Dielectric relaxation of \(\alpha\)-tocopherol acetate (vitamin E)

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Dielectric loss spectra are reported for \(\alpha\)-tocopherol acetate (an isomer of vitamin E) in the supercooled and glassy states. The \(\alpha\)-relaxation times, \(\tau_{\alpha}\), measured over a 190° range of temperatures, \(T\), at pressures, \(P\), up to 400 MPa can be expressed as a single function of \(TV^{1.9}\) (\(V\) is specific volume, measured herein as a function of \(T\) and \(P\)). At ambient pressure, there is no dynamic crossover over eight decades of measured \(\tau_{\alpha}\). The relaxation spectra above the glass transition temperature \(T_g\) show ionic conductivity and an excess wing on the high-frequency flank of the \(\alpha\)-relaxation loss peak. Temperature-pressure superpositioning is valid for the \(\alpha\) process; moreover, the peak shape is constant (stretch exponent equal to 0.65). However, application of pressure changes the shape of the dielectric spectrum at higher frequencies due to the shift of the excess wing to form a resolved peak. Additionally, another relaxation process, absent at atmospheric pressure, emerges on the high-frequency side of the \(\alpha\)-process. We propose that this new peak reflects a more compact conformation of the \(\alpha\)-tocopherol acetate molecule. Drawing on the coupling model, the experimentally determined relaxation times, activation energy, and activation volume for the Johari-Goldstein process are compared to values calculated from the properties of the \(\alpha\) relaxation. The agreement is generally satisfactory, at least for \(T<T_g\).

I. INTRODUCTION

In recent years there has been increasing interest in dielectric relaxation measurements among pharmaceutical scientists [1–5]. Dielectric spectroscopy is an important tool for investigating the molecular mobility of vitrifying liquids, enabling observation of the dynamics of molecular dipoles over many decades of frequency. This characterization of the amorphous phase is relevant not only to manufacturing and storage, but even affects dosage through the latter’s dependence on the physical and chemical stability of the pharmaceutical.

The majority of solid drugs are utilized in the crystalline state, associated with an ordered lattice structure. The state is generally thermodynamically stable and relatively simple to study. Some pharmaceuticals are prepared in an amorphous form [6–8]. The high internal energy and specific volume of the amorphous state relative to the crystal enhances dissolution and bioavailability [9], as well as chemical reactivity [10]; these features can improve product performance. However, the physical structure of glassy materials is more difficult to characterize, affecting quality assurance. Amorphous material may also be thermodynamically unstable, with a tendency to crystallize on storage [11,12]. An understanding of the nature and characterization of the glassy state and glass transition behavior is essential to realizing the predictability and stability of amorphous pharmaceuticals necessary for their optimal utilization.

Since the amorphous state is usually thermodynamically metastable relative to the crystalline form, the potential for crystallization during handling and storage may be present. This has lead to a number of studies of this problem. Fukuoka et al. [11] and Yoshioka et al. [12] showed that crystallization can take place even below the glass transition temperature \(T_g\) in dry amorphous indomethacin (a nonsteroidal anti-inflammatory drug). Hancock et al. [13] concluded from enthalpy recovery experiments that glassy indomethacin still exhibits significant molecular mobility, leading to crystallization. Ali et al. [14] showed that the crystal growth process in SSR, a low-molecular-weight model drug compound, is controlled by intramolecular dynamics involving the \(\beta\)-relaxation mode, rather than the motions involving all atoms in the molecule responsible for the \(\alpha\) relaxation above \(T_g\). Hancock and Zografi [15] also showed that trace levels of water may plasticize the sample sufficiently to bring the \(T_g\) value below the storage temperature, whereby crystallization commences. Usually this crystallization is undesirable, so commonly a high-\(T_g\) glass former such as PVP is cosolidified to stabilize an amorphous drug by raising the \(T_g\) value in the supercooled and glassy states.

