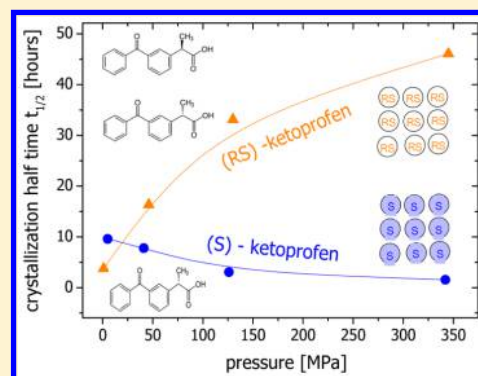


Crystallization Behavior and Relaxation Dynamics of Supercooled *S*-Ketoprofen and the Racemic Mixture along an IsochroneKarolina Adrjanowicz,^{*,†,‡} Kamil Kaminski,[§] Marian Paluch,[§] and Kristine Niss[‡][†]NanoBioMedical Centre, Adam Mickiewicz University, Umultowska 85, 61-614 Poznan, Poland[‡]DNRF Centre "Glass and Time", IMFUFA, Department of Sciences, Roskilde University, Postbox 260, DK-4000 Roskilde, Denmark[§]Institute of Physics, University of Silesia, Uniwersytecka 4, 40-007 Katowice, Poland

Supporting Information

ABSTRACT: In this paper, we study crystallization behavior and molecular dynamics in the supercooled liquid state of the pharmaceutically important compound ketoprofen at various thermodynamic conditions. Dielectric relaxation for a racemic mixture was investigated in a wide range of temperatures and pressures (up to 350 MPa), whereas crystallization kinetics for racemic and single enantiomers was studied along a (T, p) curve characterized by the same structural relaxation time, $\tau_\alpha \cong 10^{-6}$ s, a so-called isochrone. The aim was to investigate the effect of pressure on the crystallization tendencies of pure enantiomers and their 50–50 equimolar mixture in the metastable supercooled liquid state. Crystallization kinetic studies revealed that at the same isochronal conditions the behavior of the *S*-enantiomer and *R,S*-racemic mixture of ketoprofen is entirely different. This was examined in the context of previous results and in view of the possibility of inducing changes in the enantiomeric composition or enantiomers separation from a racemic mixture as the effect of high pressure.



I. INTRODUCTION

The process of crystal formation is fundamentally important from a scientific point of view but also in many practical applications. Understanding why some liquids can be easily supercooled and reach the glassy state, whereas the others may not, is a longstanding problem of condensed matter physics. Crystallization is very complex and nonequilibrium phenomenon, stochastic in its nature. It is influenced by many factors at the same time, and there are still many aspects that are poorly recognized or even completely nonaddressed. One of them is certainly the effect of pressure on the overall crystallization behavior of glass-forming materials.

It is well-known that pressure, just like temperature, is one of the most essential thermodynamic variables that control molecular dynamics and the glass-forming ability of liquids.^{1,2} It can therefore have an important impact on the crystallization behavior of glass-forming liquids, though it also implies introducing an additional element of uncertainty particularly if used in an uncontrolled way. In the past decade compression of liquid has turned out to be an extremely powerful method to achieve organic and inorganic materials with interesting physicochemical properties, sometimes not attainable by any other experimental attempt performed at atmospheric pressure.^{3–7} Unfortunately, the exact effect of pressure on slowing down or speeding up the crystal formation from the supercooled liquid state has not been fully established yet because most of these studies are performed at randomly selected combinations of temperature and pressure without

taking into account the relative impact of fundamental parameters governing its progress at various thermodynamic states. Therefore, a number of contradictory examples can be found in the literature.^{8–11} On the other hand, one can also take the advantage of high pressure studies to get better understanding of the crystal formation and access some of its features unattainable otherwise, e.g., controlling fundamental parameters governing crystallization progress as established by some of us recently. This involves a novel protocol of studying crystallization phenomenon at various thermodynamic conditions (i.e., various combinations of temperature and pressure) along an isochronal curve having the same time scale of the global molecular mobility.^{12,13} The valuable asset of such approach is that it provides a unique opportunity to disentangle thermodynamic effects on crystallization from kinetic ones which cannot be achieved by any other known experiment performed at ambient pressure.

