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Solvent effects on chemical processes. 9. Energetic contributions to the complexation of 4-nitroaniline with α-cyclodextrin in water and in binary aqueous-organic solvents

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Solvent effects on chemical processes. 9. Energetic contributions to the complexation of 4-nitroaniline with α-cyclodextrin in water and in binary aqueous-organic solvents

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The phenomenological theory of solvent effects partitions the free energy change of a process into contributions from solvent-solvent interactions (the general medium or solvophobic effect), solvent-solute interactions (the solvation effect), and solute-solute interactions (the intersolute or intrasolute effect). This approach is applied to complex formation between α-cyclodextrin and 4-nitroaniline in water and many aqueous-organic solvent mixtures; the organic solvents were methanol, ethanol, 2-propanol, ethylene glycol, dimethylsulfoxide, acetonitrile, and acetone. Complex stability constants were measured spectrophotometrically. The parameters of the phenomenological model were extracted by nonlinear regression or by graphical analysis. It is observed that there are two classes of cosolvents, distinguished by their polarity. If the pure solvent has log P < -0.3 (where P is the 1-octanol/water partition coefficient), the system behaves "normally," with parameter values typical of nonelectrolyte solutes, whereas if log P > -0.3, unusual parameter values, attributed to strong interaction between the organic solvent and α-cyclodextrin, are observed. The α-cyclodextrin cavity is inferred to have a polarity corresponding to log P = -0.3. The energetic contributions to complex stability in water suggest that essentially all of the stability is derived from the general medium (hydrophobic) effect. Addition of organic cosolvents weakens the complex through both general medium and solvation effects.

INTRODUCTION

Our laboratory has developed a phenomenological model of solvent effects in mixed solvent systems[1]. Instead of describing deviations from ideal behavior in terms of activity coefficients or excess thermodynamic functions, we postulate chemical bases for observed behavior, and write explicit expressions for free energy changes as functions of solvent composition. We consider observed solvent effects to arise from combinations of solvent-solvent interactions, which give rise to a *general medium effect*; solute-solvent interactions, giving the *solvation effect*; and solute-solute interactions (the *intersolute effect*). This approach has been applied to solvent effects on nonelectrolyte solubility[1,2], surface tension[3], molecular complex formation[4,5], and absorption spectra[6]. In one of these applications[4] we interpreted solvent effects on the stability of the complex between methyl orange and α-cyclodextrin. We have now made a deeper analysis of such effects; in the present paper we describe this theory in the context of solvent effects on cyclodextrin complex formation, and we apply it to data on the 1:1 complex of 4-nitroaniline with α-cyclodextrin in many aqueous-organic solvent systems.

THEORY

Solvent effects on complex stability

We will consider the equilibrium formation of complex C (with 1:1 stoichiometry) from substrate S (the guest) and ligand L (the host). From measurement of the equilibrium constant (binding or stability constant) for this process we calculate the free energy of complex formation, ΔG^*_{comp}. The phenomenological theory expresses this free energy change as a function of the mole fraction x_1 and x_2 of solvent component 1 (water) and component

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2 (the organic cosolvent). In earlier work[5] we showed how the solvent effect on complex formation can be related to solvent effects on the equilibrium solubilities of the species S, L, and C. The free energies of solution are themselves given as sums of the effects described in the introduction. Thus for species S we write eq. (1), and similarly for L and C.

$$\Delta G^{S}_{soln} = \Delta G^{S}_{intersol} + \Delta G^{S}_{gen\ med} + \Delta G^{S}_{solv} \qquad (1)$$

In eq. (1), $\Delta G^{S}_{intersol}$ includes the crystal lattice energy and any significant solute-solute interactions in the solution phase.

Our analysis[5] of the complex formation process provided eq. (2) as the connection between ΔG^{*}_{comp} and the quantities in eq. (1).

$$\Delta G^{*}_{comp} = \Delta G_{comp}(g) + (\Delta G^{C}_{gen\ med} + \Delta G^{C}_{solv}) - (\Delta G^{S}_{gen\ med} + \Delta G^{S}_{solv}) - (\Delta G^{L}_{gen\ med} + \Delta G^{L}_{solv}) \qquad (2)$$

In eq. (2), $\Delta G_{comp}(g)$ is the free energy change for complex formation in the vapor state. This quantity can therefore be interpreted as the substrate-ligand interaction energy *within* the complex; we label this $\Delta G^{C}_{intrasol}$:

$$\Delta G^{*}_{comp} = \Delta G^{C}_{intrasol} + (\Delta G^{C}_{gen\ med} + \Delta G^{C}_{solv}) - (\Delta G^{S}_{gen\ med} + \Delta G^{S}_{solv}) - (\Delta G^{L}_{gen\ med} + \Delta G^{L}_{solv}) \qquad (3)$$

The solvation effect is modelled as a competitive stoichiometric equilibrium between water (W) and cosolvent (M) for solute (R):

$$RW + M \underset{}{\overset{K_1}{\rightleftharpoons}} RM + W$$

where K_1 is the dimensionless solvation equilibrium constant. In solubility studies covering the full range of solvent composition it is necessary to invoke a 2-step (3-state) solvation scheme, but in the present studies x_2 was seldom larger than 0.05, and the above 1-step (2-state) solvation scheme suffices. Development of this concept leads[1] to eq. (4) for the solvation energy of a solute species,

$$\Delta G_{solv} = \frac{(-kT\ln K_1)K_1x_2}{x_1 + K_1x_2} + \Delta G_W \qquad (4)$$

where ΔG_W is the solvation energy in the fully aqueous system ($x_2 = 0$).

