SOLVENT EFFECTS ON CYCLODEXTRIN CHEMISTRY

An Investigation of α-Cyclodextrin Complex Stability in Binary Aqueous Organic Mixtures

by

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To Some of My Professors

To: KAC

From: MM

I sincerely appreciate all of your help and support during my stay at Wisconsin.

Best Regards,

Michael Mulcahy

P.S You're included in the dedication!

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TABLE OF CONTENTS

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M. Mulski

Under the supervision of Professor Kenneth A. Connors at the University of Wisconsin-Madison

We have investigated the stability of the α-cyclodextrin-Methyl Orange and α-cyclodextrin-4-nitroaniline complexes in many binary aqueous organic mixtures; the cosolvents were methanol, dimethyl sulfoxide, ethylene glycol, ethanol, isopropanol, dioxane, acetonitrile, and acetone. Solubility studies of 4-nitroaniline and α-cyclodextrin were also carried out in some of these solvent systems.

The complexation and 4-nitroaniline solubility profiles were successfully described by phenomenological solvent effect models which were developed by regarding solvent effects on chemical processes as the contribution of three effects. These effects arise from solute-solute interactions (the intersolute effect), solute-solvent interactions (the solvation effect) and solvent-solvent interactions (the

general medium effect). The solvation effect was modelled as stepwise competitive equilibria between the organic cosolvent and water for the solute. The general medium effect was associated with the energy required to create a cavity in the solvent. The intersolute effect was assumed to be composition independent.

The model parameters generated by the solvent effect models for complexation and solubility were in general physically reasonable and provide a measure of predictability for these chemical processes. Furthermore, we postulate that the solvation exchange equilibrium constants for the complexation process reflect the cosolvent's ability to partition into the cyclodextrin cavity and is therefore associated with the polarity of the cyclodextrin interior.

I. INTRODUCTION

A. INTRODUCTION TO CYCLODEXTRINS

Cyclodextrins (cycloamyloses) are oligosaccharides consisting of six or more D-glucose units connected by α-1,4 linkages to form a torus. The most common cyclodextrins, α, β, and γ cyclodextrin, are made of six, seven and eight D(+) - glucopyranose units respectively. A list of some of their physical properties is presented in Table 1.1.

NMR (1,2,3) and X-ray crystallography (4) have been used to elucidate cyclodextrin structure. The molecular structure of α-cyclodextrin is presented in Figure 1.1. The numbering scheme of the carbon atoms in the glucose unit is presented in Figure 1.2. Primary hydroxyl groups line one end of the rim. The other end of the rim is occupied by the secondary hydroxyl groups. The primary hydroxyl groups are free to rotate about the 5,6 C-C bond and can therefore partially occlude the cavity. The secondary hydroxyl groups do not possess this rotational freedom. Because of these rotational differences, cyclodextrins are often depicted as a truncated cone with the smaller rim representing the primary hydroxyl rim. The interior of the ring is lined with glycosidic ether linkages, making it non-polar relative to water.

Table 1.1 Physical properties of Cyclodextrins

Cyclodextrin	Number of glucose units	Molecular Weight	Aqueous Solubility at 25°C (g/100mL)	Cavity Dimensions (Å)	
				internal diameter	depth
α	6	972	11.78[a]	4.7[b] 6[c] 4.7-5.2[d]	6.7[b]
β	7	1135	1.850[a]	8[c] 6-6.4[d]	7[e]
γ	8	1297	21.76[a]	10[c] 7.5-8.3[d]	7[e]

[a] reference 15
[b] reference 16
[c] reference 17
[d] reference 18
[e] reference 19

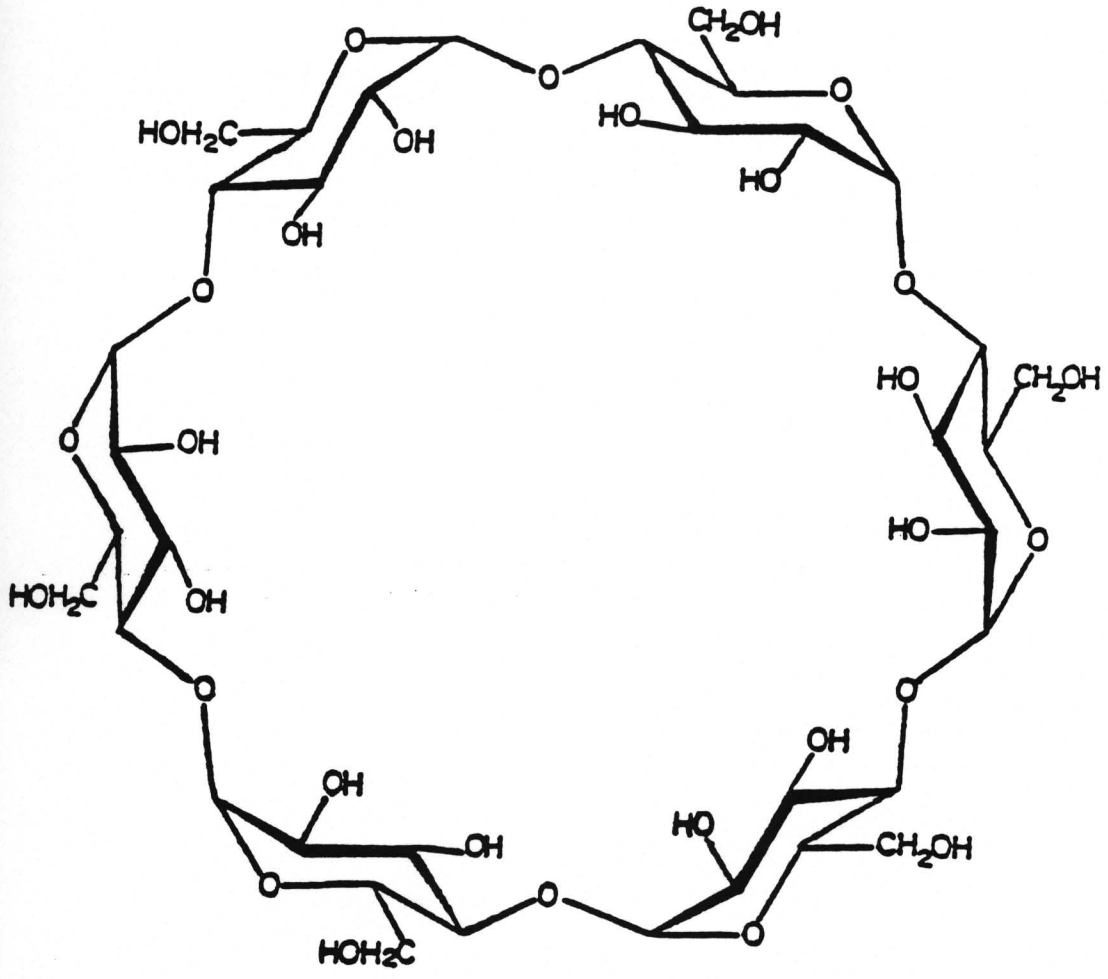

Figure 1.1: Structure of α-cyclodextrin

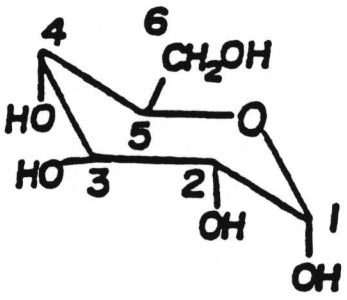

Figure 1.1: Glucose Carbon Numbering Scheme

An unusual feature of cylodextrins is their ability to form inclusion complexes with various compounds. This has lead to the development of a number of industrial (5) and analytical applications (6) for cyclodextrins and their complexes. Because the present work involves solvent effects on cyclodextrin inclusion complexation, a presentation of the forces postulated to be responsible for cyclodextrin inclusion complexation is of value.

B. FORCES INVOLVED IN CYCLODEXTRIN COMPLEXATION

There is considerable debate over the major forces responsible for cyclodextrin complex formation and stability.

Cyclodextrin complexation is generally enthalpically driven (7). The standard entropy change (ΔS°) is either negative or positive (although the majority of calorimetric studies report a negative value). Classical hydrophobic interactions (8), where the solvent is the driving force for complexation, are entropically driven and are associated with a negligible standard enthalpy change (ΔH°). The enthalpically favourable process for cyclodextrin complexation has been used to support the hypothesis that host-guest interactions, that is

interactions between the cylodextrin and the included guest molecule, are the main driving force for cyclodextrin complexation (9-10). Others argue (11-14) that despite the atypical thermodynamics of cyclodextrin complexation the solvent plays a major role in the complexation process.

This discussion will therefore divide proposed mechanisms and forces for cyclodextrin complexation into two categories, those attributed to host guest interactions and those related to solvent effects.

1. Mechanisms and Forces Associated with Host-Guest Interactions

Gelb and coworkers (9,20) obtained 2 linear profiles of ΔH° against ΔS° for the complexation of various carboxylic acids with α-cyclodextrin and β-cyclodextrin respectively. Profile linearity was interpreted as evidence of the existence of a common complexation mechanism for these reactions. They proposed that the main driving force for complexation is polar interactions between the cyclodextrin and the included guest molecule. They also postulated a torsional constraint of the cyclodextrin molecule which is associated with the large negative entropy change found in these systems.

Although the proposed mechanisms for complex formation seem plausible , Gelb and coworkers suggest that there is no change in the solvation of the guest and host molecule upon complexation. This conflicts with X-ray crystallographic data of cyclodextrin complexes (18). The most stable complexes leave little if any room for solvent molecules in the cyclodextrin cavity. Complexation would therefore cause a significant change in the solvation of the cyclodextrin molecule.

Saenger and coworkers also proposed a mechanism based on cyclodextrin conformational change (21). Analysis of the crystal α-cyclodextrin hexahydrate revealed that one of the D-glycosyl units was rotated into an almost orthogonal position relative to the other five in order to form hydrogen bonds with the included water. They suggest that the α-cyclodextrin ring is "strained" in water and that upon complexation there is a transformation of the ring to a relaxed state. This strain relief is believed to contribute to the enthalpy of association and stability of the complex.

Evidence of a conformational change of α-cyclodextrin upon complexation was obtained by optical rotation measurements. Schlenk and Sand (22) observed a decrease in the optical rotation of α-cyclodextrin in the presence of various straight chain alkanoic acids. The magnitude of the

change appeared to be associated with alkyl chain length. Rees (23) attributed the shift in optical rotation to the formation of an inclusion complex and the relief of conformational distortion. Analysis of NMR data (24) revealed that certain C-1 and C-4 sites were shifted relative to the remainder, indicating some ring assymetry. Ultrasonic relaxation techniques (25-27) revealed two relaxation steps associated with aqueous α-cyclodextrin. The first relaxation step was associated with conformational change of the ring. The second relaxation process was attributed to reorientation of water within the ring.

Ring strain conformation appears to be only operative for α-cyclodextrin. β-cyclodextrin and γ-cyclodextrin rings in the crystal hydrates are not strained (21). Bergeron and Meeley (28) showed that methylation of the primary hydroxyl groups of α-cyclodextrin (which should significantly affect the ease of rotation of the D-glucosyl unit) had little effect upon complex stability. This suggests that conformational change plays only a minor role in stabilising the complex.

Van der Waals forces appear to play a significant role in complex formation. Van Etten and coworkers (29) studied the complexation of a series of phenyl acetates with α-cyclodextrin. They obtained a linear relationship between

the logarithm of the dissociation constant and the molar refraction of the guest. Because the molar refraction is related to polarizability, this suggests that Van der Waals forces are associated with the complexation process. Connors and coworkers (12,31) have found correlations between complexation constants and Hammett substituents (which can be used as a measure of polarizability).

The importance of Van der Waals forces in complexation is supported by the theoretical work of Kitagawa and coworkers (32). They calculated a dipole moment of 13.5D for α-cyclodextrin. The dipole moment passed through the center of the cavity. In support of their hypothesis dipole moments were calculated for substituted benzenes included in the cyclodextrin cavity. The dipole moments of the guest molecules were found to be oriented antiparallel to that of α-cyclodextrin.

Van der Waals forces are approximately proportional to the reciprocal of the sixth power of the distance between the two components. Because of the small diameter of the cyclodextrin cavity there is not much distance between the included guest molecule and the cavity walls. This generates significant Van der Waals forces. It therefore appears that Van der Waals forces have a significant role in the formation and stability of the cyclodextrin complex.

Hydrogen bonding between the substrate and complex may also play a role in cyclodextrin inclusion complex formation in some cases. *t*-Butyl alcohol forms hydrogen bonds less easily than does *t*-butyl hyperperoxide. Matsui and coworkers (33) reported the formation of cyclodextrin inclusion complexes with the latter substrate but none was found with the former.

Cyclodextrins have been shown to form complexes with alkanes and rare gases (34). These molecules are unable to hydrogen bond. This suggests that the role of hydrogen bonding in complex formation is substrate[f] dependent and not universal.

All of the above outlined mechanisms generally disregard the role of the solvent in complex formation. The mechanisms and forces associated with solvent effects will be reviewed in the next section.

2. Solvent Effects on Cyclodextrin Complexation

Because the complexation process is enthalpically driven, Griffiths and Bender (11) suggest that cyclodextrin complexation in aqueous solution is an example

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[f] The substrate refers to the included guest and the ligand refers to cyclodextrin throughout this text.

of an "atypical hydrophobic effect". The mechanism they use to explain cyclodextrin complexation thermodynamics is based upon the argument that water included in the cyclodextrin cavity is unable to form its full complement of hydrogen bonds. In the process of complexation these included water molecules are released, leading to a net increase in hydrogen bond formation and an enthalpically favourable change.

The release of "enthalpically rich" water molecules does not explain the wide range of association constants found in the literature for different substrates complexed with the same type of cyclodextrin. It also offers little explanation for the formation of complexes in non-aqueous environments (13,35). This suggest that the contribution of this mechanism to cyclodextrin complexation is minor.

Evidence of the importance of solvophobic interactions on cyclodextrin complexation was reported by Connors and Pendergast (12). An inverse relationship was obtained between cyclodextrin complex stability and the solublility of the guest molecule. A direct relationship between complex stability and the octanol - water partition coefficient (which can be used as a measure of hydrophobicity (36)) was also reported.

Further evidence of the importance of the solvent in complex formation was provided by Mochida and coworkers

(37). They obtained association constants for an azo dye-β-cyclodextrin complex in various salt solutions. An apparent increase in the association of the complex was observed with salt concentration.

Orstan and Ross (38) obtained stability constants in conjunction with surface tension values for the β-cyclodextrin - indole complex. The association constant was found to increase upon the addition of calcium chloride to the aqueous solution and was associated with an increase in surface tension. A decrease in the association constant was reported upon the addition of dimethyl formamide or ethanol, which lead to a decrease in the surface tension.

The correlation between complex formation and solvent surface tension suggests that one of the main driving forces for complexation is solvophobic. Complexation appears to be driven by the reduction in free energy resulting from the net decrease in surface area exposed to solvent upon complexation of substrate with ligand.

Orstan and Wojcik (39) obtained a linear profile when they plotted the log of the forward rate constant (in mole fraction units) for azo dye-α-cyclodextrin complexation against surface tension for various water-dimethyl sulfoxide (DMSO) mixtures. Although this result supports the importance of the solvophobic driving force, the complexation constants were obtained over a very narrow

surface tension range of 72-62 dynes/cm.

A study which analysed cyclodextrin complexation over a wider surface tension range (72-29 dynes/cm) was conducted by Harrison and Eftink (13). They studied the complexation of adamantane carboxylate with β-cyclodextrin in various methanol-water cosolvent mixtures. A decrease in the free energy of complexation was observed with solvent surface tension. There was also considerable curvature of the profile. The authors forced a straight line through the data and proceeded to partition the free energy of complexation into a hydrophobic driving force term and a surface tension independent term. This latter term was believed to be associated with substrate-cyclodextrin Van der Waals forces in the associated complex. The problem with these authors' analysis is the forced linearisation of the curved profile. The curvature indicates that an analysis of cyclodextrin complexation forces based only on a linear surface tension term and a solvent - independent term is inadequate.

Solvation of the participating molecules in the complexation process may also be significant. Analysis of NMR data of anhydrous and aqueous α, β and γ cyclodextrins (40,41) suggests that water is essential in maintaining cyclodextrin conformation.

NMR studies (42,43) on pyrene-β-cyclodextrin and

acridene-β-cyclodextrin complexes in dilute alcohol solutions revealed the formation of a ternary complex. Fluorescence studies revealed a significant increase in the association complex when alcohol was added to the pyrene system. A decrease in the association constant was found when alcohol was added to the acridine system. The authors conclude that alcohols act as a "space regulator" in complex formation and are intimately involved in the association process.

We have seen that a number of mechanisms for cyclodextrin complexation have been proposed. Analysis reveals that there are three major driving forces for cyclodextrin complexation. These are

1. Substrate-ligand interactions.
2. The solvophobic effect, arising from solvent-solvent interactions.
3. Solvation effects, namely solute - solvent interactions.

Therefore any model used to interpret complexation must include all these forces.

The study of solvent effects on cyclodextrin complex stability has the potential to be a valuable means of

gaining further insight into the forces responsible for cyclodextrin complexation formation and stability. The work presented in this thesis investigates cyclodextrin complex stability in binary aqueous organic mixtures. Previous work conducted in this area (10,13,35,39,42-47) has been cosolvent limited and generally lacked sufficient data to adequately characterise the complexation profile. Moreover, as the preceding paragraphs have shown, prior work was based on inadequate theoretical or interpretrive bases. Therefore cyclodextrin complexation in cosolvent mixtures merits further investigation.

A phenomenological model used to describe and interpret solvent effects on complexation is presented in the next section.

C. SOLVENT EFFECT MODELS FOR SOLUBILITY AND COMPLEXATION

1. Introduction

Our laboratory has developed a fairly general phenomenological model of solvent effects in mixed solvent systems. In this model, the total standard free energy change for solubility and complexation is partitioned according to Equation 1.1.

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Intersol.} + \Delta G^{\circ}_{Gen.med.} + \Delta G^{\circ}_{Solvation} \qquad (1.1)$$

where the free energy change arising from solute-solute interactions is assigned to $\Delta G^{\circ}_{Intersol.}$, that from solvent-solvent interactions to $\Delta G^{\circ}_{Gen.med.}$, and that from solute-solvent interactions to $\Delta G^{\circ}_{Solvation}$. The terminology used to describe the effects arising from these three types of interactions is *the intersolute effect*, *the general medium effect*, and *the solvation effect*. Solvent composition dependent expressions will be derived for the two latter terms and it will be assumed that *the intersolute effect* is solvent composition

independent.

The interested reader is referred to Khossravi (48) for a detailed presentation of the solubility and complexation models. The purpose of this description is to give the reader a fundamental understanding of the model and the derivation of the terms associated with it. The model used to interpret cyclodextrin complexation in cosolvent mixtures is a modification of the solubility model. Therefore a description of the complexation model will follow a presentation of the solubility model.

2. The Solubility Model

The dissolution process is outlined in Scheme 1.1 and consists of four steps. The variable f_2 refers to the composition of the organic in the surface phase surrounding the solute. An explicit expression for this term will be derived later.

The total free energy change is written as Equation 1.2.

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Crystal} + \Delta G^{\circ}_{Gen.med.} + \Delta G^{\circ}_{Insertion} + \Delta G^{\circ}_{Solvation} \quad (1.2)$$

The form of this equation appears to be inconsistent with Equation 1.1. However we will see that when we analyse the different free energy components of Equation 1.2 in terms of their contribution to the inersolute effect, the general medium effect, and the solvation effect, that we end up with an equation which is identical in form to Equation 1.1.

Step 1.	Crystalline Solute	$\Delta G^{\circ}_{Crystal}$	Gaseous Solute
Step 2.	Bulk Solvent (no cavity)	$\Delta G^{\circ}_{General\ Medium}$	Solvent with Molecular cavity (surface phase composition f_2)
Step 3.	Solvent with Molecular cavity (surface phase composition f_2) + Gaseous Solute	$\Delta G^{\circ}_{Insertion}$	Unsolvated solute in the cavity (surface phase composition f_2)
Step 4.	Unsolvated Solute in cavity (surface phase composition f_2)	$\Delta G^{\circ}_{Solvation}$	Solvated Solute in cavity (surface phase composition f_2)
Sum	Crystalline Solute + Bulk Solvent	ΔG°_{Total}	Solvated Solute

Scheme 1.1 The four step dissolution process.

The intersolute term includes the crystal lattice energy and any effects arising from solute-solute interactions in solution (which are negligible for dilute solutions). The general medium effect term is a measure of the energy required to create a cavity of surface phase composition f_2. The solvation term is a measure of the energy of interaction between the solute and a "solvation shell" of surface phase composition f_2 and is the sum of $\Delta G^\circ_{Insertion}$ and $\Delta G^\circ_{Solvation}$. We can set $\Delta G^\circ_{Insertion}$ to zero because all solute - solvent interaction terms can be included in the $\Delta G^\circ_{Solvation}$ term. We therefore write the total standard free energy for solubility as

$$\Delta G^\circ_{Total} = \Delta G^\circ_{Crystal} + \Delta G^\circ_{Gen.med.} + \Delta G^\circ_{Solvation} \qquad (1.3)$$

We now have an equation which describes the dissolution process that is consistent with Equation 1.1.

The solvation and general medium effect terms are composition dependent and explicit expressions for these terms will be derived shortly. Because $\Delta G^\circ_{Crystal}$ is assumed to be composition independent, it will be eliminated by a Leffler-Grunwald delta operator. The operator will be discussed after the derivations of $\Delta G^\circ_{Solvation}$ and $\Delta G^\circ_{Gen.med.}$.

The Solvation Effect

The solvation effect can be described as a series of stepwise competitive exchange equilibria of water (W) and organic (M) with solute (R). This is represented by Scheme 1.2,

$$RW_k + M \overset{K_1}{\rightleftharpoons} RW_{k-1}M + W$$

$$RW_{k-1}M + M \overset{K_2}{\rightleftharpoons} RW_{k-2}M_2 + W$$

$$\vdots$$

$$RWM_{n-1} + M \overset{K_k}{\rightleftharpoons} RM_n + W$$

Scheme 1.2

where K_k represents the equilibrium constants and k represents the number of solvation steps. The solvation effect will be derived using a two - step process because

this was all that was required to describe solubility data (48,49). The scheme then becomes

$$RW_2 + M \underset{}{\overset{K_1}{\rightleftharpoons}} RWM + W$$

$$RWM + M \overset{K_2}{\rightleftharpoons} RM_2 + W$$

Scheme 1.3

Scheme 1.3 indicates that the solute is capable of existing as three solvated species RW_2, RWM, and RM_2. Using the postulate that the solvation effect is a weighted average of these species,

$$\Delta G^\circ_{solv} = \Delta G^\circ_{WW} F_{WW} + \Delta G^\circ_{WM} F_{WM} + \Delta G^\circ_{MM} F_{MM} \qquad (1.4)$$

where F_{WW}, F_{WM}, and F_{MM} are the the fractions of the solute in the RW_2, RWM, and RM_2 forms. Because

$$F_{WW} + F_{WM} + F_{MM} = 1 \qquad (1.5)$$

we can combine Equations 3.5 and 3.6 to obtain

$$\Delta G^{\circ}_{solv} = (\Delta G^{\circ}_{WM} - \Delta G^{\circ}_{WW})\ F_{WM} + (\Delta G^{\circ}_{MM} - \Delta G^{\circ}_{WW})\ F_{MM} + \Delta G^{\circ}_{WW} \qquad (1.6)$$

which can be expressed as Equation 1.7.

$$\Delta G^{\circ}_{solv} = S_1\ F_{WM} + S_2\ F_{MM} + \Delta G^{\circ}_{WW} \qquad (1.7)$$

where the definitions of S_1 and S_2 are obvious. The equilibrium constants in Scheme 1.3 can be used to obtain explicit equations for F_{WM} and F_{MM}.

$$F_{WM} = \frac{K_1 x_1 x_2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (1.8)$$

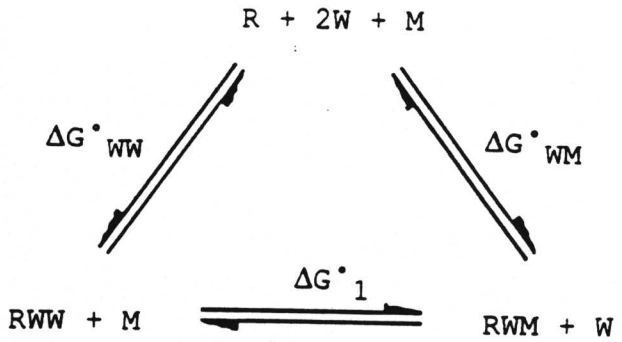
$$F_{MM} = \frac{K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (1.9)$$

where x_1 and x_2 are the bulk mole fractions of water and the organic cosolvent. Combining these last three equations

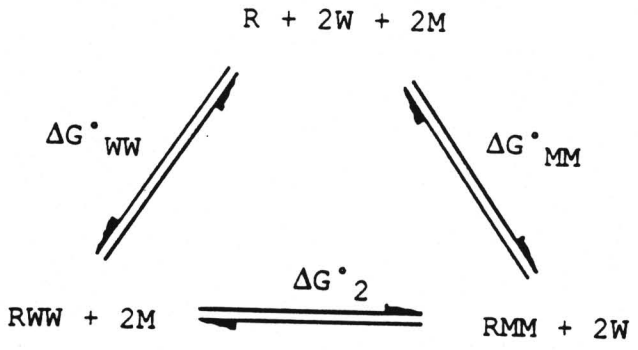
gives

$$\Delta G^{\circ}_{solv} = \frac{S_1K_1x_1x_2 + S_2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + \Delta G^{\circ}_{WW} \qquad (1.10)$$

S_1 and S_2 are related to the solvation parameters K_1 and K_2 by the thermodynamic cycles in Schemes 1.4 and 1.5.



Scheme 1.4.



Scheme 1.5

Equation 1.11 is obtained from Schemes 1.3 and 1.4.

$$S_1 = \Delta G^\circ_{WM} - \Delta G^\circ_{WW} = \Delta G^\circ_1 = -\mathbf{k}T \ln K_1 \qquad (1.11)$$

Similarly

$$S_2 = \Delta G^\circ_2 = G^\circ_{MM} - \Delta G^\circ_{WW} = -\mathbf{k}T \ln K_1 K_2 \qquad (1.12)$$

The contribution of the solvation effect to the solubility process is then obtained by combining Equations 1.10, 1.11, and 1.12.

$$\Delta G^{\circ}_{solv} = \frac{(-\mathbf{k}T \ln K_1)\, K_1 x_1 x_2 + (-\mathbf{k}T \ln K_1 K_2)\, K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} + \Delta G^{\circ}_{WW} \qquad (1.13)$$

The General Medium Effect

The general medium effect is described by a modified version of a model proposed by Uhlig (50),

$$\Delta G^{\circ}_{Gen.\ med.} = gA\gamma \qquad (1.14)$$

which describes the work done for cavity formation as the product of the solvent surface tension and the solute surface area. Because both of these terms are positive quantities, this energetic contribution to solubility is unfavourable. A curvature correction term (g) has been added to take into account the effect of curvature at the molecular level on the effective surface tension. The area term (A) refers to the contact surface area. This is defined as the locus of all exterior points of the Van der Waals surface of the solute molecule that could be in contact with the Van der Waals surface of a solvent

molecule. It is treated as a composition independent term. The surface tension (γ) is that for a cavity of surface phase composition f_2. An explicit expression for f_2, defined as the mean fractional composition of the solvation shell with respect to the organic, can be derived by denoting the solvation stoichiometry as RW_iM_j, where i + j = k (where k represents the number of solvation steps from Scheme 1.2).

$$f_2 = \frac{1}{k} \sum j \, F_{RW_iM_j} \qquad (1.15)$$

In a similar manner f_1 is defined as the mean fractional composition of the solvation shell with respect to water,

$$f_1 = \frac{1}{k} \sum i \, F_{RW_iM_j} \qquad (1.16)$$

The surface tension of the solvation shell is defined by Equation 1.17,

$$\gamma = \gamma_1 f_1 + \gamma_2 f_2 = \gamma_1 + (\gamma_2 - \gamma_1) f_2 \qquad (1.17)$$

where γ_1 and γ_2 are the bulk surface tensions of pure water and organic cosolvent. The surface tension of the solvation shell of composition f_2 is then found by combining Equations 1.8,1.9,1.15 and 1.17. This leads to Equation 1.18.

$$\gamma = \gamma_1 + \gamma' \left[\frac{K_1 x_1 x_2 + 2K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \right] \qquad (1.18)$$

where $\gamma' = (\gamma_2 - \gamma_1)/2$.

