratation préférentielle du lysozyme est cohérente avec le petit nombre de liaisons hydrogènes formées entre les sucres et la protéine (voir tableau 2.3). Celle-ci semble aussi plus importante en présence du tréhalose que des autres sucres en bon accord avec le modèle de Timasheff [22].

Une étude de la structure du solvant similaire à celle réalisée pour les solutions binaires permet de clarifier ce comportement. La figure 2.13 représente le nombre d'hydratation n_H , le nombre de liaisons hydrogènes intramoléculaires $\langle n_{HB} \rangle_{intra}/N_S$ et la taille des agrégats de sucres $\langle n_S \rangle/N_S$. On observe que ces différents paramètres dans le mélange ternaire présentent une évolution globalement analogue au mélange binaire qui valide l'étude réalisée préalablement sur l'homogénéité des solutions. Pour le tréhalose, le nombre d'hydratation

n_H présente une valeur supérieure à celle du maltose ou du sucrose, son nombre de liaisons hydrogènes intramoléculaires $\langle n_{HB} \rangle_{intra}/N_S$ est le plus faible et la taille de ses agrégats de sucres $\langle n_S \rangle / N_S$ est intermédiaire. Des différences par rapport au système binaire sont toutefois observées en raison de l'action de la protéine sur les propriétés du solvant car des liaisons hydrogènes sont possibles entre l'eau et la protéine qui réduisent en particulier les valeurs des nombres d'hydratation n_H où la taille des agrégats $\langle n_S \rangle / N_S$.

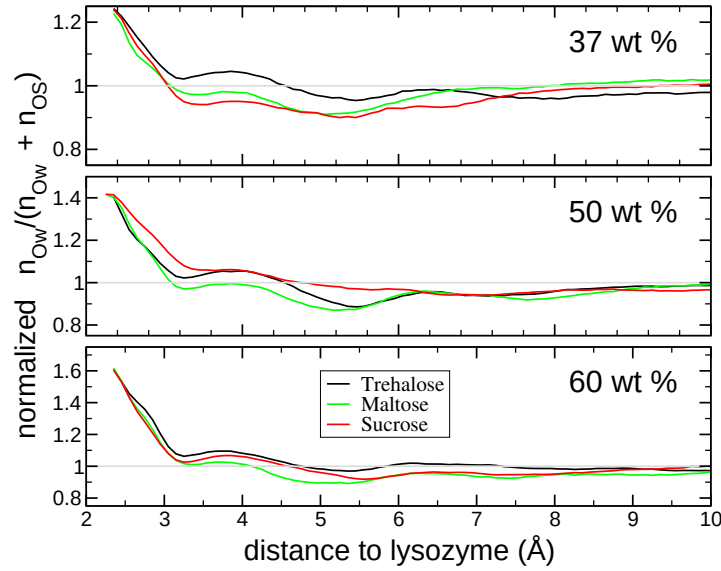


FIG. 2.12 – Fonction $g_{N,Ow} = n_{Ow}/(n_{Ow} + n_{Os})(r)/(N_{Ow}/(N_{Ow} + N_{Os}))$ où n_{Ow} et n_{Os} sont les nombres d'atomes d'oxygène des molécules d'eau et de sucres situés à la plus petite distance r d'un atome lourd de la protéine. N_{Ow} et N_{Os} représentent le nombre total d'atomes d'oxygène de l'eau et des sucres dans le système.

La figure 2.14 représente les fluctuations des déplacements carrés moyens (MSF) de l'ensemble des résidus du lysozyme à différentes concentrations en sucre et pour l'eau pure. La forte variation des MSFs démontre la grande hétérogénéité des environnements locaux dans lesquels sont placés les résidus. Les résidus avec les plus hauts MSFs sont localisés principalement à la surface de la protéine. Ils correspondent à des éléments de structure I, II, III, IV et V de la figure 2.14 (boucles, hélices et feuillets) capables de former de liaisons hydrogènes avec le solvant. Les faibles MSFs peuvent être associés à deux domaines A et B (hélice et boucle) localisés à l'intérieur de la protéine et difficilement accessible par le solvant. Leur fluctuation est aussi réduite par des encombrements stériques dus aux résidus voisins. A basse concentration, la présence des sucres réduit nettement les valeurs des MSFs mais ne révèle pas d'effets spécifiques. A plus haute concentration, on observe une réduction des MSFs plus importante pour le maltose qui sera discutée dans la section 2.3.2 sur la dynamique.

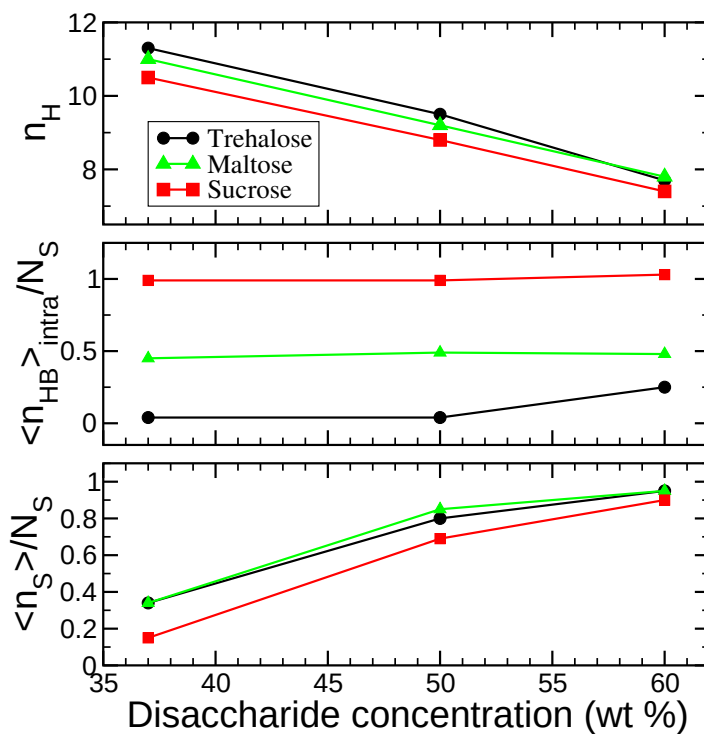


FIG. 2.13 – Trois paramètres décrivant la structure du solvant (tréhalose, maltose et sucrose) en fonction de la concentration en sucre à 300 K (de haut en bas) : le nombre d'hydratation n_H , le nombre de liaisons hydrogènes intramoléculaires des sucres $\langle n_{HB} \rangle_{intra} / N_S$ et la taille des agrégats de molécules de sucres $\langle n_S \rangle / N_S$. La définition de $\langle n_S \rangle / N_S$ est indiquée figure 2.6).

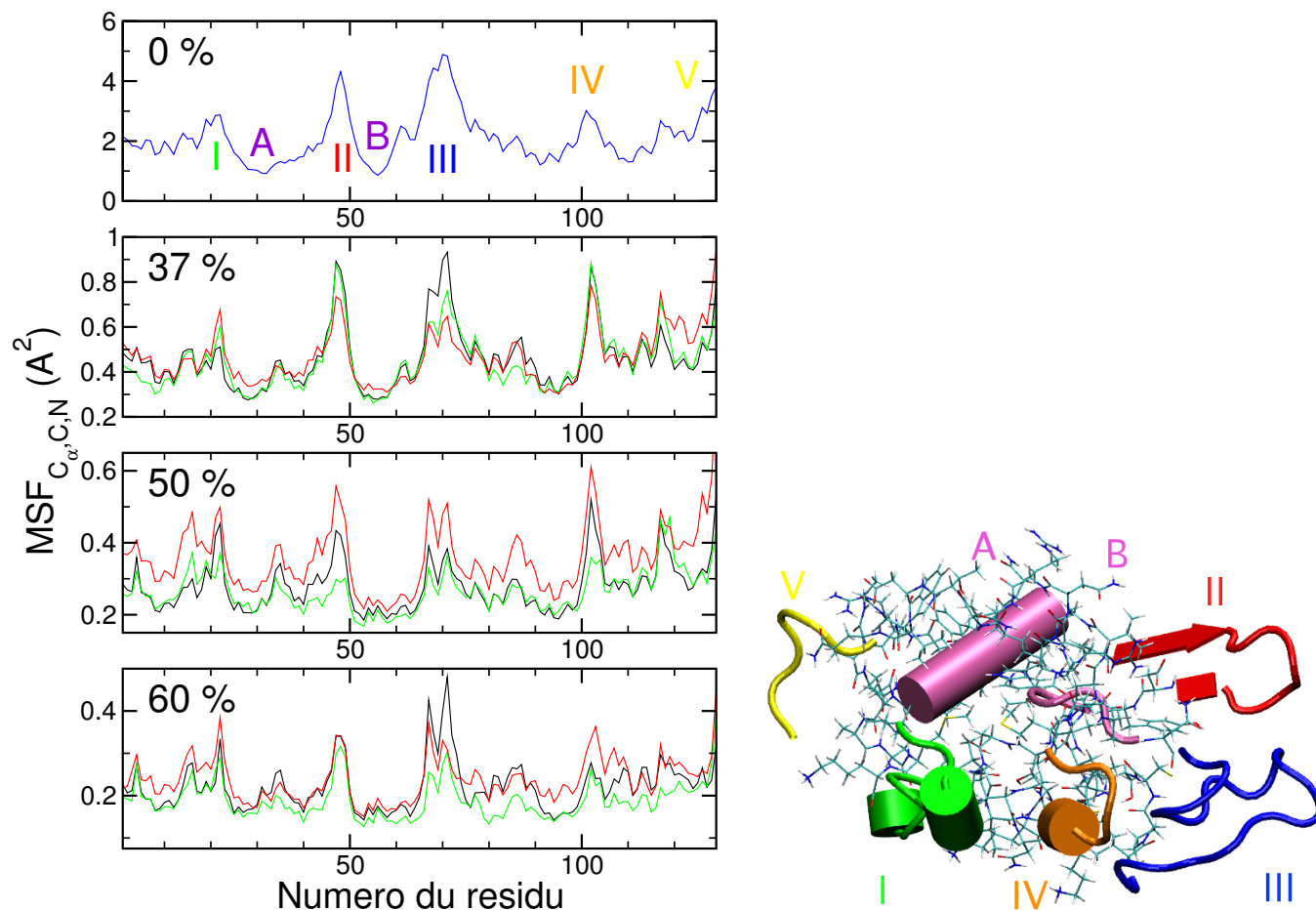


FIG. 2.14 – Gauche : Fluctuations des déplacements carrés moyens (MSF) de l'ensemble des résidus du lysozyme à différentes concentrations en sucre et pour l'eau pure à 300 K. Droite : localisation des régions correspondantes aux MSFs les plus importants situés à la surface du lysozyme (I, II, III, IV et V) et aux plus faibles localisés dans le coeur (A et B).

2.3.2 Dynamique

Par simulation MD, le spectre vibrationnel $g(\nu)$ basse fréquence ($\nu < 300 \text{ cm}^{-1}$) de l'eau seule dans le système ternaire lysozyme/sucre/eau a été calculé à partir de la fonction d'autocorrélation des vitesses atomiques et il est représenté sur la figure 2.15. Il révèle la présence de deux bandes de vibrations à $\nu_1 \sim 50 \text{ cm}^{-1}$ et à $\nu_2 \sim 200 \text{ cm}^{-1}$ en bon accord avec les données expérimentales. Le premier mode est souvent attribué à l'effet de cage (voir chapitre précédent) et il est commun à tous les liquides moléculaires. Le seconde mode, en revanche, résulte des mouvements de libration des molécules d'eau liées par liaisons hydrogènes avec leurs voisines. Un ajustement du spectre représenté en figure 2.15 par une fonction log-normale pour le mode ν_1 et gaussienne pour le mode ν_2 donne un résultat satisfaisant et permet d'estimer la fréquence des deux modes en fonction de la concentration en sucre (voir figure 2.15). On observe une nette augmentation des deux modes avec la concentration en sucre en bon accord avec les études Raman réalisées au laboratoire qui suggèrent que le principal effet des sucres bioprotecteurs est de stabiliser la structure tertiaire de la protéine, via un renforcement du réseau de liaison hydrogène de l'eau [27]. Les faibles différences observées entre les sucres ne permettent cependant pas de tirer des conclusions sur une éventuelle capacité supérieure du tréhalose à renforcer le réseau de liaison hydrogène de l'eau.

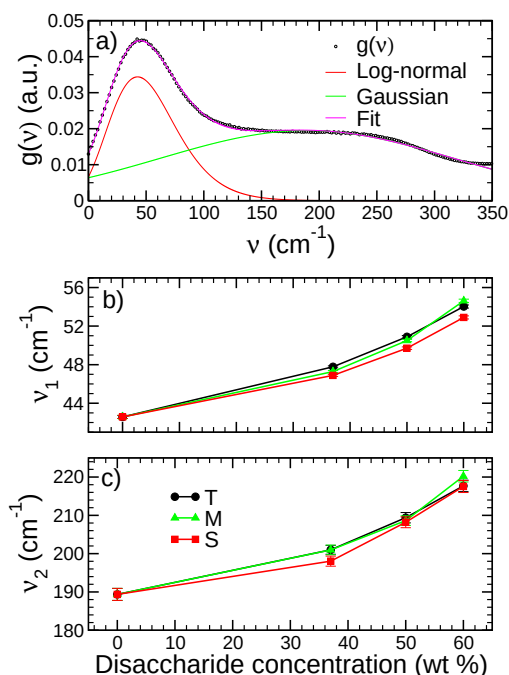


FIG. 2.15 – Exemple de densité d'état vibrationnelle de l'eau seule dans les solutions ternaires à 300 K (a). Dépendance en concentration des modes ν_1 (b) et ν_2 (c) de l'eau en présence de tréhalose, sucrose et maltose.

Nous nous sommes intéressés à l'influence du sucre sur la dynamique du lysozyme et

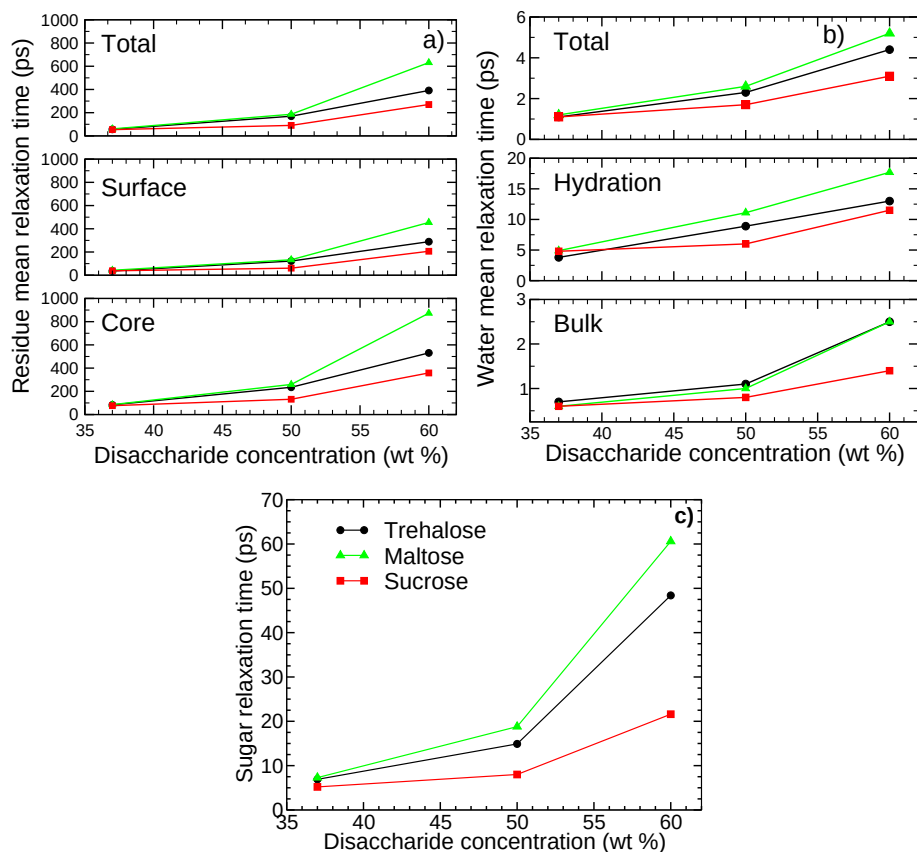


FIG. 2.16 – Temps de corrélation de la protéine (a), de l'eau (b) et des sucres tréhalose, sucrose et maltose seuls (c), à 300 K. Pour l'eau, on a décomposé le temps (total) où l'on prend en compte toutes les molécules d'eau en deux contributions tenant compte des seules molécules d'eau d'hydratation (hydratation) et de toutes les molécules d'eau à l'exclusion des molécules d'eau d'hydratation (bulk). De la même manière pour la protéine, on a décomposé le temps (total) en une contribution des atomes du coeur de la protéine (core) et de la surface (surface).

de l'eau dans le cadre de l'hypothèse de Green et Angell portant sur la vitrification. La figure 2.16 montre les temps de corrélation extraits des fonctions de corrélation dynamique individuelles $F_S(q, t)$ calculées pour les sucres, l'eau et la protéine (voir équation 2.3). La dynamique de la protéine et celle de l'eau est clairement esclave de celle des sucres. Le maltose apparaît comme le plus efficace à réduire la mobilité de la biomolécule (cœur et surface) et l'eau l'hydratation. Cependant, la dynamique des molécules d'eau éloignées de la surface de la protéine continue d'être dominée par celle du tréhalose certainement en raison de son nombre d'hydratation n_H supérieur de manière similaire aux résultats obtenus sur les mélanges binaires. La dynamique du sucrose apparaît plus rapide que celle du tréhalose et du maltose en bon accord avec les résultats de la littérature et les investigations précédentes sur les solutions binaires. Cependant, on constate ici une inversion entre le tréhalose et le maltose (voir figure 2.9) qui demeure mal comprise mais cohérente avec le comportement des MSFs (voir figure 2.14). Cet effet a déjà été observé par d'autres simulations MD [107] et son origine pourrait provenir de l'absence de mutarotation entre les formes α et β dans notre modèle du maltose où seul la forme α est considérée.

2.4 Perspectives

Les investigations par simulation MD des mélanges binaires sucre/eau et ternaires biomolécule/sucre/eau montrent des perspectives encourageantes sur la compréhension des mécanismes de la bioprotection. Je souhaite vivement les poursuivre en liaison avec les travaux de diffusion Raman menés au laboratoire.

Il s'agira en particulier de mener des investigations sur les états profondément déshydratés à forte concentration en protectant qui n'ont pas encore été réalisées dans l'unité. Green et Angell [20] ont suggéré que les composés moléculaires possédant une température de transition vitreuse T_g élevée ($\sim 120^\circ$ C pour le tréhalose par exemple) formaient de meilleurs bioprotecteurs : l'activité biologique serait plus réduite à des températures très en dessous de T_g . Une valeur élevée de T_g n'implique cependant pas nécessairement la suppression de dynamiques à l'échelle de la pico-nanoseconde. Des travaux expérimentaux récents de diffusion neutronique [80] ont révélé que le mélange tréhalose/glycérol présentait des capacités bioprotectrices supérieures au tréhalose seul alors qu'il possède une T_g plus faible. Il a été en effet montré que l'addition d'une petite quantité de glycérol au tréhalose permettait de réduire les mouvements locaux de faibles amplitudes $\langle u^2 \rangle$ qui seraient fondamentaux pour la stabilité des protéines. Ces mouvements rapides de la matrice vitreuse tréhalose/glycérol se couplent à la dynamique de la protéine et pourraient inhiber des changements conformationnels beaucoup plus lents et de grande amplitude responsables de la dénaturation. Mes objectifs prioritaires seront donc : i) d'étudier différents plastifiants de faibles poids moléculaires (polyols, eau) afin d'évaluer l'importance des dynamiques « lentes » et de la structure de la matrice vitreuse sur la stabilité des protéines. ii) de comprendre comment les dynamiques de la protéine se couplent avec celles de la matrice vitreuse et identifier les sites d'interactions privilégiés s'ils existent. iii) d'analyser le rôle de l'eau résiduelle des lyophilisats qui semble fondamentale. Des taux de déshydra-

tation extrêmes sont en effet très défavorables à la stabilité du lyophilisat même dans des formulations utilisant de bons bioprotecteurs.

L'étude du mélange binaire glycérol/tréhalose serait de plus directement liée aux investigations portant sur les propriétés intrinsèques des liquides formateurs de verre comme la fragilité et l'anharmonicité que nous avons effectué. Ce travail sera facilité par la mise au point au laboratoire (stage Master J. Blicq 2003-2004) d'un nouveau champ de force pour le glycérol qui reproduit correctement à la fois la structure et la dynamique de ce liquide contrairement aux modèles disponibles jusqu'à présent. Des études de solutés comme le glycérol dans le régime à plus haute hydratation permettraient de plus de mieux comprendre le rôle du volume exclu des osmolytes sur la dynamique des protéines. Ceci nous indiquerait la part respective des interactions spécifiques et du couplage protéine-solvant dans le phénomène de bioprotection.

Les investigations réalisées jusqu'à présent m'amènent aussi à aborder le problème de la stabilité des protéines aux basses températures et celui de la dénaturation froide. Les protéines sont stables d'un point de vue thermodynamique sur un intervalle de température déterminé. A haute température, le phénomène de dépliement des protéines (dénaturation chaude) a fait l'objet de nombreuses études. A basse température le phénomène de dénaturation froide, directement impliqué dans les procédures de lyophilisation, a été beaucoup moins étudié. Une des raisons est que ce phénomène se superpose à un autre phénomène de dénaturation inhérent à la formation de cristaux de glace. Afin d'analyser sélectivement ces deux phénomènes on a recours à l'application de pression ou à l'addition de dénaturants qui ont pour effet d'augmenter la température de dénaturation froide au-dessus de 0°C. Les mécanismes microscopiques de la dénaturation froide demeurent mal compris mais ils sont classiquement attribués à la diminution de l'effet hydrophobe engendrée par la dépendance en température de la structure de l'eau. Les simulations MD offrent des possibilités intéressantes de clarifier ce phénomène et d'atteindre notamment des états physiques difficilement accessibles expérimentalement comme dans le cas de la dénaturation froide sans avoir à ajouter des dénaturants ou changer la pression. Un projet de recherche qui m'intéresse particulièrement porte sur la caractérisation à l'échelle microscopique de la structure de l'eau (haute densité, basse densité, cristal) aux très basses températures et son influence sur les propriétés structurales et dynamiques de la biomolécule.

Comparative study of trehalose, sucrose and maltose in water solutions by molecular modelling

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(received 4 September 2003; accepted 28 October 2003)

PACS. 61.20.Ja – Computer simulation of liquid structure.

PACS. 64.60.Ht – Dynamic critical phenomena.

PACS. 64.70.Pf – Glass transitions.

Abstract. – A systematic study of three well-known bioprotectant sugars —trehalose, sucrose and maltose— in water solutions has been performed at different concentrations and temperatures using molecular-dynamics simulations. A variety of relevant probes such as the size of hydrogen-bonded water clusters, the orientational order parameter q , the Voronoi volume and the dynamical structure factor have been determined to describe the effect of the three disaccharides on water quantitatively. This investigation points out different structural and dynamical behaviours for which a threshold concentration ϕ_A and a crossover temperature T_A emerge. A “destructuring” effect on the water network and a slowing-down of its dynamics are highlighted. These results suggest narrow links between the different scenarios tentatively explaining bioprotection.

Introduction. – Sugars are often used in pharmaceutical, food and biomedical applications to prepare glassy matrices for long-term storage of biological materials [1]. In recent years, trehalose, which is naturally produced by several organisms that are able to survive severe external stresses (temperature changes and/or dehydration), has received considerable attention [2]. Indeed, this non-reducing disaccharide of glucose was shown to be particularly effective to preserve and maintain activity of biomolecules during drying and over long-term storage. Despite its importance in cryopreservation and desiccation protection, the properties that make trehalose an effective protective agent are still poorly understood. Several hypotheses have been suggested to explain the superior effectiveness of trehalose. The “water-replacement” hypothesis, first proposed by Crowe *et al.* [3], assumes that sugars hydrogen-bond to biomolecules during dehydration or freeze-drying, acting as substitutes of hydration water molecules. Alternative scenarios have been proposed in which some specific properties of sugar/water solutions are responsible for the bioprotective capability. Similarly to the encapsulation of insects in amber, Green and Angell [4] advanced that biomolecule motions are inhibited due to the vitrification upon cooling of the sugar/water solutions. The very high glass transition temperature of trehalose could explain its superior cryoprotective ability. The most efficient inhibition of ice formation by trehalose compared to sucrose and maltose has

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also been emphasised by Magazù *et al.* [5] and related to its greater “destructuring effect”. Recently, Cesàro *et al.* [6] referred to the role of the formation of the trehalose dihydrate crystal and the subsequent reversible transformation into an anhydrous state (α phase) during water removal. However, none of these assumptions is fully satisfactory regarding the numerous experimental observations [7–10] as well as numerical simulations [11–13].

In this work, a careful comparative study of disaccharides trehalose, sucrose and maltose in aqueous solutions by MD simulations is presented. We focus on both the structure and dynamics of water in the presence of these three disaccharides. Our goal is to point out relevant parameters able to differentiate trehalose effects from those of homologous maltose and sucrose molecules in order to understand the molecular mechanisms at the origin of bioprotection. This paper also aims at clarifying the outstanding bioprotective effectiveness of trehalose in the framework of the Green and Angell, Magazù and Cesàro models.

Computational setup. – MD simulations have been carried out with the molecular-dynamics package DL-POLY-2 [14] on a system composed of 512 water molecules and 0, 1, 5, 13, 26 or 52 sugar molecules (either trehalose, sucrose or maltose) corresponding to weight concentrations of 0, 4, 16, 33, 49 or 66%, respectively. The sizes of these systems have been chosen to give size-independent results. The investigated temperatures ranged from 273 K up to 373 K in steps of 20 K. The SPC/E model [15] for water and the force field developed by Ha *et al.* [16] for carbohydrates are used. Electrostatic interactions were handled by the reaction-field method (with $\epsilon_{\text{RF}} = 72$). We worked in the NPT statistical ensemble (the pressure was set to 1.0 bar). We have performed simulations of 200 ps up to 2 ns depending on concentrations with a time step of 0.5 fs for mixed solutions and 2 fs for pure water. The cutoff radius is 10 Å and cubic periodic boundary conditions have been applied.

