The Stability of Some Molecular Complexes in Aqueous Mixed Solvents. Correlation with Solvent Surface Tension

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Abstract: The stability of the molecular complex between methyl *trans*-cinnamate and theophylline can be correlated with the surface tension of the solvent for various mixed solvents containing water. Among the solvents used were aqueous binary mixtures with methanol, dioxane, acetonitrile, and ethylene glycol, as well as aqueous solutions of sodium chloride and lithium chloride. A linear relationship exists between the standard free-energy change for the complexation equilibrium and the surface tension of the solvent. This was extrapolated to zero surface tension, presumably eliminating the solvent contribution to the overall complex stability. This extrapolation procedure was applied to five complex systems: methyl *trans*-cinnamate–theophylline; methyl *trans*-cinnamate–theophylline anion; methyl *trans*-cinnamate–8-chlorotheophylline anion; naphthalene–theophylline; and methyl 2-naphthoate–8-nitrotheophylline anion. The extrapolated intercepts, interpreted as free energies of substrate–ligand interaction, were found to be linearly related to the vertical deviations for the same complexes from the average regression line in the correlation between complex stability and maximal overlap area as described earlier. This extrapolation procedure may provide an approach for separating overall complex stability into a solvent contribution (which is dependent upon surface tension) and a substrate–ligand interaction contribution. These experimental results are consistent with the functional relationships proposed by Sinanoğlu and coworkers to account for solvent effects on association equilibria.

Recently a linear correlation has been described between the standard free-energy change for organic molecular complex formation in aqueous solution and the "maximal overlap area" between the substrate and ligand molecules oriented in a plane-to-plane manner.[1] More than 50 neutral and ionic complexes were correlated in this way, and it was observed that, *on the average*, there is no difference in behavior between neutral and ionic complexes. (This is a "first-order" description only; moreover, for any specific complex, the ionic state is important in determining complex stability.) Deviations from the line are significant, and were attributed to a "second-order" effect of variable structural contributions to the stability.

The slope of this maximal overlap correlation of free-energy change with area is equivalent to 64 dyn/cm. The dimensions and magnitude of this quantity suggest the possible involvement of a surface or interfacial tension as a factor in controlling complex stability. This inference led to the present study, in which the stabilities of several molecular complexes have been studied in mixed aqueous solvents. It has been found that complex stability is related to solvent surface tension in a simple way, as first proposed by Sinanoğlu and his coworkers.[2]

Experimental Section

Most of the materials, equipment, and experimental methods have been described in detail earlier.[1,3] Specific gravity measurements were made with a 50.0-ml vacuum-jacketed pycnometer (Sargent S-9225). Surface and interfacial tensions were determined at 25.0° with a Du Noüy ring tensiometer (Cenco 70535) having a platinum–iridium ring 5.992 cm in circumference, with the ring-to-wire diameter 53.6.

Complex stability constants K_{11} were evaluated by the spectral,[4] solubility,[5] and kinetic[3b,6] techniques. Unitary standard free-energy changes were calculated from the apparent 1:1 stability constants K_{11} (which are evaluated on the molar concentration scale and have the units M^{-1}) with eq 1,[7] where ρ_0 is the density

$$\Delta G_u^\circ = -RT \ln K_{11} M^* \rho_0 \qquad (1)$$

of the solvent and M^* is the number of moles of solvent contained in 1000 g of solvent. (For example, in 12.50% (w/w) acetonitrile in water, $M^* = 125/41.054 + 875/18.016 = 51.608$.) The unitary free-energy change, which is the free-energy change calculated on the mole fraction scale, does not include the contribution from entropy of mixing.

Results

The following five complexes (listed in the order substrate–ligand) were studied: methyl *trans*-cinnamate–theophylline; methyl *trans*-cinnamate–theophylline anion; methyl *trans*-cinnamate–8-chlorotheophylline anion; naphthalene–theophylline; and methyl 2-naphthoate–8-nitrotheophylline anion. All of these had been investigated earlier;[1,3] they were selected here to represent points in the maximal overlap area correlation that fall on, above, and below the regression line. The methyl cinnamate–theophylline system was studied in binary solvents consisting of water with the following additives: acetonitrile, methanol, dioxane,

(1) J. L. Cohen and K. A. Connors, *J. Pharm. Sci.*, **59**, 1271 (1970). The *substrate* S is that interactant whose properties are measured, and the *ligand* L is the interactant whose concentration is the independent variable, in experimental studies. *Maximal overlap areas* are estimated from tracings of molecular models by maximizing the molecular superposition of planar portions of substrate and ligand, with no account being taken of other factors (such as local group interactions).

