

Influence of Alkali Metal Counterions on the Glass Transition Temperature of Amorphous Indomethacin Salts

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Purpose. To test the hypothesis that the choice of counterion in salt formation would generally result in a change in the glass transition temperature, T_g , in relation to the nature of the interaction between the ionized parent structure and its counterion.

Methods. Various alkali metal salts of indomethacin (IMC), lithium (Li^+), sodium (Na^+), potassium (K^+), rubidium (Rb^+), and cesium (Cs^+) IMC were prepared as amorphous solid powders by lyophilization. The T_g was measured using differential scanning calorimetry or modulated-temperature differential scanning calorimetry. The spectroscopic properties of these salts were analyzed using Fourier transform-Raman and Fourier transform-infrared spectroscopy.

Results. A comparison of the T_g values of the five salts showed T_g values in the order of $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$, which is consistent with an order of decreasing ionic radius, and hence an increased charge density and an increased electrostatic interaction energy between the carboxylate ion and the alkali metal cation. Spectroscopic data support this interpretation by showing that the different salts exhibit spectral differences only in the region of the carboxylate group.

Conclusions. Changes in T_g due to salt formation for alkali metal salts of IMC mainly result from differences in ionic interaction between the oppositely charged ions that appear to be related to the size/charge ratio of the counterion.

KEY WORDS: amorphous; alkali metal salts; indomethacin; glass transition temperature, vibrational spectroscopy.

INTRODUCTION

A common strategy for improving the aqueous solubility of relatively hydrophobic crystalline drugs, which exist as free acids or bases, is to prepare a suitable water-soluble salt (1,2). Such salts, when prepared in oral solid dosage forms or as lyophilized parenterals, often are caused to lose part or all of their crystallinity because of various processing conditions. Drugs intended for oral use are often unintentionally rendered amorphous by grinding, compaction, and drying, and this can lead to unanticipated changes in physical and chemical stability. Such changes arise because of the increased energy of molecules in the amorphous state relative to that in the crystalline form. This, in turn, gives rise to an enhanced molecular mobility, as reflected in an increase in translational and rotational diffusion, relative to that in the crystalline state

(3,4). Such increases in molecular mobility provide the basis for enhanced instabilities over timescales of pharmaceutical interest (5–7).

A critical parameter for characterizing the amorphous state is the glass transition temperature, T_g . It is at this temperature that the amorphous material upon cooling converts from an equilibrium supercooled liquid to an unstable glassy solid. Relative to molecular mobility, as the supercooled liquid is cooled to and through the glass transition, the timescales of molecular motion can increase by many orders of magnitude, so that where the operating temperature T is relative to T_g is an important factor in establishing optimal conditions for handling and storing amorphous materials.

In a previous study, two of us reported a comparison of the amorphous properties for indomethacin (IMC) and its sodium salt (8). We were able to show that the T_g of IMC in the dry state is about 45°C, whereas that of its sodium salt is about 120°C. Thus, on this basis alone, it can be seen that a much higher temperature would be required to convert the drug from its viscous glassy state to the more molecularly mobile supercooled liquid, and that under the usual storage conditions encountered pharmaceutically in the dry state, amorphous sodium IMC would be expected to have much less molecular mobility than its corresponding free acid. This 75°C difference in T_g (with a greater tendency to remain in the glassy state for the sodium salt) was believed to be due in part to an ionic interaction between the sodium and IMC ions, which leads to less molecular mobility relative to that of its free acid form. To test this hypothesis in more detail, we have now prepared and studied the amorphous characteristics of the lithium (Li^+), sodium (Na^+), potassium (K^+), rubidium (Rb^+), and cesium (Cs^+) salts of IMC. We would expect, based on our earlier conclusions, that the T_g of these salts would increase as the tendency for cation-anion interaction increases (i.e., $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+ > \text{Cs}^+$). Using vibrational spectroscopy, the possible effects of the counterion on the molecular structure of the drug in the amorphous state was also probed. Although we would normally expect that only the sodium and potassium ions in this group would be used in practical situations, the choice of this series of alkali metal cations, we believe, provides a systematic basis for better understanding of the extent to which such counterions influence an important solid-state property linked to the potential physical or chemical instability of a drug.