In this paper we present broadband dielectric relaxation and pressure-volume-temperature (PVT) data on \(\alpha\)-tocopherol acetate measured at ambient and at elevated pressure. \(\alpha\)-tocopherol acetate is the most biologically active of the eight isomers composing vitamin E, an essential human nutrient reputed to have anticancer properties. Recent studies have suggested this compound may induce apoptosis (arrest of uncontrolled cell proliferation) in a variety of epithelial cancer cell types [18]. The relaxation spectra at atmospheric pressure of \(\alpha\)-tocopherol acetate are similar to com-
molecular glass-forming substances, showing the structural \( \alpha \) relaxation with both an excess wing and a \( \gamma \) relaxation; however, the dielectric spectra measured for elevated pressure exhibit an additional process on the high-frequency flank of the \( \alpha \)-relaxation peak. These secondary relaxation processes can serve as a mechanism for localized nucleation and consequent crystallization \cite{19-21}; thus, their analysis is directly relevant to the use of amorphous pharmaceuticals. One result of the appearance of secondary relaxations at elevated pressure is a breakdown of temperature-pressure superposition of the structural \( \alpha \)-relaxation peak; that is, while recent studies have shown that at a fixed value of \( \tau_\alpha \) (representing widely different combinations of temperature and pressure), the \( \alpha \) peak for most glass formers is constant \cite{22,23}, in the case of \( \alpha \)-tocopherol acetate, the emergence of a new relaxation process, obscured at low pressure, changes the apparent shape of this relaxation peak.

II. EXPERIMENTAL

The \( \alpha \)-tocopherol acetate, purchased from Merck and used as received, has the chemical structure shown in Fig. 1. Ambient pressure measurements were performed in the frequency range from \( 10^{-2} \) to \( 10^6 \) Hz using a Novocontrol Alpha dielectric spectrometer, with the sample in a parallel plate cell (diameter 20 mm, gap 0.1 mm). Temperature control of better than 0.1 K was achieved using a dry-nitrogen thermostated flow. For the high-pressure measurements the capacitor filled with the test material was placed in the high-pressure chamber and compressed using silicone fluid via a piston in contact with a hydraulic press (SITEC). The sample capacitor was sealed and mounted inside a Teflon ring to separate it from the silicone oil. Pressure was measured by a Nova Swiss tensometric meter (resolution \( \sim 0.1 \) MPa) and temperature controlled to 0.1 K by means of liquid flow from a thermostatic bath. PVT measurements were carried out with a Gnomix apparatus, with volume changes determined isothermally from 10 to 200 MPa over a temperature range from 300 to 360 K. The data were converted to specific volumes, \( V \), using the value of \( V \) measured for ambient conditions with a pycnometer. A TA Instrument Q100 with liquid nitrogen cooling was employed for scanning calorimetry at 10 K/min.

III. RESULTS AND DISCUSSION

A. Ambient pressure

From cooling at 10 K/min, the calorimetric glass transition temperature of \( \alpha \)-tocopherol acetate is 223 K.

![FIG. 1. Chemical structure of \( \alpha \)-tocopherol acetate, the most biologically active isomer of vitamin E.](image)

![FIG. 2. (Color online) Dielectric loss curves for \( \alpha \)-tocopherol acetate at the indicated temperatures and ambient pressure.](image)

Representative dielectric loss spectra measured above \( T_g \) and at 0.1 MPa are shown in Fig. 2. There is a dc conductivity from mobile ionic contaminants and the prominent \( \alpha \) peak (structural relaxation), both spectral features moving toward lower frequencies as \( T \) decreases. The shape of the \( \alpha \) peak is essentially invariant to temperature. In Fig. 3, three spectra measured below \( T_g \) have been shifted along the frequency axis, superposing with the spectra for 235 K (although the overlap is primarily on the high-frequency side). We fit these superimposed peaks to the one-sided Fourier transform of the Kohlrausch-Williams-Watts (KWW) function \cite{24,25},

\[
\phi(t) = \exp\left(-\frac{t}{\tau_{KWW}}^{\beta_{KWW}}\right), \quad 0 < \beta_{KWW} \leq 1
\]

with the best-fit stretch exponent \( \beta_{KWW} = 0.65 \). A deviation of the fit is noted on the high-frequency side of the \( \alpha \) peak; this

