Anomalous Electrical Conductivity Behavior at Elevated Pressure in the Protic Ionic Liquid Procainamide Hydrochloride

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Anomalous electrical conductivity behavior at elevated pressure in the protic ionic liquid, procainamide hydrochloride

Z. Wojnarowska[1], C. M. Roland[2], A. Swiety-Pospiech[1], K. Grzybowska[1] and M. Paluch[1]

[1]*Institute of Physics, Silesian University, ul. Uniwersytecka 4, 40-007 Katowice, Poland*

[2]*Naval Research Laboratory, Chemistry Division, Code 6120, Washington DC 20375-5342, USA*

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ABSTRACT Using broadband dielectric spectroscopy we investigated the effect of hydrostatic pressure on the conductivity relaxation time, τ_σ, of the supercooled protic ionic liquid, procainamide hydrochloride, a common pharmaceutical. The pressure dependence of τ_σ exhibited anomalous behavior in the vicinity of the glass transition T_g, manifested by abrupt changes in activation volume. This peculiar behavior, paralleling the change in temperature dependence of τ_σ near T_g, is a manifestation of the decoupling between electrical conductivity and structural relaxation. Although the latter effectively ceases in the glassy state, free ions retain their mobility but with a reduced sensitivity to thermodynamic changes. This is the first observation of decoupling of ion migration from structural relaxation in a glassy conductor by isothermal densification.

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The morphology, solubility, wettability, and other properties of drugs and their carriers depend on the physical form, so modification of the latter offers a means to regulate bioavailability and pharmaceutical performance. Although most pharmaceutical materials are crystalline, the amorphous glass is the highest energy state and thus able to provide solubility advantages. However, "supercooled" materials are metastable and susceptible to chemical or physical changes, such as crystallization. These changes are governed largely by the molecular mobility, which means that exploiting amorphous drug systems entails understanding glass formation and the dynamic properties of the materials near and below their glass transition temperature, T_g. This is a complex topic, since pharmaceuticals are organic compounds with complex molecular structures, extensive hydrogen bonding, and a variety of conformational states. A number of methods can be utilized to stabilize the amorphous, glassy state, including additives that bind nucleating sites, chemical reaction of the material, and anti-plasticization (i.e., raising T_g).

In this work we focus on the effect of the thermodynamic variables temperature and pressure on the dynamic properties of procainamide hydrochloride, a salt used pharmaceutically as a cardiac depressant. The drug can be injected as an aqueous solution or, more typically, delivered orally by tablet or capsule in crystalline form. The melting point of procainamide hydrochloride is 442K [1]; however, it can be readily quenched into the amorphous state. The present study describes dielectric relaxation measurements of the glassy material. We characterize the translational mobility of (primarily) the chloride ions, which transpires on a time scale almost three orders of magnitude faster than the structural relaxation process. The latter involves molecular rearrangements that are largely frozen out in the glassy state. Although diffusion of ions is usually coupled to rotations of the host molecules, on approach to the glass transition the proportionality of the respective time constants is lost, with the former enhanced relative to the reorientational motions [2,3,4,5,6,7,8]. In this work we show the further disconnect between the two dynamics as the glass transition is traversed. This effect is well known on cooling glassy ionic conductors, the prototypical example being CKN [9,10,11]. We report herein the qualitatively same effect induced by increasing the pressure, the first demonstration of this strong decoupling under isothermal conditions; that is, when vitrification is induced solely by densification. Below T_g displacement of mobile ions continues but with a

markedly weaker sensitivity to thermodynamic variables. This decrease of both the activation energy and activation volume is a consequence of the freezing out of translational and rotational motions of the procainamide hydrochloride, which inhibits ion migration and increases the bulk modulus of the material. Possible changes in the dissociation equilibrium of the procainamide hydrochloride, which would affect the concentration of free ions and thus the conductivity, is an ancillary factor in the observed behavior.

The conductivity relaxation data were measured using a Novocontrol Alpha analyzer. High-pressure experiments utilized a Unipress system, with a custom flat parallel capacitor. A detailed description of the equipment can be found in ref. [12]. Temperature-modulated differential scanning calorimetry (TMDSC) was also implemented with a Mettler-Toledo TOPEM, to analyze the dynamic behavior of the sample in the frequency range from 4mHz to 400 mHz in a measurement using a heating rate of 1K/min. The procainamide hydrochloride was obtained from Aldrich Chemicals and used as received.

