Debye Process in Ibuprofen Glass-Forming Liquid: Insights from Molecular Dynamics Simulation

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By means of molecular dynamics simulations, dynamical properties of racemic ibuprofen glass-forming liquid are investigated at different temperatures from 360 to 500 K. The origin of the peculiar low amplitude Debye-type relaxation observed experimentally by dielectric relaxation spectroscopy is addressed (Bras, A. R.; Noronha, J. P.; Antunes, A. M. M.; Cardoso, M. M.; Schönhals, A.; Affouard, F.; Dionisio, M.; Correia, N. T. *J. Phys. Chem. B* **2008**, *112*, 11087). Single and total dipolar autocorrelation functions are calculated. It is found that the behavior of the total dipole correlation is dominated at short and long times by the single function. It mainly originates from the antiparallel dipoles correlations in agreement with a value of the Kirkwood correlation factor slightly smaller than unity. The simulation suggests that the long time Debye-type decay of the dipole−dipole correlation is dominated by the internal cis−trans conversion of the O═C−O−H group coupled to the change of the intermolecular linear/cyclic HB structures. The overall rotation of the molecules is about 1−2 decades faster than the cis to trans transformation, so all the O═C−O−H group environments are equal on average. The effective rotational potential energy barriers of the O═C−O−H groups due to the surroundings are thus averaged and dipolar relaxation follows a simple Debye law. It is found that cyclic dimers inhibit the cis to trans conversion unlike the linear dimers and trimers which favor this conversion and stabilize the trans isomer. It is well in line with the very low amplitude of the dielectric strength associated with the Debye relaxation observed experimentally and its increase when the liquid is maintained isothermally above the melting temperature since this amplitude mainly relates to the low fraction of ibuprofen molecules in the trans conformation. A comparison is made with the Debye-type relaxation found in microstructured monohydroxy alcohols.

I. Introduction

In the framework of the glass transition phenomena, there has been recently revived interest for hydrogen-bonded (HB) liquids composed of molecules of low molecular weight such as alcohols, polyols, or sugars. An important issue is to characterize the complex mechanisms underlying the different relaxation dielectric processes and to precisely identify the dielectric contribution truly resulting from the structural relaxation.[1−8] From dielectric relaxation spectroscopy (DRS) investigations, most of the molecular glass-formers show multiple non-single exponential (non-Debye) relaxation processes.[8] In most cases, the lowest frequency and dominant process (i.e., the slowest one) is identified to the so-called α-relaxation associated to the cooperative molecular motions and the dynamic glass transition. Some other higher frequency secondary processes corresponding to localized motions are also usually observed, such as the so-called β-Johari−Goldstein and γ-processes.[8,9]

For unclear reasons, it is known for decades that some monohydroxy alcohols or amides hydrogen bonded (HB) glass-forming systems in which the −OH or the −NH group is sterically accessible behave differently. At the lowest frequencies, they exhibit a surprising very intense peak corresponding to a purely exponential or Debye-type decay.[10−17] This peak (noted process I in the following) is always accompanied by a few decades smaller amplitude and a few decades higher frequency mainly non-exponential relaxation (process II). At higher frequencies, another relaxation is also frequently detected and often attributed to the Johari−Goldstein process β_{J-G}[9] (process III). The problem of the origin of the Debye-type relaxation and the way it contributes to the liquid structural relaxation or its viscosity continues to be a matter of debate and has motivated many experiments and models, but a complete understanding is still lacking.

In fact, some models have been postulated but none of them can be considered as fully accepted since they cannot completely describe all the features observed for the liquids exhibiting Debye-type relaxation. It was originally proposed that Debye-type dielectric relaxations mainly originate from the rates of breaking and reforming of hydrogen bonds linked to the rotation of the permanent dipole moment of the hydroxyl group.[14,18,19] As postulated by Johari and Dannhauser,[15] the lower frequency Debye process should be at the origin of the true structural relaxation since it contributes to about 90% of the total dielectric relaxation strength. It would result from simultaneous and

