than alkyl vinyl ethers owing to the presence of the carbonyl group and that as a result the critical transition state is reached when proton transfer to the olefin is complete; the mechanism of hydrolysis is then the same as for vinyl ethers with the provision that proton transfer be complete.

The mechanism of eq 3 satisfies the data. Further experimentation is required in order to accommodate the proton-transfer reactions of **1** within the framework of what is known of the mechanisms of vinyl ether hydrolysis and the hydrations of α,β-unsaturated ketones.

Interactant Structure and Complex Stability for Complexes of Theophylline with Cinnamate Esters and Related Compounds in Aqueous Solution[1]

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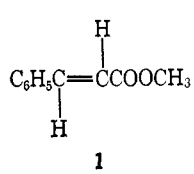
Abstract: Complex stability was evaluated by means of the spectral, solubility, and kinetic techniques for interactions between many esters and related compounds with theophylline and its anion. Stability constants were determined in aqueous solution at 25.0° and ionic strength 0.30 *M*. A plot of standard unitary free energy change for complex formation (for complexes of neutral interactants) against estimated planar area of the smaller interactant gives a rough but reasonable linear correlation over two orders of magnitude range in stability constant. A simple model of the complex formation process is consistent with this observation. It is suggested that these 1–1 complexes have a plane-to-plane orientation, that the solvent is important in determining complex stability, and that the complex structures probably do not involve maximum π-orbital overlap, but do permit extensive local dipole and induced dipole interactions.

It is not yet possible to make general statements about the stability of organic complexes in solution, though numerous limited correlations of complex stability with interactant properties have been described.[2] In an earlier paper[3] we reported stability constants for complex formation between methyl *trans*-cinnamate (**1**) (the *substrate*, or interactant whose property is measured in the solution) with numerous



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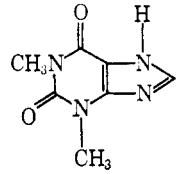

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heterocyclic *ligands* (the second interactant, whose concentration is the independent variable). The present paper describes studies on many substrates chosen as systematic variants of the methyl *trans*-cinnamate structure. Theophylline (**2**) or its anion (theophyllinate) was the ligand in most of these studies. Comparative studies by more than one technique were employed when possible to aid in detecting multiple equilibria and higher stoichiometries.[4]

Experimental Section

Materials. Methyl *trans*-cinnamate, *trans*-cinnamic acid, theophylline, and imidazole have been described earlier.[3] Ethyl *trans*-cinnamate (Eastman) was distilled; bp 122–123° (5–6 mm) (lit.[5] 128–133° (6 mm); 138–140° (10 mm)). Isopropyl *trans*-cinnamate (K & K) was distilled; bp 107° (1–2 mm) (lit.[6] 107.5–108° (2 mm)). *p*-Nitrophenyl *trans*-cinnamate was recrystallized from ethanol–water; mp 145–146.5° (lit.[7,8] 146°, 146.5–147.5°). *N*-*trans*-Cinnamoylimidazole was prepared by the method of Schonbaum, *et al.*,[9] mp 133° (lit.[9] 133–133.5°). *trans*-Cinnamaldehyde (Eastman) was shaken with 10% sodium carbonate solution, washed with water, dried over magnesium sulfate, and then distilled; bp 93–94° (1–2 mm) (lit.[10] 98–100° (3–4 mm)). *trans*-Benzalacetone (Eastman) was recrystallized twice from Skellysolve B; mp 40–41.5° (lit.[11] 41–42°). *p*-Methoxyphenyl *trans*-cinnamate was prepared from cinnamoyl chloride and *p*-methoxyphenol and recrystallized from 95% ethanol; mp 97.5–98.5°. *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.66; H, 5.49. *trans*-Cinnamyl acetate (J. T. Baker Chemical Co.) was distilled; bp 111–112° (2 mm) (lit.[12] 111–112° (2 mm)). Phenacyl acetate (East-

(1) Part IV in the series "Modification of Reaction Rates by Complex Formation." For part III see P. A. Kramer and K. A. Connors, *J. Amer. Chem. Soc.*, **91**, 2600 (1969).

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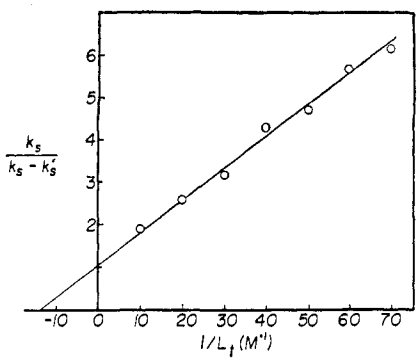

Figure 1. Kinetic plot according to eq 4 for the alkaline hydrolysis of phenyl *trans*-cinnamate in the presence of theophyllinate as ligand: pH 11.78, ionic strength 0.30 *M*, 0.40% acetonitrile, 25.0°.

man) was distilled, bp 130–132° (4 mm), mp 47–48.5° (lit.[13] 46–48°). α-Methyl *trans*-cinnamic acid (Aldrich) was recrystallized twice from Skellysolve B; mp 79.5–80.5° (lit.[14] 79–80.5°). β-Methyl *trans*-cinnamic acid (Eastman) was recrystallized twice from Skellysolve B; mp 95.5–96.5° (lit.[15] 94–96°). *trans*-Cinnamamide was prepared from cinnamoyl chloride and ammonium hydroxide and was recrystallized from ethanol–water; mp 147° (lit.[16] 147°). Benzamide was recrystallized from water, mp 130° (lit.[17] 128–130°).