The general medium effect is treated in terms of the energy required to create a cavity in the solute for the solute molecule; the expression is

$$\Delta G_{gen\ med} = gA\gamma \qquad (5)$$

where g is an empirical curvature correction factor that adjusts the surface tension γ to the highly curved cavity surface, and A is the cavity surface area. The surface tension is postulated to be that value appropriate to the composition of the solvation shell, which gives eq. (6), for a 1-step solvation model, where $\gamma' = \gamma_2 - \gamma_1$, γ_1 and γ_2 being the surface tensions of pure components 1 and 2.

$$\gamma = \gamma_1 + \frac{\gamma' K_1 x_2}{x_1 + K_1 x_2} \qquad (6)$$

Combining eqs. (3–6) gives eq. (7), which relates the free energy of complex formation to the solvent composition and the model parameters.

$$\Delta G^{*}_{comp} = \Delta G^{C}_{intrasol} + (\Delta G^{C}_{W} - \Delta G^{S}_{W} - \Delta G^{L}_{W}) + (gA^{C} - gA^{S} - gA^{L})\gamma_1 + \frac{(gA^{C}\gamma' - kT\ln K_1^{C})K_1^{C}x_2}{x_1 + K_1^{C}x_2} - \frac{(gA^{S}\gamma' - kT\ln K_1^{S})K_1^{S}x_2}{x_1 + K_1^{S}x_2} - \frac{(gA^{L}\gamma' - kT\ln K_1^{L})K_1^{L}x_2}{x_1 + K_1^{L}x_2} \qquad (7)$$

Now, in the fully aqueous system eq. (7) becomes eq. (8).

$$\Delta G^{*}_{comp}(x_2 = 0) = \Delta G^{C}_{intrasol} + (\Delta G^{C}_{W} - \Delta G^{S}_{W} - \Delta G^{L}_{W}) + (gA^{C} - gA^{S} - gA^{L})\gamma_1 \qquad (8)$$

We define the solvent effect, $\delta_M \Delta G^{*}_{comp}$, by eq. (9).

$$\delta_M \Delta G^{*}_{comp} = \Delta G^{*}_{comp} - \Delta G^{*}_{comp}(x_2 = 0) \qquad (9)$$

Combining eqs. (7–9) gives eq. (10).

$$\delta_M \Delta G^{*}_{comp} = \frac{(gA^{C}\gamma' - kT\ln K_1^{C})K_1^{C}x_2}{x_1 + K_1^{C}x_2} - \frac{(gA^{S}\gamma' - kT\ln K_1^{S})K_1^{S}x_2}{x_1 + K_1^{S}x_2} - \frac{(gA^{L}\gamma' - kT\ln K_1^{L})K_1^{L}x_2}{x_1 + K_1^{L}x_2} \qquad (10)$$

Eq. (10) relates the solvent effect on complex formation to the solution composition. However, the equation contains six unknown parameters (gA and K_1 for C, S, and L), too many for practical use. It is necessary to reduce the number of parameters in order to obtain a useful relationship.

The cancellation approximations

Let us apply the condition $K_1^C = K_1^S = K_1^L = K_1$ to eq. (10). The result is eq. (11),

$$\delta_M \Delta G^*_{comp} = \frac{(kT\ln K_1 + \Delta gA\gamma')K_1 x_2}{x_1 + K_1 x_2} \quad (11)$$

where $\Delta gA = gA^C - gA^S - gA^L$. We call this case the *full cancellation approximation*. When $x_2 = 0$, from eq. (8):

$$\Delta G^*_{comp}(x_2 = 0) = \Delta G^C_{intrasol} + (\Delta G^C_W - \Delta G^S_W - \Delta G^L_W) + \Delta gA\gamma_1 \quad (12)$$

The data from the present study have led us to examine another special case, namely $K_1^C = K_1^S < K_1^L$. Applying this condition to eq. (10) provides eq. (13).

$$\delta_M \Delta G^*_{comp} = \frac{(kT\ln K_1^L - gA^L\gamma')K_1^L x_2}{x_1 + K_1^L x_2} + \frac{(gA^C - gA^S)\gamma' K_1^S x_2}{x_1 + K_1^S x_2} \quad (13)$$

Since $K_1^L > K_1^S$, we write eqn. (13) in this approximate form:

$$\delta_M \Delta G^*_{comp} = \frac{(kT\ln K_1 - gA\gamma')K_1 x_2}{x_1 + K_1 X_2} \quad (14)$$

where it is understood that K_1 and gA refer to species L. (Of course, the designations substrate and ligand are arbitrary, and these assignments might be interchanged.) This case is called the *partial cancellation approximation*. When $x_2 = 0$, from eq. (8) we find

$$\Delta G^*_{comp}(x_2 = 0) = \Delta G^C_{intrasol} + (\Delta G^C_W - \Delta G^S_W - \Delta G^L_W) + (gA^C - gA^S)\gamma_1 - gA^L\gamma_1 \quad (15)$$

The different forms of eqns. (12) and (15) reflect the different kinds of information available in the two cases.