Cluster size. – Clusters of water molecules are considered using a definition given in [17]. A cluster is defined as a set of water molecules connected to each other by at least one hydrogen bond identified by a geometric criterion (oxygen-oxygen distance less than 3.4 Å and O-H $\cdots$ O angle greater than 160°). The average cluster size $\langle n_w \rangle$ was computed as

$$\langle n_w \rangle = \sum_n n \times W_n. \quad (1)$$

The size n of a given cluster is the number of water molecules and W_n is the probability of the clusters of size n . In fig. 1, we show $\langle n_w \rangle$ as a function of the sugar concentration for the three investigated disaccharides. At low temperatures and at concentrations below $\phi_A \simeq 40\%$, which appears to be a threshold value, more than 300 water molecules among the 512 ones in the simulation box are linked to each other by one hydrogen bond (HB) at least. So, the disaccharides slightly perturb the hydrogen bond network (HBN) of water. Moreover, the same cluster sizes are obtained in the presence of the three sugars. This shows that water is hardly sensitive to the nature of a given disaccharide, at these concentrations. Above $\phi_A \simeq 40\%$, $\langle n_w \rangle$ strongly decreases and reaches a value of about 20 at a concentration of 66%. At high concentrations, the aqueous solution is composed of many small clusters as shown in the distribution of clusters size W_n displayed in the inset of fig. 1. Furthermore, a very interesting point is that the decrease of the cluster size above the threshold concentration ϕ_A allows us to distinguish the different disaccharides. Indeed, we observe in fig. 1 that trehalose reduces the cluster size more than sucrose and maltose. This result is confirmed in the inset where the number of water clusters W_n of small size is larger in the presence of trehalose than with sucrose or maltose, while W_n for large size clusters is smaller in the case of the trehalose/water solution. This suggests that trehalose prevents more efficiently the percolation of the HBN of water.

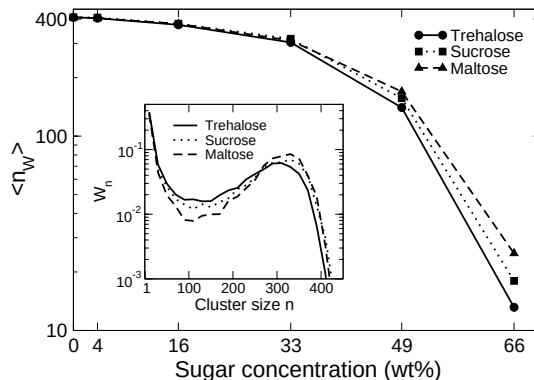


Fig. 1 – Concentration dependence of the weight-averaged cluster size $\langle n_w \rangle$ of water in the presence of the three disaccharides (trehalose, sucrose and maltose) at $T = 273$ K. W_n is given in the inset for the three 49 wt% disaccharide solutions at $T = 273$ K.

Thus, the tetrahedral structure of water in the presence of trehalose should be more confined into small spatial regions. Trehalose appears to be the most “destructuring” solute among the three homologous disaccharides, in good agreement with a Raman investigation performed by Magazù *et al.* [5]. This feature occurs in experiments [5] above a sugar concentration of about 50% close to the threshold value obtained in the present MD investigation.

Orientational order parameter. – The orientational order parameter q has been extensively discussed for pure water by Debenedetti *et al.* [18]. According to [18], q quantifies the deviation of the arrangement of a given water molecule and its four nearest neighbours from a perfect tetrahedral network. It is defined as

$$q = 1 - \frac{3}{8} \sum_{j=1}^3 \sum_{k=j+1}^4 \left(\cos(\Psi_{j,k}) + \frac{1}{3} \right)^2, \quad (2)$$

where $\Psi_{j,k}$ denotes the angle formed by the lines joining the oxygen atom of a given water molecule to those of the j -th and k -th nearest neighbours. For a perfect tetrahedral organisation, $q = 1$. Conversely, for a random arrangement with uncorrelated uniform angular distributions, $q = 0$. However, in case of mixed solutions, water molecules in close vicinity to sugars cannot adopt a regular tetrahedral arrangement —particularly at high concentrations— for straightforward steric reasons. Therefore, water molecules H-bonded to sugars are not accounted for in the following q analysis. Nevertheless, the remaining water molecules should not be considered as true bulk water as they may still be near sugars and/or influenced by them. The q distribution of trehalose/water solutions at different concentrations at 273 K is displayed in fig. 2. At low concentrations, the q distribution presents two peaks, similar to those of pure water at low temperatures. The high- q peak may be ascribed to structured (or “ice”-like) water molecules, whereas the low- q peak accounts for unstructured (or “liquid”-like) water. As trehalose concentration increases, the high- q peak decreases in favour of the low- q peak. This trend becomes particularly significant for concentrations above $\phi_A \simeq 40\%$. It mimics the behaviour of a temperature increase, observed by Debenedetti *et al.* [18]. At the highest sugar concentration (66%), water molecules are predominantly disordered, as indicated by the large amplitude of the low- q peak and the global shift towards low- q values. The comparison of the q distribution for the three disaccharides (shown in the inset of fig. 2) reveals no shift among the

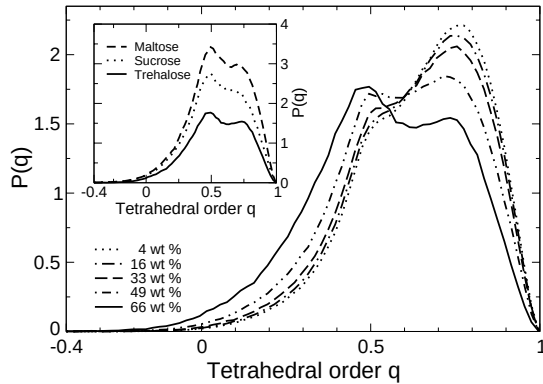


Fig. 2 – Distributions of the orientational order parameter q [18] of water molecules not H-bonded to trehalose for different trehalose wt% concentrations at $T = 273$ K. The distribution for pure water is very similar to that of the 4 wt% solution, and therefore is not shown. The inset presents the distributions of the three 66 wt% disaccharide solutions at $T = 273$ K. Sucrose and maltose curves are not normalised in order to show the influence of the hydration numbers.

three disaccharides, suggesting that, on average, water molecules adopt comparable configurations in the three solutions. However, the number of water molecules not H-bonded to trehalose (proportional to the total integrated area) is clearly reduced compared to that of sucrose and maltose. Accordingly, trehalose is likely to perturb the tetrahedral HBN of water more deeply than sucrose and maltose because of its more extensive hydration, as reported in [19].

Voronoi tessellation. – We have investigated the distributions of Voronoi volumes, which may provide useful information about the local molecular environment or the local free volume. This technique has recently been used quite successfully by Starr *et al.* [20] on a glass-forming polymer melt. We have calculated this parameter to quantify the change of the water structure in these solutions compared to pure water and to probe the near neighbourhood of the solutes. The distributions of the Voronoi volumes of water P_w in the presence of the three sugars are shown in fig. 3. These distributions have been calculated for mixed solutions at $T = 293$ K and

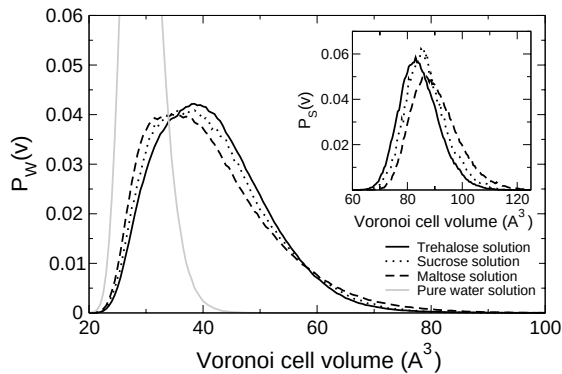


Fig. 3 – Distributions of Voronoi cell volumes of water P_w and of sugars P_s (displayed in the inset) in the 49 wt% disaccharide solutions at $T = 293$ K. The P_w of pure water (in gray) is given as reference (the maximum is about 0.13).

for a concentration of 49%. P_w are clearly shifted towards the large volumes and broadened compared to the distribution of pure water (gray line). These two findings stem from the heterogeneity of the mixed solutions due to the inclusion of sugars. It ensues both a dilation and a distortion of the HBN of water from its tetrahedrality. Moreover, P_w mixed with trehalose is more shifted than the other two ones. Thus, the water network is more perturbed by trehalose than by the other two disaccharides. As previously demonstrated, a larger number of water molecules (in relation with the hydration number) is affected by trehalose.

Another important point, revealed in the inset of fig. 3, concerns the Voronoi volume distribution of sugars P_s which allows us to distinguish the effects of the three sugars at the sugar concentration of 49%, above the threshold value $\phi_A \simeq 40\%$. This result is all the more interesting as the three disaccharides —trehalose, maltose and sucrose— are homologous (same chemical formula, similar conformations and thermodynamical properties) and as other parameters (*e.g.*, diffusion coefficients) are not sensitive enough for pointing out slight differences among them. In fig. 3, the mean Voronoi volume for trehalose (roughly the maximum of the P_s distribution) is smaller than for the other sugars. This implies that trehalose molecules possess a smaller free volume than sucrose and maltose. This result is in good agreement with the apparent partial molar volumes of the three sugars determined in previous results [10]. Since water in the presence of trehalose exhibits the largest Voronoi volume while trehalose shows the smallest one, it can be suggested that water molecules mixed with trehalose are less bounded to each other due to their greater affinity with trehalose. This remark is compatible with the existence of a dihydrated trehalose crystal in which two water molecules are linked to the sugar in a specific manner so that the complex is stabilised. This idea is in keeping with the hypothesis proposed by Cesàro *et al.* [21]. Further analyses are currently led to check whether the water sites of the trehalose dihydrate crystal are more likely to be occupied in trehalose/water solutions at high sugar concentrations.

Dynamics of the mixed solutions. – The dynamical behaviour of water has been investigated by means of the dynamical structure factor $F_S(Q, t)$ defined as

$$F_S(Q, t) = \frac{1}{N} \left\langle \sum_i b_i^2 \cdot e^{i \cdot \mathbf{Q} \cdot [\mathbf{r}(t) - \mathbf{r}(0)]} \right\rangle, \quad (3)$$

where N denotes the number of atoms, b_i the scattering length of atom i , $\mathbf{Q}$ the transfer momentum, and $\mathbf{r}_i(t)$ the position of atom i at time t . The brackets $\langle \dots \rangle$ stand for the average over all time origins. Figure 4 shows $F_S(Q, t)$ of water in the presence of trehalose at different temperatures (water behaves similarly in the presence of maltose or sucrose). At very short times, below 0.1 ps, a first decay is observed for all solutions and all temperatures. It corresponds to vibrational dynamics and does not exhibit significant changes as a function of sugar concentrations. Therefore, we will only discuss dynamics for times longer than 0.1 ps in the following. At high temperatures, $F_S(Q, t)$ decays mono-exponentially to zero. When lowering the temperature, the dynamics slows down dramatically and a two-step process is seen, as expected for supercooled liquids [22]. This behaviour is classically interpreted in terms of α – β dynamical decoupling as described by the Mode Coupling Theory (MCT) [23]. The long-time relaxation (α), fitted with a Kohlrausch-Williams-Watts exponential, is separated from the short-time regime (β) by a plateau-like region, which can be associated to the *cage effect*. From $F_S(Q, t)$, we can estimate a crossover temperature, noted T_A , which corresponds to the onset of slow dynamics where non-exponential and non-Arrhenius relaxations emerge. T_A has been identified on binary Lennard-Jones liquids [24] above the critical temperature T_c predicted by MCT and is interpreted as the temperature where the dynamics of the system starts being influenced by the potential energy landscape. We have roughly identified T_A as the temperature

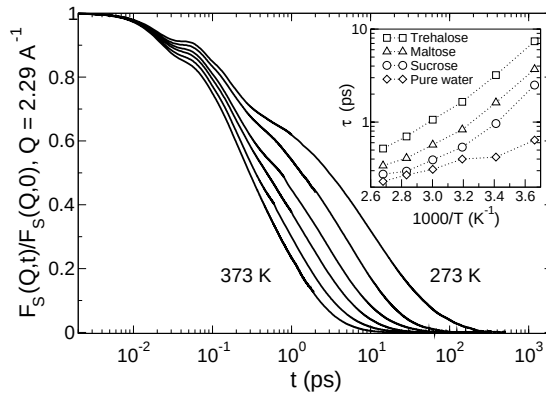


Fig. 4 – Incoherent intermediate scattering function of water $F_S(Q, t)$ in the 49 wt% trehalose solution for all temperatures investigated (from left (373 K) to right (273 K) in steps of 20 K). The inset shows the temperature dependence of the relaxation times τ determined from the $F_S(Q, t)$ of water in the 49 wt% sugar solutions and in pure water. We define τ as the time at which $F_S(Q, t)$ has decayed by a factor e^{-1} , at the Q value of $2.29 \text{ \AA}^{-1}$, corresponding to the position of the first main peak of the partial structure factor S_{O-O} of water.

at which the plateau observed on $F_S(Q, t)$ appears. Above T_A , the mixed solutions behave like a simple liquid with no unusual properties. Below T_A , the dynamics of water is slowed down and the matrix becomes very viscous. For the trehalose/water solution at a sugar concentration of 49%, T_A is estimated around 320 K. For aqueous mixtures with maltose and sucrose, we have found $T_A \simeq 300$ K. This means that water in the presence of trehalose can be maintained in a slow-dynamics situation at higher temperatures than with maltose or sucrose. Therefore, upon a temperature change, trehalose protects earlier biomolecules by reducing their conformational relaxations. Then, in addition to the glass transition temperature T_g playing a key role in the Green and Angell model, T_A would be a relevant temperature for bioprotection.

From $F_S(Q, t)$, we have extracted a relaxation time of water mixed with the three different sugars at the six investigated temperatures as displayed in the inset of fig. 4. The relaxation times of pure water are also given for comparison. Those of water in the presence of the sugars are 1.2 to 10 times longer than the ones of pure water, depending on temperature. Moreover, a salient issue is that we can discriminate the homologous disaccharides by the relaxation times. Indeed, the trehalose/water solution has the longest relaxation times. Thus, trehalose slows down the water liquid more efficiently. Hence, trehalose must have a stronger influence than sucrose and maltose on the dynamics of water, *i.e.* the dynamics of trehalose molecules is imposed to a larger number of water molecules.

Conclusion. – As a conclusion, this work has combined several analysis tools such as the size of H-bonded water clusters, the Voronoi tessellation, the orientational order parameter or the dynamical structure factor to differentiate the actions of the homologous disaccharides — trehalose, sucrose and maltose. This work shows that trehalose has superior effects in “destructuring” the network of water and in slowing down its dynamics. These two properties could play a key role in the understanding of the microscopic mechanisms of bioprotection. This work also highlights the narrow links between the various hypotheses listed in the introduction, which are not fully satisfactory when taken individually. Further investigations on binary (sugar/water and polyol/water) and ternary (protein/sugar/water) solutions are in progress.

* * *

Prof. A. CESÀRO and Prof. K. NGAI are gratefully acknowledged for fruitful discussions. All computations were performed on the IBM Power 4 computers of the CRI (Université Lille I) and of the IDRIS (Paris). This work was supported by the INTERREG III program (Nord-Pas de Calais/Kent).

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How Homogeneous Are the Trehalose, Maltose, and Sucrose Water Solutions? An Insight from Molecular Dynamics Simulations

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Received: July 15, 2004; In Final Form: March 23, 2005

The structural properties resulting from the reciprocal influence between water and three well-known homologous disaccharides, namely, trehalose, maltose, and sucrose, in aqueous solutions have been investigated in the 4–66 wt % concentration range by means of molecular dynamics computer simulations. Hydration numbers clearly show that trehalose binds to a larger number of water molecules than do maltose or sucrose, thus affecting the water structure to a deeper extent. Two-dimensional radial distribution functions of trehalose solutions definitely reveal that water is preferentially localized at the hydration sites found in the trehalose dihydrate crystal, this tendency being enhanced when increasing trehalose concentration. Over a rather wide concentration range (4–49 wt %), the fluctuations of the radius of gyration and of the glycosidic dihedral angles of trehalose indicate a higher flexibility with respect to maltose and sucrose. At sugar concentrations between 33 and 66 wt %, the mean sugar cluster size and the number of sugar–sugar hydrogen bonds formed within sugar clusters reveal that trehalose is able to form larger clusters than sucrose but smaller than maltose. These features suggest that trehalose–water mixtures would be more homogeneous than the two others, thus reducing both desiccation stresses and ice formation.

1. Introduction

Disaccharides have received a huge interest over the past few decades for their preservation capabilities of biosystems such as cells, vaccines, or therapeutic proteins employed in the food, pharmaceutical, or cosmetics industry.^{1–4} Indeed, disaccharides such as trehalose (α -D-glucopyranosyl- α -D-glucopyranoside), maltose (4-O-(α -D-glucopyranosyl)- β -D-glucopyranoside), or sucrose (β -D-fructofuranosyl- α -D-glucopyranoside) can be added to biologically active solutions to overcome the limited stability range of proteins (in pH, in temperature, in salt concentration, etc.). These additives prevent the partial or even total degradation of biomolecules due to the lethal thermal or dehydration stresses encountered during industrial conservation methods (lyophilization), where trehalose has been found the most effective.⁵ Trehalose is also found in high concentrations in organisms that enter into a state called *anhydrobiosis*, where almost any biological activity is suspended, thus allowing them to survive conditions of extremely low water content and high or low temperatures.

However, the molecular mechanisms at the origin of the superior capabilities of trehalose and, more generally, of the biopreservation phenomenon itself still remain unclear, despite various experimental and theoretical works. Several hypotheses have been proposed, but none of them can be considered as fully accepted since they have sometimes led to contradictory conclusions.

Green and Angell⁶ suggested that dehydrated sugar solutions convert to a glassy state,⁷ which has been pictured as acting like amber, encaging molecules and membranes in the same way that amber traps insects. The higher glass transition temperature T_g of trehalose ($T_g \approx 393$ K^{8,9}) could explain its

greater preservation efficiency compared to maltose ($T_g \approx 373$ K^{8,9}), sucrose ($T_g \approx 348$ K^{8,9}), or other protectants (glucose, sorbitol, xylitol, etc.).^{9–11} Nevertheless, it is now well-accepted that biopreservative efficiency does not necessarily scale with the glass transition temperature, as was shown for glycerol,¹² trehalose–glycerol mixtures,¹³ or poly(vinylpyrrolidone) (PVP) and dextran polymers.^{2,14} Thus, other glass properties such as fragility, anharmonicity, or intimate interactions of cosolvents with biomolecules via hydrogen bonds (HBs) must be involved.

Crowe et al.¹⁵ suggested that sugar molecules were able to directly interact with the polar groups of membranes¹⁶ or proteins¹⁵ via HBs, by substituting for the hydration water shell, essential for proteins structure, dynamics, and activity. This would preserve the three-dimensional structure of biomolecules even at low water content and is referred to as the “water replacement” hypothesis.¹⁶ Trehalose would be able to replace more water molecules than other sugars and even to bind to nonpolar groups of proteins owing to its higher flexibility as proposed by Oku et al.¹⁷ The water replacement hypothesis seems reasonable for water-binding sites at the protein surface, and indeed, it has been demonstrated from a myriad of experiments^{15,14} that trehalose can be directly hydrogen-bonded to proteins. However, it is less plausible for internal water molecules. Indeed, it seems improbable that one trehalose molecule could enter into confined regions of proteins.¹⁸

Moreover, Timasheff et al.¹⁹ have shown that many cosolvents are *preferentially excluded* from the first hydration shell of proteins, at moderate concentrations. Among these osmolytes, trehalose was found to be the most preferentially excluded,²⁰ thus inducing the greatest thermodynamic stabilization. Although this mechanism might not hold at low water contents, Belton and Gil,²¹ in view of Raman results, proposed that the protein hydration layer is preserved, even at very high dehydration levels. These water molecules trapped in the glassy matrix

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formed by trehalose would allow a protein to preserve its native structure and its internal dynamics necessary to accomplish its biological function.

Alternatively, an approach based on the *destructuring effect* of sugars on the water hydrogen bond network (HBN) has been proposed by Magazù et al.²² from numerous experiments such as infrared and Raman spectroscopies,^{22,23} NMR, and ultrasound measurements.²³ They particularly demonstrated that trehalose promotes a more extended hydration than other disaccharides and binds more strongly to water molecules, thus preventing more efficiently the crystallization of ice, which causes lethal damage to biosystems. This hypothesis seems well-suited to explain the enhanced cryoprotective efficiency of trehalose but not its lyoprotective one.

Finally, Cesàro et al.²⁴ point out the possible role of the polymorphic forms of sugars in the anhydrobiosis phenomenon. The metastable α form of trehalose, T_α , is actually produced from the dihydrate crystal T_{2H_2O} ²⁵ only below a given threshold rate of water removal above which dehydrated regions become amorphous.²⁶ Depending on humidity levels, T_α may reversibly transform into T_{2H_2O} within time scales compatible with the anhydrobiotic protection, i.e., that does not induce rapid changes in the volume or internal pressure of cells. This dehydration–hydration mechanism may play a key role in anhydrobiosis because crystallization of trehalose is easier in NaCl salt aqueous solutions²⁷ and thus in cells, owing to the probable presence of charged solutes or macromolecules.

A considerable amount of simulation results has been accumulated on binary sugar–water solutions^{28,29,30–38} or ternary protein or membrane–sugar–water systems.^{39–42} Most studies of binary mixtures deal with the dilute case (a few wt %)^{28,29,31–33,36} and analyze at ambient temperature (~ 300 K), e.g., sugar hydration properties via radial and orientational distribution functions, hydration numbers, intrinsic conformations through adiabatic maps, radii of gyration, autocorrelation functions of glycosidic dihedral angles, and sugar and water mobilities by means of translational and rotational diffusion coefficients. Investigations of concentrated mixtures are much fewer. Roberts et al.³⁰ studied 4–80 wt % aqueous solutions of three homologous monosaccharides (namely, β -D-glucose, β -D-mannose, and D-fructose) and pointed out significant effects of the sugar stereochemistry on the diffusion coefficient of water and on the structure and relaxation of the HBN in these solutions. Moreover, Ekdawi-Sever et al.^{35,37} and Conrad et al.³⁴ have investigated sucrose and trehalose aqueous solutions from 6–80 wt % and even above. They found a larger hydration number for trehalose³⁵ for each concentration investigated as well as a diffusion coefficient of sucrose consistently larger than that of trehalose at high concentration (72 wt % or above).³⁷ Finally, Molinero et al.³⁸ studied concentrated water–sucrose systems (50–100 wt %). They showed percolation of the sucrose HBN in the range of 60–67 wt % at 333 K and suggested that the formation of the sucrose network may increase both the mixture resistance to shear deformation and mechanical stability observed experimentally.

Simulations of ternary systems have also provided relevant results. Sum et al.³⁹ and Pereira et al.⁴⁰ published results on simulations of a lipid membrane in the presence of sugars and found evidence for direct HBs with specific parts of the lipid molecules, consistent with previous experiments. Moreover, Lins et al.⁴¹ proposed a model of trehalose–lysozyme interaction on the nanosecond scale and at moderate concentration (18 wt %) in agreement with the suggestion of Belton and Gil,²¹ which

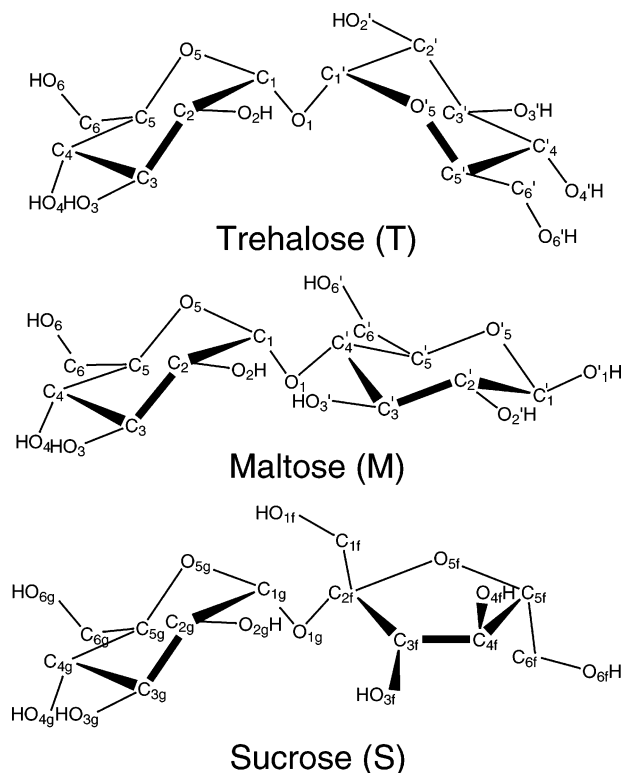


Figure 1. Schematic representation of the studied disaccharides: trehalose (T), maltose (M), sucrose (S). Only hydrogen atoms belonging to hydroxyl groups have been represented for clarity reasons. Moreover, the glucose and fructose rings of sucrose are identified by the g and f subscripts, respectively.

was also inferred by Cottone et al.⁴² from simulations of carboxymyoglobin in trehalose (50–89 wt %).

To obtain a deeper understanding of disaccharide–water solution structural properties in the framework of the biopreservation problem, we have carried out a careful comparative study of trehalose, maltose, and sucrose in aqueous solutions by molecular dynamics (MD) simulations. The hydrogen-bonding capabilities of these three sugars are directly comparable since they possess the same chemical formula $C_{12}H_{22}O_{11}$ and the same number of OH groups. Water–water, water–sugar, and both intra and inter sugar–sugar properties and their relationships have been probed to measure the homogeneity of the different mixtures. Different relevant structural parameters have been used: partial static structure factors, two-dimensional (2D) radial distribution functions, probability of HB formation, water cluster size, hydration number, molecular flexibility, and sugar cluster size. The main goal of this work was to analyze the physical property changes of the water–sugar solutions upon increasing the sugar concentration, to identify pertinent parameters aiming to explain the superior bioprotective effectiveness of trehalose, and to discuss these results in the framework of the different suggested hypotheses. A schematic model of the structure of sugar–water mixtures showing the destructuring effects of the different sugars on the water HBN is proposed.