The total solvent effect on solubility is obtained by substituting the specific expressions for the solvation effect (Equation 1.13) and the general medium effect (Equations 1.14 and 1.18) into Equation 1.2.

$$\Delta G^{\circ}(x_2) = gA\gamma_1 +$$

$$\frac{(-\mathbf{k}T \ln(K_1)+gA\gamma') K_1x_1x_2 + (-\mathbf{k}T \ln(K_1K_2)+2gA\gamma') K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}$$

$$+ \Delta G^{\circ}_{WW} + \Delta G^{\circ}_{Intersol.} \qquad (1.19)$$

In the fully aqueous medium this becomes

$$\Delta G^{\circ}(x_2=0) = gA\gamma_1 + \Delta G^{\circ}_{WW} + \Delta G^{\circ}_{Intersol.} \qquad (1.20)$$

Using the Leffler-Grunwald delta operator (51), the solvent effect is defined as

$$\delta_m\Delta G^{\circ} = \Delta G^{\circ}(x_2) - \Delta G^{\circ}(x_2=0) \qquad (1.21)$$

The use of this operator eliminates the solvent independent terms, and reduces the number of adjustable parameters. The total solvent effect is then defined by Equation 1.22.

$$\delta_m \Delta G^\circ = \frac{(-\mathbf{k}T \ln(K_1) + gA\gamma')\, K_1 x_1 x_2 + (-\mathbf{k}T \ln(K_1 K_2) + 2gA\gamma')\, K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (1.22)$$

This equation has three adjustable parameters: K_1 and K_2 are the solvation exchange constants and gA is the surface area with the curvature correction factor. These parameters are obtained by fitting the solubility data to Equation 1.22 by nonlinear regression. This model has already been used to successfully describe solubility profiles of a number of different solutes in various binary aqueous organic systems (49).

3. The Complexation Model

Complexation between a substrate (S) and ligand (L) can be represented by Scheme 1.6,

$$mS + nL \underset{}{\overset{K_{mn}}{\rightleftharpoons}} S_m L_n$$

Scheme 1.6

where S_mL_n represents the complex (52). The equilibrium constant (also called the complexation, stability, association, binding, or formation constant) is defined as

$$K_{mn} = \frac{[S_mL_n]}{[S]^m[L]^n} \qquad (1.23)$$

where [S] is the free substrate concentration, [L] is the free ligand concentration, and $[S_mL_n]$ is the concentration of the complex. The substrates used in this thesis, methyl orange and 4-nitroaniline, form one to one complexes (53,54) with α-cyclodextrin. Therefore the binding constant for this process is defined by Equation 1.24.

$$K_{11} = \frac{[SL]}{[S][L]} \qquad (1.24)$$

The next task is to relate the standard free energy change of complexation to solvent effects. The total free energy change for complexation is partitioned into the same terms used to describe solubility.

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Intersol.} + \Delta G^{\circ}_{Gen.med.} + \Delta G^{\circ}_{Solv.} \qquad (1.1)$$

The major contribution to the intersolute effect arises from the interactions between the substrate and ligand in the associated complex. Once again it is assumed that the intersolute effect is composition independent. Therefore substrate-ligand orientation in the complex is assumed to be unaffected by solvent composition.

The composition dependent terms $\Delta G^{\circ}_{Gen.med.}$ and $\Delta G^{\circ}_{Solvation}$ are addressed in the next sections.

The Solvation Effect

A one - step solvation exchange process is adopted to describe the solvation effect for complexation; as shown earlier, this can be generalised if required.

$$RW + M \underset{}{\overset{K_1}{\rightleftharpoons}} RM + W \qquad (1.25)$$

Using the concepts developed earlier, the solvation term for the one step process is found to be

$$\Delta G^{\circ}_{solv.(R)} = \frac{(-\mathbf{k}T \ln K_1)\ K_1 x_2}{x_1 + K_1 x_2} + \Delta G^{\circ}_{WW(R)} \qquad (1.26)$$

There are three solvated species involved in complexation, namely the substrate, the ligand, and the complex. Therefore the solvation effect must include a solvation term of the form of Equation 1.26 for each of these three species.

The process of complexation involves solvated substrate and ligand species coming together to form a solvated complex. This results in a net decrease in the number of solvated species. The solvation effect on complexation is then written as

$$\Delta G^{\circ}_{Solv.} = \Delta G^{\circ}_{Solv(SL)} - \Delta G^{\circ}_{Solv(S)} - \Delta G^{\circ}_{Solv(L)} \qquad (1.27)$$

In order to reduce the total number of parameters in the final equation, the assumption is made that the value of K_1 for all three solvated species are identical. The validity of this assumption will be discussed in later chapters. Using this assumption the solvation effect for complexation

can be written as $\Delta G^{\circ}_{Solv.} = - \Delta G^{\circ}_{Solv(S \text{ or } L)}$, or

$$\Delta G^{\circ}_{Solv.} = \frac{(\mathbf{k}T \ln K_1) K_1 x_2}{x_1 + K_1 x_2} + \Delta G^{\circ}_{WW(CSL)} \quad (1.28)$$

where

$$\Delta G^{\circ}_{WW(CSL)} = \Delta G^{\circ}_{WW(SL)} - \Delta G^{\circ}_{WW(L)} - \Delta G^{\circ}_{WW(S)} \quad (1.29)$$

The General Medium Effect

The model that will be used to describe the general medium effect combines Equation 1.14 and an idea of Sinanoglu (55-58), and is written

$$\Delta G^{\circ}_{Gen.med.} = g\Delta A(\gamma - \gamma_o) \quad (1.30)$$

where g is the curvature correction factor for the complex, ΔA is the net decrease in surface area upon complexation, and γ_o is the surface tension at which the solvophobic driving force is zero. Because there is a decrease in surface area the general medium effect term is energetically favourable.

Once again γ refers to the surface tension of a solvation shell of surface phase composition f_2. Using

previously developed concepts, for a one step solvation process this becomes

$$\gamma = \gamma_1 + \frac{\gamma'' K_1 x_2}{x_1 + K_1 x_2} \qquad (1.31)$$

where $\gamma'' = (\gamma_2 - \gamma_1)$.

The general medium effect is then obtained by combining Equations 1.30 and 1.31 to yield

$$\Delta G^\circ_{Gen.med.} = g\Delta A(\gamma_1 - \gamma_o) + \frac{g\Delta A\gamma'' K_1 x_2}{x_1 + K_1 x_2} \qquad (1.32)$$

Substituting Equations 1.28 and 1.32 into Equation 1.1 yields the total free energy change for complexation.

$$\Delta G^\circ(x_2) = \Delta G^\circ_{Intersol.} + g\Delta A(\gamma_1 - \gamma_o) + \frac{(g\Delta A\gamma'' + \mathbf{k}T \ln K_1) K_1 x_2}{x_1 + K_1 x_2} + \Delta G^\circ_{WW(CSL)} \qquad (1.33)$$

In the fully aqueous medium this becomes

$$\Delta G^{\circ}(x_2=0) = \Delta G^{\circ}_{Intersol.} + g\Delta A(\gamma_1 - \gamma_o) + \Delta G^{\circ}_{WW(CSL)} \qquad (1.34)$$

Using the Leffler-Grunwald delta operator the total solvent effect for complexation becomes

$$\delta_m \Delta G^{\circ} = \frac{(g\Delta A\gamma'' + \mathbf{k}T \ln K_1)K_1 x_2}{x_1 + K_1 x_2} \qquad (1.35)$$

This equation has two adjustable paramaters, K_1 and $g\Delta A$ which are obtained by fitting the complexation data to Equation 1.35 by nonlinear regression.

Now that the models have been presented it is appropriate to state the objectives of this work.

D. STATEMENT OF THE PROBLEM

The work presented in this thesis is part of a series of systematic studies of solvent effects on chemical processes (48,49 59). These studies have been conducted in

binary aqueous organic cosolvent mixtures. These organic cosolvents are completely miscible with water, and display a range of chemical types and behaviours.

A major purpose of the present work is to use solvent effects as a tool for understanding the molecular forces responsible for cyclodextrin complexation. A second, more practical, reason for these studies was to gain predictability. A goal is to be able to specify quantitatively the effect of any organic cosolvent on complex stability.

The methyl orange - α-cyclodextrin complex was initially investigated. The complexation model was successfully applied to this system. However, questions arose about the magnitude, range, and chemical significance of the model parameters obtained for this system. In order to answer these questions and develop a more rigorous test of the model, the 4-nitroaniline system was investigated in conjunction with 4-nitroaniline and α-cyclodextrin solubility experiments. The results from all four of these studies are discussed in the succeeding chapters.

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II. EXPERIMENTAL

A. MATERIALS

The complexation experiments were conducted using α-cyclodextrin obtained from American Tokyo Kasei. American Maize supplied the cyclodextrin (which was recrystallised once in water) for the solubility experiments. All cyclodextrin was dried at 105°C for at least 24 hours to obtain the anhydrous form. Methyl orange (Aldrich) was recrystallised from water, and washed with 95% ethanol followed by diethyl ether. 4-Nitroaniline (Aldrich, 99.9% purity) was used as received. The organic cosolvents used were acetone, dioxane, dimethyl sulfoxide, acetonitrile (all spectrophotometric grade Baker products), ethylene glycol (Baker, reagent), methanol (Mallinkrodt, reagent), and ethanol (Quantum Chemical Corporation, reagent). The distilled water was further treated with a Sybron/Barnstead PCS ion exchange purification system.

B. APPARATUS

Complexation experiments were conducted with an On Line Instrument Systems (OLIS) - modified Cary 14 or a Beckman DU-65 spectrophotometer. The cell compartments of these instruments were connected to a circulating water

bath maintained at 25°C. A Hitachi U-3000 spectrophotometer was used for the 4-nitroaniline solubility experiments. Cyclodextrin solubility measurements were performed with a Perkin Elmer Model 241 polarimeter equipped with a sodium lamp source and a 589 nm filter.

C. EXPERIMENTAL PROCEDURES

1. Solvent Preparation

All cosolvent mixtures were prepared gravimetrically on an Ohaus model GT4100 analytical balance (accurate to a hundredth of a gram). Apart from the cosolvent, the only other component of the cosolvent mixtures for the solubility studies was water.

The cosolvent mixtures prepared for the complexation studies were buffered. In order to repress the ionisation of methyl orange, which has a pKa of 3.4 (1,2), the cosolvent mixtures used for these complexation studies contained 0.1 N HCl. The 4-nitroaniline complexation studies were initially part of a larger study investigating solvent effects on cyclodextrin catalysis of 4-nitrotrifluoroacetanilide hydrolysis. Consequently a pH 10,

0.4 M carbonate buffer was used in cosolvent mixture preparation of these solutions to yield a final carbonate concentration of 0.01 M.

2. Density Measurements

All densities were determined gravimetrically by obtaining the weight of a known volume of the liquid at 25°C and were the average of 4-5 determinations. Density values were obtained for the cosolvent mixtures in the complexation studies. The densities of the solute-saturated filtrate were determined in the solubility studies.

3. Binding Constant Measurement

The spectrophotometric method was used for the methyl orange and 4-nitroaniline cyclodextrin complexation studies. Solutions consisting of the same substrate concentration but different ligand (cyclodextrin) concentrations (including a solution containing no ligand) were prepared. Each of these solutions was matched with a reference solution containing the identical ligand concentration. All sample solutions were equilibrated at

25°C. Samples were analysed with respect to the reference by visible spectrophotometry at 25°C.

The substrate concentration for the methyl orange studies varied from 1.6 x 10^{-5} to 5.5 x 10^{-5} M, which was below the concentration (1 x 10^{-4} M) reported for its dimerization (3). The range of ligand concentration was 1.6 x 10^{-4} to 3.4 x 10^{-2} M. The analytical wavelength used was 508 nm.

Substrate concentrations for the 4-nitroaniline studies ranged from 7.1 x 10^{-5} to 7.7 x 10^{-5} M, while ligand concentrations varied from 9.4 x 10^{-4} to 3.4 x 10^{-2} M. The analytical wavelength used for these studies was 410 nm.

4. 4-Nitroaniline Solubility

Samples were prepared by adding approximately 6 ml of cosolvent mixture to ampuls containing solute in excess of its solubility. The ampules were chilled in a dry ice-acetone bath (in order to minimize the evaporation of the organic portion of the cosolvent) prior to sealing. The sealed ampuls were placed in a 25° C water bath and rotated for at least 48 hours.

The contents of each ampul were filtered through a 0.22 μm polytetrafluoroethylene (Teflon®) membrane filter (Gelman Sciences, Inc., Ann Arbor, Mi). After the density of each filtrate was determined, the samples were diluted for spectrophotometric analysis. The cosolvent composition of the analysed samples was duplicated in the spectrophotometric standards. The analytical wavelength used was 381 nm. Each solubility value was an average of 4-5 separate determinations.

5. α-Cyclodextrin Solubility

The procedure used for cyclodextrin solubility was similar to that used for the 4-nitroaniline studies, with two differences. Solute-saturated samples were initially filtered through 8 μm glass wool (Corning glassware) before Teflon® membrane filtration. Second, samples and standards were analysed by polarimetry. Apart from these two differences the cyclodextrin and 4-nitroanaline procedures were identical.

E. CALCULATIONS

1. Complexation Constant Determination

Derivation of Equations Used in Complexation

In order to gain insight into the methods used to determine the complexation constant, the equations on which the analysis was based will be derived. The method is based on a shift in the ultraviolet or visible spectrum upon complexation. Therefore it will only work at a wavelength where the molar absorptivity of the bound and unbound substrate species are significantly different. The derivation also assumes that Beer's law holds for all species in solution. The equilibrium constant for one - to - one complexation was written in Chapter One as

$$K_{11} = \frac{[SL]}{[S][L]} \qquad (1.24)$$

The mass balance equations for this complexation process are defined by equations 2.1 and 2.2.

$$S_t = [S] + [SL] \qquad (2.1)$$

$$L_t = [L] + [SL] \qquad (2.2)$$

The absorbance (A_o) of a solution of the substrate in the absence of ligand is written as

$$A_o = \varepsilon_S b S_t \qquad (2.3)$$

where ε_S is the molar absorptivity of the substrate solution and b is the path length. The absorbance (A_L) in the presence of ligand is

$$A_L = \varepsilon_S b[S] + \varepsilon_L b[L] + \varepsilon_{11} b[SL] \qquad (2.4)$$

where ε_L and ε_{11} are the molar absorptivities of the ligand and complex, respectively. Equation 2.5 is obtained by combining Equations 2.2, 2.3 and 2.4.to yield

$$A_L = \varepsilon_S b S_t + \varepsilon_L b L_t + \Delta\varepsilon_{11} b[SL] \qquad (2.5)$$

where $\Delta\varepsilon_{11} = \varepsilon_{11} - (\varepsilon_S + \varepsilon_L)$. If the absorbance A_L is measured against a reference with a matching ligand concentration, then Equation 2.5 becomes

$$A_L = \varepsilon_S b S_t + \Delta\varepsilon_{11} b [SL] \qquad (2.6)$$

Equation 2.7 is obtained when Equations 2.6 and 1.24 are combined,

$$\Delta A = K_{11} \Delta\varepsilon_{11} b [S][L] \qquad (2.7)$$

where $\Delta A = A - A_o$. Combining equations 2.1 and 2.7 yields an equation which relates the change in substrate absorbance to the binding constant and free ligand concentration.

$$\frac{\Delta A}{b} = \frac{S_t K_{11} \Delta\varepsilon_{11} [L]}{1 + K_{11}[L]} \qquad (2.8)$$

Equation 2.9 is another form of this equation

$$\frac{b}{\Delta A} = \frac{1}{S_t K_{11} \Delta\varepsilon_{11} [L]} + \frac{1}{S_t \Delta\varepsilon_{11}} \qquad (2.9)$$

which yields a straight line when $1/\Delta A$ is plotted against $1/[L]$. K_{11} and $\Delta\varepsilon_{11}$ can be calculated from the slope and intercept.

The relationship between the free and unbound ligand can be obtained by combining Equations 1.24, 2.1, and 2.2 to yield the quadratic

$$[L]^2 + \left(S_t + \frac{1}{K_{11}} - L_t\right)[L] - \frac{L_t}{K_{11}} = 0 \qquad (2.10)$$

Now that all the relevant equations have been presented, the procedure used to determine the binding constant will be outlined.

Procedure

1) An estimate of K_{11} and $\Delta\varepsilon_{11}$ was initially obtained from the slope and intercept of a plot of $1/\Delta A$ against $1/L_t$ by assuming $[L] \approx L_t$ and using Equation 2.9.

2) The estimate of K_{11} was introduced into a BASIC computer programme (6), which used Equation 2.10 to calculate [L] for each L_t.

3) {[L},ΔA} data pairs from the second step, along with the initial estimates for K_{11} and $\Delta\varepsilon_{11}$, were introduced into a BASIC nonlinear regression programme (7), which used Equation 2.8 to obtain the final estimates of K_{11} and $\Delta\varepsilon_{11}$.

2. Free Energy Change Calculations

All complexation and solubility data were converted from a molar scale to a mole fraction scale (x_3) in order to eliminate the free energy of mixing contribution (4,5). The procedures used for these conversions will now be outlined.

Free Energy Change of Complexation

Equation 2.11 was used to determine the free energy change of complexation

$$\Delta G^\circ = - \mathbf{k}T \ln(M^*\rho_0 K_{11}) \qquad (2.11)$$

where M* is the moles of solvent per kilogram of solvent, and ρ_0 is solvent density in g/ml.

Free Energy Change of Solubility

The procedure for determining the dissolution free energy change was a little more involved than the procedure used for complexation. The step - by - step procedure is outlined below.

1) One liter of the saturated solution of the cosolvent mixture was conveniently chosen for all the calculations.

2) Equation 2.12 was used to determine the weight of one liter of the saturated solution (***A***),

$$1000 \text{ mL} \times (\rho) = \boldsymbol{A} \qquad (2.12)$$

where ρ is the density of the saturated solution.

3) The weight of solute (***B***) present in one liter of the saturated solution was calculated by using equation 2.13.

$$C \times MW_{solute} = \boldsymbol{B} \qquad (2.13)$$

where C is the solute concentration in moles per liter.

4) The next step involved calculating the weight of the solvent (***C***) in one liter of the saturated solution[a].

$$\boldsymbol{A} - \boldsymbol{B} = \boldsymbol{C} \qquad (2.14)$$

5) Equations 2.15 and 2.16 were used to calculate the weight of the organic cosolvent (***D***) and water (***E***) present in one liter of the solvent.

$$\%\ \text{w/w cosolvent} \times \boldsymbol{C} = \boldsymbol{D} \qquad (2.15)$$

$$(1 - \%\ \text{w/w cosolvent}) \times \boldsymbol{C} = \boldsymbol{E} \qquad (2.16)$$

6) This was followed by calculating the total number of moles (***F***) present in one liter of the saturated solution

$$\mathbf{C} + \frac{\boldsymbol{E}}{MW_{water}} + \frac{\boldsymbol{D}}{MW_{cosolvent}} = \boldsymbol{F} \qquad (2.17)$$

7) Equation 2.18 was used to calculate the mole fraction solubility, x_3

$$x_3 = C / \boldsymbol{F} \qquad (2.18)$$

---

[a] This procedure was used to convert solubility data since the solute weight's contribution to the total saturated solution weight could be significant, especially for the 4-nitroanaline system at higher organic concentrations.

8) The free energy change of solubility could now be calculated as

$$\Delta G^{\circ} = - \mathbf{k}T \ln x_3 \qquad (2.19)$$

3. Parameter Estimates

Parameter values were obtained by fitting the experimental data to the Solvent Effect model equations with a nonlinear regression programme (SYSTAT).

4. Surface Area Determinations

Surface area determinations of 4-nitroanaline and α-cyclodextrin were determined by a foil wrapping technique (8,9). This method involved wrapping the pertinent portions of a Corey-Pauling-Koltun (CPK) space-filling model of the molecule in aluminium foil. A minimum amount of foil was used to wrap the model in order to achieve a snug fit. Because these were contact surface area measurements, the aluminum foil was not forced into the crevices of the model. This piece of foil was then removed and weighed.

The weight was then converted to surface area by using a constructed standard curve of area against weight for

various sizes of aluminium foil and the scaling factor for the CPK model (1.25 cm = 1.0 Å).

This method was used to calculate the total surface area and the hydrophobic surface areas of the previously mentioned molecules as well as the surface area of the interior of the cyclodextrin cavity.

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III. α-CYCLODEXTRIN - METHYL ORANGE COMPLEXATION

A. RESULTS

This chapter describes a solvent study on the stability of the 1:1 α-cyclodextrin - Methyl Orange complex at 25°C in 0.10 M HCl. Tables 3.1 to 3.8 present K_{11} as a function of x_2, along with some related information, for each cosolvent system as well as the fully aqueous system. The associated error for each value is in parentheses. Each table entry represents a single binding study; the uncertainties in K_{11} are within run uncertainties. Half of the results presented in the tables were obtained by A. Paulson (1), who initiated this work. More detailed tables giving the substrate concentration, ligand concentrations, and associated absorbance values for each table entry are presented in Appendix A of this thesis and Appendix I of Paulson's Ph. D. thesis (1). The value obtained in the fully aqueous system is in very good agreement with previous values obtained in this laboratory (2,3). The model parameters for each cosolvent system are presented in Table 3.8. Figures 3.1 to 3.7 show the curve fits to Equation 1.35.

Table 3.1. 0.01N HCL

Physical Constants for Methyl Orange/α-Cyclodextrin Binding

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0	0.9993	55.506	4.63(0.07)	682(15)	4.337(0.008)

Table 3.2. Methanol System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M^* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00496	0.9952	55.292	4.69(0.04)	580(8)	4.269(0.006)
0.01340	0.9969	54.933	4.62(0.07)	383(9)	4.10(0.01)
0.01340	0.9969	54.933	4.6(0.1)	413(15)	4.13(0.02)
0.01340	0.9885	54.933	4.3(0.2)	449(34)	4.16(0.03)
0.02628	0.9830	54.394	4.7(0.2)	315(15)	4.01(0.02)
0.04886	0.9757	53.473	4.52(0.05)	195(4)	3.80(0.01)
0.07520	0.9420	52.435	4.6(0.1)	122(7)	3.60(0.02)
0.09658	0.9686	51.411	4.48(0.01)	71(1)	3.363(0.005)
0.12327	0.9653	48.830	4.28(0.02)	49(1)	3.200(0.007)
0.15443	0.9540	49.366	4.420(0.003)	31(2)	3.00(0.02)
0.18070	0.9526	48.489	4.27(0.09)	25(0.1)	2.90(0.02)

Table 3.3. DMSO System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M^* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules $molec.^{-1}$
0.01249	1.0046	53.286	4.50(0.07)	412(10)	4.117(0.008)
0.03767	1.0146	49.309	4.42(0.08)	191(6)	3.77(0.01)
0.06475	1.0372	45.644	4.57(0.02)	125(1)	3.576(0.003)
0.06518	1.0273	45.591	4.2(0.1)	118(6)	3.55(0.02)
0.06518	1.0292	45.591	4.8(0.1)	82(3)	3.40(0.02)
0.09682	1.0433	41.953	4.5(0.1)	64(3)	3.27(0.02)
0.12753	1.0472	38.817	3.70(0.03)	40(2)	3.05(0.02)
0.15439	1.0719	36.634	4.01(0.03)	42(1)	3.046(0.007)
0.17685	1.060	34.816	4.4(0.2)	16(4)	2.6(0.1)
0.23128	1.071	31.259	2.8(0.1)	16(2)	2.59(0.04)

Table 3.4. Ethylene Glycol System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00328	0.9973	54.800	2.20(0.03)	659(83)	4.32(0.05)
0.00669	0.9990	54.349	3.40(0.02)	362(9)	4.07(0.01)
0.02781	1.0080	54.394	4.7(0.2)	250(11)	3.92(0.02)
0.04968	1.0155	53.473	4.61(0.04)	149(2)	3.704(0.006)
0.00963	1.0012	54.933	4.4(0.1)	510(21)	4.22(0.02)
0.00963	1.0012	54.933	4.9(0.2)	390(23)	4.11(0.02)
0.07702	1.0256	52.435	4.7(0.1)	95(5)	3.52(0.02)
0.10009	1.0290	44.433	2.90(0.01)	78(3)	3.37(0.02)
0.12697	1.0358	42.217	3.00(0.05)	46(2)	3.13(0.02)
0.16213	1.0486	47.294	4.5(0.2)	28(2)	2.98(0.03)

Table 3.5. Dioxane System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00406	0.9966	54.379	4.436(0.006)	293(1)	3.981(0.001)
0.00519	0.9969	54.146	4.08(0.01)	219(3)	3.860(0.006)
0.00769	1.000	54.057	4.55(0.06)	190(4)	3.802(0.009)
0.01059	0.9982	53.06	4.20(0.01)	134(2)	3.651(0.005)
0.01490	1.0036	52.464	4.58(0.07)	82(2)	3.45(0.01)
0.02450	1.0067	50.676	4.6(0.3)	39(4)	3.13(0.04)
0.03730	1.0073	48.271	5.8(0.4)	15(2)	2.70(0.05)
0.03720	1.0076	48.287	4.4(0.6)	20(3)	2.83(0.06)
0.04724	1.011	46.889	4.6(0.4)	14(1)	2.68(0.03)
0.05126	1.0220	46.278	-	8.7	2.478

Table 3.6. Isopropanol System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M^* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00070	0.9928	55.415	4.61(0.07)	587(15)	4.27(0.01)
0.00117	0.9954	55.355	4.46(0.07)	549(16)	4.25(0.01)
0.00211	0.9984	55.235	4.440(0.025)	444(4)	4.160(0.004)
0.00211	0.9984	55.235	4.70(0.06)	398(9)	4.115(0.009)
0.00211	0.9984	55.235	3.91(0.06)	456(13)	4.170.01)
0.00351	0.9936	55.056	4.44(0.07)	335(10)	4.04(0.01)
0.00356	0.9928	55.050	4.502(0.007)	347(2)	4.055(0.002)
0.00515	0.9954	54.581	2.06(0.01)	300(23)	3.99(0.03)
0.00538	0.9920	54.551	4.120(0.007)	258(8)	3.93(0.01)
0.00646	0.9922	54.417	2.88(0.02)	228(29)	3.88(0.05)
0.00901	0.9901	54.102	4.40(0.07)	169(4)	3.749(0.009)
0.01137	0.9895	53.813	2.6(0.3)	141(23)	3.67(0.07)
0.01219	0.9837	53.972	4.53(0.02)	119(1)	3.602(0.003)
0.01390	0.9880	53.508	6.222(0.002)	105(1)	3.550(0.003)
0.01603	0.9811	53.252	4.46(0.02)	76(2)	3.41(0.01)
0.01709	0.9990	53.127	3.92(0.01)	86(3)	3.46(0.01)
0.02293	0.9827	52.443	2.35(0.04)	56(9)	3.28(0.07)

Table 3.7. Acetonitrile System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00228	0.9950	55.074	4.68(0.08)	390(3)	4.10(0.003)
0.00442	0.9930	54.925	2.81(0.01)	285(4)	3.972(0.005)
0.00444	0.9953	55.194	4.74(0.01)	305(2)	4.004(0.003)
0.00671	0.9920	54.767	4.34(0.03)	216(6)	3.86(0.01)
0.00893	1.0100	54.615	4.73(0.02)	164(3)	3.751(0.007)
0.01118	0.9928	54.726	4.62(0.03)	164(3)	3.744(0.008)
0.01316	0.9910	54.327	4.41(0.03)	102(2)	3.54(0.01)
0.01681	0.988	54.081	4.8(0.1)	76(8)	3.42(0.04)
0.01797	0.988	54.003	3.75(0.04)	110(4)	3.57(0.01)
0.01842	0.9876	53.973	4.0(0.2)	96(8)	3.52(0.03)
0.02268	0.9877	53.946	4.63(0.08)	62(2)	3.34(0.01)
0.02741	0.9827	53.378	2.88(0.04)	57(2)	3.29(0.01)
0.02764	0.9836	53.364	4.36(0.03)	49(1)	3.23(0.01)
0.02869	0.9826	53.295	4.25(0.02)	48(1)	3.226(0.003)
0.03770	0.98015	52.714	4.25(0.02)	29(1)	3.01(0.01)
0.04663	0.9803	52.391	4.6(0.3)	23(2)	2.91(0.04)

Table 3.8. Acetone System

Physical Constants for α-Cyclodextrin - Methyl Orange Binding

x_2	ρ_o g/ml	M^* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.00171	0.9967	55.296	4.6(0.1)	483(19)	4.19(0.02)
0.00438	0.9956	54.971	4.5(0.1)	330(9)	4.04(0.01)
0.00776	0.9917	54.565	4.61(0.03)	235(3)	3.890(0.005)
0.01291	0.9985	53.962	4.61(0.02)	158(1)	3.725(0.003)
0.01326	0.9902	53.910	4.57(0.08)	138(4)	3.66(0.01)
0.01736	0.9879	53.193	4.12(0.55)	114(1)	3.582(0.004)
0.01915	0.9873	52.992	4.72(0.04)	86(7)	3.46(0.04)
0.02327	0.9816	52.533	3.620(0.005)	94(1)	3.492(0.005)
0.02708	0.9827	52.117	3.72(0.02)	75(3)	3.34(0.02)
0.03026	0.9812	51.774	4.258(0.007)	54(1)	3.262(0.003)
0.03953	0.9847	51.021	4.63(0.07)	50(2)	3.22(0.02)

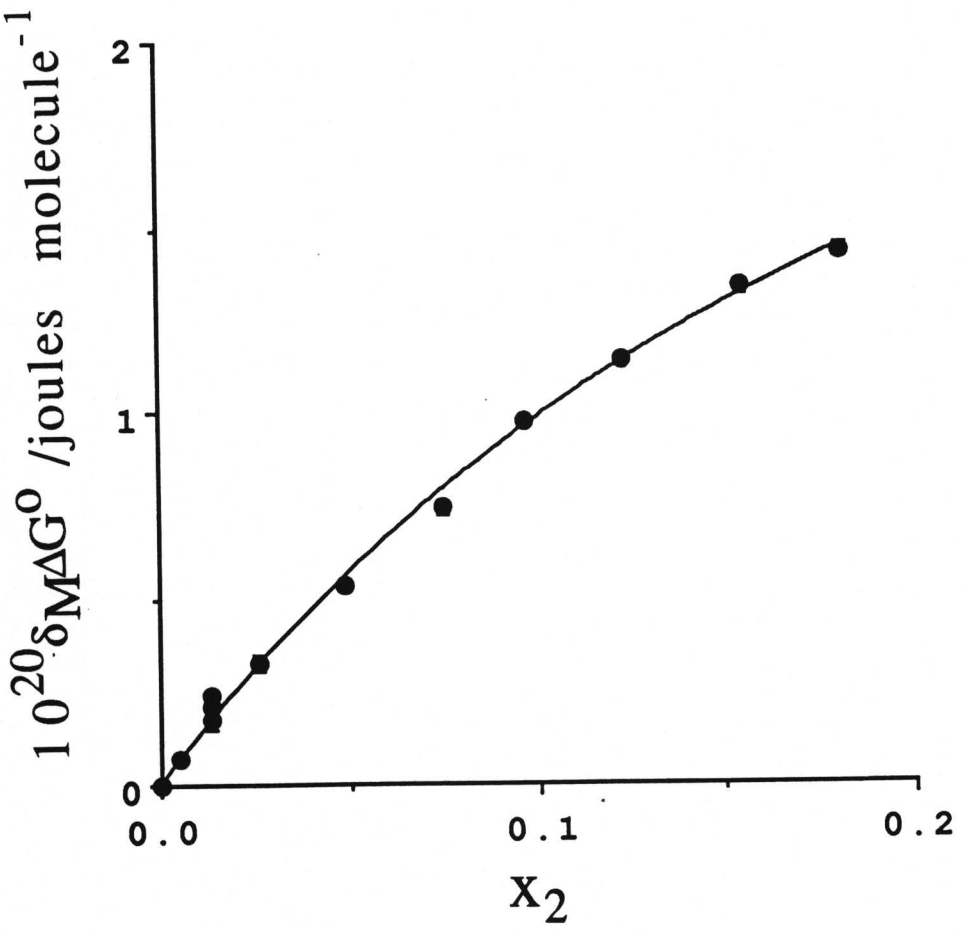


Figure 3.1. Solvent effect on the stability of the α-cyclodextrin - Methyl Orange complex in the methanol system, showing the experimental data points and the fitted curve.