MATERIAL AND METHODS

Materials

Crystalline IMC (the stable γ form) was obtained from Sigma Chemical Co. (St. Louis, Missouri). Alkali hydroxides of American Chemical Society grade were used to make different salts of IMC. They include sodium hydroxide (Sigma Chemical Co.), potassium hydroxide (Fisher Scientific, Co., Hanover Park, Illinois), lithium hydroxide (Sigma Chemical Co.), rubidium hydroxide (Aldrich Chemical Co. Inc., Milwaukee, Wisconsin), and cesium hydroxide (Aldrich Chemical Co. Inc., Milwaukee, Wisconsin). They were stored in a -20°C freezer and used as received.

Poly(vinylpyrrolidone) (PVP K-12), was obtained from the BASF corporation, (Ludwigshafen, Germany) with a

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weight-average molecular weight of about 2,000–3,000 reported by the supplier. Deionized water was used to make all aqueous solutions. Anhydrous methanol (Aldrich Chemical Co. Inc., Milwaukee, Wisconsin; water < 0.005%) was used to prepare a coprecipitated amorphous mixture of LiIMC and PVP.

Methods

Formation of Amorphous Alkaline IMC Salts

The preparation of amorphous NaIMC by freeze-drying its aqueous solution has been described in detail in earlier work (8). The alkaline salts of IMC in this work, including NaIMC, were made by titrating an aqueous suspension of IMC with the aqueous solutions of LiOH, KOH, NaOH, RbOH, and CsOH. An amount of the corresponding alkali hydroxide equivalent to 0.045 mol was dissolved in 25 ml of water. This alkaline solution was added dropwise with stirring to an aqueous suspension of IMC that contained 0.045 moles IMC in the crystalline γ form. The pH of the solution during the reaction was monitored using a model 701A/digital ion-analyzer (Orion Research Incorporated, Cambridge, Massachusetts) equipped with a Corning semi-micro combination electrode (catalog No. 476541). The pH of the reaction solution was kept below 9.0 to avoid any chemical degradation. After complete addition of the alkaline solution, the system was stirred for another 2 h before the solution was filtered.

For all the salts prepared, the pH of the aqueous solution was found to be in the range 7.9–8.3. The solution then was dispensed into 15-ml scintillation vials and freeze-dried using an FTS Dura-Stop tray drier (Dura-Stop, FTS Systems, Stone Ridge, New York) coupled with a condenser module (Dura-Dry-MP, FTS Systems). The solution was frozen at -40°C for 12 h before a vacuum was applied. At a residual pressure of 50 millitorr, the temperature of the freeze-drier was programmed to -25°C (48 h), -10°C (48 h), 0°C (24 h), 25°C (24 h), and 45°C (24 h). Following this procedure, the freeze-dried cake was dried under vacuum at 60°C for 48 h to remove any residual water. In all cases, Karl Fischer analysis revealed water content of less than 0.1% (w/w).

The stoichiometries of the different IMC salts formed were confirmed by elemental analysis of C, H, N, and the counterions, which was conducted by Quantitative Technologies Inc. (Whitehouse, New Jersey). The counterions were analyzed using ion chromatography. The elemental analysis results are presented in Table I.

The formation of a completely amorphous phase was confirmed in all cases by examination for the presence of any crystallinity (i.e., presence of birefringence) using an Olym-

pus BH-2 optical microscope (Olympus Optical Co., LTD, Tokyo, Japan) equipped with a thermal hot stage and polarized light accessories, and by an x-ray scanning powder diffractometer (Scintag Inc., Santa Clara, California).

The sodium salt prepared with IMC and NaOH, as described above, gave identical values of T_g and enthalpy relaxation (to be described below) as the sample of sodium salt previously used, obtained by lyophilizing solutions of crystalline NaIMC trihydrate (8).

