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The Effect of Temperature on Hydrogen Bonding in Crystalline and Amorphous Phases in Dihydropyrine Calcium Channel Blockers

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Purpose. To investigate the effect of temperature on hydrogen bonding in a series of structurally related amorphous and crystalline compounds to gain a better molecular-level understanding of structural differences in the various phases.
Methods. FT-infrared spectra of seven 1,4-dihydropyridine calcium channel blockers were obtained at temperatures between 0 and 200°C using a temperature-controlled attenuated total reflection accessory. Thermal behavior was characterized using differential scanning calorimetry.
Results. Hydrogen bonding was investigated by monitoring the position of the NH stretching vibration, where an increase in peak wavenumber was taken to indicate a weakening of hydrogen bonding. Heating resulted in a reduction in hydrogen bonding strength, which was greatest for liquids and less for glassy and crystalline phases. For the amorphous samples, a plot of NH peak position vs. temperature displayed a discontinuity in the region of the glass transition (determined using differential scanning calorimetry) indicating that hydrogen bonding weakened abruptly as the material passed through the glass transition. This effect was more pronounced for some samples than for others.
Conclusions. The variation in the decrease in hydrogen-bonding interactions with increasing temperature for the different phases is consistent with greater configurational freedom as one moves from crystal to glass to liquid.

KEY WORDS: crystalline; amorphous; hydrogen bonding; vibrational spectroscopy.

INTRODUCTION

Amorphous materials are characterized by complex behavior with respect to both temperature and time (1). Liquids at temperatures below the melting point are termed supercooled liquids. Cooling of a supercooled liquid to below the glass transition temperature (Tg) results in a glass. Although the supercooled liquid can be regarded as an equilibrium state (albeit metastable with respect to the crystalline phase), the glass is not in configurational equilibrium and is thermodynamically unstable with regard to both the lower energy glassy state and the crystalline state (2). The experimentally observed glass transition event is a kinetic event marking the onset of high mobility and configurational equilibrium on heating rather than a thermodynamic transition and occurs over a range of temperatures. On heating, as Tg is approached the specific volume begins to increase more rapidly because the thermal expansion coefficient in the liquid state is considerably larger than in the glassy state, which has a thermal expansion coefficient more akin to that found for the crystalline state (2). These volume differences will affect intermolecular distances and hence intermolecular interactions.

Pharmaceutical formulations containing amorphous drugs, particularly in the form of solid dispersions, are considered an attractive way of enhancing bioavailablity (3). However, problems with chemical and physical stability have limited the usefulness of this approach (4) and efforts are being made to gain a better fundamental understanding of amorphous pharmaceutical materials (5, 6). The patterns of self association within amorphous materials are considered to be important in influencing the properties of the pure phase and the interaction with other components. In a previous article, we have compared the hydrogen bonding interactions within a group of amorphous compounds and with their crystalline counterparts (7). In this study, we extend that work to investigate the effect of temperature on hydrogen-bonding interactions in the same group of compounds (1,4-dihydropyridine calcium channel blockers), an important aspect given the temperature-dependent behavior of amorphous phases. It was anticipated that the intermolecular interactions in amorphous materials would vary with temperature in a different manner from those in the crystal. In particular, the change in hydrogen bonding as the amorphous materials passed from the glassy to the supercooled liquid was of interest. One might expect hydrogen bonds to abruptly weaken as the system is heated through the glass transition. Indeed, we find this behavior.

Infrared (IR) spectroscopy was used to monitor the changes. IR spectroscopy is a well-established technique for investigating effects of temperature on hydrogen bond interactions (8–10).

MATERIALS AND METHODS

Materials

All materials were as described previously (7).