2. Details of the Simulation

MD simulations have been performed using the molecular dynamics package DL_POLY_2.⁴³ α , α -trehalose, β -maltose, and sucrose disaccharides (Figure 1) have been investigated and are referred to in the remaining part of the paper as trehalose (T), maltose (M), and sucrose (S), respectively. Disaccharide molecules have been considered flexible and have been modeled

TABLE 1: System Compositions, Densities, and Equilibration/Simulation Times at $T = 293$ K at Different Sugar Concentrations ϕ^a

ϕ (wt %)	no. sugars/no. H ₂ O	density(g cm ⁻³)			equilibration/simulation time (ns)		
		T	M	S	T	M	S
0	0/512	1.005	1.005	1.005	0.1/0.3	0.1/0.3	0.1/0.3
4	1/512	1.020	1.020	1.020	0.1/0.4	0.1/0.4	0.1/0.4
16	5/512	1.076	1.078	1.076	0.1/0.4	0.1/0.2	0.05/0.15
33	13/512	1.167	1.168	1.168	0.1/0.4	0.15/0.35	0.125/0.375
49	26/512	1.269	1.276	1.273	0.2/0.8	0.3/0.7	0.125/0.375
66	52/512	1.379	1.392	1.377	0.25/1.75	0.5/1.0	0.25/1.75

^a Data corresponding to $\phi = 0$ wt % result from only one simulation of pure water.

using the well-known all-atom force field designed for carbohydrates developed by Ha et al.,⁴⁴ which has been extensively employed.^{28,29,45} The SPC/E model⁴⁶ has been used to represent water molecules whose geometry has been constrained using the SHAKE algorithm.⁴⁷ This model is known to give a too stiffly structured water, but it realistically describes the diffusion coefficient of water at ambient temperature. To check the dependence of our results on the water model, some additional simulations have been performed using the TIP3P water model.⁴⁸ A cutoff radius of 10 Å has been used to account for nonbonded interactions. Electrostatic interactions have been handled by the reaction-field method using the permittivity constant $\epsilon = 72$. Since a concentrated disaccharide solution has a relatively low dielectric constant, we checked the validity of the reaction-field method by performing one MD simulation of the 66 wt % sucrose solution at $T = 373$ K using an Ewald summation. No significant structural or dynamical difference has been found between both techniques. The compressibility of the simulated solutions was that of water (it is a parameter of the DL_POLY_2 program). A Lennard-Jones potential has been employed to represent van der Waals interactions, and Lorentz–Berthelot mixing rules have been used for cross-interaction terms. MD simulations have been realized in the *NPT* statistical ensemble where the number of molecules N , pressure P , and temperature T are fixed. The pressure has been set to 1.0 bar using weak coupling to a pressure bath (Berendsen barostat⁴⁹) with a relaxation time of 1.0 ps. The investigated temperatures range from 273 to 373 K in steps of 20 K. They have been maintained constant during a given simulation using weak coupling to a heat bath (Berendsen thermostat⁴⁹) with a relaxation time of 0.1 ps. Newton's equations of motion have been integrated using the Verlet leapfrog algorithm.⁵⁰ The simulation lengths range from 200 ps to 2 ns depending on concentrations and temperatures with a time step of 0.5 fs for the binary aqueous solutions and 2 fs for pure water. The 0.5-fs time step is justified by the flexible O–H bonds of the carbohydrates hydroxyl groups. The disaccharide initial conformations have been deduced from neutron and X-ray studies (trehalose,²⁵ maltose,⁵¹ and sucrose⁵²). Starting positions of the sugar and the water molecules have been arbitrarily chosen on a cubic lattice. To remove local contacts that result from this construction, short simulations with a thermostated temperature of 0 K and a small time step have been performed. Simulated systems are composed of $N_w = 512$ water molecules and $N_s = 0, 1, 5, 13, 26$, or 52 sugars molecules (either trehalose, maltose, or sucrose) corresponding to weight concentrations of 0, 4, 16, 33, 49, or 66%, respectively. These systems have been considered to be large enough to give size-independent results. Moreover, they cover a relatively broad concentration range. Depending on the temperature and concentration, each system has been equilibrated from 50 to 500 ps, and configurations have then been saved with time intervals that ranged between 0.05 and 0.5 ps. Table 1 summarizes simulation data for $T = 293$ K.

3. Water–Sugar Interactions

3.1. Comparison of Experimental and Simulated Static Structure Factors. As a means to obtain some insights on the structure of disaccharide–water solutions, we have computed the static structure factor $S(\mathbf{Q})$, which can be classically obtained from coherent neutron scattering experiments⁵³ from $S(\mathbf{Q}) = \langle |\rho_{\mathbf{Q}}|^2 \rangle$, where $\rho_{\mathbf{Q}}$ is the time-dependent density correlator defined as $\rho_{\mathbf{Q}}(t) = \sum b_{\alpha} \exp(i \cdot \mathbf{Q} \cdot \mathbf{r}_{\alpha})$. The sum is over all the α atoms of the system, b_{α} and $\mathbf{r}_{\alpha}$ are the coherent scattering length and the position of the α atom, respectively. An average over isotropically distributed $\mathbf{Q}$ -vectors that have the same modulus Q is performed to obtain $S(Q)$. Partial static structure factors $S_{HH}(Q)$ and $S_{XX}(Q)$ are obtained by only including or only excluding in the summation both the hydrogen atoms of sugar and water molecules.

Figure 2 shows a comparison between the partial static structure factors $S_{HH}(Q)$ and $S_{XX}(Q)$ of the 49 wt % trehalose–water solutions and of pure water obtained experimentally from neutron diffraction^{54,55} and those from the present MD study. The $S_{HH}(Q)$ and $S_{XX}(Q)$ of the 49 wt % sucrose and maltose aqueous solutions are also given for comparison, although no experimental data is available. The agreement found between both techniques is good and found better for the $S_{XX}(Q)$ than for the $S_{HH}(Q)$, particularly at $Q \leq 3 \text{ Å}^{-1}$. This arises from the difficulty to reproduce precisely relative positions of hydrogen atoms, which strongly depend on the orientation of water molecules and of sugar hydroxyl groups. The peak observed at $Q \approx 2 \text{ Å}^{-1}$ for pure water seems to decrease with the addition of sugars. This could be representative of a lowered tetrahedral order of water molecules. Nevertheless, no striking and meaningful difference is observed between the partial $S_{HH}(Q)$ of the three sugar–water solutions. Similarly, the modification of the peak observed at $Q \approx 2.2 \text{ Å}^{-1}$ in the $S_{XX}(Q)$ of pure water, representative of hydrogen-bonded water molecules, may suggest a decrease of the tetrahedrality of water upon increasing the sugar concentration. However, the rather large contributions from sugar molecules in the $S_{HH}(Q)$ and $S_{XX}(Q)$ of mixed solutions (about one-third and one-half of the number of considered atoms for the calculations, respectively) makes this kind of analysis quite hazardous. Therefore, the shift observed in the $S_{XX}(Q)$ of the peak at about $Q \approx 2 \text{ Å}^{-1}$ for pure water may be attributed to differences in the conformation and topology of sugars. Interestingly, significant discrepancies are observed between the three studied solutions at $Q \leq 1 \text{ Å}^{-1}$, which represents distances of intermolecular interactions between sugars, and where the water contribution is quite low. This motivates a more detailed analysis, which could be performed by separating contributions from both sugar and from water molecules, therefore probing their complex structures. However, a careful analysis of the HBN of these solutions will be presented in a different manner in the following.

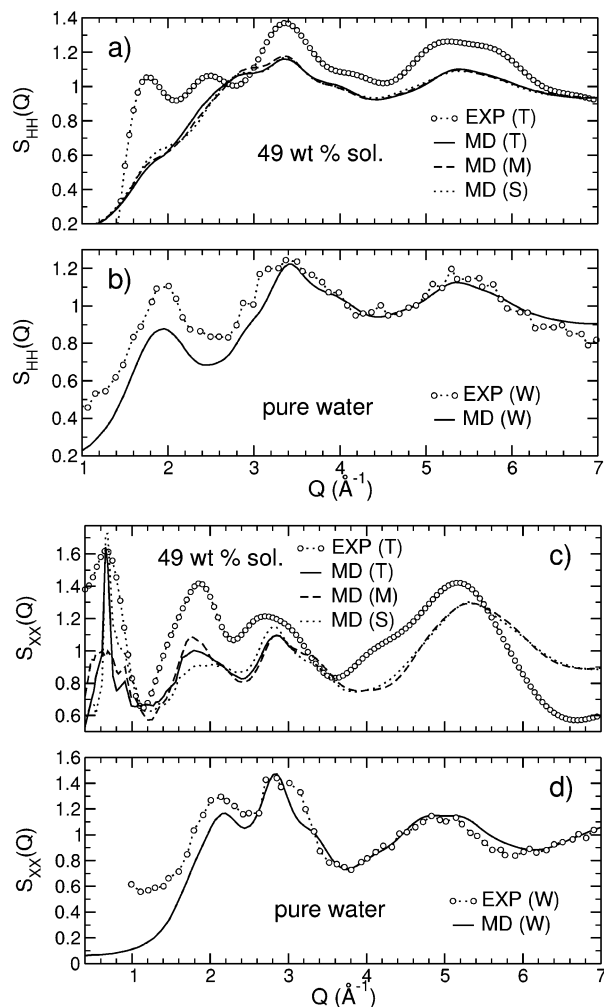


Figure 2. Partial static structure factors $S_{HH}(Q)$ of hydrogen atoms (a) and $S_{XX}(Q)$ of all atoms distinct from hydrogen (c) for the 49 wt % sugar–water solutions obtained from the present MD investigation at $T = 293$ K and from experiments (for trehalose only) at $T = 300$ K.^{54,55} Data for pure water obtained from MD simulation and experiment⁵⁶ are also included (parts b and d).

3.2. Crystallinity of Trehalose–Water Solutions. As indicated in the Introduction, some authors suggested that the rich crystalline polymorphism of trehalose could be involved in the origin of its superior bioprotective capability.²⁴ From neutron scattering experiments, Magazù et al. recently showed that trehalose possesses a more crystalline character than sucrose and maltose, which could provide a more rigid environment for protecting biological structures.⁵⁷ Furthermore, Engelsen et al.⁵⁸ demonstrated that the trehalose hydration pattern in dilute solution (~ 4 wt %) resembles that of the trehalose dihydrate crystal.²⁵ Inspired by this latter work, we compared the hydration sites of highly concentrated water–trehalose solutions with those of the trehalose dihydrate crystalline phase. Two-dimensional radial $g(r_1, r_2)$ distribution functions have been computed and are defined as

$$g(r_1, r_2) = \frac{N(r_1, r_2)}{\rho_W V_{\text{intersect}}(r_1, r_2, \Delta r)} \quad (1)$$

An exhaustive description of $g(r_1, r_2)$ functions is given in ref 58, so we give here only the essential details. $g(r_1, r_2)$ gives the probability of finding a water oxygen atom at a distance r_1 and r_2 from two selected solute oxygen atoms, O_2 and O'_2 (Figure 1), relative to the probability expected for a random

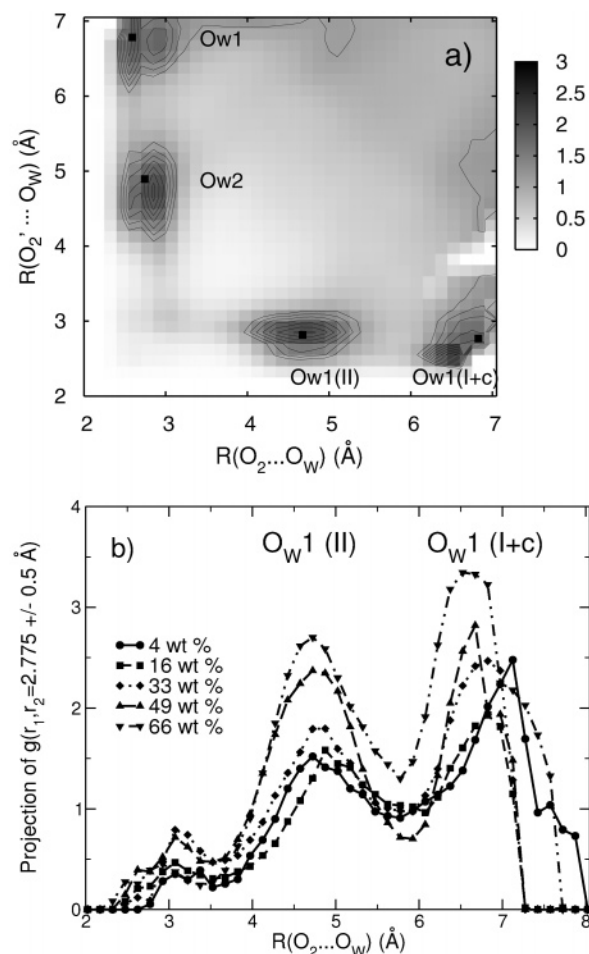


Figure 3. (a) Normalized $g(r_1, r_2)$ pair distribution of the 49 wt % trehalose–water solution at 293 K. r_1 and r_2 correspond to the distance between the water oxygen atoms and the O_2 and O'_2 oxygen atoms of the trehalose molecules, respectively. Black squares indicate the position of the two water molecules of the trehalose dihydrate crystal, $Ow1$ and $Ow2$. Symmetries are indicated in parentheses (see text and ref 58). (b) Projection of $g(r_1, r_2)$ at $r_2 = 2.78 \pm 0.5$ Å for the different trehalose–water solutions at 293 K.

distribution. $N(r_1, r_2)$ denotes the number of water oxygens at distances r_1 and r_2 from the two selected solute atoms, averaged over all of the solute molecules and the configurations of the simulation. $\rho_W = N_W/V$ stands for the mean water density of the simulated system, and $V_{\text{intersect}}(r_1, r_2, \Delta r)$ designates the intersection volume between the two shells of inner radii r_1 and r_2 and thickness Δr . Figure 3a shows the normalized $g(r_1, r_2)$ pair distribution of the 49 wt % trehalose–water solution at 293 K. It is clearly seen that water molecules are localized in particular regions of the 2D distribution, the maximum of which corresponds to the hydration sites found in the dihydrate crystal. Four sites are particularly observed, $Ow1$, $Ow2$, $Ow1(II)$, and $Ow1(I+c)$, following the same nomenclature as in ref 58 where I and II denote the trehalose dihydrate $P2_12_12_1$ symmetry operations (x, y, z) and $(-x + 1/2, -y, z)$, respectively. A good agreement has been found with the $g(r_1, r_2)$ of ref 58 for the 4 wt % solutions, with both the TIP3P and SPC/E water models (data not shown). The symmetry observed in the hydration pattern of trehalose is consistent with the approximate 2-fold symmetry found in the trehalose dihydrate crystal.²⁵ This means that the most probable trehalose conformation in solution is rather close to the conformation in the dihydrate crystal, as shown in refs 29 and 58. The concentration dependence of the water density at 293 K is depicted in Figure 3b, which shows

the $g(r_1, r_2)$ at $r_2 = 2.78 \pm 0.5$ Å, i.e., in the region where the O_{W1} water molecule of the dihydrate structure should be found.

A significant increase in the localization of water molecules at the O_{W1} and O_{W2} (not shown) hydration sites of the trehalose dihydrate crystal is observed. This result reveals that the position of the water molecules is more and more sterically restricted as the concentration of sugar increases. It clearly supports the results obtained by Magazù et al. on the crystallinity of trehalose–water solutions.⁵⁷ It should be noted that similar results were obtained for a maltose–water solution for which water molecules are found to be preferentially localized on the water site of the monohydrate structure (data not shown).⁵¹ The localization of water molecules seen in the present investigation is consistent with the suggestion of Aldous et al.⁵⁹ that the dihydrate trehalose state works as a sponge for water molecules. Indeed, the air-exposed part of the glassy trehalose may quite easily transform into the dihydrate crystal form, which could further stabilize the sugar matrix. On the contrary, a small amount of absorbed water will readily plasticize the sucrose matrix, since it cannot form any hydrated crystalline phase. Finally, maltose should be intermediate between trehalose and sucrose, since it may exist in a monohydrate crystalline form. Hydration properties of sugars will be analyzed in the following.

3.3. Hydration Numbers. Since trehalose, maltose, and sucrose possess the same number of hydroxyl groups, the average number of water molecules hydrogen-bonded per disaccharide provides a useful parameter to quantify the water–disaccharide interaction. This parameter will be identified as the hydration number n_H in the following although in the literature it often refers to the total number of water molecules in the solvation sphere.⁵⁸

Two different geometric criteria commonly used in molecular dynamics studies^{29,30} were defined and called I and II in the following. In the present study, two molecules are considered to be hydrogen-bonded if the oxygen–oxygen distance d_{OO} is less than 3.4 Å and the $O-H\cdots O$ angle is larger than 160° or 120° for the criterion I or II, respectively. The criterion I³⁰ relates to relatively well-formed and thus strong HBs whereas the less stringent criterion II²⁹ also includes more deformed, weaker HBs. Owing to the strong dependence of the HB energy on the $O-H\cdots O$ angle, both criteria may probe different populations of HBs and will therefore be used in the present paper. Moreover, we have not considered the energetic criteria because of the difficulty to define with any ambiguity water–solute HBs, as pointed out by Brady et al.²⁸

Figure 4 shows the hydration number n_H of the three studied disaccharides as a function of the disaccharide concentration at $T = 273$ and 373 K. We clearly see that n_H decreases monotonically by a factor of about 2 for both criteria when the concentration increases from 4 to 66 wt %. For the most dilute solutions, disaccharides are surrounded by several hydration layers, and their structure mainly results from their intrinsic interaction with water. At higher concentrations, disaccharides begin to share water molecules and to form sugar–sugar HBs. Table 2 presents the sugar–sugar HBs statistics (criterion II) at $T = 293$ K. As expected, the normalized mean number of intermolecular sugar–sugar HBs steadily increases with concentration. But most important, significant differences appear among sugars. Indeed, sucrose (maltose) forms the lowest (largest) number of HBs in the concentration range where intermolecular HBs become meaningful, i.e., 33–66 wt %. Trehalose forms slightly fewer intermolecular HBs than maltose does. This has direct consequences in the clustering differences between sugars, as will be shown in section 4.2 of this paper.

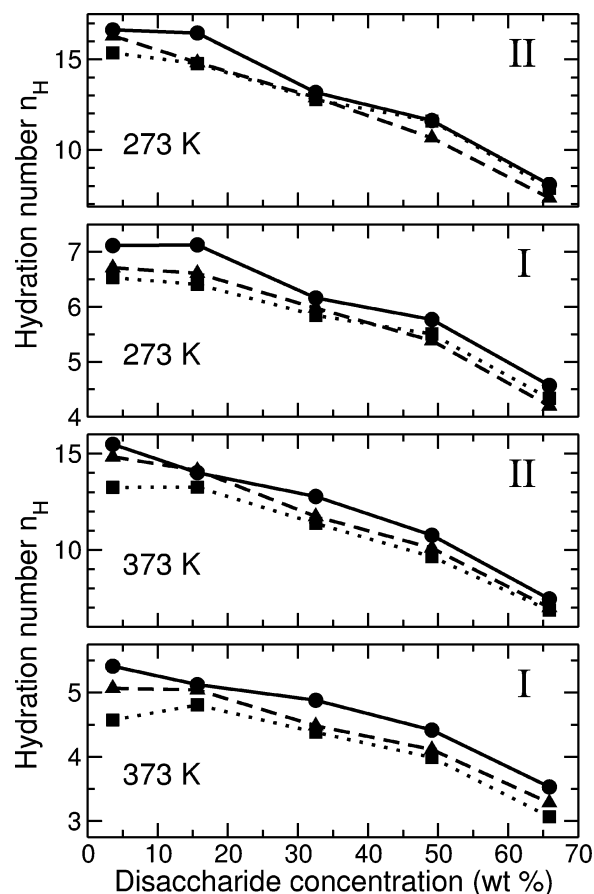


Figure 4. Hydration number n_H of trehalose (solid line), maltose (dashed line), and sucrose (dotted line) as a function of their concentration at two temperatures (273 and 373 K) and for both geometric criteria I and II (see text for definition of geometric criteria).

TABLE 2: Normalized Mean Number of Sugar–Sugar Intermolecular $\langle n_{HB} \rangle_{inter}/N_S$ and Intramolecular $\langle n_{HB} \rangle_{intra}/N_S$ HBs for the Sugar–Water Solutions at $T = 293$ K at Different Sugar Concentrations ϕ^a

ϕ (wt %)	$\langle n_{HB} \rangle_{inter}/N_S$			$\langle n_{HB} \rangle_{intra}/N_S$		
	T	M	S	T	M	S
4	0.000	0.000	0.000	0.304	0.739	2.490
16	0.153	0.361	0.266	0.146	0.455	1.962
33	0.767	0.853	0.435	0.141	0.373	2.058
49	1.322	1.942	0.738	0.451	0.346	2.210
66	2.689	2.985	2.293	0.175	0.400	1.979

^a The broken brackets denote time-averaging over stored configurations, and N_S designates the number of sugars in the simulation box.

From Figure 4, trehalose is found to be more hydrated than sucrose and maltose, whatever the concentration and the geometric criterion considered, in good agreement with Ekdawi-Sever et al.³⁵ They have obtained similar results when comparing sucrose and trehalose at 353 and 360 K, respectively, in the 6–90 wt % concentration range. They particularly suggested that the intramolecular HBs were at the origin of the difference observed between both sugars. Table 2 clearly confirms this hypothesis. It is indeed well-known that maltose and sucrose form intramolecular HBs in their crystalline state on the contrary to trehalose.^{25,51,52} The crystalline β -maltose forms one intramolecular HB between O_2-HO_2 and O_3' . Two intramolecular HBs, namely, $O_{6f}-HO_{6f}\cdots O_{5g}$ and $O_{1f}-HO_{1f}\cdots O_{2g}$ are present in crystalline sucrose. As a consequence, the disaccharide HB centers (i.e., hydroxyl hydrogen and oxygen atoms) involved in intramolecular HBs no longer remain available for water–

TABLE 3: Hydration Numbers n_H of Trehalose, Maltose, and Sucrose Molecules Computed from the Present Investigation Using Both SPC/E and TIP3P Models at $T = 293$ K

n_H	SPC/E	TIP3P	other MDs ^a	experiments ^d
trehalose	6.5 (I)	6.1 (I)	7.8, ^b 58 ^{13.4} , ³⁴ 18.9 ³²	7.95, ⁶² 10.9, ⁶³ 12.1 ⁶¹
	16.4 (II)	16.8 (II)	22.5, ²⁹ 27.5 ^c 58	15.2 ⁶¹ , 15.3 ⁶⁰
maltose	6.5 (I)	5.7 (I)	10–11, ⁶⁴ 22.6 ²⁸	6.50, ⁶² 9.5, ⁶³ 11.7 ⁶¹
	16.1 (II)	16.1 (II)		14.2, ⁶¹ 14.5 ⁶⁰
sucrose	6.2 (I)	5.6 (I)	7.0, ^b 65 ^{11.7} , ³⁵ 24.7 ^c 65	6.33, ⁶² 8.5, ⁶³ 11.2 ⁶¹
	14.8 (II)	15.1 (II)		13.8, ⁶¹ 13.9 ⁶⁰

^a n_H obtained from other computer simulations. ^b $d_{OO} \leq 3.5$ Å. ^c $d_{OO} \leq 2.8$ Å. ^d Experiments (acoustic,^{60,61} viscosity,⁶¹ and calorimetric^{62,63} measurements) are also indicated for comparison.

disaccharide HBs. The large number of intramolecular HBs of sucrose relative to trehalose and maltose for the 4 wt % concentration explains why its hydration number is significantly lower, while those of maltose and trehalose are rather similar. Moreover, a crossover between maltose and sucrose hydration curves is found at temperatures lower than 353 K, as exemplified in Figure 4 at $T = 273$ K. This could arise from different concentration dependences of the relative number of intramolecular HBs and intermolecular HBs between sucrose and maltose. Indeed, the difference between $\langle n_{HB} \rangle_{\text{inter}}/N_S$ of maltose and sucrose steeply increases above 33 wt % disaccharide concentration. Meanwhile, the difference between $\langle n_{HB} \rangle_{\text{intra}}/N_S$ of maltose and sucrose changes moderately. Therefore, the overall effect is a more pronounced decrease of maltose hydration numbers compared to sucrose when increasing disaccharide concentration.

Hydration numbers of the 4 wt % disaccharide solutions at $T = 293$ K are given in Table 3. Trehalose clearly binds to a larger number of water molecules, and consequently the water structure will be more affected by this sugar than the others as will be shown in the next section of this paper devoted to water structure. The higher hydration number of trehalose is also seen to be independent of the choice of the model of water as proven by the additional calculations performed using the TIP3P water model (Table 3). A good agreement is particularly obtained between both SPC/E and TIP3P models. $n_H(I)$ obtained from the SPC/E water model is slightly higher than that obtained with TIP3P. This may be understood as the stronger water–disaccharide HBs formed with SPC/E by means of the larger water partial charges. In addition, hydration numbers calculated in this study may rather be dependent on the potential energy landscape (PEL) of sugars explored within the length of simulations. For computation time reasons, it was not possible to explore each minima of the adiabatic map of sugars. Moreover, only the β -anomeric form of maltose was considered here, whereas an equilibrium between the β - and the α -form of maltose establishes in reality. Several hydration numbers found in the literature from experimental and other numerical studies are also reported in Table 3 for comparison. A fair agreement is obtained with our present results, which confirms that trehalose always possesses the higher hydration number. Discrepancies can be due to the very different definitions of the hydration number found in the literature and the various approaches and models used to derive hydration numbers from ultrasound, density scanning calorimetry, viscosity, or water activity measurements. Nevertheless, the two geometric criteria employed in this study seem to be well-suited to distinguish, within the first hydration shell, strongly hydrogen-bonded (I) water molecules from weakly hydrogen-bonded (II) water molecules. These two types of HBs could be at the origin of the differences observed experimentally.

