Journal of Molecular Liquids 205 (2015) 74–77

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Local molecular organizations of ibuprofen, flurbiprofen and ketoprofen in the liquid phase: Insights from molecular dynamics simulations

M.T. Ottou Abe [a,b], N.T. Correia [a,c], L.-C. Valdes [a], J.M.B. Ndjaka [b], F. Affouard [a,*]

[a] Unité Matériaux et Transformation (UMET), UMR CNRS 8207, UFR de Physique, BAT P5, Université Lille 1, 59655 Villeneuve d'Ascq, France
[b] Département de Physique, Faculté des Sciences, Université de Yaoundé I. B.P. 812, Yaoundé, Cameroon
[c] REQUIMTE/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

ARTICLE INFO

Available online 23 August 2014

Keywords:
Molecular dynamics
Simulations
Dielectric relaxation spectroscopy
Molecular liquids
Hydrogen bonding
Pharmaceuticals

ABSTRACT

In this paper, the local molecular organization of ibuprofen, flurbiprofen and ketoprofen in the liquid state have been investigated using molecular dynamics simulations. The different hydrogen bonding associating structures have been characterized. Dipolar correlations between molecules have been probed by calculating the Kirkwood factor. For the three liquids, the present investigation performed at relatively high temperatures from 500 to 380 K revealed the presence of a specific local molecular organization composed of small hydrogen bonding aggregates corresponding to cyclic dimers possessing anti-parallel dipolar organization. This organization becomes more and more probable upon decreasing temperature and it is suggested that this trend would continue to lower temperatures for which cyclic dimers would become the dominant organization i.e. precursor of the crystalline structures. At all investigated temperatures, the probability of forming the cyclic dimers association is significantly lower in ketoprofen than in ibuprofen or flurbiprofen. This difference would suggest why a peculiar low frequency Debye process is detected in ibuprofen and flurbiprofen and not in ketoprofen.

1. Introduction

Structural, dynamical and thermodynamical properties of molecular liquids are strongly influenced by their capability to form hydrogen bonds (HBs). For a long time, it is well known that some monohydroxy alcohols or amides exhibit an extremely large amplitude low frequency Debye peak as observed from dielectric relaxation spectroscopy (DRS) experiments [1,2]. This unexpected relaxation corresponding to a simple exponential decay of the polarization is puzzling since it contributes to about 90% of the total dielectric relaxation strength but it does seem very weakly coupled to the structural relaxation or viscosity of the liquid [3]. So far, the Debye-type relaxations have been mainly observed in the HB liquids. This type of process should be thus intrinsically related to some specific structural HB organizations. Due to the strong directional hydrogen bonding, HB liquids tend to be locally more organized than the ordinary van der Waals liquids. The presence of some aggregates is often suggested. However, their precise structures remain unclear [4,5]. Ring and open chains have been suggested from DRS investigations [6–10]. Cyclic structures are also suggested from X-ray and neutron diffraction studies [11] and heats of vaporization [12] measurements of liquid alcohols. From molecular dynamics (MD) simulation, a rich variety of HB aggregates are usually seen such as open chains or ring [5]. The physical mechanism at the origin of the Debye peak continues to be a matter of debate and has motivated many experiments and models but a complete understanding is still lacking. A few 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 the Debye-type relaxation.

An interesting possibility to investigate the link between structure and dynamics of HB liquids and thus the microscopic origin of relaxation processes in a different class of HB liquids is offered by the members of the 2-arylpropionic acid derivatives (profens). Molecular mobility of some profens has been investigated by DRS covering a wide temperature and frequency range [13,14]. A rich relaxation map was obtained with an identification of different relaxational processes including a Debye type process as observed in alcohols but with a much lower amplitude. Since these compounds are composed of simple molecules possessing a carboxylic acid group O═C–O–H, they may form a rich distribution of HB multimers – cyclic dimers above all – in the liquid state [13,15]. Fundamental similarities and differences thus exist between profens and alcohols in their dielectric properties as it will be confirmed in the following.