Methyl hydrocinnamate was prepared from methanol and hydrocinnamoyl chloride (Eastman); bp 73.5° (3 mm), 233° (lit.[18] 82–86 (0.3 mm)); saponification equivalent: calcd, 164.21; found, 163.7, 164.2. Hydrocinnamic acid (Eastman) was recrystallized from water, mp 47–48° (lit.[19] 47.5–48°). Methyl acetate was distilled from phosphorus pentoxide; bp 56.5° (lit.[20] 57.1°). Methyl benzoate (Matheson Coleman and Bell) was distilled: bp 196.5–197° (lit.[21] 199.45° (760 mm)). Methyl crotonate (Matheson Coleman and Bell) was distilled; bp 117–118° (744 mm) (lit.[22] 118.6–119.6° (760 mm)). Methyl 1-naphthoate was prepared by treating 1-naphthoyl chloride (Eastman) with methanol in pyridine; the product was purified by distillation; bp 171–172° (17 mm) (lit.[23] 159–160° (10 mm)). Methyl 2-naphthoate was prepared from 2-naphthoyl chloride and methanol and was recrystallized from water–ethanol; mp 78° (lit.[24] 76°). Methyl 2,6-dichloro-*trans*-cinnamate was prepared by refluxing 2,6-dichloro-*trans*-cinnamic acid (Aldrich) with methanol for 10 hr in the presence of sulfuric acid. The product was purified by a short-path vacuum distillation, being collected as white needles on a cold-finger condenser; mp 51.5–52°. *Anal.* Calcd for $C_{10}H_8Cl_2O_2$: C, 51.98; H, 3.49; Cl, 30.69. Found: C, 52.11; H, 3.55; Cl, 30.72. The nmr spectrum in $CDCl_3$ yielded a singlet at τ 6.15 (methyl), two sets of doublets at 3.42 and 2.20 (olefinic protons, J = 16 Hz), and a multiplet at 2.72 (aromatic). The integration yielded 3:1:1:3 for the four types of protons.

cis-Cinnamic acid was prepared by catalytic hydrogenation of phenylpropiolic acid on Lindlar-type catalysts.[25] The product was purified by Liebermann's aniline salt precipitation,[26] and was recrystallized from ligroin; mp 67–68° (lit.[27] 68°). Methyl *cis*-cinnamate was obtained by treating *cis*-cinnamic acid with diazomethane in ether. The ester was distilled; bp 126.5–128° (17–18 mm) (lit.[28] 129–130° (17 mm)); mp −3 to −2° (lit.[29] −3.5°, −2°). The nmr spectrum in $CDCl_3$ gave a singlet at τ 6.35 (methyl), two sets of doublets at 4.10 and 3.12 (olefinic protons, J = 13 Hz), and a multiplet at 2.61 (aromatic). Integration gave the ratio 3:1:1:5 for these types of protons.

Phenyl *trans*-cinnamate was recrystallized from ethanol–water; mp 75.5–76.5° (lit.[30] 75–76°).

Many ultraviolet spectral data, solubilities, and rate constants for these compounds are reported elsewhere.[31]

Procedures. The spectral and solubility techniques were used for studying complex stability as described earlier.[1,3] For spectral studies with a few substrates (cinnamic acid and cinnamate anions) the total substrate concentration, S_t, was an appreciable fraction (up to 0.1) of the total ligand concentration, L_t, so an iterative procedure was used to find the stability constant.[32]

The kinetic method[1,4] is less familiar and will be briefly outlined. If substrate S and ligand L interact to form the 1:1 complex SL, the kinetic scheme is

$$S + L \underset{}{\overset{K_{11}}{\rightleftharpoons}} SL \qquad (1)$$

$$S + R \xrightarrow{k_S} \text{products} \qquad (2)$$

$$SL + R \xrightarrow{k_{11}} \text{products} \qquad (3)$$

where k_S is the second-order rate constant for reaction of S with reagent R, and k_{11} is the corresponding constant for reaction of SL. The experimental technique requires evaluation of the apparent second-order rate constant k_S' as a function of the molar ligand concentration. Equation 4 describes the behavior of the system[4] (k_{11} is smaller than k_S for the systems described here)

$$\frac{k_S}{k_S - k_S'} = \frac{1}{q_{11}K_{11}[L]} + \frac{1}{q_{11}} \qquad (4)$$

where $q_{11} = 1 - k_{11}/k_S$; q_{11} can be interpreted as the fractional decrease in reactivity of the complexed substrate relative to uncomplexed substrate. From a plot of $k_S/(k_S - k_S')$ *vs.* $1/L_t$ (where L_t is total ligand concentration, which in these systems is very close to [L]), q_{11} is found as the reciprocal of the intercept on the ordinate, and K_{11} as the negative of the intercept on the abscissa. Figure 1 shows a typical application of the plotting method. Stability constants evaluated in this way have a reproducibility of 10–25%, and q_{11} (which is constrained to lie in the range 0–1 for 1:1 complexes) can be determined with an uncertainty of about 0.1 unit. Data were treated as in earlier work.[1] In this study R was hydroxide ion, and the reactions were therefore hydroxide ion catalyzed hydrolyses.

