Solvent Effects on Chemical Processes. 2. Binding Constants of Methyl Orange with α-Cyclodextrin in Binary Aqueous-Organic Solvents

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Received July 30, 1991 (Revised Manuscript Received November 18, 1991)

The standard free energy change for complex formation is written as a sum of effects arising from solvent–solvent interactions (the general medium effect), solvent–solute interactions (the solvation effect), and solute–solute interactions (the intersolute effect). The general medium effect is given by $g\Delta A\ (\gamma - \gamma_o)$, where g is a curvature correction factor to the solvent surface tension γ, ΔA is the change in surface area as the two solvent cavities containing the substrate (Methyl Orange) and ligand (α-cyclodextrin) collapse into a single cavity containing the complex, and γ_o is the value of surface tension at which there is no net solvophobic interaction; γ is defined to be the value appropriate to the equilibrium mean solvation shell composition. The solvation effect is modeled by equilibrium stoichiometric formation of solvated species. All data are related to the fully aqueous system to give $\delta_M\Delta G°$, the solvent effect on the free energy change, as an explicit function of solvent composition. Complex stability data (obtained spectrophotometrically) on seven aqueous–organic cosolvent systems were fitted to this relationship to obtain estimates of $g\Delta A$ and K_1, the solvation exchange constant.

We are carrying out systematic studies of solvent effects on chemical rates and equilibria, and because our laboratory has developed considerable experience in cyclodextrin chemistry, it seemed reasonable to us to examine the solvent dependence of the stability of a cyclodextrin complex. This paper describes an experimental study of the binding constant between Methyl Orange (the substrate or guest) and α-cyclodextrin (the ligand or host) in binary solvents composed of water and an organic cosolvent. We also develop a theoretical framework for the interpretation of such data.

Theory

Our approach[1] to interpreting medium effects in mixed solvent systems is to divide the observed effect into contributions from solvent–solvent interactions (the *general medium effect*), solvent–solute interactions (the *solvation effect*), and solute–solute interactions (the *intersolute effect*). We obtain explicit expressions for the general medium and solvation effects and then relate all data to the fully aqueous system.

First we consider the solvation effect. Other authors[2,3] have interpreted the effects of organic cosolvents in cyclodextrin complexes in terms of competitive complexing, so we address the relationship between solvation and competitive complexing in these systems. Our basic postulate is that solvation is a stoichiometric equilibrium process. Let S ≡ substrate, L ≡ ligand, W ≡ water, M ≡ organic cosolvent. We treat only 1:1 stoichiometries here, though generalization is easily possible. Consider the formation of the possible solvated forms of L, the cyclodextrin:

$$L + W \xrightleftharpoons{K_W} LW$$

$$L + M \xrightleftharpoons{K_M} LM$$

These equilibria can be combined into the exchange process

$$LW + M \xrightleftharpoons{K_1} LM + W$$

where

$$K_1 = \frac{K_M}{K_W} \tag{1}$$

Now we write equilibria involving the substrate-ligand complex:

$$LW + S \xrightleftharpoons{K_{11W}} SL + W$$

$$LM + S \xrightleftharpoons{K_{11M}} SL + M$$

It follows that

$$K_1 = \frac{K_{11W}}{K_{11M}} \tag{2}$$

These reactions incorporate the concept of competitive complexing. Now, inasmuch as we shall find that we are able only to measure K_1, eq 1 and 2 show that the solvation of L and the competitive complexing descriptions are operationally equivalent in the present context.

The system contains three solutes, namely S, L, and SL, connected by the equilibrium

$$S + L \rightleftarrows SL$$

We make the assumption of a cancellation of solvation effects between S and SL, leaving only the solvation effect on L to consider. This assumption is not required, but it simplifies the form of the relationships, it reduces the number of adjustable parameters, and it is chemically acceptable as an approximation.