According to classical theory of nucleation and crystal growth the overall crystallization rate proceeds in two steps via nucleation and crystal growth which are determined by kinetic and thermodynamic barriers that in a very simplified form are expressed as^{7,14–17}

Received: March 18, 2015

Revised: May 5, 2015

Published: May 26, 2015

$$I(T, p) = C_1 \exp\left(-\frac{\Delta G_D}{kT}\right) \exp\left(-\frac{W^*}{kT}\right) \quad (1)$$

$$U(T, p) = C_2 \exp\left(-\frac{\Delta E}{kT}\right) \left[1 - \exp\left(-\frac{\Delta G}{kT}\right)\right] \quad (2)$$

I denotes nucleation rate, U is crystal growth rate, W^* and ΔG refer to thermodynamic barriers to nucleation and crystal growth, ΔG_D and ΔE refer to kinetic free energies to nucleation and crystal growth, C_1 and C_2 are pre-exponential constants. W^* is usually discussed in the context of work required to form critical nuclei, whereas ΔG_D and ΔE are often discussed in terms of a diffusion coefficient D related to the viscosity η via Stokes–Einstein relation ($D \approx 1/\eta$). The value of the thermodynamic driving force for growth of crystals ΔG can be replaced by $\Delta\mu$.¹⁸

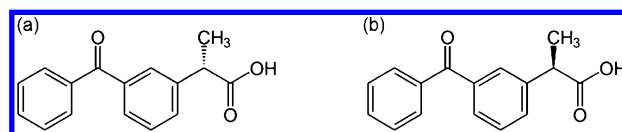
Upon lowering temperature/increasing pressure both exponential terms describing kinetic and thermodynamic driving factors exhibit completely opposite effects on the overall kinetics, which makes it very difficult to control. If the kinetic terms are coupled to the viscosity we can write $\exp\left(-\frac{\Delta G_D}{kT}\right) \propto \frac{1}{\eta}$ and $\exp\left(-\frac{\Delta E}{kT}\right) \propto \frac{1}{\eta}$. Hence, by studying crystallization along the isochrone one has an exceptional opportunity to the kinetic factor via controlling viscosity/structural relaxation time. This implies that all the changes in the crystallization rate along the isochrone must originate exclusively from the variation of the thermodynamic factors, because the kinetic barriers for nucleation and crystal growth are expected to be invariant. The second components in both equations describe thermodynamic driving force for nucleation and crystal growth. They depend on many parameters, primarily the difference in the free energy between liquid/crystalline phases and specific surface energy on the liquid/crystal interfaces. While keeping the kinetic factor under control thermodynamic forces are expected to facilitate the crystallization progress because the difference in the energy between liquid/crystalline phases increases and the specific surface energy should decrease with increasing pressure/decreasing temperature.^{12,13}

The idea of controlling the kinetic factor of the crystallization process makes sense only if (i) the viscosity (relaxation dynamics) is coupled to the diffusion, and (ii) the crystallization rate is controlled by the diffusion. For some glass-forming liquids it well established that on approaching the glass transition the Stokes–Einstein equation becomes invalidated and the self-diffusion coefficient does not follow any more the same dependence as the viscosity.¹⁹ Typically above the temperature $1.1\text{--}1.2T_g$, both quantities are coupled, and in this temperature region we have carried out our crystallization studies. However, it is completely unknown if this empirical relation also holds on increased pressure. For the purposes of our studies we assume that pressure does not modify significantly the relationship between viscosity and the self-diffusion coefficient. However, one should also be aware that under compression a decoupling might occur or intensify, as happens sometimes with the viscosity and structural relaxation,²⁰ or conductivity and the structural relaxation.²¹

