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Communication: Synperiplanar to antiperiplanar conformation changes as underlying the mechanism of Debye process in supercooled ibuprofen

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In this Communication, we present experimental studies that put new insight into the puzzling nature of the Debye relaxation found in the supercooled liquid state of racemic ibuprofen. The appearance of D-relaxation in the loss spectra of non-hydrogen bonding methylated derivate of ibuprofen has proven that Debye relaxation is related solely with conformational changes of the carboxyl group, termed in this paper as synperiplanar-antiperiplanar. Our studies indicate that the presence of hydrogen bonding capabilities is not here the necessary condition to observe Debye process, however, their occurrence might strongly influence α- and D-relaxations dynamics. Interestingly, the activation energy of the D-process in ibuprofen methyl ester on approaching T_g was found to be perfectly consistent with that reported for ibuprofen by Affouard and Correia [J. Phys. Chem. B **114**, 11397–11402 (2010)] (∼39 kJ/mol). Finally, IR measurements suggest that the equilibrium between conformers concentration depends on time and temperature, which might explain why the appearance of D-relaxation in supercooled ibuprofen depends on thermal history of the sample. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4820492]

In the classical picture, glassy phenomenon is accompanied by drastic slowing down of cooperative motions of molecules with lowering temperature. This universal process, termed as structural relaxation, is closely connected with the dynamic glass transition and can be probed by many techniques.[1–3] However, for unknown reasons in dielectric response of some supercooled liquids these classical observations are significantly modified by the presence of an additional low frequency relaxation peak, which unlike α-relaxation has Debye-like decay. The most prominent Debye-like process is characteristic feature of monohydroxyl alcohols, for which its amplitude might be high enough to overlap almost completely structural relaxation response associated "truly" with the glassy dynamics.[4–6] As the appearance of well-pronounced Debye relaxation was confirmed experimentally for low molecular weight hydrogen-bonded liquids, it is believed that its presence is due to hydrogen bonded structures.[7] Unfortunately, the microscopic origin of the Debye-type relaxation remains still unclear. The first problem arose when studying Debye-like liquids is that the presence of an exponential decay was confirmed experimentally only by dielectric technique.[8,9] It is also remarkable that in hydrogen bonded systems Debye relaxation appears only if in a close vicinity of sterically accessible –OH (or –NH) center there is no neighboring hydroxyl groups.[10]

The importance of hydrogen bonded systems in pharmaceutical and biological science makes important to understand the fundamental nature of Debye-relaxation and its dynamics. Thus, in this Communication, we have made an attempt to reveal the nature of Debye-relaxation observed in the supercooled liquid state of widespread pharmaceutical substance, ibuprofen (IBU). Ibuprofen, being a racemic mixture of R and S enantiomers was recently a subject of detailed dielectric studies as it possesses strong ability to form hydrogen bonded aggregates.[11–15] Brás *et al.*[11] have reported that in the supercooled liquid state of hydrogen bonded ibuprofen, except of α-relaxation an additional Debye-type appears. However, in contrast to monohydroxyalcohols the amplitude of D-relaxation is much lower than structural relaxation. Brás *et al.*[11] have associated D-process observed in supercooled liquid state of racemic ibuprofen with hydrogen-bonded cyclic structures. Later, theoretical simulation studies performed by Affouard and Correia[16] revealed that this process might result from the internal *cis-trans* conversion of the O=C–O–H group (with the energy barrier of ∼9.5 kJ/mol) coupled to the change of the intermolecular linear/cyclic HB structures.

In order to put some new insight into the origin of D-relaxation in supercooled ibuprofen we have played with

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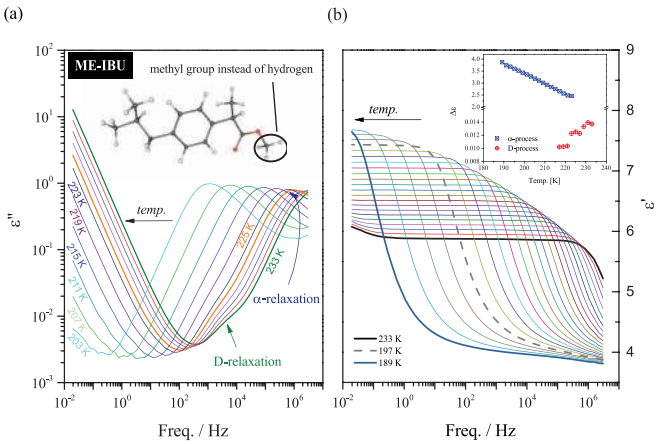

FIG. 1. (a) Dielectric loss spectra ε'' of Me-IBU for temperatures from 233 K to 203 K as indicated (b) storage component of complex dielectric permittivity ε' recorded above glass transition temperature of Me-IBU. The inset shows dielectric strength $\Delta\varepsilon$ for α- and D-relaxation of Me-IBU plotted versus 1/T.