Methods

Fourier Transform IR Spectroscopy

IR spectra were obtained using a Biorad FTS 575C spectrometer equipped with a KBr beamsplitter and a Peltier cooled DTGS detector. The wavenumber accuracy was monitored using a reference sample of polystyrene. The sample compartment and beamsplitter were purged with dry nitrogen. Spectra were obtained using a Golden Gate attenuated total reflection (ATR) accessory with a single reflection diamond crystal (Specac, Kent, UK), which was also equipped with a temperature controller (0–200 ± 1°C). The resolution was 4 cm^{-1} and 128 scans were acquired. The ATR accessory enables spectra to be obtained from solid materials pressed into contact with a diamond crystal, thus minimum sample handling is required and the use of KBr is avoided. The freshly prepared glass or crystalline powder was loaded onto

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the ATR cell at room temperature (22°C) and the cell was heated (or cooled) to the analysis temperature followed by data acquisition. The entire ATR accessory was enclosed within the sample compartment and purged with dry nitrogen. Samples that were heated to the highest temperatures were also scanned again after cooling and the spectra compared with unheated samples. No visible signs of degradation were observed as a result of heating. Duplicate measurements were performed for a number of samples and reproducibility was good.

Differential Scanning Calorimetry

The glass-transition temperatures of amorphous materials and the heats of fusion of crystals were determined using a differential scanning calorimeter (DSC). Approximately 5 mg of powdered crystalline sample was weighed into an aluminum sample pan with a vented lid (Mettler Toledo Schwerzenbach, Switzerland). Differential scanning calorimetric measurements were carried out using a Mettler Toledo 820 DSC. Dry nitrogen at 50 ml min^{-1} was used as purge gas and the scanning rate was 10°C min^{-1}. The instrument was calibrated using indium. Amorphous samples were prepared *in situ* by quenching of the melt. All Tg values were determined from the second scan after heating the sample to 10°C above Tg to erase the previous thermal history and the onset, midpoint, and endpoint temperatures are reported. Samples were analyzed in duplicate.

RESULTS

Thermal Characterization

Data from the thermal characterization are summarized in Table I. For the crystalline materials, all samples were characterized by one endotherm, which corresponded to melting. For amorphous compounds, Tg could be evaluated from the characteristic stepwise change in heat capacity over the glass transition region. It can be seen from Table I that, despite having similar chemical structures and molecular weights, there is still a variation of up to 30°C in the melting points and Tg values between the various compounds. The ratio Tg/Tm in Kelvin is, however, reasonably constant at approximately 0.72 and this value is very close to that normally observed for pharmaceutical materials (11). Knowledge of the Tg and melting point defines temperature regions for the crystal, glass, supercooled liquid, and liquid, necessary for meaningful interpretation of the spectroscopic data.

Characteristics of the NH Stretching Vibration in the Crystalline, Glassy, and Liquid States of Felodipine

Hydrogen bonding in the model compounds occurs between the NH function of the dihydropyridine ring and an acceptor group in another molecule as described in detail previously (7). The position of the NH stretching peak, measured using IR spectroscopy, can be used to indicate changes in hydrogen bonding as a function of temperature. Figure 1 shows how this peak varies with temperature in crystalline and amorphous felodipine. In crystalline felodipine (Fig. 1a), the NH group is involved in a relatively weak hydrogen bond (12) and gives rise to a reasonably sharp peak at approximately 3370 cm^{-1}, which varies little with temperature until melting. For amorphous felodipine (Fig. 1b), the main NH peak is at 3330 cm^{-1}, indicating stronger average hydrogen bonding than in the crystal (7). There is an additional NH peak at 3420 cm^{-1}, assigned to non-hydrogen bonded NH (7). Both NH peaks in the amorphous material change more with temperature than in the crystalline material. The spectrum of the melt resembles that of the amorphous phase. These results are discussed in more detail below.