Thermal Analysis

The T_g of the various amorphous samples was measured using a Seiko 220C DSC (Seiko Instruments, Horsham, Pennsylvania) and a Seiko DSC 5200 data station, as described in detail elsewhere (8). Temperature and enthalpy calibration were carried out at each heating rate used using high-purity indium and gallium (Aldrich Chemical Co. Inc.). In all cases, T_g was reported as the onset temperature of the glass transition.

A modulated-temperature differential scanning calorimeter (MTDSC; TA Instruments, New Castle, Delaware) also was used to identify the T_g of LiIMC because of the difficulty in detecting a significant heat capacity change by conventional DSC. The MTDSC was calibrated for temperature and enthalpy using indium, and for heat capacity using sapphire, at the heating rate used for this study. Samples in the amount of 10 mg or slightly more were weighed into aluminum DSC pans in a glove box under nitrogen flow. The pans were crimped, and a pinhole was put in the lid. The sample was first heated at $10^{\circ}\text{C}/\text{min}$ to 120°C , held isothermally at 120°C for 1 min, and cooled to 0°C . Then with oscillation amplitude of 0.5°C per 100 s, the sample was heated to 150°C at a heating rate of $1^{\circ}\text{C}/\text{min}$, under a nitrogen purge of 50 ml/min.

To further confirm a value of T_g for LiIMC, oven-dried PVP K-12 was mixed with the freeze-dried LiIMC at ratios of 1:1 (w/w) and then dissolved in anhydrous methanol in a round-bottom flask. Upon complete dissolution, the solvent was rapidly rotaevaporated under vacuum at room temperature. The resultant amorphous mixture was further dried in a vacuum oven, without heating, for up to 3 h to remove residual methanol. The T_g of this mixture was measured by conventional DSC, as described above.

Determination of the heating rate dependence of T_g for the purpose of estimating the fragility of NaIMC and KIMC (9) using DSC was carried out at the same cooling and heating rates of 5, 10, 20, 30, and $40^{\circ}\text{C}/\text{min}$. Enthalpy relaxation was measured for the purpose of estimating a mean relaxation time below T_g by subjecting amorphous NaIMC and KIMC to three storage temperatures (i.e., 16, 24, and 32°C below their T_g values for various lengths of time) and applying an analysis that is described in detail elsewhere (8).

Fourier Transform (FT)-Raman Spectroscopy

FT-Raman spectra were collected on a Perkin-Elmer System 2000 instrument (Beaconsfield, Buckinghamshire, United Kingdom) with a near-infrared Nd:YAG laser operating at 1064 nm. The laser power was typically 500 mW, and a InGaAs detector was used. Backscattered radiation at an angle of 180°C was collected, and the Stokes radiation was reported. Indene was used as a reference standard to monitor

Table I. Elemental Analysis Results for the Various Salts of IMC^a

Salts of IMC	C	H	N	Counterion
Li	62.10 (62.74)	4.22 (4.16)	3.72 (3.85)	1.90 (1.91)
Na	59.66 (60.09)	4.17 (3.98)	3.52 (3.69)	6.05 (5.63)
K	57.65 (56.55)	3.82 (4.12)	3.54 (3.33)	8.98 (9.88)
Rb	48.98 (51.60)	3.54 (3.42)	2.82 (3.17)	18.08 (19.33)
Cs	45.64 (46.60)	3.39 (3.09)	2.66 (2.86)	27.29 (27.14)

^a Results are the average of two measurements. Values given as the percentage (theoretically estimated value).

wavenumber accuracy. One hundred twenty-eight scans at a resolution of 2 cm were averaged for each sample. Samples were dried under vacuum at 50°C for 24 h and then were analyzed in sealed nuclear magnetic resonance tubes with continuous rotation.