(2) (a) O. Sinanoğlu and S. Abdulnur, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 24, Suppl. 15, S-12 (1965); (b) O. Sinanoğlu in "Molecular Associations in Biology," B. Pullman, Ed., Academic Press, New York, N. Y., 1968, pp 427–445; (c) T. Halicioğlu and O. Sinanoğlu, *Ann. N. Y. Acad. Sci.*, **158**, 308 (1969).

(3) (a) J. A. Mollica, Jr., and K. A. Connors, *J. Amer. Chem. Soc.*, **89**, 308 (1967); (b) P. A. Kramer and K. A. Connors, *ibid.*, **91**, 2600 (1969); (c) K. A. Connors, M. H. Infeld, and B. J. Kline, *ibid.*, **91**, 3597 (1969); (d) H. Stelmach and K. A. Connors, *ibid.*, **92**, 863 (1970).

(4) H. Benesi and J. H. Hildebrand, *ibid.*, 70, 2832 (1948); 71, 2703 (1949).

(5) T. Higuchi and K. A. Connors, *Advan. Anal. Chem. Instrum.*, 4, 117 (1965).

(6) K. A. Connors and J. A. Mollica, Jr., *J. Pharm. Sci.*, **55**, 772 (1966).

(7) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill, New York, N. Y., 1953 (Dover Publications, New York, N. Y., reprint, 1962), Chapter 6. Unitary thermodynamic quantities were introduced to us by Professor P. Mukerjee, in helpful discussions that we wish to acknowledge.

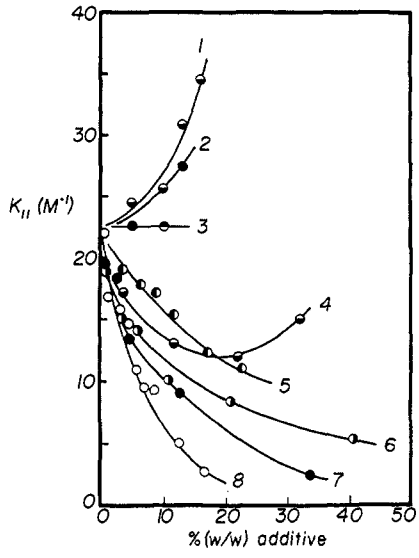

Figure 1. Stability constants for complex formation between methyl cinnamate and theophylline in aqueous solvent mixtures: 1, lithium chloride; 2, sodium chloride; 3, glycerol; 4, DMSO (note atypical behavior); 5, ethylene glycol; 6, dioxane; 7, methanol; 8, acetonitrile. Data from Table I.

ethylene glycol, glycerol, dimethyl sulfoxide, lithium chloride, and sodium chloride. The other complexes were investigated in fewer solvents, mainly methanol–water and acetonitrile–water mixtures. Deuterium oxide was the solvent in a study of the methyl cinnamate–8-chlorotheophylline anion complex.

Table I lists the experimental results for the methyl cinnamate–theophylline system. The variation of stability constant with percentage of additive in the mixed solvents is shown in Figure 1. (The lines connecting the experimental points in this figure have no theoretical significance; they merely indicate trends.) Most of the organic solvents clearly decrease the complex stability. Inorganic salts significantly increase the experimental stability constant. Obviously, and not surprisingly, the percentage composition of the binary solvent system inadequately relates complex stability to solvent character. A plot of K_{11} against the dielectric constant reveals similar behavior, showing that the macroscopic dielectric constant does not solely control the complexation process.[8]

In Figure 2 the same K_{11} values are plotted against the solvent surface tension. This plot indicates that, for the methyl cinnamate–theophylline complex in solvents containing water, complex stability is determined primarily by the solvent surface tension. The standard free-energy change for complex formation is a linear function of surface tension (Figure 3). Stability constants for the other four complexes are gathered in Table II. The complex stability–surface tension correlation includes these two observations: (1) that surface tension is a "master variable" determining the stability of a given complex; (2) that a linear free-energy relationship exists between stability and surface tension. Both of these are demonstrated with the methyl cinnamate–theophylline system. The correlations with the other four systems have not been as rigorously tested, but the data are fully consistent.

Although surface tension was found to be a serviceable independent variable in these correlations, it seemed that the interfacial tension between the mixed aqueous solvent and an immiscible organic liquid might also be an appropriate parameter. Such data are less accessible than are surface tensions. One difficulty is that the

(8) This plot strikingly resembles a plot of a spectral frequency function for charge transfer in 1-ethyl-4-carbomethoxypyridinium iodide against the macroscopic dielectric constant of several solvent mixtures.[9] This correspondence may reflect partial control by local solvent polarity or the "microscopic" dielectric constant. We thank Mr. N. R. Desai for pointing out this similarity.