In considering the solvation effect, we make use of our earlier results.[1] We provisionally adopt this "one-step" solvation model:

$$LW + M \xrightleftharpoons{K_1} LM + W$$

The solvation free energy change is postulated to be a weighted average of contributions by species LW and LM

$$\Delta G°_{solvation} = \Delta G°_W F_W + \Delta G°_M F_M \tag{3}$$

where F_W and F_M are the fractions of solute in the LW and LM forms, respectively. Development of this concept, as shown previously,[1] leads to eq 4. (In ref 1, $\Delta G°_{solvation}$ is

$$\Delta G°_{solvation} = \frac{(kT \ln K_1)K_1x_2}{x_1 + K_1x_2} - \Delta G°_W \tag{4}$$

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0022-3263/92/1957-1794$03.00/0

shown with sign opposite to that in eq 4. This is because ref 1 treats the dissolution process, in which the solute is a *product*, whereas in the present case the solute is a *reactant*.) In eq 4, x_1 and x_2 are the bulk mole fractions of water and organic cosolvent, respectively.

Now we turn to the general medium effect. We model this by means of the key concept of Sinanoglu's theory of the solvophobic effect,[4] according to which the solvophobic driving force for molecular association is the product of the solvent surface tension γ and the decrease in surface area ΔA resulting from the coalescence of two solvent cavities (containing substrate and ligand molecules) into a single cavity (containing the complex). We write

$$\Delta G^\circ_{\text{gen.med}} = g\Delta A(\gamma - \gamma_o) \tag{5}$$

where g is a curvature correction factor to the surface tension, recognizing that the surface tension of a highly curved surface is different from that of a planar surface, and γ_o is defined to be that value of the surface tension at which the solvophobic driving force is zero. In our first use[5] of this solvophobic concept we set $\gamma_o = 0$; later Harrison and Eftink,[6] studying cyclodextrin–adamantanecarboxylate complexes, chose $\gamma_o = 23$ dyn cm^{-1}, this value being the mean surface tension of 15 organic solvents.

We have elsewhere[1] cited theoretical estimates of the curvature factor g; here, we treat it as an empirical parameter. We have also discussed the appropriate value of γ and have concluded that a value calculated to reflect the solvent composition of the solvation shell (which is usually different from the bulk composition) should be used. In the present case, which invokes only 1:1 solvation stoichiometry, the result is

$$\gamma = \gamma_1 + \frac{(\gamma_2 - \gamma_1)K_1x_2}{x_1 + K_1x_2} \tag{6}$$

where γ_1 and γ_2 are the surface tensions of pure water and pure organic cosolvent, respectively. The general medium effect is obtained by combining eqs 5 and 6.

We can now write the total free energy change as

$$\Delta G^\circ = \Delta G^\circ_{\text{intersolute}} + g\Delta A(\gamma - \gamma_o) - \Delta G^\circ_W + \frac{(kT \ln K_1)K_1x_2}{x_1 + K_1x_2} \tag{7}$$

In the fully aqueous system this becomes

$$\Delta G^\circ\ (x_2 = 0) = \Delta G^\circ_{\text{intersolute}} + g\Delta A(\gamma_1 - \gamma_o) - \Delta G^\circ_W \tag{8}$$

Using the Leffler–Grunwald symbolism,[7] the solvent effect is defined as

$$\delta_M\Delta G^\circ = \Delta G^\circ - \Delta G^\circ\ (x_2 = 0) \tag{9}$$

which gives

$$\delta_M\Delta G^\circ = \frac{[g\Delta A(\gamma_2 - \gamma_1) + kT \ln K_1]K_1x_2}{x_1 + K_1x_2} \tag{10}$$

In obtaining eq 10 we have assumed that the intersolute effect is composition-independent, so that it vanishes in the subtraction.

Experimentally, we measure ΔG° as a function of x_2 and then fit $\delta_M\Delta G^\circ$ to x_1 and x_2 using nonlinear regression and eq 10. The regression analysis provides estimates of the parameters K_1 and $g\Delta A$. ΔG° is calculated on the mole fraction basis to eliminate the free energy of mixing.[8,9]

Experimental Section

Materials. α-Cyclodextrin (Sigma or American Tokyo Kasei) was dried at 105 °C for at least 3 h to obtain the anhydrous form. Methyl Orange (Aldrich) was recrystallized from water, washed with 95% ethanol, and then washed with anhydrous diethyl ether. Distilled water was further treated with a Sybron/Barnstead PCS ion exchange purification system. The organic solvents were 2-propanol, acetone, dioxane, dimethyl sulfoxide, acetonitrile (all Baker products, spectrophotometric grade), ethylene glycol (Baker, reagent), and methanol (Mallinckrodt, reagent).