Increase in the Fraction of Free NH in Amorphous Felodipine

As seen from Fig. 1b, the small peak assigned to nonhydrogen bonded NH increases in intensity relative to the hydrogen bonded NH peak as the temperature is increased. Using a peak fitting procedure, the areas of the free and bonded NH peaks of amorphous felodipine were estimated as a function of temperature and the results are shown in Fig. 2. It can be seen that the area of the bonded NH peak is initially fairly constant and then decreases with temperature, whereas that of the free NH peak, is also initially constant and then increases. Both of these changes occur just above the glass transition temperature. Thus the amount of free NH appears to increase somewhat as the temperature is raised. The decrease in the area of bonded NH peak is consistent with a decrease in absorption coefficient [which is known to occur with temperature (9)] and/or decrease in the amount of bonded NH.

Table I. Thermal Characterization Data for the Different Crystalline and Amorphous Compounds, Determined Using DSC

Compound	MW	Tm (°C)	Tg (°C) Onset	Mid point	End point	ΔCp ($\text{Jg}^{-1}\text{K}^{-1}$)	Tg/Tm
Felodipine	384.3	142.9	43.7	44.6	46.5	0.41	0.76
Nifedipine	346.3	171.0	43.2	44.5	48.3	0.41	0.71
Nimodipine	418.5	124.5	12.2	14.0	16.2	0.36	0.72
Nitrendipine	360.4	152.6	28.6	30.4	32.7	0.36	0.71
Nicardipine	479.5	—	11.6	13.4	16.1	0.34	—
Isradipine	371.4	167.0	40.2	41.3	43.1	0.37	0.71
Nisoldipine	388.4	150.2	34.1	35.5	36.9	0.33	0.73

Note. The melting points (Tm) and the onset values and Tg/Tm is calculated after conversion of the data to °K. MW, molecular weight.

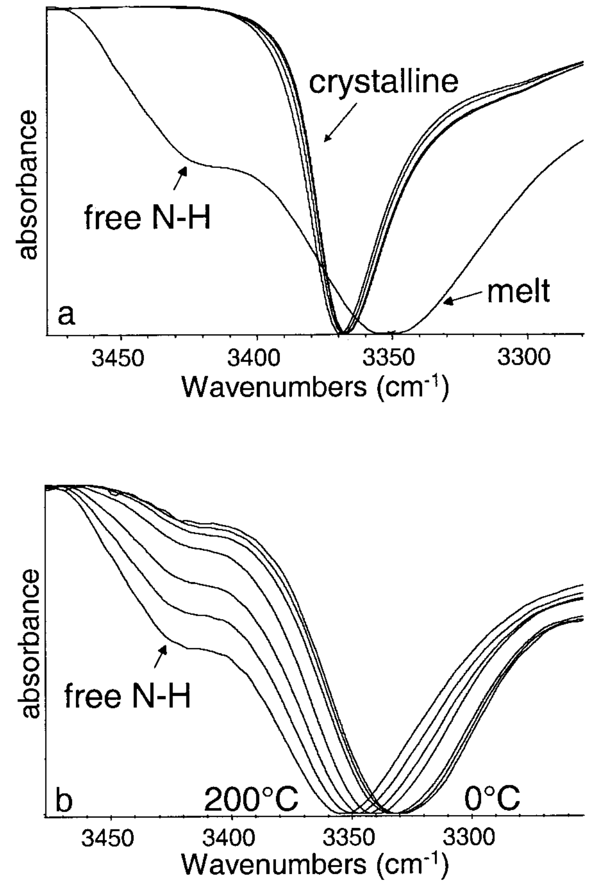

Fig. 1. a) NH stretch of crystalline felodipine at 25, 40, 80, 120, 160, and 200°C. b) NH stretch of amorphous felodipine at 0, 20, 40, 80, 120, 160, and 200°C (from right to left). For crystalline and amorphous felodipine, the peak position shifts to a higher wavenumber with increasing temperature.