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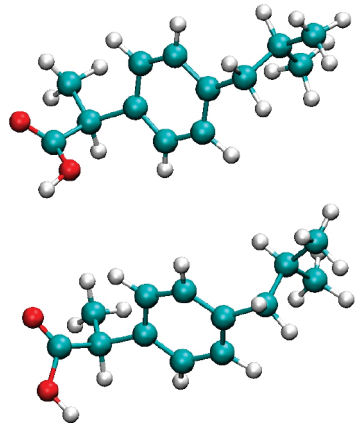

Figure 1. Snapshots of an instantaneous configuration of one ibuprofen molecule where the O═C—O—H carboxylic group shows the cis (top) ($\langle\mu\rangle$ = 1.6 D) or the trans (bottom) ($\langle\mu\rangle$ = 4.6 D) conformation.

cooperative reorientations of the OH groups between nearest neighbors in the intermolecular HB structures mainly made of linear chains. The higher frequency process II should be identified with the rotation of the group around the OH bond.[10,20] Alternatively, it was also suggested that process II couples much more to viscosity and structural relaxation of the liquid than process I.[12,21−23] Indeed, process II possesses most of the classical features associated with the so-called α-relaxation seen in HB or non-HB glass-forming materials such as nonexponentiallity and dynamical crossover.[24,25] The low intensity of peak II implies that a surprisingly low fraction of molecules contributes to the α-relaxation process. It is thus not obvious to understand how it would be responsible alone to the supercooled liquid's viscosity and structural relaxation.[20]

However, a small dielectric peak does not automatically imply that only few molecules are involved, it could also be that all molecules participate with a small angle of reorientation or lower net dipole. In addition, formation of clusters of molecules forming micelles structures has been also proposed.[26] In this case, process I will be associated with the relaxation of the net dipole of the micelle clusters and process II to the alkyl chains contribution exhibiting motions about a relatively immobile hydroxyl end. Rotational blocking of dipoles for a long period residence time in the HB network,[27] transition between states that differ in energy only if an external electric field is applied,[28] and cyclic tetramers[29] have been also postulated as the origin of the Debye process in monohydroxy alcohols.

An interesting possibility to investigate the origin of relaxation processes in a different class of HB liquids is offered by racemic ibuprofen (2*RS*)-2[4-(2-methylpropyl)phenyl]propanoic acid, $C_{13}H_{18}O_2$ (see Figure 1). This widely used pharmaceutical compound can be easily supercooled and forms a glass at the temperature T_g = 228 ± 2 K.[2,30,31] The molecular mobility of ibuprofen has been recently investigated by DRS covering a wide temperature and frequency range.[2] A rich relaxation map was obtained with an identification of different relaxational processes such as α-relaxation (process II) and β_{J-G} (process III) mentioned above. Moreover, an additional Debye type relaxation (process I), noted D-relaxation in ref 2, was also found, which unlike to that observed in monohydroxy alcohols and amides, possesses an amplitude much lower than the faster process II. Since this compound is composed of simple molecules possessing a carboxylic acid group O═C—O—H, it may form a rich linear/cyclic HB multimers distribution, cyclic dimers above all, in the liquid state.[2] Fundamental differences thus exist between ibuprofen and alcohols in their dielectric properties as it will be confirmed in the following. The great ability of ibuprofen to form such HB aggregates were suggested by IR spectroscopy, electrospray ionization mass spectrometry, and preliminary molecular dynamics (MD) simulations and were suspected to be linked to the particular dynamic behavior of ibuprofen.[2]

In this paper, molecular dynamics of racemic ibuprofen in the liquid state is analyzed in the light of results from simulation studies, in order to gain deeper insights into the mechanism of molecular reorientation in hydrogen bonded systems. The origin of the peculiar Debye-type relaxation is particularly addressed. An explanation based on intramolecular cis−trans isomerism of the carboxylic group which differs from that proposed for monohydroxy alcohols and amides[10−15] is suggested.