Eqs. (11) and (14) both have the form

$$\delta_M \Delta G^*_{comp} = \frac{(kT\ln K_1 + G\gamma')K_1 x_2}{x_1 + K_1 x_2} \quad (16)$$

Thus data analysis proceeds in the same manner for both special cases: the solvent effect $\delta_M \Delta G^*_{comp}$ is fitted to solvent composition x_1 and x_2 by nonlinear regression or graphical analysis, and the adjustable parameters K_1 and G are evaluated. G is called the general medium parameter; in the full cancellation case $G = \Delta gA$, whereas in the partial cancellation case $G = -gA$. The assignment of individual systems to either of these cases is discussed later.

EXPERIMENTAL

Materials

α-Cyclodextrin (American Tokyo Kasei) was recrystallized from water and dried at 105°C for at least 3 hr to obtain the anhydrous form. 4-Nitroaniline (Aldrich, 99.9% purity) was used directly. The organic solvents were 2-propanol, acetone, dimethylsulfoxide, acetonitrile (Baker, spectrophotometric grade); ethylene glycol (Baker, reagent); methanol (Mallinckrodt, reagent), and ethanol (Quantum Chemical, reagent). Distilled water was further treated with a Sybron/Barnstead PCS ion exchange purification system.

Apparatus

Complex stability constants were measured with the aid of an On Line Instrument Systems (OLIS)-modified Cary 14 or a Beckman DU-65 spectrophotometer. The cell compartments of these instruments were maintained at 25°C by connection to circulating water baths.

Measurement of complex stability constants

All cosolvent mixtures were prepared gravimetrically. The complexation studies were carried out in solutions prepared from a pH 10 (in water) carbonate buffer such that the final total concentration of carbonate was 0.01 M.

K_{11}, the stability constant for 1:1 complex formation between 4-nitroaniline (the substrate) and α-cyclodextrin (the ligand), was measured spectrophotometrically. The procedure has been described in detail elsewhere[7]. K_{11}, which is in M^{-1} units, was converted to a mole fraction basis with the expression $K_{11}\rho M^*$, where ρ is the solvent density and M^* is the number of moles of solvent per kg.

All constants were measured at 25°C. The analytical wavelength was 410 nm. The 4-nitroaniline concentration was 7.1×10^{-5} M to 7.7×10^{-5} M, and the α-cyclodextrin concentration ranged from 9.4×10^{-4} M to 3.4×10^{-2} M.

Estimation of parameters

The unitary free energy change for complex formation is calculated from the stability constant on a mole fraction basis, eq. (17),

$$\Delta G^*_{comp} = -kT\ln K_{11}\rho M^* \quad (17)$$

where ΔG^*_{comp} is on a per molecule basis. The solvent effect is then calculated with eq. (9). Finally the parameters K_1 and G are evaluated by applying eq. (16) to the solvent effect $\delta_M \Delta G^*_{comp}$ as a function of x_2.

The parameter estimates were obtained by two methods. In one of these nonlinear regression analysis was carried out with the program Systat®, Version 5.2.1.

Because of the considerable scatter in the data, smoothing was necessary, thus introducing some subjectivity into the process.

A graphical method was also applied. Let $y = \delta_M \Delta G^*_{comp}$ and $a = kT \ln K_1 + G\gamma'$. Then eq. (16) becomes eq. (18).

$$y = \frac{aK_1x_2}{x_1 + K_1x_2} \tag{18}$$

Using $x_1 + x_2 = 1$, eq. (18) can be put into the linear plotting form of eq. (19).

$$y/x_2 = aK_1 - y(K_1 - 1) \tag{19}$$

As with nonlinear regression, this graphical technique required smoothing of the data (of y vs. x_2) before making the plot according to eq. (19).

RESULTS

The 1:1 stoichiometry of the 4-nitroaniline/α-cyclodextrin complex is supported by the observation of isosbestic points and the independence of K_{11} on wavelength[8]. (Armstrong et al[9] have reported a weak 1:2 complex in this system.) Table I lists K_{11} values in aqueous-organic solvent mixtures, the organic cosolvents being methanol, dimethylsulfoxide (DMSO), ethylene glycol, ethanol, 2-propanol, acetonitrile, and acetone; the table also gives the free energy of complexation calculated with eq. (17). The pKa of 4-nitroaniline (NA) is 1.00[10], so it is in the conjugate base form in all of these studies. It has been shown that the nitro group is the substrate site that enters the cyclodextrin cavity[8].