In this paper, MD simulation studies have been performed on three molecular liquids composed of ibuprofen $C_{13}H_{18}O_2$, flurbiprofen $C_{15}H_{13}FO_2$ and ketoprofen $C_{16}H_{14}O_3$ molecules. The main goal was to reveal the differences of the HB characteristics between the three profens

* Corresponding author.
E-mail address: frederic.affouard@univ-lille1.fr (F. Affouard).

http://dx.doi.org/10.1016/j.molliq.2014.08.015
0167-7322/

and relate them to the differences in dipolar Kirkwood factors aiming to discuss the existence of the puzzling Debye peak seen in ibuprofen and flurbiprofen and not in ketoprofen.

2. Simulations details

Computations of ibuprofen, flurbiprofen and ketoprofen in the liquid state have been performed using the DL_POLY package and the all-atom OPLS force-field to model the intra- and intermolecular interactions [16,17]. Schematic models of the three molecules are displayed in Fig. 1. Ibuprofen, flurbiprofen and ketoprofen are chiral molecules but only the enantiomer S was considered in the present simulations. For each compound 64 molecules were first located on a pseudo crystal ($4 \times 4 \times 4$ simple cubic cells) which was rapidly melted at 500 K in order to generate an initial amorphous configuration. Periodic boundary conditions were imposed, to overcome the problem of surface effects. The equations of motion were integrated using the Verlet leap-frog algorithm [18], with a time step of 1 fs, and bond lengths were constrained by means of the SHAKE algorithm [19]. A Lennard–Jones potential has been employed to represent the van der Waals interactions. For the electrostatic interactions, a pairwise damped shifted method developed by Wolf [20,21] was used. The same cutoff radius of 9 Å has been used for both van der Waals and coulombic interactions.

Dielectric properties were particularly investigated in the present study so we carefully compared some dipolar properties obtained from the present simulation with reported experimental values. Calculations of the static permittivity [22] lead to $\varepsilon_s = 2.05$ at T = 380 K for ibuprofen in fair agreement with the experimental value 2.65 reported in [23] determined at T = 274 K. For flurbiprofen, the value obtained $\varepsilon_s = 3.17$ at T = 380 K is also in agreement with the experimental value 3.22 reported in [14] determined at T = 372 K. For ketoprofen, the value obtained $\varepsilon_s = 5.21$ at T = 380 K is also consistent with the experimental value 10.0 reported in [24] determined at T = 298 K since ε_s is expected to increase upon decreasing temperature. We also checked the validity of the damped shifted method used in the present study by performing one MD simulation at T = 500 K using an Ewald summation known to be one the most correct methods to handle long range electrostatic interactions. No significant structural, dynamical or thermodynamical differences have been found between both damped shifted and Ewald techniques. Calculations of the static permittivity ε_s using methods described in [22] lead to similar values for ibuprofen $\varepsilon_s = 1.7, 1.79$, for flurbiprofen $\varepsilon_s = 2.4, 2.44$ and ketoprofen $\varepsilon_s = 2.9, 2.99$ at the temperature T = 500 K from MD simulations using Ewald summation and damped shifted method, respectively.

MD simulations have been performed at four temperatures: 500, 450, 400 and 380 K. Thermalization was carried out in isobaric-isothermal NPT ensemble at a pressure P of 1.0 bar. The Nosé Hoover thermostat and barostat relaxation times have been chosen as 0.2 and 2.0 ps respectively [25]. The stabilized volume of the simulation box during the NPT simulation was considered to compute the averaged volume of the system and used to perform the subsequent production simulation in the NVT ensemble (constant number of particles, volume, and temperature). Production simulation time ranges from 40 ns at 500 K to 200 ns at 380 K.