II. Computer Simulations Details

MD simulations of racemic ibuprofen in the liquid state have been performed using the DL POLY program[32] and the all-atom OPLS force-field[33] to model the intra- and intermolecular interactions. The starting conformation of the R and S enantiomers was taken from the neutron diffraction determination of the crystalline racemic ibuprofen.[34] The initial configuration of the system was constructed from a 50:50 mixture of each ibuprofen enantiomer randomly located and oriented in a cubic simulation box. The total number of molecules is N = 54. The length of all covalent bonds was kept fixed using the SHAKE algorithm,[35] with a relative tolerance of 10^{-8}. A 1 fs time step has been used to integrate the equations of motion with the Verlet leapfrog algorithm.[36] A cutoff radius of 10 Å has been used to account for van der Waals interactions. 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 reaction-field method[37] using the dielectric permittivity of the medium outside the cutoff sphere ε_{RF} = 2 (reaction field correction). Ibuprofen can exhibit isomerism of the O═C—O—H group (see Figure 1). The dipole moment vector of each ibuprofen molecule was calculated from the position of each atom and from the partial electrostatic charge assigned to each atom in the molecule[38] in the all-atom OPLS force-field.[33] A calculation of the average dipole moment in space and time yields ≃1.64 D for the cis isomer, in agreement with the value reported in the literature[39] from ab initio calculation. As expected, the dipole moment is also close to the values usually reported for other carboxylic acids since it mostly originates from the O═C—O—H group.[40] The average dipole moment of the trans isomer is found to be 4.6 D.

Calculations of the static permittivity[41] lead to ε_S = 2.0 at T = 360 K in fair agreement with the reported experimental value 2.6 determined at T = 274 K.[2,31] Thermalization was obtained by means of constant number of particles N, pressure (P), and temperature (NPT) simulations. The pressure has been set to 1.0 bar using weak coupling to a pressure bath (Berendsen barostat[42]) with a relaxation time of 2.0 ps. The investigated temperatures have been maintained constant during a given simulation using weak coupling to a heat bath (Berendsen thermostat[42]) with a relaxation time of 0.2 ps. The stabilized volume of the simulation box during the NPT simulation was considered to compute the averaged density of the system and used to perform the subsequent production simulation in the NVT ensemble (constant number of particles, volume, and temperature). The density values are found in fair agreement with the results reported in the literature.[43] Table 1 summarizes some simulation data for the different temperatures considered in the present study.

TABLE 1: Densities and NPT/NVT Simulation Times in Nanoseconds for the Different Temperatures T Investigated in the Present Study

T (K)	density (g cm^{-3})	NPT/NVT times (ns)
500	0.888	3/40
450	0.926	3/60
400	0.964	3/100
380	0.978	5/160
360	0.995	5/200

III. Results and Discussion

A. Molecular Dynamics. Molecular dynamics as it can be classically obtained from dielectric spectroscopy experiments is related to the total electric dipole moment of the sample $\vec{M}(t) = \sum_{i=1}^{N} \vec{\mu}_i(t)$, where $\vec{\mu}_i(t)$ is the permanent dipole moment of the molecule i at time t and N the total number of molecules. Some induced dipole terms are also to be added if individual molecules are polarizable. However, these terms are difficult to calculate from MD simulations since they are not pairwise additive and hence they are not taken into account in this study.[38] The complex dielectric permittivity $\varepsilon^*(\omega)$ measured experimentally is proportional to the Fourier transform of the normalized autocorrelation function $\Phi_M(t) = \langle \vec{M}(t)\cdot\vec{M}(0)\rangle / \langle \vec{M}^2(0)\rangle$ of the total dipole moment.[44] $\Phi_M(t)$ time-dependent correlation functions have been calculated for ibuprofen at different temperatures and are shown in Figure 2a. The time-dependence follows the classical two-step decay separated with a plateau region as expected for glass-forming liquids.[45,46] In the following, only the long time decay will be investigated for comparison with the DRS results. In addition to the total dipole functions, single molecule autocorrelation functions $\Phi_\mu(t) = \langle \vec{\mu}(t)\cdot\vec{\mu}(0)\rangle / \langle \vec{\mu}^2(0)\rangle$ have been also computed and are shown in Figure 2b. These figures show that $\Phi_M(t)$ behaves closely as $\Phi_\mu(t)$ at all times. The time decay of both $\Phi_M(t)$ and $\Phi_\mu(t)$ functions can be fitted with the so-called stretched exponential law classically used for glass-forming liquids, $\exp[-(t/\tau_M)^{\beta_M}]$ and $\exp[-(t/\tau_\mu)^{\beta_\mu}]$, respectively. The stretching parameters $\beta_M = 0.50$ and $\beta_\mu = 0.48$ allowed us to fit data at all investigated temperatures. These values are also in fair agreement with the experimental data $\beta = 0.52$ reported for the α-relaxation[2] (process II). The characteristic times τ_M and τ_μ are reported in Table 2 and are represented in Figure 3. A good agreement with the experimental data reported for the α-relaxation[2] (process II) is also obtained.