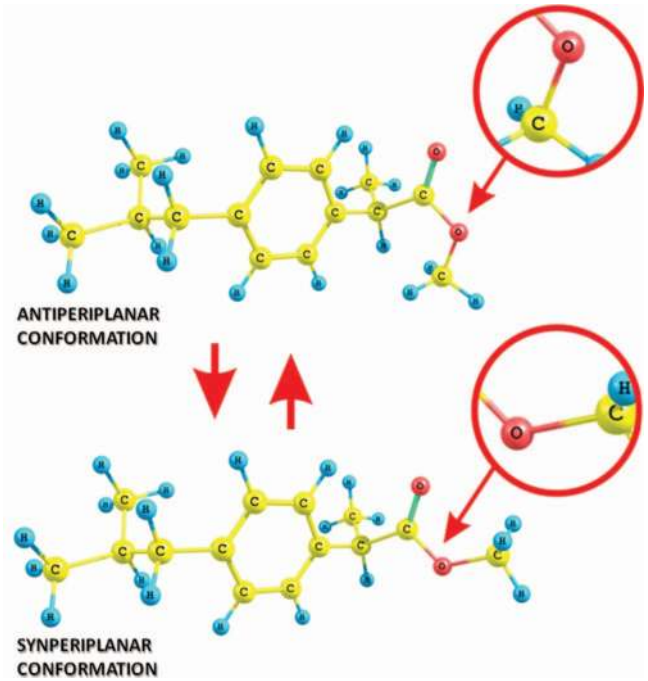

FIG. 2. The antiperiplanar and synperiplanar conformers of methyl ibuprofen ester. Upper panel, synperiplanar isomer; lower panel, antiperiplanar isomer.

hydrogen bonding abilities of examined compound. Intermolecular HB abilities of ibuprofen were removed by chemical substituting hydrogen atom from the hydroxyl group by the methyl $-CH_3$ moiety (see scheme in Figure 1). Obtained in this way methylated form of racemic ibuprofen was confirmed to consist of only non-hydrogen bonded ibuprofen *monomers, with no possibility to form intermolecular HB structures*. The synthesis method and purity verification procedure are given in the supplementary material.[17] Dielectric measurements were carried out using Novocontrol Alpha analyzer. Transmission infrared spectra were measured using a Biorad FTS-6000 spectrometer. Temperature infrared measurements were carried out using Linkam THMS600 stage with the temperature accuracy of ± 0.1 K/s. The infrared analysis was supported by the theoretical calculation using the B3LYP/6-311G** level of theory and Gaussian09 software. Dipole moment calculations were carried out on the B3LYP/6-311G* level of theory using Orca 2.9 package.