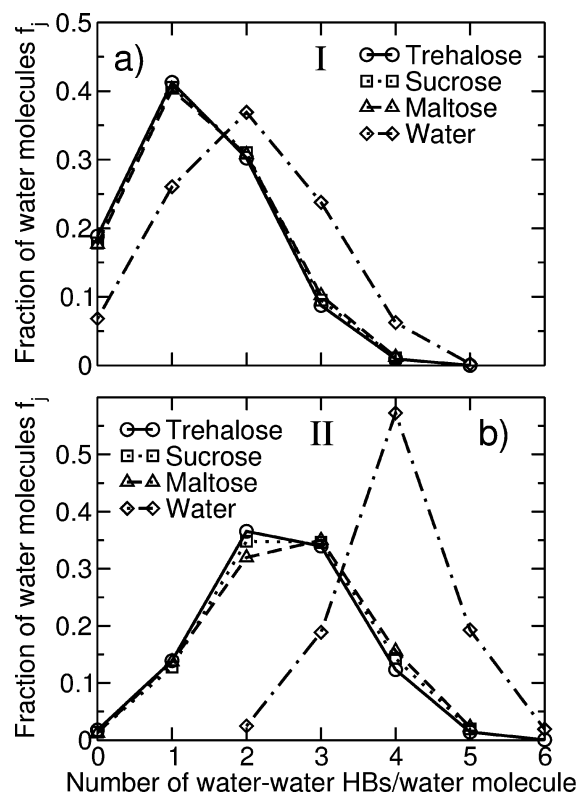


Figure 5. Fractions f_j of water molecules forming j HBs with other neighboring water molecules for the 66 wt % solutions and for pure water (dot-dashed line) at $T = 293$ K: (a) using criterion I, (b) using criterion II.

3.4. HB Probability. The hydrogen bond network of water may be described by the fractions f_j of water molecules that form j HBs with their neighboring water molecules.⁶⁶ Indeed, water molecules would be involved in four water–water linear HBs (two as proton donor and two as proton acceptor) in perfect ice, because each one is surrounded by four neighbors that form a perfect tetrahedron. In real water, deviations from this ideal view occur, and bifurcated HBs as well as non-hydrogen-bonded hydroxyl groups exist.⁶⁷ Raman scattering studies on the O–H stretching band of water as function of temperature reveal the existence of an isobestic point.⁶⁸ From this observation, some authors proposed an arbitrary decomposition of the Raman spectrum of water into two temperature-independent classes of water molecules, denoted as “open” (or intact bond) and “closed” (or broken bond). The former was assigned to tetrahedrally bonded water molecules, while the latter to the remaining water molecules, including bifurcated HBs, free OH groups, etc.

Figure 5 shows the populations f_j of water molecules that form j HBs with their neighboring water molecules for the 66 wt % solutions and for pure water at $T = 293$ K, using the two criteria previously defined. Distributions using criterion II show a shift to larger numbers of water–water HBs compared to criterion I because it is less stringent. As expected, the maximum of the distribution for pure water is 4 for criterion II. Nevertheless, the distribution is quite broad as a consequence of thermal disorder and may exceed 4 owing to the bifurcated HBs that are likely to occur. Addition of disaccharide molecules to the solutions leads to a significant shift of the maximum of the distribution toward lower values because of the formation of water–disaccharide HBs. Trehalose appears to increase populations of water molecules with low j (below 2 and 3 with I and II, respectively) and to decrease populations of water molecules

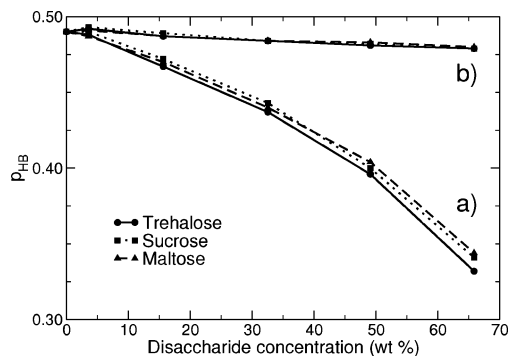


Figure 6. Concentration dependence of the probability of HB formation p_{HB} as deduced from eq 2 for the disaccharide solutions at $T = 293$ K using criterion I: (a) for all water molecules, (b) excluding water molecules of the first hydration shell (defined using criterion II).

with high j (above 2 and 3 with I and II, respectively) more than sucrose and maltose. This result is a direct consequence of the difference observed in the hydration numbers. Therefore, the tetrahedral HBN of water will be more disrupted in the presence of trehalose than with sucrose or maltose. This agrees with numerous experimental studies showing a higher *destruc-turing effect* of trehalose compared to sucrose and maltose as has been particularly demonstrated by Magazù et al.²² from Raman scattering experiments.

When the concept of intact and broken bonds is referred to, it is possible to deduce p_{HB} , the probability of forming an intact bond from the previous distributions. Indeed, assuming that the HB formation is not cooperative⁶⁹ and the coordination number in liquid water is 4, the fraction f_j follows the binomial distribution⁶⁶

$$f_j = \binom{4}{j} p_{HB}^j (1 - p_{HB})^{4-j} \quad (2)$$

Figure 6 shows the concentration dependence of p_{HB} of the disaccharide solutions at 293 K obtained from eq 2 using the geometric criterion I, which was chosen so that j ranges from 0 to 4 for pure water (f_5 is negligible with criterion I). Attempts to compute p_{HB} with criterion II did not lead to satisfactory fits of eq 2 using 5 or 6 as the maximum coordination number and thus are not presented. The observed decrease of p_{HB} mainly arises from the substitution of water–water HBs with water–sugar HBs when increasing disaccharide concentration. As a consequence, the evolution of p_{HB} as function of the concentration is directly controlled by the sugar hydration numbers discussed previously. This is well-demonstrated in Figure 6b when water molecules from the first shell were excluded. Indeed, p_{HB} clearly becomes less dependent on the sugar concentration and nearly constant. This figure also shows that the difference between sugars is largely reduced beyond the first-neighbor water layer. When the first hydration shell is excluded, no difference between sugars is observed. This conclusion was already highlighted in our preliminary numerical work⁷⁰ from the distributions of the orientation parameter q defined by Debenedetti et al.⁷¹ As a consequence, it appears that hydration numbers mainly rule the difference observed among sugars, within the investigated concentration range. The higher hydration number of trehalose explains its enhanced ability to disturb the HBN of water, revealed by the lowest p_{HB} for trehalose–water solutions. It should be noted that these results are in fair agreement with those obtained experimentally by Branca et al.²²

3.5. Water Clusters. Finally, we consider water clusters formed in the disaccharide–water solutions. Clusters of class i

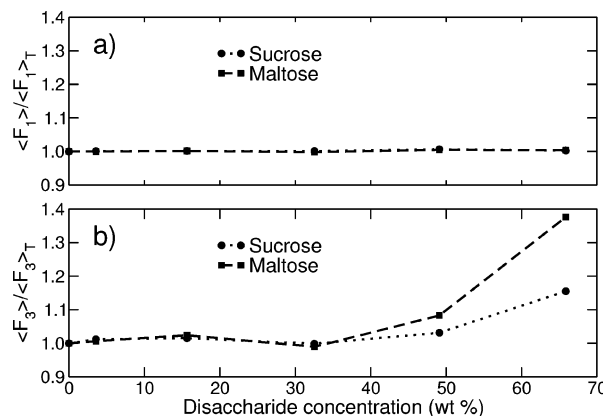


Figure 7. Concentration dependence of the normalized ratios (a) $\langle F_1 \rangle / \langle F_1 \rangle_T$ and (b) $\langle F_3 \rangle / \langle F_3 \rangle_T$ of sucrose and maltose solutions at $T = 273$ K, using criterion I. $\langle F_i \rangle$ stands for the time-averaged fraction of water molecules involved in clusters of class i , and the subscript T refers to the trehalose solutions.

were defined as ensembles of water molecules hydrogen-bonded with each other and forming at least i water–water HBs according to criterion I. Criterion I is more suited to probe the local tetrahedral arrangement of water molecules since it characterizes well-formed HBs, contrary to criterion II which allows distorted configurations of water molecules. Alternatively, clusters could be defined using an order parameter such as the orientation parameter q suggested by Debenedetti et al.⁷¹ In this case, a cluster is defined as an ensemble of water molecules that have a q parameter greater than a threshold value q_c ⁷² and are separated by a distance smaller than r_c .

On one hand, clusters of class 1 encompass both water molecules in a tetrahedral arrangement and in more distorted configurations. Ambient water may then be described as a space-filling percolating HBN, as shown in previous papers.^{70,73} On the other hand, clusters of class 3 or 4 involve only water molecules in nearly tetrahedral configurations. Such clusters are thus relatively small at ambient temperature and may be viewed as precursor nuclei of the crystallization of ice. The addition of sugars makes the probability of finding large numbers of such clusters very small. Therefore, we focus our attention on the analysis of the proportion of water molecules included in each class i as a means to clearly distinguish the effects of the three disaccharides. We define $\langle F_i \rangle$ the fraction of water molecules involved in clusters of class i (broken brackets mean time-averaging over the simulation length). Figure 7 shows the fraction of water molecules $\langle F_i \rangle$ of sucrose and maltose for clusters of classes 1 and 3 at $T = 273$ K normalized by $\langle F_i \rangle_T$, the fraction of water molecules forming clusters of class i in the presence of trehalose. $\langle F_1 \rangle$ of trehalose, maltose, or sucrose are found identical at all concentrations. This indicates that the total number of water molecules involved in clusters is nearly independent of the studied sugars whatever the considered concentration, at $T = 273$ K. In other words, the fraction of water molecules not hydrogen-bonded with at least one water neighbor is essentially the same in the various disaccharide solutions. However, water molecules reorganize in clusters of different sizes in the trehalose, sucrose, and maltose solutions at concentrations above $\phi_A \approx 40$ wt %.⁷⁰ Indeed, the mean cluster size $\langle n_W \rangle$ of water clusters at these concentrations is the lowest in trehalose solutions, trehalose breaking clusters into smaller ones more efficiently (see Figure 1 of ref 70), well in line with its higher hydration number. As shown in Figure 7b, the $\langle F_3 \rangle / \langle F_3 \rangle_T$ ratios of sucrose and maltose exhibit a significant departure from 1.0 at concentrations above ϕ_A . Most of the water

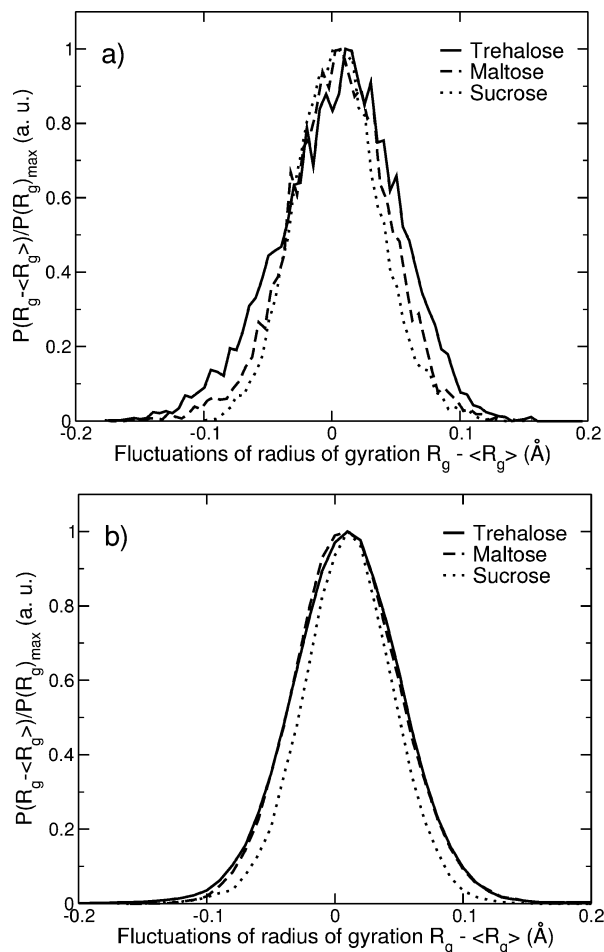


Figure 8. Rescaled distributions of fluctuations of the radius of gyration R_g of trehalose, sucrose, and maltose at $T = 293$ K for (a) the 4 wt % solutions and (b) the 49 wt % solutions. $\langle R_g \rangle$ denotes the time-averaged radius of gyration, and $P(R_g)_{\max}$ stands for the maximum of probability of the distribution $P(R_g)$.

molecules feel the presence of disaccharides above ϕ_A , owing to comparable numbers of water–sugar and water–water HBs. That is the reason why discrepancies among the three disaccharides increase and why trehalose is found to reduce the number of locally tetrahedral water regions, precursors of ice crystallization, more than sucrose and maltose (see also Figure 6). These ice nucleators become small and rare at these high concentrations, at $T = 273$ K. For example, only 6–9% of water molecules participate in clusters of classes 3 and 4 in the 66 wt % solutions at $T = 273$ K. This may be understood as the very low probability of finding a water molecule surrounded by four other neighboring water molecules not forming too many HBs with sugars, so that they can adopt positions and orientations compatible with a regular hydrogen-bonded water tetrahedron. Moreover, sucrose is found to disturb the tetrahedral water structure more than maltose, as discussed above for hydration numbers. Consequently, the hydration numbers of disaccharides play a key role at these concentrations.

4. Sugar Intramolecular and Intermolecular Interactions

4.1. Molecular Flexibility. The intrinsic size of disaccharides can be roughly estimated from their radii of gyration R_g , defined as $R_g^2 = \sum(m_i r_i^2)/\sum m_i$, where i denotes the index number of atoms within a given molecule and m_i and r_i the related mass and distance from the center of mass of the molecule, respectively. Figure 8 shows the disaccharide radius of gyration

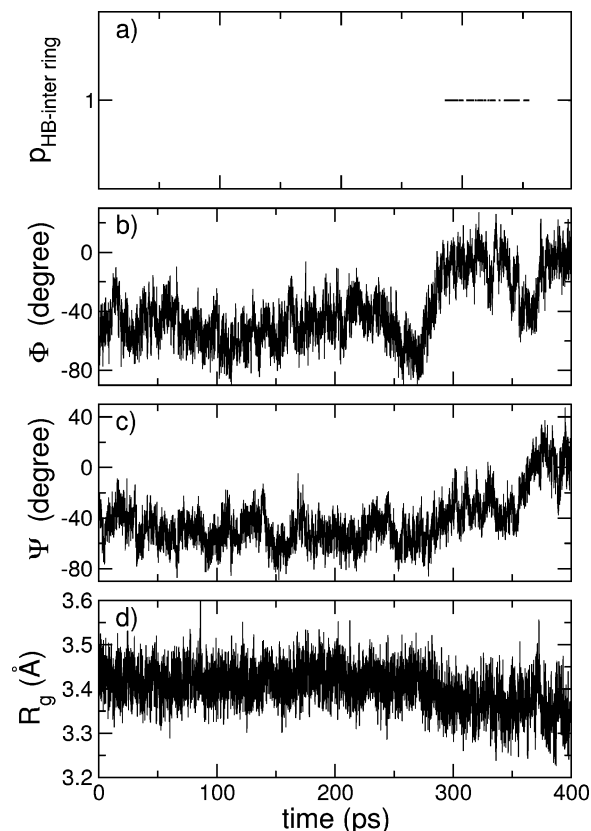


Figure 9. Time dependence of different parameters obtained for trehalose in the 4 wt % solution at $T = 293$ K: (a) probability of the formation of an interring HB $p_{\text{HB-inter ring}}$, (b) and (c) Φ and Ψ glycosidic torsion angles defined as the dihedral angles between atoms $\text{H}_1\text{—C}_1\text{—O}_1\text{—C}'_1$ and $\text{C}_1\text{—O}_1\text{—C}'_1\text{—H}'_1$, respectively (Figure 1), (d) radius of gyration R_g .

rescaled distributions $P(R_g - \langle R_g \rangle)/P(R_g)_{\max}$ for the 4 and 49 wt % solutions at $T = 293$ K. Fluctuations of R_g for trehalose molecules are broader and more asymmetric than for maltose or sucrose. This higher asymmetry may reflect the greater anharmonicity of the region of the PEL explored by trehalose and is consistent with the larger amplitudes of the ring motions. Indeed, the number of intramolecular HBs in trehalose is fewer compared to maltose and sucrose. These HBs restrict movements of disaccharide rings and of hydroxyl groups involved in HBs, thus confining sucrose and, to a lesser extent, maltose into more harmonic regions of the PEL, i.e., closer to the local minimum. Consequently, trehalose seems to be more flexible than maltose and sucrose, in the 4 and 49 wt % solutions at $T = 293$ K. Most of this flexibility arises from small variations of the torsional angles about the glycosidic linkage bonds, since rings are relatively rigid and stabilized by high-energy barriers.²⁹ It should also be mentioned that the radius of gyration R_g corresponding to the maxima of the $P(R_g)$ distributions are equal to 3.40, 3.45, and 3.13 Å for trehalose, maltose, and sucrose, respectively. The lower radius of sucrose comes from its more spherical structure compared to maltose and trehalose. Moreover, it contains a glucose ring and a smaller fructose ring, whereas maltose and trehalose possess two glucose rings. The lower R_g of trehalose stems from the higher degree of symmetry of glucose rings relative to the glycosidic bond. Indeed, glucose rings are linked through $\text{C}_1\text{—O}_1$ and $\text{O}_1\text{—C}'_1$ bonds for trehalose and $\text{C}_1\text{—O}_1$ and $\text{O}_1\text{—C}'_4$ bonds for maltose (Figure 1).

In Figure 9, fluctuations of the glycosidic dihedral angles and the gyration radius R_g are compared for trehalose. It should be noted that fluctuations are larger for trehalose than those for

maltose and sucrose, in good agreement with the R_g distributions discussed previously. ($\Delta\Phi, \Delta\Psi$) within the main minimum are ($13^\circ, 12^\circ$), ($9^\circ, 10^\circ$), ($11^\circ, 7^\circ$) and ($11^\circ, 13^\circ$), ($9^\circ, 9^\circ$), ($9^\circ, 10^\circ$) for the trehalose, maltose, and sucrose 4 and 49 wt % solutions, respectively. Φ and Ψ are defined as the dihedral angles between atoms $H_1-C_1-O_1-C'_1$ and $C_1-O_1-C'_1-H'_1$ for trehalose, $H_1-C_1-O_1-C'_4$ and $C_1-O_1-C'_4-H'_4$ for maltose, and $O_{5g}-C_{1g}-O_{1g}-C_{2f}$ and $C_{1g}-O_{1g}-C_{2f}-O_{5f}$ for sucrose (Figure 1). This is indicative of a greater conformational flexibility and suggests that the free energy minimum that trehalose explores during our simulations is broader than that of maltose and sucrose. This is also in agreement with the number of intramolecular HBs, which is the lowest for trehalose and the highest for sucrose. Within a given well, intramolecular HBs prevent large motions of the rings. This is illustrated over the 400 ps simulation of a 4 wt % trehalose solution at $T = 293$ K in Figure 9. During the first 260 ps of the simulation, no HB forms between the rings of trehalose (Figure 9a). Meanwhile, the glycosidic dihedral angles Φ and Ψ and the radius of gyration R_g fluctuate around rather stable values: $\Phi = -50 \pm 13^\circ$, $\Psi = -51 \pm 12^\circ$, $R_g = 3.42 \pm 0.04$ Å (Figures 9b, 9c, and 9d, respectively). After 260 ps, the dihedral angle Φ shows a transition to $\Phi = -14 \pm 16^\circ$ while for Ψ the transition is less pronounced until $t = 350$ ps ($\Psi = -22 \pm 22^\circ$). This transition is connected with the formation of an intramolecular HB between O_2 and O'_6 oxygen atoms. This intramolecular HB was observed by Conrad et al. at high concentrations (50 wt % or more) at 358 K.³⁴ As a direct consequence of this conformational transition, the radius of gyration R_g of trehalose is reduced, $R_g = 3.37 \pm 0.05$ Å, suggesting a more compact conformation, with the rings becoming closer to each other. We also expect smaller fluctuations of R_g . However, the short time during which this new conformation is observed does not allow us to confirm this.

Besides, the intrinsic enhanced flexibility of trehalose is not contradictory with its lower mean-square fluctuations ($\langle u^2 \rangle$) compared to sucrose, as experimentally observed.⁵⁷ Indeed, the motions of the hydrogen atoms both depend on the global molecular translation and rotation and on the internal vibrations. Therefore, trehalose may show a greater flexibility (probed, e.g., by the radius of gyration fluctuations) and a smaller ($\langle u^2 \rangle$) compared to sucrose. This point will be described in more detail in a paper devoted to the dynamical features of sugar–water solutions.⁷⁴

Figure 9 underlines the close relation between intramolecular HBs and molecular conformational fluctuations. In particular, it may confirm the hypothesis of Oku et al.¹⁷ who investigated the mechanism of the antioxidant function of trehalose by means of NMR and quantum chemistry. They proposed that trehalose interacts specifically with one cis double bond of an unsaturated fatty acid via the $O_6-H'_6$ and either O_2-H_2 or O_3-H_3 hydroxyl groups of trehalose. The complex formed was also stabilized by $O-H \cdots \pi$ and $C=H \cdots O$ types of HBs. The greater conformational flexibility that we observe for trehalose in the present study might favor these kinds of interactions compared to sucrose and maltose. Indeed, it may allow the hydroxyl groups mentioned above to adopt the required conformation, while trehalose remains in the gauche conformation before and after complexation, i.e., in the same energy well. Furthermore, the occurrence of an interring HB between O_2 and O'_6 oxygen atoms of trehalose observed in the 4 wt % solution may indicate that the stable conformation of trehalose is favorable to form such a complex. On the contrary, the more frequent interring HBs found in maltose and sucrose as well as their intrinsic

topology might prevent such interactions. Accordingly, the enhanced conformational flexibility of trehalose may favor HBs with polar groups of membranes or proteins as proposed by Crowe et al.⁷⁵ and referred to as the water replacement hypothesis.

4.2. Sugar Clusters. As the sugar content increases in the studied solutions, sugar–sugar interactions become more and more likely (Table 2). At a given concentration threshold, sugar clusters may even percolate, forming a continuous space-filling network. The percolation of the sugar HBN may explain the decoupling of water and sugar diffusions. Indeed, it has been observed experimentally that sucrose and water diffusions decouple at water contents below ~ 50 wt %.⁷⁶ Moreover, Goddard et al.³⁸ have suggested from simulations that the formation of a sucrose network in highly concentrated solutions may increase both the resistance to shear deformation and the mechanical stability of the mixture.

The formation of a sugar network should be favored by a low number of intramolecular HBs, since this kind of HB involves OH groups that are not available for intermolecular HBs. Moreover, the number of sugar–sugar intermolecular HBs should reveal clustering tendencies. The largest number of intermolecular sugar–sugar HBs found for maltose (see statistics given in Table 2) may imply that the molecules of this sugar tend to organize themselves into larger clusters than for sucrose or trehalose. To describe the sugar cluster formation suggested by these HB data, we define a cluster as a set of sugar molecules connected to each other by at least one HB according to criterion II. This geometric criterion was preferred to criterion I to avoid scarce clusters and consequently very poor statistics. The mean sugar cluster size ($\langle n_s \rangle$) was computed as $\langle n_s \rangle = \sum n_s W_s$, where n_s is the number of sugars composing a given cluster and W_s is the probability of the formation of clusters of size n_s . Isolated sugar molecules are considered as clusters of size 1. Since sugar dynamics are much slower than water dynamics³⁷ and their number is relatively small in our simulation boxes (between 1 and 52), the statistics of cluster formation are rather poor for a given simulation. Therefore, since no significant differences of $\langle n_s \rangle$ as function of the temperature were observed, we have averaged $\langle n_s \rangle$ over the (293–373 K) temperature range at a given concentration (the results at $T = 273$ K have not been used because of the lack of sugar diffusion at high concentrations). Four aberrant values over 60 were discarded (two for sucrose and one for maltose and trehalose, among the four concentrations and five temperatures considered for these calculations). Consequently, $\langle n_s \rangle$ provides a rough trend of the sugar cluster formation as a function of concentration.

Figure 10a shows the evolution of the ratio $\langle n_s \rangle / N_s$, where N_s is the total number of sugars in the simulation boxes, for the three disaccharide solutions as a function of concentration. At low concentrations (16 and 33 wt %), small clusters may appear in the solutions, $\langle n_s \rangle / N_s$ remaining roughly constant around 0.2–0.3. Therefore, the mean size of the cluster $\langle n_s \rangle$ is rather proportional to the total number of sugars N_s . This behavior changes radically at higher disaccharide concentrations, where sugar clusters grow more than linearly with N_s and $\langle n_s \rangle / N_s$ increases to 1 for the solutions at 66 wt %, which can be considered as the threshold concentration of percolation, ϕ_p . Accordingly, the percolation of the sugar HBN has been achieved at this concentration, i.e., most of the sugars of the simulation box belong to the same large cluster. Notwithstanding the quite large error bars, differences below ϕ_p between maltose or trehalose on one hand and sucrose on the other hand emerge. Indeed, sucrose is found to form clusters of smaller sizes than

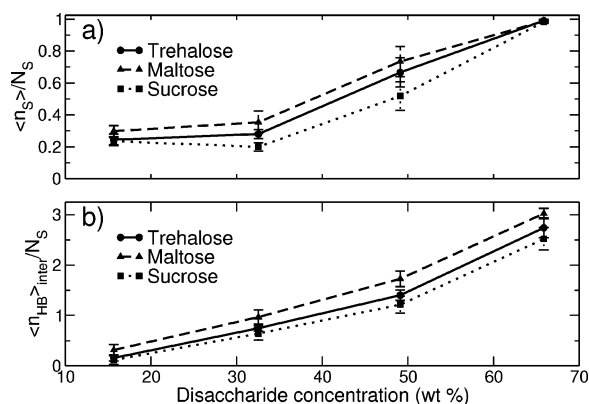


Figure 10. Concentration dependence of (a) the normalized mean sugar cluster size $\langle n_s \rangle / N_s$ and (b) of the normalized mean number of sugar-sugar HBs $\langle n_{HB} \rangle_{inter} / N_s$ of the disaccharide solutions, averaged over the (293–373 K) temperature range to improve statistics. (Table 2 gives $\langle n_{HB} \rangle_{inter} / N_s$ at $T = 293$ K.) Error bars are calculated from the standard deviations. $\langle n_s \rangle / N_s$ and $\langle n_{HB} \rangle_{inter} / N_s$ cannot be calculated for our most diluted solutions (4 wt %), because there is only one sugar in the simulation box.

trehalose or maltose. This is probably related to the higher number of intramolecular HBs of sucrose molecules compared to maltose and trehalose, since hydroxyl groups involved in these intramolecular interactions do not remain available for other intermolecular interactions (with water or sugar molecules). As a consequence, a higher sucrose concentration is needed to reach a given cluster size compared to maltose or trehalose. Furthermore, $\langle n_s \rangle$ of maltose and trehalose are found to be relatively close to each other, consistent with their very similar topology. Nevertheless, maltose molecules have a propensity to form a larger number of HBs with each other than trehalose molecules. This is illustrated in Figure 10b, which presents the normalized averaged number of intermolecular sugar-sugar HBs $\langle n_{HB} \rangle_{inter} / N_s$ (see also Table 2). At low concentrations, this number is limited by the quite low probability of forming intersugar HBs, which prevents multiple HBs between two given sugars. It increases with sugar concentration but is restricted at high concentrations by the maximum number of intermolecular HBs that sugars may form owing to sterical hindrance. The averaged number of intermolecular sugar-sugar HBs is found larger in the maltose clusters than in the trehalose ones. Thus, maltose favors more sugar-sugar HBs than trehalose and sucrose. This explains in part the lower hydration number of maltose relative to trehalose at high concentrations since sugar-sugar HBs reduce the possibility that the water molecules have to bind to sugars.