(9) P. Mukerjee and N. R. Desai, *Nature (London)*, **223**, 1056 (1969).

Table I. Stability Constants of the Methyl Cinnamate–Theophylline Complex in Aqueous Mixed Solvents[a]

% (w/w) additive	K_{11}, M^{-1}	γ, dyn/cm	d_4^{25}
	Acetonitrile–Water		
0.62	22.0	71.9	0.9960
1.24	16.9	69.2	0.9948
3.11	15.8	63.3	0.9920
4.52	14.7	59.0	0.9895
5.62	10.9	56.6	0.9877
6.89	9.5	54.1	0.9855
8.48	9.3	51.4	0.9828
12.50	5.0	46.0	0.9758
16.57	2.7	42.0	0.9680
	Methanol–Water		
0.62	19.5	70.0	0.9957
2.59	18.4	66.0	0.9920
4.58	13.5	62.6	0.9885
12.64	9.1	52.4	0.9757
33.81	5.0	38.3	0.9420
	Dioxane–Water		
0.81	19.2	70.2	0.9976
3.36	15.1	64.9	1.0000
5.90	14.2	62.1	1.0023
10.94	10.1	58.2	1.0067
20.90	8.4	51.0	1.0220
40.47	5.3	43.0	1.0288
	Ethylene Glycol–Water		
0.88	21.8	71.2	0.9976
3.53	19.1	70.0	1.0010
6.35	17.9	68.8	1.0047
8.97	17.1	67.8	1.0080
11.75	15.4	66.6	1.0117
17.09	12.3	64.7	1.0188
22.33	11.1	62.8	1.0256
	Glycerol–Water[f]		
10.1	22.5	71.5[c]	1.0220[c]
	Dimethyl Sulfoxide–Water		
0.87	19.3	71.5	0.9976
3.58	17.2	70.4	1.0010
11.60[d]	13.1	67.5	1.0116
22.02[d]	12.0	64.4	1.0263
32.12[d]	15.1	61.8	1.0420
	Lithium Chloride–Water[b]		
4.94	27.1	74.0[e]	1.0252
10.00	28.2	76.2[e]	1.0541
12.99	30.9	77.6[e]	1.0706
15.98	34.6	79.0[e]	1.0879
	Sodium Chloride–Water[f]		
4.76	22.6	73.5[g]	1.0320
13.04	27.5	76.6[g]	1.0919

[a] 25.0°; pH 6.6 phosphate buffer; ionic strength maintained at 0.3 M with KCl (except as noted). [b] Also contains 0.62% (w/w) acetonitrile. [c] R. W. Gallant, *Hydrocarbon Process.*, **46**, 212 (1967). [d] pH 5.0 phosphate buffer; ionic strength 0.15 M. [e] "Handbook of Chemistry and Physics," 49th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1968–1969. [f] Also contains 0.62% (w/w) methanol. [g] J. W. Benton, *Trans. Faraday Soc.*, **31**, 1413 (1935).

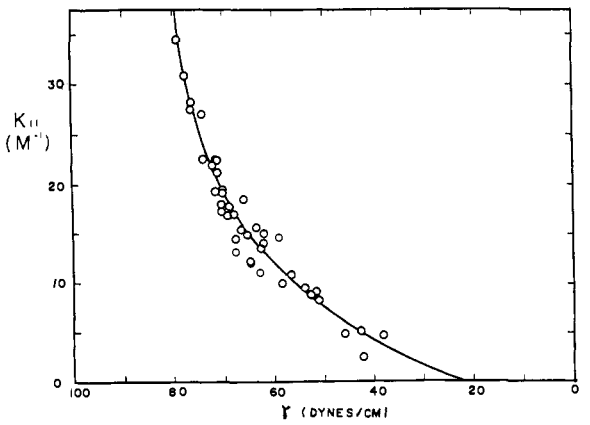

Figure 2. Relationship of stability constant to surface tension for methyl cinnamate–theophylline in mixed aqueous solvents. Data from Table I.