Apparatus. Spectra were recorded on an On Line Instrument Systems (OLIS)-modified Cary 14, a Perkin-Elmer 559A, or a Beckman DU-64 spectrophotometer. The cell compartments were connected to external water baths; all measurements were made at 25 °C.

Procedures. Solvent Preparation. Solvent mixtures were prepared either volumetrically (using densities of the pure components to calculate weights) or gravimetrically; all experimental solvents contained 0.10 M HCl.

Measurement of Binding Constants. For each determination nine sample solutions were prepared with a fixed total concentration (1.6×10^{-5} to 3.0×10^{-5} M) of Methyl Orange. (This is below the concentration at which dimerization is reported to occur.[10]) One of these solutions contained no ligand and the other eight contained varying concentrations of ligand, from 1×10^{-4} to 5×10^{-2} M, the upper cyclodextrin concentration being chosen so that the fraction of substrate bound did not exceed 0.6 (owing to a loss of sharply defined isosbestic points at higher extents of binding). For each solution a reference was prepared to contain a matching ligand concentration but no substrate. All solutions were equilibrated at 25.0 °C. The visible spectrum of each sample solution was recorded relative to its reference solution. The analytical wavelength was 508 nm.

The spectrophotometric data were analyzed with eq 11, where

$$\frac{\Delta A}{b} = \frac{S_tK_{11}\Delta\epsilon_{11}[L]}{1 + K_{11}[L]} \tag{11}$$

ΔA is the change in absorbance at the (fixed) analytical wavelength at fixed Methyl Orange concentration S_t, path length b, when the free cyclodextrin concentration is changed from zero to [L]. In eq 11 K_{11} is the binding constant for 1:1 complex formation (molar scale) and $\Delta\epsilon_{11}$ is the difference in molar absorptivities of the complexed and free Methyl Orange. Since only L_t, the total cyclodextrin concentration, is known, [L] is found by an iterative process.[11] First a linearized form of eq 11 was used, with the approximation [L] = L_t, to obtain initial estimates of K_{11} and $\Delta\epsilon_{11}$. The K_{11} estimate was used to calculate estimates of [L] corresponding to each value of L_t. These [L] estimates, together with the estimates of K_{11} and $\Delta\epsilon_{11}$, were then used in a nonlinear regression analysis according to eq 11. This generated an improved estimate of K_{11}, which led to improved estimates of [L], and so on. The iteration was terminated when the last changing digit in the parameter estimates was the fourth significant figure for two consecutive calculations.

K_{11} in M^{-1} units was converted to a mole fraction basis with the expression $K_{11}\rho M^*$, where ρ is solvent density and M^* is the number of moles of solvent per kg.

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Table I. Binding Constants for the Methyl Orange/α-Cyclodextrin System in Aqueous–Organic Solvents[a,b]