This peculiar interplay between the capability of a sugar to hydrogen-bond to other sugars or to water seems critical for the homogeneity of the system and could probably play a significant role in the preservation of biomolecules. Indeed, it suggests that below the percolation concentration ϕ_p trehalose may form more homogeneous matrixes with water with respect to sucrose or maltose. Trehalose would be able to form large clusters with itself while maintaining higher hydration numbers than sucrose or maltose. Moreover, since trehalose forms HBs with a larger number of water molecules than sucrose and maltose do, less *bulk* water molecules (marked by a star in Figure 11) would exist in the trehalose solutions. Therefore, both the ice formation probability and the dehydration stresses arising from the water escape would be reduced. However, this new insight suggests experiments to probe the influence of the sugar-water matrix nanostructure on the dehydration kinetics. Figure 11 outlines schematic 2D views of concentrated trehalose

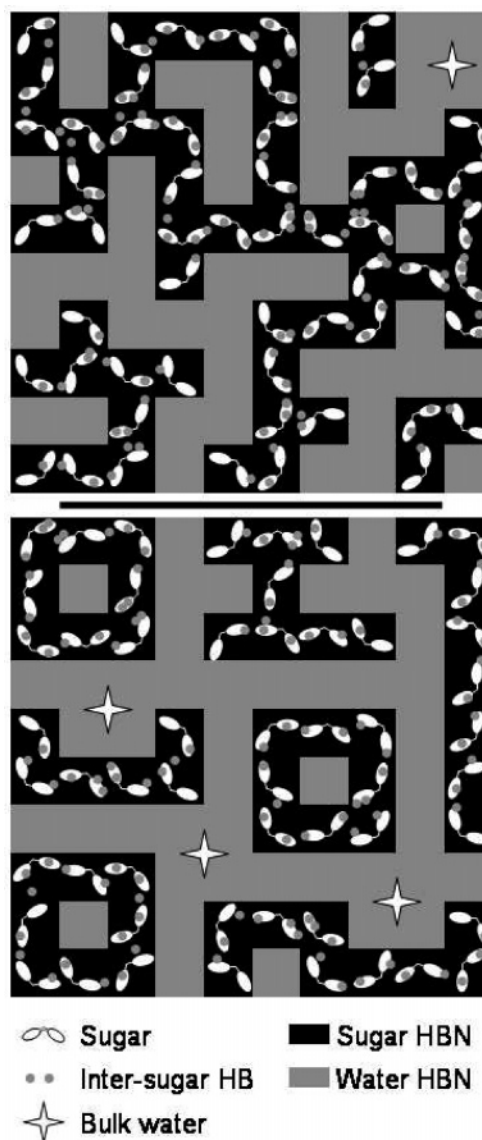


Figure 11. Schematic 2D representation of a microscopic region of trehalose (top) and sucrose (bottom) solutions in the intermediate concentration range (33–66 wt %), i.e., below the percolation threshold ϕ_p . The differences between these two cartoons are purposefully magnified to clearly distinguish the structural features of trehalose and sucrose solutions. Gray parts represent water molecules (whether they are hydrogen-bonded to sugars or not), while black parts stand for the sugar molecules. Stars designate sites where *bulk* water, not in the first hydration shell of sugars, may exist. Trehalose molecules form quite large and interconnected clusters, whereas sucrose arranges itself into smaller, isolated clusters. This makes trehalose molecules less mobile than sucrose ones. Moreover, owing to the larger number of water-trehalose HBs, water molecules diffuse less in trehalose-water mixtures, and sites where water may crystallize (*bulklike*) are more scarce than in sucrose solutions. This makes water-trehalose mixtures more homogeneous, from a structural point of view at least.

and sucrose aqueous solutions to illustrate this hypothesis. These representations are based on the interpretation of the statistical calculations shown in Figure 10 and therefore are difficult to observe for an instantaneous configuration of our simulation trajectories. It should also be reminded that sugar clusters reorganize continuously until percolation has been achieved.

5. Summary and Conclusion

The structural properties of trehalose, maltose, and sucrose disaccharides in water have been investigated by MD computer simulations.

The crystallinity of sugar–water solutions has been studied from calculations of the partial static structure factor found in good agreement with neutron diffraction experiments and 2D radial distribution functions. A significant increase in the localization of water molecules at the hydration sites of the trehalose dihydrate crystal is observed. It strongly supports the more crystalline character of the trehalose solution suggested in ref 57. Hydration numbers have been accurately determined for two different models of water (SPC/E and TIP3P, for the 4 wt % solutions) and different geometrical criteria aiming to distinguish both well-formed and less-formed water HBs. We have clearly shown that trehalose binds to a larger number of water molecules than do maltose and sucrose, for all studied concentrations. Our data have also been successfully confronted to experimental and other MD simulation results of hydration numbers. The structure of the water HBN in the presence of sugars has been studied using the concept of broken HBs proposed by Teixeira and Stanley.⁶⁶ Our results prove that the presence of disaccharide molecules in the investigated solutions leads to a significant decrease in water populations with high coordination numbers and to a smaller probability p_{HB} of forming an intact bond, this effect being more salient in trehalose solutions. However, the evolution of p_{HB} as function of the concentration was also found to be directly controlled by the sugar hydration numbers. The discrepancy between the different sugars is largely reduced beyond the first hydration shell. Statistics of cluster sizes made of hydrogen-bonded waters have been investigated and reveal that above a concentration $\phi_A \approx 40$ wt % trehalose is able to reduce the water cluster size more efficiently than sucrose and maltose. This confirms the superior capability of trehalose to disturb the HBN of water and is consistent with the *destructuring effect* model suggested by Magazù et al.²²

From the fluctuations of the radii of gyration and of the glycosidic angles for the 4 and 49 wt % solutions, we have also shown that trehalose exhibits a higher flexibility with respect to maltose and sucrose, consistent with its lower number of intramolecular HBs and thus with its higher hydration number. This enhanced flexibility would confirm the hypothesis of Oku et al.,¹⁷ suggesting that trehalose is able to form HBs with nonpolar residues of proteins. Sugar–sugar interactions have been analyzed in terms of sugar clusters. Sugar molecules form a percolating HBN in the 66 wt % solutions. At intermediate concentrations, the average size of clusters $\langle n_s \rangle$ of trehalose and maltose is larger than $\langle n_s \rangle$ of sucrose owing to fewer intramolecular HBs. Moreover, trehalose favors to a lower extent intersugar HBs compared to maltose, thus preserving more efficiently HBs with water molecules. The trehalose–water solution is found to be more homogeneous than the others. This particular property should play a major role in the biopreservation efficiency of water–trehalose mixtures against desiccation stresses and ice formation.

To conclude, the results reported here show that maltose–water systems are less homogeneous owing to the tendency of maltose molecules to form clusters and thus reducing their possibility to destructure the water HB network. For sucrose–water solutions, the higher probability of sucrose molecules to form intramolecular HBs strongly reduces their interaction with both water or other sugar molecules. Unlike maltose or sucrose, trehalose molecules possess similar capabilities to interact with both sugar and water molecules, which makes trehalose–water systems more homogeneous. This homogeneity of the disaccharide–water matrixes due to the reciprocal interactions between sugar and water molecules may rule their biopreser-

vative efficiency. It may also be of the utmost importance in the interactions between sugars and biomolecules. Lysozyme–disaccharide–water simulations are currently being conducted to shed more light on disaccharide–protein interactions. Results obtained in the present paper also call for new investigations to clarify the influence of the solution structural homogeneity on dynamic properties.⁷⁴

Acknowledgment. The authors are grateful to Professor A. Cesàro for fruitful discussions and wish to acknowledge the use of the facilities of the IDRIS (Orsay, France) and the CRI (Villeneuve d'Ascq, France) where calculations were carried out. This work was supported by the INTERREG III (FEDER) program (Nord-Pas de Calais/Kent).

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Molecular dynamics simulations of glycerol glass-forming liquid

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Received 6 January 2005; accepted 18 May 2005

Available online 22 August 2005

Abstract

Structural and dynamical properties of liquid glycerol have been investigated by Molecular Dynamics simulations. An improved model based on a slight reparametrisation of the all-atoms AMBER force field used in [R. Chelli, P. Procacci, G. Cardini, R.G.D. Valle, S. Califano, *Phys. Chem. Chem. Phys.* 1 (1999) 871] is presented. The structure remains satisfactory, qualitatively similar to that obtained from the original model. This new model is also found to reproduce significantly better the diffusion coefficient and the correlations times as they can be deduced from neutron spin echo (NSE) experiments. Structural heterogeneities revealed as a pre-peak of the static structure factor $S(Q)$ close to $Q \sim 0.6 \text{ \AA}^{-1}$ are observed. Our results are also found compatible with predictions of the Mode Coupling Theory.

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Keywords: Molecular dynamics; Simulation; Supercooled liquids; Glass transition

1. Introduction

Glycerol ($\text{C}_3\text{H}_8\text{O}_3$) has been the subject of numerous experimental studies in glass physics [1–8]. Indeed, this weak hydrogen-bonded (HB) liquid composed of small and highly flexible molecules can be easily supercooled and reach the glassy state at about $T_g = 187 \text{ K}$ [4]. Transport coefficients of glycerol exhibit a non-Arrhenius behaviour quantified by a fragility index $m = 57$ [9] which is intermediate between the so-called “strong” glassformers (e.g., silica) and some very “fragile” molecular van der Waals liquids such as *ortho*-terphenyl [10]. In recent years, glycerol has also been widely studied for its capabilities in the long-term preservation of proteins and is considered as one of the best cryoprotectant solvents [11,12].

In the last two decades, a significant progress on glass-forming systems in the high temperature regime

has been obtained from molecular dynamics simulations [13–17]. These works were strongly correlated to the development of the mode coupling theory (MCT) [18] which provides a microscopic description of weakly viscous liquids. The intrinsic basis of MCT states that the behaviour of any time-dependent correlators describing the dynamics of the system is only controlled by its static density correlator, i.e., $S(Q)$ and predicts the existence of a critical temperature T_c indicating a bifurcation from ergodic to non-ergodic dynamics. However, no sharp transition is observed at T_c itself owing to some activated processes not included in MCT which restore ergodicity. It should be noted that MCT predictions have been checked in many experimental works [19] and in particular on glycerol [20].

Surprisingly, only a few MD investigations of glycerol have been performed so far. Root and Stillinger [21] proposed a force field designed for reproducing the crystalline structure of glycerol, where the aliphatic CH groups were represented as united atoms. This model was particularly used to investigate structural properties of pure glycerol and pressure effects on the

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hydrogen-bond network [22]. More recently, Chelli et al. [23,24] used the more realistic all-atom AMBER force field [25] and obtained an excellent agreement with several structural, vibrational and thermodynamical experimental data. This model was also employed to investigate the conformations and the hydrogen bonding of glycerol. However, some discrepancies between the experimental [26] and numerical [24] diffusion coefficient are clearly observed using this model [23,24]. Moreover, a comparison of the total intermediate scattering function $S(Q, t)$ obtained from MD using the Chelli et al. model [23,24] and from NSE experiments [27] shows that the numerical characteristic times are significantly shorter than the experimental ones.

The molecular mobility is an important parameter to account for the development of a realistic model of the so widely used glycerol glass-forming liquid. The development of a model able to reproduce the dynamical features of glycerol is also fundamental in order to check the generic predictions of MCT or of the Coupling Model [28] in the supercooled regime. Owing to the weak HB network of glycerol, relatively complex dynamics can be expected and could explain the disagreement found between MD and experimental data. It clearly motivates a reparametrisation of the Chelli et al. [23,24] force field. As the latter model has been efficient to reproduce various data (structural as well as thermodynamical), we have only made slight modifications to better fit the diffusion coefficient and characteristic times obtained from NSE experiments. A small change of the van der Waals parameters and of the atomic charges of the hydroxyl groups has turned out to be sufficient. The new model is described in the following and used to investigate some structural and dynamical properties of glycerol.

2. Computational details

MD simulations have been carried out with the molecular dynamics package DL_POLY [29] on a system composed of $N = 108$ flexible glycerol molecules (see Fig. 1). Size-independent effects have been checked with a larger system composed of $N = 500$ molecules at $T = 400$ K. Glycerol has been modelled using the all-atom AMBER force field [25] employed by Chelli

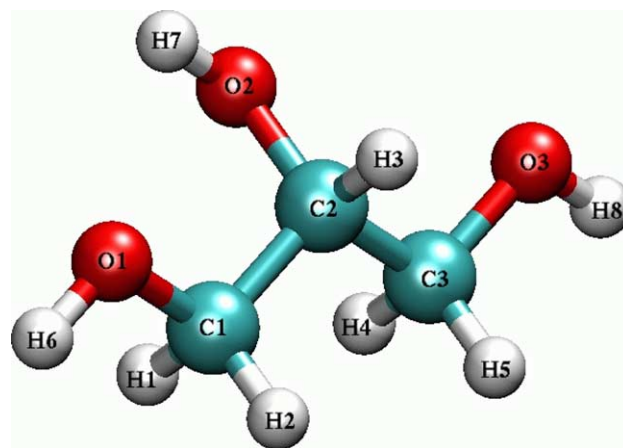


Fig. 1. Glycerol molecule.

et al. [23]. Some parameters of this force field, i.e., atomic charges and Lennard-Jones parameters of the hydroxyl groups, have been reparametrised in order to reproduce more realistically the diffusion coefficient D [26] and the characteristic times τ_Q obtained from NSE experiments [4]. Five models of glycerol have been investigated at different temperatures: (i) the original Chelli et al. model [23], (ii) a model inspired from the glucose model [30] for van der Waals interactions of the hydroxyl groups and from the Root and Stillinger [21] for atomic charges, (iii) a model identical to (ii) but where atomic charges of model (i) were used, (iv) a model identical to (iii) where hydroxyl group atomic charges were reduced by 5% and (v) a model identical to (iii) where hydroxyl group atomic charges were reduced by 10%. The best agreement with experimental data were obtained for model (iv) which will be discussed in the following. All parameters are summarized in Table 1. The main difference with the Chelli et al. model [23] is a small increase of the atomic charges of the hydroxyl groups: -0.6048 and 0.4158 compared to -0.585 and 0.396 for the oxygen and the hydrogen atoms, respectively (see Table 1). Electrostatic interactions were handled by the reaction-field method with the relative dielectric constant $\epsilon = 40$ close to the values found in the literature [31]. We checked the validity of the reaction-field method by performing one MD simulation using an Ewald summation at $T = 400$ K. No significant structural or dynamical difference has been found be-

Table 1

Parameters of the Lennard-Jones potential and atomic charges of the glycerol forcefield

Lennard-Jones site	σ (Å)	ϵ (kcal/mol)	q (electronic units)
C1 and C3	3.816	0.1094	0.182
C2	3.816	0.1094	0.055
Aliphatic hydrogen atoms	2.774	0.0157	0.026
Hydroxyl H6, H7 and H8	1.4254	0.0498	0.4158 (0.396)
Hydroxyl O1, O2 and O3	2.8508 (3.442)	0.1591 (0.21)	-0.6048 (-0.585 or -0.581)

Parameters of the Chelli et al. model [23] are given in parenthesis if different from the present model.

tween both techniques. The time step is 0.5 fs (justified by the flexibility of the model) and the cutoff radius is 10 Å. Cubic periodic boundary conditions have been applied. MD simulations have been performed in the NPT statistical ensemble where the number of molecules N , pressure P and temperature T are fixed. The pressure has been set to 1.0 bar using a weak coupling to a pressure bath (Berendsen barostat [32]) with a relaxation time of 1.0 ps. The temperature has been maintained constant during a given simulation using a weak coupling to a heat bath (Berendsen thermostat [32]) with a relaxation time of 0.2 ps. Simulations have been performed at ten different temperatures : 493, 473, 453, 433, 413, 400, 393, 353, 333 and 313 K. The simulation lengths range from 0.7 to 6 ns and equilibration periods from 100 to 500 ps depending on temperatures.

3. Results and discussion

The intermediate scattering function usually obtained from coherent neutron scattering experiments, given by the following expression [33]:

$$S(\vec{Q}, t) = \langle \rho_{\vec{Q}}(t) \rho_{\vec{Q}}(0) \rangle, \quad (1)$$

has been analysed in order to investigate numerically collective dynamics where in Eq. (1), $\rho_{\vec{Q}}(t)$ is the time-dependent density correlator defined as:

$$\rho_{\vec{Q}}(t) = \sum_{\alpha} b_{\alpha} \exp[i\vec{Q} \cdot \vec{r}_{\alpha}(t)], \quad (2)$$

where the sum is over all the atoms α of the system. b_{α} and $\vec{r}_{\alpha}$ are the coherent scattering length and the position of the α atom, respectively. An average over isotropically distributed Q -vectors having the same modulus Q is performed in order to obtain $S(Q, t)$. The static structure factor is defined as $S(Q) = S(Q, t = 0)$ and displayed in Fig. 2(a). A qualitative agreement with experimental data extracted from [3] is observed. Indeed, the present model is able to reproduce the main features of the experimental $S(Q)$ but some discrepancies concerning the intensities and widths of the peaks remain. However, a relatively good agreement concerning the intensity and the width of the first peak between simulation and experiment is obtained. It indicates that both real and model systems exhibits similar ordering. This result also shows that the small changes made on the original force field do not alter the capability of the model to mimic successfully the glycerol inter- and intra-molecular structure, as already discussed by Chelli et al. [23,24]. An interesting new point revealed from the present investigation is the existence of a pre-peak close to $Q \simeq 0.6 \text{ Å}^{-1}$ located below the first sharp diffraction peak at $Q = Q_{\text{max}} \simeq 1.4 \text{ Å}^{-1}$. A closer look at the experimental data in the small Q region in [3] at a lower temperature seems to con-

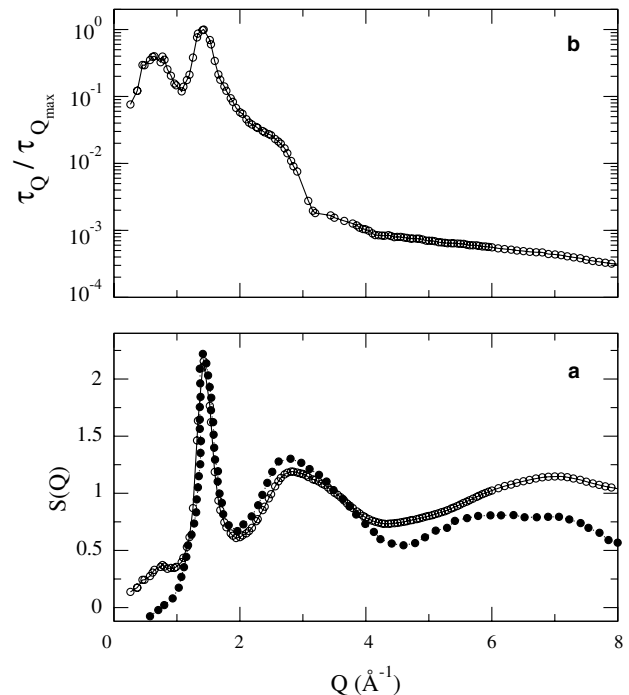


Fig. 2. (a) Static structure factor $S(Q)$ obtained from experiment (full circle) at $T=296 \text{ K}$ [3] and from MD simulation (open circle) at $T=333 \text{ K}$. (b) Relaxation times $\tau_Q / \tau_{Q_{\text{max}}}$ extracted from $S(Q, t)$ at $T=333 \text{ K}$, where $\tau_{Q_{\text{max}}}$ is about 148 ps.

firm this result. This feature has already been observed in some other hydrogen-bonded glass-forming molecular liquids such as metatoluidine and metacresol [34,35]. In such liquids, the pre-peak has been interpreted as a signature of structural heterogeneities corresponding to clusters of hydrogen-bonded molecules and forming a medium range order.

The coherent intermediate scattering function $S(Q, t)$ has been calculated from MD simulations at different temperatures and different Q wave-vectors and is compared with the NSE data [4] in Fig. 3 at the arbitrary wave-vector $Q = Q_{\text{max}}$. Despite slight discrepancies at the highest and the lowest temperatures, a reasonable agreement between experimental and numerical $S(Q, t)$ is found. The discrepancy found at the lowest temperature investigated $T = 313 \text{ K}$ could arise from an aging effect. Indeed, at this temperature, it takes about 1 ns for the $S(Q_{\text{max}}, t)$ to relax while only a 500 ps equilibration period is used. The authors have no clear explanation about the high temperature discrepancy at $T = 413 \text{ K}$. It seems surprising since the agreement between numerical and experimental diffusion coefficient remains fair at this temperature and even at higher temperatures (see below). Upon cooling, $S(Q, t)$ displays a decay typically observed in MD simulations [17] and in NSE experiments on glass-forming molecular liquids [27,36]. This decay process is often interpreted in terms of $\alpha - \beta$ relaxations in the framework of MCT [18]. In the α long time relaxation regime, we define the characteristic time τ_Q of the

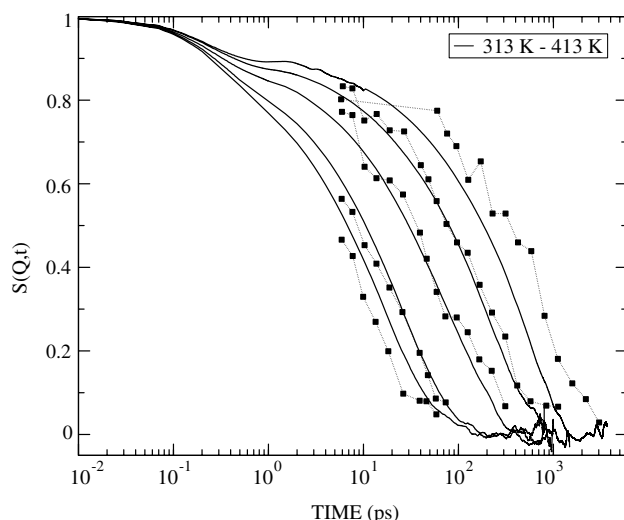


Fig. 3. Coherent intermediate scattering function $S(Q, t)$ at $Q = Q_{\max}$ obtained at $T = 313, 333, 353, 393$ and 413 K from experiment (full square) and MD simulation (solid line).

dynamics as the time it takes for $S(Q, t)$ to decay from 1 to $1/e$. This arbitrary definition is chosen in order to fully compare both NSE and MD data. The characteristic times $\tau_{Q_{\max}}$ and the diffusion coefficient D obtained experimentally and numerically are shown in Fig. 4. We found that both $\tau_{Q_{\max}}$ and D are consistent with previous experiments [4,26] and exhibit a non-Arrhenius dynamical behavior. The discrepancies observed at the highest and lowest temperatures may come from the reparametrisation that seems to underestimate the activation energy of $\tau_{Q_{\max}}(T)$ and $1/D(T)$ in a simple Arrhenius law at first approximation, although it is an important

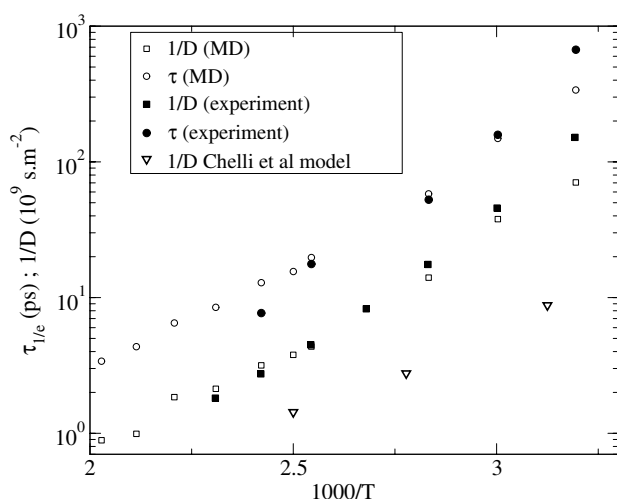


Fig. 4. Temperature dependence of the relaxation time τ_Q at $Q = Q_{\max}$ obtained from experiment [4] (full circle) and MD simulation (open circle). Temperature dependence of the diffusion coefficient D obtained from experiment [26] (full square), the present MD simulation (open square) and the MD investigation performed by Chelli et al. [24] (open triangle).

improvement for the dynamics of liquid glycerol. According to MCT, any characteristic relaxation times should yield asymptotically the same temperature dependence $\sim (T - T_c)^{-1/\gamma}$. Owing to the limited temperature range investigated in this study, an accurate determination of T_c is difficult. Fits of $\tau_{Q_{\max}}$ and D have been performed and our results are found compatible with the critical temperature around $T_c \simeq 288$ K and $\gamma \simeq 2.87$ found in the literature [20].

Another intrinsic basis of MCT states that the behaviour of any time-dependent correlators such as $S(Q, t)$ describing the dynamics of the system is only controlled by its static density correlator $S(Q)$. This result has been nicely demonstrated both experimentally and numerically for the pure van der Waals glass-forming orthoterphenyl system [37,14,17]. Since a good agreement between experiments and simulations has been found for the static structure factor (see Fig. 2(a)), we study this MCT prediction for glycerol, a molecular system where intermolecular interactions are mainly controlled by hydrogen bonds and which possesses this infrequent pre-peak. The Q -dependence of the relaxation time τ_Q has been calculated and results are shown in Fig. 2(b). We find that τ_Q oscillates in phase with $S(Q)$. Four main oscillations are clearly observed at the positions of the pre-peak $Q \simeq 0.6 \text{ \AA}^{-1}$, $Q = Q_{\max}$ and two others at around $3 \text{ \AA}^{-1}$ corresponding to the intra- and intermolecular hydrogen bonds [24]. A thorough analysis of the higher Q data above $4 \text{ \AA}^{-1}$ (not displayed in the present paper) also shows that τ_Q is modulated by $S(Q)$. Moreover, the value of τ_Q close to the position of the pre-peak provides an estimation of the lifetime of the hydrogen-bonded molecules clusters $\tau \simeq 80$ ps, i.e., of the same order of magnitude as $\tau_{Q_{\max}}$.