![FIG. 3. (Color online) Ambient pressure dielectric loss spectra shifted along the abscissa to superpose the high-frequency side of the \( \alpha \) peak. The solid line is the fit to the transform of Eq. (1), with \( \beta_{KWW} = 0.65 \). In the inset are the same spectra as measured; the arrows denote the frequencies of the JG relaxation \((= 1/2 \pi T_g)\) calculated from Eq. (2).](image)
extra loss is the well-known excess wing of the structural relaxation. Various experiments including high-pressure measurements [26,27], physical aging [28,29], and mixtures with another glass former [30] have all shown unambiguously that the excess wing is the Johari-Goldstein (JG) secondary relaxation [31,32]. The JG relaxation is a specific secondary process having intermolecular character and seeming to serve as the precursor to the α relaxation [26]; thus, it has an important role in vitrification. When the JG relaxation time, \( \tau_{JG} \), is close to the calorimetric glass transition of 223 K, the excess wing is the Johari-Goldstein (JG) process, which makes explicit that the separation in frequency of the JG relaxation, which we refer to as the secondary relaxation, is on the order of the symbol size.

To verify that the properties of the excess wing in \( \alpha \)-tocopherol acetate are consistent with those of a JG relaxation, we apply the coupling model (CM) [33] to calculate \( \tau_{JG} \) from the values of \( \tau_{\alpha} \) and \( \beta_{KWW} \) for the \( \alpha \) relaxation using [26,34].

\[
\tau_{JG}(T, P) = \tau_{\alpha}^{1-\beta_{KWW}} \tau_{\alpha}(T, P)^{\beta_{KWW}},
\]

(2)

where \( \tau_{\alpha} = 2 \text{ ps} \) for molecular and polymeric glass formers [35]. These calculated JG relaxation times are shown in the inset to Fig. 3 (indicated by arrows corresponding to \( (2 \pi \tau_{JG})^{-1} \)). The frequencies of the JG relaxation predicted by Eq. (2) fall within the vicinity of the (broad) excess wing, supporting the identification of the latter as an unresolved JG process. Equation (2) can be rewritten as [36]

\[
\Delta = (1 - \beta_{KWW}) (\log \tau_{\alpha} + 11.7),
\]

(3)

which makes explicit that the separation in frequency of the \( \alpha \) and JG peaks, \( \Delta \), is governed (inversely) by the magnitude of \( \beta_{KWW} \); that is, larger \( \Delta \) for broader \( \alpha \) peaks. Similar behavior is seen with eugenol (\( \beta_{KWW} = 0.68 \)), isoeugenol (\( \beta_{KWW} = 0.62 \)) [37], dioctyl phthalate (\( \beta_{KWW} = 0.65 \)) [38], and tripropylene glycol (\( \beta_{KWW} = 0.63 \)) [39]. All have narrow \( \alpha \) dispersions (\( \beta_{KWW} > 0.6 \)) and thus exhibit an excess wing rather than a distinct, resolved secondary peak.

Although structural relaxation is arrested at the glass transition, the JG process exhibits activated behavior below \( T_g \), giving rise to greater separation between the two peaks. This is shown in the loss spectra measured for \( T < T_g \) (Fig. 4). With decreasing temperature, the excess wing becomes resolved as a distinct peak. At low temperatures another secondary relaxation, which we refer to as the \( \delta \) process, appears at higher frequencies. This presumably is due to pendant group (intramolecularly correlated) motion.

Figure 5 shows the relaxation map for \( \alpha \)-tocopherol acetate. The structural relaxation times can be described over the entire measured range with a single Vogel-Fulcher-Tamman-Hesse equation [40–42]

\[
\tau_{\alpha}(T) = \tau_{\alpha,0} \exp \left( \frac{DT_{\alpha}}{T - T_0} \right)
\]

(4)

with \( \tau_{\alpha,0} = 2.40 \times 10^{-13} \text{ s}, D = 773, \) and \( T_0 = 173 \text{ K}. \) There is no evidence of a change in dynamics (“dynamic crossover”) [43–45] over the more than eight decades of \( \tau_{\alpha} \). A modest extrapolation of the data using Eq. (4) yields \( T_g = 226 \text{ K} \), defined as the temperature at which \( \tau_{\alpha} \) equals 100 s. This close to the calorimetric glass transition of 223 K. The steepness or “fragility” index \( \left( = d \log \tau_{\alpha} / d(T_g/T) \right) \) reflecting the rapidity of the change of \( \tau_{\alpha} \) in the supercooled regime, is equal to 63. Thus, \( \alpha \)-tocopherol acetate is an intermediate glass former, although the narrowness of its \( \alpha \) peak (\( \beta_{KWW} = 0.65 \)) is more in accord with that of strong liquids [46].