x_2	ρ/g mL^{-1}	M^*/mol kg^{-1}	$-10^{-4}\Delta\epsilon_{11}$/ M^{-1} cm^{-1}	K_{11}/M^{-1}	$-10^{-20}\Delta G°$ /J molec^{-1}	x_2	ρ/g mL^{-1}	M^*/mol kg^{-1}	$-10^{-4}\Delta\epsilon_{11}$/ M^{-1} cm^{-1}	K_{11}/M^{-1}	$-10^{-20}\Delta G°$ /J molec^{-1}
					Water						
0	0.9993	55.506	4.63 (0.07)	682 (15)	4.34 (0.01)						
					Methanol						
0.00496	0.9952	55.292	4.69 (0.04)	580 (8)	4.27 (0.01)	0.07520	0.9420	54.435	4.6 (0.1)	122 (7)	3.60 (0.02)
0.01340	0.9969	54.933	4.62 (0.07)	383 (9)	4.10 (0.01)	0.09658	0.9686	51.411	4.48 (0.01)	71 (1)	3.36 (0.01)
0.01340	0.9969	54.933	4.6 (0.1)	413 (15)	4.13 (0.02)	0.12327	0.9653	48.830	4.28 (0.02)	49 (1)	3.20 (0.01)
0.01340	0.9885	54.933	4.3 (0.2)	449 (34)	4.16 (0.03)	0.15443	0.9540	49.366	4.42 (0.003)	31 (2)	3.00 (0.02)
0.02628	0.9830	54.394	4.7 (0.2)	315 (15)	4.01 (0.02)	0.18070	0.9526	48.489	4.27 (0.09)	25.0 (0.1)	2.90 (0.02)
0.04886	0.9757	53.473	4.52 (0.05)	195 (4)	3.80 (0.01)						
					Dimethyl Sulfoxide						
0.01249	1.0046	53.286	4.50 (0.07)	412 (10)	4.12 (0.01)	0.09682	1.0433	41.953	4.5 (0.1)	64 (3)	3.27 (0.02)
0.03767	1.0146	49.309	4.42 (0.08)	191 (6)	3.77 (0.01)	0.12753	1.0472	38.817	3.70 (0.03)	40 (2)	3.05 (0.02)
0.06475	1.0372	45.644	4.57 (0.02)	125 (1)	3.58 (0.003)	0.15439	1.0719	36.634	4.01 (0.03)	42 (1)	3.05 (0.01)
0.06518	1.0273	45.591	4.2 (0.1)	118 (6)	3.55 (0.02)	0.17685	1.060	34.816	4.4 (0.2)	16 (4)	2.6 (0.1)
0.06518	1.0292	45.591	4.8 (0.1)	82 (3)	3.40 (0.02)	0.23128	1.071	31.259	2.8 (0.1)	16 (2)	2.59 (0.04)
					Ethylene Glycol						
0.00328	0.9973	54.800	2.20 (0.03)	659 (83)	4.32 (0.05)	0.04968	1.0155	53.473	4.61 (0.04)	149 (2)	3.70 (0.01)
0.00669	0.9990	54.349	3.40 (0.02)	362 (9)	4.07 (0.01)	0.07702	1.0256	52.435	4.7 (0.1)	95 (5)	3.52 (0.02)
0.00963	1.0012	54.933	4.4 (0.1)	510 (21)	4.22 (0.02)	0.10009	1.0290	44.433	2.90 (0.01)	78 (3)	3.37 (0.02)
0.00963	1.0012	54.933	4.9 (0.2)	390 (23)	4.11 (0.02)	0.12697	1.0358	42.217	3.00 (0.05)	46 (2)	3.13 (0.02)
0.02781	1.0080	54.394	4.7 (0.2)	250 (11)	3.92 (0.02)	0.16213	1.0486	47.294	4.5 (0.2)	28 (2)	2.98 (0.03)
					Dioxane						
0.00406	0.9966	54.379	4.44 (0.01)	293 (1)	3.98 (0.001)	0.02450	1.0067	50.676	4.6 (0.3)	39 (4)	3.13 (0.04)
0.00519	0.9969	54.146	4.08 (0.01)	219 (3)	3.86 (0.01)	0.03720	1.0076	48.287	4.4 (0.6)	20 (3)	2.83 (0.06)
0.00769	1.000	54.057	4.55 (0.06)	190 (4)	3.80 (0.01)	0.03730	1.0073	48.271	5.8 (0.4)	15 (2)	2.70 (0.05)
0.01059	0.9982	53.060	4.20 (0.01)	134 (2)	3.65 (0.01)	0.04724	1.011	46.889	4.6 (0.4)	14 (1)	2.68 (0.03)