Table II shows the parameters evaluated by fitting the data of Table I to eq. (16). Some of the results obtained by means of nonlinear regression are disquieting—particularly for the DMSO and ethylene glycol systems. Examination of the plots of $\delta_M \Delta G^*_{comp}$ against x_2 for these systems shows that they are essentially linear. It is not possible to evaluate two parameters from a straight line passing through the origin, so we must conclude that the K_1 and G for DMSO and ethylene glycol are curve-fitting artifacts. This conclusion leads to doubts about the validity of the rest of the nonlinear parameter estimates in Table II, and this is why the graphical method was developed; Table II also lists the parameters found by applying eq. (19).

Table I Binding constants for the 4-nitroaniline/α-cyclodextrin system in aqueous-organic solvents at 25°C

x_2	K_{11}/M^{-1a}		$-\Delta G^*_{comp}/10^{-20}$ J molecule^{-1}
	Water		
0	431	(39)	4.15
	Methanol		
0.0256	197	(21)	3.81
0.0491	126	(7)	3.62
0.0804	66	(7)	3.34
0.1041	68	(5)	3.34
0.1070	54	(7)	3.24
0.1236	24	(2)	2.90
0.1307	28	(1)	2.97
	Dimethylsulfoxide		
0.0122	256	(28)	3.92
0.0250	296	(57)	3.96
0.0540	115	(4)	3.55
0.0896	57	(4)	3.22
0.1332	16	(1)	2.66
	Ethylene glycol		
0.0245	256	(16)	3.91
0.0521	128	(17)	3.61
0.0830	78	(3)	3.38
0.1197	51	(3)	3.18
0.1646	13	(1)	2.58
	Ethanol		
0.0045	254	(15)	3.92
0.0118	135	(19)	3.65
0.0195	102	(7)	3.54
0.0276	66	(4)	3.35
0.0417	52	(3)	3.24
0.0528	31	(1)	3.02
0.0599	24	(1)	2.92
	2-Propanol		
0.0030	355	(15)	4.06
0.0062	154	(12)	3.72
0.0090	151	(9)	3.70
0.0123	77	(3)	3.43
0.0153	79	(11)	3.43
0.0187	61	(6)	3.32
0.0248	63	(7)	3.33
0.0309	42	(6)	3.15
	Acetonitrile		
0.0045	228	(30)	3.88
0.0114	140	(9)	3.68
0.0178	73	(2)	3.40
0.0268	44	(3)	3.19
0.0360	44	(3)	3.19
0.0558	30	(3)	3.03
	Acetone		
0.0031	360	(28)	4.07
0.0055	270	(15)	3.95
0.0120	188	(28)	3.79
0.0196	107	(9)	3.55
0.0236	75	(3)	3.40
0.0332	43	(3)	3.16
0.0385	38	(3)	3.10

[a] Standard deviation in parentheses.

DISCUSSION

The parameter estimates

Table II gives the parameters K_1 and G obtained by fitting the solvent effect data of Table I to eq. (16). The results from nonlinear regression and from graphical analysis are shown. We have commented on the artifactual nature of the nonlinear regression results for ethylene glycol and DMSO. Another peculiar feature of these

Table II Parameter estimates for the 4-nitroaniline/α-cyclodextrin system[a]

Cosolvent	*Nonlinear regression*[b]				*Graphical analysis*	
	K_1		G		K_1	G
Ethanol	25	(0.3)	-11	(0.3)	29	-9
2-Propanol	52	(0.7)	-0.2	(0.3)	46	-3
Acetone	8	(nil)	-77	(nil)	10	-57
Acetonitrile	47	(nil)	-0.7	(nil)	55	+3
Methanol	2.9	(nil)	-67	(0.1)	3.1	-68
Ethylene glycol	0.7	(0.02)	-500	(16)	-	-
Dimethylsulfoxide	0.5	(nil)	-706	(4)	-	-

[a] The parameters appear in eq. (16); the units of G are $Å^2$ $molecule^{-1}$.
[b] Quantities in parentheses are standard deviations.

nonlinear regression results is their extremely small error estimates, which may be a consequence of using smoothed data. For this reason we attach no significance to the uncertainty estimates.

Aside from these issues, there appears to be fairly reasonable agreement between the nonlinear regression and the graphical estimates. In the following we will use the graphically determined parameters.

Eq. (16) successfully describes the solvent effect, as shown in Fig. 1; similar curve-fits for the methyl orange (MO)/α-cyclodextrin system are shown in ref.[4].