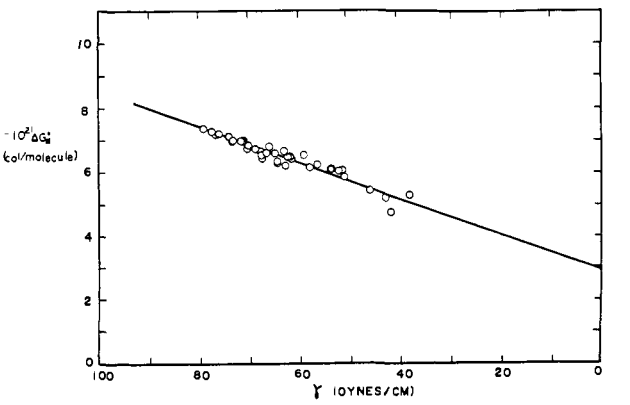

Figure 3. Standard unitary free-energy change for complex formation between methyl cinnamate and theophylline as a function of solvent surface tension.

organic component of the binary solvent may partition into the organic phase. Despite this ambiguity, interfacial tensions were measured[10] for the following two-phase systems: benzene–water–methanol; carbon tetrachloride–water–methanol; isooctane–water–methanol; isooctane–water–dioxane; and isooctane–water–acetonitrile. Reasonable correlations were obtained in plots of ΔG_u° against interfacial tension. As a practical parameter for developing empirical correlations, however, the surface tension is superior to interfacial tension.

Table II. Stability Constants for Some Complexes at 25°

Additive	% (w/w) additive	K_{11}, M^{-1}
Methyl Cinnamate–Theophylline Anion[a]		
Acetonitrile	0.62	14.7
	4.52	5.7
	8.48	3.8
	12.50	1.6
Methanol	4.58	7.7
	8.58	7.3
	16.74	4.1
	25.15	2.6
Methyl Cinnamate–8-Chlorotheophylline Anion		
Acetonitrile[b]	0.62	20.9
	4.52	11.5
	8.48	8.7
	16.57	2.1
Methanol[b]	4.58	15.5
	8.58	12.4
	12.64	10.4
	16.74	8.6
	25.15	6.2
	33.81	3.8
Deuterium oxide[c]	99	18.7
Naphthalene–Theophylline		
Methanol[d]	0.00	67.3
	3.97	56.0
	8.00	54.8
	16.22	33.8
	24.66	25.8
	33.37	18.2
Methyl 2-Naphthoate–8-Nitrotheophylline Anion		
Methanol[e]	0.00	241
	3.97	173
	8.00	158
	16.22	102

[a] pH 10.7, μ = 0.3 M. [b] pH 9.2, μ = 0.2 M. [c] pD 9.66, μ = 0.2 M, also contains 0.99% (v/v) CD_3CN. Surface tension = 67.6 dyn/cm. [d] pH 6.6, μ = 0.3 M. [e] pH 7.7, μ = 0.3 M.

Discussion

Hydrophobic Bonding and Surface Tension. Several years ago Sinanoğlu and Abdulnur[2a] proposed that the stability of molecular aggregates (the DNA double helix in particular) is determined largely by the solvent surface tension. Their theory was later extended by Sinanoğlu[2b,c] to simpler association complexes in solution. Sinanoğlu's essential viewpoint is that the observed solvent effect is governed by two contributing factors. One of these is a solvent effect term that is a function of solvent surface tension. The other is a solute–solvent interaction term. The major energetic feature of the solvent contribution to the association process is the collapse of two solvent cavities (each enclosing one of the interactant molecules) into a single cavity, with a resultant decrease in surface area; the consequent decrease in surface free energy is the driving force for the molecular aggregation. Several experimental studies have been made related to this concept; most of these have been summarized by Sinanoğlu.[2b] Wacker and Lodemann[11] studied the photodimerization of thymines in thymidylyl-thymidine. This reaction occurs within the "stacked" form of the solute, so the extent of photodimerization is a measure of the extent of stacking. This was found to be correlated with a solvophobic force sequence of several solvents, as determined primarily by solvent surface tension. Moser and Cassidy[12] observed a qualitative correspondence between complex stability and solvent surface tension for the interaction of hydroquinone and *p*-benzoquinone. The relationship was not quantitatively satisfactory, however, possibly because of the very low complex stabilities, which present difficulties of determination and interpretation. Kristiansen, *et al.*,[13] noted a rough correlation of complex stability with surface tension in several aqueous mixed solvents; two complex systems were studied, and the magnitudes of the stability

(10) S. Sun, Ph.D. Thesis, University of Wisconsin, Madison, Wis., 1971.

(11) A. Wacker and E. Lodemann, *Angew. Chem., Int. Ed. Engl.*, 4, 150 (1965).

(12) R. E. Moser and H. G. Cassidy, *J. Amer. Chem. Soc.*, 87, 3463 (1965).