Figure 1 shows the electric modulus spectra at ambient pressure at various temperatures (upper) and at fixed $T = 333$K at various pressures (lower). The (complex) modulus function, $M^* = 1/\varepsilon^*$ where ε^* is the complex permittivity, is employed herein to emphasize the dc conductivity contribution [13,14]. (This is distinct from the higher frequency ac conductivity, which in addition to ion diffusion can include non-relaxing, subdiffusive processes, such as local excursions and vibrations of the ions within a cage of the host molecules.) The frequencies of the maximum in the M'' peak, f_{max}, all fall several decades higher than the frequency at which the real and imaginary components of the dielectric permittivity are equal, indicating these peaks, from migration of charge carriers, are intrinsic to procainamide and not artifactual (not due to grain boundaries or other dielectric heterogeneities within the material). The peak breadth increases slightly with increasing temperature, by about a quarter decade over the range of temperatures in the figure. Such insensitivity to temperature is common to glassy ionic conductors [9,10,13]. The dispersion can be fitted to the Kohlrausch function, yielding a stretch exponent $\beta_K = 0.64$ (Figure 2), which falls in the middle of the range reported for various pharmaceuticals, $0.46 < \beta_K < 0.80$ [15]. The breadth of the structural relaxation dispersion is known to correlate with many properties [16], possibly including the crystallization rate [17].

f_{max} shows the usual decrease with decreasing T or increasing P. However, for peak frequencies less than about 1 Hz, these dependences become much weaker; that is, a decrease is observed in both the apparent activation energy, E_{act} (from values in the range 150 - 350 kJ/mol at higher T to about 75 kJ/mol at low T) and activation volume, $\Delta V^{\#}$ (from 101±3 ml/mole at low pressures to 48±3 ml/mole at high pressure). This behavior, illustrated in Figures 3 and 4 respectively, reflects vitrification of the procainamide hydrochloride, since under these conditions the molecular relaxation times become very long compared to the diffusional times of the chloride ion. The decoupling of the conductivity and structural relaxation in the vicinity of the glass transition is illustrated in Fig. 3, with the structural relaxation times determined from the temperature dependences of the real part of the complex heat capacity c_p' measured by TMDSC. It is seen that the conductivity is more than 100-fold faster than structural relaxation (τ_α=38s and τ_σ=0.1s at the calorimetric T_g). This effect is not related to crystallization, as evidenced by the glass transition at 316K (Fig. 3 inset) and the absence of crystallization during heating over the temperature range of the dielectric measurements.

Such rotational-translation decoupling is known to occur in liquids near their glass transition. Angell [18] has shown that the magnitude of the β_K measured around the glassy state correlates with the degree of decoupling of ion and structural mobilities. In the present case the ion diffusion is enhanced near T_g by almost 3 orders of magnitude in comparison to the host dynamics. This change in temperature-dependence of ion translation has been seen previously in molten salts and related compounds [9,15,19]. The behavior is caused by the freezing of the structure below T_g, so that temperature changes primarily alter only the thermal energy of the diffusants. Ion migration proceeds via a thermally activated, hopping mechanism, with no mitigation of local barriers through reorientation of the host species. The weaker effect of pressure below T_g is due to its reduced effectiveness at densifying the solidified material (the bulk modulus being more than an order of magnitude larger than that of the corresponding supercooled liquid). Defining T_g as the temperature at which the activation volume changes, we obtain the pressure-dependence of T_g plotted in the inset to Figure 4.

There is a second mechanism that would give rise to different structural and ion transport behaviors. The measured conductivity is proportional to the product of the diffusivity of the ions and their concentration. As temperature is reduced, the dissociation equilibrium of the protic liquid shifts towards the salt, reducing the number of free ions. This chemical effect alters the

measured conductivity in a fashion unrelated to the dynamics *per se*. The phenomenon and its connection to perceived deviations from the Debye-Stokes-Einstein relation in supercooled ion-containing liquids have been analyzed in detail by Johari et al. [20,21]. Note that this contribution would *reduce* the conductivity herein, tending to counter the enhancement of translational motions relative to reorientations. The effect of increasing pressure on the ion concentration in procainamide hydrochloride is unknown.