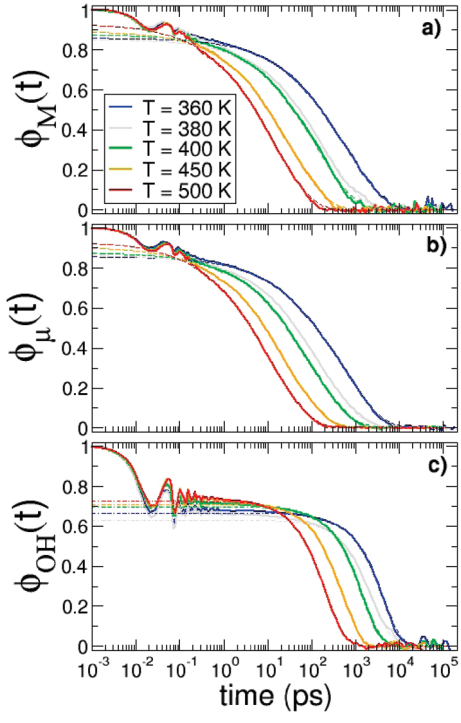

Figure 2. Time-dependent correlation functions as a function of time are represented at different temperatures $T = 360$, 380, 400, 450, and 500 K. (a) Total dipole correlation $\Phi_M(t)$, (b) single molecule self-correlation $\Phi_\mu(t)$, and (c) single molecule self-correlation $\Phi_{OH}(t)$ for the dipole of the OH group in the molecular frame of the carboxylic group (see text). Fits using the stretched exponential law are represented by dashed lines (a and b) and fits using the single exponential law by dotted−dashed lines (c).

TABLE 2: Relaxation Times τ_M, τ_μ, and τ_{OH} Extracted from Their Respective Dipolar Correlation Functions (See Text and Figure 2)[a]

temperature (K)	τ_M (ps)	τ_μ (ps)	τ_{OH} (ps)	G_k
500	12	11	215	1.03
450	30	25	504	0.99
400	123	92	1444	0.98
380	186	160	2544	0.92
360	582	473	4165	0.94

[a] Kirkwood correlation factors G_k are also given. The value of the standard deviations of G_k is about 0.02 determined from calculations of the Kirkwood correlation factor G_k over several 20 ns simulation blocks (see Table 1 for total simulation times).

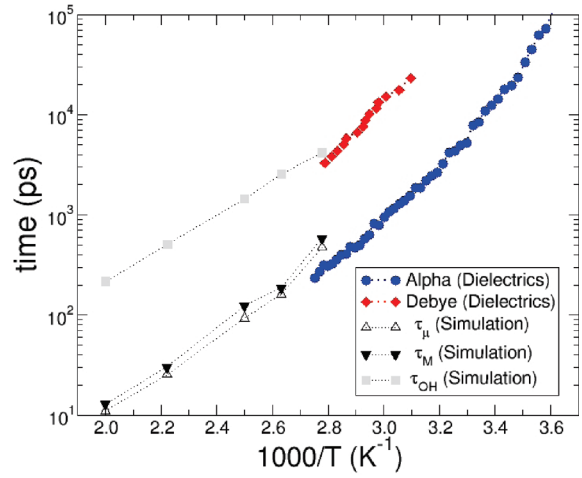

Figure 3. Relaxation times τ_M, τ_μ, and τ_{OH} versus $1000/T$ computed in the present study. Relaxation times obtained from DRS experiments for D- (process I) and α-relaxation (process II) are also indicated for comparison (extracted from ref 2).

