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Received January 4, 1979.
Accepted for publication January 25, 1980.
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Charge Transfer Effect through Hydrogen Bonding in Caffeine–*p*-Cresol and Theophylline–*p*-Cresol Complexes

Keyphrases ☐ Charge transfer effect—hydrogen bonding in caffeine–*p*-cresol and theophylline–*p*-cresol complexes ☐ Caffeine—hydrogen bonding in complex with *p*-cresol ☐ Theophylline—hydrogen bonding in complex with *p*-cresol

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

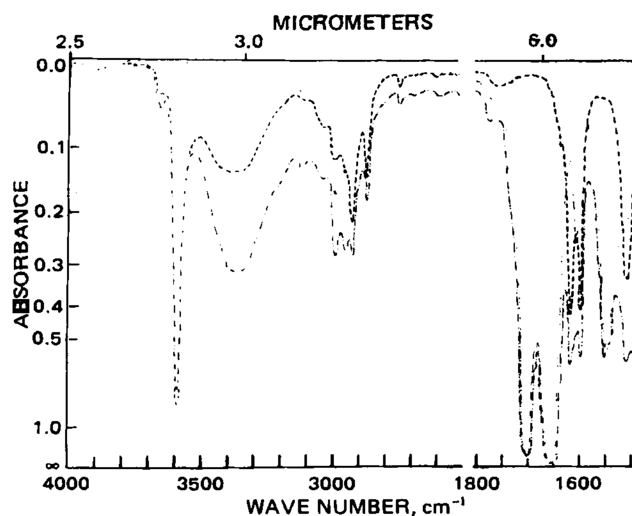

Figure 1—*IR spectra of chloroform solutions containing 4 × 10^{-2}* M *caffeine (-—-), 1.5 × 10^{-1}* M *p-cresol (- - -), and an equimolar mixture of the pure components (-·-·-). The baseline of the solvent is represented by the dotted line. Measurements were taken in the sodium chloride cells with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

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

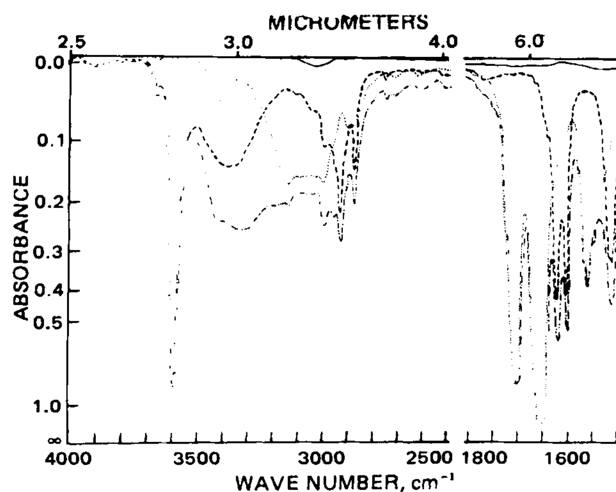

Figure 2—*IR spectra of chloroform solution containing 2 × 10^{-2}* M *theophylline (. . .), 1.5 × 10^{-1}* M *p-cresol (- - -), and an equimolar mixture of the pure components (-·-·-). The baseline of the solvent is represented by the solid line. Measurements were taken in sodium chloride cells with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