FT-Infrared (IR) Spectroscopy

Infrared spectra were obtained using a Biorad FTS 575C spectrometer (Cambridge, Massachusetts) 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 N₂. Spectra were obtained using an attenuated total reflectance (ATR) accessory (single-reflection diamond crystal; Golden Gate, Specac, Orpington, Kent, United Kingdom). The resolution was 4 cm, 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. Prior to acquiring spectra, samples were dried under vacuum at 50°C for 24 h followed by rapid loading onto the accessory (approximately 30 s), which was then enclosed in the nitrogen-purged sample compartment. The peak positions for both the FT-Raman and FT-IR spectra were determined using the Perkin-Elmer Spectrum software peak picking function for Windows v2.00.

RESULTS

T_g of Alkali Salts of IMC

Using the conventional DSC, the amorphous form of the alkali salts of IMC all exhibited a distinct glass transition, with the exception of LiIMC, and the T_g values are shown in Table II.

Also shown in Table II is the T_g for LiIMC obtained by MTDSC. As stated in the Methods section, an MTDSC had to be used to identify the T_g of LiIMC due to the difficulty in detecting a significant heat capacity change by conventional DSC. The reversing signal curve in the MTDSC thermogram for LiIMC, as shown in Fig. 1, shows a reversible thermal event at 139°C, which is characteristic of a T_g. This T_g value of LiIMC was confirmed by making a coprecipitated amorphous mixture of LiIMC with PVP K-12 at a 1:1 weight ratio. Such a mixture exhibited a single T_g at 115°C, demonstrating the formation of a molecular dispersion (10). It has been shown by earlier studies in this and other laboratories that the amorphous molecular dispersions of some pharmaceutical compounds with PVP K-12 usually exhibit reasonably ideal mixing behavior that can be described by an equation such as that reported by Gordon and Taylor (see e.g. ref. 6). Using

Table II. T_g and Heat Capacity of Different Salts of IMC Measured by DSC or MTDSC

Salts of IMC	T _g (°C)	ΔC _p (mJ/mg/K)
Li	139 ± 3.6	0.27 ± 0.11
Na	121 ± 1.0	0.33 ± 0.03
K	109 ± 1.2	0.46 ± 0.08
Rb	77 ± 2.1	0.45 ± 0.07
Cs	69 ± 3.0	0.33 ± 0.07

* Error ± one SD

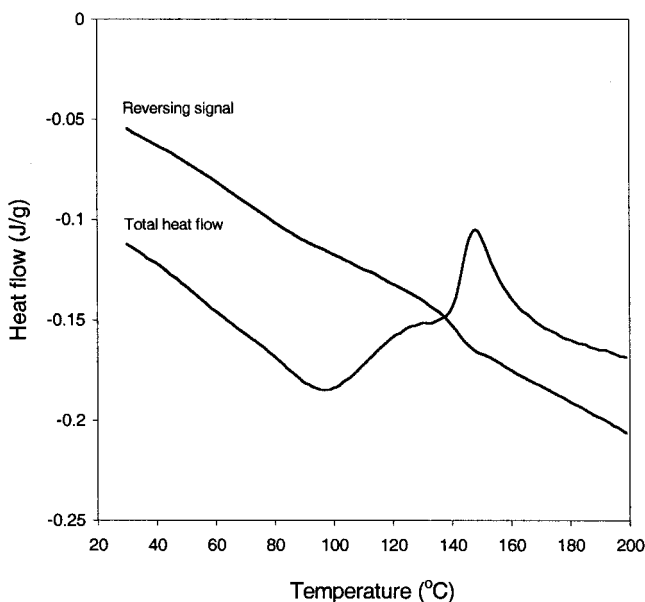


Fig. 1. Modulated temperature DSC thermogram for LiIMC (using an oscillation amplitude of 0.5°C per 100 s, at a 1°C/min heating rate).

the density of LiIMC, which was determined to be 1.37 g/cm³, and a reported density value of 1.23 g/cm³ for PVP K-12 (11), and using 139°C (see Table II) and 99°C (6) as the T_g values for LiIMC and PVP K-12, respectively, the T_g of the LiIMC/PVP K-12 1:1 (w/w) amorphous solid dispersion was estimated to be 116°C, which is in good agreement with the result from the MTDSC analysis of this mixture (115°C).