Wavenumber-Temperature Correlation for Crystalline vs. Amorphous Felodipine

Plotting the NH peak position as a function of temperature provides a convenient monitor of the change in hydrogen bonding with temperature, whereby a shift to a higher wavenumber represents a decrease in hydrogen bond strength and a shift to a lower position an increase in strength. Lutz and Maas (13) have termed this change in peak position with temperature the wavenumber-temperature correlation or WTC (i.e. $\Delta\nu$ °C^{-1}, where $\Delta\nu$ is the shift in peak position). Figure 3 shows a wavenumber vs. temperature plot for crystalline and amorphous felodipine. For crystalline felodipine there is a slight upward shift in peak position with increasing temperature and from the slope of the data, the WTC can be calculated (Table II). On heating, intermolecular distances will increase, resulting in an upward shift of peak position because of reduced hydrogen-bond strength (10). Hence the data indicate that crystalline felodipine experiences a small decrease in hydrogen bond strength as the temperature is increased. At around 140°C, a sharp decrease in peak position occurs, corresponding to the melting point of the substance. The data suggest that the liquid phase of felodipine contains shorter average hydrogen bonds than the crystalline phase, as evidenced by the lower peak frequency. However, the broadness of the peak also suggests that the distribution of hydrogen bond lengths and angles is much greater in the melt, than in the crystal, as would be anticipated.

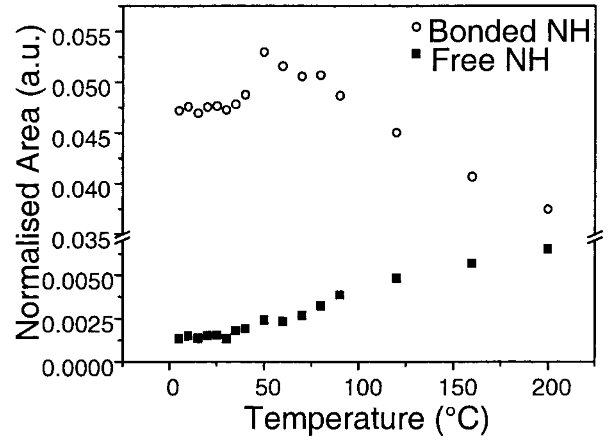

Fig. 2. Plot of the estimated area of the free and hydrogen bonded NH stretching peaks of amorphous felodipine as a function of temperature. The areas of each peak were estimated using a peak fitting procedure and are normalized against the area of the peak at 775 cm^{-1}, which was used as an internal reference.

For the amorphous material (Fig. 3) there is little change in NH peak position with temperature when the material is below 40°C and in the glassy state, similar to the corresponding crystalline data. Between 40°C and 65°C there is a sharp increase in the peak position and this corresponds to the temperature region where felodipine passes through the glass transition (see Table I), although the calorimetrically determined Tg event is much sharper. Above the glass transition region, where felodipine is a supercooled liquid, the slope decreases somewhat but the WTC is much higher than for either the glass or the crystal (Table II). The upward trend in peak position is continuous as the temperature increases and the supercooled liquid passes above the melting point. Spectra from the melt of the crystalline material and those from the heated amorphous substance are identical at any temperature above the melting point, as expected.

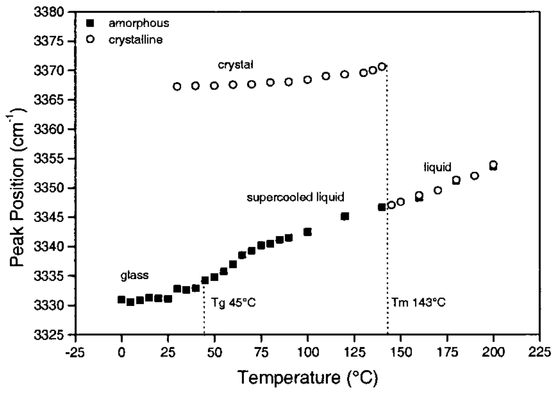

Fig. 3. Wavenumber vs. temperature plot of the NH stretching vibration of crystalline and amorphous felodipine. The melting temperature (Tm) and glass transition temperature (Tg) for the crystalline and amorphous phases respectively are indicated (as determined from DSC measurements).