(13) H. Kristiansen, M. Nakano, N. I. Nakano, and T. Higuchi, *J. Pharm. Sci.*, 59, 1103 (1970).

constants were within the extremes encountered in the present study. Crothers, *et al.*,[14] studied the solvent effect on the ORD of actinomycin solutions, finding a smooth correlation of intensity with surface tension. Mukerjee and Ghosh[15] have recently commented on some weaknesses of the surface tension argument. The correlations presented in this paper, especially Figures 2 and 3, appear to be among the best examples yet reported of the relationship of molecular complex stability to solvent surface tension.

These surface tension correlations are relevant to the concept of hydrophobic bonding. Two extreme points of view could be taken in attempting to account for the association of nonpolar groups in aqueous solution. One of these is the cavity model,[2a] which ascribes the attraction between nonpolar solute molecules to the large cohesive forces between water molecules; aggregation of the solute molecules permits minimization of the cavity surface area. Water, with its unusually high surface tension, therefore promotes "solvophobic" bonding, and any additive that decreases the surface tension will decrease the extent of aggregation. The driving force for association is largely a favorable enthalpy contribution.

The second viewpoint (which antedates the cavity model)[16] concentrates attention on the structure of the water and extent of hydrogen bonding in the vicinity of the solute molecules, or rather upon changes in the solvent structure. Introduction of a nonpolar solute into water induces local increases in solvent ordering, which lead to a negative entropy change; upon association of two such solute species, some of the ordered water molecules are released into the bulk of the solution, giving a positive entropy change for the association process. This provides the principal driving force for the formation of the hydrophobic association.

Crothers and Ratner[17] attempted to differentiate between these alternative pictures by measuring the changes in free energy, enthalpy, and entropy of complex formation between actinomycin and deoxyguanosine in a series of methanol–water mixtures. They argued that if solvent structuring is the main effect, passing from water to a nonaqueous medium should result in a more negative ΔS and a more negative ΔH of complexing (as the solvent structure becomes less important). The cavity model was interpreted as leading to less negative ΔS and ΔH terms with a decrease in solvent surface tension. As the methanol content of the solvent was increased, the experimental $\Delta S°$ became markedly more negative, and $\Delta H°$ became somewhat more negative; the net result was a more positive $\Delta G°$. It was concluded that solvent structuring plays the dominant role (though not necessarily the only one) in this association process.[18]

Table III. Thermodynamic Data for the Methyl Cinnamate–8-Chlorotheophylline Anion System[a]

t, °C	% (w/w) acetonitrile	K_{11}, M^{-1}	$\Delta S°$,[b] eu	$\Delta S_u°$,[c] eu	$\Delta H°$, kcal/mol
15.5	0.62	25.8			
25.0	0.62	20.9	−5	+3	−3.3
40.0	0.61	18.4			
50.0	0.61	13.1			
15.5	4.55	15.8			
25.0	4.52	11.5	−14	−6	−5.7
40.0	4.46	7.1			
50.0	4.43	5.6			
15.5	8.51	11.6			
25.0	8.48	8.7	−17	−9	−6.3
40.0	8.36	5.9			
50.0	8.32	3.4			

[a] At 25.0° in pH 9.2 borate buffers; ionic strength 0.2 M. [b] On a molar concentration scale. [c] Unitary standard entropy change.

Table III shows thermodynamic data obtained for the methyl cinnamate–8-chlorotheophylline anion system in the present study. A similar pattern is seen for this complex, with an increasingly negative entropy change partially compensated by a negative enthalpy change, resulting in net destabilization of the complex.

A difficulty in interpreting such data arises because of the impossibility of independently varying the surface tension and the temperature without altering some other system property, such as solvent composition. This can be demonstrated by the following analysis of the cavity model applied to an association process. Constant pressure is assumed. Then $\Delta G = f(\Delta A,\gamma,T)$, where ΔA is the change in cavity surface area in the process, γ is solvent surface tension, and T is the absolute temperature. Writing the total differential and using the identity $\mathrm{d}(\Delta G)/\mathrm{d}T = -\Delta S$

$$-\Delta S = \left[\frac{\partial \Delta G}{\partial \Delta A}\right]_{\gamma,T}\frac{\mathrm{d}\Delta A}{\mathrm{d}T} + \left[\frac{\partial \Delta G}{\partial \gamma}\right]_{\Delta A,T}\frac{\mathrm{d}\gamma}{\mathrm{d}T} + \left[\frac{\partial \Delta G}{\partial T}\right]_{\Delta A,\gamma} \quad (2)$$