To describe the two secondary peaks, the loss spectra below \( T_g \) were fit to a superposition of two Cole-Cole functions [47]. For both processes, the obtained relaxation times exhibit Arrhenius behavior (Fig. 5). For the \( \delta \) relaxation, the prefactor \( \tau_{\alpha,0} = 3 \times 10^{-11} \text{ s} \) and \( E_{\delta} = 17 \pm 2 \text{ kJ/mol} \); the small activation energy is consistent with motion of only some atoms in the \( \alpha \)-tocopherol acetate molecule. For the JG relaxation, \( \tau_{JG} = 4.9 \times 10^{-14} \text{ s} \) and the activation energy \( E_{JG} = 39.7 \pm 0.6 \text{ kJ/mol} \). Various proposals have been made relating the magnitude of the JG activation energy to prop-

\[
FIG. 4. (Color online) The frequency dependence of the dielectric loss \( \varepsilon'' \) at five temperatures below \( T_g \).
\]

\[
FIG. 5. (Color online) Arrhenius plot of the relaxation times for the \( \alpha \) (squares), JG (circles), and \( \delta \) process (triangles). Stars represent \( \tau_{JG} \) for the liquid state calculated using Eq. (2) with \( \beta_{KWW} = 0.65 \). Dashed line is the fit of \( \tau_{\alpha} \) to Eq. (4), while solid lines are linear fits of the secondary relaxation data. The uncertainty in the secondary relaxation times is on the order of the symbol size.
\]
properties of the \( \alpha \) relaxation. According to the CM [48,49] the ratio of the respective activation energies for \( \tau_B \) and \( \tau_\alpha \) should equal the value of \( \beta_{KWW} \) describing the \( \alpha \) peak,

\[
E_{\alpha} = E_{\alpha} \times \beta_{KWW}.
\]  

This equation follows directly from Eq. (2). The activation energy of the \( \alpha \)-process is non-Arrhenius, but at \( T_g \) we obtain from Eq. (4) an apparent \( E_a = 270 \) kJ/mol. Equation (5) then gives a predicted value of \( E_{\alpha} \) that is more than a factor of 4 larger than the experimental result for the glassy state. Consistent with this result, \( \tau_{\alpha} \) calculated from Eq. (2) for \( T > T_g \) (shown in Fig. 5) exhibits a substantially steeper Arrhenius slope than the JG relaxation times measured for \( T < T_g \). The calculated JG relaxation times are also larger in magnitude than the experimental \( \tau_{\alpha} \), and by an amount exceeding the uncertainties (which are ca. 50% or less).

A related CM prediction for \( \tau_{\alpha} \) in the glassy state is [50]

\[
E_{\alpha} = 2.303RT_g(13.7\beta_{KWW} - \log_{10} \tau_{\alpha,JG} - 11.7),
\]  

which overestimates the experimental \( E_{\alpha} \) for \( T < T_g \) by 13%. These various results are collected in Table I. Although the value from Eq. (5) for the liquid is not accurate, both Eqs. (6) and (7) yield \( E_{\alpha} \) that are close to the JG activation energy measured for the glass. It is known that in the vicinity of \( T_g \) JG relaxation times become more sensitive to temperature [52–55]; for sorbitol and xylitol, for example, the activation energy for \( \tau_\alpha \) above \( T_g \) is \( \sim 40\% \) larger than \( E_{JG} \) in the glassy state [52]. This may account for some of the difference between the predictions of Eqs. (5) and (6).