It is apparent from Table II that all of the salts of IMC have higher T_g values than that of the free acid, and that the T_g of the salt is very dependent on the counterion, with the T_g decreasing significantly as one goes from Li⁺ to Na⁺ to K⁺ to Rb⁺ to Cs⁺.

Spectroscopic Properties of Alkali Metal Salts of IMC

On the formation of an alkali metal salt of IMC, it would be expected that the largest perturbation of the spectrum would occur in the region of the COOH stretch, and this has been reported previously (8). Thus, the acid carbonyl stretch is lost and is replaced by vibrations arising from the carboxylate ion. The carboxylate ion vibration has two components, an asymmetric and a symmetric stretch. The asymmetric stretch is typically strong in IR spectroscopy but weak in Raman spectroscopy, while the converse is true of the symmetric stretch (12). Formation of the carboxylate ion requires the presence of a counterion, and it is of interest to investigate the influence of this counterion on the structure of the molecule, since it clearly influences the properties of the amorphous phase. Alkali metal salts themselves have no vibrational spectrum, so spectra obtained from the different IMC salts are composed only of the anionic species, albeit influenced by the different cations.

Figures 2 and 3 show the Raman and IR spectra, respectively, of the series of amorphous alkali metal salts of IMC. Generally, it can be seen that the spectra are similar, and this is not unexpected given that the molecular species that gives rise to the vibrational spectrum are identical in each instance. Moreover, since all samples are amorphous, there are no in-

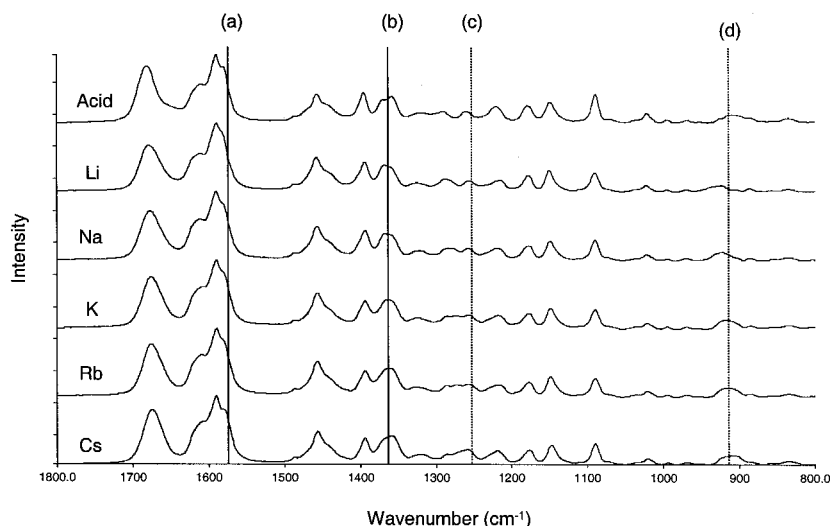


Fig. 2. FT-Raman spectra of the alkali metal salts of IMC. Solid lines: (a) νCO^- asymmetric stretch peak around 1580 cm; (b) νCO^- symmetric stretch peak around 1367 cm. Dashed lines: (c) the CH deformation peak around 1260 cm; and (d) the C-C stretch peak around 930 cm. See the text for detailed description.

fluences from dissimilar arrangements in different crystal lattices that will contribute to the spectra. It is of interest to examine the carboxylate stretching regions more closely, since it is anticipated that changing the cation would primarily perturb vibrations arising from this group. The asymmetric carboxylate stretch band is usually seen at 1650–1540 cm, while the symmetric stretch occurs between 1450 and 1360 cm (12).

In Figs. 2 and 3, the assignments for the IMC carboxylate stretches are shown by the solid lines. A comparison of the spectrum of the neutral form of amorphous IMC with those obtained from the salts in both figures suggests that the asymmetric carboxylate stretch peak also contains a contribution from the aromatic groups present, as shown by the enhanced νCO^- asymmetric peak intensity, thus it is a band of mixed origin. The aromatic contribution is greater in the Raman

spectrum, where the asymmetric carboxylate is expected to be weak. However, in the IR spectrum the asymmetric carboxylate band is expected to dominate.