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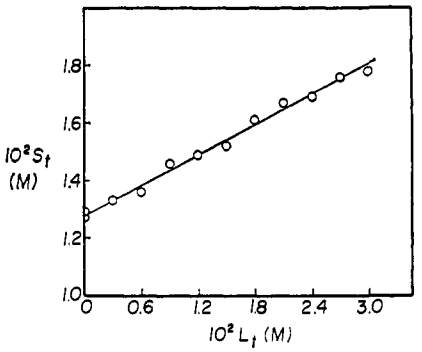

Figure 2. Total molar solubility of methyl benzoate (S_t) as a function of total theophylline concentration (L_t) at 25.0° in pH 6.60 phosphate buffer.

The stability constant obtained by these methods is labeled K_{11}' and is called the apparent 1:1 stability constant until sufficient evidence is obtained to warrant its consideration as the actual K_{11}.

Many of the substrates in this study are liquids, and the determination of their equilibrium solubilities presents problems in phase separation prior to analysis of the solution. Both filtration and centrifugation were employed for this purpose. Figure 2 shows that good results can be obtained. Ultraviolet spectrophotometry (with Cary 14 and 15 spectrophotometers) was usually used for analysis of solutions (sometimes after preliminary separations by solvent extraction) and for following reaction kinetics. pH measurements were made with equipment and techniques as given earlier.[1,3] Some reaction rates were studied by the pH-Stat method, using a pH meter as a manually operated pH-Stat.[33]

Stability constants are expressed on the molar concentration scale and refer to aqueous solution of ionic strength 0.30 *M*. Solutions employed in the spectral and kinetic methods usually contained up to 1% acetonitrile.

Results

Table I gives apparent 1:1 stability constants for theophylline and theophyllinate complexes. A few of these systems require comment on unexpected observations.

Figure 3 shows van't Hoff plots of log K_{11}' *vs.* $1/T$ for the methyl *cis*-cinnamate and methyl *trans*-cinnamate complexes with theophylline.[3,4] These constants were obtained by the solubility method. The scatter about the line for the *cis* ester is greater than for the *trans* ester, but the difference is even more marked than this, for the precision of the individual points is considerably better than their deviation from the line would indicate. Thus the K_{11}' values for the *cis* ester at 35.0°, in three independent determinations, were 9.1, 9.7, and 9.4 M^{-1}; for three studies at 25.0°, 11.9, 11.1, and 11.2 M^{-1}; and for two studies at 15.0°, 10.5 and 10.6 M^{-1}. It is therefore possible that the data in Figure 3 reflect a complicated system. The discrepancy between the solubility value (11 M^{-1}) and the spectral result (16 M^{-1}, both at 25°) also indicates that multiple

(33) B. J. Kline and K. A. Connors, *Am. J. Pharm. Educ.*, 32, 54 (1968).

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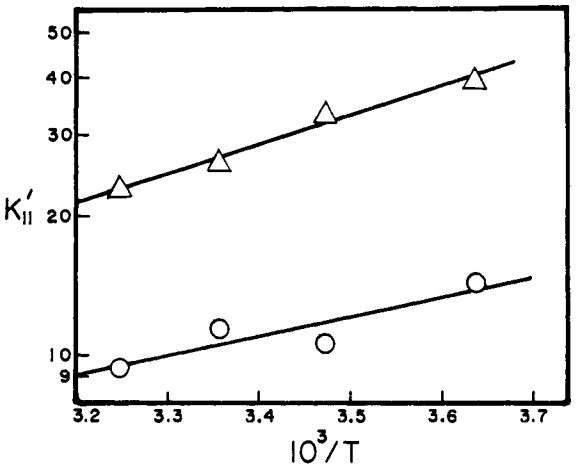

Figure 3. Temperature dependence of apparent 1:1 stability constants for theophylline complexes of methyl *trans*-cinnamate (triangles) and methyl *cis*-cinnamate (circles).

complexes may be present,[4] although variation in the wavelength did not change the stability constant found by the spectral method. At any rate, from the least-squares lines shown in Figure 3 the apparent thermodynamic quantities $\Delta H_{11}°$ and $\Delta S_{11}°$ can be calculated. For the *trans* ester these quantities are $\Delta H_{11}° = -2.9$

Table I. Apparent Stability Constants with Theophylline and Theophyllinate[a,b]