It should be noted that for both $\Phi_M(t)$ and $\Phi_\mu(t)$ functions, the existence of an additional relaxation process is highly suspected from the fitting procedure: the fit with the stretched exponential is not perfect in the very long time tail of the different functions (see below). These results thus show that in ibuprofen the behavior of the total dipole correlation function $\Phi_M(t)$ is mainly dominated at all times by the single dipole function $\Phi_\mu(t)$ unlike to monohydroxy alcohols where $\Phi_\mu(t)$ only dominates $\Phi_M(t)$ at short times.[47,48]

This effect can be understood from the cross-terms between distinct molecules ($i \neq j$) in which $\Phi_M(t)$ differs from $\Phi_\mu(t)$. Indeed, $\Phi_M(t)$ can be rewritten as a sum of single and distinct dipoles contributions weighted by the so-called Kirkwood correlation factor G_k[2,29,47−52]

$$\Phi_M(t) = \frac{1}{G_k}\Phi_\mu(t) + \left(1 - \frac{1}{G_k}\right)\Phi_{dist}(t) \quad (3)$$

where $\Phi_{dist}(t) = \langle\vec{\mu}_i(t)\cdot\vec{\mu}_j(0)\rangle/\langle\vec{\mu}_i(0)\cdot\vec{\mu}_j(0)\rangle$ represents the distinct dipole correlation function and the averages of the product $\vec{\mu}_i\cdot\vec{\mu}_j$ are performed for different molecules ($i \neq j$). The Kirkwood correlation factor G_k is given by the relation

$$G_k = \frac{\langle|\vec{M}(0)|^2\rangle}{N\mu^2} = 1 + \frac{N-1}{\mu^2}\langle\vec{\mu}_i(0)\cdot\vec{\mu}_j(0)\rangle \quad (4)$$

G_k mainly accounts for orientational correlation of neighboring dipoles. Parallel and antiparallel dipoles orientation leads to $G_k > 1$ and $G_k < 1$, respectively. If orientations of individual dipoles are completely random, one finds $G_k = 1$.

The Kirkwood correlation factor G_k was calculated from eq 4, and it is given in Table 2 as a function of the temperature. Except at the highest temperature, these values are found to be smaller than 1. They also slightly decrease upon decreasing temperature indicating an increasingly antiparallel correlation of the dipoles. This is a significant difference of the ibuprofen properties compared to the dielectric behavior observed in some monohydroxy alcohols for which the Kirkwood correlation factor G_k is significantly larger than unity.[11,20,53,54] It should be noted that some alcohols may also have Kirkwood correlation factors smaller than unity, although this is more the exception.[48] A Kirkwood correlation factor larger than unity, $G_k \gg 1$, is often interpreted as the capability of these HB liquids to form associating structures showing multimers with parallel dipole orientations. Moreover, chains of double hydrogen-bonded molecules with increasing effective dipole moment in alcohols are often suggested as the origin of the high amplitude Debye-type relaxation (process I). Oppositely, the decreasing G_k values ($G_k < 1$ for the lowest temperatures) of ibuprofen points to the existence of small multimers such as cyclic dimers and trimers with antiparallel dipoles as it was previously reported in ref 2. It should be mentioned that several DRS experiments have been performed on ibuprofen,[2,31] but to the authors' knowledge, the Kirkwood correlation factor has not been determined.

Using the estimated Kirkwood correlation factors G_k reported in Table 2 as prefactors of $\Phi_\mu(t)$ and $\Phi_{dist}(t)$ in eq 3, one confirms that $\Phi_\mu(t)$ influences almost exclusively $\Phi_M(t)$, unlike to monohydroxy alcohols where the long time decay of $\Phi_M(t)$ is found to be mainly dominated by $\Phi_{dist}(t)$.[47,48] This feature is thus consistent with the absence in ibuprofen of collective dynamics associated with linear HB winding chains controlling the dynamics at long times.