**Table I. Activation energy for \( \tau_{\alpha} \).**

<table>
<thead>
<tr>
<th></th>
<th>Experimental ((T&lt;T_g))</th>
<th>Eq. (5) ((T=T_g))</th>
<th>Eq. (7) ((T&lt;T_g))</th>
<th>Eq. (6) ((T&lt;T_g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_{\alpha} ) (kJ/mol)</td>
<td>39.7 ( \pm ) 0.6</td>
<td>175</td>
<td>45</td>
<td>46</td>
</tr>
</tbody>
</table>

B. Elevated pressure

Dielectric measurements were carried out for elevated pressures at \( T = 298 \) and 253 K, with representative spectra shown in Fig. 6. In addition to the usual shift of the relaxations toward lower frequencies with increasing \( P \), a new process (which we designate the \( \beta' \) peak) appears on the high-frequency side of the \( \alpha \) peak. As a result, ambient and elevated pressure spectra obtained at respective temperatures such that \( \tau_\alpha \) is constant (Fig. 7) do not superpose. This breakdown of superpositioning is at odds with the usual result that the frequency dispersion of the \( \alpha \) relaxation together with the excess wing are invariant for widely different combinations of \( P \) and \( T \), provided the \( \alpha \)-peak frequency does not change [22,23]. However, this absence of superpositioning for

\[
\alpha-\text{tocopherol acetate is due to the pressure-induced emergence of a new relaxation peak.}
\]

As seen in Fig. 6, the relaxation time of this \( \beta' \) process is insensitive to pressure. The peak amplitude decreases with pressure, even though the peak itself becomes more visible in the spectra. The latter is the result of a strong diminution of the amplitude of the \( \alpha \)-relaxation dispersion with pressure. From dielectric measurements alone, we cannot deduce the

\[
\text{FIG. 6. (Color online) Dielectric loss spectra measured at } T = 298 \text{ K at various pressures from 20 MPa to 420 MPa (upper panel), and at } T = 253 \text{ K in the pressure range from 0.1 MPa to 300 MPa (lower panel).}
\]

\[
\text{FIG. 7. (Color online) Dielectric loss spectra at 0.1 MPa and 239 K (squares), 80 MPa and 258 K (stars), and 300 MPa and 298 K (circles), showing the apparent change in shape of the } \alpha \text{ peak due to the emergence of the } \beta' \text{ relaxation at high pressure.}
\]
origin of this $\beta'$ relaxation. One possibility is that the application of hydrostatic pressure generates a meta phase, involving greater molecular compaction; i.e., a conversion of trans to gauche conformers (see Fig. 1), with a more compact structure exhibiting faster dynamics. Although evidence for this meta phase might be expected in the PVT data, those measurements do not extend to sufficiently high pressures ($>325$ MPa for $T=298$ K) or low temperatures ($T=253$ K for $P<200$ MPa).

In the data of Fig. 6 for 253 K, the excess wing can be seen to emerge as a resolved peak due to the stronger $P$ dependence of the $\alpha$ peak (although the excess wing has some sensitivity to pressure, consistent with its identity as a JG process). The relaxation times measured at $T=253$ and $298$ K are plotted vs pressure in Fig. 8 (note for $298$ K the uncertainty is too large to yield reliable values for $\tau_{\alpha}$). This $P$ dependence can be characterized by an activation volume, defined as $\Delta V=RT\left(\partial \ln \tau/\partial P_T\right)$. While $\Delta V_{\beta'} \sim 0$, the activation volume for the $\alpha$ and JG relaxations are substantial, $=157 \pm 8$ and $83 \pm 4$ ml/mol, respectively. From the CM, the two quantities are related by an expression analogous to Eq. (5),

$$\Delta V_{\alpha} = \Delta V_{\tau} \times \beta_{\text{KWW}},$$

which overestimates the experimental $\Delta V_{\alpha}$ by 23%, which is significant. This small discrepancy is seen in the values of $\tau_{\alpha}$ calculated using Eq. (2) (Fig. 8), which are slightly steeper than the experimental data (in addition to being a factor of 10 larger).