Classification of systems

It is apparent that there are two classes of behavior in these α-cyclodextrin systems. We first demonstrate this "non-parametrically" with Fig. 2, which plots the initial slope (that is, the slope at $x_2 = 0$) of the plot of $\delta_M \Delta G^*_{comp}$ against x_2, for both the NA and MO systems. This quantity is plotted against log P_M, where P_M is the 1-octanol/water partition coefficient of the organic cosolvent[11]. This graph is model-independent in the sense that it is not based on any theory of solvent effects. We interpret Fig. 2 to be a description of a practically discontinuous function, the discontinuity occurring at about log $P_M = -0.3$. Our interpretation of this behavior is that the cosolvents may be divided into two classes, those more polar than log $P_M = -0.3$, and those less polar than this value. We go further to suggest that log P = -0.3 may correspond to the effective polarity of the α-cyclodextrin cavity; those solvents less polar than this are able to partition into the cavity effectively, whereas more polar solvents are ineffective in competing for the interior of the cyclodextrin.

Division of cosolvents into two classes can also be demonstrated with the parameter values of the phenomenological model, K_1 and G. Table III lists the systems studied for both NA and MO. (Throughout this discussion the analysis is enhanced by considering the NA and MO results together, so the MO parameters from ref. 4 are given in Table III.) It is apparent that there are two extreme classes of behavior: in one of these K_1 is large and -G is small, whereas in the other class K_1 is small and -G is large. (One system, MO in dioxane, seems to fit neither class. NA could not be studied in dioxane owing to the development of a yellow color unrelated to cyclodextrin complexation.)

In the Theory section we described the concepts of the full cancellation and partial cancellation approximations, which are closely related to the foregoing observations. We wish to determine if these approximations are valid descriptions of the solvent effect behavior. We may first note that eq. (16), which arises from the cancellation approximations, is capable of fitting the experimental data, though because of the limited solvent composition range this is not a demanding test.

To the present time our laboratory has subjected 56 solubility studies to analysis by the phenomenological model. These 56 studies comprise 36 different solutes and 10 different cosolvents. The average K_1 value is 4.5, with standard deviation 3.0 and range 1.5 to 15.1. These values provide us with a criterion of "normal" nonelectrolyte behavior in aqueous-organic solvent mixtures: K_1 is typically small, seldom exceeding 10.

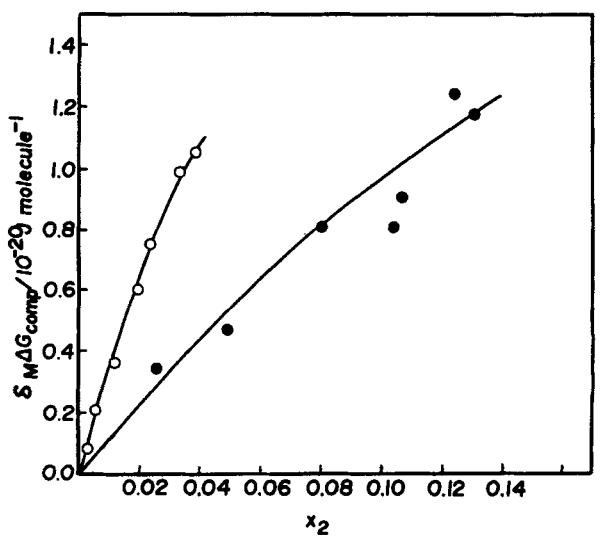

Figure 1 Solvent effect on the stability of the 4-nitroaniline/α-cyclodextrin complex in acetone-water (upper curve) and methanol-water (lower). The points are experimental; *the smooth curves were* drawn with eq. (16) and the parameter values in Table II.

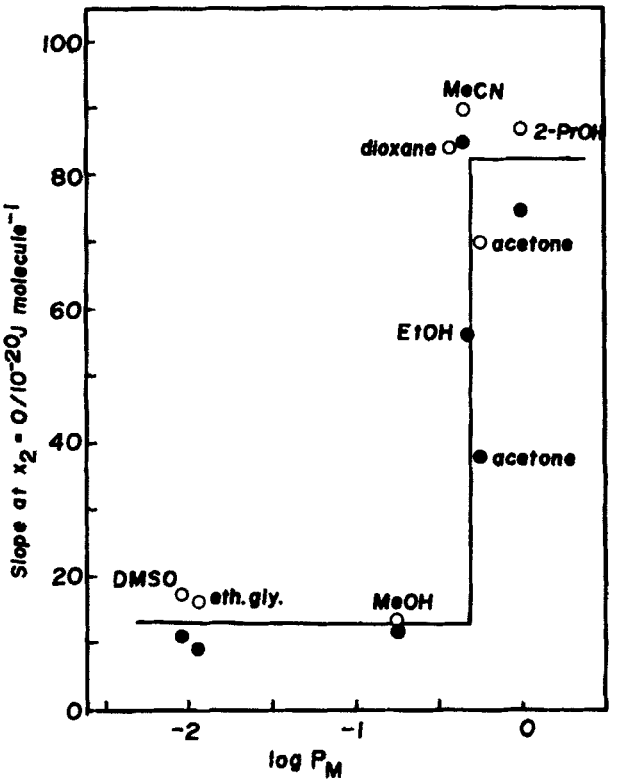

Figure 2 The initial slope of the solvent effect $\delta_M\Delta G^*_{comp}$ against x_2 as a function of log P_M of the organic cosolvent. Open circles are from the methyl orange/α-cyclodextrin system [4]; full circles are from the 4-nitroaniline/α-cyclodextrin system.