B. Origin of the Debye Relaxation in Ibuprofen. A thorough analysis of the long-time tails of $\Phi_M(t)$ and $\Phi_\mu(t)$ functions (data not shown) suggest the existence of an additional low amplitude process. Because of the noisy behavior of both correlation functions, additional MD simulations are clearly required in order to fully validate this result. In the following, we used an alternative way to demonstrate the existence of such a process. The dipole moment of the ibuprofen molecule mostly originates from the O═C−O−H group as usually reported in the literature.[39] This is confirmed by the similar behavior found between the self-correlation functions calculated from the total dipole moment of each individual molecule or only from the dipole moment of each carboxylic group (data not shown). In addition to the overall rotation of the molecule, ibuprofen can also exhibit internal motion due to the cis−trans isomerism of the O═C−O−H group (see Figure 1). The fraction of trans isomer is found to continuously decrease from about 10 to 5% from 500 to 360 K with a conversion between cis and trans isomers and vice versa clearly seen at all temperatures. The population of each isomer and the energy barrier of the conversion can be well investigated from the free energy profile of the O═C−O−H group. This latter can be probed from the potential of mean force (PMF) $A(\psi)$ calculated along the reaction coordinate chosen as the torsion angle ψ of the carboxylic group:[55]

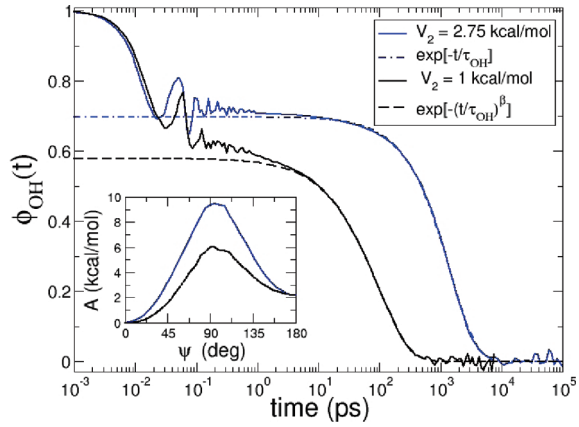

Figure 4. Dipolar self-correlation functions $\Phi_{OH}(t)$ (solid lines) calculated from the OH dipoles in the molecular carboxylic group frame are represented at the temperature $T = 400$ K for the original OPLS force-field and the slightly modified version in which the O═C−O−H torsion barrier is lower (see below). Fits using the stretched exponential law and single exponential law are represented by dashed lines and dotted−dashed lines, respectively. The potential of the mean force $A(\psi)$ as function of the O═C−O−H torsion angle ψ is shown in the inset. Values are shifted with respect to the most stable cis isomer $\psi = 0°$. PMFs were obtained from MD calculations using the original OPLS[33] force-field (solid line) and a slightly modified version of this force-field (dashed line) in which the parameter V_2 associated with the O═C−O−H torsion energy $E(\psi) = V_2[1 - \cos(2\psi)]$ is $V_2 = 1$ kcal/mol instead of the original value 2.75 kcal/mol.[33] No significant temperature dependence for $A(\psi)$ was found in the investigated temperatures range.

$$A(\psi) = -k_B T \ln[P(\psi)] \quad (5)$$

where k_B is the Boltzmann constant and $P(\psi)$ the probability of configuration for a given value of the reaction coordinate ψ in a canonical ensemble of the remaining coordinates. The MD simulation runs (see Table 1) performed in the present work ranging from 40 to 200 ns are long enough to sample roughly all values of ψ associated with the probability of configuration $P(\psi)$. The potential of mean force $A(\psi)$ is represented in the inset of Figure 4.