Ingram and coworkers [22] have found that for various polymer electrolytes and glasses the ratio $E_{act}/\Delta V^{\#}$ is a material constant that measures the resistance to spatial separation of the constituent molecules (i.e., a local "modulus"). From the data in Figs. 3 and 4, $E_{act}/\Delta V^{\#} \approx 2$ GPa above T_g, increasing to about 4 GPa in glassy procainamide. These magnitudes and the increase for the glassy state are in accord with values reported for various organic and inorganic materials [23].

The other processes detected in the glassy procainamide are two weak secondary relaxations. Secondary motions, although localized, can be significant because of their connection to structural relaxation [16,24,25,26] and their potential role in nucleating crystallization, which affects the storage stability of a pharmaceutical [27,28,29]. The lower frequency of two secondary relaxations can be seen in Figure 2 at frequencies higher than the conductivity peak. The most probable relaxation times, taken as the inverse of $2\pi f_{max}$, are plotted in Arrhenius form in Fig. 3 for all processes in glassy procainamide at ambient pressure. The activation energies are 15 and 68 kJ/mol for the higher and lower frequency secondary relaxations, respectively. Note these E_{act} are much smaller than the T-dependent activation energy for the conductivity (shown in the inset to Fig. 3), the latter related to, if not directly coupled with, structural relaxation.

Below T_g very slow structural rearrangement occurs that brings the material towards its equilibrium state. This physical aging causes a progressive increase in the structural relaxation time, and as illustrated in Figure 5, a concomitant retardation of ion translational motions. Also seen toward higher frequencies in the spectra in Fig. 5 is a change in the intensity of the β-relaxation peak; as the material densifies during physical aging, the amplitude of this secondary process is reduced. It was recently shown that changes in the secondary relaxation due to physical aging can be used to follow the structural dynamics in the glassy state; that is, the time constant characterizing the change in β-peak height is a measure of the structural relaxation time

[24,25,30]. In the inset to Fig. 5, *M''(t)* normalized by its initial value at a fixed frequency within the β-peak is plotted versus aging time. Using the method of ref. [31] and fitting the peak, we determined the time constant for structural relaxation in the glassy state: log τ_α (s) = 4.41 at 200 MPa and 323K, which is 10 degrees below T_g. This is commensurate with the time scale of the shift of the conductivity relaxation peak due to physical aging, demonstrating the connection of the two effects.

In summary, vitrification of procainamide hydrochloride causes changes in the temperature and pressure dependences of the conductivity relaxation time. This is the first observation of decoupling of ion migration from structural relaxation in a glassy conductor induced by isothermal densification. Physical aging of the glass reduces the ion mobility, concomitant with a reduction in intensity of the secondary relaxation; thus, both quantities provide a measure of the structural relaxation in the glass, a dynamical process too slow for direct determination.

Acknowledgments

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Figure 1.

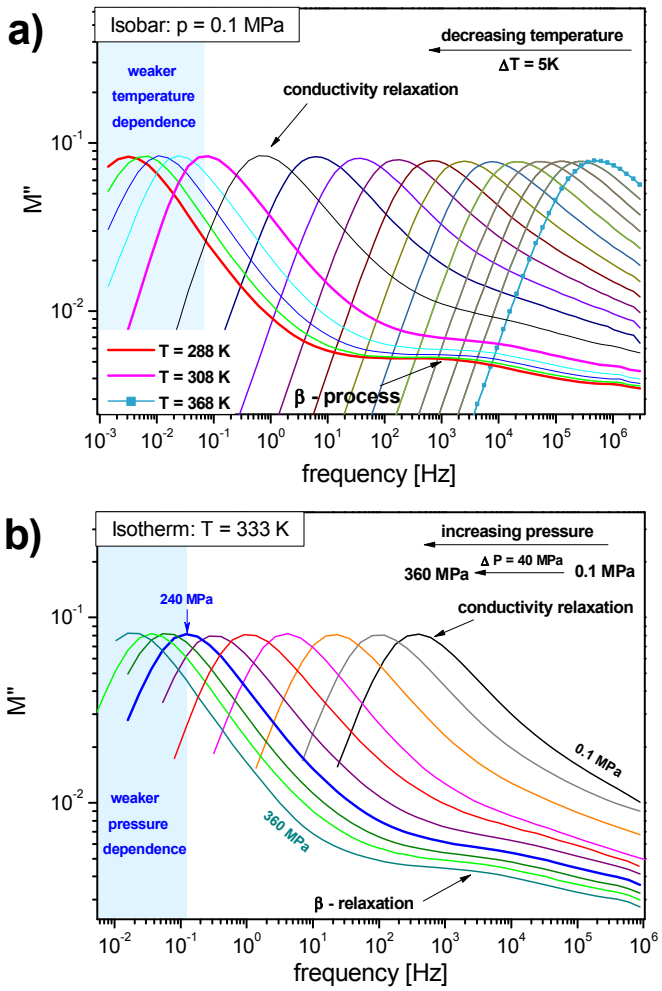
a)
Isobar: p = 0.1 MPa
decreasing temperature
ΔT = 5K
weaker
temperature
dependence
conductivity relaxation
M"
T = 288 K
T = 308 K
T = 368 K
β - process
frequency [Hz]
b)
Isotherm: T = 333 K
increasing pressure
360 MPa
Δ P = 40 MPa
0.1 MPa
240 MPa
conductivity relaxation
0.1 MPa
360 MPa
weaker
pressure
dependence
β - relaxation
M"
frequency [Hz]

