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BRIEF ARTICLE

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Temperature and Volume Effect on the Molecular Dynamics of Supercooled Ibuprofen at Ambient and Elevated Pressure

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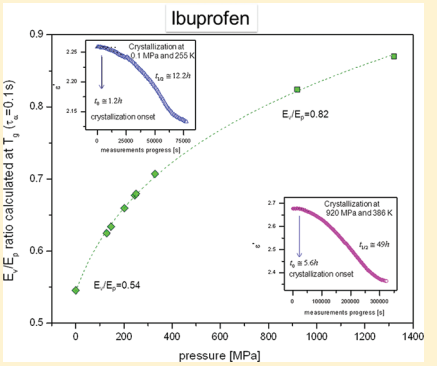
ABSTRACT: In this paper we have studied the relative importance of thermal effects and volume in controlling structural relaxation of supercooled ibuprofen at ambient and elevated pressure. The relative contribution of both parameters on the structural relaxation times was estimated by means of the ratio E_V/E_P (i.e., the activation energy at constant volume to enthalpy of activation at constant pressure), which can be simply estimated from dielectric relaxation and pressure−volume−temperature (PVT) measurements. We found out that at ambient pressure the effect of thermal energy and molecular packing on structural relaxation dynamics is practically equaled. However, with increasing pressure the role of thermal effects in governing molecular dynamics becomes more prominent, leading to its complete domination in the pressure region of around 1 GPa. These results are discussed in the context of remarkably different behavior of supercooled ibuprofen crystallized at various thermodynamic conditions, as reported in our previous paper. The implication is that, when molecular mobility of supercooled ibuprofen is governed primarily by the thermal energy, significant slowing down of crystallization progress at isostructural relaxation conditions is observed.



KEYWORDS: supercooled liquid state, glass transition, dielectric spectroscopy, crystallization, amorphous pharmaceutical

Amorphous solids pervade virtually all aspects of contemporary life as well as major technological sectors. Although the best-known example of glass is the window glass made from silica, one should remember that amorphous or glassy behavior can be also found for a broad group of materials ranging from ceramics, polymers, and metals to soft matter or biological systems.[1−3] Glass formation is also ubiquitous in nature, allowing preservation of numerous insects and small organisms in extremely cold or dehydrated conditions.[4] Many pharmaceuticals and food materials are unintentionally created partially or completely in the disordered amorphous state during manufacturing processing. When improvement of solubility and bioavailability is desired, pharmaceuticals are deliberately formed in the amorphous state.

In the past decade it has been demonstrated that drugs delivered in the amorphous form can be more than several times as active as their crystalline counterparts, basically because of greater solubility and enhancement of dissolution profile.[5] However, production of the amorphous active pharmaceutical ingredients (APIs) on mass scale is possible only if their long-term physical and chemical stability are ensured. This seems to be the most challenging task to handle, since thermodynamic instability of the glassy state is an irresistible factor which prompts the amorphous system to revert to the more stable crystalline structure. As crystallization from the glassy state proceeds, crucial and beneficial features given by the amorphous state are completely lost. Nevertheless, it is commonly believed that if we thoroughly understood what causes crystallization of the amorphous systems and were able to control it, development of stable organic as well as nonorganic glassy systems with a variety of promising applications would be possible.

Ongoing studies have shown that principal factors affecting crystallization from the amorphous state are kinetic factor (degree of molecular mobility), thermodynamic factor, moisture content (the presence of water content decreases the glass transition of respective glass and makes it more susceptible for crystallization) and method of preparation.[6−8] On the other hand one should also remember that the crystallization phenomenon is a very tough and complicated problem and there are also other things that might affect crystallization tendencies of supercooled liquids or glassy materials such as specific surface area (samples with larger surface area are generally less stable) or surface mobility.[9] Since for nucleation as well as crystal growth the movement of molecules is a necessary condition, the very natural way is considering molecular mobility as probably the most important factor determining physical and chemical stability of amorphous drugs. Indeed, many scientific reports have shown that crystal growth rate directly couples with molecular mobility of either global or local origin.[10,11]