Substrate	Ligand: Theophyllinate Kinetic	Ligand: Theophylline Solubility	Ligand: Theophylline Spectral
Methyl *trans*-cinnamate	12[c,d]	25[d]	22[d]
Methyl *cis*-cinnamate	7	11	16
Methyl benzoate	16	17	
Methyl crotonate	5	2[e]	
Methyl acetate	~0		
Methyl 2,6-dichloro-*trans*-cinnamate		39	
Methyl 1-naphthoate		104[f]	
Methyl 2-naphthoate		116[g]	
Methyl hydrocinnamate		6	
Ethyl *trans*-cinnamate	9, 11[h]	26	
Isopropyl *trans*-cinnamate	12	28	
Phenyl *trans*-cinnamate	15		
p-Nitrophenyl *trans*-cinnamate	15		
p-Methoxyphenyl *trans*-cinnamate	17		
Benzamide		15	
trans-Cinnamamide	10,[h] 17[i]	28	17
N-*trans*-Cinnamoylimidazole	14		
trans-Cinnamyl acetate		17	
trans-Cinnamaldehyde			23
trans-Benzalacetone		24	27
Phenacyl acetate		8	
trans-Cinnamic acid			16
trans-Cinnamic acid anion	7[h]		12
α-Methyl *trans*-cinnamic acid anion	6[h]		
β-Methyl *trans*-cinnamic acid anion	8[h]		
Acetophenone		17	

[a] Expressed as K_{11}' (M^{-1}); method given in parentheses, except as noted. [b] At 25.0° in water; ionic strength 0.30 *M*. [c] Mean of spectral and kinetic methods. [d] Reference 3. [e] Reversed system: theophylline was the substrate. [f] $K_{12} = 16\ M^{-1}$. [g] $K_{12} = 17\ M^{-1}$. [h] Spectral method. [i] Solubility method.

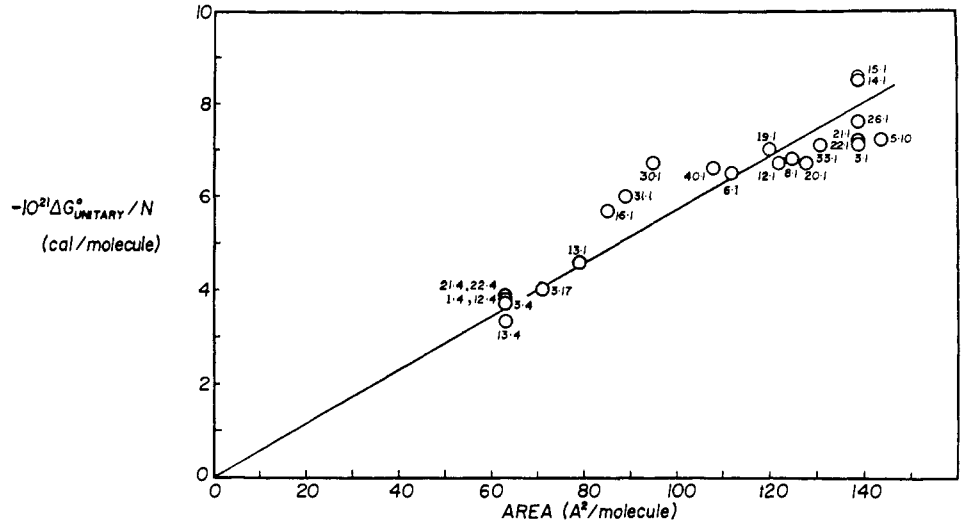

Figure 4. Plot of standard unitary free energy change per molecule against estimated planar area per molecule (one side only) of the smaller interactant for 25 complexes of neutral interactants. Symbols designate the complex identity (see Table II); thus 5·10 is the methyl *trans*-cinnamate·caffeine complex (usually the substrate is listed first). Stability constant data are from Table I, from ref 1, 3, and 31, or from P. A. Kramer, Ph.D. Dissertation, University of Wisconsin, Madison, 1968. (Point 31·1 has been misplotted, and 41·1 was omitted.)

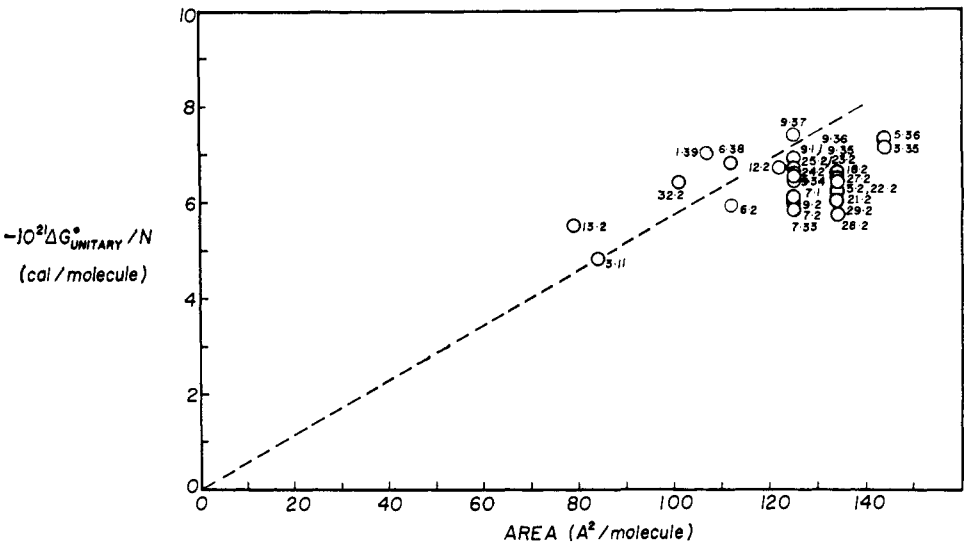

Figure 5. Plot of standard unitary free energy change per molecule against estimated planar area per molecule for 20 complexes between one neutral and one monoanionic interactant and 8 complexes between two monoanions. See Figure 4 for details.