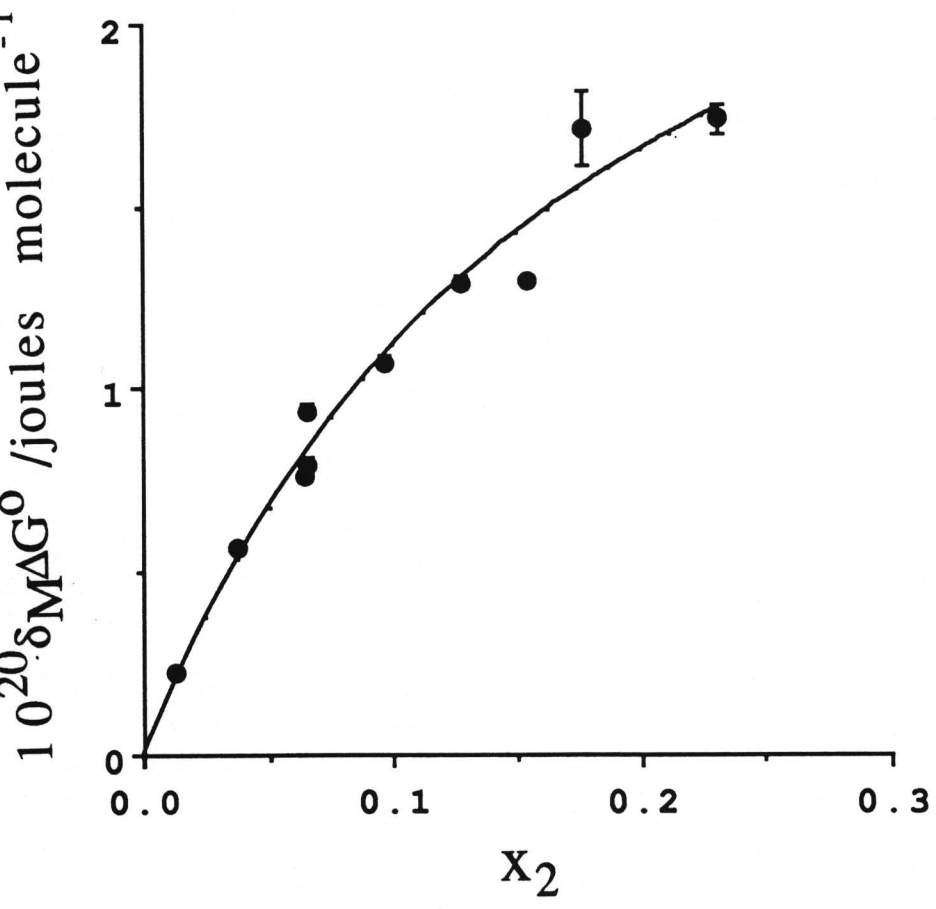


Figure 3.2. Solvent effect on the stability of the α-cyclodextrin - Methyl Orange complex in the DMSO system, showing the experimental data points and the fitted curve.

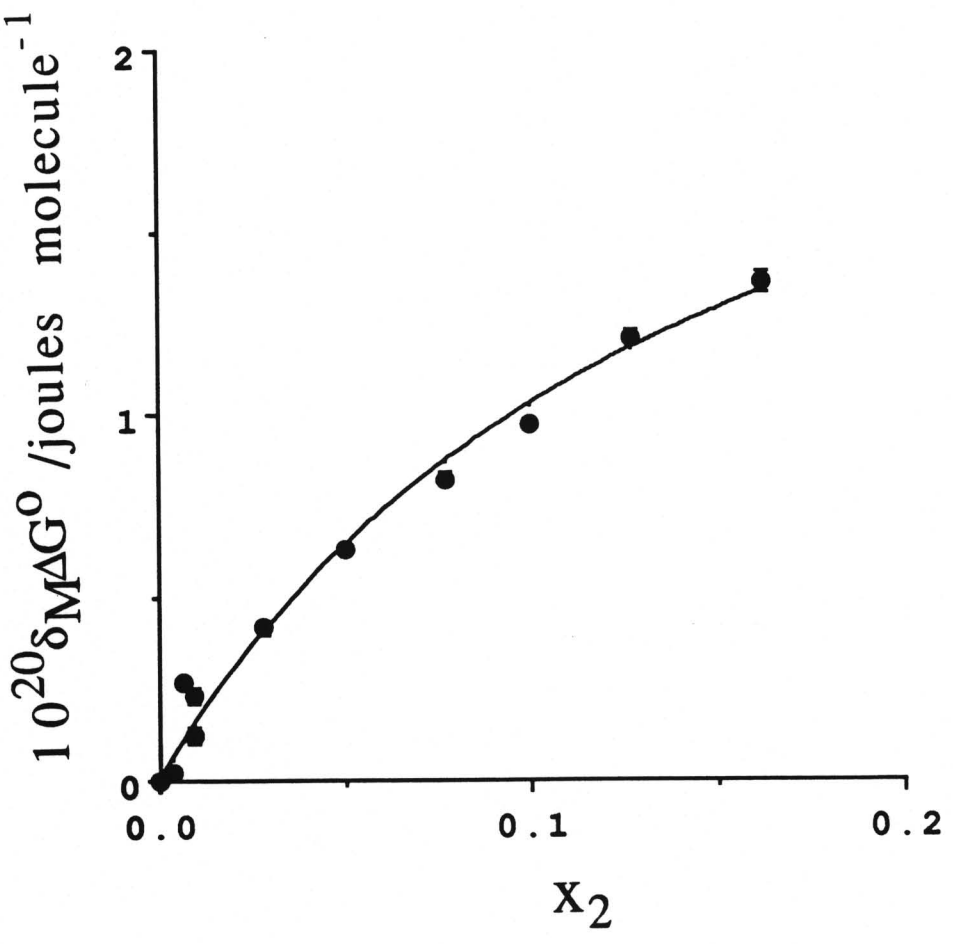


Figure 3.3. Solvent effect on the stability of the α-cyclodextrin - Methyl Orange complex in the ethylene glycol system, showing the experimental data points and the fitted curve.

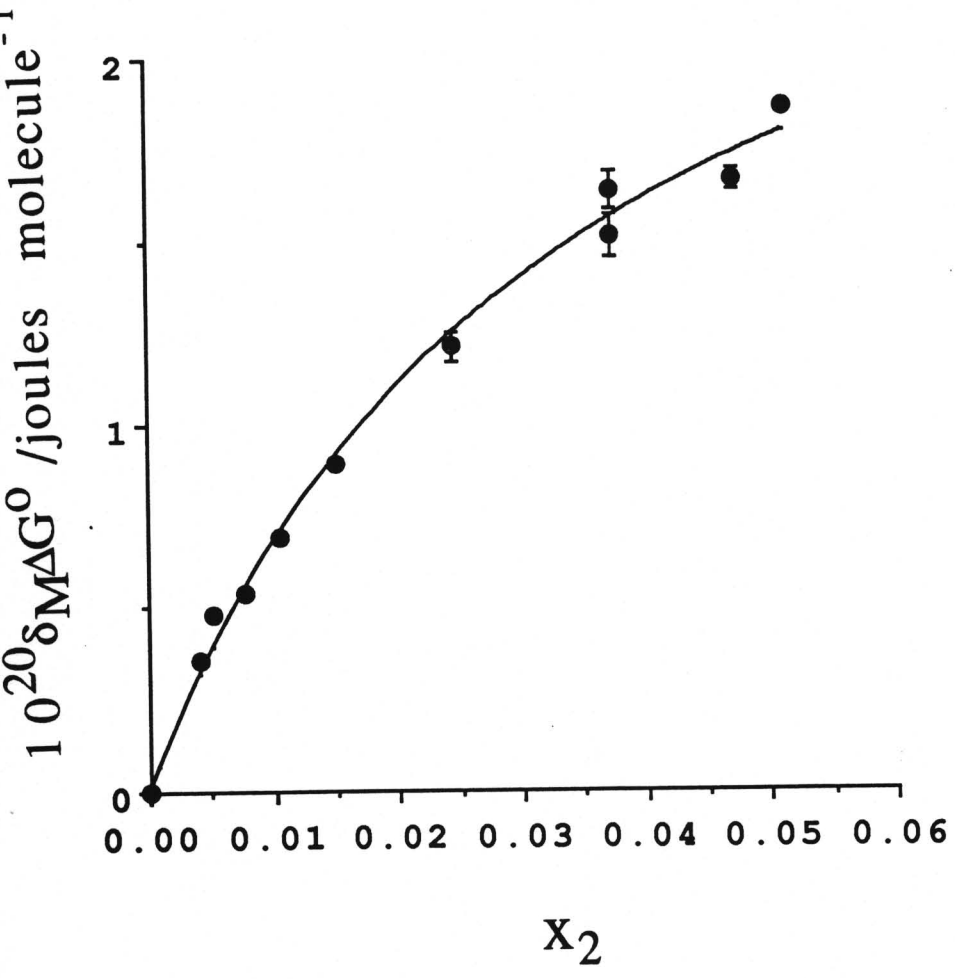


Figure 3.4. Solvent effect on the stability of the α-cyclodextrin - Methyl Orange complex in the dioxane system, showing the experimental data points and the fitted curve.

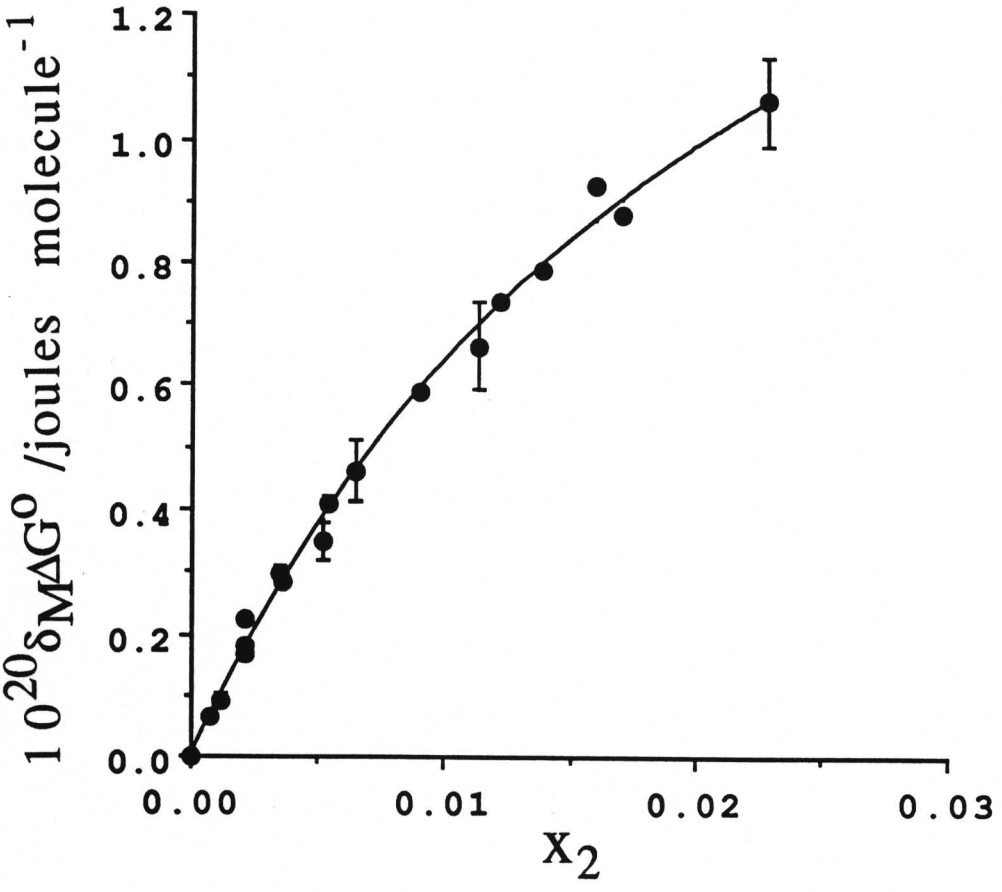


Figure 3.5. Solvent effect on the stability of the α-cyclodextrin-Methyl Orange complex in the isopropanol system showing the experimental data points and the fitted curve.

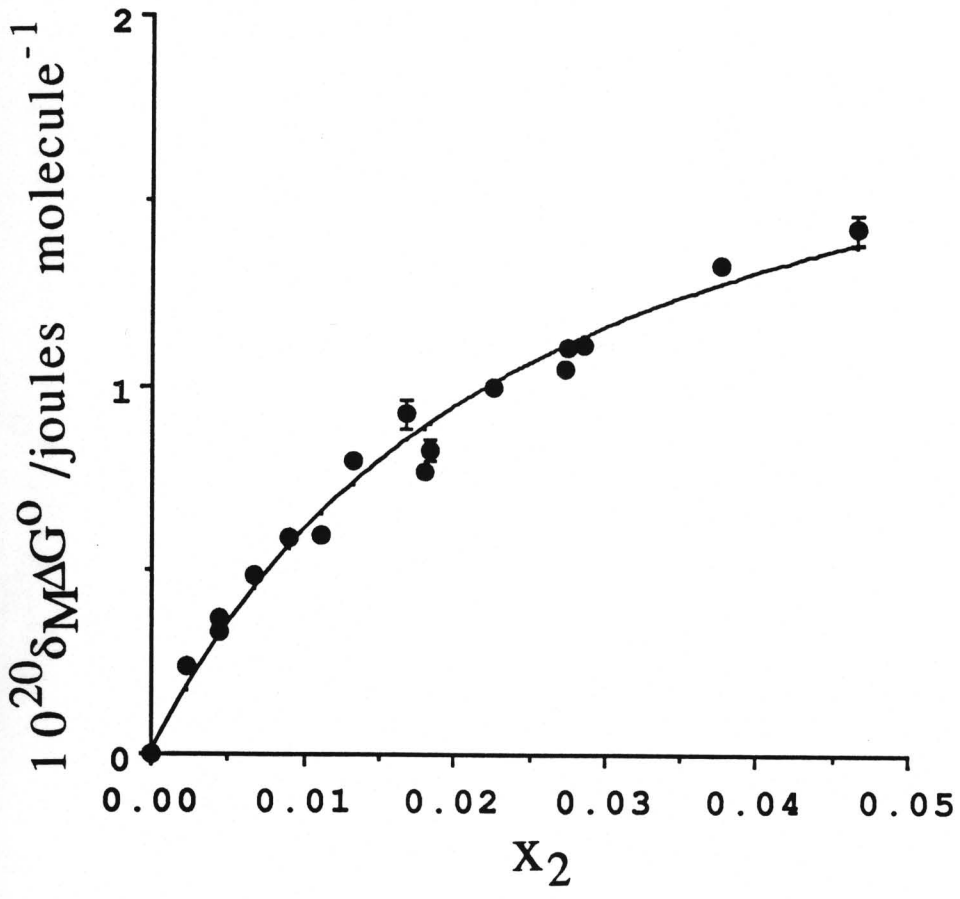


Figure 3.6. Solvent effect on the stability of the α-cyclodextrin-Methyl Orange complex in the acetonitrile system, showing the experimental data points and the fitted curve.

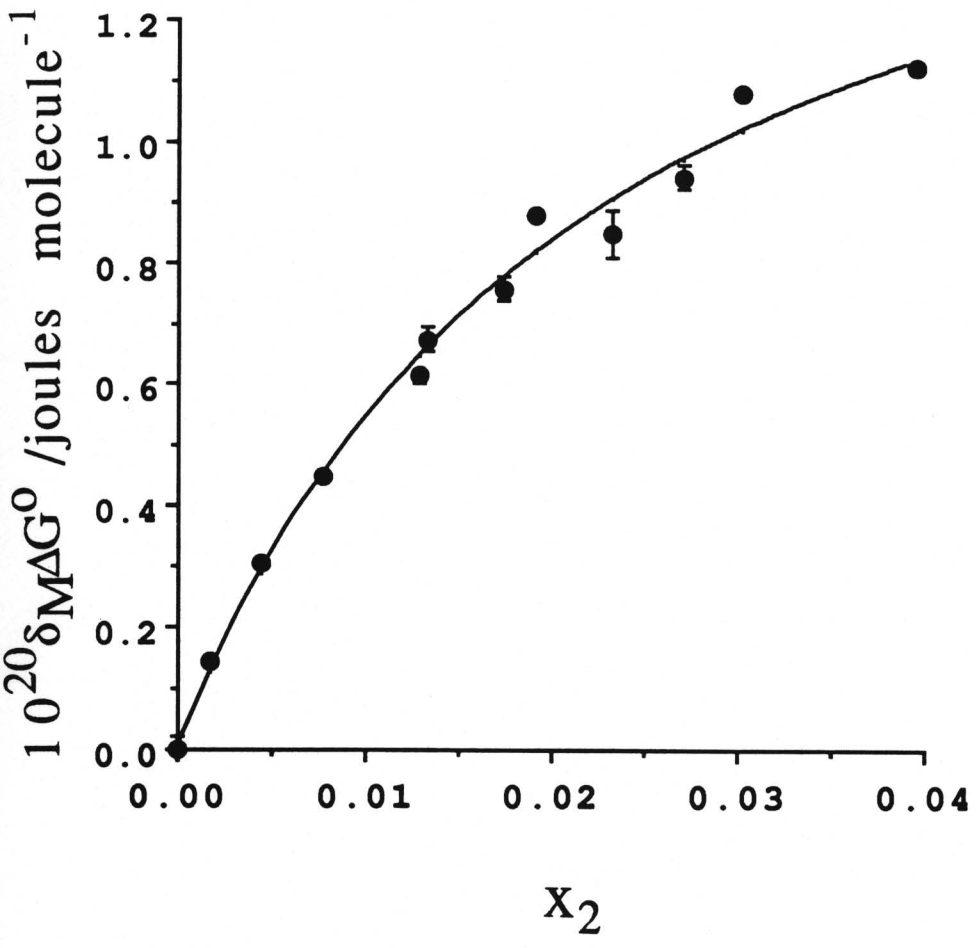


Figure 3.7. Solvent effect on the stability of the α-cyclodextrin-Methyl Orange complex in the acetone system showing the experimental data points and the fitted curve.

Table 3.8. Parameter Estmates for the Methyl Orange/ α - Cyclodextrin Cosolvent Systems Obtained by Fitting the Complexation Data to Equation 1.35.

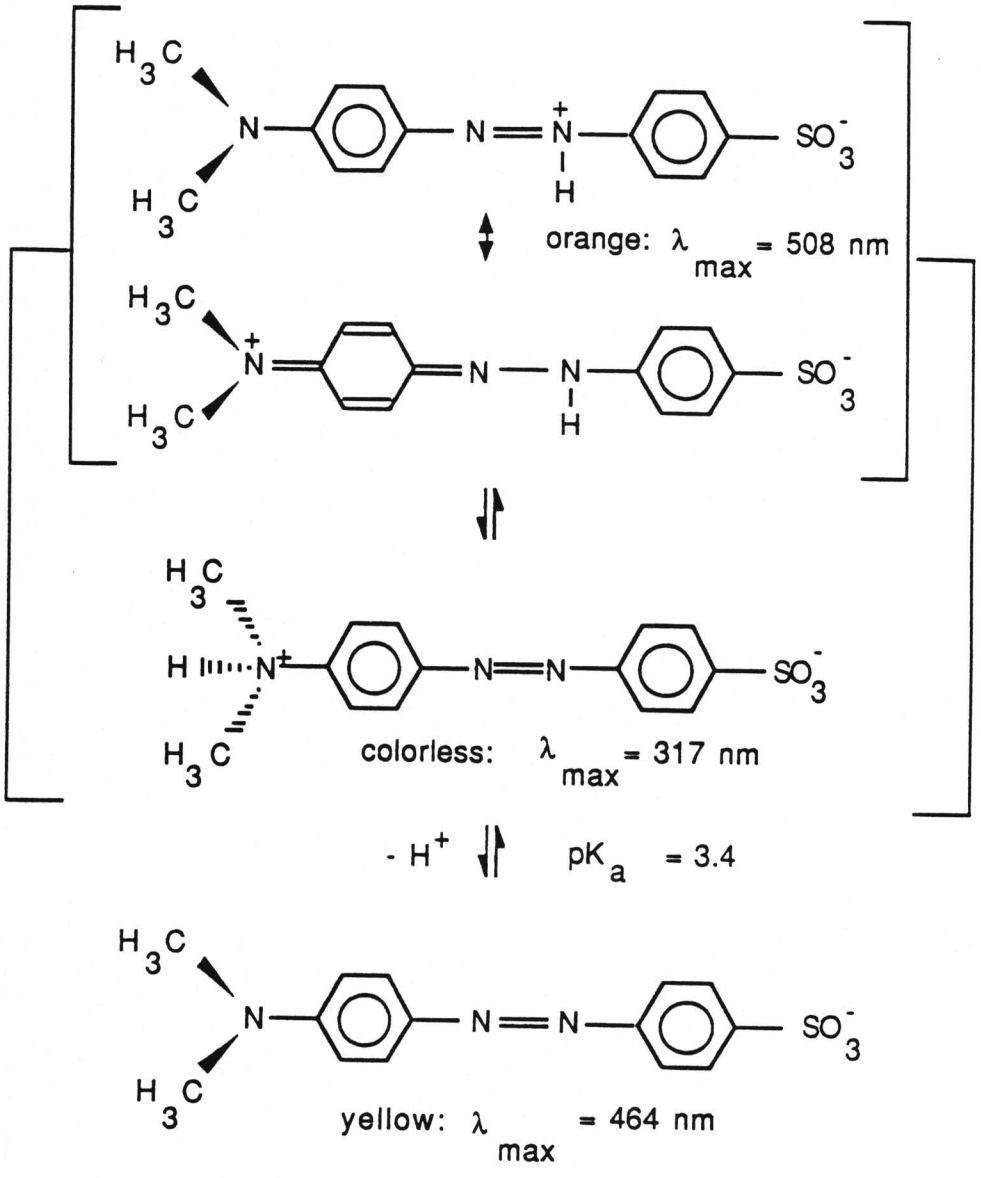
COSOLVENT SYSTEM	K_1	$-g\Delta A$ /$A^{o2}molecule^{-1}$	curve fit criterion[a] \%
methanol	4.9(0.5)	43(4)	1
DMSO	6.4(1.2)	66(12)	3
ethylene glycol	7.7(1.8)	58(15)	2
dioxane	30.6(2.3)	38(4)	2
isopropanol	43(3.6)	11(3)	1
acetonitrile	40.3(5.7)	13(5)	2
acetone	45.7(3.9)	3(2)	1

[a] Curve fit criterion = 100(standard deviation of points about the fitted line divided by the mean of the ordinate values).

B. DISCUSSION

1. Introduction to α-Cyclodextrin - Methyl Orange Complexation

A thorough discussion of solvent effects on α-cyclodextrin - Methyl Orange stability requires knowledge of the properties of Methyl Orange associated with complex formation. Methyl orange has a pK_a of 3.4 (4,5) and the protonated species exists in two tautomeric forms. The tautomerism is shown in Scheme 3.1 In 0.1N HCl the absorption at 508 nm, the predominant band, has been attributed to the quinoid resonance form of the azonium tautomer and the band at 317 nm to the ammonium tautomer (4,6). Mochida and coworkers (7) have concluded from Raman spectroscopy that Methyl Orange in 0.1 N HCl is almost exclusively in the azonium quinoid resonance form. A sharp decrease in the absorption at 508 nm is observed upon complexation of Methyl Orange with α-cyclodextrin in acidic solution. The loss in visible absorbance has been attributed to a shift in the tautomeric equilibrium toward the ammonium form (8,9), which is due to the tight fit of the α-cyclodextrin about the azobenzene moiety. The close association between the azo moiety and the cyclodextrin



Scheme 3.1

Dissociation and Tautomeric Equlibria of Methyl Orange

cavity has been confirmed by Higuchi and coworkers (10,11) using circular intensity differential and Raman optical activity spectra. The results are also consistent with the structure of the solid Methyl Orange - α -cyclodextrin complex (12).

All cosolvent mixtures in our study were buffered with 0.1 N HCl to prevent the dissociation of Methyl Orange. It has been shown that for the aqueous rich organic cosolvent mixtures used in these studies, there is a shift in the pK_a of less than one unit in the negative direction (13,14). Therefore the 0.1 N HCl buffer effectively maintains Methyl Orange in the protonated form in all the cosolvent mixtures used in this work.

The introduction of ions raises concerns about possible ionic effects upon complexation. There have been some reports of cyclodextrin complexation with anions (15-18). However, Wojcik and Rohrbach (15) determined, by conductance methods, that the chloride ion does not bind to α-cyclodextrin in aqueous solutions. Therefore we need not be concerned with ionic effects on complexation in these studies.

2. Review of Previous Applications of the Solvent Effect Model

Because some of the ideas and concepts proposed in the present study are based on results of previous applications of the Solvent Effect Model to solubility and complexation, a review of this past work is warranted.

Khossravi and Connors (19,20) first used the Solvent Effect Model (Equation 1.22) to successfully describe the solubility of naphthalene over the entire cosolvent range in binary aqueous organic mixtures of ethylene glycol, methanol, and acetonitrile. Based on these initial results, it was suggested that K_1 and K_2 are cosolvent dependent terms which are independent of solute identity. Second, it was proposed that the gA term was a reflection of the hydrophobic surface area of the solute.

These hypotheses were supported by the results obtained from solubility studies of substituted biphenyls in methanol cosolvent mixtures. The solvation exchange constant terms for these studies matched those obtained for naphthalene solubility in the methanol system. Furthermore, a linear profile was obtained from a plot of the gA terms against their corresponding hydrophobic surface area.

Reasonable K_1, K_2, and $g\Delta A$ values were obtained by

using a solvent effect model to describe the complexation of napthalene with theophylline, in methanol, acetonitrile, and ethylene glycol cosolvent systems (19). The complexation model required a 2-step solvation exchange process owing to the cosolvent range covered. The studies in methanol and acetonitrile were conducted to cosolvent mole fractions of 0.46 and 0.22 respectively. The studies in ethylene glycol were conducted over the entire cosolvent range. The Cancellation Approximation, which eliminated the solvation terms of the substrate and complex, was also invoked. This approximation is only valid if the solvation exchange constants for the substrate, ligand, and complex are similar. Because solubility studies had been performed with naphthalene and theophylline in these solvents, the experimental data could also be analysed in terms of complex solubility. The complex solubility analysis allowed for an independent determination of the validity of the Cancellation Approximation. The value of the solvation exchange constants for the complex were found to be similar in magnitude to the naphthalene solubility values. Moreover, for each cosolvent system investigated, the $g\Delta A$ term was found to be identical with the value calculated by the subtracton of the napthalene and theophylline gA terms from that of the complex. These results indicated that the Cancellation Approximation is valid for these systems.