Figure 1(a) presents imaginary part of the complex dielectric permittivity measured during cooling of the sample from 233 to 203 K at every 2 K. As illustrated, above glass transition temperature a well pronounced structural relaxation is clearly visible. However, a close inspection of the loss spectra shows that in the supercooled liquid of methyl ester of ibuprofen an addition, Debye type process emerges at lower frequencies than the structural relaxation. It has much lower amplitude than the α-process and with decreasing temperature becomes practically hidden by the dominant glassy relaxation dynamics. Since the behavior of this extra relaxation process is analogical as that reported earlier for ibuprofen, we labeled it as D-relaxation (please see Ref. 17). The appearance of the Debye relaxation in the supercooled liquid state of methyl ester of ibuprofen is quite surprising finding, taking into account the origin of D-relaxation hotly discussed recently for pure ibuprofen. Our dielectric data, in fact, suggest that the presence of Debye-type relaxation in supercooled ibuprofen cannot be due to its strong ability to form hydrogen bonding aggregates, because by substituting hydrogen atom in carboxyl group by the methyl group hydrogen bonding abilities of ibuprofen have been blocked. In addition, in view of current results the interpretation of the Debye process in supercooled ibuprofen as due to internal *cis-trans* conversion of carboxyl group coupled to the change of intermolecular linear/cyclic hydrogen bonding structures needs in our opinion a slight update. Affouard and Correia[16] have suggested that cyclic dimers inhibit *cis-trans* conversion, whereas linear dimers favor it. However, it looks that the change in dipole moment generated by isomeric conversions that involves O=C–O–H group must be solely related to the D-process. As in the chemical nomenclature *cis-trans* formalism is typically reserved for isomers that contain double bonds which cannot rotate, we prefer to use a more appropriate name of it, as synperiplanar/antiperiplanar. It is worth to stress that both terms are used here to reflect the same conformational change related with torsion angle change O=C–O–X (X = H or CH_3) proposed by Affouard and Correia.[16] Nevertheless, we believe that "synperiplanar"-"antiperiplanar" terminology is probably more suitable. Isomers of methyl ester of ibuprofen in synperiplanar and antiperiplanar arrangements are shown in Figure 2. Synperiplanar conformer refers to *cis* isomer, whereas antiperiplanar to the *trans* one.

Figure 1(b) presents the real part of complex dielectric permittivity ε' for methylated derivative of ibuprofen recorded in the temperature region above T_g. As for conventional glass-formers dielectric strength $\Delta\varepsilon$ of the α-relaxation increases with lowering temperature (please see the inset in Figure 1(b)). For the structural relaxation, $\Delta\varepsilon$ increases almost twice between temperature range from 223 K to 189 K. In addition, dielectric strength for the α-relaxation in methyl ester of ibuprofen is much greater than that reported by Brás *et al.*[12] for the outcome racemic ibuprofen (less than 0.2

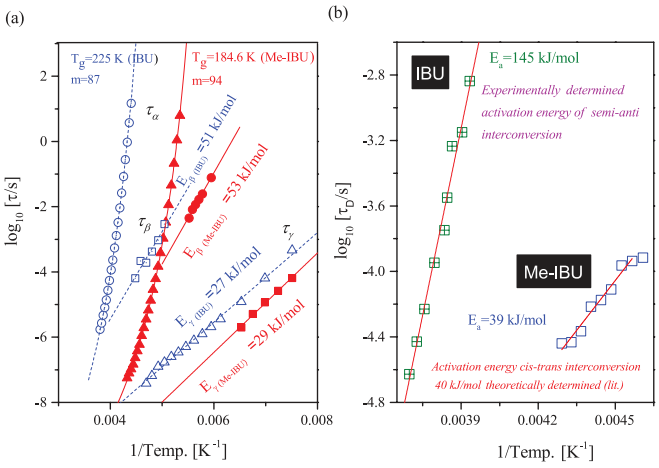

FIG. 3. (a) Relaxation map of ibuprofen (data taken from Ref. 13) and methyl ibuprofen ester (open symbols, IBU; filled symbols, Me-IBU). The temperature dependences of the structural relaxation times were described by the VFT equation. To fit the temperature dependences of secondary relaxations τ_β and τ_γ Arrhenius equation was used; (b) D-relaxation times τ_D versus 1/T for Me-IBU and IBU. The experimentally determined activation energies of synperiplanar to antiperiplanar conformational changes were obtained by fitting to the Arrhenius equation the temperature dependence of D-relaxation times. Data for ibuprofen were digitalized from Ref. 11.