Studies on the relationship between molecular motions and crystallization rate of amorphous pharmaceuticals can certainly be carried out by means of dielectric spectroscopy which allows mobility to be detected in the liquid as well as glassy state. As a matter of fact, it enables the relaxation processes of different molecular origin (such as the α-relaxation reflecting cooperative movement of the system or secondary relaxations associated with

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noncooperative mobility) to be observed in a broad range of frequencies, temperatures and even pressures. The possibility to monitor relaxation properties of pharmaceutical systems in elevating pressure is especially important, since it provides completely new insight into their relaxation behaviors. It is well-known that pressure might exert significant influence on the molecular interactions (for example reduction of hydrogen bonds), density and entropy of glass-formers, changing as a consequence also their molecular dynamics.[12] Moreover, in view of our recent studies, compressed supercooled liquids and glasses might be more stable against crystallization than that prepared at ambient conditions.[13,14] It should be also added that the measuring of structural relaxation times as a function of temperature and pressure (so the volume too) can facilitate our understanding of the dramatic change in molecular dynamics near the glass transition.

So far, the scientific community agrees that in general the increase of structural relaxation time as a supercooled system is cooled toward the glass transition is brought about by thermal and density (volume) effects.[15,16] The former reflects decreasing of kinetic energy of molecules whereas the latter reflects increasing of molecular packing. The knowledge about the relative importance of these two effects in governing the structural relaxation should be of great interest, since it provides a clear picture of supercooled liquid dynamics. More so, by experimental identification of which thermodynamic variable, temperature or specific volume (density), plays a decisive role in dramatic change of supercooled liquid dynamics in the vicinity of the glass transition region, we are able to verify which alternative approach, i.e. "free volume" (complete limitation of thermal energy effect, e.g. ref 17) or "energy landscape" (neglects volume role. e.g. ref 18), is more appropriate for its description.

Herein, it is worth pointing out that most of the studies which concern the relationship between molecular mobility and crystallization tendencies of the supercooled and glassy samples involve focusing on the coupling between translational diffusion and structural relaxation above certain temperature T_B or its lack below T_B where the crystal growth proceeds even hundreds of times faster than molecules can reorientate (e.g. ref 19). However, none of these studies concern what does actually govern the structural relaxation dynamics in these compounds in the vicinity of the glass transition.

The purpose of this paper is 2-fold: (i) first, to verify which thermodynamic variable (volume, temperature or both) has dominant influence on molecular dynamics of ibuprofen at ambient and elevated pressures, namely, 0.1, 128, 146, 201, 245, 250, 328, 920, 1321 MPa; (ii) second, to confront these results with our previous ones concerning crystallization kinetics of supercooled ibuprofen at various thermodynamical conditions.[14] To addressed this issue in detail, it was necessary to perform isobaric and isothermal dielectric relaxation measurements along with pressure−volume−temperature (PVT) measurements. For ibuprofen both types of studies were performed and described carefully elsewhere.[14,20]

In this paper the relative importance of thermal energy and molecular packing on structural relaxation dynamics of ibuprofen was evaluated by means of the E_v/E_p ratio,[21,22] i.e. the activation energy at constant volume $E_v = R[(\partial \ln \tau_\alpha)/(\partial T^{-1})]_v$ to the activation enthalpy at constant pressure, $E_p = R[(\partial \ln \tau_\alpha)/(\partial T^{-1})]_p$. The magnitude of E_v/E_p varies from 0 to 1. If the E_v/E_p tends to unity, thermal energy should fully dominate molecular dynamics, whereas the volume effect can be neglected . On the other hand, if the E_v/E_p ratio approaches zero, free volume plays a decisive role