Table II. WTC for the NH Stretching Vibration for the Compounds in Different States and the Temperature of the Tg Event as Estimated from Spectroscopic Data

	WTC values (cm^{-1} °C^{-1})			Tg (°C)		
	Glass	Liquid	Crystal	Onset	Mid point	End point
Felodipine	0.056 ± 0.010	0.106 ± 0.002	0.010 ± 0.001	40	52.5	65
Nifedipine	0.083 ± 0.021	0.161 ± 0.007	0.075 ± 0.002	40	50	60
Nimodipine	*	0.135 ± 0.003	0.047 ± 0.005	—	—	—
Nitrendipine	0.110 ± 0.010	0.146 ± 0.010	0.040 ± 0.001	32	39.5	47
Nicardipine	*	0.131 ± 0.005	—	—	—	—
Isradipine	0.078 ± 0.007	0.129 ± 0.004	0.007 ± 0.001	30	40	50
Nisoldipine	0.073 ± 0.002	0.165 ± 0.007	0.026 ± 0.002	40	46	52

Note. The error values represent the standard deviation of the linear regression analysis used to determine WTC. In all cases, the correlation coefficient was greater than 0.98. * Not enough data to determine WTC.

Peaks arising from other parts of the molecule, i.e. non-hydrogen bonding groups were much less sensitive to temperature (data not shown). For example, a peak arising from CH stretching showed a small negative WTC (total change in peak position was less than 5 cm^{-1}), typical for vibrations subject only to van der Waals forces (14)

In summary, spectral data show that the greatest decrease in hydrogen bonding occurs during the glass transition event. In the supercooled liquid/equilibrium liquid state, hydrogen bonding is more sensitive to temperature than for the crystalline or glassy states. The numerical values for WTC of felodipine in various states are listed in Table II.

WTC for Further Crystalline and Amorphous Compounds

Heating data were obtained for an additional six substances and Fig. 4 shows examples of the change in NH peak position for two of these compounds in the amorphous and crystalline states. WTC data are summarized in Table II. For crystalline isradipine (Fig. 4a), little change is seen in the NH peak position, until the compound melts. In this substance, weakening of hydrogen bonding occurs on melting as evidenced by the upward shift in NH peak position. Amorphous isradipine behaved in a similar manner to amorphous felodipine showing little change in peak position with temperature as a glass with an abrupt change in slope around the glass-transition temperature. Crystallization was observed to commence at 100°C with changes in a number of peaks in addition to the NH peak shifting towards the position found in crystalline isradipine as the temperature increased and crystallization progressed. Amorphous nisoldipine also crystallized during heating, after passing through the glass transition. This can be clearly seen in Fig. 4b where the NH peak position shifts towards that of the crystalline material. The melting transition is clearly reflected in the spectroscopic data and hydrogen bonding in the melt is weaker than for the crystal. WTC data for four further compounds are summarized in Table II and their behavior may be briefly described as follows: Nimodipine and nifedipine also crystallized during heating at 100 and 70°C, respectively. For nicardipine and nimodipine, which have the lowest Tg values, no distinct change of slope in the region of Tg could be observed from the spectral data. For all compounds, WTC for the supercooled liquid was identical with that of the melt. It can be seen from Table II that the lowest WTC value in all cases is seen for the crystalline material and the glasses. In contrast, in the supercooled liquid/liquid phase, the WTC values are larger, indicating that hydrogen bonding is most sensitive to temperature in this state.