Examination of the symmetric stretching spectral region of the salts with the spectrum of the free acid revealed a similar problem of overlap with other peaks, but in this instance it is believed that the contribution is less in the Raman spectra since the symmetric carboxylate is more Raman-active. For the reasons discussed above, it is therefore considered appropriate to use the asymmetric stretch from the IR data, and the symmetric stretch from the Raman data. It can be seen from Fig. 2 that along the series from lithium to cesium, there is a progressive decrease in the position of the symmetric carboxylate peaks and, from Fig. 3, a progressive decrease in the position of the asymmetric carboxylate peaks. A similar decrease in carboxylate stretching frequency has

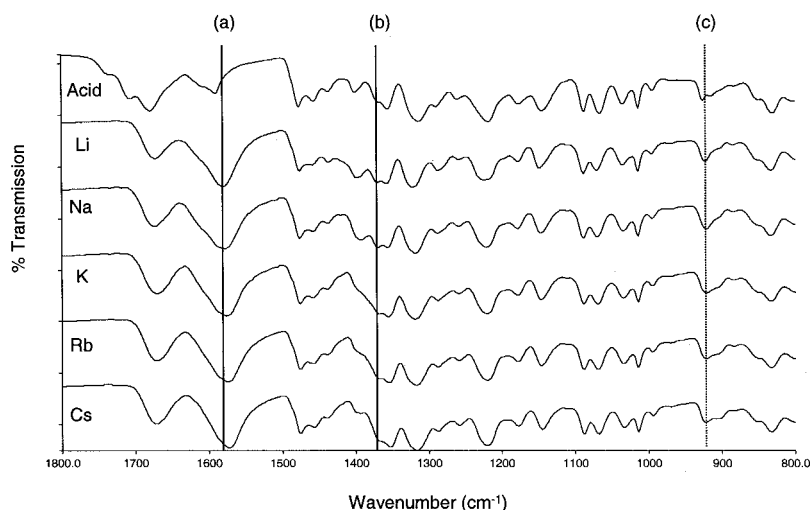


Fig. 3. FT-IR spectra of the alkali metal salts of IMC. Solid lines: (a) νCO^- asymmetric stretch peak around 1580 cm; (b) νCO^- symmetric stretch peak around 1367 cm. Dashed lines: (c) the C-C stretch peak around 930 cm. See the text for detailed description.

been observed for a series of alkali metal stearates (13,14). Attempts have been made to correlate the observed band shifts with various properties such as ionic radii, ionic mass, and electronegativity (13–15). Green *et al.* (16), however, investigated salts of several organic acids and found no simple relationships between the asymmetric and symmetric stretching positions and the properties of the cations. It was, therefore, of interest to examine the data obtained in this study more carefully. It was found for IMC salts that a linear relationship existed between the asymmetric carboxylate stretch and the ionic radius of the metal, as shown in Fig. 4. The correlation coefficient for the linear regression analysis was 0.997. The corresponding relationship for the symmetric stretch is also shown in Fig. 4, however, in this case no linear relationship could be seen, and the r^2 value for linear regression was only 0.947.

Two further spectral regions were observed to vary between the different salts, as indicated in Figs. 2 and 3 in dashed lines. The first of these is the peak, which appears between 950 and 900 cm. In the acetate ion spectrum, with the peak at 927 cm, has been assigned to C-C stretch (17). Therefore, it is reasonable to assign the peak in the IMC anion spectrum to the C-C stretch of the carboxylate carbon with the carbon positioned beta to this group, since the vibration is clearly affected by the nature of the cation. The second spectral region that shows a large variation between the different salts is between 1240 and 1280 cm. We assign the peak in this region to CH deformation and suggest that it is the CH groups that are associated with the carbon positioned beta to the carboxylate group.