With the assumption that $\mathrm{d}\Delta A/\mathrm{d}T = 0$ and the equality $[\partial \Delta G/\partial \gamma]_{\Delta A} = \Delta A$, this becomes

$$-\Delta S = \Delta A\frac{\mathrm{d}\gamma}{\mathrm{d}T} + \left[\frac{\partial \Delta G}{\partial T}\right]_{\gamma} \quad (3)$$

A similar equation can be obtained for the enthalpy change.[19]

For all ordinary liquids the derivative $\mathrm{d}\gamma/\mathrm{d}T$ is a negative quantity, and for the assumed process ΔA is negative. The first term on the right side of eq 3 therefore always makes a negative contribution to ΔS. As the solvent is made less aqueous, the quantity $\mathrm{d}\gamma/\mathrm{d}T$ may increase or decrease, depending upon the solvent mixture, though it remains negative. ΔA may undergo some change with solvent, but it too remains negative. The net result is that this first term could lead either to

(14) D. M. Crothers, S. L. Sabol, D. I. Ratner, and W. Müller, *Biochemistry*, 7, 1817 (1968).
(15) P. Mukerjee and A. K. Ghosh, *J. Amer. Chem. Soc.*, **92**, 6419 (1970).
(16) W. Kauzmann, *Advan. Protein Chem.*, 14, 1 (1959).
(17) D. M. Crothers and D. I. Ratner, *Biochemistry*, 7, 1823 (1968).
(18) Crothers and Ratner[17] add to their argument the observation that the ratio $\beta = \delta_M\Delta H°/\delta_M\Delta S°$ is 240–280°K, which is near the melting temperature of the solvent. Their interpretation of this ratio (which is usually called the isokinetic temperature) is doubtful. The demonstration and interpretation of isokinetic relationships constitutes one of the minor controversies of physical organic chemistry. For some contrasting points of view see J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp 315–342; R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Amer. Chem. Soc.*, **83**, 3819 (1961); J. E. Leffler, *J. Org. Chem.*, **31**, 553 (1966); R. C. Petersen, *ibid.*, **29**, 3133 (1964); O. Exner, *Collect. Czech. Chem. Commun.*, **29**, 1094 (1964); R. Lumry and S. Rajender, *Biopolymers*, **9**, 1125 (1970).
(19) Surface tension is also a function of surface curvature, a dependence that is neglected here. The effect may be substantial; it is calculated[20] that the surface tension of a cavity of molecular dimensions in several nonpolar solvents is about one-third that for a plane surface.
(20) D. S. Choi, M. S. Jhon, and H. Eyring, *J. Chem. Phys.*, **53**, 2608 (1970).

an increase or a decrease in the entropy change as the surface tension is decreased. The second term, $[\partial\Delta G/\partial T]_\gamma$, is the contribution to $-\Delta S$ at constant surface tension. Though this is the quantity that has attracted speculative attention in terms of hydrophobic bonding models, it seems that the condition of constant surface tension is commonly overlooked, in effect, by ignoring the $\Delta A(d\gamma/dT)$ term.

In fact, it is highly unlikely that either model alone can account for a wide range of hydrophobic effects. The relative contributions of solvent structuring and surface tension effects to the net hydrophobic interaction may vary depending upon the sizes of the interacting components.[2,15,21] Jencks[22] has given a qualitative description of hydrophobic bonding that incorporates both the cavity and solvent structure models. The extent to which the solvent structure is modified after the solute molecule is placed in the cavity is determined by the polarity of the solute, with the result that the driving force for association may appear as either a favorable entropy or a favorable enthalpy change. A simple model of complex formation has been proposed that includes solute–solute interaction and solvent effect terms, with explicit inclusion of a solute size factor.[1,3c] Sinanoğlu[2b] gave a theoretical treatment along lines indicated earlier, with the net free-energy change for association being determined by a solvent effect contribution (the solvophobic force), dependent upon solvent surface tension, and an interaction term. The relative importance of the two terms, which will be discussed below, depends upon the size and polarity of the interactants.

The successful correlation of complex stability shown in Figure 2 provides strong support for a role of solvent cohesive forces, or some related property, in promoting the association of these molecules. Thermodynamic data are difficult to interpret, in part because of the complexities described in connection with eq 3, and in part because these molecules are relatively polar, so that substrate–ligand interactions probably make an important contribution to the net stability.