DISCUSSION

The Effect of Temperature on Hydrogen Bonding

Vibrational spectroscopy offers the possibility of gaining a molecular level view of the macroscopic changes that occur

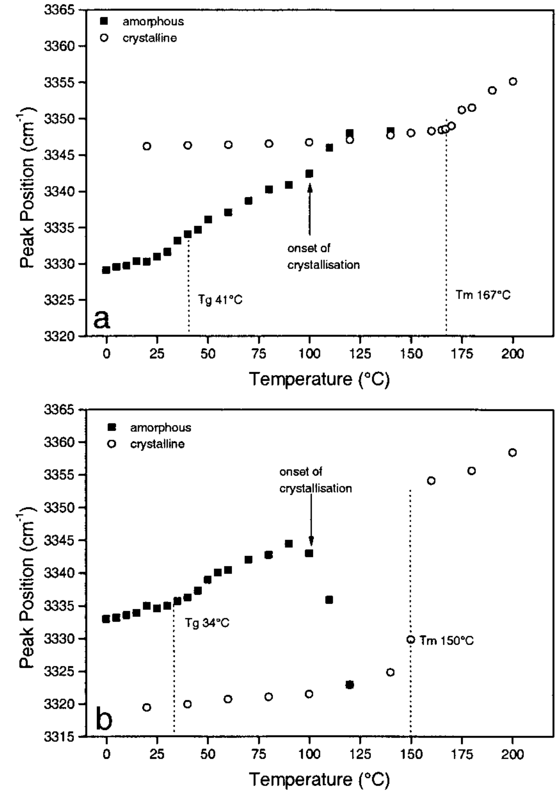

Fig. 4. Wavenumber vs. temperature plot for crystalline and amorphous a) isradipine and b) nisoldipine. The melting temperature (Tm) and glass transition temperature (Tg) for the crystalline and amorphous phases, respectively, are indicated (as determined from DSC measurements).

in crystalline and amorphous materials as they are heated. This technique has been used to investigate hydrogen bonding as a function of temperature for crystalline and amorphous materials (8,14,15), although little data exists that compares the two phases. The most straightforward way to evaluate the different compounds and phases is to compare the wavenumber-temperature coefficients (WTC). Positive WTC values with an increase in temperature are typical for hydrogen-bonded systems (13,14) and indicate a decrease in hydrogen-bond strength with increasing temperature, as would be anticipated.

Lutz and Maas (13) have studied the WTC values for crystalline sugars and concluded that the WTC for a particular hydrogen-bonded system depended primarily on the change in O····O distance with temperature. This in turn depends on the expansion of the material with temperature and on the orientation of the groups involved in hydrogen bonding. For the compounds investigated in this study, the main differences in response of the hydrogen bonding to temperature can be ascribed to differences in the thermal expansion between crystalline/glassy phases and liquid phases. The thermal expansion coefficients of crystals/glasses are lower, therefore the change in interatomic distance between the NH and acceptor group involved in the hydrogen bond is less over the temperature range studied. Therefore, only a small change in hydrogen bonding and hence a low WTC value is observed. In the liquid the thermal expansion coefficient is greater and hydrogen bonding decreases more rapidly as a function of temperature. Other factors will also contribute to the value of WTC, particularly for the crystalline compounds where the strength of the hydrogen bonding differs for the various compounds. For example, it is well recognized that a change in length of hydrogen bond for a shorter hydrogen bond has a greater effect on the strength of the hydrogen bond than does a similar change in length for a longer hydrogen bond (10).

Not only does the hydrogen bonding weaken more rapidly as a function of temperature above Tg, but it was also observed that the fraction of non-hydrogen bonded NH groups increases at temperatures above Tg. Presumably due to the increase in molecular mobility, some of the intermolecular hydrogen bonding associations are disrupted. With further rise in temperature, existing hydrogen bonding weakens further, molecular mobility increases, and a larger fraction of felodipine (at any particular moment in time) is not hydrogen bonded. It can be speculated that this non-hydrogen bonded fraction will be more chemically reactive and less physically stable due to its nonassociated state.