Based on the above observation, it appears that there is little difference in the spectra of the alkali metal salts of IMC except in the carboxylate group and the groups immediately adjacent to this group. Otherwise, the structure appears to be minimally perturbed by the cation.

Estimation of Dynamic Properties of NaIMC and KIMC

Since sodium and potassium ions are most often used in forming salts of carboxylic acid-containing drugs, it was decided to select these two salts of IMC for further comparative analysis of amorphous properties. In a previous study, a com-

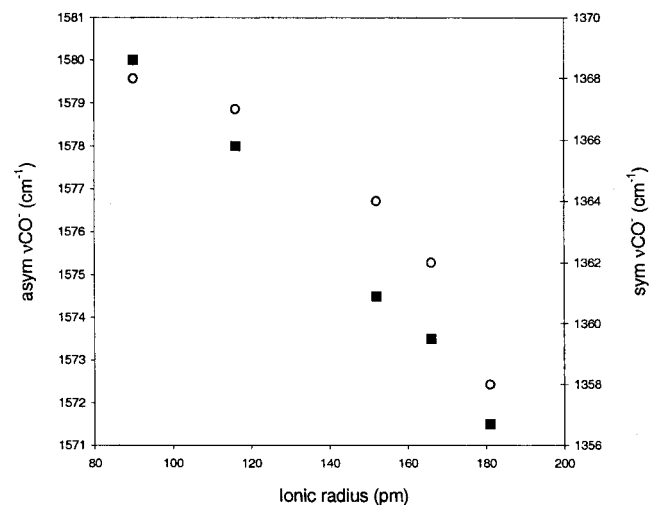


Fig. 4. Relationship between the asymmetric νCO^- (■) and symmetric νCO^- (○) frequencies and the cation ionic radius.

parison between NaIMC and IMC was made by estimating their fragilities using the scanning rate dependence of T_g and by measuring enthalpy relaxation at various temperatures below T_g , which allowed estimation of the mean relaxation time, τ , below T_g (8). From the scanning rate dependence of T_g , it was possible to estimate an apparent activation enthalpy for relaxation, ΔH^* , of 609 and 569 kJ/mol, respectively, for NaIMC and KIMC (18). These can be compared to a value of 464 kJ/mol for IMC, which was obtained earlier using the same scanning rates (8). Calculation of the fragility term m or strength parameter D using ΔH^* revealed very similar values among the three compounds, which is indicative of very similar fragilities of all three forms of IMC relative to their T_g values. Figure 5 presents a plot of τ , the average relaxation time on a log scale below T_g , which was determined using the same values of T_g - T , and indeed we see excellent agreement in relaxation behavior for all three compounds when plotted against temperature relative to their T_g values.

DISCUSSION

The T_g of a wide range of compounds, including those of biologic, food, and pharmaceutical materials, have been found to be material-specific (19). The magnitude of T_g is apparently affected by a number of factors, including structure, molecular geometry, molecular size, etc. The results from this study have highlighted that, for amorphous salt forms, the counterion also has a profound influence on T_g .

In this study, on creating the ionized form of IMC, it was observed that there is an increase in T_g , the magnitude of increase being inversely related to the ionic radius of the cation. Since the IMC salts are all monovalent, one of the direct consequences of a reduced ionic radius is an increased charge density, and it would seem likely that the increase in T_g is related to an increase in electrostatic interaction between the carboxylate anion and the alkali metal cation. Indeed, the spectroscopic data indicate that, although the different salts are remarkably similar in structure, they do exhibit differences in the region of the carboxylate group.