kcal/mol, $\Delta S_{11}^{\circ} = -3.0$ eu; for the *cis* ester, $\Delta H_{11}^{\circ} = -1.9$ kcal/mol, $\Delta S_{11}^{\circ} = -1.9$ eu. (Entropy changes are based on the molar concentration scale.) An earlier determination[3] of these quantities for the methyl *trans*-cinnamate–8-chlorotheophyllinate system yielded $\Delta H_{11}^{\circ} = -3.4$ kcal/mol and $\Delta S_{11}^{\circ} = -4.8$ eu. These values are too small and too similar to be mechanistically useful at this time.

A spectral anomaly was observed with methyl hydrocinnamate. At concentrations of this ester below saturation, in aqueous solution, a characteristic absorption spectrum (say A) is obtained. Solutions prepared with an excess of the pure ester present display a qualitatively different spectrum, B. Dilution of such a saturated solution failed to produce spectrum A; on the other hand, it was easy to convert A to B by placing a solution having spectrum A in contact with neat ester. When solutions displaying either A or B were extracted with isooctane, a single spectrum was produced, and this was identical with that of a solution prepared by dissolving methyl hydrocinnamate in isooctane. These observations were not pursued, but they may affect the reliability of the estimated stability constant. It is conceivable that this spectral behavior reflects changes in rotamer distribution; the *skew* form of methyl hydrocinnamate may be of significantly different energy from the *trans* form because of the possible interaction between the carbonyl oxygen and the phenyl ring in the *skew* rotamer. Wittstruck and Trachtenberg[35] propose such an interaction to account for nmr chemical shifts of substituted hydrocinnamic acids.

Solubility studies with methyl 1-naphthoate and with methyl 2-naphthoate gave phase diagrams with slight positive curvature, which is indicative of the presence of complexes containing more than one molecule of ligand. These systems were analyzed in terms of SL and SL_2

(35) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, 89, 3803 (1967).

complexes,[2b] with the stability constants for the SL_2 complex being defined as stepwise constants.

trans-Cinnamamide yielded apparent stability constants whose values depended upon the method of study. Disagreement of stability constants evaluated by different experimental techniques is evidence for the presence of complexes of stoichiometry other than 1:1.[3,4] *trans*-Cinnamaldehyde showed spectral evidence of instability in solution, so absorbance measurements were made within 2 min of the preparation of each solution. Among the substrates whose study was attempted but abandoned (because of marked instability or erratic solubility or spectral behavior) were styrene, *t*-butyl *trans*-cinnamate, *trans*-cinnamyl *trans*-cinnamate, *trans*-cinnamononitrile, and methyl *p*-nitro-*trans*-cinnamate.

Within the limits of the experimental method, the q_{11} values for those complexes studied kinetically were essentially unity for attack by hydroxide ion. This result agrees with earlier reports of the effectiveness of the ligand in blocking attack at the carboxylic group in these substrates.[1,3]

Discussion

A Stability-Area Correlation. Many authors have noted that complex stability is promoted by planarity of the interacting molecules,[1,2a,36] but no quantitative demonstration seems heretofore to have been reported.[37] Figure 4 shows a plot of the standard unitary free energy change for complex formation[38] against the estimated planar area of the interactant with the smaller area; all data refer to aqueous solution at 25.0°. Most of the data are from Table I, and therefore represent various substrates with theophylline as ligand, but some points are included for other complexes. The correlation is surprisingly good.

Planar areas were estimated from tracings of CPK molecular models;[40] obviously the area of a molecule that is considered to lie essentially in one plane is a matter of judgement, so the areas used in Figure 4 are listed in Table II. The rationale for selecting the smaller of the two possible areas as the abscissa is that the energy of interaction should be related to the area of substrate–ligand overlap, and this will be limited by the molecule with the smaller area. Consideration of the shapes of the planar areas suggests that for some complexes the area of overlap will be substantially smaller than the area of the smaller planar surface, so some of the points in Figure 4 may lie to far to the right; however we cannot yet make an estimate of overlap area with any confidence, so the crude plotting method shown in Figure 4 must suffice for the present.

Figure 5 shows a similar plot for complexes in which one or both of the interactants is a monovalent anion (often theophyllinate or a substituted theophyllinate). The correlation is poorer than that observed for neutral complexes, and the differences between Figures 4 and 5 are not presently understood. It is probable that solvation is an important factor in modifying complex stability in charged species.