A useful way to analyze the combined $T$ and $P$ dependences is to determine the variation in $\tau_{\alpha}$ with the product $TV^\gamma$, in which $\gamma$ is a material constant (independent of $T$, $P$, and $V$) [56,57]. The exponent on the specific volume is a measure of the contribution of volume (density) to the supercooled dynamics relative to the effect of temperature. It has been shown for more than 50 glass formers that $\tau_{\alpha}$ is a unique function of $TV^\gamma$ [57,58], with $\gamma$ related to the steepness of the intermolecular repulsive potential [59,60].

We calculate the specific volume for any $T$ and $P$ from the equation of state for $\alpha$-tocopherol acetate. The latter was obtained by fitting the PVT data to the Tait equation [61],

$$V(T,P) = V(T,0)(1 - C \ln[1 + P/B(T)]),$$

with $C=0.0894$ and the temperature dependence at ambient pressure given by

$$V(T,0) = 1.0312 + 0.00067 T + 8.429 \times 10^{-7} T^2$$

in units of ml/g and temperature in Celsius. The pressure dependence (in units of MPa) was described by

$$B(T) = 183 \exp(-4.44 \times 10^{-3} T).$$

The $\alpha$-relaxation times are plotted in Fig. 9 as a function of the scaling variable $TV^\gamma$, with $\gamma=3.9$ yielding superposition. This is a typical value for liquids having a bulky structure [58,62]. A more traditional measure of the contribution of volume and temperature to the dynamics is the relative magnitude of the isochoric, $(E_\alpha)_V$, and isobaric, $(E_\alpha)_P$, activation enthalpies [58,63,64]. This ratio varies from 0 (jammed, or volume-dominated, dynamics) to unity (thermally activated relaxation). Using the relation [56,65]

$$(E_\alpha)_V/(E_\alpha)_P = (1 + \gamma \alpha \rho T)^{-1},$$

where $\alpha \rho$ is the isobaric thermal expansion coefficient ($=5.896 \times 10^{-4}$ K$^{-1}$ at $T_\alpha$ and 0.1 MPa), we calculate $(E_\alpha)_V/(E_\alpha)_P=0.66$ at $T_\alpha=226$ K. This is large for a molecu-
lar glass former, but emphasizes that both volume and temperature govern the dynamics, with a stronger effect from the latter. The volume dependence of $\tau_\alpha$ per se is shown in the inset to Fig. 9.

IV. SUMMARY

Dielectric relaxation measurements were carried out on an isomer of vitamin E at both ambient and elevated pressure. The $\alpha$ relaxation has a peak shape that is invariant to thermodynamic conditions, apart from the separation of an excess wing for longer $\tau_\alpha$. The $\alpha$ peak is rather narrow ($\beta_{\text{KWW}}=0.65$), even though $\alpha$-tocopherol acetate is a moderately fragile glass former. At low temperature and high pressure, two new secondary relaxations ($\delta$ and $\beta'$) are observed. The former involves motion of only a part of the molecule (thus its high frequency), while the latter likely reflects development with $P$ of a more compact molecular structure. The $\alpha$-relaxation times superpose when plotted vs $TV^{3.9}$, in accord with behavior common to unassociated liquids and polymers. From the value of the scaling exponent, $n=3.9$, we calculate an activation enthalpy ratio $E_a/E_p=0.66$ at $T_g$, indicating that temperature exerts a somewhat stronger influence on $\tau_\alpha(T)$ than does volume.

From $\tau_\alpha$ and the magnitude of the stretch exponent, we use the coupling model to calculate properties of the JG relaxation. The predicted $\tau_{\text{JG}}$ are consistently larger, by about an order of magnitude, than values deduced from the frequency of the maximum of the JG peak, although the calculated $\tau_{\text{JG}}$ fall within the range of the broad JG dispersion. The JG activation energy measured for the glass and the experimental JG activation volume are both close to values calculated from the CM, which in turn is consistent with an empirical relation between $E_{\text{JG}}$ and $T_g$. For the liquid state the CM overestimates the activation energy, although quantitative determination of $E_{\text{JG}}$ for $T>T_g$ is problematic given the proximity of $\tau_{\text{JG}}$ and $\tau_\alpha$.

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