Relationship between H-Bonding Change and the Thermodynamics of Fusion

Phase transitions are frequently characterized in terms of thermodynamics and it is of interest to see if and how the hydrogen bonding changes during fusion relate to the thermodynamic parameters. The enthalpy of fusion represents the energy difference between the liquid and crystalline states at the melting point (1 atm pressure). In Fig. 5, the enthalpy of fusion is plotted against the NH peak shift observed on melting (i.e. νNH liquid-νNH crystal). This peak shift provides an indication of how the hydrogen bonding changes on passing from a crystalline to a liquid phase; a positive NH peak shift is consistent with a weakening of hydrogen bonding, whereas a negative peak shift indicates stronger hydrogen bonding in the melt. From Fig. 5a, it can be seen that although there are significant differences in peak shift on melting for the different compounds, there is no simple relationship with the heat of fusion. A clearer trend is seen when the peak shift is plotted against the entropy of melting (Fig. 5b) where a reasonably linear correlation appears to exist ($R^2 = 0.96$). The entropy of melting is positive, since there is more disorder in the liquid state than in the crystalline state. The smallest entropy of fusion is seen for felodipine where the strength of hydrogen bonding is known to increase on melting. Our results suggest that the extent of hydrogen bonding in the liquid, not unexpectedly, plays a role in determining the entropy difference between crystal and liquid. An increasing difference in hydrogen bonding between melt and crystal thus appears to correlate with a greater entropy difference, as would be anticipated.

Glass Transition Temperature and Hydrogen Bonding

The variation in the glass-transition temperatures of the seven compounds investigated was around 30°C. There was no correlation between the Tg and the molecular weight of the compound, as can be seen from Table I. Moreover, it has been observed that the average hydrogen bonding strength in all compounds is approximately the same (when in the amorphous state) (7) suggesting that the difference in Tg cannot be accounted for by any variation in hydrogen bonding. Our

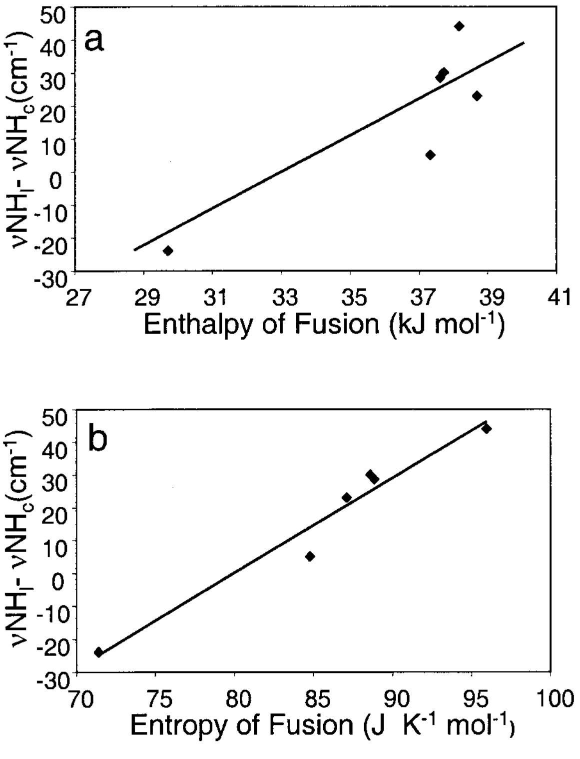

Fig. 5. Relationship between the peak shift of the NH stretching vibration (νNH_l-νNH_c) during melting with a) the enthalpy change during melting and b) the entropy change during melting.

results thus suggest that differences in molecular geometry or other noncovalent interactions most likely result in the observed variations in Tg.