This is why the full cancellation approximation, whose conditions of $K_1^C = K_1^S = K_1^L$ may seem very limiting, is expected to be quite widely satisfied as an approximation. It is also the criterion for assignment of a system to the full cancellation class; if K_1 is "normal," presumably the full cancellation conditions are reasonably satisfied.

It follows that, if the experimentally determined K_1 lies substantially beyond the normal range, the full cancellation approximation is unlikely to be appropriate. However, the partial cancellation condition may be satisfied, and this is the assignment made in Table III for many of the systems. The "abnormal" feature of these systems is of course the presence of α-cyclodextrin (the ligand, L); the cosolvents that are less polar than the cyclodextrin interior (see Fig. 1) are able to compete effectively with water for the cyclodextrin cavity, leading to the abnormally high K_1 value. At the same time, S (the substrate, NA or MO) and C (the complex) do not possess cavities, so they may be expected to behave as normal solutes.

Table III reveals some substrate control, since acetone gives full cancellation with NA but partial cancellation with MO. Dioxane appears to fit neither profile, having both a large K_1 and a large G value. Solvents having polarities very similar to that of the cyclodextrin cavity may play transitional roles, as suggested by the placement of systems along the discontinuity in Fig. 2.

With these classification assignments made, it becomes possible to interpret G. With full cancellation, G = ΔgA, whereas with partial cancellation G = -gA.

Table III Parameter values of the 4-nitroaniline/α-cyclodextrin and methyl orange/α-cyclodextrin systems

Cosolvent	K_1	G^a	*Cancellation assignment*
	4-Nitroaniline		
Acetonitrile	55	+3	Partial
2-Propanol	46	-3	Partial
Ethanol	29	-9	Partial
Acetone	10	-57	Full
Methanol	3.1	-68	Full
	Methyl orange[b]		
Acetone	46	-3	Partial
2-Propanol	43	-11	Partial
Acetonitrile	40	-13	Partial
Dioxane	31	-38	(Unassigned)
Ethylene glycol	7.7	-58	Full
DMSO	6.4	-66	Full
Methanol	4.9	-43	Full

[a] Units are Å^2 molecule^{-1}.
[b] From ref. [4].

Interpretation of the parameters

Fig. 3 is a plot of log K_1 against log P_M, where P_M is the 1-octanol/water partition coefficient of the organic cosolvent. We had earlier[4] presented this plot for the MO data alone; the NA results appear to be fully consistent with the interpretation, already given in connection with Fig. 2, that a characteristic system polarity corresponding to log P_M = -0.3 divides solvents into two classes. We propose that this value constitutes the effective polarity of the α-cyclodextrin cavity.

It was not possible to evaluate parameters for the DMSO and ethylene glycol systems with NA, but the behavior shown by these systems in Fig. 2 suggests very strongly that their K_1 values would fall in the "normal" range, consistent with the MO results for these cosolvents.

Interpretation of the general medium parameter G depends upon the system classification. First we consider those systems that can be assigned to the full cancellation approximation (Table III). For these systems G = ΔgA; if g is substantially constant, this can be interpreted as gΔA, where ΔA is the decrease in area exposed to the solvent as the two solvent cavities enclosing substrate and ligand coalesce into one cavity containing the complex. Thus ΔA is negative, and this results in a driving force of gΔAγ for complex formation; this is the hydrophobic effect in water, or the solvophobic effect in general[12]. All of the full cancellation systems gave substantial negative values of gΔA.

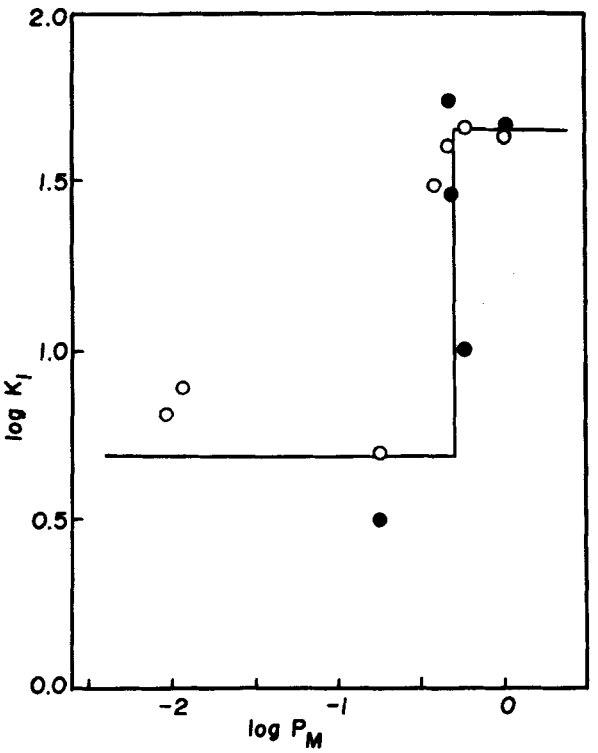

Figure 3 A plot of log K_1 against log P_M of the organic cosolvent. Open circles: methyl orange systems; full circles: 4-nitroaniline systems. Data from Table III.