0.01490	1.0036	52.464	4.58 (0.07)	82 (2)	3.45 (0.01)	0.05126	1.0220	46.278		8.7	2.48
					2-Propanol						
0.00070	0.9928	55.415	4.61 (0.07)	587 (15)	4.27 (0.01)	0.00646	0.9922	54.417	2.88 (0.02)	228 (29)	3.88 (0.05)
0.00117	0.9954	55.355	4.46 (0.07)	549 (16)	4.25 (0.01)	0.00901	0.9901	54.102	4.40 (0.07)	169 (4)	3.75 (0.01)
0.00211	0.9984	55.235	4.44 (0.03)	444 (4)	4.16 (0.004)	0.01137	0.9895	53.813	2.6 (0.3)	141 (23)	3.67 (0.07)
0.00211	0.9984	55.235	4.70 (0.06)	398 (9)	4.12 (0.01)	0.01219	0.9837	53.972	4.53 (0.02)	119 (1)	3.60 (0.003)
0.00211	0.9984	55.235	3.91 (0.06)	456 (13)	4.17 (0.01)	0.01390	0.9880	53.508	6.22 (0.002)	105 (1)	3.55 (0.003)
0.00351	0.9936	55.056	4.44 (0.07)	335 (10)	4.04 (0.01)	0.01603	0.9811	53.252	4.46 (0.02)	76 (2)	3.41 (0.01)
0.00356	0.9928	55.050	4.50 (0.01)	347 (2)	4.06 (0.002)	0.01709	0.9990	53.127	3.92 (0.01)	86 (3)	3.46 (0.01)
0.00515	0.9954	54.581	2.06 (0.01)	300 (23)	3.99 (0.03)	0.02293	0.9827	52.443	2.35 (0.04)	56 (9)	3.28 (0.07)
0.00538	0.9920	54.551	4.12 (0.01)	258 (8)	3.93 (0.01)						
					Acetonitrile						
0.00228	0.9950	55.074	4.68 (0.08)	390 (3)	4.10 (0.003)	0.01797	0.9880	54.003	3.75 (0.04)	110 (4)	3.57 (0.01)
0.00442	0.9930	54.925	2.81 (0.01)	285 (4)	3.97 (0.01)	0.01842	0.9876	53.973	4.0 (0.2)	96 (8)	3.52 (0.03)
0.00444	0.9953	55.194	4.74 (0.01)	305 (2)	4.00 (0.003)	0.02268	0.9877	53.946	4.63 (0.08)	62 (2)	3.34 (0.01)
0.00671	0.9920	54.767	4.34 (0.03)	216 (6)	3.86 (0.01)	0.02741	0.9827	53.378	2.88 (0.04)	57 (2)	3.29 (0.01)
0.00893	1.0100	54.615	4.73 (0.02)	164 (3)	3.75 (0.01)	0.02764	0.9836	53.364	4.36 (0.03)	49 (1)	3.23 (0.01)
0.01118	0.9928	54.726	4.62 (0.03)	164 (3)	3.74 (0.01)	0.02869	0.9826	53.295	4.25 (0.02)	48 (1)	3.23 (0.003)
0.01316	0.9910	54.327	4.41 (0.03)	102 (2)	3.54 (0.01)	0.03770	0.9802	52.714	4.25 (0.02)	29 (1)	3.01 (0.01)
0.01681	0.9880	54.081	4.8 (0.1)	76 (8)	3.42 (0.04)	0.04663	0.9803	52.391	4.6 (0.3)	23 (2)	2.91 (0.04)
					Acetone						
0.00171	0.9967	55.296	4.6 (0.1)	483 (19)	4.19 (0.02)	0.01915	0.9873	52.992	4.72 (0.04)	86 (7)	3.46 (0.04)
0.00438	0.9956	54.971	4.5 (0.1)	330 (9)	4.04 (0.01)	0.02327	0.9816	52.533	3.62 (0.01)	94 (1)	3.49 (0.01)
0.00776	0.9917	54.565	4.61 (0.03)	235 (3)	3.89 (0.01)	0.02708	0.9827	52.117	3.72 (0.02)	75 (3)	3.34 (0.02)
0.01291	0.9985	53.962	4.61 (0.02)	158 (1)	3.73 (0.003)	0.03026	0.9812	51.774	4.26 (0.01)	54.3 (0.4)	3.26 (0.003)
0.01326	0.9902	53.910	4.57 (0.08)	138 (4)	3.66 (0.01)	0.03953	0.9847	51.021	4.63 (0.07)	50 (2)	3.22 (0.02)
0.01736	0.9879	53.193	4.12 (0.55)	114 (1)	3.58 (0.004)						