Potential of mean force computations yield to a cis−trans energy barrier of about ≃9.5 kcal/mol. The trans isomer is about ≃2 kcal/mol less stable than the cis isomer, consistent with the equilibrium population of trans and cis isomers directly calculated in the present study. These values are also comparable to those obtained from the ab initio calculation of formic acid.[56] As already mentioned, a calculation of the average dipole moment yields to ≃1.6 and 4.6 D for the cis and the trans isomers, respectively, in agreement with the values reported in the literature.[39] This cis−trans conversion thus generates a dipolar active mode of motion which results in a second dielectric relaxation whose amplitude is directly related to the low fraction of trans isomers. The self-correlation function $\Phi_{OH}(t)$ of the dipoles of OH groups in the molecular frame of

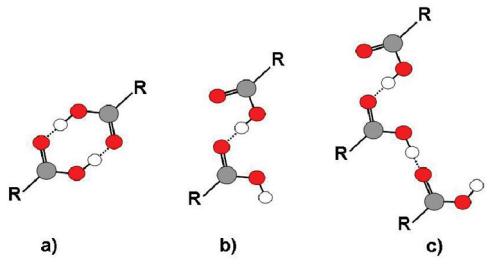

Figure 5. Schematic representation of ibuprofen HB associating structures: cyclic dimer (a), linear dimer (b), and trimer (c). In part a, both monomers are in the cis conformation, while in parts b and c one monomer is in the trans conformation and the others in the cis conformation. Only the carboxylic group O═C—O—H is represented for clarity.

the carboxylic groups, shown in Figure 2c, provides an estimation of the dipolar motion resulting only from the rotational motion between the cis and the trans isomers. It is clear in Figure 2c that for all studied temperatures, the dipolar functions $\Phi_{OH}(t)$ exhibit a Debye-type decay which can be well adjusted with a single exponential law exp $[-t/\tau_{OH}]$. The characteristic times τ_{OH} are represented in Figure 3 and are found in good agreement with the relaxation times of the Debye process obtained from DRS experiments.[2] In the high temperature range investigated in the present study, the evolution of the characteristic times τ_{OH} is found almost Arrhenian with an activation barrier of about 7.6 kcal/mol. This value is consistent with the PMF computations from which an activation barrier of about $9.5 - 2 = 7.5$ kcal/mol was expected.

An important feature is that in each ibuprofen molecule the carboxylic group is able to form intermolecular HBs. Therefore, the internal reorientation of the carboxylic group in the ibuprofen molecule is strongly coupled with the overall rotation of this group. The great ability of ibuprofen to form HB aggregates, cyclic dimers above all, has been suggested from IR spectroscopy, electrospray ionization mass spectrometry, and previous MD simulations.[2] From the present MD calculations, as expected, it is found that the formation of cyclic dimers inhibits the cis to trans conversion while linear dimers and trimers favor this conversion and stabilize the trans isomer by intermolecular HBs (see Figure 5). At $T = 360$ K, the fraction of trans isomers for non-HB ibuprofen molecules is about 3% while this fraction is about 15% for linear dimers and trimers. It may be thus suggested that the interplay between the internal cis−trans O═C—O—H conversion and the intermolecular HBs associations might be at the origin of the peculiar low-intensity Debye peak observed experimentally.[2] In fact, it is well in line with the very low amplitude of the dielectric strength associated with the Debye relaxation and its increase when the liquid is maintained isothermally above the melting temperature since this amplitude mainly relates to the low fraction of ibuprofen molecules in the trans conformation, which increases upon increasing temperature (data to be published).