A cyclodextrin complex differs from molecular complexes of the "stacking" kind in that the quantity ΔA is related to an "internal" molecular area. From an estimate of the total internal area we can calculate g. The dimensions of the α-cyclodextrin internal space ("cavity") are somewhat ambiguous, but molecular models and X-ray crystal data suggest a cavity about 8 Å long and 4–6 Å in diameter[13]. An internal area of 125 ± 25 Å^2 is a reasonable estimate. Taking the ratio $|g\Delta A|/125$ as an estimate of g gives g = 0.47 (standard deviation 0.08). This appears to be a reasonable value[5,14].

Turning to partial cancellation systems (Table III), we note that G = -gA, where gA presumably refers to the solute, α-cyclodextrin, responsible for the abnormally large K_1 values. We expect gA to be positive, as it is for most systems in Table III, though one negative value, which is probably not significantly different from zero, is seen. The considerable variation in gA values that has been observed in solubility studies appears to be related to the polarities of cosolvents and solutes, and eq. (20) has been proposed[14] as an empirical relationship between gA and the partition coefficients of cosolvent (P_M) and solute (P_R).

$$gA = -33.4 \log P_M + 13.4 \log P_R \qquad (20)$$

According to eq. (20), it is possible for gA to be negative, although the physical meaning of such a result is not presently defined. At any rate, we can apply eq. (20) to the gA values in Table III to calculate log P_R, which we interpret as an estimate of the partition coefficient of α-cyclodextrin; the result is log P_R = -0.03 (standard deviation 0.57). Though rather imprecise, this estimate seems to be chemically reasonable.

Energetic contributions to complex formation

In earlier descriptions of solvent effects on complex formation we wrote the general medium contribution as the product $g\Delta A(\gamma-\gamma_o)$ rather than $g\Delta A\gamma$, as we have done here. The quantity γ_o was interpreted to be that value of surface tension below which there is no further solvophobic driving force for association[4,5,15]. We have now (eq. 3) related solvent effects on complex formation to solvent effects on solubility, and the presence of γ_o in the complex formation expression requires its presence in the solubility relationships. In calculating $\delta_M\Delta G^*$ quantities, γ_o is subtracted off, so the problem does not arise, but the ΔG^* quantities themselves may contain γ_o. We now address this question of the physical reality of γ_o. We do this by means of the thermodynamic concept of ideal solubility, which is the equilibrium solubility of a solute in a solvent in which solute-solvent interactions are energetically equivalent to solvent-solvent interactions. In such a system the solubility is entirely controlled by the crystal lattice energy, or $\Delta G_{intersolute}$ in the present terminology. According to eq. (1), $\Delta G_{gen\ med} + \Delta G_{solv} = 0$ in such a system. This condition can be met either if $\Delta G_{gen\ med}$ and ΔG_{solv} are both equal to zero, or if $\Delta G_{gen\ med} = -\Delta G_{solv}$. But according to the cavity model approach, the creation of a cavity in a solvent must require some energy, which we have written as $\Delta G_{gen\ med} = gA\gamma$; replacement of γ with $(\gamma-\gamma_o)$ leads to the unphysical result that cavity formation requires no work when $\gamma = \gamma_o$. We thus reject the condition that $\Delta G_{gen\ med}$ and ΔG_{solv} are identically equal to zero in the ideal solubility case, and instead accept the alternative, namely that $\Delta G_{gen\ med} = -\Delta G_{solv}$, which implies that the γ_o concept is unneeded. Hence in the following we set $\gamma_o = 0$.

Let us calculate the energetic contributions to the free energy of complex formation in the fully aqueous solution. For full cancellation systems eq. (12) is applicable, whereas eq. (15) is used for partial cancellation systems. The quantity ΔG^*_{comp} ($x_2 = 0$) is -4.15 for NA (Table I) and -4.34 for MO[4], both being given in units of 10^{-20} J molecule^{-1}. Table IV shows the results of the calculations.