0022-3549/80/0500-0613$01.00/0
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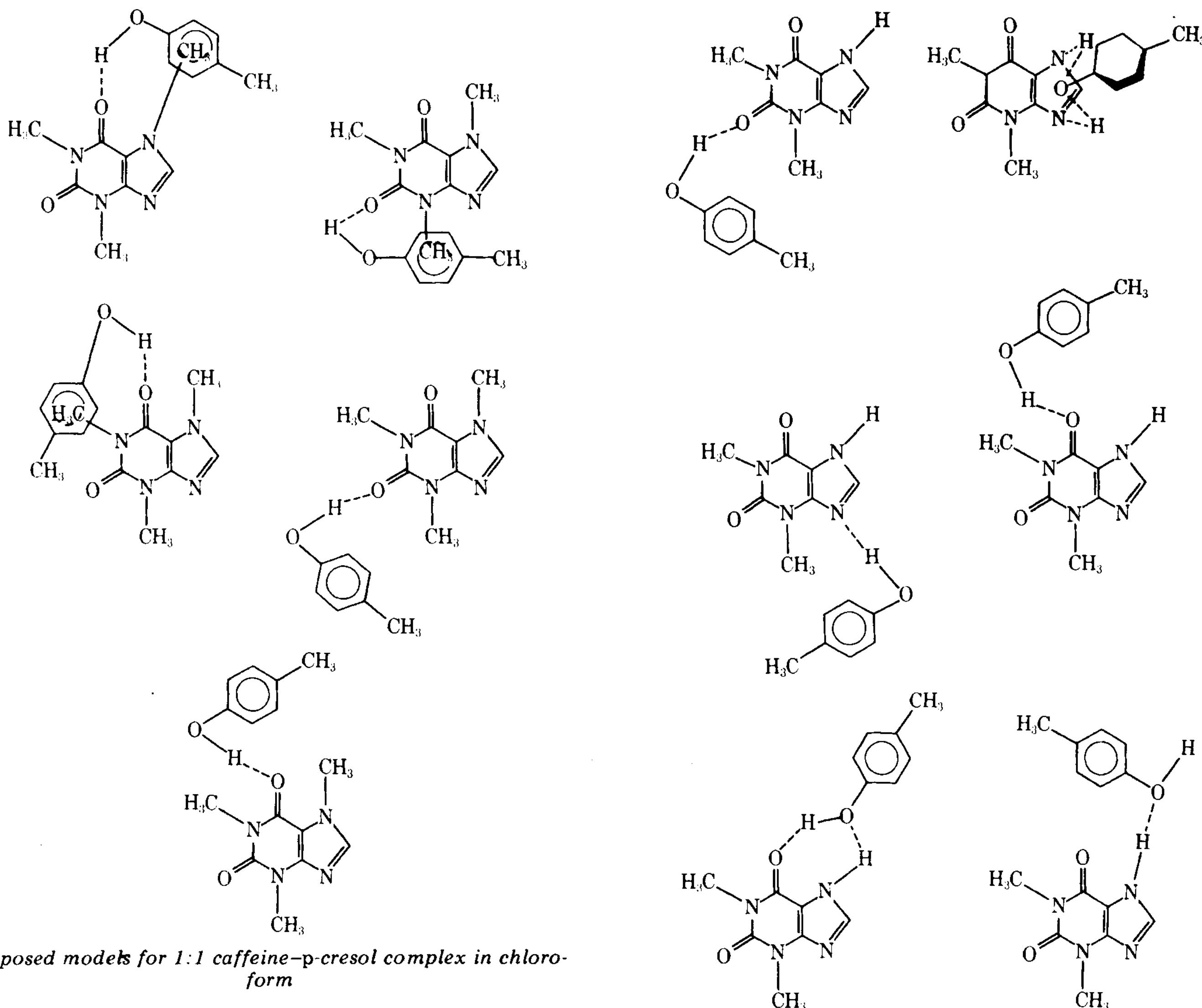

*Proposed models for 1:1 caffeine–*p*-cresol complex in chloroform*

*Proposed models 1:1 theophylline–*p*-cresol complex in chloroform*

indicated that the band at 3590 increased while the band at 3370 decreased. These results are further evidence that the first band can be attributed to the free OH stretching vibration while the second one can be assigned to the hydrogen-bonded OH of the self-associated species. The band at 2990 of the aromatic CH stretching vibration also increased. However, bands belonging to the CH stretching vibrations of the methyl groups (2920 and 2860) were unaffected; those of the in-plane skeletal stretching vibrations (1615, 1595, and 1502) all increased. The band at 1502 was shifted toward shorter wavelength (1512) with a drastic increase in absorption.

All of these results indicate the presence of self-associated molecules. The groups involved in bonding are the hydroxyl group and the benzene ring. However, it is difficult to propose an exact geometry or a stoichiometry of such self-associated species. Nevertheless, the following geometries of the self-associated aggregates may be proposed: hydrogen-bonded dimers, stacks of hydrogen-bonded dimers with methyl groups projected away from each other, stacked hydrogen-bonded dimers, and spherically oriented polymers with the OH groups projected inward and the nonpolar methyl groups oriented outside.

It is evident from changes in the IR spectrum (Fig. 1) of the solution containing caffeine–*p*-cresol that the areas that contribute most to the formation of the complex are the OH group and the skeletal carbons of *p*-cresol and the $C_2{=}O$, $C_6{=}O$, and CH_3 groups of caffeine. The models proposed for the geometry of a 1:1 complex are presented.

When theophylline is mixed with *p*-cresol, a complex appears to be formed (Fig. 2). The groups predominantly involved in formation of such a complex are the OH group and the aromatic CH group of *p*-cresol and the NH, aromatic CH, methyl CH, $C_2{=}O$, and $C_6{=}O$ groups of theophylline. The formation of a planar complex where hydrogen bonding is the dominant attractive force contributing to its formation may be proposed.

The increase in the intensity of the band corresponding to the free NH stretching vibration at 3425 may be due to overlapping with the hydrogen-bonded hydroxyl group of *p*-cresol or may result because dimers and polymers of theophylline, held together through hydrogen bonds with their NH groups, dissociate to interact with molecules of *p*-cresol and to free some of the bonded NH groups.