For almost all liquids where the crystallization behavior was tested along isochrones, we have observed the ease of crystallization tendency with subsequent compression.^{12, 22} The only one exception from this empirical finding was reported for pharmaceutical drug, ibuprofen,²³ which reveals

greater resistivity against crystallization with increasing pressure and temperature along an isochrone. Formerly this was believed to be a very promising finding, opening a novel route of producing extraordinary stable glassy pharmaceuticals.²⁴ However, the peculiar behavior of ibuprofen under pressure could not be explained in the same way as for other glass forming materials, and these point to something else that could also affect crystallization behavior. Since commercially available ibuprofen is a racemate, i.e., it contains equimolar mixture of optical isomers (enantiomers), whereas the other studied molecular liquids do not, this leads naturally to questioning the effect of chirality. The aim of this work is to shed some light on the crystallization behavior of pure enantiomers and their binary mixtures under pressure. For the present studies we have selected a chiral compound, ketoprofen, having a very similar molecular backbone as ibuprofen (see Scheme 1). Ketoprofen

Scheme 1. Chemical Structure of Ketoprofen (a) S-Enantiomer and (b) R-Enantiomer^a



^aTheir equimolar mixture is called a racemate.

is widespread nonsteroidal anti-inflammatory drug with analgesic effect. It is available on the market in the form of racemic mixture, although its biological activity results only from S-enantiomer.²⁵ Herein, isochronal crystallization studies were carried out in the supercooled liquid state of racemic (1:1 ratio of R- and S-isomers) and enantiopure S-isomer. The obtained results emphasize the difference between the crystallization behavior of single enantiomers and their racemic mixture helping to improve our understanding of the possible way of evolving crystallization progress for various molecular systems under compression. The dielectric relaxation studies were carried out only for RS-ketoprofen, however, in a wide range of temperature and pressure.

II. MATERIALS AND METHODS

Materials. Racemic ketoprofen ((R,S)-2-(3-benzoylphenyl)-propionic acid, purity >98%) and S-enantiomer ((S)-2-(3-benzoylphenyl)-propionic acid, purity >99%) were purchased from Sigma-Aldrich and used as received. Both starting materials were completely crystalline with melting points at around 93.5 and 75 °C, respectively. According to the definition enantiomers are defined to be optical isomers with no difference in chemical and physical properties. However, they can differ in many features including biological activity.^{26,27} A laboratory polarimeter was used to verify the optical inactivity of the racemic compound (zero net rotation of plane-polarized light) and the optical activity of pure S-enantiomer before and after melting. For the crystalline form of the S-isomer the specific rotation was found to be $[\alpha]_D^{22} = +46.8$ and for the amorphous analogue $[\alpha]_D^{22} = +46.2$.

Methods. For high pressure studies we used a Unipress system (Institute of High Pressure Physics, Polish Academy of Sciences) connected to an impedance analyzer (Novocontrol GmbH) with a homemade flat parallel capacitor (20 mm diameter, gap 0.07 mm). The pressure was generated by a manual pump and transmitted with the use of nonpolar silicon oil via systems of capillars (Nova Swiss) to high pressure vessel. For temperature stabilization we use thermal bath (Julabo) connected to a heating jacket on the pressure chamber. Pressure was measured by tensometric pressure meter (resolution ± 0.1 MPa) and temperature by a platinum resistor (PT-100) placed inside the pressure chamber (accuracy ± 0.1 K) using a Keithley 195A