Having given this background, we will now proceed with our analysis of solvent effects on α-cyclodextrin - Methyl Orange complex stability.

3. Analysis of K_1 and $g\Delta A$

An analysis of the solvation exchange constant term is not complete without a discussion of the physical significance of this term. K_1 was presented in chapter 1 as a one - step solvation equilibrium constant in which a water molecule associated with the solvation shell is replaced by an organic cosolvent molecule. This is an overly simple model of the solvation exchange process in binary aqueous solutions, which must involve multiple equilibria. Therefore a more realistic view of the K_1 term is that it is some composite average of these multiple equilibria for a solute molecule going from a fully hydrated to a partially cosolvated state, as shown in Scheme 3.2.

Fully Hydrated Solute $\rightleftharpoons$ Partially Cosolvated Solute

Scheme 3.2

However, we will continue to treat K_1 as a one step solvation equilibrium constant, because this treatment is a convenient way of analysing mechanisms associated with the solvent - exchange process. Using this treatment, it will now be shown that K_1 term takes into account competitive complexation. The one step solvation exchange for the ligand is defined by Equation 3.1.

$$LW + M \overset{K_1}{\rightleftharpoons} LM + W \qquad (3.1)$$

We can write equilibria involving the substrate - ligand complex as

$$LW + S \overset{K_{11W}}{\rightleftharpoons} SL + W \qquad (3.2)$$

and

$$LM + S \underset{}{\overset{K_{11M}}{\rightleftharpoons}} SL + M \qquad (3.3)$$

It follows that

$$K_1 = \frac{K_{11W}}{K_{11M}} \qquad (3.4)$$

Therefore the K_1 term incorporates competitive complexation.

Figures 3.1-3.7 indicate that the model successfully describes the complexation data for each cosolvent system. The cosolvent systems appear to fall into two categories. The first category consists of the cosolvent systems DMSO, methanol, and ethylene glycol, whereas the second contains the acetone, acetonitrile, isopropanol, and dioxane cosolvent systems. These categories are also reflected in the K_1 values in Table 3.8. The first category contains K_1 values ranging from 5-8, while the second has values between 30 - 50.

We will now discuss the significance of the K_1 values. Although the values obtained for K_1 are within an order of magnitude of 1, which is chemically reasonable for cosolvents which are completely miscible with water, the values of K_1 for the Methyl Orange cyclodextrin systems are significantly higher than those obtained from the

napthalene solubility work, which ranged from 2.3 to 3.0 for the acetonitrile, methanol, and ethylene glycol cosolvent systems. The highest mole fraction at which a complexation constant could be determined, in the present work, ranged from 0.02 for the isopropanol system to 0.23 for DMSO. This is in contrast to the solubility studies, which could be carried out over the entire cosolvent range. However, the difference in cosolvent range covered between the two systems does not appear to account for the discrepancy between the K_1 values. Biphenyl solubility in methanol-water mixtures has been extensively characterised in the water rich region (19). Khossravi has applied a 1-step solubility model over the cosolvent ranges that match those in the complexation studies. The maximum K_1 value achieved in this analysis was 2.0, which was significantly smaller than the value of 4.9 obtained for the methanol complexation complexation.

We have proposed that the unusual K_1 values for cyclodextrin complexation reflect the cosolvent's ability to partition into the cyclodextrin cavity and is therefore a measure of the chemical nature of cyclodextrin's interior. The octanol/water partition coefficient can be used as a measure of polarity (21). A plot of log K_1 against log P of the pure cosolvent is presented in Figure 3.8. If this interpretation is correct, we could determine

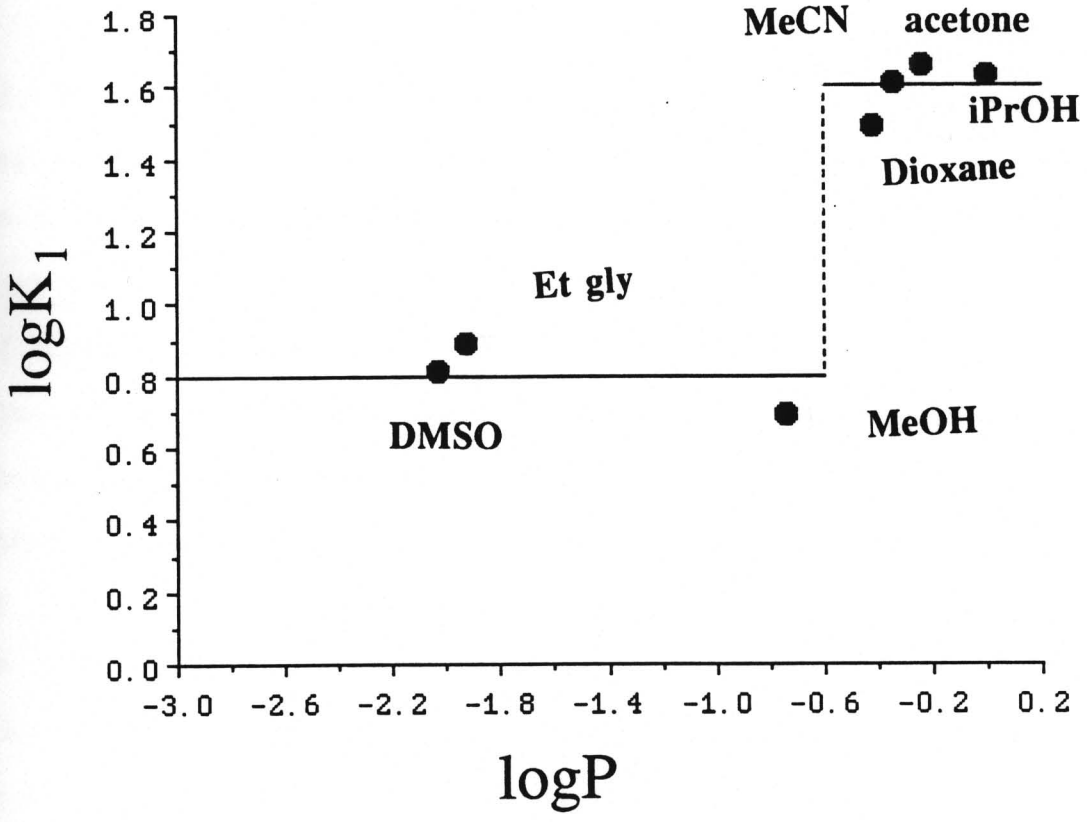


Figure 3.8. Plot of log K_1 against log P where P is the octanol/water partition coefficient in the pure cosolvent.

which category the cosolvent belongs to based only on its log P value. Moreover, the position of the discontinuity in the curve may be an indication of the effective polarity of the cyclodextrin cavity.

Various methods have been used to elucidate the nature of the cyclodextrin interior. Van Etten and coworkers (22) reported similar absorption spectra for p-*tert*-butylphenol in dioxane and in aqueous α-cyclodextrin solutions. This work has often been cited as evidence that the properties of the cyclodextrin interior are similar to dioxane. Fluorescence studies suggest that the cyclodextrin interior resembles *tert*-butyl alcohol (23), ethylene glycol (23), or ethanol (24,25). Paulson and Connors (26) obtained spectra of 1,4-disubstituted benzenes in a variety of solvents and in aqueous α-cylodextrin solutions. They showed that their conclusions on the nature of the cyclodextrin cavity were probe dependent. Cox and coworkers (23) have suggested that the disparity is the result of the individual probes interacting with different regions of the cyclodextrin cavity. Our solvent effect result may be useful since it constitutes an estimate of the polarity of the cyclodextrin interior that is based on a physical phenomenon that is different from the previous estimates.

The variations in the $g\Delta A$ values are considerable, ranging from 3 $Å^2 molecule^{-1}$ for acetone to 66 $Å^2 molecule^{-1}$

for DMSO. There also appears to be an inverse association between the magnitudes of the K_1 and $g\Delta A$ values. However it is not precise. We therefore seek to further investigate the significance of the $g\Delta A$ values and determine if its variation and association with K_1 is real or simply a curve fitting artefact. We will base our analysis of the $g\Delta A$ term on the conclusions from the naphthalene solubility studies, which are, as follows:

1. The effective area A is the nonpolar surface area of the solute.
2. The g value is only dependent on cosolvent identity and is solute and composition independent.

This analysis will therefore treat ΔA as a constant, and any differences in the $g\Delta A$ values from cosolvent system to cosolvent system will be attributed to variations in the cosolvent dependent g term. We can therefore compute estimates for $g\Delta A$ using the g terms determined for naphthalene solubility in the ethylene glycol, methanol and acetonitrile systems. The ΔA value used for these computations is 105(3) $Å^2 molecule^{-1}$, which is the hydrophobic area of the internal cavity of α-cyclodextrin determined by the foil wrap method. The results, presented in Table 3.9, indicate that the values of $g\Delta A$ obtained from

Table 3.9. Estimates of the $g\Delta A$ Term Calculated by Using the g Values Obtained from the Napthalene Solubility Studies (19,20) and an Estimate of the Hydrophobic Surface Area of the Cyclodextrin Cavity

Cosolvent System	$-g\Delta A$ Estimate
Methanol	38.4(2.0)
Ethylene Glycol	71.3(2.8)
Acetonitrile	40.5(3.2)

this analysis match those in Table 3.8 for the methanol and ethylene glycol systems. However, the value of $g\Delta A$ for the acetonitrile system is three times larger than that obtained from the curve fit. This suggests that the small value of $g\Delta A$ is an artefact of curve fitting. In an attempt to elucidate the association between the K_1 and $g\Delta A$ magnitudes, we reanalysed the acetonitrile complexation data with Equation 1.3 while fixing $g\Delta A$ at 40.5 $Å^2 molecule^{-1}$. The analysis yielded a value of 21.6(0.6) for K_1 and a fitted curve which matched that described in Figure 3.6, where K_1 and $g\Delta A$ were both treated as adjustable parameters. There are two inferences from this treatment for cosolvent systems defined by large K_1 and small $g\Delta A$ values. The analysis suggests that part of the association between the parameters arises from an artefact of the curve fitting procedure, which inappropriately inflates K_1 and decreases the magnitude of $g\Delta A$. Second, when the curve fitting artefact is taken into account, we still obtain a K_1 value that is significantly larger than was obtained for the methanol, ethylene glycol, and DMSO systems. This suggests that the discontinuity observed in the K_1 values between the cosolvent systems is real and not a curve fitting artefact.

If the assumptions made in our analysis are invalid, $g\Delta A$ may actually be a composite of terms. Khossravi (27) proposed that this parameter can be expanded to

$$g\Delta A = g_{SL}A_{SL} - g_S A_S - g_L A_L \qquad (3.5)$$

where A_{SL}, A_S, and A_L are the surface areas of the subscripted species. Equation 3.5 can be combined with $\Delta A = A_{SL} - A_S - A_L$ to yield

$$g\Delta A = g_{SL}\Delta A + (g_{SL} - g_S)A_S + (g_{SL} - g_L)A_L \qquad (3.6)$$

Equation 3.6 suggests that a more appropriate designation for $g\Delta A$ is ΔgA.

Next we will investigate some of the approximations used in the derivation of the model equation that describes complexation. The Cancellation Approximation, which we invoked to reduce the number of parameters in our complexation model equation, will be discussed first.

The Cancellation Approximation is only valid for systems in which the exchange constants for the substrate, ligand, and complex are similar. We have suggested that the K_1 terms for complexation reflect the cosolvent's ability to partition into the interior of the cyclodextrin cavity.

This implies that the solvation exchange constant of α-cyclodextrin is different from those of the substrate and complex. Nevertheless, the Cancellation Approximation may still be used in the solvation process for cyclodextrin complexation if the following postulates are invoked:

1. The cavity of cyclodextrin endows this molecule with solvation characteristics which are different from other "non-cavity containing" solutes.

2. The complex is regarded as a "non-cavity containing" solute (because now the cavity is occupied by the substrate).

Applying these postulates to Equation 1.27,

$$\Delta G^{\circ}_{Solv.} = \Delta G^{\circ}_{Solv(SL)} - \Delta G^{\circ}_{Solv(S)} - \Delta G^{\circ}_{Solv(L)} \qquad (1.27)$$

which defines the solvation process for complexation, permits the cancellation of the substrate and complex solvation terms. This results in an equation for the solvation process that is identical to Equation 1.28, which was used in the original development of the complexation model. The only deviation from the original model

development is the assumption used to justify the Cancellation Approximation.

Where this argument fails is in the description of the general medium effect term. This is shown by an alternate derivation of the general medium effect for the complexation process initially proposed by Connors and Khossravi (19). This derivation uses the general medium effect term for cavity formation derived from the solubility model and associates the general medium effect for the complexation process with the net change in the free energy of cavity formation. Using these concepts, the general medium effect for complexation, in a one step solvation exchange process, becomes

$$\Delta G^{\circ}_{Gen.med.} = \frac{gA_{SL}\gamma''K_{1(SL)}x_2}{x_1 + K_1x_2} - \frac{gA_S\gamma''K_{1(S)}x_2}{x_1 + K_1x_2} - \frac{gA_L\gamma''K_{1(L)}x_2}{x_1 + K_1x_2} \qquad (3.7)$$

We immediately see from this equation that the general medium effect term is a function of the gA and K_1 values of the solute species in solution. Second, $\Delta G^{\circ}_{Gen.med.}$ only

collapses to the general medium effect term used in our complexation model when the solvation exchange constants of the individual solute species are identical. We have postulated that the K_1 values associated with cyclodextrin are different from the substrate and complex because they reflect the ability of the cosolvent to partition into the cyclodextrin cavity and therefore the Cancellation Approximation would not be valid for these systems. If this postulate is correct, Equation 7.3 suggests that the model parameter values for our complexation data generated by Equation 1.35, an equation in which the Cancellation Approximation was invoked, are a composite of the solvation exchange constant and gA values of the individual solute species.

A second approximation involves our definition of g, the curvature factor, which we treat as a composition independent term. The weakness of this approximation is shown by Equation 1.34.

$$\Delta G^{\circ}(x_2=0) = \Delta G^{\circ}_{Intersol.} + g\Delta A(\gamma_1 - \gamma_o) + \Delta G^{\circ}_{WW(CSL)} \qquad (1.34)$$

$\Delta G^{\circ}(x_2=0)$, $\Delta G^{\circ}_{WW(CSL)}$, γ_1, and γ_o are all constants. Based on our model development, $\Delta G^{\circ}_{Intersol.}$ and ΔA also have fixed values. Therefore Equation 1.34 requires g be a

constant, independent of cosolvent identity. Yet we have obtained a range of $g\Delta A$ values for the different cosolvent systems.

This weakness in the model can be overcome by treating the curvature factor as a composition dependent term. Connors (28) has shown that if we treat the composition dependence of the curvature factor in the same manner that the surface tension term was treated, we obtain Equation 3.7.

$$\Delta G^{\circ}(x_2) = \Delta G^{\circ}_{\text{Intersol.}} + g_1\Delta A(\gamma_1 - \gamma_o) + \frac{[g_1\Delta A\gamma' + \mathbf{k}T \ln K_1 + (g_2-g_1)\Delta A(\gamma_1 - \gamma_o)]K_1x_2}{x_1 + K_1x_2} + \frac{[(g_2-g_1)\Delta A(\gamma_2 - \gamma_1)](K_1x_2)^2}{(x_1 + K_1x_2)^2} + \Delta G^{\circ}_{WW(CSL)} \qquad (3.7)$$

where g_1 and g_2 are the curvature correction factors in water and the cosolvent. Setting $x_2 = 0$ we obtain

$$\Delta G^{\circ}(x_2=0) = \Delta G^{\circ}_{Intersol.} + g_1\Delta A(\gamma_1 - \gamma_o) + \Delta G^{\circ}_{WW(CSL)} \qquad (3.8)$$

All the terms in Equation 3.8 are now constant and we do not run into the same difficulties associated with Equation 1.34. Applying the Leffler-Grunwald delta operator we obtain

$$\delta_m \Delta G^{\circ} = \frac{[g_1\Delta A\gamma' + \mathbf{k}T \ln K_1 + (g_2-g_1)\Delta A(\gamma_1 - \gamma_o)]K_1x_2}{x_1 + K_1x_2} + \frac{[(g_2-g_1)\Delta A(\gamma_2 - \gamma_1)](K_1x_2)^2}{(x_1 + K_1x_2)^2} \qquad (3.8)$$

The $g_1\Delta A\gamma' + \mathbf{k}T \ln K_1$ portion of the first term constitutes the whole of model equation 1.35. An interesting aspect of Equation 3.8 is the presence of the γ_o term, which was eliminated in the original model equation. There are now four parameters to be fit in this equation: $g_1\Delta A$, K_1, $(g_2-g_1)\Delta A$, and γ_o. However, the computer programme was unable to generate meaningful parameter values when

Equation 3.8 was used to fit the experimental data, even after the value of γ_o was fixed at 25 dynes/cm to reduce the number of parameters to three. Nevertheless, Equation 3.8 may provide an estimate of the error incurred by assuming that g is a cosolvent independent term. This is achieved by subtracting Equation 1.35 from Equation 3.8 to yield

$$\delta_m\Delta G^\circ_{(Eq.3.8)} - \delta_m\Delta G^\circ_{(Eq.1.35)}$$

$$= (g_2-g_1)\left[\frac{\Delta A(\gamma_1-\gamma_o)]K_1x_2}{x_1 + K_1x_2}\right]$$

$$+ (g_2-g_1)\left[\frac{\Delta A(\gamma_2-\gamma_1)](K_1x_2)^2}{(x_1 + K_1x_2)^2}\right] \qquad (3.9)$$

Calculations based on reasonable estimates for ΔA, γ_o and K_1, covering the x_2 range used in the complexation studies, reveal that the magnitude of the sum of the free energy contribution of the terms in square brackets can approach the free energy change for complexation of Methyl Orange

with alpha cyclodextrin in water. Reasonable estimates of the g terms range from 1/3 to 3/2. This analysis suggests that for systems in which g_2 and g_1 are substanstially different the error associated with treating g as a composition independent term can be significant.

We have seen that there are some theoretical difficulties associated with the derivation of the solvent effect model used to describe complexation. Nevertheless, it successfully describes the experimental data. We therefore will continue to use this model while recognising that the value of the parameters generated from this analysis are contaminated by the approximations originally used in the derivation of the model equation. Figures 3.10 and 3.11 are representative plots of the contributions of the solvation effect and general medium effect to the total solvent effect for the methanol and acetone cosolvent systems. The figures clearly indicate that both effects are needed to describe solvent effects on complexation.

We have discussed the model parameters and speculated on their significance. The discussion indicates that

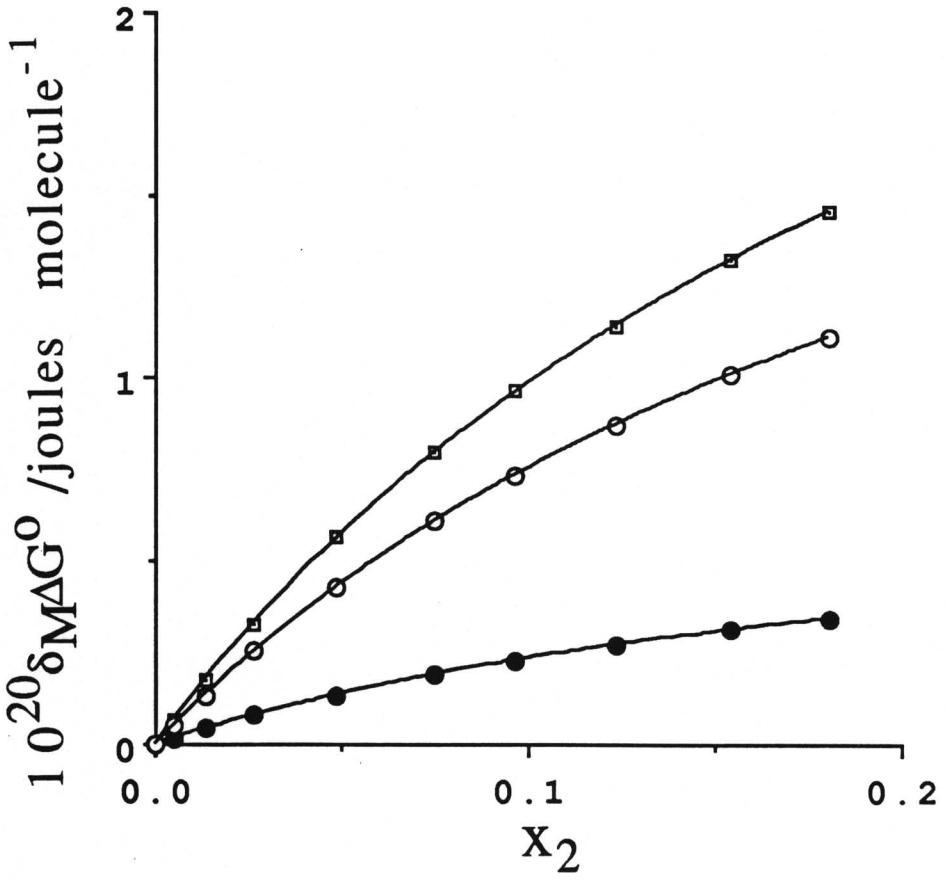


Figure 3.9. Plot of the methanol system showing the total relative solvent effect (squares), the general medium effect contribution (open circles), and the solvation effect contribution (filled circles). The points serve only to clarify the several curves.

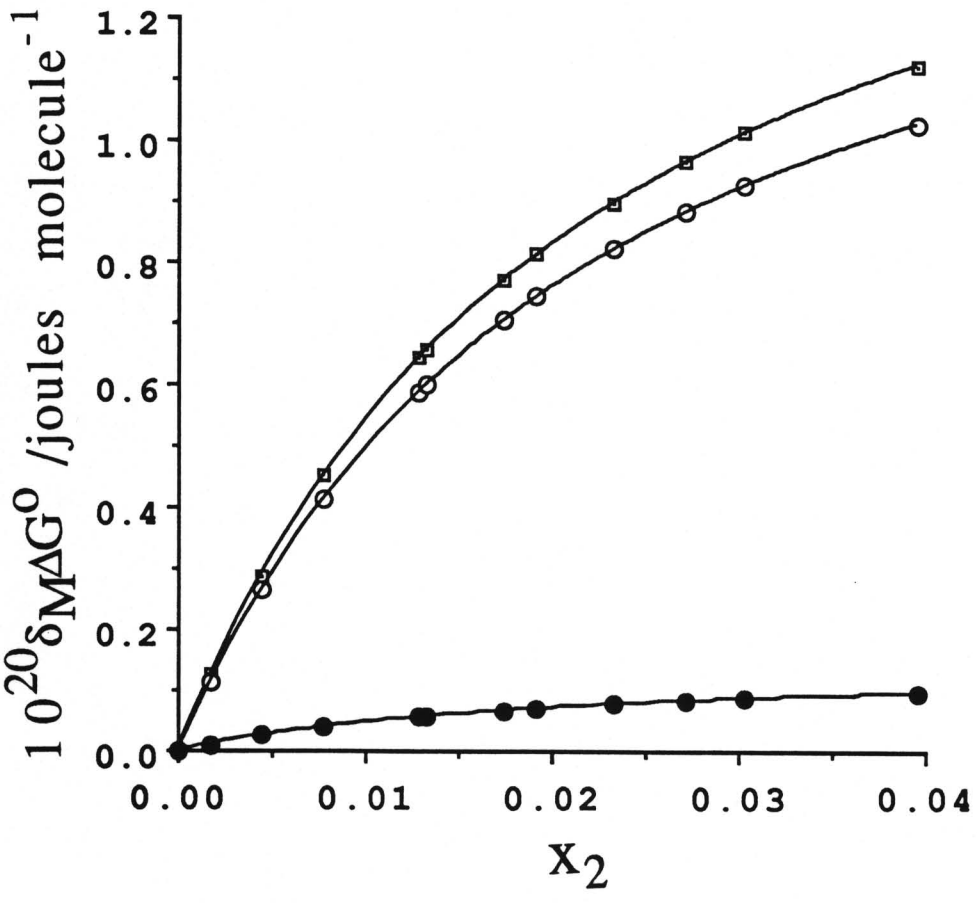


Figure 3.9. Plot of the acetone system showing the total relative solvent effect (squares), the general medium effect contribution (open circles), and the solvation effect contribution (filled circles). The points serve only to clarify the several curves.

additional studies are needed to come to any firm conclusions on the significance of the model parameters. Removal of the Cancellation Approximation requires individual solvation exchange constants for the substrate and ligand. We should be able to obtain these solvation exchange constants through solubility studies. Solubility studies will also permit further investigation of the effect of different cosolvents on g and will provide a better estimate of the expected variation of the $g\Delta A$ value from cosolvent to cosolvent.

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IV. α-CYCLODEXTRIN - 4-NITROANILINE COMPLEXATION

A. RESULTS

This chapter describes a solvent study on the stability of the 1:1 α-cyclodextrin - 4-nitroaniline complex at 25°C in 0.01 M pH 10 carbonate buffer. Tables 4.1 to 4.8 present data for α-cyclodextrin - 4-nitroaniline complexation in the various cosolvent systems. The tables are of the same format used in the methyl orange complexation studies. The cosolvents used in these complexation studies were identical to those in the Methyl Orange studies with one exception: the cosolvent dioxane was replaced by ethanol because it was observed that introduction of dioxane into an aqueous solution of 4-nitroaniline banished the solution's distinctive yellow colour, indicating the operation of some not - understood (and irrelevant) chemistry. More detailed tables giving the substrate concentration, ligand concentrations and associated absorbance values for each table entry are presented in Appendix B of this thesis. There was more scatter of the experimental data in these profiles than was found in the methyl orange complexation studies. Because of this scatter, the free energy of complexation data as a function of x_2 for each cosolvent system were initially plotted out on graph paper. A curve which appeared to best

describe the profile was then drawn. Points taken from the curve were then fit to Equation 1.35 by nonlinear regression. The model parameters for each cosolvent system are presented in Table 4.9. Figures 4.1 to 4.7 show the curve fits to the actual data points.