In summary, an improved force field for glycerol is proposed and checked from MD investigations at different temperatures. Preliminary results show that dynamics could be described in the framework of MCT. The present study also reveal the existence of a pre-peak in the static structure factor $S(Q)$ which clearly motivates some new diffraction experiments in order to be confirmed. The authors hope that investigations of such intrinsic structural heterogeneities could clarify the physical mechanisms at the origin of many unclear properties of glass-forming molecular liquids associated with the existence of dynamical heterogeneities such as the breakdown of the Stokes–Einstein relation, the non-exponential relaxation ($\exp(-(t/\tau)^\beta)$) or the decoupling of the translational and the rotational dynamics.

Acknowledgements

The authors wish to acknowledge the use of the facilities of the IDRIS (Orsay, France) and the CRI (Ville-neuve d'Ascq, France) where calculations were carried

out. This work was supported by the INTERREG III (FEDER) program (Nord Pas de Calais/Kent).

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How do trehalose, maltose and sucrose influence some structural, vibrational and dynamical properties of lysozyme ? An Insight from Molecular Dynamics simulations

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Abstract

The influence on some structural, vibrational and dynamical properties of lysozyme of three well-known disaccharides, namely trehalose, maltose and sucrose, in the 37-60 wt % concentration range have been investigated by means of molecular dynamics computer simulations. The effects of sugars on the conformation of lysozyme are found to be relatively weak, in agreement with the preferential hydration of lysozyme. Conversely, sugars seem to affect significantly the low-frequency vibrational density of states and to increase the relaxation times of lysozyme. These effects are shown to be correlated to the fractional solvent accessibilities of lysozyme residues and further support the dynamic slaving of lysozyme. Moreover, a significant increase in the relaxation times of lysozyme, sugars and water molecules is observed within the studied concentration range and may result from the percolation of the hydrogen-bond network of sugar molecules. This percolation appears to be of primary importance to explain the influence of sugars on the vibrational and dynamical properties of lysozyme.

1 Introduction

The preservation of biological molecules like proteins is a fundamental goal of pharmaceutical, food, and cosmetic industries [1-4]. Indeed, they generally remain stable only under very stringent conditions of temperature, pH, hydration level or ionic strength [3, 5]. The addition of stabilizing agents is a common strategy to increase the stability of proteins both in solution or in the dry state [3, 5]. Among these compatible solutes, trehalose, a disaccharide ($C_{12}H_{22}O_{11}$), has been found particularly

efficient [2, 6]. This sugar is naturally synthesized in large amounts by plants, insects and microorganisms such as yeasts and nematodes which are able to withstand for an extended period severe environmental conditions of low/high temperatures and/or drought experienced in desert or polar regions [7, 8]. These organisms enter into a biological state where their activity is almost completely suspended as long as environmental conditions remain deleterious, and then resume their normal activity. This phenomenon is called *anhydrobiosis*. Despite the many experimental [6, 9-11] and numerical [12-14] studies which have been devoted to the *bioprotection* phenomenon, the molecular mechanisms at its origin are still not clearly understood. Several hypotheses, mostly based on the properties of trehalose - high solubility, low reactivity, good glass-former and antioxidant, etc. - have been proposed to explain why it is the most effective bioprotectant among sugars and polyols [8]. Nonetheless, none of them is fully satisfactory, since it generally covers only a limited range of temperatures and hydration levels.

In aqueous solutions proteins may be thermodynamically stabilized by the *preferential exclusion* of cosolvent molecules from the protein/solvent interface, which make thermodynamically unfavorable the increase of the solvent accessible surface area (SASA) of proteins upon denaturation [15]. This exclusion could arise from excluded volume effects and an increase in the surface tension of water induced by solutes. This may explain why among many solutes trehalose was found to be the most excluded [16, 17], given its larger hydration number in comparison to other disaccharides such as sucrose and maltose [18]. Moreover, solutes may hinder the formation of ice, which is generally lethal to organisms. Magazù *et al.* have suggested that tre-

halose would be more effective in inhibiting ice formation than other disaccharides, because it binds to a larger number of water molecules and would therefore have a greater *destructuring effect* [19].

At high temperatures or high osmotic pressures, dehydration is observed. Biological molecules may experience important stresses when *hydration* water molecules are removed [20]. The effect of the addition of stabilizing solutes may be two-fold. First, the solution is likely to vitrify before the complete removal of hydration water molecules, since the solution viscosity raises exponentially when decreasing the water content. The glass formed may kinetically maintain the conformation of proteins and prevent the fusion of membranes. Trehalose would then be a better bioprotectant than maltose or sucrose given its higher glass transition temperature T_g , as suggested by Green and Angell [21]. This hypothesis is generally well accepted, even though counter-examples have been reported [11, 22, 23]. The second effect of an increase of the concentration of stabilizing solutes upon dehydration is the formation of hydrogen bonds (HBs) between solutes and biological molecules. Crowe *et al.* have proposed that solutes were able to substitute to the hydration water of biological molecules, therefore stabilizing their solution structure and functionality [6]. This has been supported by the results from many studies [9–11]. There is a lot of debate on the relative importance of the solvent vitrification and the formation of solute-biomolecule HBs. Nevertheless, both appear necessary to achieve long-term preservation [5, 6].

Alternatively, Belton and Gil have suggested that the direct interaction of the solute glassy matrix with lysozyme is relatively limited, because the hydration water is trapped by the solute glassy matrix [24]. The role of trehalose would be to concentrate residual water molecules close to the protein. This would be consistent with the hypothesis of the preferential hydration of proteins in dilute to semi-dilute solutions [17].

Finally, Cesàro *et al.* [25] have pointed out the possible role of the interconversion between the trehalose dihydrate crystal T_{2H_2O} [26] and the metastable α phase T_α [27] upon dehydration. This interconversion may make easier the rehydration of biomolecules and occurs on time scales compatible with the anhydrobiotic protection, and thus may not induce fast changes in the volume or internal pressure of cells, on the contrary to ice formation.

Many simulation studies of ternary systems have been published in the last few years [12–14, 28–31]. Studies of membrane/sugar/water systems [12, 28–31] indicate that sugars, and trehalose in particular, interact directly with membranes, and may stabilize them by forming multiple HBs between sev-

eral adjacent phospholipids. Furthermore, Lins *et al.* [12] have studied trehalose-lysozyme interactions at a concentration of about 18 wt % and have shown that trehalose molecules do not expel hydration water. They have suggested that the presence of lysozyme induces an aggregation of trehalose molecules, which trap a thin layer at the protein surface, in agreement with the suggestion of Belton and Gil *et al.* [24] for solid lysozyme/trehalose/water samples. Similarly, Cottle *et al.* [32] have shown that trehalose is preferentially excluded from the protein surface at 50 and 89 wt %. They also observed an analogous behavior for sucrose at 89 wt %, which was found more excluded than trehalose [13]. Furthermore, Dirama *et al.* [14] have studied lysozyme in a trehalose glass at different temperatures and shown a strong coupling between lysozyme and trehalose molecules correlated with the dynamics of protein-sugar intermolecular (HBs).

This paper aims at understanding how proteins are influenced at room temperature (300 K) by stabilizing solutes at intermediate concentrations, *i.e.* high enough so that the solvent structure and dynamics are quite different from those of pure water, but low enough to allow relatively large-scale motions of protein surface atoms. This concentration range is particularly important since it may link the protein properties in dilute solutions to those in solid matrices. For this purpose, we have probed the influence on some structural, vibrational and dynamical properties of hen egg-white lysozyme, a model globular protein, of three well-known homologous disaccharides, namely trehalose [α -D-glucopyranosyl- α -D-glucopyranoside], maltose [4-O-(α -D-glucopyranosyl)- β -D-glucopyranoside] and sucrose [β -D-fructofuranosyl- α -D-glucopyranoside], in the 37–60 wt % concentration range by means of molecular dynamics computer simulations. This specific concentration range was chosen because it corresponds to the range of concentrations where the HB network of the present sugars was shown to percolate in our previous numerical study of disaccharide/water solutions [33]. It should also be reminded that lysozyme remains in its flexible native state [34] in the studied solutions, so that neither the dynamical transition nor the denaturation process are covered by this study.

2 Details of the simulation

Molecular Dynamics simulations of hen egg-white lysozyme (hereafter referred to as lysozyme) in sugar/water solutions have been performed using the CHARMM program [35], version 29b1. The all-atom CHARMM22 force field [36] has been used to

model the protein. The CSFF carbohydrate force field [37] has been considered for disaccharides and water molecules were represented by the SPC/E model [38]. The production simulations were performed in the isochoric-isothermal (N,V,T) ensemble. The length of all covalent bonds involving an hydrogen atom as well as the geometry of water molecules were kept fixed using the SHAKE algorithm [39], with a relative tolerance of 10^{-5} . A 2-fs timestep has been used to integrate the equations of motion with the verlet leapfrog algorithm [40].

During the different stages of the simulations, the temperatures have been maintained constant with weak coupling to a heat bath (Berendsen thermostat [41]) with a relaxation time of 0.2 ps. A cutoff radius of 10 Å has been used to account for van der Waals interactions, which were switched to zero between 10 and 11.5 Å. A Lennard-Jones potential has been employed to represent van der Waals interactions and Lorentz-Berthelot mixing-rules have been used for cross-interaction terms. Electrostatic interactions have been handled by the particle mesh Ewald (PME) [42] method with $\kappa = 0.32 \text{ Å}^{-1}$ and the fast-Fourier grid densities set to $\sim 1/\text{Å}$ (48 and 64 grid points in the X/Y and Z directions, respectively).

The starting structure of lysozyme was obtained from the X-ray crystal structure solved at 1.33 Å (193L entry of the Brookhaven Protein Data Bank) [43]. Most probable charge states at pH 7 were chosen for ionizable residues. The total charge of lysozyme (+8 e) was then neutralized by uniformly rescaling the charge of protein atoms, similarly to ref. [44]. The disaccharide initial conformations have been deduced from neutron and X-ray studies of trehalose [26], maltose [45] and sucrose [46]. The sugar concentrations on a protein-free basis are 37, 50 and 60 wt %. These concentrations have been purposefully chosen based on our previous study of sugar/water solutions [47, 48]. Indeed, we showed that the relative effect of sugars on water may be distinguished above a threshold concentration of about 40 wt%. Therefore, their relative influence on lysozyme at ambient temperature may be characterized above this concentration. Lysozyme and its 142 crystallographic hydration water molecules were first placed in an orthorhombic box with cell parameters $a = b = 46.7 \text{ Å}$ and $c = 62.2 \text{ Å}$. Then, disaccharide molecules were located and oriented randomly around lysozyme, with minimum sugar-protein and sugar-sugar distance criteria, which ensure an isotropic distribution of sugars around lysozyme. Finally, water molecules non-overlapping with either lysozyme or sugars were randomly added in the simulation box. Initial configurations were minimized in three steps, keeping first lysozyme and sugars fixed, then keep-

ing only lysozyme fixed and finally keeping free all molecules. This minimized configuration was heated to 473 K in the canonic ensemble during 1 to 3 ns, while maintaining fixed the conformation of lysozyme to prevent conformational changes. This aimed at equilibrating solvent configurations, particularly the position and orientation of sugars. Then, the resulting configurations were thermalized at 300K and simulated in the isobaric-isothermal (N,P,T) ensemble. The stabilized volume of the simulation box during this simulation was considered to compute the averaged density of the system and used to perform the subsequent simulations in the (N,V,T) ensemble. A steepest-descent minimization procedure of 1000 iterations was then performed, whilst applying a decreasing harmonic potential on atoms of lysozyme. After the minimization procedure, the temperature was raised from 0 to 300 K, with a 5-K temperature increase every 250 steps. Then, an equilibration at 300 K was performed during about 80 ps. Finally, simulations of 10, 12 and 17 ns were performed for the systems at concentrations of 37, 50 and 60 wt %, respectively, and configurations were saved every 0.25 ps. A control simulation of lysozyme in pure water was done in an analogous way as the one described above. In this simulation, the orthorhombic box was directly filled with water molecules. Moreover, this system was not heated at 473 K, since water molecules are much more mobile than sugars. The first two and four ns were not considered to compute the structural and dynamical properties presented in this paper for the 0-50 and 60 wt % systems, respectively. Table 1 summarizes some simulation data for the different systems considered in the present study.

3 Structural properties.

3.1 Lysozyme

3.1.1 Control parameters

The influence of sugars on the conformation of lysozyme has first been checked by computing the root-mean-square deviation (RMSD) from the crystallographic structure, of either the C_α carbon atoms of the protein backbone or of all protein atoms. The averaged values for all studied systems are shown in table 2. The values for the pure water system are in fair agreement with those reported in previous studies [12, 44], which employed the TIP3P water model [49]. The presence of sugars at the studied concentrations reduces conformational changes of lysozyme, as seen from the significant decrease of the C_α and the all-atom RMSDs, which tends to be more important when disaccharide concentration increases. A comparable effect

Table 1: System compositions (where N_L , N_S and N_W denote the number of lysozyme, sugar and water molecules, respectively), densities, and equilibration/simulation times for the different sugar concentrations ϕ (on a protein-free basis). Data corresponding to $\phi = 0$ wt % result from only one simulation of lysozyme/pure water.

ϕ (wt %)	$N_L/N_S/N_W$	density ($g.cm^{-3}$)			Eq./Sim. time (ns)
		T	M	S	
0	1/0/3800	1.04	1.04	1.04	2/8
37	1/85/2800	1.16	1.16	1.15	2/8
50	1/125/2400	1.20	1.21	1.20	2/10
60	1/165/2100	1.24	1.25	1.24	4/13

has been observed by Lins *et al.* [12] for lysozyme in presence of trehalose at a concentration of ~ 18 wt % compared to the pure water system, where the all-atom RMSD of lysozyme in presence of trehalose was found about $0.2 \text{ \AA}$ lower. The fact that the reduction is also seen for the C_α RMSD may arise from the slowing-down of the solvent dynamics observed at these concentrations, which will be shown later in this article. No major difference is observed among the three sugars, whatever the concentration considered. This suggests that the studied sugars have a similar influence on lysozyme from a structural point of view. This is expected in the framework of the preferential hydration hypothesis [17], which suggests that sugars are preferentially excluded from the protein surface. The conformation of lysozyme in the different solutions has also been characterized via its radius of gyration R_g and its total solvent accessible surface area (SASA) - see the remaining part of table 2. The program DSSP [50] has been used to computed the SASA of protein residues. The R_g and SASA of lysozyme seem to slightly increase in the presence of sugars. This may stem from the non-negligible interaction of surface residues of lysozyme with sugars, as will be shown in the section 3.1.3. Again, a clear discrepancy among the studied sugars does not emerge. These three parameters show that the structure of lysozyme in presence of sugars remains relatively close to that in pure water.

3.1.2 Protein fluctuations

The influence of sugars on the internal motions of lysozyme has been investigated by the computation of atomic mean-square fluctuations (MSFs). Similarly to Maragliano *et al.* [51], MSFs were calculated by averaging over 250-ps time blocks to limit the effect of conformational changes during simulations. The figure 1 presents the MSFs of lysozyme main-chain atoms (C_α , C, and N) for the different studied systems, averaged by residue. These

MSFs are in qualitative agreement with the experimental temperature factors of lysozyme in its tetragonal form [52]. The high diversity of fluctuations reflects the heterogeneity of local environments experienced by lysozyme residues. This is consistent with the three kinds of residues identified by Lumry [53], based on temperature factors and also with the *knot/matrix* classification in the description of Gregory *et al.* [34] from exchange rate distributions : residues with low and intermediates B-factors are identified to *knot* and *matrix* residues, respectively, whereas residues with the highest B-factors are located on the surface of lysozyme. In figure 1, five main parts of lysozyme, centered on residues 20, 48, 70, 102 and 129, have rather high MSFs. These residues correspond to loops, 3-10 α -helices, and some residues of the β -sheet. They are all located at the protein surface, and are therefore likely to form HBs with the solvent. Two zones of the lysozyme residue sequence centered on residues 30 and 55 have lower MSFs than the average. They correspond to a α -helix and a loop located in the core of lysozyme. These residues are not extensively accessible to the solvent (see section 3.1.3) and their motions are sterically constrained by the presence of other protein residues. The addition of sugars significantly reduces lysozyme fluctuations, but their distributions remain qualitatively the same for all sugar concentrations. The MSFs at 37 wt % do not reveal clear differences among the three sugars, even if maltose tends to globally reduce slightly more protein fluctuations than trehalose and sucrose. At 50 wt %, sucrose clearly allows slightly larger fluctuations than trehalose and maltose for nearly every protein residue. This suggests that the protein-solvent interactions in this system differ, as will be shown later. Finally, the MSFs at 60 wt % show that maltose reduces slightly more lysozyme fluctuations than do trehalose and sucrose.

Table 2: Parameters describing the structure of lysozyme : (i) Root-mean-square deviation (RMSD) from the crystallographic structure of C_α carbon atoms or of all atoms, (ii) radius of gyration R_g of lysozyme, and (iii) total solvent accessible surface area (SASA). Standard deviations from mean values are given in parentheses.

ϕ (wt %)	Sugar	RMSD (Å)		R_g (Å)	SASA (Å ²)
		Backbone	All atoms		
0		1.40 (0.13)	2.27 (0.11)	14.07 (0.07)	7280 (144)
37	T	1.01 (0.10)	1.80 (0.08)	14.21 (0.10)	7380 (208)
	M	1.09 (0.07)	1.93 (0.06)	14.20 (0.10)	7310 (135)
	S	1.06 (0.06)	1.84 (0.06)	14.25 (0.05)	7335 (122)
50	T	0.96 (0.07)	1.73 (0.06)	14.14 (0.07)	7167 (102)
	M	1.02 (0.06)	1.71 (0.06)	14.21 (0.05)	7290 (91)
	S	0.97 (0.11)	1.66 (0.12)	14.19 (0.07)	7358 (189)
60	T	0.97 (0.07)	1.70 (0.07)	14.26 (0.06)	7437 (96)
	M	0.96 (0.07)	1.66 (0.08)	14.28 (0.04)	7325 (91)
	S	0.94 (0.06)	1.63 (0.05)	14.23 (0.05)	7283 (73)

3.1.3 Fractional solvent accessibilities f_{sa}

The fluctuations of lysozyme residues clearly reveal distinct local environments, which may arise from differences in local packing and interactions with the solvent. Indeed, residues from the core should be more densely packed and less accessible to the solvent than residues from the surface, whose motions are also less sterically constrained. The time-averaged fractional solvent accessibilities [54] f_{sa} of lysozyme residues have been calculated to know how they may interact with the solvent. The DSSP program has been used for this purpose [50]. f_{sa} is equal to the ratio $A_{protein}/A_{free}$, where $A_{protein}$ is the SASA of a particular residue in the presence of the other surrounding residues of lysozyme, while A_{free} is the related surface area of the *free* residue, *i.e.* without the presence of other amino acids. Figure 2 shows the f_{sa} of the different lysozyme residues in pure water and in the 50 wt % trehalose solution (the distributions for the remaining solutions are similar and are thus not shown). The distributions for the pure water and the 50 wt % trehalose solution are close to each other and further evidences that the presence of sugars do not modify significantly the conformation of lysozyme. This is expected since sugars are well-known protein stabilizers. A more important point is that the distributions mimic those of MSFs (see figure 1), and thus confirms that residues with low solvent accessibilities fluctuate much less than residues exposed to the solvent. Figure 2c presents the distributions probabilities of f_{sa} . These distributions show a bimodal behavior : (i) a first relatively sharp contribution for f_{sa} lower than about 0.15, and (ii) a second much broader band, centered at ~ 0.3 . These

two contributions have been arbitrarily attributed to lysozyme *core* and *surface* residues, respectively. The sharper contribution from core residues may indicate that the environments they experienced is much homogeneous than that of surface residues. This again shows that surface residues may exhibit larger motions than core residues, because sterical constraints imposed by other protein residues are lower. This result also suggests that the exposition of residues to the solvent may have important consequences on their vibrational and dynamical properties (see section 4).

In the following, residues of lysozyme in pure water with f_{sa} lower and higher than 0.15 are considered as *core* and *surface* residues, respectively. This arbitrary criterion was chosen because it corresponds approximately to the minimum between the two contributions of the f_{sa} distributions of figure 2c. 59 and 70 residues belong to these two categories in the lysozyme/water solution, respectively, so that the statistical accuracy of their related properties should be comparable. This ratio between core and surface residues is similar for each system considered. This is the reason why the residues which belong to these categories were assumed to be the same for each ternary system.

3.2 Protein-solvent interactions.

3.2.1 Water-protein and sugar-protein HBs

The way sugars interact with biomolecules, and in particular with globular proteins and membrane phospholipid bilayers, has been largely debated over the last two decades [6]. According to the *water replacement* hypothesis, sugars form HBs with

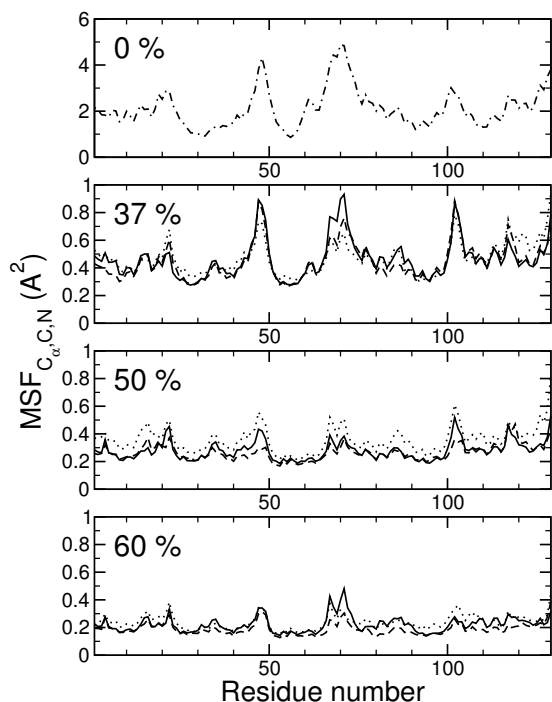


Figure 1: Residue-averaged mean square fluctuations (MSFs) of atoms from the backbone of lysozyme (C_α, C, N) in the lysozyme/pure water solution, and in the different ternary solutions at $T = 300$ K. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

biomolecules by substituting to their hydration water. In the present study, the HBs formed at the lysozyme-solvent interface have been analyzed. Two molecules were considered to be H-bonded if the donor-acceptor distance d_{DA} is less than $3.4 \text{ \AA}$ and if the D-H...A angle is larger than 120 deg . [55]. The table 3 summarizes the time-averaged number of HBs formed between lysozyme and water and disaccharide molecules. In the investigated concentration range, sugars form between 10 and 20 % of the total number of protein-solvent HBs. This is much fewer than the number of HBs they could form, assuming that water and sugar molecules were equally able to form HBs with lysozyme. In addition, the total number of protein-solvent HBs tends to slightly decrease when sugar concentration increases. This suggests that sugars are not able to substitute perfectly to water molecules. Probably because of sterical hindrance and topological constraints, they cannot access as easily as water molecules to polar groups located in cavities of lysozyme.

The number of disaccharide-protein HBs and the number of water molecules shared between lysozyme and disaccharides increases with sugar

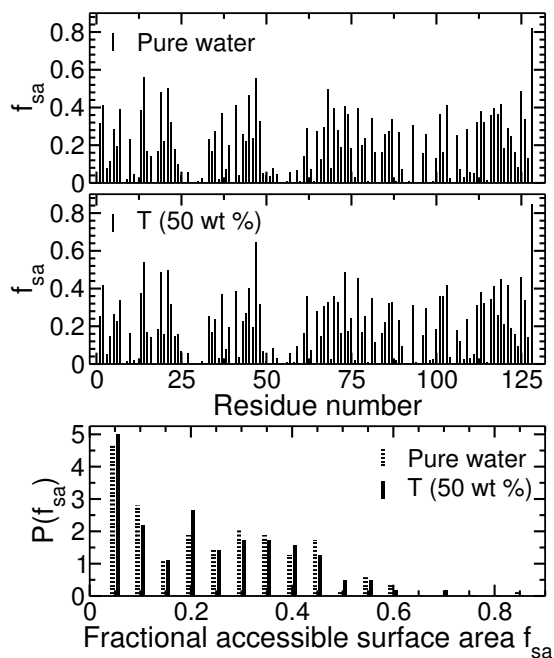


Figure 2: Fractional solvent accessibilities f_{sa} as a function of residue number sequence for the lysozyme/pure water (top) and for the trehalose 50 wt % (middle) solutions at $T = 300$ K. The related probability densities are displayed in the bottom part of the figure. They show a bimodal behavior, from which *core* and *surface* residues have been defined (see text).

concentration, since sugar-protein interactions are more likely. Slight differences are observed among the three sugars. First, sucrose molecules seem to form a lower number of HBs with lysozyme in the 50 wt % solution. But, this discrepancy may lay within simulation errors and is likely to occur from a lack of configurational sampling. Indeed, sucrose form more comparable numbers of HBs with lysozyme at lower or higher concentrations. Consequently, care must be taken when comparing the results for the three sugars. Moreover, it does not seem that trehalose forms more HBs with lysozyme than sucrose and maltose at the studied concentrations, although this may be the case in the completely dehydrated case. This result would be consistent with the simulation results of Lins *et al.* [12] which showed that trehalose clusters at the protein surface and does not expel the water molecules closest to the protein surface. It would therefore confirm the *preferential hydration* hypothesis proposed by Timashoff *et al.* [16,17], which suggests that trehalose is more excluded - in the relatively diluted solutions - than other osmolytes, and would thus increase the thermodynamical stabilization of the proteins compact native state relative to their extended denat-

urated state [3]. The larger hydration number of trehalose (see figure 4a) would then explain why it does not interact more than do maltose and sucrose with lysozyme in our simulations. These results also appear in line with those of a recent simulation study [31], which shows that maltose forms a larger number of HBs with a phospholipid membrane than trehalose, at a 2 m concentration, both at 325 and 475 K.