Possible Separation of Solvent Contribution. The linear plots, as in Figure 3, of the standard free-energy change for complex formation against solvent surface tension can be extrapolated to zero surface tension.[10] Though this is a long and questionable extrapolation, it should be explored as a potential method for separating the solvent contribution to complex stability from the substrate–ligand contribution. At the point where $\gamma = 0$, the surface free energy between two phases is zero, and the dependent variable presumably has the same value in both phases. In the present case, therefore, where $\gamma = 0$ the solvent has been reduced to the character of the second phase (air containing solvent vapor), with respect to its cohesive character. The simplest interpretation is to assume that the observed standard free-energy change ΔG° is an additive function of a solvent independent contribution ΔG°_{SL} due to substrate–ligand interaction, and a surface tension dependent solvent contribution $\Delta G^\circ_{solvent}$; thus $\Delta G^\circ = \Delta G^\circ_{SL} + \Delta G^\circ_{solvent}$. Then the value of ΔG° extrapolated to $\gamma = 0$ is interpreted as ΔG°_{SL}.

(21) P. Mukerjee, *Advan. Colloid Interface Sci.*, 1, 241 (1967).
(22) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 417–436.

This treatment leads to surprisingly large substrate–ligand interaction contributions. For example, ΔG°_{SL} for the methyl cinnamate–theophylline complex is 56% of the total complex stability in fully aqueous medium. It is probable that these extrapolated ΔG°_{SL} values are influenced by the nature of the solvent through which the extrapolation is made; that is, ΔG°_{SL} may represent the substrate–ligand interaction energy in an aqueous environment, or of the hydrated reactants. In this connection the theory of Sinanoğlu[2b] is relevant. For the association equilibrium $S + L \rightleftharpoons SL$, the following approximate expression has been given (eq 4).[2b] In eq 4, ΔG° is the experimental standard unitary free

$$\Delta G^\circ \approx a'' - b'\Delta\left(\frac{\mu_i^2}{v_i}\right) + c'\Delta(v_i^{2/3})\gamma_1 \qquad (4)$$

energy change for complex formation, γ_1 is the solvent surface tension, μ_i is the dipole moment of solute i (i = S, L, SL), v_i is the molecular volume of solute i, and a'', b', and c' are quantities that in this approximation are treated as constants independent of solvent or solute. The last term in eq 4 is the solvent effect (cavity) term; the first two terms give the interaction contribution. It has been pointed out[2b] that if a'' and b' are in fact independent of solvent, a plot of ΔG° against γ_1 should be linear. Figure 3 shows such a reasonably linear plot, which is in sharp contrast with the results of Halicioğlu and Sinanoğlu on the cis–trans isomerization rate of azobenzene,[2c] which did not correlate with solvent surface tension, although a full calculation of solvent effect and interaction term magnitudes gave a good account of the results. Although the complete theory applies to solvent effects in pure solvents, it appears from the present paper to be applicable in its approximate form to mixed aqueous solvents. This may be, as noted above, because of specific solvation effects, so that in a series of aqueous solvents the solute species are hydrated, whereas comparisons among different pure solvents introduce the complication of differently solvated solutes, a complication amenable to the full theoretical treatment but not to the approximate equation.

The development thus far has been independent of the maximal overlap area correlation,[1] but the two treatments are related. The surface tension extrapolation procedure yields a quantity ΔG°_{SL} that is tentatively considered to be a solvent-independent measure of the substrate–ligand interaction. The regression line in the area correlation, on the other hand, seems to be an average description of all effects on the complex stability, and deviations of individual points from the line were ascribed to variable substrate–ligand interactions. If both views are valid, there should be a relationship between ΔG°_{SL} and the deviation from the maximal overlap area correlation line. Figure 4 is a plot of d, the vertical deviation described, against ΔG°_{SL} for the five complexes studied. A reasonable linear relationship is observed over a wide range. The equation of this line is $d = m\Delta G^\circ_{SL} + b$, where $m = +0.375$ and $b = +1.40 \times 10^{-21}$ cal/molecule. Since ΔG°_{SL} will only appear as an attractive contribution, it appears that the limiting value of d is b. The equation of the average area correlation regression line[1] in water is $\Delta G^\circ_{H_2O} = kA$, where $k = -0.149 \times 10^{-21}$ cal/Å^2 and A is the maximal overlap area in Å^2/molecule. This