In order to be sure that the different systems are at equilibrium at all investigated temperatures, we performed calculations of different single and collective time-dependent auto-correlation functions and checked that the expected behavior at long time is reached. For example, we checked that the diffusion regime is reached by the mean-squared displacement and that the dipole–dipole functions decrease to zero at long times. We also checked that the temperature dependence of some thermodynamical parameters such as density or potential energy shows a monotonic behavior. A change of slope that is not observed in our simulations would actually indicate a change to an out-of-equilibrium state i.e. glassy state.

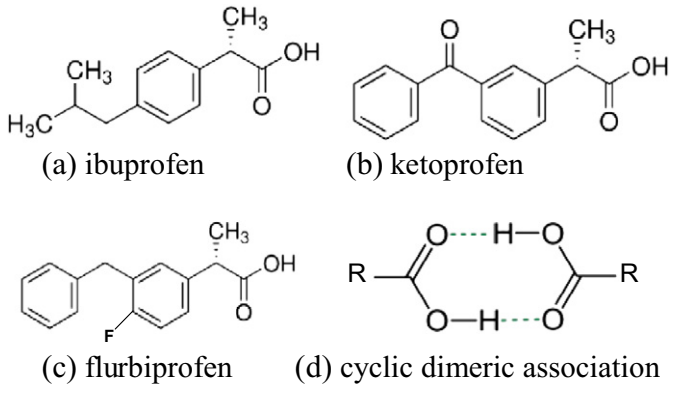

Fig. 1. Schematic representation of the ibuprofen (a), ketoprofen (b) and flurbiprofen (c) molecules. A schematic cyclic dimeric association is also shown (d). Only the carboxylic acid group O═C–O–H is displayed. R represents the remaining part of the profen molecule.

3. Results and discussion

3.1. Hydrogen-bonding statistics

HB statistics can be easily obtained from MD simulation [26,27]. This will allow determining the population of different HB associating structures and probing the structure of the different investigated liquids. The investigated molecules have in common a carboxylic group O═C–O–H. They thus similarly possess two oxygen atoms localized in the carboxylic acid group which may form HBs. For the three molecules, the only donor is the hydroxyl oxygen site (O–H) of the carboxylic group. This site may thus form an HB either with the carbonyl oxygen (···O═C) or with the hydroxyl oxygen (···O–H) of another carboxylic group. For ibuprofen, this is the only possibility. For flurbiprofen, it may also form an HB with the additional fluorine atom, and for ketoprofen with the additional oxygen atom of the ketone functional group.

In the present study, two oxygen atoms are considered to be H-bonded if *i*) they do not belong to the same molecule, *ii*) the oxygen–oxygen distance is less than 3.4 Å and *iii*) the (O···H–O) angle is larger than 120°. This classical criterion allows including more deformed and weaker HBs in statistics [26]. The same criterion is used for HBs involving the fluorine atom. The fraction of multimers composed of n profen molecules detected on average during the MD simulation is displayed in Fig. 2. These figures similarly show that a large variety of aggregates are theoretically possible. Upon decreasing temperature, the fraction of isolated molecules (n = 1) decrease significantly while the population of n > 3 multimers increases. At the lowest investigated temperatures T = 380 K, dimeric association (n = 2) is expected to be the most probable structure. The fraction of trimers (n = 3) and tetramers (n = 4) are significantly smaller. Additional larger associated structures are also observed but their fraction is really very small at this temperature as shown in previous MD simulations of ibuprofen [15].

Most important is the contribution of cyclic geometries (see Fig. 1) to the total number of dimers associating structures which is reported in the insets of Fig. 2. Cyclic structures of larger multimers are not considered in the following since their fraction is very small. Moreover, cyclic aggregates with a large number of molecules are also unlikely to exist for entropic reasons. Fig. 2 reveals that the contribution of cyclic structures becomes increasingly important when temperature is decreased.

At T = 380 K, 30% and 39% of the dimers are already made of cyclic arrangements for ibuprofen and flurbiprofen respectively. This evolution of the fraction of cyclic structures reported in Fig. 2 suggests that the same trend will continue at lower temperatures at which the population of cyclic structure might be even higher than the population of