From eq. (12) we find, for both NA and MO, that $\Delta G^C_{intrasol} + (\Delta G^C_W - \Delta G^S_W - \Delta G^L_W) \approx 0$. That is, the substrate-ligand interaction energy combined with the solvation component make no significant contribution to the complex stability in water; either these two energetic components offset each other, or both are negligible. In consequence, the entire complex stability of these α-cy-

Table IV Energetic contributions to the 4-nitroaniline and methyl orange a-cyclodextrin complexes in water at 25°C

Substrate	*Cosolvent*	ΔgA^a	$100\Delta gA\gamma_1/\Delta G^*_{comp}(x_2=0)$
NA	Acetone	-57	98.6
NA	Methanol	-68	117.6
MO	Ethylene glycol	-58	96.0
MO	DMSO	-66	109.2
MO	Methanol	-43	71.1

[a]From Table III.

clodextrin complexes in water can be ascribed to the general medium (hydrophobic) effect; the average contributions are 108% for NA and 92% for MO, with uncertainties of about 20%. Our conclusion that complex stability is entirely controlled by the general medium effect is dependent on the validity of our theory of solvent effects, and the finding applies only to these MO and NA complexes with α-cyclodextrin. Other complexes may well yield different quantitative distributions of energetic contributions.

Many authors have discussed the energetics of cyclodextrin complex formation, but most of these discussions have been based on structural considerations. Our theory and experiments provide another approach to the problem, an approach that we have shown to be capable of generating quantitative estimates of energetic contributions. It is important to observe that we do not draw any inferences concerning the forces of interaction; our method is designed for, and is limited to, seeking the distribution of pairwise interactions that contribute to the process.

Let us next turn to calculations of the energetic roles of organic cosolvents when they are incorporated into the aqueous system. Adding these organic solvents weakens these cyclodextrin complexes. With eqs. (11) (full cancellation) and (14) (partial cancellation) and the parameter estimates in Table III we can calculate the contributions of $\delta_M\Delta G_{solv}$ and $\delta_M\Delta G_{gen\ med}$ to $\delta_M\Delta G^*_{comp}$; that is,

$$\delta_M\Delta G^*_{comp} = \delta_M\Delta G_{solv} + \delta_M\Delta G_{gen\ med} \qquad (21)$$

and, from eq. (16),

$$\delta_M\Delta G_{solv} = \frac{(kTlnK_1)K_1x_2}{x_1 + K_1x_2} \qquad (23)$$

$$\delta_M\Delta G_{gen\ med} = \frac{G\gamma'K_1x_2}{x_1 + K_1x_2} \qquad (24)$$

The results show that, for full cancellation systems, complex weakening from addition of cosolvents arises mainly from the general medium effect, because $g\Delta A\gamma'$ is much larger than is kT ln K_1. For partial cancellation systems, however, complex weakening comes mainly from the solvation effect, because of the anomalously large K_1 value, which we have associated with the interaction of the organic solvent with α-cyclodextrin. It is interesting to note that, although the complex stability in water can be attributed entirely to the general medium effect, the complex weakening caused by the addition of organic solvents receives contributions from both the general medium and the solvation effects.

The partial cancellation cases allow the quantity $(gA^C - gA^S)$ to be estimated, and with this quantity it is possible to assess the error introduced by neglecting the final term in eq. (13). Using typical values for the parameters shows that the final term constitutes 20 – 30% of the total. Thus its neglect generates some error in the parameter estimates, but within the context of these approximate methods of data interpretation this error seems acceptable and comparable to the corresponding uncertainties embodied in the full cancellation approximation.

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REFERENCES

1 Khossravi, D.; Connors, K.A.; *J. Pharm. Sci.* **1992**, *81*, 371.
2 Khossravi, D.; Connors, K.A.; *J. Pharm. Sci.* **1993**, *82*, 817.
3 Khossravi, D.; Connors, K.A.; *J. Solution Chem.* **1993**, *22*, 321.
4 Connors, K.A.; Mulski, M.J.; Paulson, A.; *J. Org. Chem.* **1992**, *57*, 1794.
5 Connors, K.A.; Khossravi, D.; *J. Solution Chem.* **1993**, *22*, 677.
6 Skwierczynski, R.D.; Connors, K.A.; *J. Chem. Soc., Perkins Trans. 2* **1994**, 467.
7 Connors, K.A.; *Binding Constants: the Measurement of Molecular Complex Stability*, Wiley-Interscience, New York, **1987**, Chap. 4.
8 Wong, A.B.; Lin, S.-F.; Connors, K.A.; *J. Pharm. Sci.* **1983**, *72*, 388.
9 Armstrong, D.W.; Nome, F.; Spino, L.A.; Golden, T.D.; *J. Am. Chem. Soc.* **1986**, *108*, 1418.
10 Biggs, A.I.; Robinson, R.A.; *J. Chem. Soc.* **1961**, 388.
11 Leo, A.; Hansch, C.; Elkins, D.; *Chem. Rev.* **1971**, *71*, 525.
12 Sinanoglu, O.; *Molecular Associations in Biology*, Pullman, B. ed., Academic, New York, **1968**, p. 427.
13 Szejtli, J.; *Cyclodextrins and their Inclusion Complexes*, Akadémiai Kiàdó, Budapest, **1982**, pp. 25, 34.
14 LePree, J.M.; Mulski, M.J.; Connors, K.A.; *J. Chem. Soc., Perkin Trans. 2* **1994**, 1491.
15 Harrison, J.C.; Eftink, M.R.; *Biopolymers* **1982**, *21*, 1153.