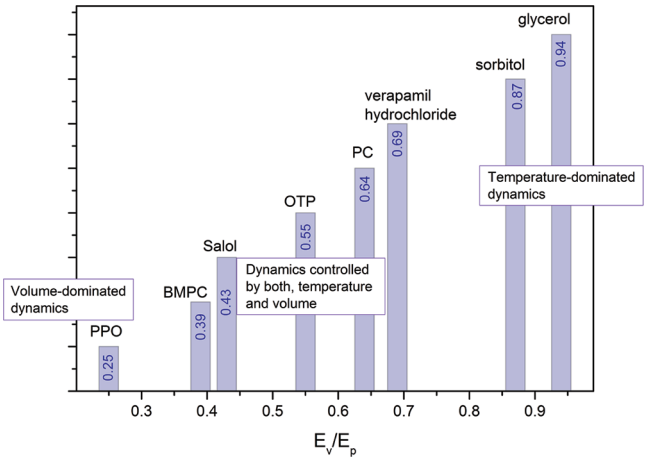

Figure 1. The ratio of isochronic and isobaric activation enthalpies E_v/E_p calculated for several compounds differing in the roles played by volume and temperature in controlling their structural relaxation while approaching the glass transition. All dynamics refer to ambient pressure. The values of E_v/E_p for glycerol, sorbitol, propylene carbonate (PC), *o*-terphenyl (OTP), salol, and BMPC were taken from ref 12, the E_v/E_p for PPO was taken from ref 23, and the value of E_v/E_p for verapamil hydrochloride was taken from ref 31.

in controlling molecular dynamics. Based on the value of the E_v/E_p ratio the nature of the structural relaxation process in glass-forming liquids can be divided into 3 categories: practically volume-dominated (found mostly for polymers, like BMMPC,[12] BMPC[12] or PPO[23]), practically temperature-dominated (characteristic for associated liquids such as glycerol or sorbitol[12]) and dominated by both temperature and volume ($E_v/E_p \sim 0.5$). Ongoing studies have revealed that for most glass-forming liquids the temperature and volume control relaxation dynamics in a practically equal way and both quantities should be taken into account. The representative values of the E_v/E_p ratio found for several compounds according to the role played by thermal effects and volume in governing their relaxation dynamics are presented in Figure 1.

Herein, it should be mentioned that as an alternative measure of the importance of V and T in governing relaxation dynamics one can use scaling exponent γ from the following equation:

$$\tau_\alpha(T,p) = F(TV^{-\gamma}) \quad (1)$$

where F is a function. As demonstrated by plotting relaxation times versus scaling product $T^{-1}V^{-\gamma}$ for most of the glass-formers superposition of data onto one master curve is obtained, irrespective of thermodynamic conditions. The parameter γ is a unique material constant; it varies from 0 to ∞. Large values of parameter γ are associated with systems whose dynamics is influenced more by intermolecular free volume, while small values of γ are characteristic of thermally activated dynamics. The parameter γ was found to correlated with the E_v/E_p ratio, as presented by Casalini and Roland.[24]

The E_v/E_p ratio can be calculated in several different ways (see for example ref 25). However, in this paper we have assessed the enthalpy ratios at various (T, p) conditions in terms of the isobaric $\alpha_p = V^{-1}(\partial V/\partial T)_p$ and isochronic $\alpha_\tau = V^{-1}(\partial V/\partial T)_\tau$ thermal expansion coefficients[26]

$$\left.\frac{E_v}{E_p}\right|_{T_g} = \frac{1}{1 + \alpha_p/|\alpha_\tau|} \quad (2)$$

Table 1. Values of α_p, E_v/E_p Calculated for Ibuprofen at Glass Transition Temperatures $T_g = T(\tau_\alpha = 0.1s)$ and Pressures Ranging from 0.1 MPa to 1321 MPa

pressures [MPa]	T_g [K] ($\tau_\alpha = 0.1$ s)	α_p [K^{-1}] at T_g	$\left.\frac{E_v}{E_p}\right\|_{T_g}$
0.1	234.70	7.4×10^{-4}	0.54
128	260.15	5.33×10^{-4}	0.62
146	263.15	5.13×10^{-4}	0.63
201	273.15	4.58×10^{-4}	0.66
245	280.15	4.23×10^{-4}	0.67
250	281.09	4.19×10^{-4}	0.68
328	293.15	3.68×10^{-4}	0.71
920	349.07	1.89×10^{-4}	0.82
1321	378.15	1.32×10^{-4}	0.87

Thermal expansion coefficients at constant pressure and constant relaxation time can be estimated from isobaric and isothermal dielectric relaxation studies and isobaric $V(T)$ curves recorded in the liquid state of ibuprofen during PVT measurements, which were parametrized later by means of the Tait equation of state (appropriate parameters can be found in ref 20).