Figure 2.

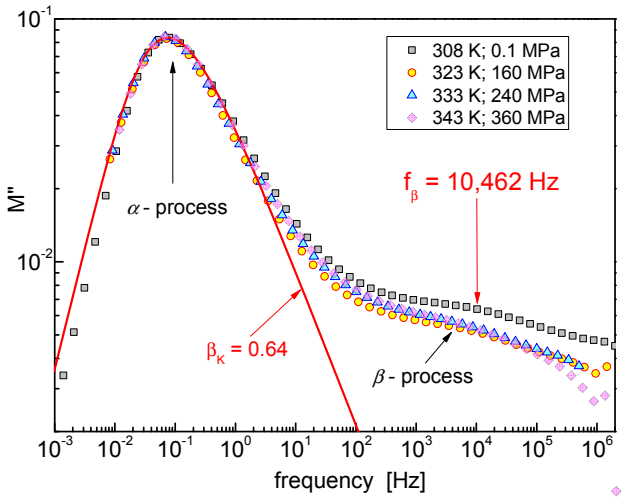

Figure 3.

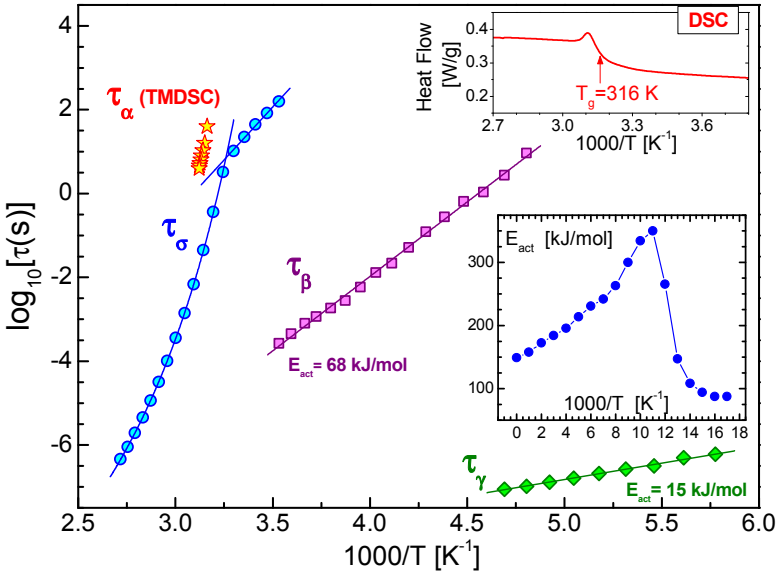

Figure 4.