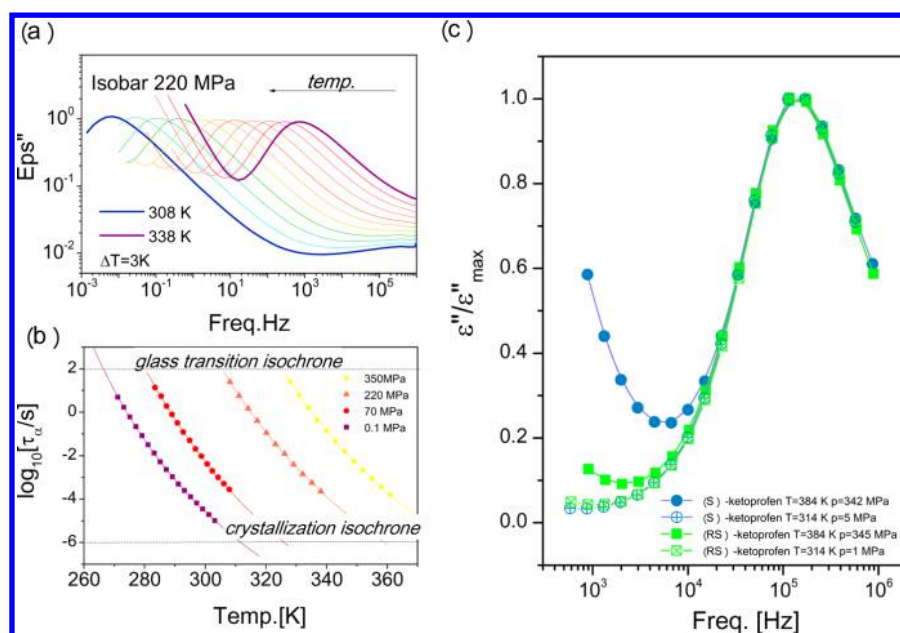


Figure 1. (a) Dielectric spectra for RS-ketoprofen measured upon cooling from 338 to 308 K at 220 MPa in the step of 3 K. (b) The temperature dependence of the α -relaxation times for racemic ketoprofen measured under various isobaric conditions as indicated. Isobaric data were fitted with the VFT equation. The dashed lines indicate isochrones corresponding to the glass transition ($\tau_\alpha = 100$ s) and crystallization conditions ($\tau_\alpha = 10^{-6}$ s), respectively. (c) Comparison of the dielectric loss spectra for RS- and S-ketoprofen measured at various thermodynamic conditions along same isochrone $\tau_\alpha = 10^{-6}$ ($\pm 1 \times 10^{-7}$) s.

multimeter. The details of the pressure setup for dielectric studies can be found in ref 1. The procedure of preparing (RS) and (S) samples for high pressure studies was exactly the same in both cases and consists of the following steps. The crystalline material was melted at ambient pressure and cooled down to the temperature ~ 20 K above T_g . The dielectric cell was filled after melting and transferred to the high pressure vessel which was held at the same temperature. Teflon was used to separate the sample from the pressure transmitting silicon oil.

The crystallization kinetics studies were carried out for different combinations of temperature and pressure while keeping the structural relaxation time constant. The time-dependent changes in the amplitude of the dielectric signal were used to track the crystallization progress. To ensure the most reliable comparison between data coming from various conditions and samples, the same experimental environment and capacitor were used. Each time after finishing crystallization at a selected (T_c, p_c) condition the sample was removed and prepared all over again for the next isochronal measurement. The desired thermodynamic conditions were reached by adjusting temperature and pressure, however, always remaining in the supercooled regime and following the same path. This one has involved increasing pressure first and then heating the sample and repeating this procedure in a few steps until the final stage was reached. Each crystallization kinetics experiment was performed twice to ensure reproducibility. Crystallization times were determined with the precision of $\pm 2h$ and $\pm 4h$ for S-ketoprofen and RS-ketoprofen, respectively. To avoid impractically long crystallization times, isochrones with $\tau_\alpha \approx 10^{-6}$ s were selected. This was achieved by carrying out a number of trial measurements before the exact crystallization kinetics studies were performed. Spectra were recorded with a very lapse of 60 s within the same frequency range, which ensured that the changes in the crystallization rate are not affected by the time of a single measurement.

III. RESULTS AND DISCUSSION

On the T, p phase diagram, the isochrone is defined as a curve along which all points have exactly the same structural relaxation time (i.e., the time scale of cooperative molecular motions). Herein, it is worth remembering that viscosity