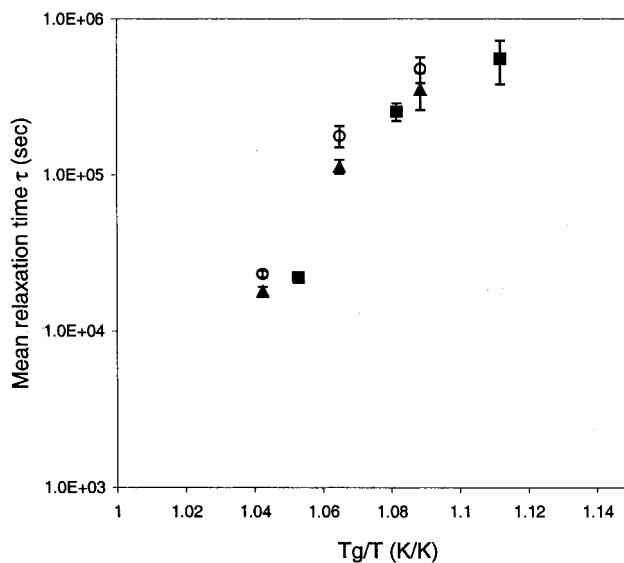


Fig. 5. Relaxation times τ against T_g/T for IMC (■), NaIMC (○), and KIMC (▲).

Furthermore, these spectral changes show a good correlation with the ionic radius of the cation (Fig. 4). These results suggest that the change in T_g observed with the different cations cannot therefore be attributed to any change in molecular conformation and support the assumption that it is some variation in ionic interactions that is important in affecting T_g .

The Li salt has the highest T_g of the series. It would be expected that this ion has the strongest electrostatic interaction with the IMC anion since, being the smallest cation, it has the highest charge density. It can be envisaged that the IMC anions and metal cations do not exist solely as ion pairs but interact further with other ion pairs. For ionic polymers, spectroscopic studies have shown that in such systems aggregates of ions are formed from ion pairs consisting of the anion and cation (20). An increase in the ion-ion interaction, which would be expected with a decrease in cation radius, would therefore be expected to result in a decrease in the molecular mobility of the molecules and an increase in the T_g , as was indeed observed. The increase in T_g on going down the series from Cs^+ to Li^+ therefore can be attributed to an increased electrostatic interaction between the carboxylate ion and the alkali metal cation.

Furthermore, packing may well be influenced by the cation/anion radius ratio, which gives an approximate measure of the degree of shielding of the cations by the anion, and, since Li has the smallest ionic radius, we suggest that packing is able to be more efficient in the Li salt, due to minimized charge repulsions between Li molecules. As the cation increases in size, the IMC anion is less able to shield the charge, therefore, packing becomes less efficient and has a negative effect on T_g . The choice of cation will thus impact an important material property, the T_g .

For the two pharmaceutically acceptable salts that were investigated in this study (i.e., Na^+ and K^+), if all other factors are equal, we might expect a sodium salt to be more stable in the amorphous form than a potassium salt at a particular storage temperature. Furthermore, based on the apparent importance of the electrostatic interaction between anion and cation, it might also be anticipated that salts from the alkali earth metal series, such as calcium and magnesium, would result in a further increase in T_g . The choice of counterion for amorphous salts should therefore be carefully considered not just in the context of the effect on solubility, but also with regard to the influence on material properties, such as reflected in the properties determined by the nature of the amorphous state, considered in this article.

It is interesting to note that despite the significant differences in T_g for these compounds, which would produce different molecular mobilities at a given storage temperature, the temperature dependency of such molecular mobility relative to T_g (i.e., fragility (9)), is very similar for these two salts (and the free acid form), indicating that no significant differences exist in the organization of the various molecules relative to one another, as might occur, for example, in a system with a significant network structure of ionic bonding, such as SiO_2 . Rather, differences primarily arise out of the strength of interaction between the cationic and anionic species.

CONCLUSIONS

The results of this study suggest that the ionic interaction, which is determined by the type of ions in an amorphous salt,

is important in influencing the T_g of the material. Thus, for the different salts of IMC, the T_g was found to decrease with the increase of the ionic radius of the alkaline cation. This decrease in T_g is believed to be caused by a decrease in the charge density of the cation, thus yielding a decrease in the electrostatic interaction between the oppositely charged ions. Spectroscopic analysis further supports that the interaction is mainly between the carboxylate ion and the alkali metal cation.

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