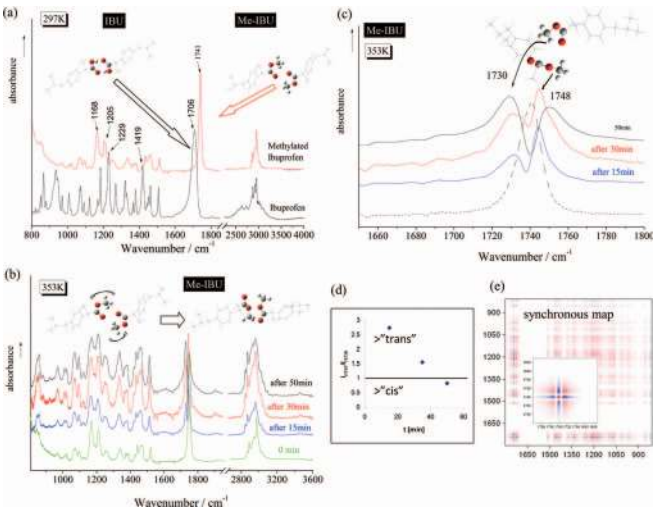

FIG. 4. (a) Comparison of infrared spectra of ibuprofen and methyl ibuprofen; (b) infrared difference spectra of methyl ibuprofen during time dependent measurements at 353 K; and (c) the difference IR spectra (absolute value) of two bands (0 min and after some part of time) with a FWHM of 20 cm^{-1}, intensity of 2.5 a.u., and frequency gap of 2 cm^{-1} in 353 K. Original spectrum (dash line) is also presented for a better comparison the absolute value of the difference spectrum; (d) ratio of the integral intensity of I_{i1748}/I_{i1730} in time; (e) 2D synchronous IR correlation spectra constructed based on changes between original and difference IR spectrum of methyl ibuprofen in the two spectral region (1800–810, 1800–1600 cm^{-1}) measured over a time range of 0–50 min at 353 K.

in the whole supercooled region). The reason for that might be twofold. First, as a result of removing hydrogen bonds dipolar molecules of methyl ester of ibuprofen will not align in antipararallel orientations, as it happens for pure ibuprofen. Second, much higher value of the dielectric strength of the α-relaxation for methylated ibuprofen might be due to the fact that in the supercooled liquid state the equilibrium between both conformers is shifted towards antiperiplanar one having higher value of the dipole moment. In present studies, we have applied DFT computation methods to calculate dipole moments for synperiplanar and antiperiplanar conformers of methyl ester of ibuprofen. Obtained values, 1.55 D and 4.55 D for, respectively, synperiplanar and antiperiplanar conformers confirm that replacement hydrogen atom in the carboxyl group by the methyl one practically does not change the total dipole moments of both ibuprofen's isomers (1.6 D and 4.6 D). Affouard and Correia[16] have shown that with decreasing temperature the fraction of less stable antiperiplanar conformer decreases in favor of synperiplanar one. We suppose that the opposite situation might happen in the case of methylated ibuprofen. In regard to the dielectric strength of D-process, its values as well as the opposite behavior to the α-relaxation are analogical for both, ibuprofen and its methyl ester (appropriate data for ibuprofen can be found in Ref. 11).

In the next step, molecular dynamics of supercooled ibuprofen methyl ester was studied in detail by dielectric technique. As can be seen in Figure 3(a) substitution of the hydrogen atom in –COOH of ibuprofen by the –CH_3 group causes its glass transition to decreases of almost 40°. Apart from that, its relaxation dynamics reflected by the α-, β-, and γ- relaxations dependences does not change significantly. As mentioned previously, theoretical work given by Affourard *et al.*[16] yields to energy barrier ≅40 kJ/mol (≅9.5 kcal/mol) for the *cis-trans* conversion. This result encouraged us to verify experimentally whether the D-relaxation observed in dielectric spectra of supercooled Me-IBU is due to conformational changes. For that purpose, relaxation times of D-process, τ_D, were plotted versus inverse of temperature, as illustrated in Figure 3(b). The activation barrier of D-process on approaching T_g was determined from the fit of experimental data to the Arrhenius equation, and it is perfectly consistent (E_a = 39 kJ/mol), with that calculated for "cis-trans" isomerism of the –COOH group for ibuprofen. As pointed out by a very helpful reviewer the value of the energy barrier determined from MD simulations was calculated in the pico-nanosecond regime, far above T_g. In this high temperature domain the hydrogen bonding associations are precisely the weakest, and thus a situation for ibuprofen is similar as the one reported for ibuprofen methyl ester. We have also made an attempt to compare experimentally determined activation energies of D-relaxation for IBU and Me-IBU. In order to do that the appropriate temperature dependence of D-relaxation times τ_D (data for ibuprofen covering approximately the same range of relaxation times were taken from Ref. 11) were fitted to the Arrhenius equation, as shown in Figure 3(b). The value of E_a for D-relaxation in hydrogen bonding ibuprofen is much higher and equal to 145 kJ/mol which suggests that the presence of hydrogen bonds might strongly affect its relaxation dynamics. Interestingly, we have also found out that the separation between D- and α-relaxations does not depend on the hydrogen bonding capabilities of investigated material (please see Ref. 17 for details).