controls structural relaxation; therefore typically the same structural relaxation time corresponds to the same viscosity. In order to control the mobility factor upon the crystallization progress, it is necessary to find isochronal states, and this typically involves molecular dynamics studies. Therefore, dielectric relaxation measurements were performed at various combinations of temperature and pressure to extract the most important features of the α -relaxation dynamics on approaching the glassy state. Here, we have conducted dielectric studies along the following isobars $p = 0.1, 70, 220,$ and 350 MPa, and isotherms $T = 282, 308,$ and 338 K. Representative dielectric loss spectra measured for racemic ketoprofen (RS) in the frequency range from 10^{-2} Hz to 10^6 Hz and pressure $p = 220$ MPa are shown in Figure 1a. On lowering temperature the characteristic peak systematically shifts toward lower frequencies indicating slowing down of the structural relaxation. From the frequency corresponding to its maximum, the characteristic relaxation time was determined and plotted versus temperature as demonstrated in Figure 1b. Similar procedures were also applied for isothermal data, as shown in Figure S1 in the Supporting Information. The temperature dependence of τ_α were then fitted with the use of VFT formula $\tau = \tau_\infty \exp[B/(T - T_0)]$,²⁸ whereas isothermal pressure dependence with the use of its pressure counterpart $\tau = \tau_\infty \exp[D_p P/(P_0 - P)]$.²⁹ By extrapolating the temperature and pressure dependences of the structural relaxation times to 100 s, the glass transition points T_g and p_g were identified, respectively. The value of the glass transition temperature determined for racemic ketoprofen at ambient pressure ($T = 266.5$ K) correlates very well with previously published dielectric data by Sailaja et al. ($T = 267$ K)³⁰ and heat capacity data by Shibata et al. ($T = 266$ K)³¹. The pressure coefficient of the glass-transition temperature was found to be $dT_g/dp = 0.200$ K/MPa (see Figure S2a in the Supporting Information.). Similarly as for other non-hydrogen bonding liquids the isobaric fragility m ³² decreases slightly with

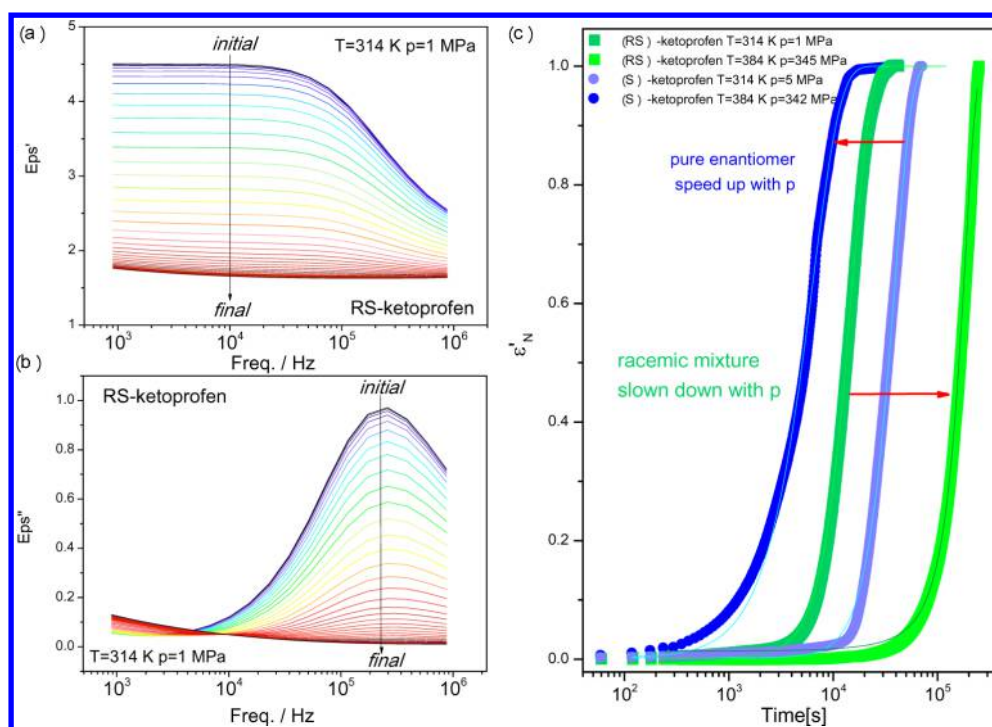


Figure 2. Time-dependent changes in the real (a) and (b) imaginary parts of complex dielectric permittivity upon crystallization of RS-ketoprofen at $T = 314$ K and $p = 1$ MPa. (c) Comparison of the time evolution of ϵ'_N for racemic and nonracemic ketoprofen at different (T, p) combinations located on the same isochrone. Solid lines are Avrami fits.

increasing pressure from 76 at 0.1 MPa to 72 at 350 MPa, and the activation volume increases with lowering temperature from $160 \text{ cm}^3/\text{mol}$ at 338 K to $244 \text{ cm}^3/\text{mol}$ at 282 K. Figures showing their pressure dependences are shown in Figure S2 in the Supporting Information.