The temperature dependence of the NH vibration of the different glasses, known to be involved in hydrogen bonding, has been monitored around the expected glass transition region. The WTC was observed to undergo a discontinuity in the region of the expected Tg, as seen in Fig. 3, and it is therefore reasonable to conclude that the changes are directly related to the glass-transition event and the subsequent modification in material properties. The Tg event has been observed previously using vibrational spectroscopy and monitoring groups involved in hydrogen bonding (8,15). The stepwise change observed at Tg indicates that hydrogen-bonding strength decreases most rapidly as the material undergoes the glass transition. Moreover, it was noted that the total peak shift on passing from the glassy to the supercooled liquid state varied somewhat between the compounds. In Fig. 6 this peak shift (calculated by extrapolating the linear WTC for the glass and supercooled liquid and measuring the difference in peak position at the beginning and end of the Tg event) is plotted vs. the calorimetrically measured glass-transition temperature. There appears to be a reasonably linear relationship between these two parameters. The abrupt weakening in hydrogen bonding observed in the region of the Tg event has been observed previously (8,15) and is unsurprising given that the Tg marks a co-operative structural change. Moreover, the results shown in Fig. 6 indicate that there is a possible relationship between the extent of hydrogen bond weakening and the Tg value. Thus the samples that have a higher Tg, change more in terms of hydrogen bonding as they pass through the glass transition than the compounds having a lower Tg, that, from a hydrogen bonding perspective, are more similar in the glass and supercooled liquid. As can be seen by comparing data in Table I and Table II, somewhat surprisingly we found no correlation between the decrease in hydrogen-bonding strength and the change in heat capacity on passing through Tg.

The observations made in this study contribute to an improved molecular level understanding of the glass transition process and the differences between glassy and liquid phases. In the glassy state, the formation of a more extensive hydrogen bonding network than in the supercooled liquid, presumably contributes to its greater physical stability and reduced molecular mobility. The observation that the fraction of non-hydrogen-bonded molecules is lower in the glass than in the supercooled liquid also suggests that the short-range orientational order will be greater in the glass (16). Moreover, the observation that there is more than one population of molecules, i.e. hydrogen bonded and non-hydrogen bonded, may well contribute to the non-exponential relaxation behavior often displayed by organic glasses (17). Changes in molecular associations as a function of temperature are likely to be important factors in determining not only the physical and chemical stability of amorphous materials but also the ability to form molecular level mixtures with other components during processes such as melt extrusion and solid dispersion formation.

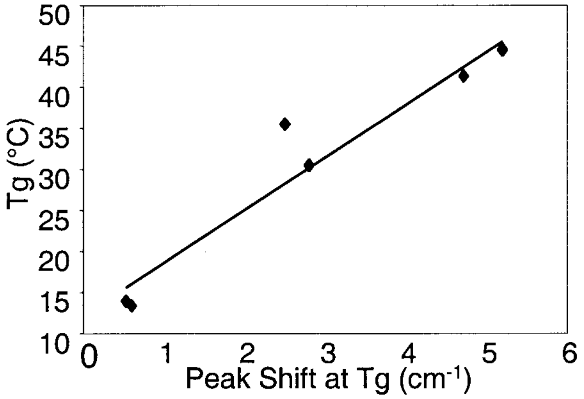

Fig. 6. Correlation between glass transition temperature and the peak shift of the NH stretching vibration during the glass transition event.

SUMMARY

The variation in hydrogen bonding with temperature has been studied for a group of compounds. For crystalline materials, a slight decrease in hydrogen bond strength was observed on heating. For the amorphous counterparts, when in the glassy state, only a small decrease in hydrogen bond strength was also observed with increasing temperature, whereas for the liquids, this decrease was more considerable. However, the temperature dependence of the hydrogen bonding decrease reaches a maximum in the region of the calorimetric Tg. Thus as materials pass through the glass transition, they undergo an abrupt weakening in hydrogen bonding. However, it was also observed that the compounds with a lower Tg have a smaller change in hydrogen bonding on passing through the glass transition than the substances with higher Tg. The amount of non-hydrogen bonded NH in amorphous felodipine was also observed to increase as a function of temperature, particularly above Tg. Infrared spectroscopy was found to be a useful method to characterize the molecular level changes in materials during heating and subsequent phase changes.

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