The equilibrium constants, calculated at 22°, of both

complexes were 0.22 and 0.16 M^{-1} for caffeine–p-cresol and theophylline–p-cresol, respectively, at 308 nm (1). On the other hand, the molar absorptivities of these complexes at the intermolecular hydrogen-bonded OH stretching vibration band, 3370 cm^{-1}, were $\sim 3 \times 10^3$ and $\sim 4.3 \times 10^3$ for caffeine–p-cresol and theophylline–p-cresol, respectively.

The present work supported the theory that hydrogen bonding is a type of charge transfer phenomenon (8–10).

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Received August 27, 1979.
Accepted for publication December 3, 1979.
The authors thank Professor Hatif H. Al-Jalil for encouragement.

Pilocarpine Ocular Distribution Volume

Keyphrases □ Pilocarpine—ocular volume of distribution □ Volumes of distribution—ocular distribution of pilocarpine □ Ophthalmic drugs—pilocarpine, ocular volume of distribution

To the Editor:

It is well established that drugs introduced into the body by various routes distribute to and equilibrate with the blood as well as numerous body tissues. Thus, the apparent volume of distribution has become a useful parameter in explaining the drug concentrations achieved in the blood after dosing and for determining the extent of absorption of various agents administered in different formulations or dosage forms.

Similarly, apparent distribution volumes also are useful in describing the ocular disposition characteristics of drugs administered topically to the eye. To make meaningful statements regarding the bioavailability of an ophthalmic preparation, it is necessary to know the apparent volume of distribution for that drug in the eye.

As with volumes of distribution obtained for drugs administered by other routes, various factors can affect apparent volumes of distribution of ocular drugs. These factors include protein binding, tissue distribution, pigmentation of the eye, and, of course, any pharmacological action the drug itself might exert. Therefore, the following discussion is limited to pharmacokinetic data obtained in albino rabbits of approximately the same weight.

Conrad and Robinson (1) developed a method of quantitating apparent ocular drug distribution volumes in experimental animals by injecting drug directly into the anterior chamber and monitoring the decline in the aqueous humor concentration as a function of time. The data from the study were used subsequently[1] (2, 3) to quantitate and describe the disposition of drugs in the eye.

Conrad and Robinson (1) determined the apparent volumes of distribution and elimination rate constants for both a therapeutically active substance (pilocarpine) and a nondistributing species (inulin). From the relationship:

$$Cl = V_d K \qquad \text{(Eq. 1)}$$

and the values obtained for inulin, a clearance of 4.59 μl/min from the aqueous humor was obtained. Since inulin neither binds nor distributes into the tissues and exits the anterior chamber solely *via* aqueous humor drainage, this value should represent normal aqueous humor turnover. The calculated value is consistent with values reported by other investigators (4, 5) for aqueous humor turnover in rabbits. Similarly, unless an agent is known to decrease aqueous humor turnover, the value of 4.59 μl/min also should represent the slowest possible clearance of any compound from the aqueous humor.

Following intracameral injection, the aqueous humor concentration of pilocarpine declined monoexponentially with an apparent first-order elimination rate constant of 0.059 min^{-1}. Based on the reported volume of distribution of 575 μl, a clearance value of 33.9 μl/min was obtained for pilocarpine. Since pilocarpine is known to facilitate aqueous humor outflow, it is not surprising that the elimination rate constant for pilocarpine and, in turn, the clearance were greater than those observed for inulin.

In a recent study by Makoid and Robinson (6), the decline of pilocarpine concentration in the aqueous humor following topical dosing was multiexponential when followed for 12 hr. Conrad and Robinson (1) only followed the aqueous humor concentration of pilocarpine for 1 hr after direct intracameral injection. The effect that this apparent discrepancy might have in determining the ocular volume of distribution for pilocarpine led us to examine further the decline in the aqueous humor concentration following direct injection into the aqueous humor.

For this study, the experimental procedure of Conrad and Robinson was repeated with pilocarpine of a higher specific activity (19.7 mCi/mg). In the original study, Conrad and Robinson (1) measured aqueous humor levels of pilocarpine at 5, 10, 15, 20, 30, and 60 min after injection, but they stated that the accuracy of their 60-min time point was in doubt. In our study, the 30-min point was excluded; however, a 25-min point was added, and sampling was extended to include 45-, 60-, 90-, and 120-min points.

Figure 1 shows the results of this study when 10 μl of 1 $\times 10^{-4}$ M pilocarpine was injected intracamerally. The

[1] M. C. Makoid and J. Cobby, presented at the APhA Academy of Pharmaceutical Sciences, Anaheim meeting, April 1979.

0022-3549/80/0500-0615$01.00/0
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