Table 4.1 Complexation Data for 4-Nitroaniline with

α-Cyclodextrin in

0.01M pH 10 Carbonate Buffer

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0	0.9934(0.002)	55.509	4.73(0.02)	431(39)	4.15(0.04)

Table 4.2 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Methanol System

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02563	0.9853(0.0006)	55.424	5.09(0.03)	197(21)	3.81(0.04)
0.04906	0.9769(0.004)	53.467	4.90(0.02)	126(7)	3.62(0.02)
0.08035	0.9720(0.0001)	52.242	5.42(0.07)	66(7)	3.34(0.04)
0.10406	0.9594(0.003)	51.349	4.76(0.04)	68(5)	3.34(0.03)
0.10699	0.9610(0.003)	51.241	4.87(0.08)	54(7)	3.24(0.05)
0.12355	0.9512(0.002)	50.639	5.41(0.08)	24(2)	2.90(0.03)
0.13074	0.9549(0.0006)	50.381	6.28(0.59)	28(1)	2.97(0.02)

Table 4.3 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the DMSO System

x_2	ρ_o g/ml	M* moles kg^{-1}	$\Delta\varepsilon_{11}$ 10^{-3} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.01110	0.9594(0.003)	51.349	4.76(0.04)	68(5)	3.34(0.03)
0.01215	0.9932(0.007)	53.346	4.71(0.02)	256(28)	3.92(0.05)
0.02497	1.0039(0.001)	51.239	4.09(0.04)	296(57)	3.96(0.08)
0.05399	1.020(0.001)	47.0340	3.75(0.01)	115(4)	3.55(0.01)
0.08955	1.0337(0.0009)	42.693	3.53(0.03)	57(4)	3.22(0.03)
0.13318	1.0402(0.004)	38.428	4.61(0.06)	16(1)	2.66(0.02)

Table 4.4 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Ethylene Glycol System

x_2	ρ_o g/ml	M* moles kg^{-1}	$\Delta\varepsilon_{11}$ 10^{-3} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.02447	1.0020(0.0004)	52.375	4.43(0.01)	256(16)	3.91(0.03)
0.05205	1.0131(0.0005)	49.241	4.26(0.04)	128(17)	3.61(0.05)
0.08303	1.0214(0.001)	46.141	3.90(0.01)	78(3)	3.38(0.01)
0.11969	1.0318(0.001)	42.941	3.18(0.02)	51(3)	3.18(0.02)
0.16461	1.0394(0.0009)	39.578	5.85(0.1)	13(1)	2.58(0.03)

Table 4.5 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Ethanol System

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00449	0.9875(0.005)	55.138	4.63(0.01)	254(15)	3.92(0.02)
0.01183	0.9722(0.003)	54.541	4.61(0.04)	135(19)	3.65(0.06)
0.01952	0.9782(0.0006)	53.929	4.04(0.03)	102(7)	3.54(0.03)
0.02760	0.9766(0.005)	53.300	4.29(0.03)	66(4)	3.35(0.03)
0.04172	0.9753(0.0003)	52.237	2.98(0.02)	52(3)	3.24(0.02)
0.05284	0.9661(0.01)	51.429	3.32(0.03)	31(1)	3.02(0.02)
0.05988	0.9713(0.0004)	50.931	3.07(0.01)	24.4(0.5)	2.92(0.01)

Table 4.6 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Isopropanol System

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00304	0.9848(0.0008)	55.118	4.43(0.03)	355(15)	4.06(0.06)
0.00618	0.9894(0.0008)	54.720	4.88(0.02)	154(12)	3.72(0.03)
0.00902	0.9848(0.0008)	54.364	4.35(0.02)	151(9)	3.70(0.02)
0.01230	0.9931(0.0007)	53.959	5.48(0.03)	77(3)	3.43(0.02)
0.01525	0.9749(0.0008)	53.600	4.64(0.07)	79(11)	3.43(0.06)
0.01874	0.9823(0.0003)	53.181	5.55(0.07)	61(6)	3.32(0.04)
0.02483	0.9817(0.0004)	52.465	3.49(0.05)	63(7)	3.33(0.05)
0.03087	0.9674(0.0008)	51.776	3.46(0.08)	42(6)	3.15(0.06)

Table 4.7 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Acetonitrile System

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00445	0.9931(0.0004)	55.195	4.74(0.03)	228(30)	3.88(0.05)
0.01143	0.9936(0.002)	55.020	4.53(0.02)	140(9)	3.68(0.03)
0.01779	0.9822(0.009)	54.275	4.55(0.01)	73(2)	3.40(0.01)
0.02679	0.9855(0.0005)	53.671	4.40(0.04)	44(3)	3.19(0.02)
0.03595	0.9849(0.005)	53.070	4.40(0.04)	44(3)	3.19(0.02)
0.05580	0.9784(0.001)	53.198	3.25(0.06)	30(3)	3.03(0.05)

Table 4.8 Complexation Data for 4-Nitroaniline with α-Cyclodextrin in the Acetone System

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00306	0.9911(0.0007)	55.134	4.43(0.01)	360(28)	4.07(0.03)
0.00547	0.9925(0.002)	54.842	4.38(0.01)	270(15)	3.95(0.02)
0.01197	0.9843(0.0006)	54.070	3.90(0.03)	188(28)	3.79(0.06)
0.01958	0.9758(0.001)	53.193	3.81(0.03)	107(9)	3.55(0.04)
0.02363	0.9795(0.002)	52.738	3.92(0.02)	75(3)	3.40(0.02)
0.03318	0.9779(0.0008)	51.695	3.77(0.04)	43(3)	3.16(0.03)
0.03853	0.9765(0.0005)	51.128	3.49(0.04)	38(3)	3.10(0.03)

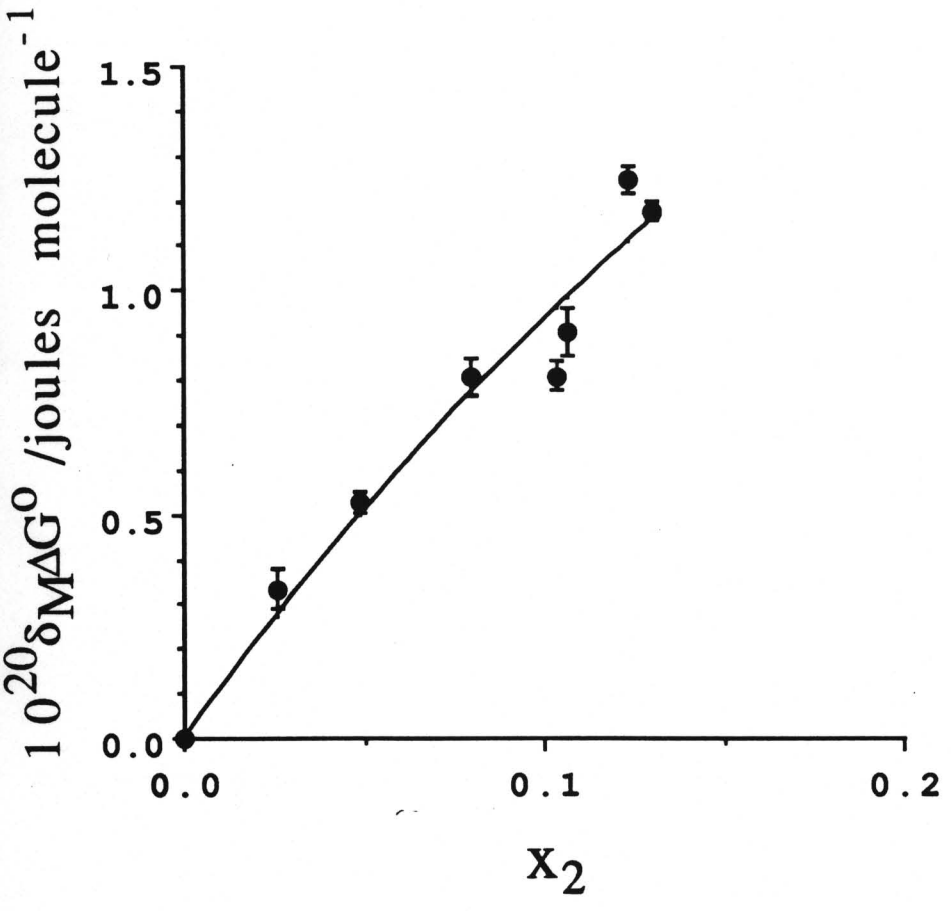

Figure 4.1. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the methanol system showing the experimental data points and the fitted curve.

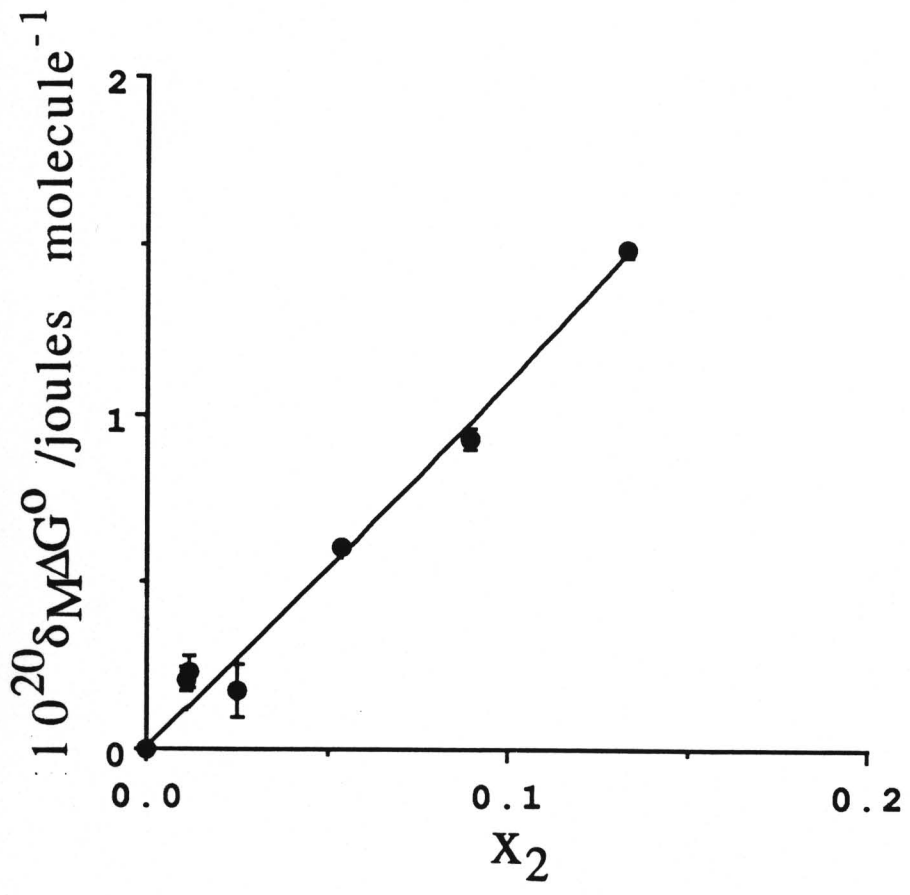

Figure 4.2. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the DMSO system showing the experimental data points and the fitted curve.

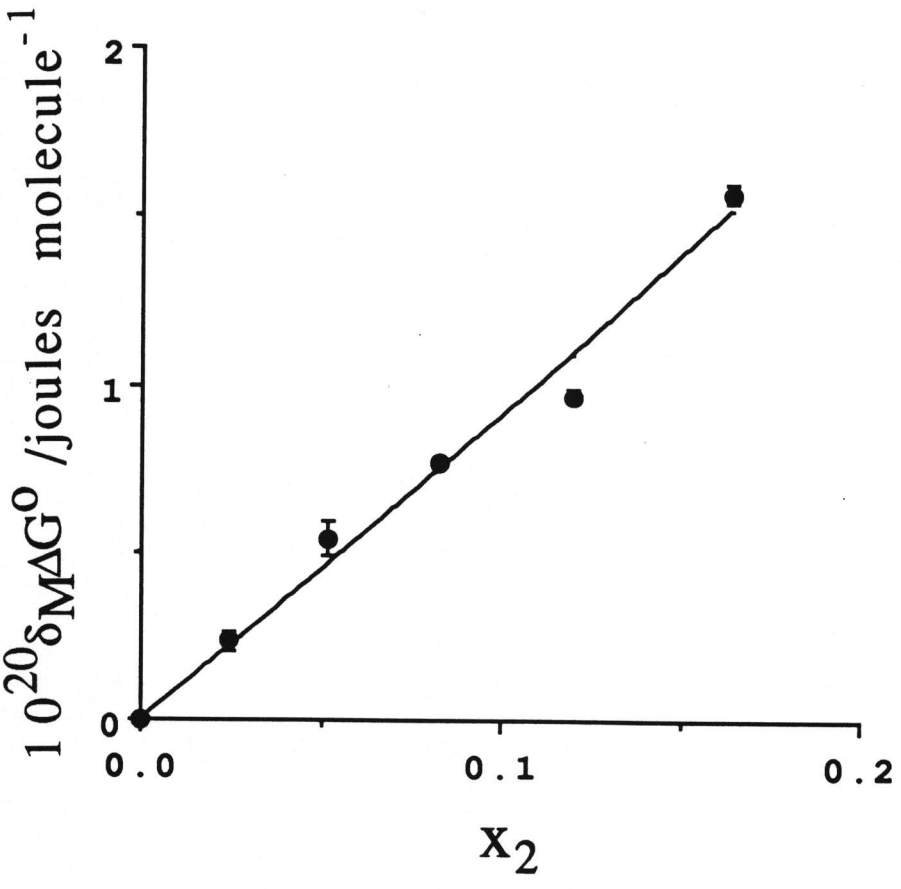

Figure 4.3. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the ethylene glycol system showing the experimental data points and the fitted curve.

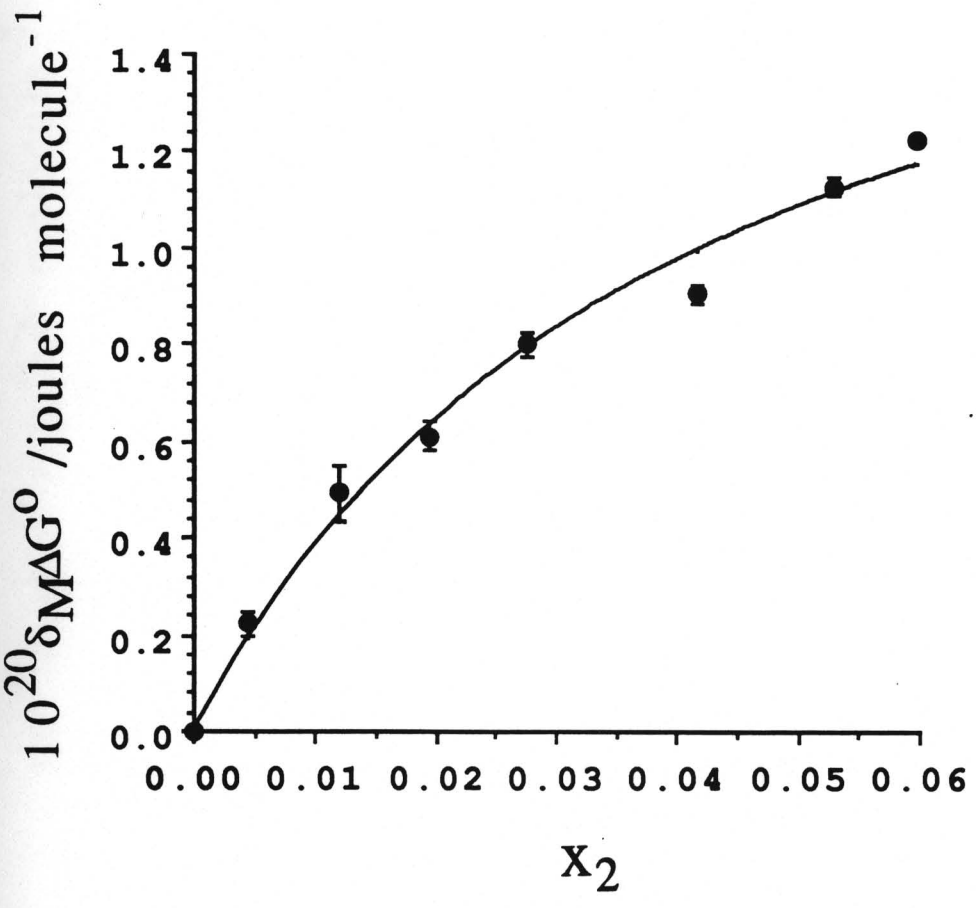

Figure 4.4. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the ethanol system showing the experimental data points and the fitted curve.

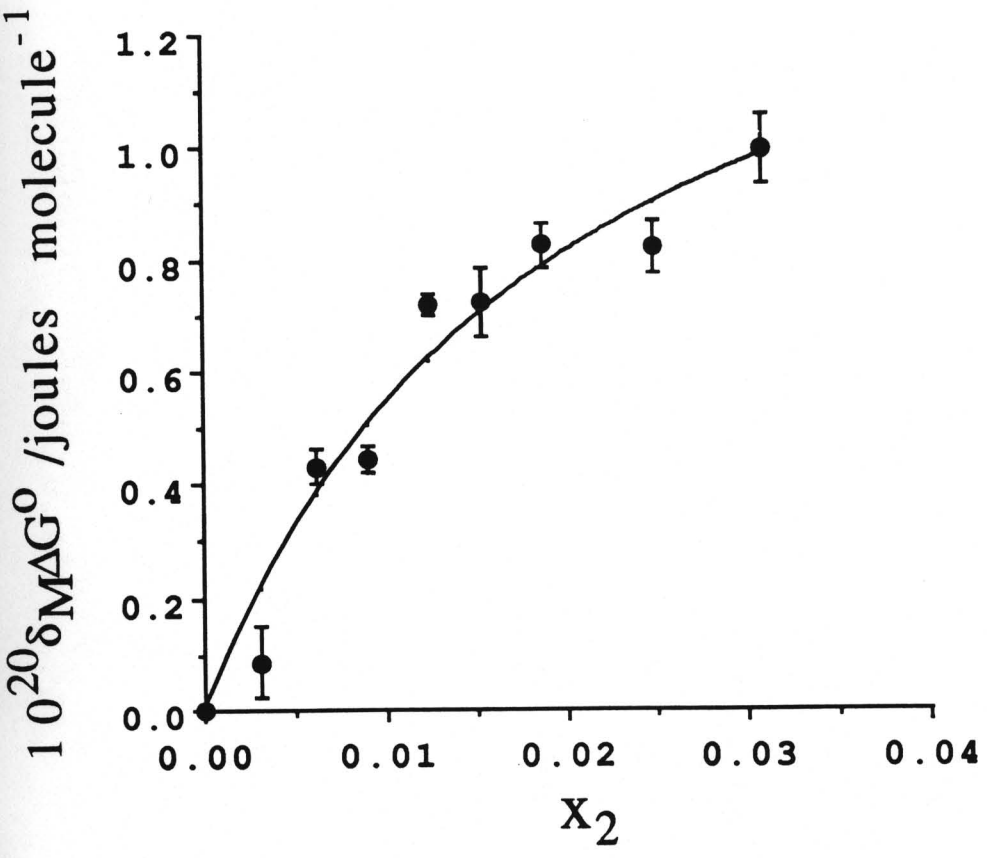

Figure 4.5. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the isopropanol system showing the experimental data points and the fitted curve.

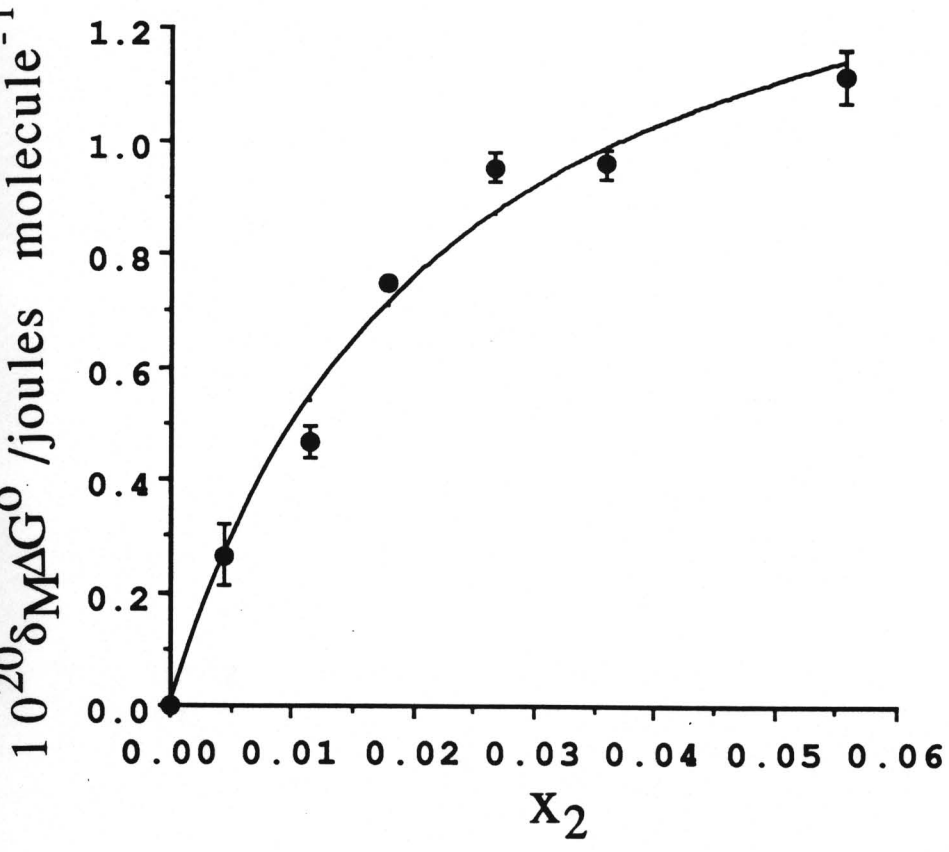

Figure 4.6. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the acetonitrile system showing the experimental data points and the fitted curve.

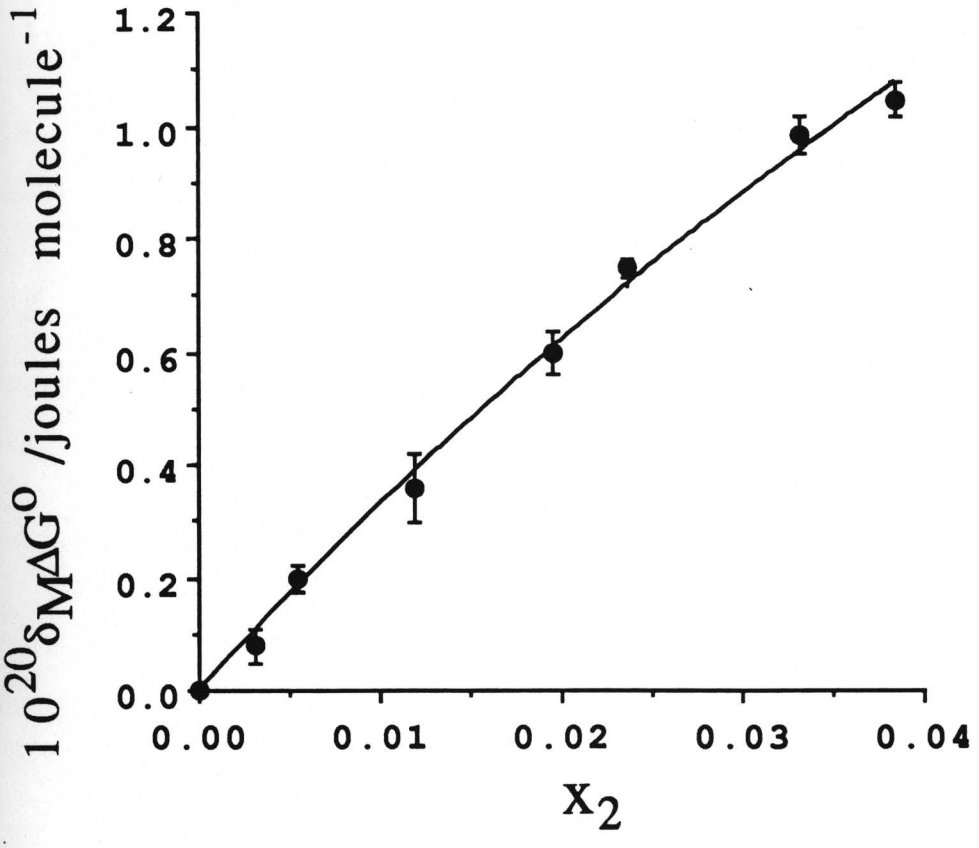

Figure 4.7. Solvent effect on the stability of the α-cyclodextrin-4-nitroaniline complex in the acetone system showing the experimental data points and the fitted curve.

Table 4.9. Parameter Estmates for the 4-Nitroaniline/ α - Cyclodextrin Cosolvent Systems Obtained by Fitting the Complexation Data to Equation 1.35.

COSOLVENT SYSTEM	K_1	$-g\Delta A$ /$A^{o2}molecule^{-1}$	curve fit criterion[a]/%
methanol	2.907(0.006)	67.0(0.1)	12
DMSO	0.508(0.003)	706(4)	14
ethylene glycol	0.74(0.02)	499(16)	10
ethanol	25.4(0.3)	11.2(0.3)	8
isopropanol	52.3(0.7)	0.2(0.3)	13
acetonitrile	46.578(0)	0.664(0)	8
acetone	7.554(0)	77.298(0)	5

[a] Curve fit criterion = 100(standard deviation of points about the fitted line divided by the mean of the ordinate values).

B. DISCUSSION

1. Introduction to α-Cyclodextrin - 4-Nitroaniline Complexation

In contrast to Methyl Orange, 4-nitroaniline is a neutral molecule. It is also an extremely weak base, the pKa of its conjugate acid is 1.00 (1). Therefore we would not expect any protonation of the amine group of 4-nitroaniline from x_2=0 to x_2=1 in our cosolvent systems. Previous work in our laboratory has indicated that 4-nitroaniline undergoes one to one complexation with α-cyclodextrin (2). An analysis by Connors and Pendergast (3) of binding constant data for a series of 4-substituted amines suggests that the nitro group enters the cyclodextrin cavity. The ability of the nitro group to be included into the cyclodextrin interior has been proven by NMR studies on the α-cyclodextrin-*p*-nitrophenolate ion complex (4,5). Therefore we conclude that α-cyclodextrin - 4-nitroaniline complexation involves the formation of a one - to - one complex formed by the inclusion of the nitro group into the cyclodextrin cavity.

Carbonate buffers have often been used in cyclodextrin complexation studies and there have been no reports of interactions between the anions of the buffer and

cyclodextrins. Therefore we would not anticipate any ionic effects upon complexation in our studies.

2. Analysis of K_1 and $g\Delta A$

In Chapter 3 we discussed the limitations associated with analyses based solely on complexation results. Therefore our discussion of the α-cyclodextrin - 4-nitroaniline complexation results will be brief. A more extensive analysis of this system will be given in Chapter 7, where we will incorporate the results from the solubility studies.

Figures 4.1-4.7 show that the model successfully describes the complexation data for each cosolvent system. The profiles of the DMSO and ethylene glycol cosolvent systems are unique in that they appear to be linear. The magnitude of the K_1 values, presented in Table 4.9, for each cosolvent system is also chemically reasonable and divides the cosolvent systems into categories which are identical to those found in the Methyl Orange complexation studies. The $g\Delta A$ values for the methanol and acetone cosolvent systems are physically reasonable, the value for the methanol system being somewhat larger than that obtained for the Methyl Orange complexation study, which

was - 43 $Å^2$ $molecule^{-1}$. For the other cosolvent systems, we observe the same inverse association between the magnitudes of the $g\Delta A$ and K_1 values found for some of the cosolvent systems in the Methyl Orange complexation work. This is particularly apparent in the DMSO and ethylene glycol cosolvent systems. The K_1 values for these systems are significantly smaller than those reported for the naphthalene solubility studies, which ranged from 2.3 to 4.8. These cosolvent systems also possess $g\Delta A$ terms which are four to seven times larger than the estimated hydrophobic surface area of the cyclodextrin interior. This suggests that these values may simply be curve fitting artefacts. A similar case can be made for the ethanol, isopropanol, and acetonitrile cosolvent systems, whose large K_1 values are offset by unusually small $g\Delta A$ terms.

Once again we can investigate the effect that a physically reasonable value of $g\Delta A$ has on the K_1 term by reanalysing the ethylene gylcol and acetonitrile cosolvent systems using a modified form of Equation 1.35 in which the $g\Delta A$ term is fixed. The $g\Delta A$ values used in this analysis were obtained from Table 3.9 and were calculated from the g values taken from the naphthalene solubility work (6) and the estimated hydrophobic surface area of the interior of the cyclodextrin cavity. This analysis yielded a K_1 of 5.8(0.3) for the ethylene glycol system, which compared

favourably with the K_1 obtained for the Methyl Orange complexation study, which was 7.7(1.8). A K_1 of 14.7(0.7) was obtained for the acetonitrile system, which approached the K_1 value of 21.6(0.6) obtained for a similar analysis of the acetonitrile cosolvent system using Methyl Orange complexation data. These analyses suggest that the inverse association between K_1 and $g\Delta A$ may simply be a curve - fitting artefact.

A plot of log K_1 against log P of the pure cosolvents is presented in Figure 4.8. This profile does not appear to exhibit the same sharp discontinuity associated with the Methyl Orange complexation system and raises questions about our postulate that K_1 is an indication of the polarity of the cyclodextrin interior. However, the difference in the profile shapes in Figures 3.8 and 4.8 may simply be due to the unusually low K_1 values obtained for the DMSO and ethylene glycol cosolvent systems. We have suggested that these low values arise from the curve fitting procedure, which inappropriately decreases the magnitude of K_1 and inflates $g\Delta A$. Replacing the K_1 values for these cosolvent systems with a K_1 of 5.8, which was the

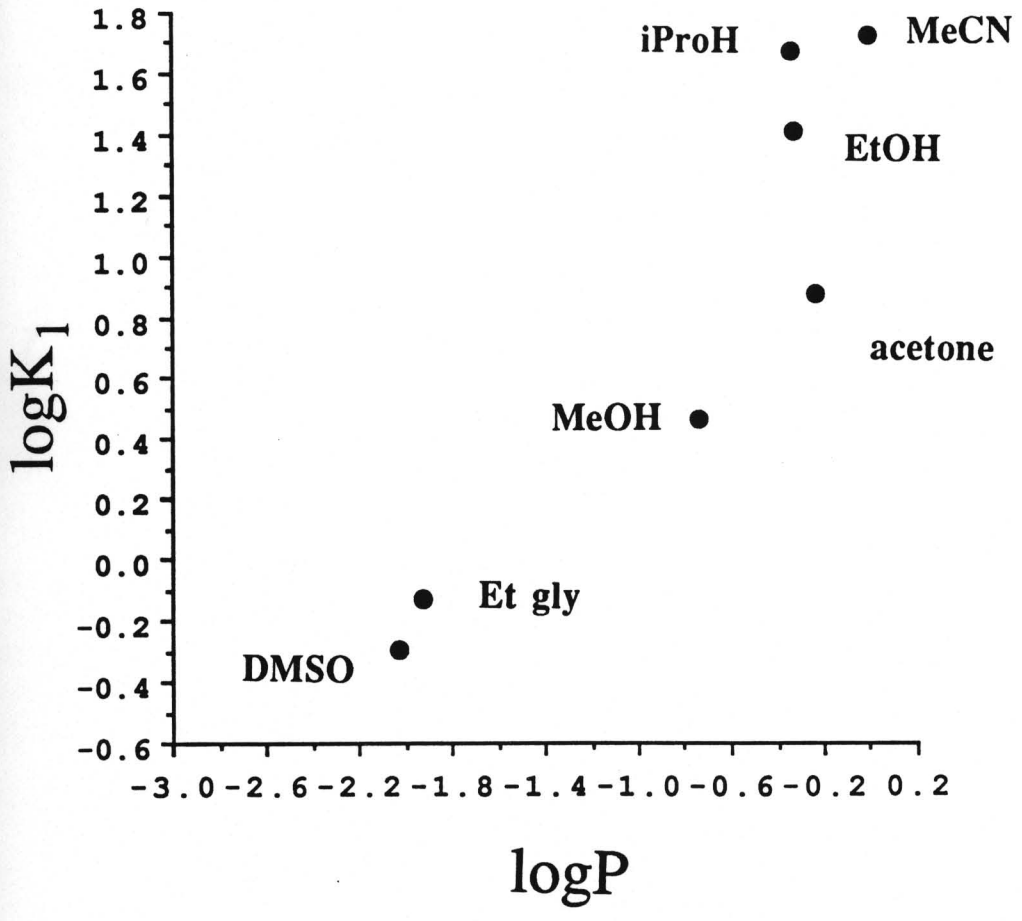

Figure 4.8. Plot of log K_1 against log P where P is the octanol/water partition coefficient in the pure cosolvent.

value obtained from our analysis in which the term was fixed at a physically reasonable value, would yield a profile that is similar to that obtained for the Methyl Orange complexation studies.