The area correlation of Figure 4 may be explicable in terms of the simple model shown in Figure 6. Let A_S and A_L be the areas of the substrate and ligand molecules, respectively (for one side). Edge effects are neglected. A_L is arbitrarily selected to be smaller than

Table II. Estimated Planar Area of Interactant Molecules

No.	Compound	Planar area (Å²/molecule)
1	Theophylline	139
2	Theophyllinate	134
3	Benzene	76
4	Imidazole	63
5	Methyl *trans*-cinnamate	144
6	Methyl *cis*-cinnamate	112
7	*trans*-Cinnamic acid anion	125
8	*trans*-Cinnamoylsalicylic acid	125
9	*trans*-Cinnamoylsalicylic acid anion	125
10	Caffeine	150
11	Purine anion	84
12	Methyl benzoate	122
13	Methyl crotonate	79
14	Methyl 1-naphthoate	148
15	Methyl 2-naphthoate	148
16	Methyl hydrocinnamate	85
17	2-Methylimidazole	71
18	N-*trans*-Cinnamoylimidazole	180
19	*trans*-Cinnamaldehyde	120
20	*trans*-Cinnamic acid	128
21	Ethyl *trans*-cinnamate	144
22	Isopropyl *trans*-cinnamate	144
23	Phenyl *trans*-cinnamate	125
24	*p*-Nitrophenyl *trans*-cinnamate	125
25	*p*-Methoxyphenyl *trans*-cinnamate	125
26	Methyl 2,6-dichloro-*trans*-cinnamate	166
27	Dimethylaminoethyl *trans*-cinnamate	144
28	α-Methyl *trans*-cinnamic acid anion	135
29	β-Methyl *trans*-cinnamic acid anion	135
30	*trans*-Cinnamyl acetate	95
31	Phenacyl acetate	109
32	*p*-Nitrophenyl benzoate	101
33	*trans*-Benzalacetone	132
34	7-(2,3-Dihydroxypropyl) theophylline	134
35	8-Chlorotheophyllinate	148
36	8-Bromotheophyllinate	151
37	8-Iodotheophyllinate	158
38	8-Nitrotheophyllinate	156
39	Salicylic acid anion	107
40	Benzamide	108
41	Acetophenone	109

(36) M. Orchin, *J. Org. Chem.*, **16**, 1165 (1951); C. E. Castro, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **80**, 2322 (1958); T. Higuchi and F. D. Pisano, *J. Pharm. Sci.*, **53**, 644 (1964); M. Nakano and T. Higuchi, *ibid.*, **57**, 183 (1968).

(37) Professor P. Mukerjee, of this school, and Dr. A. K. Ghosh have observed that the free energy of complex formation between methylene blue and some small-ring aromatic and heteroaromatic compounds varies linearly with the size of the compound.

(38) The *unitary* free energy change is the portion of the free energy change that is characteristic of the chemical process taking place, the statistical effect of change in number of particles (the *cratic* portion) being subtracted out. The unitary standard molar free energy change is given by $-RT \ln K_N$, where K_N is the equilibrium constant on the mole fraction scale. For reactions of the type shown in eq 1, in dilute aqueous solution, K_N is given by $K_N = 55.5K_{11}$, where K_{11} is the equilibrium constant on the molarity scale. Gurney[39] has described the concept of unitary quantities in detail.

(39) R. W. Gurney, "Ionic Processes in Solution," Dover Publications, New York, N. Y., 1962, Chapter 6.

(40) The Ealing Corp., Cambridge, Mass.

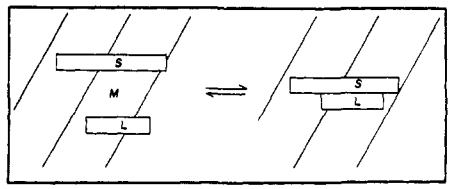

Figure 6. Model of complex formation between a planar substrate S and a planar ligand L of smaller area, in medium M. The direction of view is in the molecular planes.

A_S, $G_{MS}°$, $G_{ML}°$, and $G_{SL}°$ are standard free energies of interaction per unit area between the "surfaces" designated by subscripts. Then the standard free energy change for the process represented in the model is

$$\Delta G° = [A_S + (A_S - A_L)]G_{MS}° + A_L G_{ML}° + A_L G_{SL}° - (2A_S G_{MS}° + 2A_L G_{ML}°) \quad (5)$$

$$\Delta G° = A_L(G_{SL}° - G_{MS}° - G_{ML}°) \quad (6)$$

If the quantity $(G_{SL}° - G_{MS}° - G_{ML}°)$ is, in first approximation, a constant for a series of substrates and ligands in a common medium, eq 6 describes the type of behavior seen in Figure 4.

Since the physical significance of the "free energies per unit area" that appear in eq 6 is doubtful, the equation is equally dubious, but it will nevertheless be of utility in suggesting further experimental approaches. Thus, in a second approximation, the quantity $(G_{SL}° - G_{MS}° - G_{ML}°)$ may vary somewhat as S and L are altered, and the study of this variability (*i.e.*, some of the dispersion seen in Figure 4) may be guided by the form of this function. Again, eq 6 suggests that alterations in the medium may have major effects on complex stability. The analysis can be carried further with interesting consequences. The equation of the line in Figure 4 (which was drawn, by eye, merely to indicate the trend) is $-\Delta G°_{unitary}/N = 5.7 \times 10^{-23}$ (area). The slope value of 5.7×10^{-23} cal/Å^2 is equivalent to 23.9 dyn/cm. Interestingly, this value is within a factor of 2 of recorded interfacial tensions between water and typical hydrophobic organic compounds. This is a very suggestive observation.