3.2.2 Preferential hydration

Solvent molecules do not form HBs with apolar groups of lysozyme. Therefore, the number of protein-solvent HBs does not describe exhaustively protein-solvent interactions. We have thus characterized the relative local distribution of water molecules around lysozyme in a similar way to Cottone *et al.* [13]. We have indeed computed the time-averaged normalized ratio $g_{N,ow} = n_{ow} / (n_{ow} + n_{os})(r) / (N_{ow} / (N_{ow} + N_{os}))$, where n_{ow} and n_{os} are the local numbers of water oxygen atoms and sugar hydroxyl group oxygen, respectively, located at a minimum distance r from any heavy atom of lysozyme, and N_{ow} and N_{os} denote the total number of water oxygen atoms and sugar hydroxyl group oxygen atoms, respectively, in the simulation box. This ratio is greater than one in the close proximity of the protein surface if a given sugar is preferentially excluded from the protein surface (in other words, if the protein is preferentially hydrated). Conversely, the sugar preferentially interacts with the protein if this ratio is lower than one. This ratio is represented in the figure 3 for the different ternary studied systems. Lysozyme clearly appears more and more preferentially hydrated when increasing sugar concentration. At distances larger than ~ 5 Å there is a slight water depletion which results from the presence of sugars. This preferential hydration probably arise from excluded volume effects and is consistent with the relatively low proportion of sugar-lysozyme HBs relative to water-lysozyme HBs (see table 3). If we exclude the sucrose solution at 50 wt %, for which there may be shortcomings, we note that trehalose preferentially hydrates lysozyme slightly more than do maltose and sucrose. This seems to be especially true for the hydration of apolar groups of lysozyme, which is apparent in the small peak located around 3.7 Å. Trehalose hydroxyl oxygens were indeed systematically more excluded from these groups than those of maltose and sucrose (data not shown). This may stem from the larger hydration number of trehalose (see figure 4a), which would prevent it from remaining close to apolar groups of lysozyme. Cottone *et al.* [13] have also shown that sucrose and trehalose at a concentration of 89 wt % preferentially hydrate

carboxy-myoglobin (MbCO), but sucrose to a larger extent than trehalose. It is possible that the effect of trehalose is somewhat different at this much more elevated concentration, as exemplified by the discrepancies between the water replacement and the preferential hydration hypotheses.

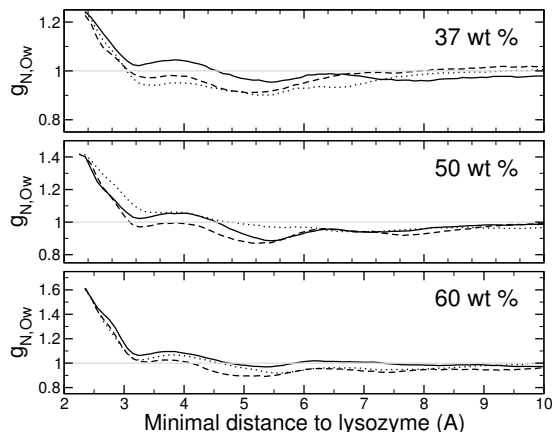


Figure 3: Normalized fraction of water oxygen atoms $g_{N,ow} = n_{ow} / (n_{ow} + n_{os}) / (N_{ow} / (N_{ow} + N_{os}))$ as a function of the minimal distance to any heavy atom from lysozyme at $T = 300$ K. n_{ow} and n_{os} denote the local numbers of water and sugar hydroxyl oxygen atoms, respectively. N_{ow} and N_{os} correspond to the total numbers of water and sugar hydroxyl oxygen atoms found in the simulation box, respectively. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

3.3 Solvent structure.

An important issue of the bioprotection phenomenon involves the role of sugar-water interactions. Indeed, the stabilizing effect of solutes is sometimes thought to depend directly on their effect on the HB network of water, although this is controverted [56]. Therefore, the larger hydration number of trehalose compared to maltose and sucrose [18,33,57] may explain its enhanced stabilizing effect. In the present solutions, the interaction of trehalose with water molecules is rather analogous to that of binary water/trehalose solutions. First, trehalose is still found to have a slightly larger hydration number than maltose and sucrose - with the exception of the 60 wt % solution, as shown in the figure 4a. It should be pointed out that the presence of the protein is likely to modify the water-sugar interactions of molecules located close to its surface, because of the formation of HBs with the protein. This is probably one of the reason why the hydration numbers of the sugars are

Table 3: Time-averaged numbers of hydrogen bonds between water and lysozyme $n_{HB}(W-L)$, disaccharides and lysozyme $n_{HB}(D-L)$, and number $n_W(L-W-D)$ of water molecules which are simultaneously hydrogen-bonded to lysozyme and disaccharides.

ϕ (wt %)		$n_{HB}(W-L)$	$n_{HB}(D-L)$	$n_W(L-W-D)$
0		329.0	-	-
37	T	290.0 (219.0)	33.9 (17.4)	46.2
	M	285.7 (207.5)	45.4 (21.3)	53.8
	S	277.1 (202.1)	35.5 (20.0)	49.4
50	T	261.4 (191.3)	50.9 (26.3)	62.4
	M	265.1 (190.0)	54.9 (27.7)	62.2
	S	281.5 (205.9)	34.1 (21.4)	57.3
60	T	259.7 (189.2)	57.0 (30.4)	73.0
	M	247.2 (177.6)	62.1 (34.0)	74.4
	S	243.6 (175.6)	64.0 (35.1)	65.7

lower than in our previous simulation study of binary sugar/water mixtures [33]. Secondly, the number of sugar intramolecular HBs, shown in figure 4b, is also in qualitative agreement with our previous study : trehalose is found to form a lower number of intramolecular HBs than does sucrose, maltose being intermediate, whatever the concentration considered. This would explain why the hydration number of trehalose is slightly larger than those of maltose and sucrose, since hydroxyl groups involved in these HBs no longer remain available for interacting with water molecules. These numbers definitely depend on the force field used and are systematically found lower in the present study. It is possible that the lower bending force constant of the glycosidic angle in the previously used carbohydrate forcefield of Ha *et al.* [58] is responsible for this discrepancy. Finally, the percolation of the HB network of sugars was suggested to play a major role in the bioprotection phenomenon, and differences between the three sugars have been observed [33]. This is particularly true for sugar concentrations above 50 wt %, where sugar-sugar interactions become important. The normalized mean sugar cluster size $\langle n_S \rangle / N_S$ has been computed in the same way as in our previous work [33] to know if the percolation of the sugar HB network occurs in the same concentration range in presence of the protein. These sizes are presented in the figure 4c. A transition clearly appears in the [37-50] wt % concentration interval, and the HB network of sugars has almost completely percolated at 60 wt %, in good agreement with our previous results [33]. Sucrose on one hand and maltose and trehalose on the other hand show quite different behaviors. Indeed, the percolation transition in sucrose systems is shifted to higher concentrations compared to maltose and trehalose ones. In other words, a higher

concentration of sucrose is needed to reach a given cluster size $\langle n_S \rangle$. This is well in line with the higher number of intramolecular HBs in sucrose (see figure 4b), as well as its slightly lower molecular volume and accessible surface area due to the presence of a furanose ring. This behavior may explain why the dynamics of lysozyme is less modified by the presence of sucrose than by the presence of maltose or trehalose. Furthermore, trehalose and maltose, which are topologically closer to each other than to sucrose, behave in a similar way. Nonetheless, it seems that the HB network of maltose tends to percolate faster than that of trehalose, as observed previously [33]. This may originate both from the less symmetric conformation of maltose and from its lower affinity for water molecules. In our previous study, maltose formed systematically larger clusters than trehalose, whereas this not always remains true in the present study. This discrepancy may stem from the presence of the protein, with which maltose seems to interact more strongly and thus less with other maltose molecules. Interestingly, the mean sugar cluster sizes $\langle n_S \rangle / N_S$ seem to be consistent with the solubility of the three disaccharides. Indeed, the experimental solubility at room temperature of sucrose is significantly larger than that of trehalose, whereas the solubility of maltose is slightly lower than that of trehalose (see fig. 4 of ref [59]). Recently, Giuffrida *et al.* [60] have suggested that this enhanced tendency of maltose molecules to form clusters could be related to their larger dipole momentum. Indeed, from ab initio calculations at the BLYP/6-31G** level, they obtained values of 5.2, 2.5 and 1.5 Debyes for the crystallographic structures of maltose, sucrose, and trehalose, respectively.

The topology of the studied disaccharides probably play a major role on their hydration numbers

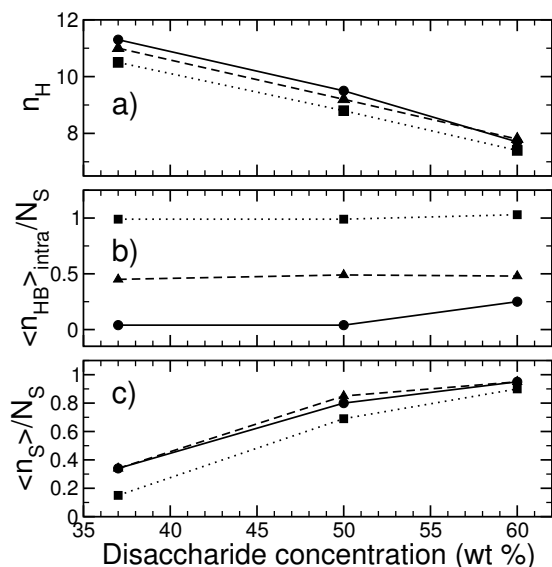


Figure 4: (a) Hydration number n_H of trehalose (solid line), maltose (dashed line), and sucrose (dotted line) as a function of their concentration at 300 K. (b) Normalized mean number of intramolecular HBs $\langle n_{HB} \rangle_{intra} / N_S$ of sugars in the different ternary solutions at 300 K. (c) Concentration dependence of the normalized mean sugar cluster size $\langle n_S \rangle / N_S$ at 300 K.

as well as their mean sugar cluster size, since these sugars have exactly the same chemical formula. The presence of a fructose ring in sucrose probably explain why several of its properties differ from those of maltose and trehalose. Nonetheless, even slighter topological discrepancies between disaccharides composed of 6-membered rings may lead to different solution properties. For instance, lactose is much less soluble than maltose [59], even though the only topological discrepancy between them is that the hydroxyl group on the C4 atom of one ring is in the axial position in lactose and in the equatorial position in maltose. As a means of interpreting the interaction of disaccharides with their neighboring molecules, we have computed their SASAs, which obviously depend on their topologies and solution conformations. The figure 5 shows the distribution of the SASAs of the three studied disaccharides in the 37 wt % solutions (the distributions at higher sugar concentrations are very similar and are therefore not shown). These SASAs have been computed according to the Lee and Richards method [61] with a probe radius of 1.4 Å. The three distributions are clearly distinct, even though the relative differences lie within about 5 %. The SASA of trehalose is found larger than that of sucrose, that of maltose being intermediate. This property may explain why trehalose interacts more with water than do maltose

and sucrose. Furthermore, the respective width of these distributions suggest that trehalose conformation is less flexible than that of maltose and sucrose. This seems to be contradictory with our previous study, which showed that trehalose was more flexible from the distributions of radii of gyration. It should however be noticed that these properties are very dependent on the force field used. It is possible that the too low force constant of the glycosidic angle in the Ha *et al.* [58] is responsible for this discrepancy, consistent with that observed on the number of intramolecular HBs.

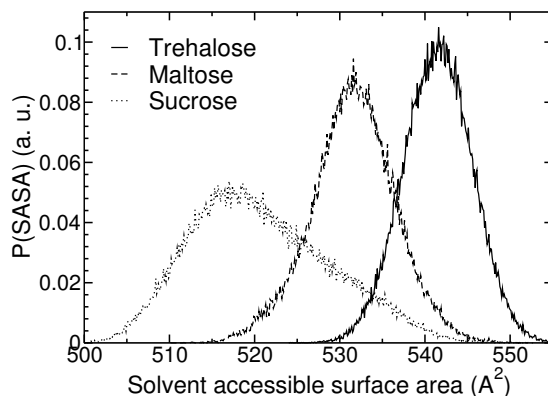


Figure 5: Solvent accessible surface area (SASA) distributions of disaccharides in the 37 wt % solutions at $T = 300$ K.

4 Vibrational and dynamical properties.

4.1 Vibrational density of states (VDOS) of lysozyme.

The low-frequency ($\omega < 1000$ cm⁻¹) vibrational density of states (VDOS) of lysozyme has been computed from the Fourier transform of the autocorrelation function of atomic velocities :

$$c_{vv}(t) = \frac{1}{M} \sum_{i=1}^N m_i \langle \mathbf{v}_i(0) \cdot \mathbf{v}_i(t) \rangle \quad (1)$$

where $\mathbf{v}_i$ is the velocity vector of atom i and m_i its mass, and $M = \sum_i m_i$ is the mass of lysozyme. The VDOS is then written as :

$$g_{vv}(\omega) = \int_0^\infty \cos(\omega t) c_{vv}(t) dt \quad (2)$$

The figure 6 shows the VDOS of lysozyme in the [0-350 cm⁻¹] range for the different studied systems. It is composed of two main bands centered on about 60 cm⁻¹ and 230 cm⁻¹. The general shape is in

qualitative agreement with the one obtained experimentally by Colaianni and Nielsen [62], although the position of the peaks are located at lower frequencies in our study. The first peak has often been attributed to the *cage* effect, and is observed in many liquids, associated or not [63,64]. It is sometimes referred to as the *boson peak*. Its width represents the heterogeneity of the local environments experienced by individual atoms, as shown for the atomic MSFs (see figure 1). Another very broad band centered at about 230 cm^{-1} appears. This band could arise from librational motions of atoms of lysozyme surface residues exposed to the solvent. The presence of sugars seems to induce two significant changes on the VDOS of lysozyme. The first one is the sharpening of the boson peak, which amplifies with sugar concentration. This effect is well in line with the reduction of protein atomic fluctuations observed in the figure 1. Sugars would therefore be likely to reduce absolute discrepancies of cage effects among the different lysozyme atoms. In pure water, the amplitude of atomic motions is limited by steric constraints imposed by the other residues of the polypeptidic chain. Motions of the surface residues are thus more free, and may be favored by HBs with water molecules. Sugars would strongly reduce the amplitude of motions of residues with which they form HBs, thus imposing an additional constraint on them in comparison to the pure water solution case. The second main consequence of the presence of sugars is that the second band is much more defined. The width of this band is lower and its amplitude raises and becomes comparable to that of the first band. Furthermore, its position shifts from $\sim 220\text{ cm}^{-1}$ up to $\sim 250\text{ cm}^{-1}$ when sugar concentration raises from 37 to 60 wt %. This band is located in about the same frequency range as the second main low-frequency band of pure water, which is generally considered to be representative of the formation of HBs. This observed effect on the second band could therefore result from the strengthening of water-lysozyme HBs, as well as the formation of sugar-lysozyme HBs, since water-lysozyme HBs lifetimes significantly increase in presence of sugars (see figure 14a). Moreover, sugar-protein HB lifetimes should be at least one order of magnitude larger than those of water-protein HBs, at a given sugar concentration. These stronger HBs would explain the shift towards higher frequencies.

4.2 Lysozyme relaxation.

The relaxational behavior of lysozyme has been investigated by means of incoherent intermediate scattering functions $S_{inc}(Q, t)$:

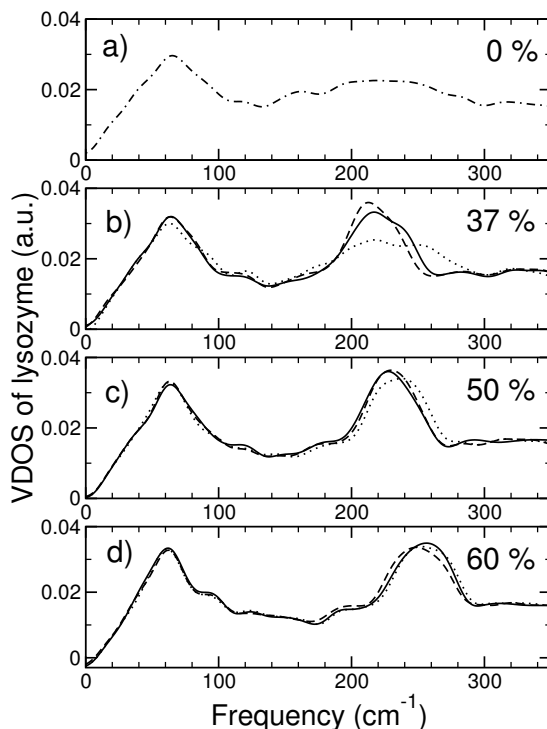


Figure 6: Vibrational density of states (VDOS) of lysozyme at $T = 300\text{ K}$ for the pure water/lysozyme solution (a) and for the different ternary solutions (b-d). The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively. Curves have been smoothed with the Savitzky-Golay algorithm of the Peakfit software version 4.02 to make easier the results analysis.

$$S_{inc}(Q, t) = \left\langle \sum_{\alpha} b_{\alpha, inc}^2 e^{i \cdot Q \cdot [r_{\alpha}(t) - r_{\alpha}(0)]} \right\rangle \quad (3)$$

where $b_{\alpha, inc}$ and r denote the incoherent scattering length and the vector position of a given atom α , respectively, and Q is the wavevector. The brackets mean averaging over every time origin of simulations. These functions correspond to the time Fourier transform of dynamic structure factors $S_{inc}(Q, \omega)$, obtained in neutron scattering experiments. We have arbitrarily chosen to probe the dynamics of lysozyme at a wavevector of $2.29\text{ \AA}^{-1}$, which corresponds to the position of the first peak in the static structure factor S_{O-O} of pure water and which was used in our study of binary sugar/water solutions [47]. Characteristic relaxation times were defined as the decay times from 1 to $1/e$ of the different $S_{inc}(Q, t)$. The figure 7 presents the $S_{inc}(Q, t)$ of lysozyme in pure water and in the different 60 wt % solutions. The decay of $S_{inc}(Q, t)$ occurs in two steps : a first fast decay down to the plateau regime, characteristic of the *cage* effect and whose length depends on the

solvent and a second one, which reflects structural relaxation motions.

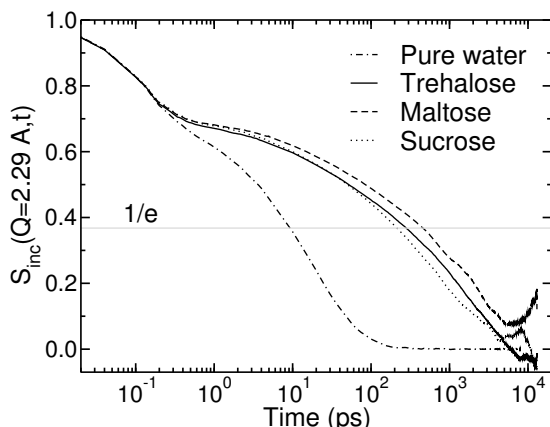


Figure 7: Incoherent intermediate scattering functions of lysozyme $S_{inc}(Q, t)$ in the 60 wt % solutions at the Q value of $2.29 \text{ \AA}^{-1}$ and for $T = 300 \text{ K}$. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively. The $S_{inc}(Q, t)$ of lysozyme in pure water (dot-dashed line) is also plotted for comparison. In this paper, relaxation times have been computed from the time decay from 1 to $1/e$ of the different $S_{inc}(Q = 2.29 \text{ \AA}^{-1}, t)$.

Since the MSFs and the f_{sa} of lysozyme residues suggest that they experience very heterogeneous local environments (see figures 1 and 2), it is interesting to know how this heterogeneity affect their relaxation times. The figure 8 shows the relaxation frequency $1/\tau_{1/e}$ of residues of lysozyme in pure water and in the different trehalose solutions. They are in good agreement with the fractional solvent accessibilities f_{sa} of residues of lysozyme, since residues which are more exposed to the solvent relax faster than those which are buried in the protein core. This may be understood as the facilitation of motions mediated by HBs with hydration water molecules. This figure shows that the relaxation of some residues is more than about 10 times slower than the relaxation of the residues close to the C-terminal amino acid, which is particularly exposed to the solvent. A similar behavior has also been observed for the other concentrated sugar solutions.

The figure 9a shows the distribution of relaxation times of lysozyme residues in the pure water and in trehalose solutions (the distributions for maltose and sucrose solutions exhibit comparable behaviors and are not shown for clarity reasons). An important broadening of distributions is observed when the sugar concentration increases. This may reflect the broadening of the energy barriers experienced by lysozyme residues resulting from an increased

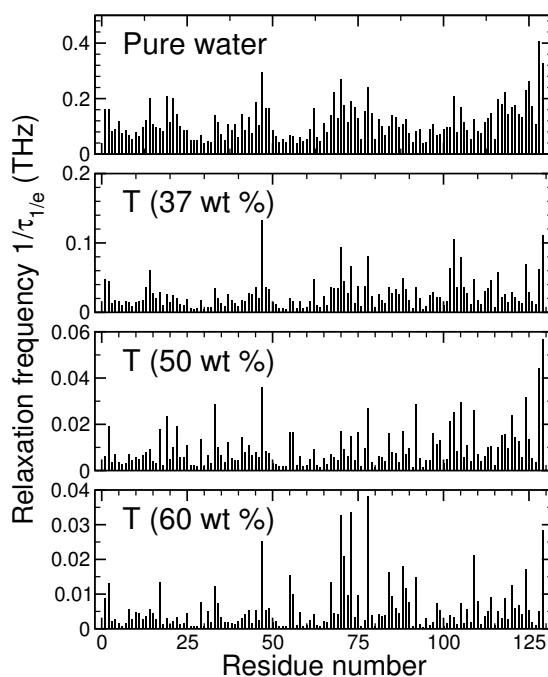


Figure 8: Relaxation frequencies $1/\tau_{1/e}$ of the different residues of lysozyme in pure water and in the different trehalose solutions at $T = 300 \text{ K}$.

dynamical coupling between solvent and protein. The figure 9b shows for the pure water and for the different trehalose solutions the evolution of the mean relaxation time of lysozyme residues as a function of their fractional accessible surface area f_{sa} , up to about 0.6 (given the low number of residues with a f_{sa} larger than 0.6, the related statistical errors are very large). The correlation between the averaged $\tau_{1/e}$ and f_{sa} of lysozyme residues is relatively well established whatever the concentration in sugars considered (data not shown), and $\tau_{1/e}$ increases almost exponentially with f_{sa} .

The figure 10 shows the mean relaxation time of lysozyme computed from the average over all residues, or over only surface or core residues - as defined in section 3.1.3 - as a function of disaccharide concentration. The addition of sugars at the considered concentrations strongly raises the relaxation time of lysozyme, up to more than one order of magnitude for the 60 wt % solutions. At 37 wt %, the relaxation time of lysozyme is very similar for each sugar solution. But at higher disaccharide concentrations - 50 and 60 wt %, lysozyme clearly relaxes faster in the sucrose solutions than in the trehalose and maltose ones. Moreover, maltose and trehalose behave quite similarly at 50 wt %, whereas maltose seems to slow down more strongly the dynamic of lysozyme at 60 wt %. This latter observation may partially arise from a lack of sampling of the dynamics of lysozyme at this concentration,

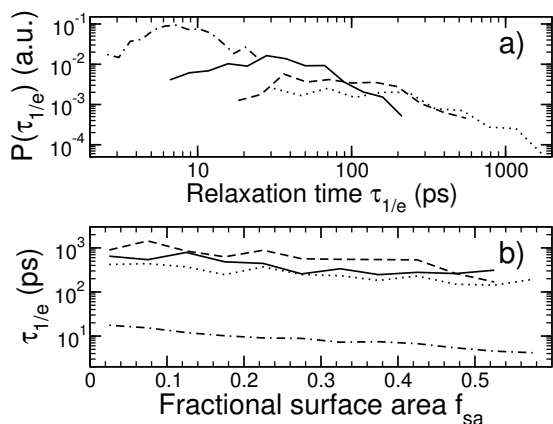


Figure 9: (a) Distributions of lysozyme residues relaxation times $\tau_{1/e}$ in the pure water/lysozyme solution (dot-dashed line) and in the 37, 50, and 60 wt % trehalose solutions (continuous, dashed, and dotted lines, respectively) at $T = 300$ K. (b) Averaged relaxation times of lysozyme residues $\tau_{1/e}$ as a function of their fractional solvent accessibilities f_{sa} for the pure water solution (dot-dashed line) and for the 50 wt % trehalose, maltose and sucrose solutions (continuous, dashed, and dotted lines, respectively) at $T = 300$ K.

i.e. when the HB network of sugars has essentially percolated (see figure 4c). The long-time part of the $S_{inc}(Q, t)$ shown in figure 7 seems to confirm this. Therefore, although the trend may be reproduced, the relative discrepancies between the relaxation times of sugars may not be as large as the ones computed. Much longer simulations should probably be required to obtain a more satisfying sampling of lysozyme dynamics at this relatively high concentration. Nonetheless, the relaxation times from figure 10 are consistent with the results from figure 4c. Indeed, the HB network of sugars has not percolated at 37 wt % and the discrepancies between the relative influence of sugars on the dynamics of the solvent are not large enough to account for significant discrepancies on the dynamics of lysozyme. At 50 and 60 wt %, the mean sugar cluster size $\langle n_S \rangle$ in the sucrose solutions are still lower than in the maltose and trehalose ones, whose HB networks have almost percolated. Therefore, the dynamics of lysozyme becomes more influenced by that of sugars (see next section), and discrepancies between sugars emerge since sugar-sugar interactions play a major role at these concentrations. In particular, the faster relaxation of sucrose compared to trehalose and maltose yields a faster relaxation of lysozyme. This could be attributed in part to the lower tendency of sucrose to form clusters. Finally, it must be pointed out that the relaxational behavior of lysozyme follows relatively well that of

the number of sugar-protein HBs, as is well exemplified with the sucrose solution at 50 wt %. But, this is not true when comparing the sucrose and trehalose solutions at 60 wt %. Indeed, sucrose form a larger number of HBs with lysozyme, which relaxes however faster than in the trehalose solution. This illustrates the fact that the slowing-down of lysozyme dynamics is both dependent on the number of HBs with sugars and on the dynamics of the solvent, which is considered in the following part of this article.