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V. 4-NITROANILINE SOLUBILITY

A. RESULTS

This chapter describes a solvent study on the solubility of 4-nitroaniline at 25°C. Tables 5.1 to 5.8 present data for 4-nitroaniline solubility, and some related information, for the various cosolvent systems as well as the fully aqueous system. The model parameters for each cosolvent system, determined by fitting the experimental data to Equation 1.22, are presented in Table 5.9. Figures 5.1 to 5.7 show the curve fits to Equation 1.22 and indicate that the solubility model effectively describes the experimental data.

Table 5.1. Solubility Data for 4-Nitroaniline

in

Water

x_2	$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
0	0.985(0.009)	0.0038(0.0005)	3.94(0.05)

Table 5.2. Solubility Data for 4-Nitroaniline

in the

Methanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.01149	1960.21	40.51	0.9767(0.004)	0.0043(0.0005)	3.881(0.049)
0.01986	1932.34	69.65	0.9639(0.002)	0.0069(0.0005)	3.683(0.03)
0.04549	1840.52	156.01	0.9737(0.001)	0.00603(0.00053)	3.733(0.036)
0.08952	840.68	147	0.9632(0.004)	0.00696(0.00002)	3.656(0.002)
0.1317	758.91	204.72	0.959(0.003)	0.0095(0.00002)	3.511(0.001)
0.176	680.85	258.64	0.9468(0.002)	0.0135(0.0001)	3.349(0.002)
0.23649	601.78	331.51	0.9168(0.003)	0.0307(0.0014)	2.981(0.018)
0.30716	527.85	416.19	0.9151(0.002)	0.0455(0.0005)	2.799(0.005)

Table 5.2 continued. Solubility Data for 4-Nitroaniline in the Methanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.38217	441.78	486.02	0.8952(0.004)	0.0823(0.0004)	2.525(0.002)
0.52271	294.68	573.97	0.8661(0.008)	0.1843(0.001)	2.140(0.004)
0.58882	241.83	615.91	0.8651(0.003)	0.1702(0.0009)	2.159(0.002)
0.64676	199.69	650.27	0.8546(0.002)	0.2051(0.0015)	2.062(0.003)
0.78534	110.74	720.57	0.8224(0.002)	0.3436(0.004)	1.797(0.005)
0.8965	50.25	774.08	0.8181(0.002)	0.3629(0.002)	1.750(0.002)
1	-	-	0.8082(0.003)	0.5554(0.003)	1.540(0.003)

Table 5.3. Solubility Data for 4-Nitroaniline

in the

DMSO System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.0048	489.99	10.31	0.969(0.01)	0.00497(0.0001)	3.818(0.008)
0.0096	479.91	20.13	0.990(0.008)	0.0056(0.0001)	3.768(0.007)
0.0202	459.66	41.14	0.984(0.013)	0.0070(0.0002)	3.661(0.012)
0.0422	839.38	160.28	0.998(0.009)	0.0103(0.0003)	3.480(0.013)
0.0675	761.38	239.05	1.004(0.012)	0.0155(0.0005)	3.287(0.014)
0.0972	681.71	318.39	1.027(0.006)	0.0248(0.0004)	3.071(0.006)
0.1345	599.88	10.31	1.041(0.005)	0.0436(0.0005)	2.806(0.005)
0.1758	489.99	404.41	1.053(0.005)	0.0864(0.0013)	2.490(0.007)

Table 5.3 continued. Solubility Data for 4-Nitroaniline in the DMSO System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.2257	441.9	558.85	1.067(0.004)	0.203(0.002)	2.097(0.004)
0.2863	365.76	636.32	1.081(0.002)	0.577(0.007)	1.613(0.005)
0.37	281.79	717.97	1.099(0.006)	1.40(0.02)	1.170(0.006)
0.4785	200.99	799.79	1.128(0.002)	2.48(0.03)	0.843(0.005)
0.6237	122.32	879.23	1.1493(0.0005)	3.39(0.01)	0.630(0.002)
0.8034	53.63	950.53	1.164(0.006)	4.13(0.03)	0.474(0.004)
1	-	-	1.153(0.012)	3.83(0.09)	0.464(0.013)

Table 5.4. Solubility Data for 4-Nitroaniline

in the

Ethylene Glycol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.00601	490.32	10.22	0.995(0.001)	0.0046(0.0001)	3.861(0.009)
0.01149	490.45	19.65	0.99(0.01)	0.0048(0.0001)	3.840(0.011)
0.02419	921.13	78.66	0.999(0.004)	0.00517(0.00005)	3.798(0.004)
0.05146	842.72	157.52	1.006(0.008)	0.00611(0.00003)	3.706(0.003)
0.08288	762.89	237.53	1.013(0.009)	0.0074(0.0002)	3.600(0.013)
0.11759	685.56	314.76	1.02(0.01)	0.0095(0.0001)	3.475(0.007)
0.16170	600.80	399.30	1.038(0.003)	0.0131(0.0001)	3.316(0.004)
0.21069	521.16	479.32	1.047(0.002)	0.0183(0.0003)	3.149(0.006)

Table 5.4 continued. Solubility Data for 4-Nitroaniline

in the

Ethylene Glycol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.26816	442.2	558.27	1.054(0.003)	0.0262(0.0001)	2.966(0.002)
0.34014	361.82	642.62	1.060(0.002)	0.0401(0.0004)	2.751(0.005)
0.42637	281.05	719.77	1.09(0.05)	0.0598(0.0007)	2.553(0.014)
0.54546	194.82	805.51	1.076(0.004)	0.096(0.002)	2.298(0.009)
0.67746	121.44	878.82	1.080(0.003)	0.138(0.005)	2.092(0.014)
0.87251	40.80	962.04	1.092(0.009)	0.2234(0.01)	1.830(0.018)
1	-	-	1.091(0.009)	0.308(0.021)	1.656(0.028)

Table 5.5. Solubility Data for 4-Nitroaniline

in the

Ethanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.00808	488.98	10.19	0.990(0.004)	0.00473(0.00003)	0.337(0.003)
0.01582	1921.61	78.99	0.983(0.007)	0.00497(0.00009)	3.820(0.008)
0.03263	1840.81	158.79	0.975(0.003)	0.00571(0.00007)	3.749(0.005)
0.06207	1680.67	284.45	0.962(0.003)	0.00850(0.00008)	3.563(0.004)
0.08856	763.36	189.67	0.958(0.002)	0.01099(0.0001)	3.440(0.004)
0.16327	632.16	315.46	0.931(0.002)	0.0424(0.0003)	2.830(0.003)
0.22220	528.04	385.76	0.916(0.004)	0.0736(0.0008)	2.566(0.005)
0.25835	475.95	423.99	0.904(0.004)	0.0978(0.009)	2.425(0.036)

Table 5.5 continued. Solubility Data for 4-Nitroaniline in the Ethanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ g/ml	Concentration M	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
	water	organic			
0.33771	380.29	495.89	0.886(0.001)	0.1655(0.0015)	2.162(0.004)
0.39629	329.78	553.59	0.877(0.003)	0.189(0.002)	2.077(0.004)
0.51515	233.92	635.58	0.855(0.002)	0.253(0.002)	1.900(0.003)
0.61682	163.99	675.09	0.836(0.003)	0.290(0.003)	1.798(0.005)
0.74072	99.53	727.16	0.820(0.002)	0.316(0.0025)	1.714(0.003)
0.90338	32.81	784.46	0.798(0.004)	0.336(0.003)	1.632(0.004)
1	-	-	0.792(0.001)	0.337(0.002)	1.603(0.002)

Table 5.6. Solubility Data for 4-Nitroaniline

in the

Isopropanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.00572	490.6	9.42	0.9872(0.002)	0.00471(0.00002)	3.849(0.002)
0.01275	480.11	20.68	0.975(0.023)	0.0051(0.00006)	3.804(0.011)
0.02523	460.28	39.75	0.979(0.001)	0.00593(0.00006)	3.733(0.004)
0.04986	422.1	73.89	0.9668(0.004)	0.00943(0.00007)	3.515(0.003)
0.09218	710.62	240.72	0.9503(0.002)	0.0268(0.00011)	3.042(0.002)
0.10984	667.51	274.78	0.9428(0.004)	0.0411(0.0003)	2.848(0.003)
0.18261	516.42	384.89	0.9127(0.002)	0.1020(0.0011)	2.404(0.005)
0.21135	480.63	429.71	0.9033(0.003)	0.1230(0.0016)	2.303(0.005)
0.23761	436.64	454	0.8955(0.001)	0.1429(0.002)	2.220(0.006)
0.36177	300.09	567.47	0.8657(0.004)	0.2105(0.002)	1.973(0.004)

Table 5.6 continued. Solubility Data for 4-Nitroaniline

in the

Isopropanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.4714	208.97	621.72	0.8477(0.003)	0.2448(0.0014)	1.847(0.002)
0.57659	150.28	682.73	0.8159(0.004)	0.2635(0.002)	1.755(0.003)
0.57844	150.15	687.33	0.8306(0.003)	0.2622(0.001)	1.764(0.002)
0.69281	86.8	653.08	0.7935(0.004)	0.2321(0.0049)	1.753(0.009)
0.71855	86.82	739.46	0.8133(0.003)	0.2504(0.0008)	1.722(0.002)
0.84595	42.1	771.28	0.7907(0.003)	0.2257(0.0017)	1.711(0.003)
0.85525	39.07	770.1	0.7985(0.002)	0.2221(0.0019)	1.719(0.004)
1	-	-	0.7873(0.003)	0.1909(0.0024)	1.733(0.006)
1	-	-	0.7773(0.002)	0.1934(0.0032)	1.722(0.007)

Table 5.7. Solubility Data for 4-Nitroaniline

in the

Acetonitrile System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.0077	489.52	8.66	0.9878(0.007)	0.00496(0.0002)	3.83(0.018)
0.01753	959.82	39.02	0.9752(0.005)	0.00864(0.0001)	3.59(0.004)
0.03595	892.31	75.83	0.9755(0.002)	0.00852(0.0001)	3.587(0.006)
0.06032	842.5	123.24	0.9623(0.004)	0.02202(0.0011)	3.177(0.021)
0.10449	761.67	202.52	0.9464(0.001)	0.06483(0.0011)	2.703(0.007)
0.17016	643.6	300.72	0.9133(0.002)	0.23397(0.0239)	2.121(0.042)
0.18939	601.35	320.14	0.9178(0.002)	0.20485(0.0009)	2.171(0.002)
0.28721	484.42	444.77	0.8962(0.002)	0.45869(0.0062)	1.776(0.006)

Table 5.7 continued. Solubility Data for 4-Nitroaniline in the Acetonitrile System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.33638	418.96	483.9	0.8861(0.002)	0.57361(0.0057)	1.654(0.004)
0.43065	320.13	551.75	0.8746(0.002)	0.99426(0.0094)	1.365(0.004)
0.5675	213.97	639.76	0.8632(0.003)	1.08089(0.0174)	1.277(0.007)
0.71041	127.11	710.53	0.8622(0.004)	1.16082(0.0102)	1.203(0.004)
0.71783	123.79	717.6	0.8559(0.004)	1.18614(0.0108)	1.187(0.004)
0.86627	52.06	768.44	0.8397(0.01)	1.21769(0.0044)	1.129(0.005)
1	-	-	0.833(0.001)	1.05424(0.0056)	1.164(0.002)

Table 5.8. Solubility Data for 4-Nitroaniline

in the

Acetone System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	Concentration M	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.00628	1960.48	39.92	0.9753(0.002)	0.0110(0.0002)	3.494(0.009)
0.01265	1920.78	79.34	0.9733(0.004)	0.0119(0.0002)	3.454(0.005)
0.0256	1840.57	155.89	0.966(0.004)	0.0172(0.0002)	3.289(0.005)
0.05413	839.85	154.94	0.9703(0.004)	0.0180(0.0004)	3.247(0.01)
0.07365	759.2	194.59	0.9597(0.004)	0.0285(0.0005)	3.038(0.008)
0.12558	639.14	295.93	0.942(0.002)	0.0981(0.0027)	2.479(0.011)
0.15871	581.13	353.46	0.953(0.04)	0.1840(0.0032)	2.197(0.017)
0.21467	487.94	430.01	0.9252(0.002)	0.4361(0.0067)	1.781(0.006)

Table 5.8 continued. Solubility Data for 4-Nitroaniline

in the

Acetone System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.30245	369.1	515.95	0.9156(0.001)	0.9337(0.0023)	1.386(0.001)
0.34006	327.99	544.88	0.9153(0.001)	0.9769(0.0092)	1.345(0.004)
0.45613	234.35	633.64	0.9143(0.002)	1.406(0.024)	1.118(0.007)
0.50103	207.26	670.97	0.9122(0.004)	1.495(0.013)	1.068(0.004)
0.71457	91.62	739.5	0.9067(0.003)	1.947(0.015)	0.857(0.004)
0.83981	45.76	773.45	0.9065(0.003)	2.075(0.011)	0.788(0.003)
1	-	-	0.896(0.003)	2.018(0.016)	0.756(0.004)

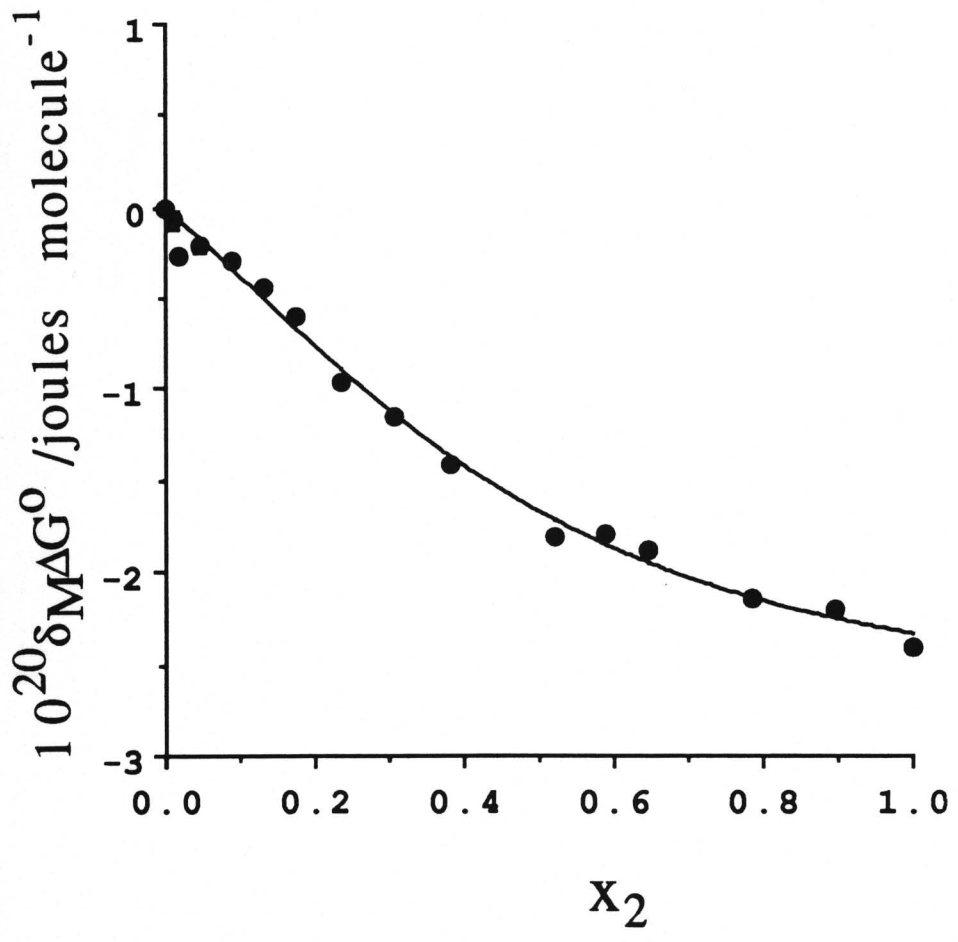

Figure 5.1. Solvent effect on the solubility of 4-nitroaniline in the methanol system showing the experimental data points and the fitted curve.

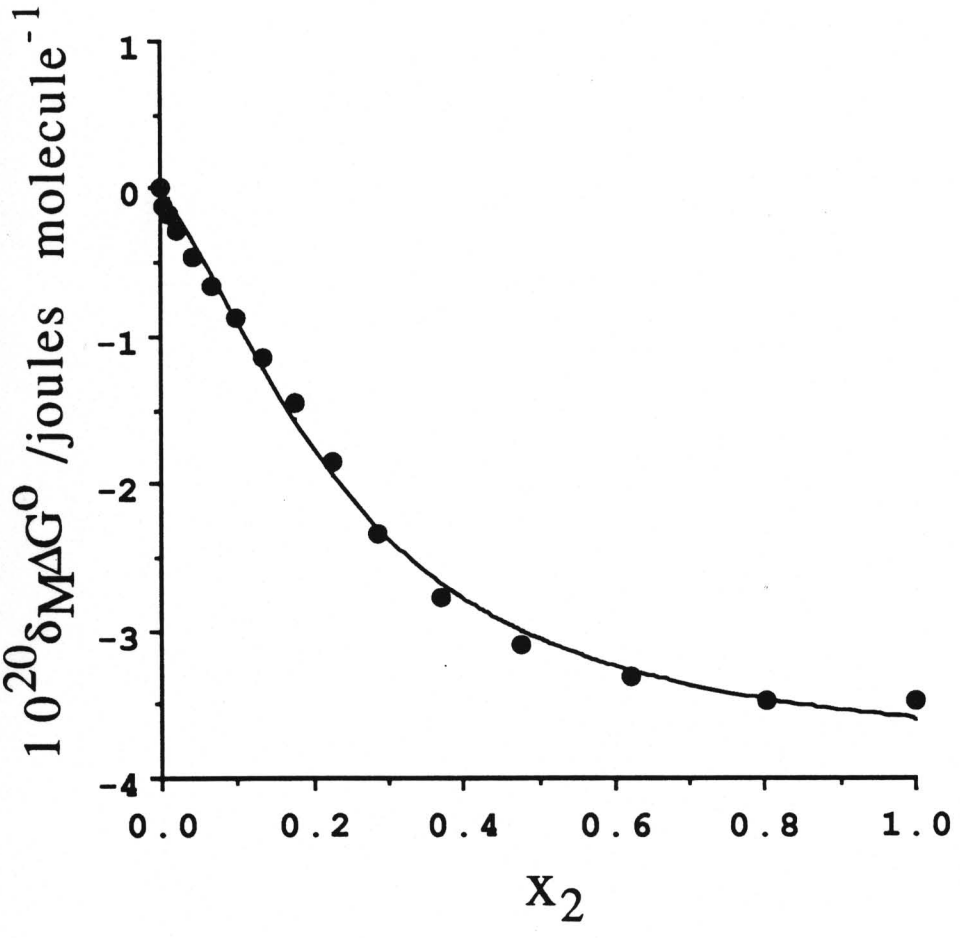

Figure 5.2. Solvent effect on the solubility of 4-nitroaniline in the DMSO system showing the experimental data points and the fitted curve.

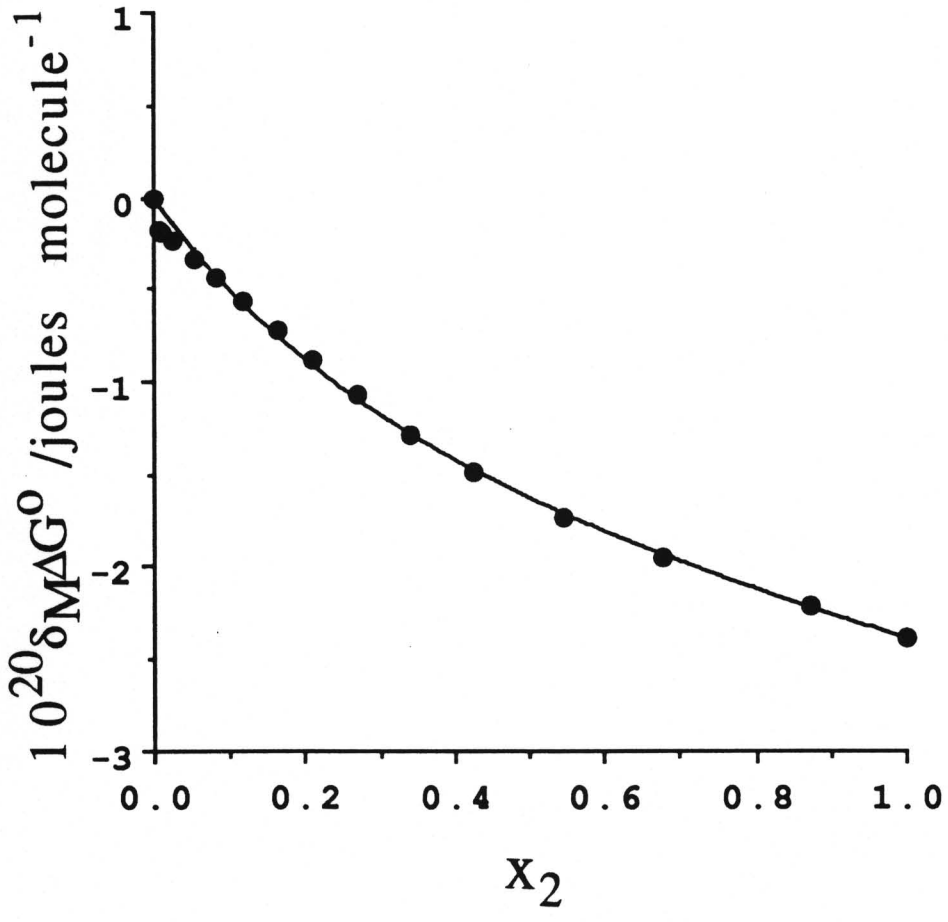

Figure 5.3. Solvent effect on the solubility of 4-nitroaniline in the ethylene glycol system showing the experimental data points and the fitted curve.

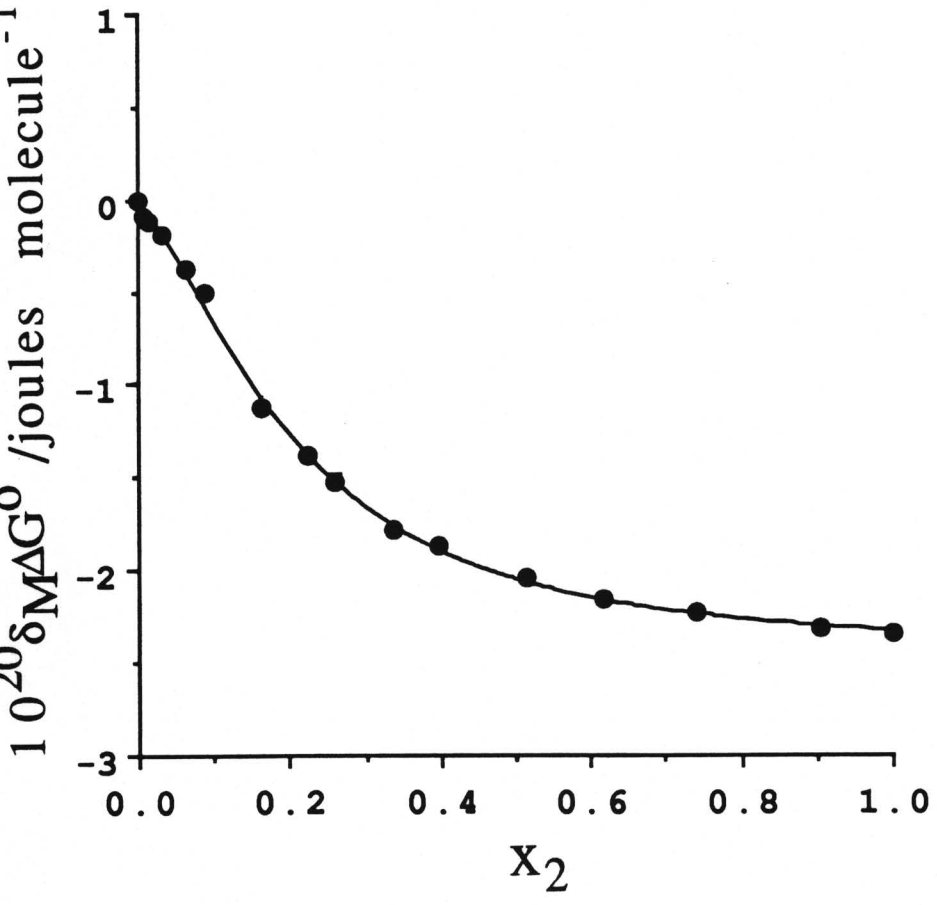

Figure 5.4. Solvent effect on the solubility of 4-nitroaniline in the ethanol system showing the experimental data points and the fitted curve.

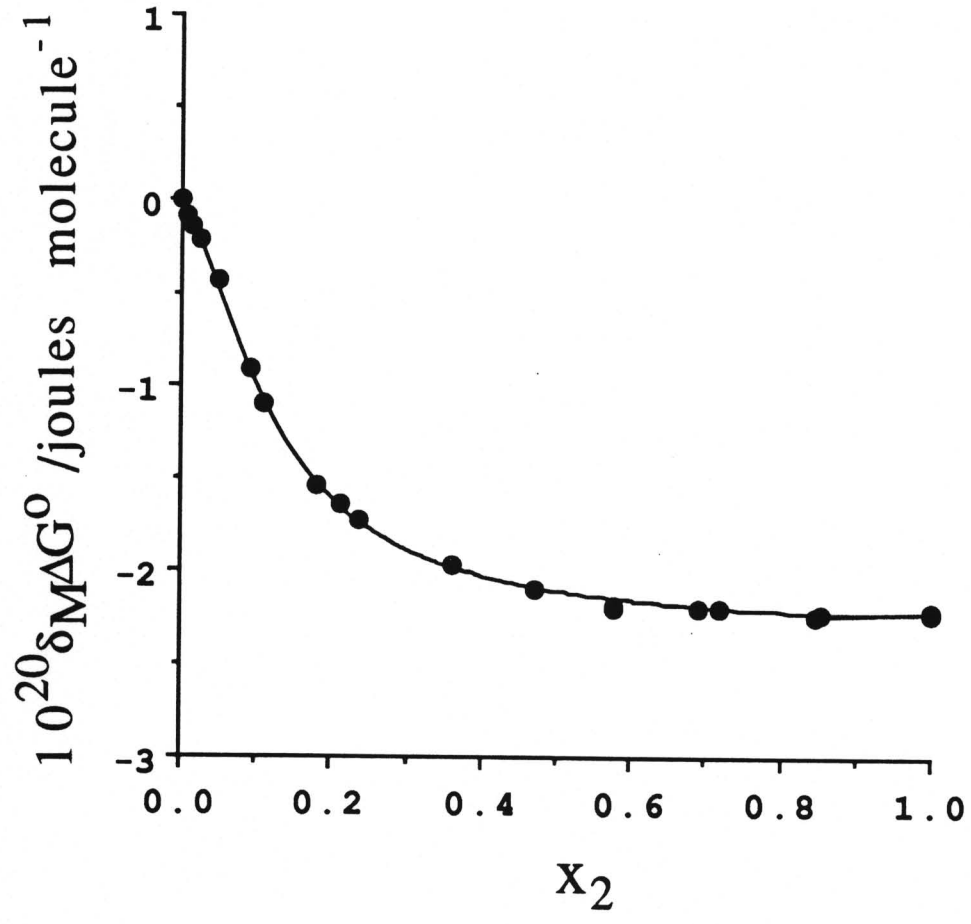

Figure 5.5. Solvent effect on the solubility of 4-nitroaniline in the isopropanol system showing the experimental data points and the fitted curve.

