tabolites is becoming necessary with several pharmacological classes of drugs (antidepressants, antiarrhythmics, antiepileptics, and steroids).

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Glass Transition Temperature of Citric Acid

To the Editor:

A recent publication (1) examined solid dispersion systems using techniques similar to those we described previously (2, 3). Discrepancies between the glass transition temperature observed by the two groups of investigators (33–36°) have been explained as being due to an artifact. We hope the present observations will clarify the matter.

The glass transition temperature cannot be given an absolute value other than that extrapolated to a zero heating rate (4), because it is dependent on the rate of quenching of the glass and the heating rate employed to measure the transition. This was shown clearly by Rötger (5), who characterized the glass transition temperature by two rate indexes applicable to the quenching and heating rates of the sample. One immediate difference between the two reported studies (1, 3) was the heating rate employed during the measurement of the glass transition. Timko and Lordi (1) used 10°/min, whereas we used 2°/min (3). We also quoted the glass transition temperature as the onset of the transition (first deviation from the thermogram[1] baseline) rather than the extrapolated onset of Timko and Lordi (1), because this approach appeared to give better precision with different sample sizes. At 2°/min, the dif-

Table I—Effect of Water on Glass Transition Temperature

Water Added to Melt, % (w/w)	Glass Transition Temperature
3	−8--−13°
4	−13--−18°
5	−23--−26°

ference between the extrapolated onset and the initial deviation is only ~0.5–1°.

However, these two differences do not account for the large discrepancy reported in the two studies. For example, with our methods, the glass transition temperature of anhydrous citric acid was 7°, rather than 10° as quoted by Timko and Lordi (1).

The second difference in the two studies was the use of citric acid monohydrate (2, 3) rather than anhydrous citric acid. We believe that the discrepancy in the glass transition temperature of the two materials is due to the water bound in the glass of the monohydrate, which is difficult to remove from the melt at 150° (the temperature used in our method). This concept is in agreement with our previous suggestion (2) that using the monohydrate is advantageous because of the formation of a citric acid solution.

Since the devitrified glasses contain anhydrous citric acid, water probably is lost during crystallization of the melt and should be detectable as a weight loss. We measured the weight loss on devitrification and drying at 60° after heating the monohydrate melt for varying periods at 140–150°. After 4 min of heating, the weight loss was 4.8–5.6% (w/w); after 10 min of heating, it was reduced only to 4.3–5.3% (w/w).

The effect of water on the glass transition temperature can be shown by incorporating water into a melt of anhydrous citric acid produced by the method outlined previously (2) and above and measuring the glass transition temperature as described previously (3). The results are shown in Table I. There is some variation in the glass transition temperature due to variation in water loss on its addition to the melt. However, if the water is added when the melt is relatively cool, it induces crystallization; therefore, the system has to be reheated, resulting again in loss of water. These results are consistent with the reported weight losses and suggest that ~4.5% moisture is in the glass. If 9% (w/w) water (the amount present in the monohydrate) is added to anhydrous citric acid before melting and the glass preparation method is repeated, the glass transition temperature is −23--−24°, which is consistent with our previous results.

The results suggest that when the monohydrate is used, an unavoidable amount of water is present in the glass, which affects the glass transition temperature. This effect is reproducible, suggesting a consistent amount of entrapment in the melt. Furthermore, the properties of the anhydrous and monohydrate glasses are similar because, as a continuation of previous work (6), we found that the effect of phenobarbital on the citric acid (monohydrate) transition temperature was similar to that reported by Timko and Lordi (1).

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Charge Transfer Effect through Hydrogen Bonding in Caffeine-*p*-Cresol and Theophylline-*p*-Cresol Complexes

Figure 1—*IR spectra of chloroform solutions containing 4×10^{-2} M caffeine (—·—), 1.5×10^{-1} M p-cresol (- - -), and an equimolar mixture of the pure components (——). The baseline of the solvent is represented by the dotted line. Measurements were taken in the sodium chloride cells with a 0.05-cm path length at ~22°. The materials and methods used were those given by Al-Ani and Borazan (1).*

To the Editor:

Charge transfer transitions were detected in the UV absorption spectra of mixtures containing caffeine-*p*-cresol and theophylline-*p*-cresol in chloroform (1). To gain more information about the bonding mechanism and the various geometries of the complexes that may exist in solution, we conducted an IR study of the two combinations.

Changes can be detected in the IR absorption bands of the compounds mixed in chloroform. [The frequencies, expressed in reciprocal centimeters, were assigned according to Cross (2) and Silverstein and Bassler (3).]