For ibuprofen, the value of α_p, referring to dynamics at different pressures, varies from 0.1 MPa up to 1321 MPa, and temperatures at which τ_α = 0.1 s are listed in Table 1 (to avoid considerable extrapolation of the VFT fits, the glass transition temperature was defined as the temperature at which structural relaxation time is equal to τ_α = 0.1 s[20]). From analysis of experimental data the isochronal expansion coefficient was assumed to be nearly constant, $\alpha_\tau(T_g) = 8.89 \times 10^{-4}$ K^{-1}, whereas the isobaric thermal coefficient decreases as the pressure increases from 0.1 MPa up to 1321 MPa (see Table 1). From the obtained thermal expansivities we have calculated the enthalpy ratios for each studied here pressure. The results are listed in Table 1. As can be seen, at ambient pressure the value of E_v/E_p was found to be equal to 0.54, which indicates that thermal energy as well as molecular packing are both important in controlling relaxation dynamics of ibuprofen near its glass transition temperature. However, as the pressure increases, the role played by thermal factors in driving molecular dynamics of compressed ibuprofen becomes more important, leading to practically thermally activated structural relaxation dynamics at pressures of around and greater than 1 GPa (E_v/E_p = 0.87 at 1321 MPa). The pressure dependence of the E_v/E_p ratio for ibuprofen is presented in Figure 2. The increase of E_v/E_p ratio with increasing pressure is a reasonable result. Since pressurization of supercooled liquid increases the sample's density, at very high pressures complete reduction of free volume contribution is expected. Consequently, the thermal effects gains importance in governing the molecular dynamics of ibuprofen at elevated pressure. This result is potentially very important, because it is a clear implication that the free volume model is not suitable to describe the glassy phenomenon in such a case, simply because of its significant decrease. Thus, for our high pressure samples the slowdown of molecular motions responsible for the glass transition cannot be connected with reduction of unoccupied free volume.

Now, the change of character of structural relaxation dynamics in the vicinity of the glass transition from being governed practically half by thermal activation and molecular packing to being almost purely temperature-dominated will be discussed in the context of crystallization tendencies of ibuprofen at ambient

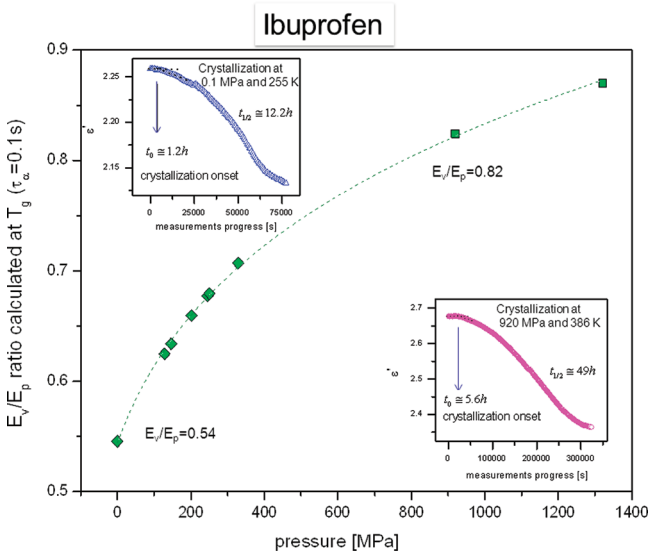

Figure 2. The pressure dependence of the E_v/E_p ratio for ibuprofen. The insets present the crystallization progress visible as the decrease of dielectric constant of the structural relaxation monitored for two ibuprofen samples crystallized at (1) 0.1 MPa and 255 K and (2) 920 MPa and 386 K but having approximately the same structural relaxation time. As illustrated for compressed sample, significant slowing down of the crystallization progress was observed.

and elevated pressure. Our previous crystallization experiments carried out at various (T,p) combinations but for approximately the same structural relaxation time (isostructural relaxation conditions) revealed significant extension of the induction time as well as overall crystallization time for the ibuprofen sample which crystallized under very high pressure (0.92 GPa), in comparison to the sample crystallized at ambient conditions (see the inset in Figure 2).[14] As we have mentioned therein, such results are a clear indication that molecular mobility related to structural relaxation process does not govern alone the crystallization process and there must be some other important factors. However, in the context of the current results, it must be pointed out that in both cases the relative importance of molecular packing and thermal effects on relaxation dynamics near T_g was completely different, so it is evident that the pressure completely modified ibuprofen's molecular dynamics.