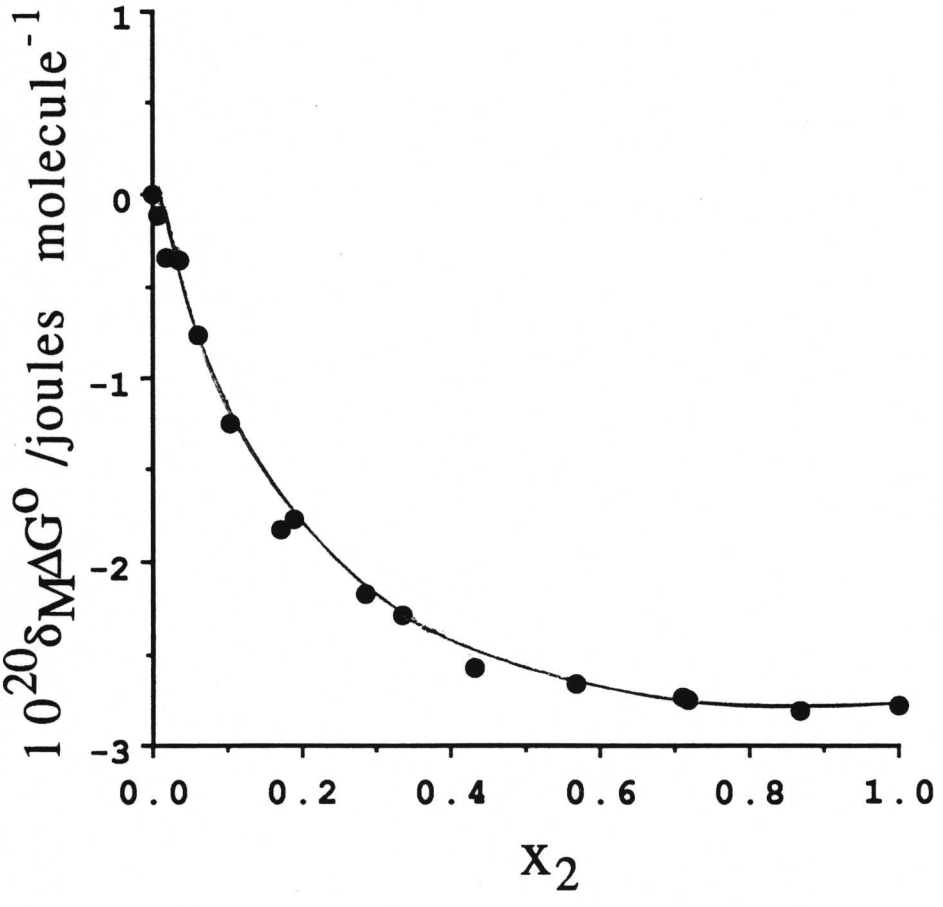

Figure 5.6. Solvent effect on the solubility of 4-nitroaniline in the acetonitrile system showing the experimental data points and the fitted curve.

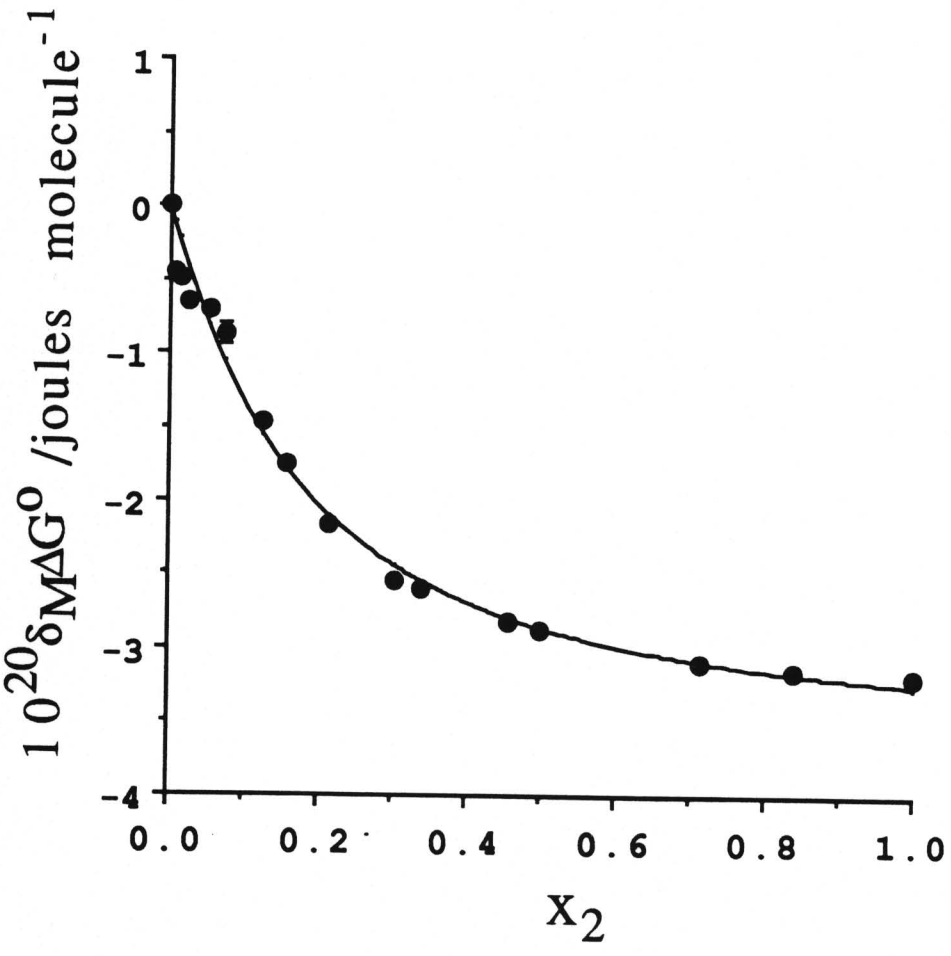

Figure 5.7. Solvent effect on the solubility of 4-nitroaniline in the acetone system showing the experimental data points and the fitted curve.

Table 5.9. Solubility Parameters for 4-Nitroaniline in the Various Cosolvent Systems

Cosolvent	K_1	K_2	$gA/Å^2$ $molecule^{-1}$	curve fit criterion[a]/%
methanol	2.73(0.35)	1.51(0.49)	35.2(3.0)	2
DMSO	3.96(0.53)	3.74(0.76)	85.5(3.6)	1
ethylene glycol	3.87(0.24)	0.65(0.21)	84.0(7.2)	2
isopropanol	5.87(0.51)	10.64(1.16)	10.64(0.5)	0.4
acetonitrile	8.13(0.90)	5.58(1.02)	29.15(1.8)	1
ethanol	4.21(0.34)	5.09(0.62)	21.20(0.86)	1
acetone	9.5(1.8)	3.5(1.3)	36.8(4.0)	2

[a] Curve fit criterion = 100(standard deviation of points about the fitted line divided by the mean of the ordinate values).

B. DISCUSSION

1. Introduction to 4-Nitroaniline Solubility

Tables 5.2 to 5.8 indicate that the solubility of 4-nitroaniline in the organic solvents is fairly high, the concentration ranging from 0.19 M in isopropanol to 3.83 M in DMSO. In the development of our model equation we postulated that any effects arising from solute-solute interactions in solution were negligible. However, this postulate assumed that only dilute saturated solutions of the solute were formed in the cosolvent mixtures. This assumption is not valid for the 4-nitroaniline systems, which formed rather concentrated saturated solutions of the solute in the binary aqueous organic mixtures. Nevertheless, the high solubility concentrations from these studies do not appear to significantly affect the model parameter values. It will be shown in Tables 5.9, 5.10, and 5.11 that for the methanol cosolvent system the model parameters obtained for the 4-nitroaniline solubility study, which possesses a maximum concentration of 0.56 M at $x_2=1$, are similar to those obtained for biphenyl. The solubility concentrations for the biphenyl system remained dilute over the entire cosolvent range, varying from 3.9×10^{-5} M at $x_2=0$ to 0.042 M at $x_2=1$.

2. Analysis of K_1 and $g\Delta A$

Table 5.9 indicates that the exchange constant values are chemically reasonable and Table 5.10 shows that these values are similar to those obtained from previous solubility studies (1,2). Table 5.9 also indicates that there is some variation in the gA term from cosolvent to cosolvent. However, it does not approach the large fluctuations associated with the $g\Delta A$ term in the complexation studies and supports our hypothesis that the model parameter values for complexation are affected by the curve fitting procedure.

Next we will use the gA values in Table 5.9 to calculate g using both the hydrophobic surface area and the total surface area of the 4-nitroaniline molecule. The estimate used for the total surface area was 147(4)$Å^2$molecule^{-1}. The hydrophobic surface area estimate was 68(4)$Å^2$molecule^{-1}; this was based solely on the surface area contribution of the phenyl ring. The g values obtained from these calculations are presented in Table 5.11 along with values obtained from the napthalene and biphenyl solubility studies. Both napthalene and biphenyl are completely hydrophobic molecules.

Table 5.10. Solvation Exchange Constants for Different Solutes in Various Cosolvent Systems

Solute	Cosolvent System	K_1	K_2
napthalene	methanol	2.28(0.04)	2.00(0.17)
biphenyl	methanol	2.45(0.07)	1.28(0.07)
4-nitroaniline	methanol	2.73(0.35)	1.51(0.49)
napthalene	acetonitrile	4.81(0.14)	5.36(0.6)
4-nitroaniline	acetonitrile	8.13(0.90)	5.6(1.0)
napthalene	ethylene glycol	3.04(0.03)	1.21(0.04)
4-nitroaniline	ethylene glycol	3.87(0.24)	0.65(0.21)

Table 5.11. Curvature Correction Factor Values for Different Solutes in Various Cosolvent Systems Using Hydrophobic and Total Surface Area Solute Estimates

Solute	Cosolvent System	g Calculated Using the Solute Hydrophobic Surface Area	g Calculated Using the Solute Total Surface Area
napthalene	methanol	0.367(0.015)	-
biphenyl	methanol	0.415(0.008)	-
4-nitroaniline	methanol	0.518(0.054)	0.239(0.021)
napthalene	acetonitrile	0.387(0.028)	-
4-nitroaniline	acetonitrile	0.429(0.037)	0.198(0.013)
4-nitroaniline	isopropanol	0.156(0.012)	0.072(0.004)
4-nitroaniline	ethanol	0.312(0.022)	0.144(0.007))
4-nitroaniline	acetone	0.541(0.066)	0.250(0.028)
napthalene	ethylene glycol	0.680(0.015)	-
4-nitroaniline	ethylene glycol	1.235(0.128)	0.571(0.051)
4-nitroaniline	DMSO	1.257(0.091)	0.582(0.029)

We will now make use of our postulate that g is a solute independent - cosolvent dependent term to analyse these g values. The g values based on the hydrophobic surface area and total surface area of 4-nitroaniline are all less than one for the methanol, ethanol, acetonitrile, acetone, and isopropanol cosolvent systems. However, for the methanol system, the g value based on the hydrophobic surface area of 4-nitroaniline is in closer agreement with those obtained for napthalene and biphenyl than the value based on the total surface area of 4-nitroaniline. The same trend is observed on comparison of the g values of 4-nitroaniline with napthalene in the acetonitrile cosolvent system. These results suggest that for the methanol, ethanol, acetonitrile, acetone, and isopropanol cosolvent systems the A term reflects the hydrophobic surface area of the solute. The g value for the DMSO and ethylene glycol cosolvent systems are greater than one when the hydrophobic surface area of 4-nitroaniline is used to calculate the g term, and g values of less than one are obtained for these systems when the total surface area is used. Moreover, comparison of the g values for 4-nitroaniline with that of napthalene in the ethylene glycol system reveals that the g value based on the total surface area of 4-nitroaniline is in better agreement with the napthalene g

value than that based on the hydrophobic surface area. This suggests that there is a hydrophilic component associated with the DMSO and ethylene glycol cosolvent systems.

This inference is supported by an analysis of surface tension data for a number of binary aqueous organic mixtures performed by Khossravi and Connors (3) using Equation 1.18, the equation we used to describe the surface tension of the solvation shell surrounding the solute.

$$\gamma = \gamma_1 + \gamma' \left[\frac{K_1 x_1 x_2 + 2K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2}\right] \qquad (1.18)$$

This treatment can be viewed in an analogous manner to solvation, where the air is treated as the solute and the air/water interface forms the solvation shell. Figure 5.8 is a copy of a plot of ln K_1 obtained from this analysis against the log P of the cosolvent for the various systems.

The plot reveals that the cosolvent systems fall into two classes. The first class of cosolvents, which include methanol, ethanol, isopropanol, acetone, and acetonitrile, show a direct relationship between surface activity and cosolvent hydrophobicity. The contrary behaviour is seen in the second class of cosolvents, which includes DMSO and

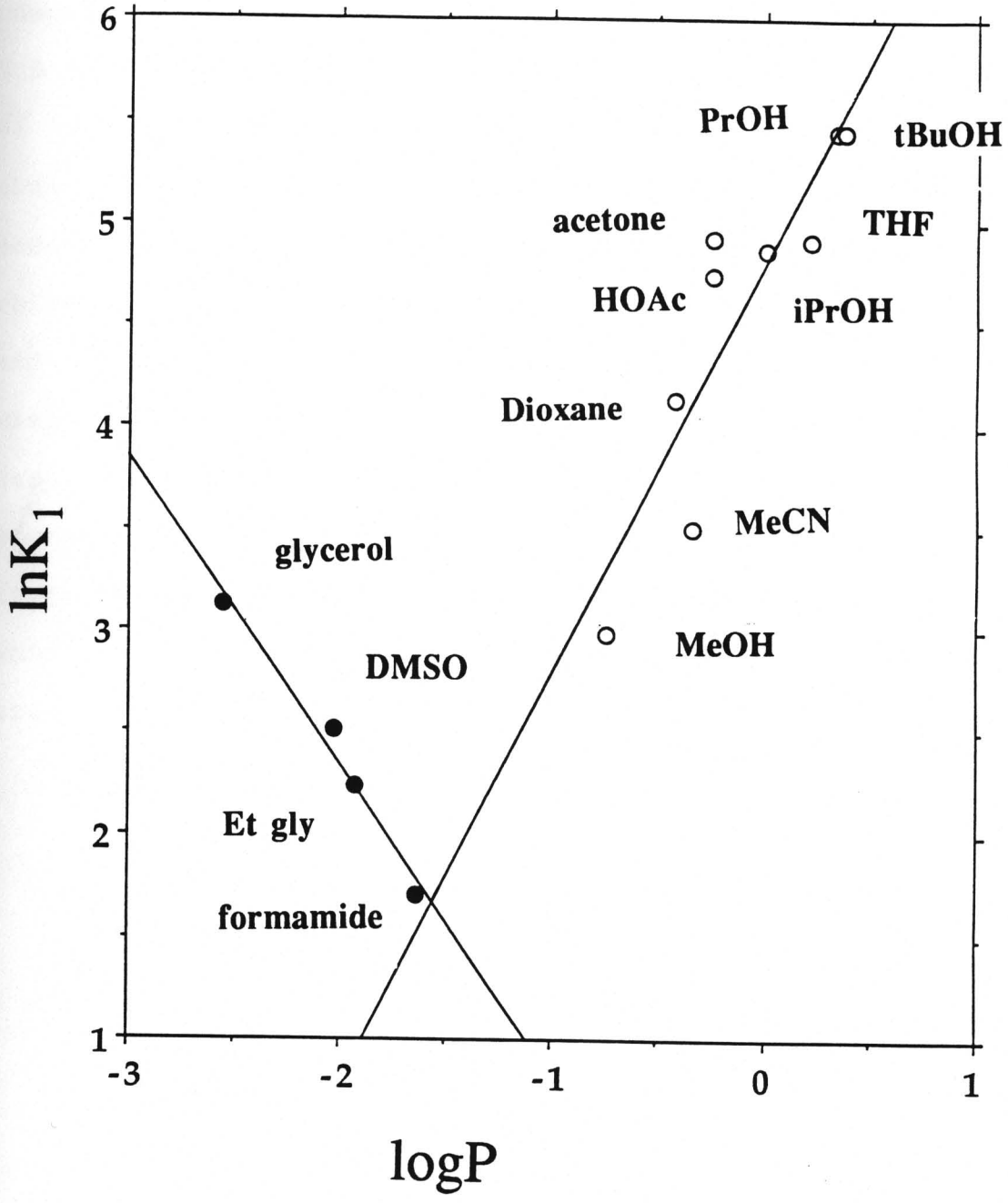

Figure 5.8. Plot of ln K_1 from the surface tension analysis vs. log P of the cosolvent.

ethylene glycol, and suggests that there is a hydrophilic component associated with these cosolvent systems. Figure 5.9 indicates that similar trends are observed with a plot of ln K_1 against log P for the 4-nitroaniline solubility studies. It therefore appears that there are two classes of cosolvents. The first class contains cosolvents which only solvate the hydrophobic portions of the solute molecule, and the second is formed by cosolvents that will interact with both the hydrophobic and hydrophilic portions. In order to further investigate this phenomenon, solubility studies (4) are currently being carried out in our laboratory with cosolvent types covering a polarity range which is as broad as those in the surface tension analysis study.

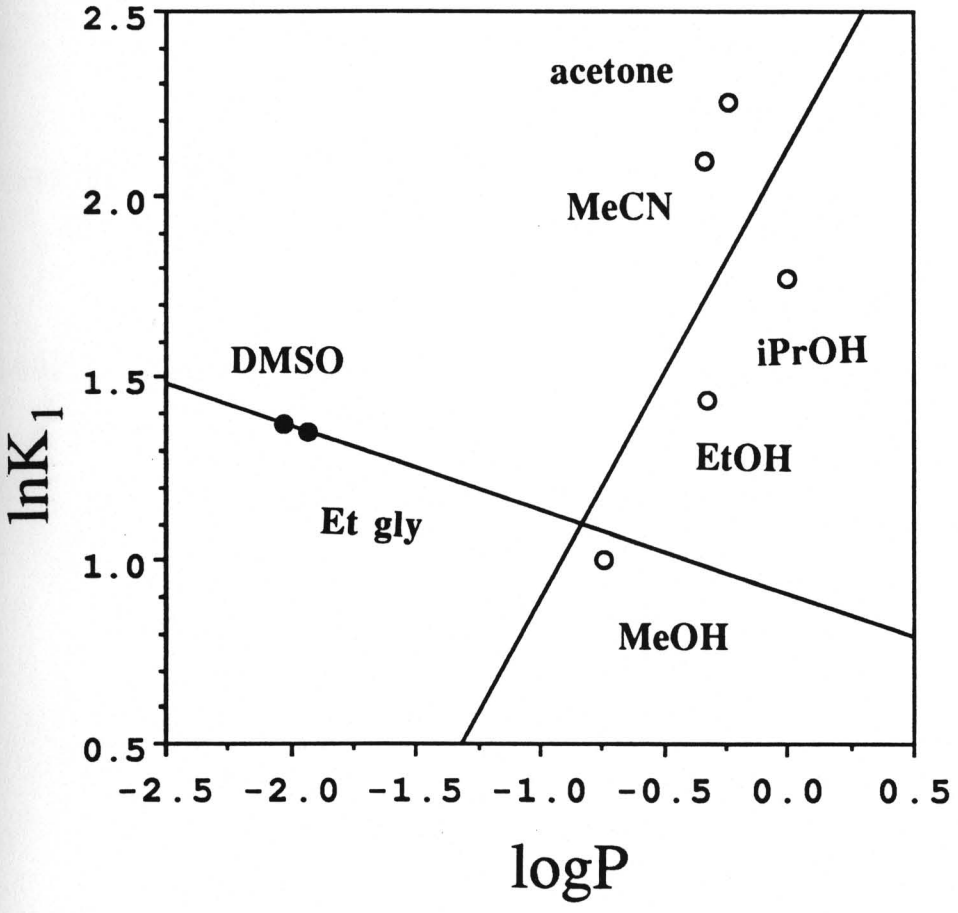

Figure 5.9. Plot of ln K_1 from the 4-nitroaniline solubility studies vs. log P of the cosolvent.

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(1) D. Khossravi, Ph.D. Thesis, University of Wisconsin - Madison 1992.

(2) D. Khossravi, K.A. Connors *J. Pharm. Sci* 1991,**81**,371.

(2) D. Khossravi, K.A. Connors *J. Soln. Chem.* 1993,**22**,321

(4) Jason Lepree, personal communication.

VI. α-CYCLODEXTRIN SOLUBILITY

A. INTRODUCTION

As early as 1949 French (1) reported the solubility of cyclodextrins in 60% propanol. Since that time there have been a number of reports in the literature (2-5) on the solubility of cyclodextrins in binary aqueous organic systems, but all of these have been limited to β-cyclodextrin. This chapter describes α-cyclodextrin solubility studies in methanol, ethylene glycol, isopropanol, and acetone cosolvent systems at 25°C.

B. RESULTS

Tables 6.1 to 6.5 present data for α-cyclodextrin solubility, and some related information, for the various cosolvent systems as well as the fully aqueous system. The value obtained in the fully aqueous system is in very good agreement with a previous value obtained in this laboratory (6). Figures 6.1 - 6.4 contain plots of the total free energy of solution as a function of x_2 for each cosolvent system.

Table 6.1. Solubility Data for α-Cyclodextrin
in
Water

x_2	$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
0	1.036(0.004)	0.125(0.002)	2.475(0.007)

Table 6.2. Solubility Data for α-Cyclodextrin in the Methanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	Concentration M	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.00203	996.08	3.61	1.032(0.010)	0.1340(0.0026)	2.440(0.009)
0.00360	991.29	6.37	1.0344 (0.0065)	0.1313(0.0035)	2.449(0.012)
0.00541	987.56	9.55	1.0376 (0.0087)	0.1277(0.0040)	2.463(0.013)
0.00578	986.03	10.20	1.0387 (0.0093)	0.1455(0.0022)	2.402(0.008)
0.00675	883.60	10.68	1.0407 (0.0062)	0.152(0.010)	2.383(0.028)
0.01090	882.71	17.30	1.0343 (0.0057)	0.1270(0.0032)	2.462(0.011)
0.01399	882.72	22.27	1.030(0.012)	0.1129(0.0037)	2.514(0.014)
0.01727	959.60	30.00	1.0154 (0.0065)	0.0873(0.0049)	2.623(0.023)
0.02289	864.46	36.01	1.0179 (0.0036)	0.0951(0.0052)	2.584(0.023)

Table 6.2 continued. Solubility Data for α-Cyclodextrin in the Methanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ g/ml	Concentration M	ΔG_u^0 10^{-20} joules molec.$^{-1}$
	water	organic			
0.02737	941.39	47.12	1.0004 (0.0055)	0.0732(0.0015)	2.692(0.009)
0.03497	846.13	54.53	1.0064 (0.0041)	0.0714(0.0021)	2.703(0.012)
0.05849	810.56	89.56	0.9886 (0.0053)	0.0563(0.0023)	2.792(0.017)
0.06006	874.34	99.37	0.9874 (0.0091)	0.0473(0.0020)	2.866(0.018)
0.16019	174.98	59.36	0.953(0.015)	0.0258(0.0005)	3.080(0.010)
0.23309	149.88	81.02	0.9380 (0.0079)	0.0220(0.0011)	3.120(0.020)
0.35872	111.47	110.90	0.9071 (0.0075)	0.0127(0.0002)	3.304(0.006)
0.44904	89.12	129.18	0.8813 (0.0058)	0.0084(0.0002)	3.441(0.012)
0.68396	42.58	163.89	0.8286 (0.0080)	0.00244(0.00003)	3.877(0.005)

Table 6.2 continued. Solubility Data for α-Cyclodextrin in the Methanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
1.000	-	-	0.7728 (0.0099)	0.00049(0.00003)	4.450(0.022)

Table 6.3. Solubility Data for α-Cyclodextrin in the Ethylene Glycol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	Concentration M	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.0000442	1022.93	0.156	1.019(0.022)	0.1205(0.0026)	2.484(0.014)
0.0000889	1020.51	0.313	1.035(0.007)	0.1215(0.0015)	2.487(0.006)
0.000135	1012.97	0.471	1.031(0.013)	0.1234(0.0017)	2.478(0.008)
0.000179	1019.16	0.627	1.031(0.011)	0.1220(0.0022)	2.483(0.009)
0.000223	1018.95	0.784	1.036(0.003)	0.1241(0.0008)	2.478(0.003)
0.00583	980.48	19.81	1.052(0.005)	0.1456(0.0010)	2.404(0.004)
0.00876	970.62	29.55	1.047(0.017)	0.1759(0.0053)	2.307(0.015)
0.01207	959.93	40.40	1.059(0.003)	0.1763(0.0024)	2.309(0.006)
0.01486	950.69	49.41	1.055(0.028)	0.1929(0.0078)	2.260(0.021)

Table 6.3 continued. Solubility Data for α-Cyclodextrin in the Ethylene Glycol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	Concentration M	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.01814	940.78	59.87	1.081(0.008)	0.2294(0.0099)	2.181(0.019)
0.03094	900.78	99.10	1.074(0.002)	0.1988(0.0018)	2.238(0.004)
0.05279	840.59	161.42	1.047(0.016)	0.1472(0.0018)	2.352(0.009)
0.08410	190.35	60.22	1.066(0.014)	0.153(0.013)	2.317(0.035)
0.11999	680.67	319.76	1.054(0.017)	0.1113(0.0017)	2.430(0.009)
0.16195	150.47	100.19	1.052(0.010)	0.1043(0.0016)	2.427(0.007)
0.28460	105.53	144.65	1.078(0.009)	0.1135(0.0005)	2.320(0.004)
0.33938	90.28	159.80	1.104(0.012)	0.1316(0.0015)	2.232(0.006)
0.34169	179.65	321.27	1.010(0.010)	0.1334(0.0042)	2.223(0.013)
0.40258	75.06	174.27	1.083(0.011)	0.0862(0.0015)	2.382(0.008)

Table 6.3 continued. Solubility Data for α-Cyclodextrin in the Ethylene Glycol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.53490	100.80	399.42	1.081(0.010)	0.0485(0.0015)	2.570(0.013)
1.00000	-	-	1.087(0.008)	0.0070(0.0001)	3.222(0.006)

Table 6.4. Solubility Data for α-Cyclodextrin in the Isopropanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.0000298	1020.11	0.102	1.021(0.018)	0.1251(0.002)	2.467(0.010)
0.0000599	1013.39	0.203	1.034(0.003)	0.1255(0.001)	2.471(0.003)
0.0000894	1019.84	0.304	1.028(0.010)	0.1239(0.001)	2.475(0.006)
0.0001192	1020.55	0.406	1.035(0.006)	0.125(0.001)	2.474(0.003)
0.00015	1014.15	0.506	1.032(0.011)	0.127(0.002)	2.466(0.007)
0.00159	994.83	5.27	1.044(0.018)	0.180(0.006)	2.302(0.016)
0.00214	991.87	7.08	1.069(0.009)	0.258(0.009)	2.130(0.017)
0.00290	990.49	9.60	1.078(0.019)	0.278(0.006)	2.093(0.013)
0.00410	981.71	13.48	1.058(0.012)	0.202(0.004)	2.248(0.010)
0.00458	975.18	14.97	1.082(0.025)	0.231(0.003)	2.191(0.013)

Table 6.4 Continued. Solubility Data for α-Cyclodextrin in the Isopropanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.00571	979.98	18.77	1.056(0.027)	0.218(0.003)	2.207(0.014)
0.00756	965.45	24.55	1.073(0.014)	0.254(0.009)	2.135(0.017)
0.01040	955.48	33.50	1.086(0.006)	0.279(0.004)	2.087(0.007)
0.01243	953.45	40.02	1.077(0.027)	0.294(0.009)	2.053(0.020)
0.02052	929.64	64.96	1.082(0.004)	0.274(0.004)	2.086(0.007)
0.03323	876.83	100.54	1.052(0.004)	0.225(0.002)	2.164(0.004)
0.06332	798.53	180.09	1.020(0.005)	0.168(0.001)	2.268(0.004)
0.12422	643.54	304.51	0.974(0.005)	0.112(0.001)	2.390(0.006)
0.17119	547.42	377.22	0.942(0.004)	0.068(0.001)	2.567(0.005)
0.23037	300.81	300.38	0.906(0.003)	0.0323(0.0001)	2.836(0.002)

Table 6.4 Continued. Solubility Data for α-Cyclodextrin in the Isopropanol System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.35046	156.55	281.79	0.869(0.001)	0.00715(0.00003)	3.381(0.002)
0.41400	62.65	147.66	0.837(0.003)	0.0032(0.00003)	3.666(0.004)
0.46052	57.51	163.78	0.824(0.005)	0.00248(0.0002)	3.742(0.027)
0.64252	59.05	354.07	0.817(0.001)	0.00016(0.00001)	4.793(0.021)

Table 6.5. Solubility Data for α-Cyclodextrin in the Acetone System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		ρ / g/ml	Concentration / M	ΔG_u^0 / 10^{-20} joules molec.$^{-1}$
	water	organic			
0.00205	992.80	6.56	1.046(0.004)	0.1562(0.0028)	2.371(0.008)
0.00296	984.97	9.42	1.020(0.012)	0.1526(0.0055)	2.370(0.016)
0.00655	974.31	20.70	1.090(0.007)	0.2231(0.0054)	2.211(0.011)
0.00927	959.88	28.97	1.064(0.010)	0.2312(0.0057)	2.178(0.012)
0.01198	955.12	37.34	1.065(0.004)	0.2262(0.0044)	2.188(0.008)
0.01818	929.80	55.50	1.051(0.016)	0.1846(0.0038)	2.278(0.011)
0.02338	912.16	70.41	1.031(0.019)	0.1744(0.0071)	2.292(0.019)
0.03856	860.43	111.26	1.024(0.014)	0.1485(0.0017)	2.354(0.008)
0.06588	195.40	44.43	0.989(0.008)	0.1035(0.0005)	2.483(0.004)
0.10532	169.48	64.32	0.968(0.011)	0.0732(0.0007)	2.600(0.006)

Table 6.5 Continued. Solubility Data for α-Cyclodextrin in the Acetone System

x_2	Weight Contributions of Water and Organic to Solvent Mixture/g		$\frac{\rho}{g/ml}$	$\frac{\text{Concentration}}{M}$	$\frac{\Delta G_u^0}{10^{-20}\text{joules molec.}^{-1}}$
	water	organic			
0.14005	152.60	80.12	0.953(0.006)	0.0381(0.0013)	2.852(0.014)
0.20263	125.82	103.08	0.911(0.006)	0.0237(0.0009)	2.994(0.016)
0.24940	107.70	115.37	0.901(0.004)	0.0081(0.0002)	3.409(0.012)
0.30259	91.59	128.12	0.878(0.009)	0.0064(0.0002)	3.462(0.015)
0.39275	69.96	145.88	0.863(0.002)	0.0015(0.0003)	4.004(0.077)

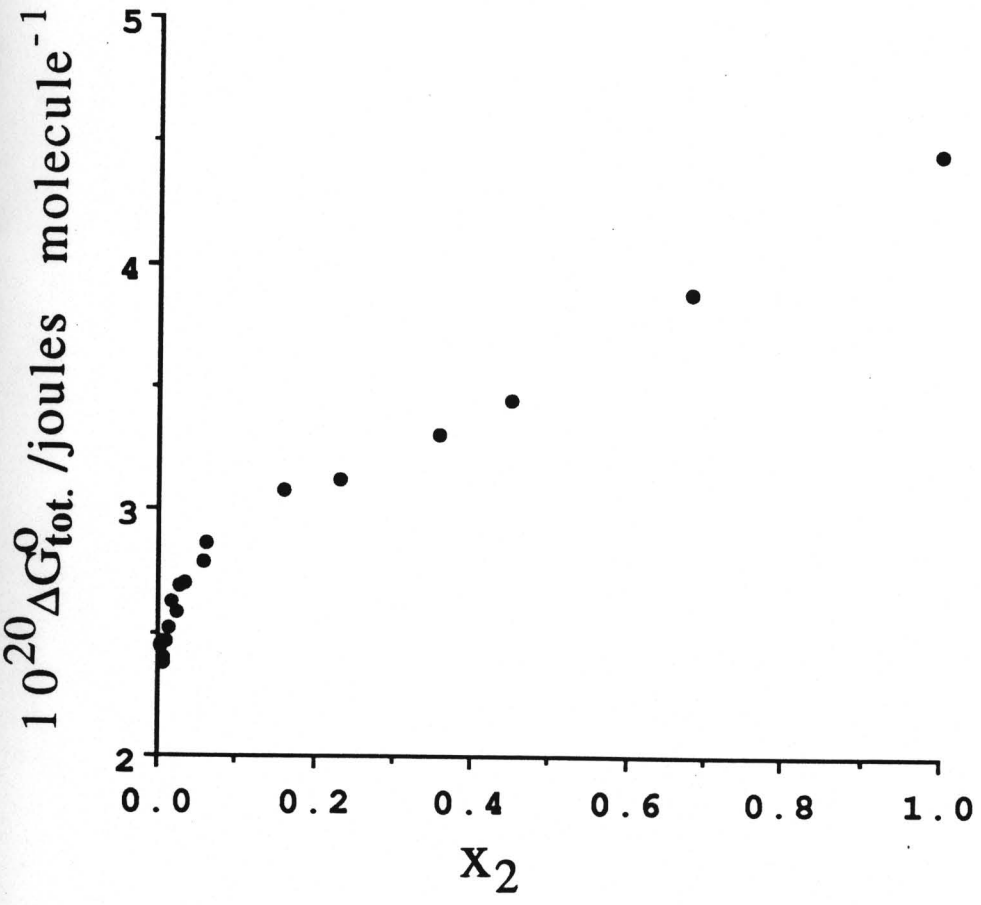

Figure 6.1. Solvent effect on the solubility of α-cyclodextrin in the methanol system.