[a] At 25.0 °C; ionic strength 0.10 M; 0.10 M HCl. [b] Standard deviations in parentheses.

Results

Table I lists values of K_{11} as a function of x_2, together with some related information, for the fully aqueous system and for seven cosolvent systems. Each entry in the table represents a separate binding study; the uncertainties in the parameters are within-run uncertainties, generated in the nonlinear regression according to eq 11. The estimates of K_{11} and $\Delta\epsilon_{11}$ in the fully aqueous system are in very good agreement with earlier values from this laboratory.[12]

The data in Table I were fit to eq 10 by nonlinear regression with the program SYSTAT, providing the parameters K_1 and $g\Delta A$, which are given in Table II. Figure 1 shows typical examples of the curve fits.

Discussion

The pK_a value of Methyl Orange is 3.4,[13,14] so in 0.1 N HCl the molecule is essentially completely protonated. In mixed aqueous organic solvents, in the water-rich region explored in the present paper, the pK_a undergoes modest shifts (less than one pK unit) in the negative direction.[15,16] In 0.1 N HCl the absorption band at 508 nm, the dominant band, has been attributed to the quinoid resonance form

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Table II. Parameter Estimates for the Methyl Orange/α-Cyclodextrin System in Aqueous–Organic Solvents[a]

cosolvent	K_1	$-g\Delta A$/Å^2 molec^{-1}	curve fit criterion[b]/%
methanol	4.9 (0.5)	43 (4)	1
dimethyl sulfoxide	6.4 (1.2)	66 (12)	3
ethylene glycol	7.7 (1.8)	58 (15)	2
dioxane	30.6 (2.3)	38 (4)	2
2-propanol	43.0 (3.6)	11 (3)	1
acetonitrile	40.3 (5.7)	13 (5)	2
acetone	45.7 (3.9)	3 (2)	1

[a] Obtained by fitting the data of Table I to eq 10. Standard deviations in parentheses. [b] Curve fit criterion = 100 (standard deviation of points about the fitted line divided by mean of the ordinate values.)

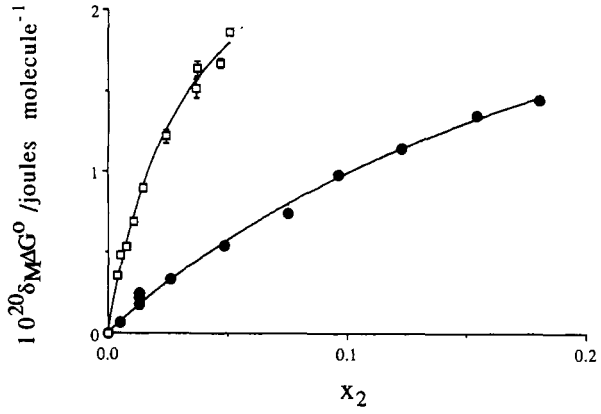

Figure 1. Solvent effect on the stability of the α-cyclodextrin–Methyl Orange complex in dioxane–water (upper curve) and methanol–water (lower). The points are experimental; the smooth lines are drawn with eq 10 and the parameters in Table II.

of the azonium tautomer, and the band at 317 nm to the ammonium tautomer.[13,17] Mochida and co-workers[18] have concluded, from resonance Raman spectroscopy, that in 0.1 N HCl Methyl Orange is almost exclusively in the azonium–quinoid form.

Upon complexation with α-cyclodextrin, in acidic solution, Methyl Orange exhibits a sharp decrease in absorption at 508 nm, with no shift in the wavelength of maximum absorption. This is attributed[19,20] to the shifting of the tautomeric equilibrium in favor of the ammonium form, owing to the tight fit of the α-cyclodextrin about the azobenzene moiety. This interpretation is consistent with Raman optical activity and circular intensity differential spectra.[21,22]

That eq 10 is capable of describing the data is a useful result, but it is not a very demanding test of the model, because the data do not cover a wide range in x_2. Extension to larger values of x_2 was limited by the ability to measure K_{11} with resonable precision. It is because of the small range in x_2 that it is unnecessary to invoke solvation stoichiometries beyond 1:1.