Nature of the Complexes. The area correlation of Figure 4 is good evidence that the gross structure of these 1:1 complexes in solution is describable as a plane-to-plane orientation of the substrate and ligand molecules. The information at hand, which can be summarized as follows, allows further inferences to be made. (1) The area correlation indicates that a plane-to-plane orientation exists in the complex, and that complex stability is promoted by planar area overlap. (2) Kinetic studies on complexed cinnamate and benzoate substrates subjected to attack by hydroxide ion give q_{11} values of essentially unity; that is, the complexed ester is relatively unreactive.[1,3] This is interpreted to mean that the ligand must be very near the ester group in these complexes. (3) Sulfite attack at the double bond of a cinnamate complex is essentially completely inhibited;[1] therefore the ligand must lie near this portion of the substrate molecule. (4) Variations in X in a series of cinnamic acid derivatives $C_6H_5CH{=}CHCOX$ result in small changes in stability constant in their complexes with theophylline; it is inferred that X is not strongly involved in the intermolecular interaction. (5) Replacement of the phenyl group by a methyl group in $C_6H_5CH{=}CHCOOCH_3$ leads to a marked decrease in complexing tendency; this implicates the ring in the complex interaction.

These observations and inferences, applied to cinnamate–xanthine complexes, restrict the number of possible structures that can be drawn for the complex. Models and scale drawings, based on X-ray structural data for cinnamates[41] and theophylline,[42] indicate that these inferences are consistent with all of the interactants' dimensions. There remain, of course, many alternative arrangements of the substrate and ligand molecules that cannot yet be eliminated.[31]

Some attempts were made to investigate the effects of relatively subtle modifications in substrate structure. In *trans*-cinnamate-type compounds two arrangements of the double bonds relative to each other are possible because of restricted rotation about the intervening single bond. The two isomers are described by specifying the single-bond geometry as *s-cis* or *s-trans*. In the crystalline state many α,β-unsaturated acids and their derivatives have the *s-cis* conformation, including methyl *m*- and *p*-bromo-*trans*-cinnamates,[41] vitamin A acid,[43] and acrylic acid.[44] *trans*-Cinnamic acid, however, exists in the *s-trans* form.[41] Dipole moment data have been interpreted to mean that *trans*-cinnamaldehyde, $C_6H_5CH{=}CHCHO$, has the *s-trans* conformation, whereas *trans*-benzalacetone, $C_6H_5CH{=}CHCOCH_3$, is in the *s-cis* conformation.[45] Even if these conformational differences are preserved in aqueous solution, they lead to no meaningful differences in complexing tendencies with theophylline, as shown by the data in Table I.

We have avoided the terms "donor" and "acceptor" in discussing these interactants and their complexes because these terms imply a hypothesis, concerning the nature of the interaction, that is far from secure in the present situation. The several points listed above render improbable a substrate–ligand orientation in which maximum π-orbital overlap is achieved, therefore classical electron donor–acceptor or charge-transfer interaction seems to be unlikely as the major source of the complex stability. Instead, orientations favoring local dipole–dipole or dipole-induced–dipole interactions, with perhaps some charge-transfer contribution, can easily be postulated consistent with the points listed. This general type of orientation has been called "polarization bonding,"[46] and Wallwork and others have shown many crystalline complexes to have such structures.[47] In the crystal the complex structure is considered to be a compromise between charge-transfer forces favoring maximum orbital overlap,

(41) L. Leiserowitz and G. M. J. Schmidt, *Acta Cryst.*, **18**, 1058 (1965).
(42) D. J. Sutor, *ibid.*, **11**, 83 (1958).
(43) C. H. Stamm and C. H. MacGillavry, *ibid.*, **16**, 62 (1963).
(44) M. A. Higgs and R. L. Sass, *ibid.*, **16**, 657 (1963).
(45) J. B. Bentley, K. B. Everard, R. J. B. Marsden, and L. E. Sutton, *J. Chem. Soc.*, 2957 (1949); R. J. Dolter and C. Curran, *J. Amer. Chem. Soc.*, **82**, 4153 (1960).
(46) P. J. A. McKeown, A. R. Ubbelohde, and I. Woodward, *Acta Cryst.*, **4**, 391 (1951); T. T. Harding and S. C. Wallwork, *ibid.*, **6**, 791 (1953).
(47) S. C. Wallwork, *J. Chem. Soc.*, 494 (1961); A. W. Hanson, *Acta Cryst.*, **17**, 559 (1964); A. Damiani, P. De Santis, E. Giglio, A. M. Liquori, R. Puliti, and A. Ripamonti, *ibid.*, **19**, 340 (1965); A. W. Hanson, *ibid.*, **19**, 610 (1965); C. K. Prout and S. C. Wallwork, *ibid.*, **21**, 449 (1966); R. M. Williams and S. C. Wallwork, *ibid.*, **22**, 899 (1967); C. K. Prout and A. G. Wheeler, *J. Chem. Soc., A*, 469 (1967); E. Shefter, *J. Pharm. Sci.*, **57**, 350 (1968).

local dipole–dipole interactions, and packing requirements.[48] The relevance of these results to complexes in solution is uncertain, but they at least demonstrate that orientations of the type suggested here are possible.

