Structure and Reactivity of Theobrominate and Theophyllinate Complexes with Methyl *trans*-Cinnamate

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Abstract □ The structure of the methyl *trans*-cinnamate complexes with the theophylline and theobromine anions is calculated theoretically by maximizing the binding energy of the two interacting molecules. The binding energy is calculated using the monopoles-bond polarizabilities method. The predicted structures correlate well with observed reactivity of the ester in the two complexes.

Keyphrases □ Theobromine—structure and reactivity of complexes with methyl *trans*-cinnamate, theoretical calculation by maximizing binding energy □ Theophyllinate—structure and reactivity of complexes with methyl *trans*-cinnamate, theoretical calculation by maximizing binding energy □ Methyl *trans*-cinnamate—structure and reactivity of theobrominate and theophyllinate complexes

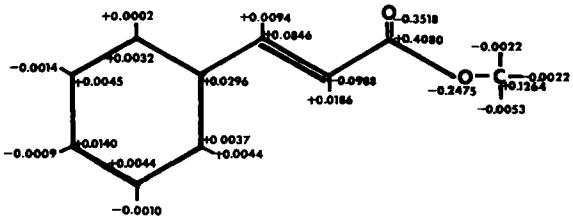
In a previous report (1), the method of monopoles-bond polarizability was discussed and applied to the calculation of the absolute interaction energy and structures of some electron donor–acceptor complexes. These results were then combined with a cavity model for the solvent to calculate the heat of complexation in solution (2). The agreement between theoretical calculations and experimental results was quite good. In this publication, attention is focused on the structure of complexes in solution.

The inhibition of a chemical reaction by a complexing ligand has frequently been observed. It was reported (3, 4) that caffeine inhibits the hydrolysis of benzocaine and procaine in aqueous solution, and this was attributed to complexation. The rate of alkaline hydrolysis of riboflavin and the ester 3-carbomethoxy-1-methylpyridinium cation was shown to be inhibited by xanthines (5, 6). The inhibition of the photodecomposition of menadione by electron donors has also been attributed to complexation (7).

Methods have been presented for separating out the reaction rate of the complexed drug (8, 9). The fractional decrease in reactivity of the complexed substrate was defined (8, 9) relative to the free substrate to be q_{11}:

$$q_{11} = 1 - \frac{k_{cs}}{k_s} \qquad \text{(Eq. 1)}$$

where k_s is the substrate reactivity, and k_{cs} is the reactivity of the substrate bound to the ligand. For the alkaline hydrolysis of the methyl *trans*-cinnamate ester–theobrominate complex, $q_{11} = 1.0$; for the corresponding theophyllinate complex, $q_{11} = 0.9$. Since the stability constants for the two ligands are about the same, a possible reversal of the xanthine–cinnamate orientation was suggested, with the theobrominate ligand occupying a position closer to the ester carbonyl (9). This orientation would be expected to lower the reaction rate on the basis of steric interference of the attacking nucleophile as well as a possible raising of the activation energy for tetrahedral intermediate formation.



I: methyl *trans*-cinnamate [(*S-cis*)]

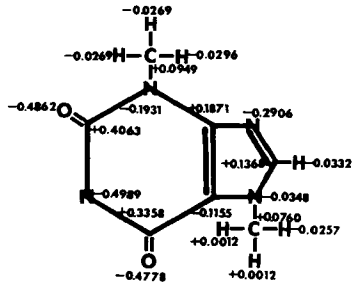
In this report this suggestion is tested by determining the structures of the two complexes theoretically.

THEORETICAL

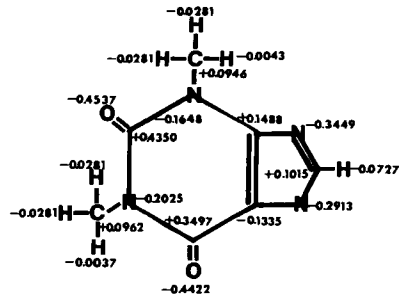
In a previous publication (2), it was concluded that the solvent term provides a general driving force toward the maximum overlapping of areas in carbon tetrachloride. This seems to be also true in aqueous solutions (2, 9, 10).

If several structures have nearly the same maximal overlap areas, then the preferred structure will be that which maximizes the absolute interaction energy. It is on this basis that a calculation of the complex structure is approached by maximizing the absolute interaction energy.