The relationships of the model parameters K_1 and $g\Delta A$ to properties of the cosolvents appear to be limited, but are suggestive. In Table II the cosolvents are listed in order of increasing K_1, the values of which seem to fall into two

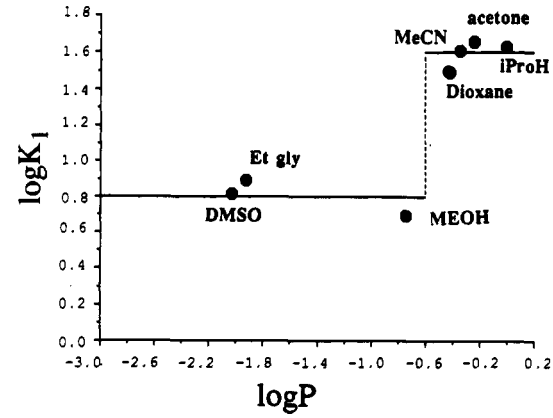

Figure 2. Plot of log K_1 (from Table II) against log P, where P is the octanol/water partition coefficient of the pure cosolvent.

classes, namely $K_1 \approx 5$–8 and $K_1 \approx 30$–50. These classes may be characterized by the polarity of the cosolvents, as measured by their octanol/water partition coefficients,[23] P. Figure 2 is a plot of log K_1 against log P. If this interpretation is valid, cosolvents having log P values less than about −0.6 will have K_1 values in the low class, whereas cosolvents with log P values above −0.6 will fall in the high class. The position of this discontinuity on the log P scale may be a measure of the effective polarity of the α-cyclodextrin cavity.

This is an interesting inference because it constitutes an estimate of the nature of the cavity that is based on a different physical phenomenon than earlier estimates, which make use of spectroscopic "probes" of the molecular environment of the cavity. Thus Van Etten et al.[24] reported that the absorption spectrum of *p-tert*-butylphenol in aqueous α-cyclodextrin solution bore a remarkable resemblance to the spectrum of *p-tert*-butylphenol in dioxane. This result has often been cited as evidence that the properties of the cyclodextrin interior are similar to the properties of dioxane. However, our laboratory[25] has shown that other probes can lead to different conclusions about the nature of the cyclodextrin cavity. Fluorescence probe studies have resulted in inferences that the cavity may resemble *tert*-butyl alcohol,[26] ethylene glycol,[26] or ethanol.[27,28] Cox et al.[26] suggest that different probes may "sample" different portions of the cyclodextrin cavity. Perhaps some of the apparent disparity in the findings depends upon one's choice of measure of solvent polarity; for example, the dielectric constants of dioxane (2.2) and ethanol (24.3) are very different, whereas their log P values are very similar (−0.42 and −0.32, respectively). The discontinuity in Figure 2, as we have sketched it, lies between, and very close to, dioxane and methanol.

There seems to be a tendency for large K_1 values to be associated with small $g\Delta A$ values, and vice versa, but the correlation is not very precise. We have argued above that K_1 is a discontinuous function, whereas $g\Delta A$ seems not to exhibit a discontinuity, so a close correlation is not expected. We do not know if the apparent relationship is a curve-fitting artifact or a real phenomenon. $g\Delta A$ is also roughly correlated with log P and with γ_2, but we will not

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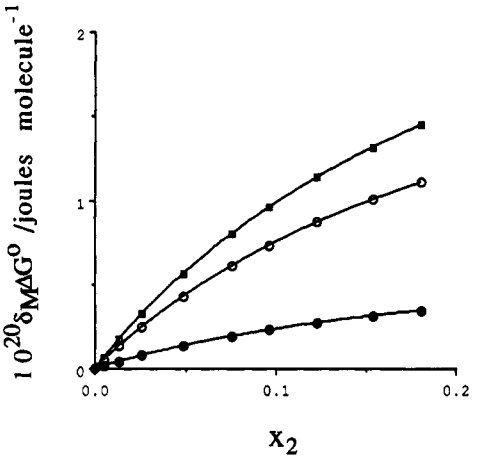

Figure 3. Plot for the methanol–water system of the total relative solvent effect (squares), the general medium effect contribution (open circles), and the solvation effect contribution (filled circles). The points serve only to clarify the several curves.