Caffeine-*p*-Cresol (Fig. 1)—p-*Cresol*—The intensity of the free OH stretching vibration of *p*-cresol at 3590 decreased. The intensity of the intermolecular hydrogen-bonded OH stretching vibration increased appreciably, with a slight shift toward a longer wavelength (~5). A measurable increase in the intensity of the in-plane skeletal stretching vibrations was detected at 1615, 1595, and 1502.

Caffeine—The intensity of the CH stretching vibrations of the caffeine methyl groups at 2980 and 2945 decreased slightly. A decrease in the intensity of the carbonyl groups at C_2 (1700) and C_6 (1655) was found, with the stretching vibration at C_6 affected more.

Theophylline-*p*-Cresol (Fig. 2)—p-*Cresol*—The intensity of the free OH stretching vibration at 3590 decreased considerably. An appreciable increase in the intensity of the hydrogen-bonded OH stretching vibration at 3370 of the self-associated species was observed, with a considerable shift toward a longer wavelength (3320). The intensity of the aromatic CH stretching vibration at 2990 decreased noticeably, while a slight decrease was observed in the bands of the CH stretching vibrations of the methyl group at 2920 and 2860. The intensity at 1615 and 1502 of the in-plane skeletal stretching vibrations decreased slightly.

Theophylline—An increase in the free NH stretching vibration at 3425 was observed. The broad band of the
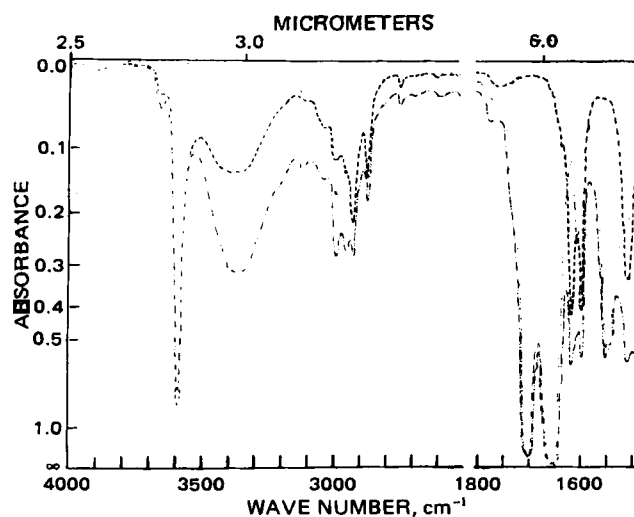
hydrogen-bonded NH overlapping the CH stretching vibration at 3300–3000 seemed to be affected to a different extent; the maximum percentage increase was at 3260, while the minimum increase was at 3150. At 3060, a noticeable decrease was found. The intensity of the bands at 2990 and 2952, representing the CH methyl stretching vibrations, was decreased. A considerable decrease was found in the intensity of the C_2=O band at 1700, while a smaller decrease was found for the C_6=O band at 1655. A decrease was observed at 1551 of the C=C and C=N stretching vibrations of the ring.

Based on theory and experimental observations (4–7), changes in the IR spectra may be explained as being due to the formation of heterogeneous complexes or to the formation of self-associated species.

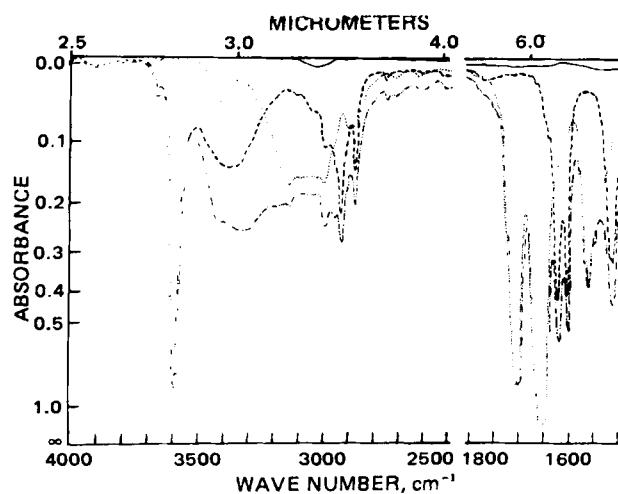Calculation of dilution effects on *p*-cresol in chloroform

Figure 2—*IR spectra of chloroform solution containing 2×10^{-2} M theophylline (. . .), 1.5×10^{-1} M p-cresol (- - -), and an equimolar mixture of the pure components (——). The baseline of the solvent is represented by the solid line. Measurements were taken in sodium chloride cells with a 0.05-cm path length at ~22°.*