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(48) S. C. Wallwork and C. J. Timmons, Abstracts, 7th International Congress and Symposium of the International Union of Crystallography, Moscow, July, 1966, *Acta Cryst. Suppl.*, **21**, A133 (1969).

Nucleophilic Substitution at Tetracoordinate Hexavalent Sulfur. The Reaction of (−)-Menthyl Phenylmethanesulfonate with *p*-Tolylmagnesium Bromide[1]

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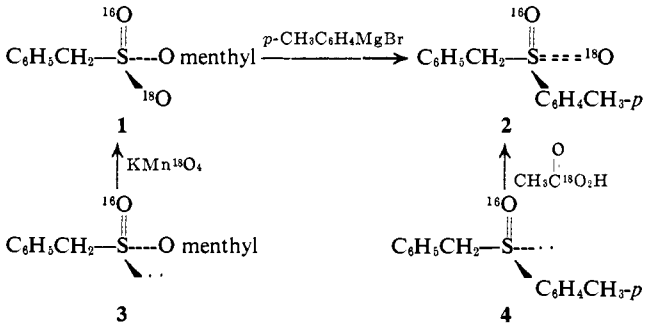
Abstract: Menthyl phenylmethanesulfinate of configuration *R* at sulfur was stereospecifically oxidized to menthyl phenylmethanesulfonate with 90.2% ^{18}O potassium permanganate. Treatment of this sulfonate ester with *p*-tolylmagnesium bromide gave (−)-benzyl *p*-tolylsulfone-^{16}O,^{18}O, presumably of configuration *S*. Since the levorotatory sulfone had been prepared by oxidation of (*R*)-benzyl *p*-tolylsulfoxide, the reaction of the sulfonate ester with the Grignard reagent proceeded with inversion of configuration at sulfur. This constitutes the first example in which the stereochemistry of nucleophilic substitution at tetracoordinate hexavalent sulfur has been established.

This article describes the stereochemistry of a nucleophilic substitution reaction of tetracoordinate hexavalent sulfur, *i.e.*, the reaction of a sulfonate ester with a Grignard reagent to form a sulfone (Scheme I, **1** → **2**). To the best of our knowledge, this is the first time that the stereochemistry of nucleophilic substitution at tetracoordinate hexavalent sulfur has been established.[3] The reaction sequence used in our study is shown in Scheme I.

Scheme I



Menthyl phenylmethanesulfinate (**3**) of configuration *R* at sulfur was oxidized to menthyl phenylmethanesulfonate (**1**) using potassium permanganate (90.2% ^{18}O) in acetone.[4] The resulting sulfonate ester was treated with *p*-tolylmagnesium bromide to give optically active benzyl *p*-tolylsulfone-^{16}O,^{18}O (**2**). In the pioneering paper demonstrating the use of ^{18}O in sulfur stereochemical studies, Stirling[5] oxidized (*R*)-benzyl *p*-tolylsulfoxide (**4**) to sulfone **2** utilizing ^{18}O-labeled peracetic acid. Both the sulfone obtained by us (**1** → **2**) and by Stirling (**4** → **2**) were levorotatory in chloroform and thus of the same configuration. If both oxidations **3** → **1** and **4** → **2** follow the same stereochemical path, then the reaction of the stereospecifically ^{18}O labeled sulfonate ester **1** with *p*-tolylmagnesium bromide to give sulfone **2** proceeds with *inversion of configuration at tetracoordinate hexavalent sulfur.*

There is evidence from similar systems that both potassium permanganate and peracids oxidize tricoordinate tetravalent sulfur to tetracoordinate hexavalent sulfur with the same stereochemistry (eq 1). In earlier work,[6] we oxidized (−)-S-methyl-S-*p*-tolyl-N-*p*-toluenesulfonylsulfilimine (**5**) to (−)-S-methyl-S-*p*-tolyl-N-*p*-toluenesulfonylsulfoximine (**6**) using potassium permanganate in pyridine. Subsequently, Rayner, von Schriltz, Day, and Cram[7] carried out the

(1) We acknowledge with gratitude support by the National Science Foundation (GP 8136 and GP 5283).

(2) This work is from the Ph.D. thesis of M. A. S., University of New Hampshire, 1968.

(3) Our assignment of the sulfur atom's covalency follows from consideration of compounds in which the ligands are monovalent fluorine or divalent oxygen atoms. The coordination number is the number of ligands. This system in which both the coordination number and covalency are designated avoids certain ambiguities in terminology; *e.g.*, the sulfur atoms in sulfones and sulfur tetrafluoride are both tetracoordinate but in the former the sulfur is hexavalent and in the latter, tetravalent.

(4) The configurations of **3** and **4** were established through the work of K. Mislow and coworkers. For a leading reference see M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 90, 4835 (1968).

(5) C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963).

(6) M. A. Sabol, R. W. Davenport, and K. K. Andersen, *Tetrahedron Lett.*, 2159 (1968).