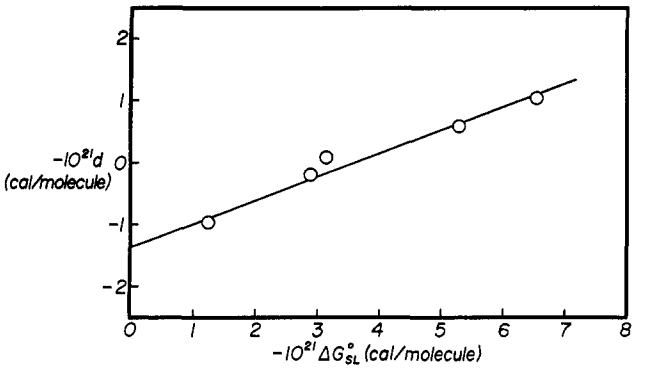

Figure 4. Relationship between d, the vertical deviation of experimental standard free-energy change from the maximal overlap area correlation line,[1] against $\Delta G°_{SL}$, the free-energy change extrapolated to zero surface tension.

treatment therefore suggests that the minimum stability of a complex in water is given by $kA + b$, or 1.4×10^{-21} cal/molecule less than that predicted by the average line. In fact, of the 50 complexes correlated earlier,[1] none falls below this lower limit.

This connection between the surface tension correlation and the overlap area correlation is evident in eq 4, as noted by Sinanoğlu.[2b] The quantity $c'\Delta(v_i^{2/3})$ can be considered an "effective surface area"; then, if a series of interactants is studied in a single solute, a plot of $\Delta G°$ against this effective surface area should reveal a dependence. In fact, the maximal overlap area correlation[1] is just such a plot, whose slope is 64 dyn/cm (close to γ_1 for water, 72 dyn/cm, and even closer to γ_1 for the usual experimental solvent, water containing a small percentage of acetonitrile) and deviations from which were attributed to specific interaction effects. The systems studied in the present paper and the preceding series[1,3] therefore seem suitable for further tests of Sinanoğlu's theory of solvent effects, the results thus far being derived independently of the theory and being fully consistent with it.

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Solvolyses in the Bishomocubane System. Multistep Rearrangements within Ion Pairs[1,2]

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Abstract: The products, rates, and activation parameters of the acetolysis of 1,1′-bishomocubyl methanesulfonate (Ia) have been determined. In turn, the rates of acetolysis of the newly formed methanesulfonates III and IVa have been determined. In the acetolysis of Ia, 61% of it underwent rearrangement with internal return to slower solvolyzing isomers. The formation of the internal-returned *endo*-methanesulfonates suggests ionization to bridged-ion pairs, followed by frontside collapse. From the slow rates of reaction of IIa, IIIa, and IVa, the extensive skeletal rearrangement with internal return of Ia requires rearrangements occurring within ion pairs. Of special significance is the fact that internal return of Ia to Va involves rebonding of the methanesulfonate group four carbons removed from its original bonding position. The rate of acetolysis of Ia is $10^{2.9}$–$10^{4.1}$ times faster than predicted for unassisted acetolysis. [If the pentacyclodecyl cations are indeed bridged, the formation of isomeric acetates of the nucleus requires both frontside and backside migration (of adjacent carbon–carbon bonds to the electron-deficient center).]

With the discovery of the intramolecular photocycloaddition, in recent years a wide variety of substituted polycyclic cage compounds have been synthesized.[3] Some of the material prepared has been subjected to detailed solvolytic studies[4,5] and, indeed, the study of the pentacyclo[5.3.0^{2,5}.0^{3,9}.0^{4,8}]decane system II has aided our understanding of the possible involvement of symmetrical bridged cations in rearrangement processes.[5a] In a preliminary communication from this laboratory,[2] the product analysis data from the acetolysis of pentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]dec-9-yl methanesulfonate (Ia), commonly called 1,1′-bishomocubyl methanesulfonate, was reported. To fully evaluate the significance of this extensive series of rearrangements the system underwent, more detailed product and kinetic investigations of the acetolysis of Ia as well as that of the related *endo*-1,2-bishomocubyl methane-

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(2) For a preliminary publication of these results, see W. G. Dauben and D. L. Whalen, *J. Amer. Chem. Soc.*, **88**, 4739 (1966).

(3) For an excellent review, see W. L. Dilling, *Chem. Rev.*, 66, 384 (1966).

(4) W. G. Dauben and C. H. Schallhorn, *J. Amer. Chem. Soc.*, **93**, 2254 (1971).

(5) (a) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *ibid.*, 91, 3404 (1969); W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, 34, 2605 (1969), and previous papers in series; (b) P. von R. Schleyer, J. J. Harper, G. C. Dunn, V. J. D. Pasquo, and J. R. E. Hoover, *J. Amer. Chem. Soc.*, **89**, 698 (1967); (c) J. C. Barborak and R. Pettit, *ibid.*, **89**, 3080 (1967); (d) for a general review, see R. E. Leone and P. von R. Schleyer, *Angew. Chem., Int. Ed. Engl.*, **9**, 860 (1970).