One may wonder why the relaxation associated with this process is of a Debye-type. This process results from the internal rotation of the O═C—O—H group in the intermolecular HB structures made of linear/cyclic multimers. This can be interpreted as the trapping of dipoles in basins of the effective potential created by the neighboring molecules. Activated jumps between the different wells should lead to reorientations of the dipole and the long time decay of the $\Phi_{OH}(t)$ functions. The internal dipolar reorientations occur only after the breaking/reforming of intermolecular HBs, which is mainly controlled by molecular mobility measured by $\Phi_M(t)$ and $\Phi_\mu(t)$. This process is about 1−2 decades faster than the cis to trans transformation ($\tau_M \approx \tau_\mu \ll \tau_{OH}$) so all O═C—O—H group environments are equal on average. With the ideas of Anderson and Ullman[57] and Johari and Dannhauser[15] followed, the potential energy barriers due to the surroundings are averaged and the relaxation follows a single time Debye relaxation. An explanation based on these fast fluctuating environments was particularly used by Huang and Richert[58] in order to explain the Debye nature of the slow rotation of the di-*n*-butylether probe immersed in 3-methylpentane solvent. In the present investigation, these ideas can be clearly checked by tuning the effective cis−trans energy barrier to a lower value of ≃5.5 kcal/mol instead of 9.5 kcal/mol (see the inset in Figure 4) while keeping the same energy difference between the cis and the trans isomers (≃2 kcal/mol). Indeed, the effective energy barrier of the O═C—O—H group as measured during MD simulations can be lowered by decreasing the original OPLS force-field parameters V_2 associated with the energy $E(\psi) = V_2[1 - \cos(2\psi)]$ of the O═C—O—H torsion from the original barrier $V_2 = 2.75$ kcal/mol to a lower barrier $V_2 = 1$ kcal/mol (see Figure 4). As shown in parts b and c of Figure 2, for the original cis−trans high energy barrier of the O═C—O—H group, the decay time of the $\Phi_\mu(t)$ function is about 1 decade faster than the cis to trans transformation as measured by $\Phi_{OH}(t)$. Moreover, $\Phi_{OH}(t)$ can be well fitted by a single exponential law while $\Phi_\mu(t)$ can only be adjusted using a stretched exponential (see Figure 2b,c). With the cis−trans energy barrier of the O═C—O—H group tuned, the decay time of the $\Phi_{OH}(t)$ and $\Phi_\mu(t)$ functions becomes clearly comparable $\tau_{OH} \approx \tau_\mu$ (data not shown) and the $\Phi_{OH}(t)$ functions cease to follow a single Debye behavior as revealed in Figure 4 and can only be adjusted with a stretched exponential with a stretching parameter of about 0.85.

IV. Summary and Conclusions

The aim of this investigation was to shed some light on some dynamical properties of racemic ibuprofen in the liquid state from MD computer simulations. From calculations of the single molecule and total dipole autocorrelation functions, we have shown that single molecule and total relaxation times are comparable. This result shows that unlike monohydroxy alcohols the behavior of the long time total dipole correlation should be dominated by the self-autocorrelation function. It is well in line with the values of the Kirkwood correlation factor found slightly below one and decreasing with a temperature decrease. Moreover, it is in agreement with the low intensity of the dielectric strength obtained from DRS measurements.[2] The ibuprofen dielectric properties are thus significantly different from the monohydroxy alcohols for which the Kirkwood correlation factor G_k is larger than unity, consistent with high dielectric strength.

In ref 2, the precise nature of the puzzling D-relaxation found in racemic ibuprofen remained unclear. From the present MD simulations, an explanation which differs from that proposed for monohydroxy alcohols and amides[10−15] was suggested. The simulation shows that the long time dipole−dipole autocorrelation function is dominated by the internal cis−trans conversion of the O═C—O—H group coupled to the change of the intermolecular linear/cyclic HB structures. It is found that cyclic dimers inhibit the cis to trans conversion, unlike the linear dimers and trimers which favor this conversion and stabilize the trans isomer. The Debye nature of the dipolar active cis−trans conversion was explained following the Anderson and Ullman[57] and Johari and Dannhauser[15] ideas. The overall rotation of the molecules is about 1−2 decades faster than the cis to

trans transformation in such way that all O═C−O−H group environments are equal on average. The effective rotational potential energy barriers of the O═C−O−H groups due to the surroundings are thus averaged and dipolar relaxation follows a simple Debye law. It was also shown, by tuning the effective cis−trans energy barrier to a lower value ≃5.5 kcal/mol instead of 9.5 kcal/mol, that the internal cis−trans conversion of the O═C−O−H group does not follow the simple Debye behavior. For the lower value of the barrier, the molecule overall rotation times become comparable to the cis to trans transformations times and so all O═C−O−H groups environments cease to be equal on average.

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