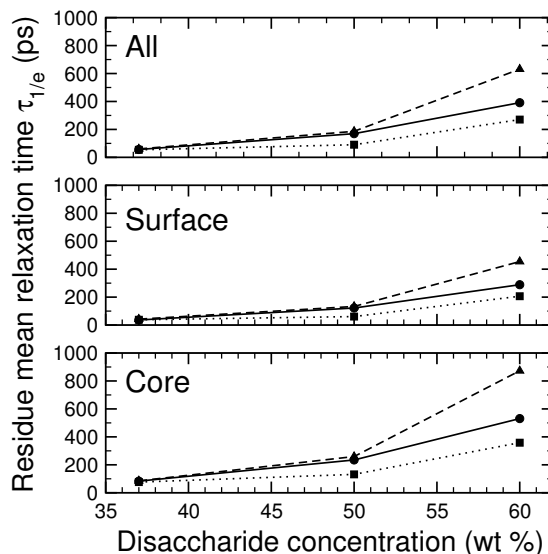


Figure 10: Mean relaxation time $\tau_{1/e}$ of lysozyme residues as a function of the disaccharide concentration at $T = 300$ K : all (top), *surface* (middle) and *core* (bottom) residues of lysozyme. Relaxation times have been computed from the time decay from 1 to $1/e$ of the incoherent intermediate scattering function at a wave vector $Q = 2.29 \text{ \AA}^{-1}$. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

4.3 Solvent dynamics

The dynamics of proteins is usually thought as *slaved* to that of the solvent [65]. Indeed, it has generally been observed that protein motions are strongly hindered in high viscosity solvents, which implies that the influence of the solvent is primarily ruled by its viscosity. However, proteins exhibit a very broad range of motions, which occur on a very broad range of timescales and amplitudes [66, 67]. High viscosity solvents may hinder large-scale motions, responsible for structural relaxation, but may be less efficient to reduce small-amplitude, vibrational motions. For instance, some counterintuitive examples such as trehalose/glycerol mixtures show

that vibrational motions of proteins may be more hindered by lower T_g matrices or solvents [22, 23].

4.3.1 Sugar dynamics

The dynamics of sugar molecules has been characterized by their incoherent intermediate scattering functions computed at the same wave vector $Q = 2.29 \text{ \AA}^{-1}$ as for protein residues. The related mean relaxation times $\tau_{1/e}$ are shown in the figure 11 as a function of sugar concentration. Sucrose clearly relaxes faster than trehalose and maltose, whatever the concentration considered. This is well in line with experimental studies, which show that the dynamics of sucrose is faster than that of maltose and trehalose [18]. Moreover, the relaxation times of maltose seem to be longer than those of trehalose. This appears to be different from experimental measurements which suggest that binary trehalose/water solutions are slightly more viscous than maltose ones [18, 68]. This may reflect a shortcoming of the simulation of maltose. Indeed, on the contrary to trehalose and sucrose, maltose is a reducing disaccharide. Therefore, it exists under two anomeric forms, α and β , which interconvert permanently. In our simulations, only the predominant β form has been considered (relative populations of the β and α forms of maltose are $\sim 66 \%$ and $\sim 34 \%$, respectively). Nonetheless, these results are relatively well in line with a recent simulation study [31] of a membrane bilayer in presence of either glucose (at 4 m), maltose or trehalose (at 2 m), where maltose was found to have a slightly lower lateral diffusion coefficient than trehalose, both at 325 and 475 K.

An interesting feature of the concentration dependence of the $\tau_{1/e}$ of sugars is the slope change observed in the [37-50] wt % concentration range, more pronounced for trehalose and maltose than for sucrose. This is probably the consequence of the percolation of the sugar HB networks, which occurs at about 40-50 wt % in both the sugar binary [33] and ternary solutions (see figure 4c). Indeed, at these relatively high concentrations, the hydration layers of sugars do not surround completely disaccharides because of sugar-sugar HBs, which strongly influence their dynamics. These dynamical changes have been observed experimentally by Rampp *et al.* [69] for a series of carbohydrates - including sucrose and trehalose - at concentrations above 50 wt %.

Solvents influence the dynamics of proteins, but proteins also affect the dynamics of solvent molecules at the protein-solvent interface. For example, it is well-accepted that the hydration water molecules of a protein behave like supercooled or confined water [70]. The figure 12 shows the evolu-

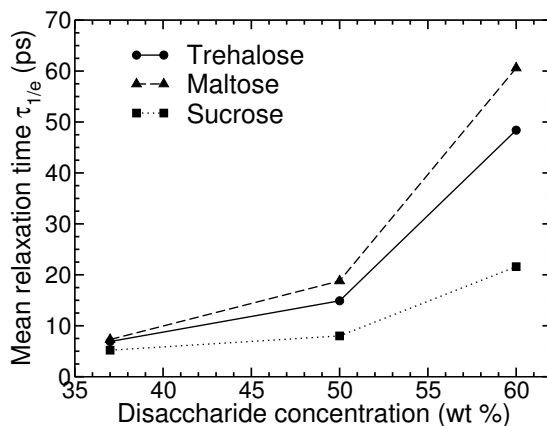


Figure 11: Mean relaxation time $\tau_{1/e}$ of disaccharides as a function of their concentration (in wt %) at $T = 300 \text{ K}$. Relaxation times have been computed from the time decay from 1 to $1/e$ of the incoherent intermediate scattering function at a wave vector $Q = 2.29 \text{ \AA}^{-1}$. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

tion of the sugar relaxation times as a function of their averaged distance to the protein. These relaxation times have been computed for each sugar on 1-ns trajectories and the averaged distance to the protein corresponds to the averaged distance from the glycosidic oxygen of sugars to any heavy atom of lysozyme during these 1-ns trajectories. Sugars within $\sim 7 \text{ \AA}$ of the protein surface clearly exhibit larger relaxation times than sugars from the *bulk*. This is probably the consequence of the presence of the protein which induces a decrease in the dimensionality of the diffusion of solvent molecules at the protein-solvent interface. It is also probable that the surface roughness of the protein as well as strong interactions with polar and charged groups play an important role. This result is consistent with those reported by Dirama *et al.* [14] for lysozyme embedded in a pure trehalose matrix at 550 K, *i.e.* above the numerical glass transition temperature $T_g \approx 460 \text{ K}$ of the pure trehalose matrix [71]. Indeed, they showed that the mean-square displacement of trehalose molecules close to the surface of lysozyme was lower than that of bulk ones at this temperature. They suggested that the viscosity seen by the protein is different from that of the bulk. This figure also shows that discrepancies between sucrose on one hand and maltose and trehalose on the other hand are observed whatever the distance to the protein.

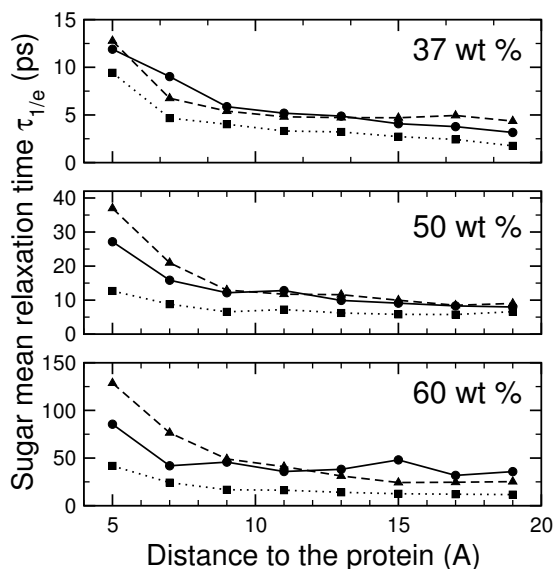


Figure 12: Mean relaxation time $\tau_{1/e}$ of disaccharides as a function of their averaged minimal distance to any heavy atom of lysozyme at $T = 300$ K. Relaxation times have been computed from the time decay from 1 to $1/e$ of the incoherent intermediate scattering function at a wave vector $Q = 2.29 \text{ \AA}^{-1}$. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

4.3.2 Water dynamics

Water molecules are known to play an important role on the structure and the dynamics of globular proteins. This remains particularly true in the present study, since the number of water-lysozyme HBs exceeds the number of disaccharide-protein HBs, even for the 60 wt % solutions (see table 3). Reciprocally, proteins modify the structure and dynamics of its hydration water molecules. There is a lot of debate about the extent of the perturbation of the dynamics of hydration water. Indeed, various experimental measurements - NMR spectroscopy, dielectric relaxation, neutron scattering, magnetic relaxation dispersion or time-resolved fluorescence - give different results, since they probe different physical phenomena [72, 73]. For instance, Marchi *et al.* [70] have shown that the water relaxational times of water close to lysozyme is about 3 to 7 times longer than bulk water, depending on the definition of hydration water, and that the diffusion of water molecules is subdiffusive. Here, the mean relaxation times of water molecules have been computed in a similar way as for sugar molecules, but for shorter trajectories (250 ps), given the faster relaxation of water molecules. The mean relaxation times of water molecules whose averaged distance to the protein is greater than $5 \text{ \AA}$ is very close to

that of bulk water (data not shown). Therefore, water molecules closer than $5 \text{ \AA}$ were considered as hydration water and the remaining water molecules as bulk water. The mean relaxation times of these two classes of molecules, as well as the global relaxation time of water molecules, are shown in figure 13. Similarly to sugars, water molecules located at the surface of the protein exhibit much longer relaxation times (from ≈ 3 times in pure water up to ≈ 10 times in sugar solutions). This probably depends on the nature of lysozyme residues and on the local rugosity of lysozyme. It must be pointed out that some molecules considered as hydration water occupy cavities within lysozyme. These internal water molecules may rigorously be best regarded as structural water molecules. Relaxation times of hydration water in disaccharides solutions tend to increase with the number of sugars found in close contact to the surface of the protein. In this sense, maltose is found to slow down to a larger extent water molecules than trehalose or sucrose do. Conversely, the dynamics of bulk water molecules follows that of sugars. In particular, bulk water dynamics is comparable for the three sugar solutions at 37 wt %, but significant discrepancies are observed for the 50 and 60 wt % solutions between sucrose on one hand and trehalose and maltose on the other hand. This seems to confirm the major role of the percolation of the HB network of sugars on the dynamics of both sugar and water molecules. Finally, the dynamics of bulk water molecules are slightly more slowed down in presence of trehalose than in presence of maltose at 37 and 50 wt %, as expected from its slightly larger hydration number (see figure 4a).

Since maltose forms larger clusters, it appears to globally slow down to a larger extent the whole dynamics of the sugar/water solvent. This may arise from a failing of the simulations of maltose which might not reproduce very well real properties of maltose. Nevertheless, it should be reminded that the structural and dynamical properties of maltose and trehalose determined from experimental measurements are generally closer to each other than to sucrose ones. Furthermore, the results of this study appear compatible with those of Pereira *et al.* [31], which showed that the lateral diffusion coefficient of water molecules is lower in presence of maltose than in presence of trehalose, for a concentration of 2 m, at both 325 and 475 K.

4.4 HB dynamics

Solvent effects on the dynamics of lysozyme may be explained by the dynamics of the intermolecular HBs formed between the different species, in particular by the water-lysozyme, sugar-lysozyme

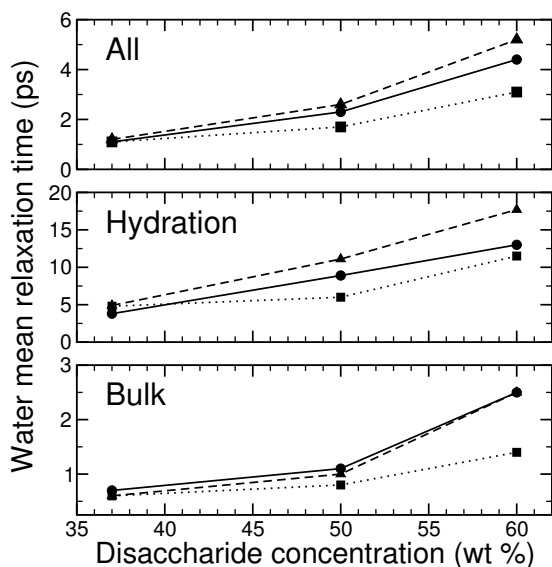


Figure 13: Mean relaxation time $\tau_{1/e}$ of water molecules as a function of disaccharide concentration (in wt %) at $T = 300$ K. Relaxation times have been computed from the time decay from 1 to $1/e$ of the incoherent intermediate scattering function at a wave vector $Q = 2.29 \text{ \AA}^{-1}$. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

or sugar-sugar intermolecular HBs. The lifetimes of HBs τ_{HB} were estimated from the time decay of the intermittent correlation function $C(t) = \langle h_i(t)h_i(0) \rangle$ where $h_i(t)$ is unity if a given HB i formed at time 0 remains intact at time t - even if it has broken in between - and is zero otherwise (the geometric criterion of HBs has been defined in section 3.2.1).

The addition of sugars significantly increases the lifetime of water-lysozyme HBs, because they hinder the diffusion of hydration water molecules, which are confined between the protein surface and sugars. About 50-70 water molecules - depending on the considered concentration, see table 3 - are simultaneously hydrogen-bonded to lysozyme and to sugars. This strengthening of water-lysozyme HBs may stabilize lysozyme, by hindering anharmonic motions of side chain residues in contact with the solvent. The hydration shell of lysozyme would thus be more stable in presence of sugars and the thermal denaturation would be shifted to higher temperatures. Maltose seems to raise more HBs lifetimes than the other two sugars, particularly at 50 and 60 wt %, in line with the longer relaxation times of maltose shown in figure 11.

The lifetimes of sugar-sugar HBs increase with the number of sugar-sugar HBs, and the larger numbers of sugar-sugar HBs in maltose and in trehalose

solutions compared to those of sucrose solutions lead to larger sugar-sugar HBs lifetimes. The dynamics of these HBs strongly affect the diffusion of sugar molecules for concentrations higher than about 40 wt % and may be responsible for the rapid increase of the viscosity of sugar/water solutions in this concentration range [69]. The lower sugar-sugar HB lifetimes observed in the sucrose solutions compared to those of maltose and trehalose may also partly stem from the presence of a furanose ring in sucrose, where two hydroxymethyl groups are present. Indeed, Baraguey *et al.* [74] have shown from a NMR study of sucrose solutions that the ^{13}C spin-lattice relaxation times of the hydroxymethyl groups of sucrose were significantly lower than those of the other hydroxyl groups, directly linked to a ring. This may result from the fact that hydroxymethyl groups have an additional rotational degree of freedom. Therefore, HBs involving two hydroxymethyl groups may be less strong than those involving a pair of hydroxyl groups directly linked to rings.

Finally, given the much lower mobilities of disaccharides with respect to water molecules and the significantly lower number of sugar-lysozyme HBs compared to water-lysozyme HBs (see table 3), large uncertainties exist on sugar-lysozyme HB lifetimes, particularly for the 60 wt trehalose and maltose % solutions. Therefore, longer simulations would be required to sample sufficiently the dynamics of sugar-lysozyme HBs by allowing a significant reorganization of sugar molecules at the lysozyme surface. This would allow us to compute reliable sugar-lysozyme HB lifetimes, which should be at least one order of magnitude longer than water-lysozyme HBs lifetimes. They may thus play a major role in the slowing-down of lysozyme dynamics, even though they are much less numerous than water-lysozyme HBs, because they are much stronger. This may explain why trehalose slows down to a larger extent the dynamics of lysozyme than sucrose does. López-Diez and Bone [75] have also suggested that trehalose may be expected to form more stable, stronger HBs than sucrose, because it is less mobile.

5 Conclusion

This article reports the results from molecular dynamics simulations of lysozyme/disaccharide/water solutions at 300 K for intermediate concentrations of sugars (37-60 wt %). This concentration range was chosen because it corresponds to the range of concentrations where the HB network of sugars was shown to percolate in our previous study of disaccharide/water solutions [33]. Several parameters

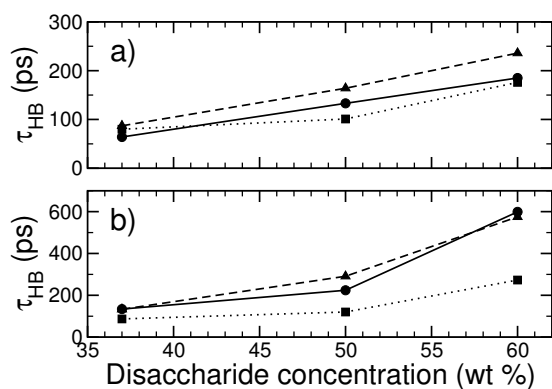


Figure 14: Relaxation times τ_{HB} of water-lysozyme (a) and sugar-sugar (b) HBs as a function of disaccharide concentration (in wt %) at $T = 300$ K. The continuous, dashed and dotted lines correspond to trehalose, maltose and sucrose solutions, respectively.

like RMSD, radius of gyration and SASA indicate that the conformation of lysozyme in presence of sugars remains very similar to that in pure water. This was expected because these sugars are protein stabilizers. Nevertheless, structural fluctuations of lysozyme as seen from mean-square fluctuations are much reduced in presence of sugars. This reduction was shown to be quite homogeneous throughout the protein and follows the fractional solvent accessibilities of lysozyme residues. This points out the direct influence of the solvent on the properties of lysozyme. The analysis of the interactions of sugars with lysozyme via HBs as well as the relative concentration of water oxygen atoms around lysozyme suggest that lysozyme is preferentially hydrated, well in line with other studies [12, 13]. When comparing the three sugars, it seems that trehalose is slightly more excluded than maltose and sucrose, although discrepancies may be not significant. This could be interpreted by the higher hydration number of trehalose compared to the other two sugars. Furthermore, the number of intramolecular HBs of trehalose was found lower than that of maltose and sucrose. In addition, the HB network of sugars was shown to percolate in the studied concentration range. Sucrose forms smaller clusters than trehalose and maltose, probably because of its larger number of intramolecular HBs. Interestingly, trehalose was also found to have the largest SASA. This may explain why it interacts more with water than maltose and sucrose. This study also reveal that sugars have a significant influence on the low-frequency vibrational density of states of lysozyme. They induce a sharpening of the first band (at ~ 60 cm^{-1}), which is related to the cage effect, and the emergence of the second band (at ~ 230 cm^{-1}),

which may reflect a strengthening of the solvent-protein interaction, caused by an increase of the solvent viscosity. These effects have been observed on both core and surface residues. Dynamical properties of lysozyme have been analyzed via incoherent intermediate scattering functions $S_{inc}(Q, t)$. Relaxation times of lysozyme residues mimic both MSFs and f_{sa} distributions. For instance, a linear correlation is observed between $\tau_{1/e}$ and f_{sa} . A broadening of the distributions of relaxation times of protein residues is also observed when increasing sugar concentration. This could reveal an enhanced dynamical coupling between solvent and lysozyme. Moreover, a significant increase of relaxation times for both surface and core residues is observed when increasing sugar concentration from 37 to 60 wt %. This increase is also apparent in the mean relaxation times of sugars and seems to arise from the percolation of the HB network of sugars, which is found consistent with our previous results on binary sugar/water solutions. Since sucrose forms smaller clusters than trehalose and maltose, it appears to slow down the dynamics of lysozyme less strongly at concentrations above ~ 40 wt %. On the contrary, maltose slows down more efficiently the dynamics of lysozyme because it forms larger clusters. It was also shown that sugars in close proximity to the protein surface exhibit much longer relaxation times than sugars from the bulk, as observed for hydration water molecules. Finally, the HB lifetimes of sugar-sugar intermolecular HBs agree with the sugar cluster sizes $\langle n_S \rangle$ and the sugar relaxation times. They are lower for the sucrose solutions, and may explain why its effects on the dynamics of lysozyme are reduced in comparison with maltose and trehalose.

Our simulations only cover a limited concentration range of disaccharides at ambient temperature (300 K). Therefore, lysozyme is not submitted to temperature and/or desiccation stresses in the studied solutions. Furthermore, the length of simulations is too short to account for phenomena which occur on much longer time scales in real systems, such as vitrification, ice formation or sugar crystalline phase transitions. Nevertheless, our results suggest that the dynamical slowing-down of lysozyme induced by the presence of sugars may stabilize biological molecules. In addition, the substitution of water-lysozyme HBs by sugar-lysozyme HBs seems limited, but may be more important in almost completely dehydrated systems. Our results would thus indicate that lysozyme remains preferentially hydrated in the studied concentration range, in agreement with the hypothesis of Timasheff *et al.* [17]. Nonetheless, sugar-lysozyme HBs are much stronger than water-lysozyme HBs, and even a partial substitution of hydration water molecules

may strongly stabilize lysozyme. Moreover, trehalose has a large hydration number, but this does not seem to be the major stabilizing source, on the contrary to the percolation of the HB network of sugars, which has major consequences on the solvent structure and dynamics. Finally, it must be pointed out that the different hypotheses proposed to clarify the bioprotection phenomenon are not necessarily conflicting. For example, it is possible that the vitrification of the solvent reduces large-scale motions, while solvent-protein HBs limit fast motions.

Acknowledgments

The authors wish to acknowledge the use of the facilities of the IDRIS (Orsay, France), the CINES (Montpellier, France) and the CRI (Villeneuve d'Ascq, France) where calculations were carried out. This work was supported by the INTERREG III (FEDER) program (Nord-Pas de Calais/Kent).

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Annexe

Collaborations

- D. Morineau - GMCM - UMR6626 - Université de Rennes 1 (France). Collaboration sur l'étude de fluides bioprotecteurs. Co-encadrement de la thèse de R. Busselez.
- K. L. Ngai - Naval Research Laboratory - Washington (USA). Collaboration sur l'influence de l'anharmonicité sur la fragilité de liquides vitrifiables. Co-organisation du « 5th International Discussion Meeting on Relaxations in Complex Systems » du 7 au 13 Juillet 2005 à Lille.
- R. Schilling - Institut für Physik - Johannes-Gutenberg-Universität - Mainz (Allemagne). Collaboration sur le développement d'une théorie de couplage de modes (MCT) pour les cristaux vitreux.
- S. Magazù - Dipartimento di fisica - Université de Messine - Messine (Italie). Collaboration sur les propriétés bioprotectrices des sucres. Programme Galileo France/Italie « préservation des biomolécules labiles ».
- S. Leharne - Department of Earth and Environmental - University of Greenwich at Medway (UK). Collaboration sur l'étude des matériaux thérapeutiques dans le cadre du contrat INTERREG IIIA Nord Pas de Calais - Kent (FEDER).
- S. Sastry - Theoretical Sciences Unit - Jawaharlal Nehru Centre for Advanced Scientific Research - Bangalore (Inde). Collaboration sur l'étude du paysage énergétique de liquides vitrifiables à anharmonicité variable.
- A. Césaro - Dept. of Biochem., Biophys., Macromol. Chem., Université de Trieste, Trieste (Italie) Collaboration sur les propriétés bioprotectrices des sucres.
- P. Bordat - Laboratoire de Chimie Structurale UMR CNRS 5624 - Pau (France). Collaboration sur la compréhension des mécanismes de la transition vitreuse, les propriétés bioprotectrices des sucres et le pre-pic de liquides moléculaires formateurs de verre.

Responsabilités d'encadrement

- Post-docs :
 - W. Zaoui sur la compréhension des mécanismes de déshydratation du tréhalose dihydrate (2005-2006).

- F. Migliardo sur des études par diffusion neutronique de disaccharides en solutions (2003-2004).
- P. Bordat sur la modélisation moléculaire de sucres en solution et les propriétés de liquides modèles vitrifiables (2002-2004).
- Thèse :
 - co-encadrement 50% d'A. Lerbret (resp. A. Hédoux) sur l'action bioprotectrice des sucres (2002-2005) .
 - co-encadrement 50% de R. Busselez (resp. D. Morineau) sur le confinement de fluides bioprotecteurs (depuis Sept. 2005).
- Master 2 (DEA) :
 - F. Vasconcelos sur l'influence de l'anharmonicité sur le paysage énergétique de liquides modèles formateurs de verre (2005 - 2006).
 - J. Blicq sur l'étude par simulation MD du glycérol (2003 -2004).

Participation à l'exécution de projets de recherches

- Porteur du projet « Amorphisation de cristaux moléculaires organiques par traitement mécanique » CNRS-SPM « jeunes chercheurs » (1999).
- Porteur du projet « Action Bioprotectrice des Sucres ». ACI 2001 « jeunes chercheurs » (2001-2004).
- Participation à l'exécution du Contrat INTEREG IIIA Nord Pas de Calais / Kent (FEDER) « matériaux thérapeutiques » (2002-2005).
Partenaire :
Prof. S. Leharne. Natural Resources Institute, University of Greenwich, Pembroke, Chatham Maritime, Kent. UK.
Prof. G. Coquerel. Sciences et Méthodes Séparatives. Université de Rouen. Mont Saint Aignan.
- Participation à l'ERT « Matériaux thérapeutiques forcés » (2003-2006).
Partenaire : Aventis-Pharma
- Participation à l'ERT « Matériaux thérapeutiques : Maîtrise des états amorphes et nanostructurés » (2006-2009).
Partenaires : Sanofi-Aventis, Roquettes Frères, Astra Zeneca et TA Instruments
- Participation au programme bilatéral Galileo-EGIDE puis MIUR (France/Italie) « préservation des biomolécules labiles » (2002-2003 et 2005-2008).
Partenaire : Prof. S. Magazù, Université de Messine, Italie.

Organisation de colloques

- Co-organisateur avec M. Descamps et K.L. Ngai du colloque : « 5th International Discussion Meeting on Relaxations in Complex Systems » du 7 au 13 Juillet 2005 à Lille (~ 600 participants). Co-éditeur des actes du colloque à paraître dans J.

Non-Crystalline Solids (Elsevier) 2006

- Co-organisateur avec D. Dangoisse, J-P. Flament, A. Legris et Y. Tinel du colloque « Calcul numérique intensif en chimie et physique » le 14 Octobre 2005 à Lille (~ 50 participants).
- Co-organisateur avec M. Descamps et A. Dzyabchenko du colloque : « Structural Modelling as a tool in assistance to experimental studies of organic states » le 3 Décembre 1999 à Lille (~ 50 participants).

Activités d'enseignement

- Travaux dirigés et pratiques de physique 1er cycle, ATER, Université Lille1 : 96 h (1996), 96 h (1997)
- Travaux pratiques de physique 1er cycle, Institut Universitaire de Technologie (IUT) de Villeneuve d'Ascq : 64 h (2003), 50h (2004), 32 h (2005)
- Cours de physique 3ème cycle « Simulations de Dynamique Moléculaire » dans le cadre de l'école doctorale de l'université de Messine (Italie) : 3h (2003)
- Cours de physique MASTER 2 Interface Physique-Chimie du Vivant (IPCV), Université Lille1, « Modélisation Moléculaire » : 10h (2005), 20 h (2006)
- Cours de physique MASTER 2 Interface Physique-Chimie du Vivant (IPCV), Université Lille1 « Thermostabilité des biomolécules » : 6h (2005), 10h (2006)
- Cours de physique MASTER 2 Science des Matériaux, Université Lille1, « Modélisation Moléculaire » : 12h (2004), 12 h (2005)