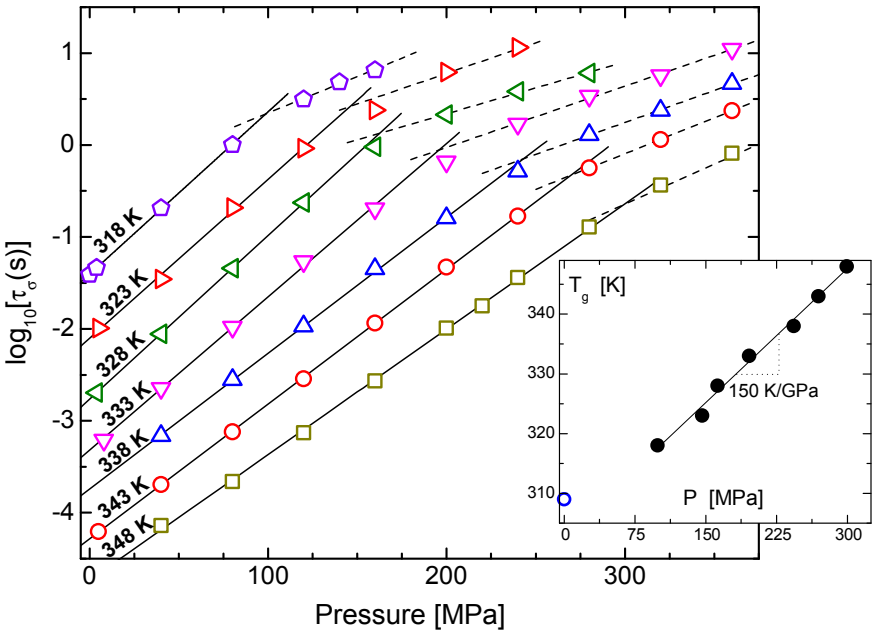
log10[τσ(s)]
Pressure [MPa]
318 K
323 K
328 K
333 K
338 K
343 K
348 K
Tg [K]
150 K/GPa
P [MPa]

Figure 5.

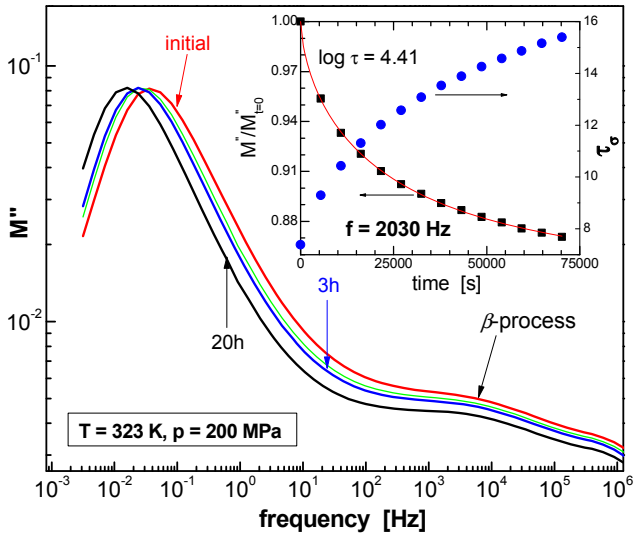
initial
3h
20h
β-process
T = 323 K, p = 200 MPa
M''
frequency [Hz]
log τ = 4.41
f = 2030 Hz
time [s]
M''/M''t=0
τσ

Figure Captions

Figure 1. Dielectric modulus spectra of procainamide HCl (a) at ambient pressure in the temperature range 288-368 K and (b) at $T = 333$ K for pressures from 0.1 to 360 MPa.

Figure 2. Comparison of dielectric spectra for different temperature and pressure combinations for which the electric modulus spectra have almost the same τ_σ. The secondary β-relaxation is seen at higher frequencies. The solid line is the fit of the Kolhrausch function to the main peak.

Figure 3. Relaxation map of procainamide hydrochloride. Circles denote conductivity relaxation times, squares and diamonds represent respectively the β- and γ-relaxation times, and stars are the structural relaxation times determined from TMDSC measurements. Solid lines are Vogel-Fulcher-Tamman (VFT) and Arrhenius fits to the data. The activation energy for the secondary relaxations is given, while that for τ_σ is plotted in the lower inset. The upper inset shows DSC measurements of procainamide hydrochloride, with $T_g = 316$ K at a heating rate of 10 K/min.

Figure 4. Conductivity relaxation time as a function of pressure at various fixed temperatures. The inset shows the temperature of the change in P-dependence (filled circles), along with the calorimetric glass transition temperature (open circle).

Figure 5. Conductivity relaxation spectra during physical aging at 323 K and 200 MPa. The inset shows the evolution of the conductivity relaxation time (circles) and the amplitude of the modulus peak at the indicated frequency (squares) during aging. The time constant for the latter, $= 2.6\times10^4$ s, is obtained from the fitted stretch exponential (solid line).