According to H. Tanaka's[27,28] explanation of the crystallization mechanism near and just below T_g (known as tension-induced interfacial mobility model), the crystallization proceeds due to tension created by the difference in densities between crystal and liquid (crystal and glass). Since the crystal has greater density than the liquid (glass), its formation in the liquid (glassy) state induces extensional stress around a nucleus due to volume contraction. That should provide (according to the Doolittle equation) an excess of free volume to molecules surrounding the crystal, resulting in the increase of their molecular mobility, and ease further crystallization. Based on Tanaka's model, we conjecture that it takes longer for ibuprofen molecules to form crystal nuclei and crystallize at very high pressure (almost 1 GPa), since the molecular mobility related to structural relaxation is governed, in that case, almost solely by thermal effects, not molecular crowding. So consequently, even if, as a result of negative pressure around the crystal nuclei, additional free volume for molecules to reorientate was being provided, it would not increase molecular

mobility and support the crystallization progress, since molecular dynamics of compressed ibuprofen was not governed by the free volume but almost entirely by thermal energy. An opposite crystallization behavior was observed at ambient pressure, where the role of free volume was substantially more important.

Preparation of highly stable amorphous systems is of great interest to the pharmaceutical community. If we learn how to inhibit recrystallization and take advantages from the glassy state, many promising applications will be possible. As can be concluded from the literature data, stabilization protocol of the glassy systems can be achieved by a sensible choice of the preparation method. This was shown previously by Ediger et al. in the case of vapor-deposited glasses with greater density, resistance to water uptake and initial stability comparable to ordinary glass aged for 7 months.[29] However, our latest research involving high-pressure experiments (for example ibuprofen,[14] indomethacin[13] or triphenyl phosphite (TPP)[30]) clearly indicate that by compression of liquid we are able to suppress the crystallization process in the supercooled regime and produce systems with greater density and stability against crystallization than at low pressures. In this paper we have directly shown that the E_v/E_p ratio increases with pressure, and the role of free volume becomes less important. Assuming the weak influence of the free volume on relaxation dynamics at high pressure and following Tanaka's explanation of the crystallization process, its slowdown or suppression at elevated pressure can be simply justified. This result is very useful for all the community, and if applied to other systems, it might give a clear protocol on how to prepare amorphous pharmaceuticals with improved stability and greater resistance against crystallization.

Summarizing, by means of the E_v/E_p ratio we have shown in this paper that with increasing pressure the role of volume (density) and thermal effects in controlling the molecular dynamics of ibuprofen in the vicinity of the glass transition becomes fundamentally different. At ambient pressure both variables, temperature and volume, govern the dynamics, while at high pressures the role of thermal effects becomes more prominent and temperature becomes the principal variable that controls its molecular mobility. The greater influence of thermal energy on structural relaxation properties of pressurized ibuprofen is due to reduction of free volume as a result of compression. These results were also confronted by us with ambient and elevated pressure crystallization data of ibuprofen. As pointed out, when molecular motions of supercooled ibuprofen are controlled almost solely by the thermal energy, significant slowing down of its crystallization progress is observed. Based on Tanaka's interpretation of the crystal formation and crystal growth in the liquid (glassy) state, we suppose that crystallization of compressed ibuprofen was significantly slowed down, since its molecular dynamics was not governed by the free volume but was almost completely temperature-dominated ($E_v/E_p = 0.82$). Thus, in contrast to the sample crystallized at ambient pressure ($E_v/E_p = 0.54$), additional free volume created around the crystal nuclei would not cause the molecules to move faster and aid crystallization. From that it is also evident that the tension-induced interfacial mobility model explaining crystal growth across T_g will not describe properly enhancement of crystallization in systems in which dynamics is completely governed by the thermal factor. Finally, the experimental evidence presented by us indicates that considerably more attention should be paid to analyzing not only molecular mobility associated with the structural relaxation process as a possible source of crystallization of supercooled and amorphous material but also, more certainly, the factors which control this type of motion.

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