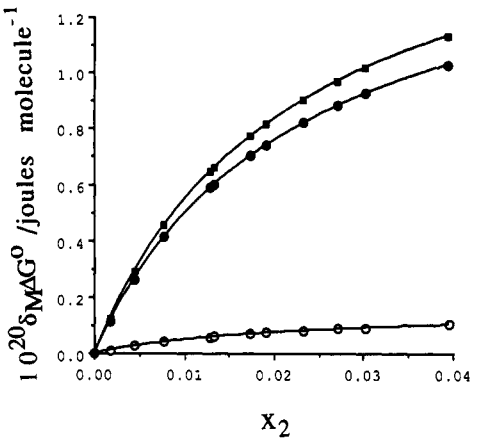

Figure 4. Plot for the acetone–water system of the total relative solvent effect (squares), the general medium effect contribution (open circles), and the solvation effect contribution (filled circles). The points serve only to clarify the several curves.

pursue these possibilities because there may be no causal connections.

We next examine more closely the nature of the parameter $g\Delta A$. According to Khossravi,[29] this can be expanded to

$$g\Delta A = g_{SL}A_{SL} - g_SA_S - g_LA_L \quad (12)$$

where A_{SL}, A_S, A_L are the surface areas of the cavities enclosing the subscripted species. Combining this with $\Delta A = A_{SL} - A_S - A_L$ gives

$$g\Delta A = g_{SL}\Delta A + (g_{SL} - g_S)A_S + (g_{SL} - g_L)A_L \quad (13)$$

Thus the g in the estimated parameter $g\Delta A$ may be a composite quantity, and a better notation for $g\Delta A$ might be $\Delta(gA)$. We make these postulates:

1. The effective area A is the area of contact of the solvation shell with the nonpolar portion of the solute. We can estimate this as the nonpolar surface area of the solute. To a first approximation, therefore, A depends only upon the solute.

2. The curvature factor g depends upon the curvature of the cavity, which may be very complex for nonspherical solutes. For a given solute, g depends upon solvent organization in the solvation shell, for this governs local radii of curvature. Thus, g depends, for a given solute, upon cosolvent identity.

There is some evidence from solubility data[1] for these dependencies. These data suggest that g is smaller than unity for molecular sized cavities and that A reflects the nonpolar area of the solute. Moreover, g appears (for a given solute) to be smaller in the less polar cosolvents. The behavior of $g\Delta A$ in the present study is consistent with these trends; we may take ΔA as essentially independent of solvent, so variation in the quantity $g\Delta A$ reflects the solvent dependence of the composite g. The correlations with log P and γ_2 indicate that, for fixed solute species, g is larger in more polar solvents. (There is some ambiguity in our interpretation, for we assume that g is independent of solvent composition.)

One further point is of interest. Figures 3 and 4 are plots of the total solvent effect, $\delta_M\Delta G°$, against x_2 for two of the cosolvent systems, together with their separate contributing factors, namely the general medium effect and the solvation effect, all relative to the fully aqueous system. Within the context of our treatment we must conclude that both the general medium and the solvation effects can make significant, and sometimes comparable, contributions to the total effect. It follows that interpretations of solvent effects must take account of both of these contributing effects. In the particular case of the α-cyclodextrin–methyl Orange complex, the destabilizing effect of organic cosolvents is a consequence both of a decreased solvophobic driving force for association (the general medium effect contribution) and a solvation destabilization. Reference to eq 7 shows that, if we assign a value to the parameter γ_o, we can calculate the contributions to the total free energy change, in any solvent mixture, of the separate terms $g\Delta A(\gamma - \gamma_o)$, which is the solvophobic contribution, $(kT \ln K_1)K_1x_2/(x_1 + K_1x_2)$, which is the cosolvent influence on the solvation contribution, and $(\Delta G°_{\text{intersolute}} - \Delta G°_W)$, which combines the intersolute effect (i.e., substrate–ligand interaction) with the aqueous solvation contribution. Equation 8 gives the corresponding relationship in the fully aqueous system.

Acknowledgment. This work was supported in part by the donors of the Petroleum Research Fund (grant 16590-AC4), administered by the American Chemical Society. A.P. was a Fellow of the American Foundation for Pharmaceutical Education and a Parke Davis/Warner Lambert Fellow. M.M. was a Pfizer Fellow, and is currently a Pharmaceutical Manufacturers Association Fellow and a Bristol-Myers Squibb Fellow. We thank Davar Khossravi for helpful discussions.

Registry No. α-Cyclodextrin, 10016-20-3.

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