The absolute interaction energies are calculated using the monopoles-bond polarizabilities method (1, 11). The necessary data are taken from the references cited in a previous paper (1). The charge distributions were calculated by the CNDO/2[1] method (1, 2) for methyl *trans*-cinnamate (I) and the theobrominate (II) and theophyllinate (III) anions. As can be observed, the negative charge on the anions (II and III) does not reside solely at the nitrogen from which the proton was removed but is considerably delocalized to



II: theobromine anion



III: theophylline anion

[1] Complete neglect of differential overlap/second parameterization.

Table I—Interaction Energies[a] for the Methyl *trans*-Cinnamate–Theobrominate Complex

Structure	R	El[b]	Pol[b]	Disp[b]	Rep[b]	E_{tot}[b]
IV	3.4	−2.879	−3.720	−17.203	8.641	−15.162
V	3.3	−2.812	−3.792	−18.540	10.167	−14.978
	3.4	−2.712	−3.544	−16.157	7.444	−14.971
VI	3.4	−2.808	−3.089	−16.635	8.267	−14.264
	3.3	−2.903	−3.294	−19.129	11.327	−14.000
VII	3.4	1.402	−3.678	−15.849	7.338	−10.787

[a] In kilocalories per mole. [b] El = electrostatic, Pol = polarization, Disp = dispersion, Rep = repulsive, and E_{tot} = total energies.

Table II—Interaction Energies[a] for the Methyl *trans*-Cinnamate–Theophyllinate Complex

Structure	R	El[b]	Pol[b]	Disp[b]	Rep[b]	E_{tot}[b]
VIII	3.5	−1.121	−2.890	−15.268	7.173	−12.107
	3.4	−1.173	−3.069	−17.521	9.913	−11.850
IX	3.5	−1.340	−2.793	−15.653	7.231	−12.556
	3.4	−1.391	−2.965	−17.968	9.996	−12.328
X	3.4	−2.603	−2.953	−16.270	8.121	−13.707
XI	3.4	−1.452	−3.351	−17.163	8.273	−13.594

[a] In kilocalories per mole. [b] See Footnote *b* of Table I.

the remaining electronegative atoms (these calculations include both σ and π electronic charges). In general, the carbon atoms became slightly less positive and the electronegative atoms became considerably more negative on ionization. The theoretically calulated ionization energy, ΔE(ionization) = E(anion) − E(neutral xanthine), is larger for theobromine than theophylline, in line with its higher experimental pKa (10.1 *versus* 8.7). The charge distribution for methyl *trans*-cinnamate (I) is that of the *(S)-cis* form, referring to the arrangement of the two double bonds (12). The CNDO/2 method predicts the *(S)-cis* form to be about 1 kcal/mole more stable than the *(S)-trans* form, with the charge distributions being nearly identical. The results reported in this paper refer to the *(S)-cis* form.

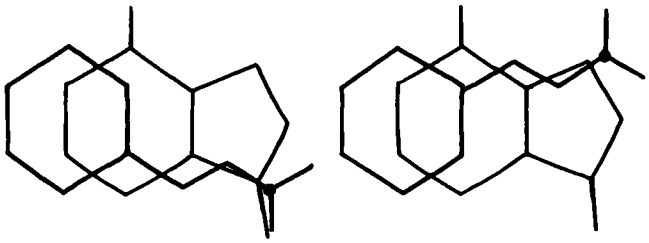
In determining the preferred structures of these complexes, an initial potential energy map was made to determine the location of the various potential energy minima and then the location and energy of each minimum were further refined. The reported results refer to the energetically preferred positions. Approximately 100 different structures for each complexing pair were considered to locate the region(s) of maximum binding.

RESULTS AND DISCUSSION

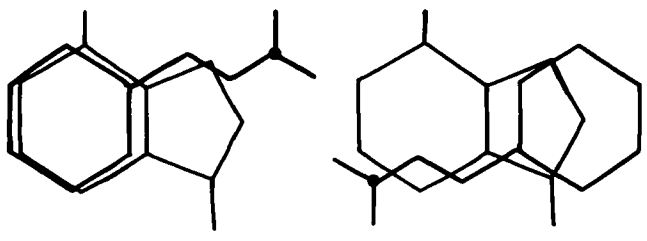
Several structures (IV–VII) were considered for the methyl *trans*-cinnamate–theobrominate complex, and the absolute interaction energies for these structures are presented in Table I. The interatomic distance, R, is the distance in Å between the planar rings of the two interacting molecules. The position of maximum binding for this complexing pair is Structure IV. Structure V shows a slightly lower interaction energy. Structure VI, with the six-membered ring of the cinnamate directly above the six-membered ring of the xanthine, is energetically less favorable due to a reduced dispersion energy. Structure VII is considerably less favorable than the other three structures due to a repulsive electrostatic energy. This results from the interaction of the negatively charged oxygens on methyl *trans*-cinnamate with the negatively charged nitrogen and oxygen of the theobrominate ion and illustrates the significant effect that complementary charge distributions in polar molecules can have on the absolute interaction energies.