Figure 1c shows comparison between the shape of α -relaxation for ketoprofen in racemic form and the single enantiomer at various thermodynamic conditions but with the same peak frequency (with same relaxation time). Temperature and pressure invariance of the α relaxation indicates validity of isochronal superposition for both materials and enables us to follow crystallization progress along the same isochrone. It is worth pointing out that although the single isomer and racemic mixture differ significantly in the values of the melting point (almost 20 K), their dynamics in the supercooled liquid state diverge only slightly. Nevertheless, to match approximately the same structural relaxation time slightly different (T, p) conditions were needed.

Having the structural relaxation dynamics in the supercooled liquid state of ketoprofen fully identified the next step of our studies has involved isochronal crystallization measurements. Both the racemic mixture and the single enantiomer were found to be very good glass formers. Generally, ketoprofen vitrifies rather easily and does not reveal significant crystallization tendencies in the supercooled liquid state, particularly close to T_g . However, it is still possible to crystallize it at higher temperatures where the driving forces toward crystallization intensify and facilitate its progress. Therefore, in order to avoid impractically long crystallization times (which can take in that case days or even weeks) our studies were carried out along the isochrone $\tau_\alpha \cong 1.10^{-6} (\pm 0.1 \times 10^{-6} \text{ s})$, i.e., about 8 decades above T_g , though still in the supercooled liquid region. The following (T, p) pairs along crystallization isochrone were considered: (314 K, 1 MPa), (323 K, 46 MPa), (343 K, 130

MPa), (383 K, 345 MPa) for racemic form, and (314 K, 5 MPa), (324 K, 41 MPa), (343 K, 126 MPa), (384 K, 342 MPa) for the S-enantiomer.

To follow the crystallization progress, dielectric spectroscopy was utilized and time-dependent changes occurring in the amplitude of the dielectric signal were recorded. In contrast to polymers, for small molecular systems like ketoprofen we can roughly imagine that the total dipole moment is associated with a molecule as whole, so changes recorded in the loss spectra during crystallization can be assumed to give equivalent information about kinetics of the crystal formation as that obtained from diffraction measurements.³³ In Figure 2a,b the time evolution of the real and imaginary parts of complex dielectric permittivity are presented. With crystallization a systematic decrease of static permittivity increment and the amplitude of the α -relaxation peak are observed. This reflects lowering the total number of actively reorienting dipoles that contribute to the relaxation process once the fraction of crystalline state systematically increases ($\Delta\epsilon \propto N\mu$). Changes occurring in the static permittivity increment were used to follow crystallization kinetics after normalization according to the following formula, $\epsilon'_N(t) = (\epsilon'_{\text{initial}} - \epsilon'(t)) / (\epsilon'_{\text{initial}} - \epsilon'_{\text{final}})$, where $\epsilon'_{\text{initial}}$ and ϵ'_{final} are initial and final values of real part of dielectric permittivity at low frequency range.

The time evolution of the $\epsilon'_N(t)$ for racemic mixture of enantiomers and pure S-enantiomer along the investigated isochrone is shown in Figure 2c. For sake of clarity, only the data from the lowest and the highest pressures are shown. As illustrated the crystallization behavior of a racemic mixture and single enantiomer at the same isochrone conditions can be completely different. For racemic mixture we have observed that all crystallization curves shift toward longer times with increasing pressure, whereas for the single enantiomer they move toward shorter times. By fitting $\epsilon'_N(t)$ data to the Avrami

equation, $\varepsilon'_N(t) = 1 - \exp(-kt^n)$, we determined the crystallization constant rate k and Avrami parameter n . It is claimed that it provides information about the rate of transformation (i.e., both nucleation and crystal growth rates, $k = Ig^{n-1}$), whereas n probably depends on the growth mechanisms and on the crystal shape.³⁴ These fits are shown as solid lines in Figure 2c. For longer crystallization time we have observed that Avrami fits deviates slightly from empirical data (i.e., they show slower increase in crystallinity). This is frequently observed and usually attributed to the secondary crystallization and crystal perfection at the late stage.