Apart from studying relaxation dynamics of ibuprofen methyl ester we have also performed IR measurements as it is a more sensitive method to study hydrogen bonding interactions and conformational changes. The IR spectra of ibuprofen (IR_{IBU}) and methyl ester of ibuprofen ($IR_{Me\text{-}IBU}$)

recorded at room temperature are presented in Figure 4(a). IR_{IBU} show lots of characteristic bands, namely, at 935, 1182, 1228, 1419, 1706 cm^{-1} and between 2500 and 3300 cm^{-1}. Three of them, i.e., 935, 1182, and 1228 cm^{-1} originate from the deformational vibrations of γCH_3 and γCH groups close to the O=CO–H.[11,18,19] It is worth to emphasize that these bands are not observed in the IR spectra of Me-IBU. On the other hand, $IR_{Me\text{-}IBU}$ points out for an additional bands at 1168 and 1205 cm^{-1} which derive from the deformational vibration of methyl groups located in the O=CO–CH_3 chain. It is worth mentioning that as a result of methylation highly intensive band originating from the stretching vibration of the νC=O group[11,18,19] shifts from 1706 cm^{-1} to 1741 cm^{-1}, such a large shift (~35 cm^{-1}) is a direct proof that ibuprofen methyl ester does not form dimers and any other internal hydrogen bonds O–H···O(=C). The lack of dimeric moieties is also confirmed by the absence of stretching vibrational bands related to the hydroxyl groups OH in the 2580–2740 cm^{-1} region. In the next step, we have performed time dependent IR measurements at 353 K, to find out what would happen with the methylated sample on increasing temperature. At first glance recorded spectra, presented in Figure 4(b), did not reveal any significant differences, indicating for the lack of changes in the sample over time. In order to establish more subtle changes the difference IR spectra analysis was performed.[20,21] As illustrated in Figure 4(c) upon isothermal measurements at 353 K the band at 1741 cm^{-1} characteristic for methyl ester of ibuprofen is shifting to 1730 cm^{-1}. Moreover, with increasing time a second band at 1748 cm^{-1} successively appears. These changes with time indicate for the presence of two different conformers that convert into each other in order to reach equilibrium population at certain temperature. The band at 1730 cm^{-1} can be associated with the presence of a "synperiplanar" form while the band at 1748 cm^{-1} with antiperiplanar form (see Figure 4(c)). It is worth mentioning that the most significant changes in the difference IR spectra are observed within first 30 min. During that time, the ratio of the integral intensity for bands associated with synperiplanar and antiperiplanar conformers $-I_{i1748}/I_{i1730}$ is rapidly changing (see Figure 4(d)). The difference IR spectra show that within the first 15 min the most intense band is observed at 1748 cm^{-1}. With increasing time this situation changes and the band at 1730 cm^{-1} becomes more intense (Figure 4(c)). This suggests that initially at this temperature there is more fraction of "*trans*" conformers than "*cis*" one. Finally, in order to show the nature and trend of changes with time 2D synchronous map (see Figure 4(e)) was made based on the IR spectrum of methyl ibuprofen and difference IR spectra. The synchronous correlation map for our experiment shows two positive cross-peaks at (1730, 1748) cm^{-1}, (1748, 1730) cm^{-1}, two negative cross-peak at (1741, 1748) cm^{-1}, (1741, 1730) cm^{-1}, and three auto-peaks at 1730, 1741, 1748 cm^{-1}. These results show that the changes that take place in the sample are at the same time and they are associated with the appearance of different conformers.

In summary, in this paper we have provided new experimental data that fulfill previous works by Brás *et al.*[11] and Affouard and Correia[16] to provide a complete picture of the molecular dynamics in supercooled ibuprofen. By preparing methyl ester of ibuprofen we have completely removed hydrogen bonding abilities of ibuprofen and shown that Debye relaxation must originate solely from synperiplanar to antiperiplanar conformational changes. We conjecture that the appearance of an additional D-relaxation in dielectric loss spectra might originate from the isomeric transformations, once significant difference in the values of their dipole moments appears and the rate of the conversion is not too fast or too long to be observed in the experimentally accessible frequency window. This type of behavior seems to be universal as observed for hydrogen and non-hydrogen bonding ibuprofen molecules.

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