These results for the methyl *trans*-cinnamate–theobrominate complex indicate that the substrate is positioned over the ligand in a broad potential energy well. The position of maximum binding, *i.e.*, the lowest point on the potential energy surface, places the reactive carbonyl carbon over the five-membered ring of the xanthine. This positioning is consistent with the proposed mechanism of reaction inhibition by the ligand.

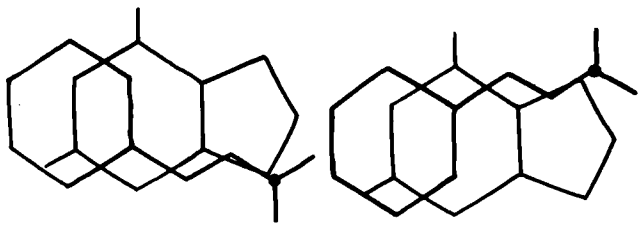
Several structures (VIII–XI) were considered for the theophylli-



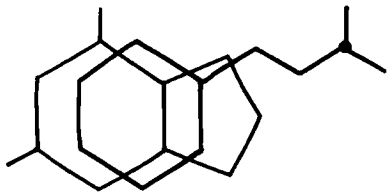
IV V



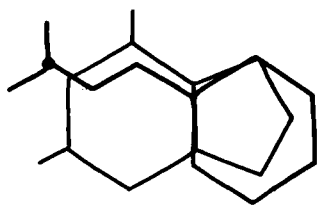
VI VII



VIII IX



X



XI

nate–methyl *trans*-cinnamate complex, and the corresponding absolute energies are given in Table II. Structures VIII and IX are similar to the preferred structures for the theobrominate–methyl *trans*-cinnamate complex but are energetically less favorable compared to Structure X. In comparing Structures VIII and IX for the two ligands (Tables I and II) at an interplanar distance of 3.4 Å, it is seen that the reduced interaction energy for theophyllinate as compared to theobrominate results from an increased repulsion. This is due to the presence of the methyl group in the 1-position on the xanthine and a reduced electrostatic attraction, which results from the repulsive electrostatic interaction of the ester oxygens with the xanthine nitrogens. Structure XI, with the carbonyl carbon of methyl *trans*-cinnamate positioned approximately over the 2-position of the xanthine, is also energetically allowed.

This shift in position of the substrate over the ligand is even more evident in comparing the potential energy curves in Fig. 1. The solid curve and energy scale on the left of the figure correspond to the theobrominate complex, and the dashed curve and the scale on the right correspond to the theophyllinate complex. These curves were calculated, holding the interplanar distance constant and displacing the substrate either to the right (positive) or to the left (negative). For example, the zero position (displacement) corresponds to Structure VI while a displacement of −1.2 Å corresponds to Structure V. From Fig. 1, it is clear that the position of the potential energy minimum moves considerably to the right for the theophyllinate complex, corresponding to Structure X. These results on the theophyllinate–methyl *trans*-cinnamate complex indicate that Structure X, with the aromatic ring of the methyl *trans*-cinnamate positioned over the center of the xanthine, is energetically the most favorable. In this position, the reactive carbonyl carbon is considerably extended into the solvent. With this being the most energetically favorable position for the theophyllinate complex, the reactivity of the ester in this complex would be expected to be greater than the theobrominate complex. However, in both complexes the double bond of the cinnamate remains over the ligand and is consistent with a $q_{11} = 1$ for sulfite attack at this position (13).