Variation of the overall crystallization rate and Avrami parameter for all studied (T, p) points located on the same isochrone are shown in the insets of Figure 3. As can be seen,

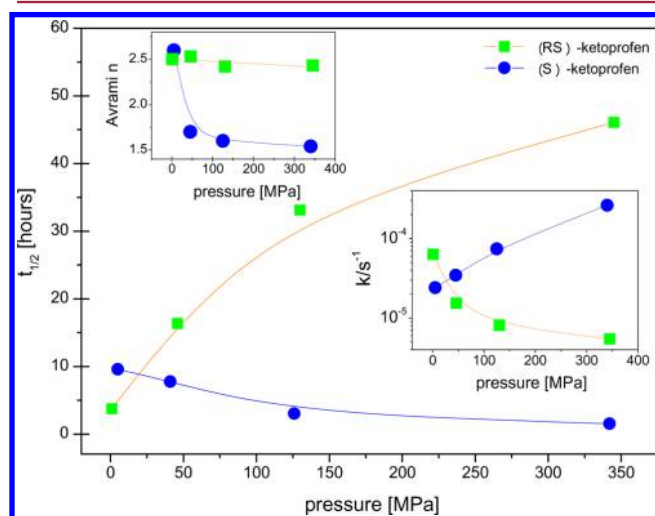


Figure 3. Pressure evolution of the crystallization half time (main), overall crystallization rate (lower inset), and Avrami parameter (upper inset) for *S*-ketoprofen and *RS*-ketoprofen crystallized along the same isochrone.

moving along isochrone toward higher pressures causes the crystallization of *RS*-ketoprofen to slow down with increasing compression, and this becomes even more straightforward when the pressure variation of crystallization half time (i.e., time after which changes in the crystallinity of the sample reaches 50%) is analyzed. As demonstrated in Figure 3, for the racemic sample maintained at 345 MPa and 384 K the half time is almost 5 times longer when compared to its ambient pressure value. Meanwhile the evolution of the Avrami exponent seems to be almost temperature- and pressure-independent (Figure 3, upper inset). On the other hand, for single *S*-enantiomer crystallization along the same isochrone speeds up with increasing pressure and half time decreases. Remarkably, crystallization tendencies of the racemic mixture and pure isomer diverge already at low pressure where crystallization from the supercooled liquid state of *RS*-ketoprofen proceeds faster ($t_{1/2} \cong 4$ h) than for its pure enantiomer ($t_{1/2} \cong 10$ h). However, with subsequent compression this trend has completely changed and crystallization of racemic mixture drastically slows (at pressure of around 345 MPa $t_{1/2} \cong 46$ h for *RS* while for the pure *S* form $t_{1/2} \cong 1.5$ h), or even halts with further compression. On the other hand it is worth to point out that relative changes in the crystallization rate along isochrones are in fact considerably smaller than changes in the crystallization rate along the isobar or isotherm. Meanwhile

the change in the density of the liquid along isochrone is definitely more pronounced, which was recognized based on PVT data.

In contrast to the racemic system, for a single enantiomer one can possibly expect changes in the crystallization morphology, as indicated by lowering the Avrami exponent with pressure. In some cases experimental evidence shows that different values of the Avrami parameter can correlate with different morphology of crystals or changes in the activation barrier or crystal growth.³⁵ However, because of the simplicity of that model precise elucidation the mechanism of crystal growth is highly uncertain.

On the basis of only the dielectric analysis of single enantiomers and its racemic mixture, it is unfortunately impossible to attempt in-depth insight into the origin of differences in the crystallization mechanism for single enantiomer and racemic mixture. This is left for the future, more detailed studies. Nevertheless, the observation that we have made together with appropriate literature support can be used to gain some elementary understanding of the high pressure crystallization behavior of chiral compounds.

As explained earlier, according to the theory of nucleation and crystal growth if kinetic factor is under control, crystallization will be driven solely by thermodynamic force. Indeed, this is what we have observed for other molecular liquids studied in the past. It can also explain the ease of crystal formation with increasing pressure for *S*-ketoprofen. However, such argumentation fails to justify increasing crystallization time for a racemic system under pressure, which as we presume must be related to the fact that racemate is a mixture of two “kinds” of molecules, not a single one. So in that case another aspect must be taken into account, i.e., possibility of spontaneous separation of enantiomers from racemate as the effect of crystallization on increased pressure. As speculated by Jacques, Collet and Wilen³⁶ at certain thermodynamic conditions for those systems which invalidate the Wallach rule³⁷ a more densely packed structure of individual enantiomers might become suddenly more preferable than their racemate. As a consequence, by the application of pressure it is possible to invoke spontaneous enantiomers resolution meaning that instead of racemate crystals the one’s characteristic for separate enantiomers would appear. In the past few years such a scenario was hotly discussed for the *DL*-mandelic acid system because the pure enantiomer appears to have greater density than the racemic form.³⁸ Unfortunately, there is still lack of convincing experimental proof of that hypothesis since crystallization from the aqueous solutions revealed only transformations between polymorphic forms of racemates which at high pressure are more preferable than at ambient conditions.^{39,40} Greater stability of racemate at a positive range of pressures was anticipated by Rietveld and co-workers⁴¹ for ibuprofen; nevertheless the polymorphism scenario cannot be excluded here. On the other hand, pressure-induced preferential crystallization of racemate and enantiomers seems to be more intriguing for ketoprofen, particularly in the context of Gonnade et al.’s findings who demonstrated that racemic ketoprofen displays appropriate polymorphism and can be spontaneously resolved into the two enantiomers by crystallization under nonequilibrium conditions.⁴² However, an open question remains here if the same effect can be obtained by high pressure crystallization from the metastable supercooled liquid state, and whether the eutectic equilibrium between the

racemate and S-enantiomer follows the same lines as their melting transitions.

IV. CONCLUSION

In order to get complete overview on the molecular dynamics and crystallization behavior of glass forming liquids, not only temperature-dependent but also pressure-dependent studies are needed. This can be a very challenging task particularly without a thought-out protocol. Therefore, a bit better understanding of the crystallization tendencies of supercooled liquids at varying conditions can be given by the isochronal approach. As demonstrated in this contribution compression exerts a completely different effect on the crystallization behavior of racemic ketoprofen and its single enantiomer studied at different (T, p) points located along the same isochrone. It was found that pressure facilitates crystal formation for a single enantiomer of ketoprofen and slows down the crystallization progress for a racemic mixture of enantiomers. Slowing down of the crystallization tendencies for racemic mixtures with increasing pressure seems to be not a coincidence as it is also reported previously for RS-ibuprofen.

The problem of physicochemical stability of racemic compounds on increased pressure is an intriguing topic, though very poorly realized. For example, it is completely unknown if (or how) pressure changes the affinity of enantiomers for each other and whether the same behavior for a racemic mixture can be observed for a 1:1 ratio physical mixture (separate R and S enantiomers mixed together). Therefore, a more detailed investigation is needed in the future to understand the effect of pressure on the crystallization behavior of racemates, but probably also in more general the impact of pressure on the crystallization of eutectic compositions. Finally, the observation from previous and current studies is that pressure influences crystallization behavior of glass forming liquids. This can be either slowing down or speeding up crystallization progress along the isochrone. However, we wish to mention that relative changes in the crystallization rate along the isochrone are in fact considerably smaller than corresponding changes in the crystallization rate along the isobar or isotherm, which indicates that the mobility factor has in fact an important role in controlling the crystallization rate.

■ ASSOCIATED CONTENT

Supporting Information

Results of dielectric relaxation studies measured on increased pressure for racemic ketoprofen. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.5b00373.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kadrjano@us.edu.pl. Present address: DNRFCentre "Glass and Time", IMFUFA, Department of Sciences, Roskilde University, Postbox 260, DK-4000 Roskilde, Denmark.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is primarily supported by the Polish National Science Centre (Grant No. DEC-2012/05/B/NZ7/03233). Authors wish to thank Dr. Lukasz Popena from NanoBioMedical Centre (Adam Mickiewicz University) and Dr. Blazej Graczyk

from Department of Chemistry (Adam Mickiewicz University) for polarimetry measurements. K.A would like to also give special thanks to Dr. Marek Kempka (Department of Physics, Adam Mickiewicz University) for his immeasurable support in conducting high pressure experiments.

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