From Table II it is also evident that Structure XI is energetically almost as favorable as Structure X. In this position it might be expected that the carbonyl carbon would be hindered and less reactive. Hence, there are at least two and probably more complex structural isomers that may have differing reactivities as well as equilibrium constants. The experimentally determined fractional decrease in reactivity, q_{11}, is obtained from the intercept of a plot of $k_s/(k_s - k_{s'})$ *versus* $1/L$, where k_s is the reactivity of the uncomplexed substrate, $k_{s'}$ is the observed reactivity in the presence of the ligand, and L is the ligand concentration (8, 13). If more than a single 1:1 complex exists (*e.g.*, isomeric 1:1 complexes or 2:1 complexes), the interpretation of the intercept is more complex (13). In the general case, if K_i is the equilibrium constant for the ith type of complex, either a 1:1 (of which there may be several) or 2:1, *etc.*, the equation becomes:

$$\frac{k_s}{k_s - k_{s'}} = \frac{1}{\Sigma q_i K_i(L)} + \frac{K}{\Sigma q_i K_i} \qquad \text{(Eq. 2)}$$

where q_i is the fractional decrease in reactivity of complex i:

$$K = \Sigma K_i \qquad \text{(Eq. 3)}$$

and the sum, Σ, is over all complexes[2]. Hence, in the general case:

$$\frac{1}{\text{intercept}} = \frac{\Sigma q_i K_i}{\Sigma K_i} \qquad \text{(Eq. 4)}$$

and is a weighted (according to the K_i) average of the q_i. Thus, the observed $q = 0.9$ for the theophyllinate–methyl *trans*-cinnamate complex could be ascribed to a $q_1 = 1$ for Structure XI, a $q_i = 0$ for all other complexes, and a ratio of $K_1/\sum_i K_i = 0.9$.

SUMMARY

A comparison of the theoretical results for the complexes of the theobrominate and theophyllinate anions with methyl *trans*-cinnamate indicates that the side chain of the methyl *trans*-cinnamate does not interact as strongly with the theophyllinate ligand as with the theobrominate ligand. This places the reactive carbonyl carbon of the substrate in a position more accessible to the solvent (and the nucleophile) when the ligand is the theophyllinate ion and, therefore, a more reactive complex. On the other hand, with the strong interaction of the substrate side chain with the theobrominate-ion ligand, the expected reactivity of the complex would be relatively low. These results are thus consistent with the proposed mechanism of reaction inhibition through complexation and indicate that the theoretical method may be a useful tool in studying such complexes.

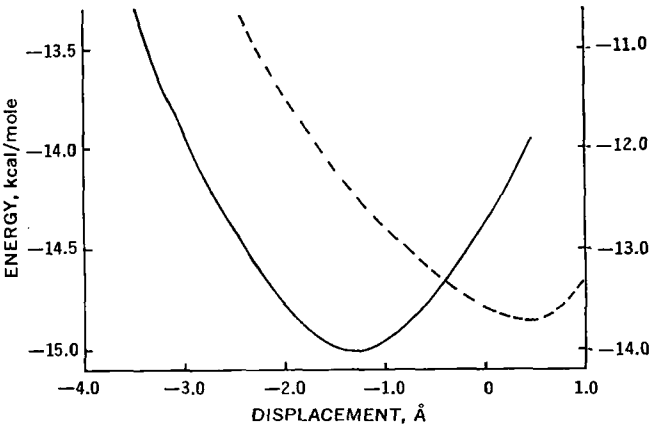


Figure 1—*Potential energy curves for the theobrominate (——) and theophyllinate (- - -) complexes with methyl* trans*-cinnamate.*

REFERENCES

(1) G. L. Amidon, *J. Pharm. Sci.*, **63**, 1514(1974).
(2) *Ibid.*, **63**, 1520(1974).
(3) T. Higuchi and L. Lachman, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 521(1955).
(4) L. Lachman, L. J. Ravin, and T. Higuchi, *ibid.*, **45**, 290(1956).
(5) P. A. Wadke and D. E. Guttman, *J. Pharm. Sci.*, **54**, 1073(1965).
(6) D. Brooke and D. E. Guttman, *ibid.*, **57**, 1677(1968).
(7) S. Hata, K. Mizano, and S. Tomioka, *Chem. Pharm. Bull.*, **16**, 1(1968).
(8) K. A. Connors and J. A. Mollica, *J. Pharm. Sci.*, **55**, 772(1966).
(9) J. L. Cohen and K. A. Connors, *ibid.*, **59**, 1271(1970).
(10) O. Sinanoglu, in "Molecular Associations in Biology," B. Pullman, Ed., Academic, New York, N.Y., 1968, p. 427.
(11) P. Claverie, *ibid.*, p. 115.
(12) K. A. Connors, M. H. Infeld, and B. J. Kline, *J. Amer. Chem. Soc.*, **91**, 3597(1969).
(13) P. A. Kramer and K. A. Connors, *ibid.*, **91**, 2600(1969).

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[2] This is a straightforward extension of Eq. 49 in Ref. 8, in which there is a typographical error.