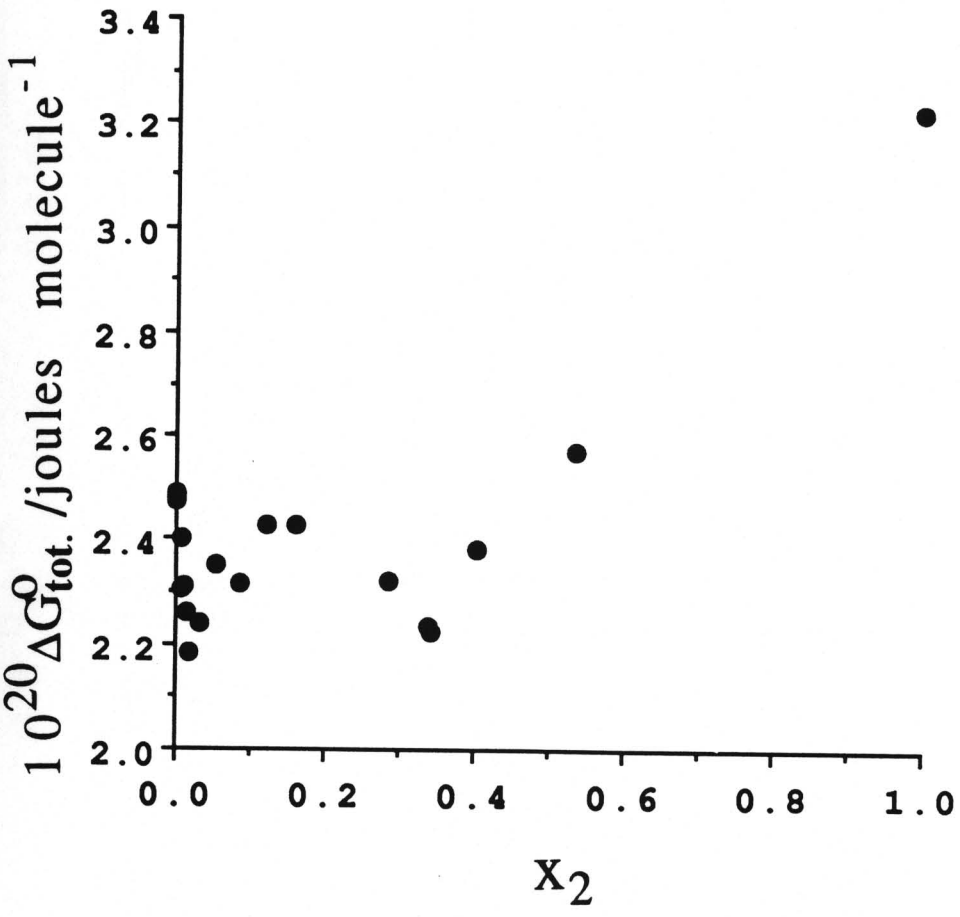

Figure 6.2. Solvent effect on the solubility of α-cyclodextrin in the ethylene glycol system.

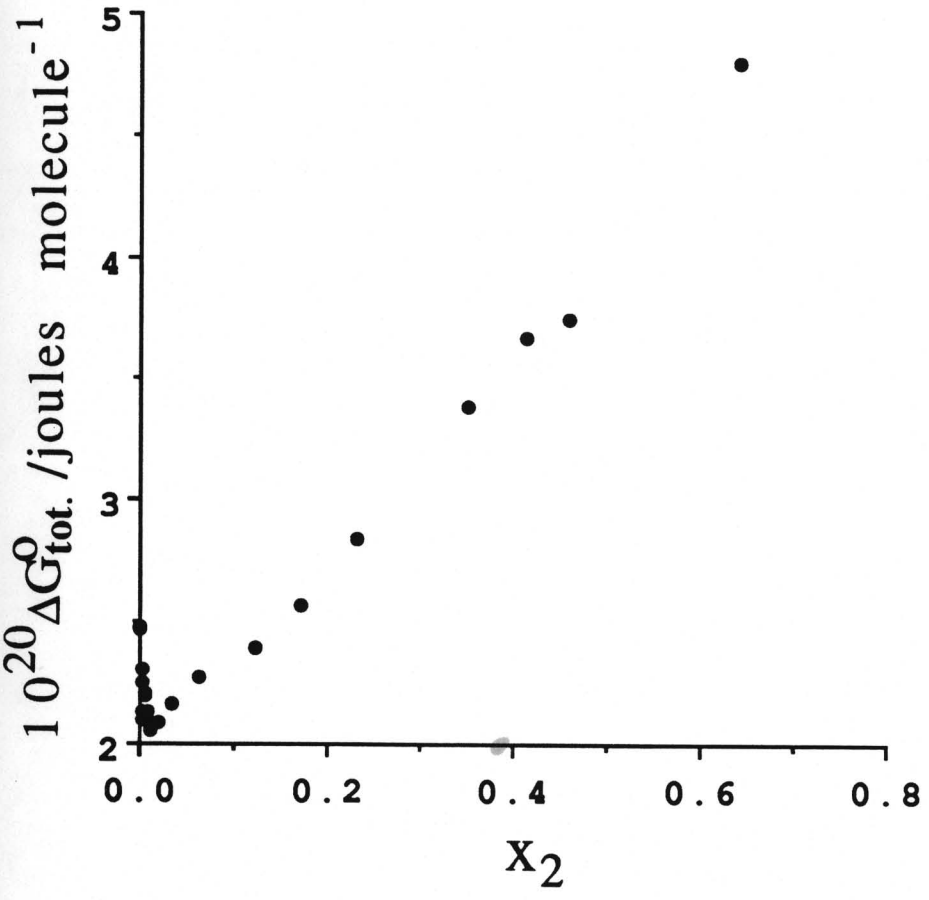

Figure 6.3. Solvent effect on the solubility of α-cyclodextrin in the isopropanol system.

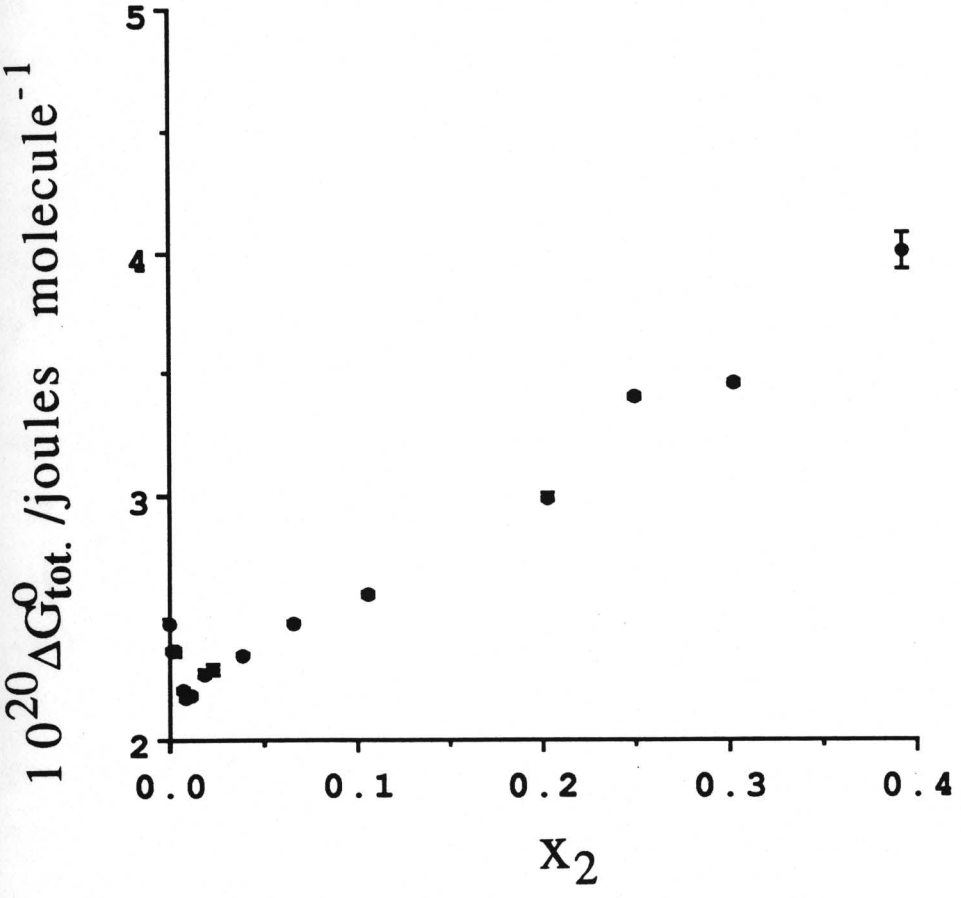

Figure 6.4. Solvent effect on the solubility of α-cyclodextrin in the acetone system.

C. DISCUSSION

We see immediately from Figures 6.1-6.4 that the shapes of the solubility profiles are radically different from those obtained for 4-nitroaniline solubility, and for many other solutes (7). Unlike the 4-nitroaniline systems, there is a significant decrease in solute solubility compared to the aqueous phase in organic rich cosolvent mixtures. The cyclodextrin solubility profiles and Tables 6.2 to 6.5 indicate that these systems are also characterised by one or more minima in the free energy of solution. All minima occur in the water rich regions, ranging from $x_2 = 0.003$ for the isopropanol cosolvent system to $x_2 = 0.34$ for the ethylene glycol system.

These apparent discontinuities in the solubility profiles are indicative of a change in the solid state in equilibrium with the solution (8). This behaviour is supported by the solubility profile for theophylline in the acetonitrile cosolvent system (7), which yielded a minimum for this cosolvent system. Furthermore, it is known that the crystal structure of theophylline is dependent upon the concentration of water in the cosolvent mixture (9). Apparently theophylline exists as the crystalline monohydrate in water-rich regions, while the anhydrous state is the most stable form of theophylline in water-

poor regions. Supporting evidence for the dependency of α-cyclodextrin crystal structure on cosolvent composition has been reported by X-ray analysis, which revealed the formation of 1:1 organic-α-cyclodextrin inclusion complexes in crystals generated from binary aqueous isopropanol solutions (10). There have been similar findings in crystals prepared from binary aqueous methanol solutions (11). Our laboratory is presently investigating the solid phase composition of the various cosolvent systems using a method that will be described later in this chapter. The present form of the phenomenological solubility model assumes that the crystal structure is constant over the entire cosolvent range in calculating $\delta_m\Delta G^\circ$, and does not take into account changes in crystal structure. Because there are indications in these studies that the crystal structure of α-cyclodextrin is cosolvent composition - dependent, we cannot use our model to describe these systems. We have already used our model to generate parameters for the solubility profiles of the substrate 4-nitroaniline and we had hoped that we could complete our complexation studies with an analysis of cyclodextrin solubility parameters. These results would then have been used to gain further insight into the complexation process. Nevertheless, although we are unable to generate model parameters for the cyclodextrin solubility profiles, the

profiles themselves are significant in that they are the first attempt at complete characterisation of α-cyclodextrin solubility in these cosolvent systems.

In order to further elucidate the relationship between α-cyclodextrin and the cosolvent, calculations were made of the mole ratio of organic to cyclodextrin in these systems in the region where the solubility was maximal. These calculations were based on estimates of the weight of cyclodextrin and volume of cosolvent mixture added to the ampuls used in these solubility studies. The results for each of the cosolvent systems are presented in Tables 6.6 to 6.9. Table 6.6 reveals that the maximum solubility of α-cyclodextrin is achieved when the mole ratio of methanol to cyclodextrin is approximately 1:1. Similar results are obtained with the isopropanol and acetone systems, and we obtain a mole ratio of two associated with the maximum solubility in the ethylene glycol system. A representative profile of these systems is presented in Figure 6.5 which consists of a plot of cyclodextrin solubility as a function of the mole ratio for the isopropanol system. We can only speculate on the significance of these values, but they appear to suggest that the quantity of the solid phase may affect cyclodextrin solubility. Studies which investigate this possible effect are in the process of being designed.

Table 6.6. Ratio[a] of Moles of Organic to Moles of α-Cyclodextrin for Various Cosolvent Mixtures in the Methanol System

x_2	Concentration M	Ratio of moles of cosolvent to moles of cyclodextrin
0.00203	0.1340(0.0026)	0.395(0.095)
0.00360	0.1313(0.0035)	0.70(0.17)
0.00541	0.1277(0.0040)	1.6(0.5)
0.00578	0.1455(0.0022)	1.1(0.3)
0.00675	0.152(0.010)	1.3(0.3)
0.01090	0.1270(0.0032)	2.1(0.5)
0.01399	0.1129(0.0037)	2.7(0.7)
0.01727	0.0873(0.0049)	5.1(1.5)

[a] Based on estimates of the weight of cyclodextrin and volume of cosolvent mixture added to the ampuls used in the solubility studies.

Table 6.7. Ratio of Moles of Organic to Moles of α-Cyclodextrin for Various Cosolvent Mixtures in the Ethylene Glycol System

x_2	Concentration M	Ratio of moles of cosolvent to moles of cyclodextrin
0.00583	0.1456(0.0010)	0.707(0.16)
0.00876	0.1759(0.0053)	1.01(0.23)
0.01207	0.1763(0.0024)	1.40(0.31)
0.01486	0.1929(0.0078)	1.68(0.38)
0.01814	0.2294(0.0099)	2.01(0.45)
0.03094	0.1988(0.0018)	3.42(0.76)
0.05279	0.1472(0.0018)	2.85(0.32)

Table 6.8. Ratio of Moles of Organic to Moles of α-Cyclodextrin for Various Cosolvent Mixtures in the Isopropanol System

x_2	Concentration M	Ratio of moles of cosolvent to moles of cyclodextrin
0.00571	0.218(0.003)	0.64(0.14)
0.00756	0.254(0.009)	0.83(0.19)
0.01040	0.279(0.004)	1.12(0.25)
0.01243	0.294(0.009)	1.29(0.29)
0.02052	0.274(0.004)	2.15(0.48)
0.03323	0.225(0.002)	3.47(0.78)
0.06332	0.168(0.001)	6.4(1.4)

Table 6.9. Ratio of Moles of Organic to Moles of α-Cyclodextrin for Various Cosolvent Mixtures in the Acetone System

x_2	Concentration M	Ratio of moles of cosolvent to moles of cyclodextrin
0.00205	0.1562(0.0028)	0.246(0.055)
0.00296	0.1526(0.0055)	0.346(0.077)
0.00655	0.2231(0.0054)	0.76(0.17)
0.00927	0.2312(0.0057)	1.03(0.23)
0.01198	0.2262(0.0044)	1.33(0.30)
0.01818	0.1846(0.0038)	2.06(0.46)
0.02338	0.1744(0.0071)	2.59(0.58)
0.03856	0.1485(0.0017)	4.22(0.95)

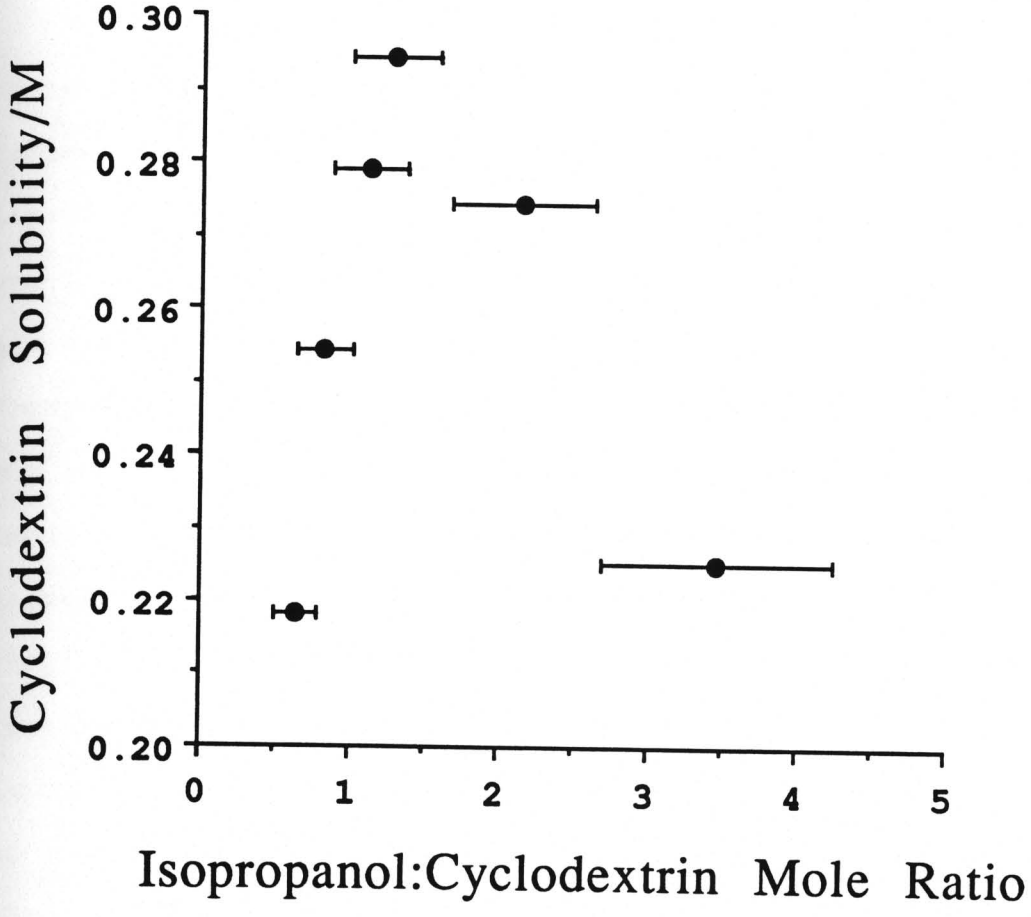

Figure 6.5. Cyclodextrin Solubility as a Functon of the Mole Ratio of Isopropanol to Cyclodextrin for Cosolvent Mixtures in the Region Of Maximum Cyclodextrin Solubility

These considerations take us considerably beyond the problem attacked in this thesis, and they lead to new investigations that, as noted above, are now being initiated in this laboratory.

We will now discuss the method that will be used to determine the composition of the solid phase. The method involves equilibrating an excess quantity of cyclodextrin with a cosolvent mixture in an identical manner to that used in the solubility studies. The samples are then dried in a vacuum oven at room temperature to drive off any excess water not associated with the crystal structure. Two sets of experiments will then be performed on the dried sample. The first involves performing a Karl Fischer titration with the dried sample in order to ascertain the quantity of water present in the solid phase. The second experiment uses polarimetry on a solution of the dried sample to determine the amount of cyclodextrin present. We now can calculate the amount of cosolvent present in the solid phase by difference. We should be able to detect a change in solid phase composition with this method. The limitation of this method is that it offers no insight into crystal structure. The two methods that could produce this information are X-ray crystallography and thermogravimetic analysis in conjunction with hot stage microscopy. X-ray

analysis would yield the most information on the crystal structure of the solid phase but there are also difficulties associated with this method. The first is an experimental one. In order to ensure that the crystals from a given cosolvent mixture are the same as those found in equilibrium with the solution phase used to determine cyclodextrin solubility, the conditions used to produce these crystals have to match those used for solute equilibration (12). Under these conditions it may be difficult to generate crystals of sufficient size for X-ray analysis. Moreover quite sophisticated analysis of the X-ray data is required to produce any meaningful information. These difficulties are not associated with the second method. Thermogravimetric analysis in conjunction with hot stage microscopy could not only be used to confirm the presence of an organic-α-cyclodextrin inclusion complex, but it could also give us its stoichiometry. The author will have access to both of these methods at the Department of Chemical Engineering and Materials Science at the University of Minnesota- Minneapolis, where this work will be continued.

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VII. ANALYSES OF COMPLEXATION AND SOLUBILITY WITH MODIFIED SOLVENT EFFECT MODELS

A. INTRODUCTION

In this chapter we present alternative solvent effect models for solubility and complexation. These models were developed as part of an effort to pinpoint the cause of the large variability in the $g\Delta A$ terms observed in the various cosolvent systems.

B. THE MODIFIED SOLUBILITY AND COMPLEXATION MODELS

The development of a model equation describing solvent effects on complexation necessitates a reexamination of the solubility process. We begin with our description of the total free energy change for the dissolution process, which is written as

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Crystal} + \Delta G^{\circ}_{Gen.med.} + \Delta G^{\circ}_{Insertion} + \Delta G^{\circ}_{Solvation} \qquad (1.2)$$

In the development of our original solubility equation we justified setting $\Delta G^{\circ}_{Insertion} = 0$ by stating that its energetic contribution was already taken into account in

$\Delta G^{\circ}_{Solvation}$. A similar argument can be used to eliminate $\Delta G^{\circ}_{Solvation}$, because it can be argued that this term is already taken into account in $\Delta G^{\circ}_{Gen.med.}$. The general medium effect term is a measure of the energy required to create a solute-sized cavity whose surface phase composition matches that of the solvation shell and is therefore a function of the solvation exchange constants. Hence this author argues that any energetic contribution from the solvation effect is already taken into account in $\Delta G^{\circ}_{Gen.med.}$ and we can set $\Delta G^{\circ}_{Solvation} = 0$. A separate term for $\Delta G^{\circ}_{Solvation}$ is not only redundant but also exaggerates its energetic contribution. Applying this concept to our model for the dissolution process we obtain

$$\delta_m \Delta G^{\circ} = \delta_m \Delta G^{\circ}_{Gen.med.} \qquad (7.1)$$

and our model equation for solubility becomes

$$\delta_m \Delta G^{\circ} = \frac{gA\gamma' K_1 x_1 x_2 + 2gA\gamma' K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (7.2)$$

The only difference between this modified solubility equation and the original equation is the absence of the natural log functions. Applying Equation 7.3 to the complexation process yields

$$\delta_m \Delta G^\circ = \frac{g \Delta A \gamma' ' K_1 x_2}{x_1 + K_1 x_2} \qquad (7.3)$$

Tables 7.1 and 7.2 present the model parameters generated by these modified model equations for the various cosolvent systems. The curve fits yielded profiles which were identical to those obtained for the original model equation for solubility and complexation.

Table 7.3 compares the solvation exchange constants generated by the original and modified solvent effect models for various cosolvent systems. The table shows that the solvation exchange constants remain largely unaffected by the modification of the solvent effect model.

Table 7.4 lists the g values of the original and modified models. The g values for the solubility studies were calculated using the gA values in Table 7.1 and our estimates of the hydrophobic surface areas of the solute

molecules. Similarly, g values for the complexation studies were calculated from the $g\Delta A$ values and our estimate of the hydrophobic surface area of the interior of the cyclodextrin cavity, $105(3) A^{o2} molecule^{-1}$. Table 7.4 is an abbreviated form of a more detailed table which also gives the g values based on total solute surface area and the error associated with the calculated g values; this table is presented in Appendix C. Table 7.4 indicates that, with the exception of the 4-nitroaniline DMSO and ethylene glycol cosolvent systems, the modified models produce an increase in the g value estimate for all cosolvent systems. This is particularly apparent in the complexation studies, where we see a large increase in the g terms for cosolvent systems in which the original model equation generated unexpectedly low g values. The modified complexation model now generates $g\Delta A$ terms for these systems which approach the hydrophobic surface area of the cyclodextrin interior. A second effect, associated with this observation, is seen on comparison of the g terms for different solvent effect processes in the same cosolvent system. We find that, for most of the cosolvent systems, the modified model produces more consistent g values. Therefore the g values generated by the modified models are in better agreement with our postulate that g is only dependent upon the cosolvent system and is independent of the solute species. The

Table 7.1. Solubility Parameters for Solutes in Various Cosolvent Systems Generated by the Modified Form of the Solubility Model

Solubiliy System[a]	Cosolvent	K_1	K_2	$gA/Å^2$ $molecule^{-1}$
biphenyl	methanol	2.595(0.079)	1.333(0.058)	83.64(0.35)
napthalene	methanol	2.341(0.045)	1.964(0.146)	67.3(1.3)
4-nitroaniline	methanol	2.95(0.52)	1.61(0.40)	47.1(1.2)
4-nitroaniline	DMSO	3.87(0.63)	3.86(0.75)	123.4(2.2)
napthalene	ethylene glycol	3.421(0.038)	1.327(0.025)	123.84(0.34)
4-nitroaniline	ethylene glycol	5.35(0.58)	0.96(0.16)	99.9(2.1)
4-nitroaniline	isopropanol	5.53(0.54)	10.4(1.0)	43.83(0.22)
napthalene	acetonitrile	4.80(0.17)	5.19(0.83)	89.2(4.0)
4-nitroaniline	acetonitrile	8.4(1.2)	5.78(0.90)	65.28(0.82)
4-nitroaniline	ethanol	4.15(0.41)	5.00(0.55)	46.32(0.39)
4-nitroaniline	acetone	10.6(2.8)	3.9(1.1)	66.3(2.0)

[a] Data for the biphenyl and napthalene solubility systems were obtained from reference 1.

Table 7.2. Complexation Parameters in the Various Cosolvent Systems Generated by the Modified Form of the Complexation Model

Substrate Complexed with Cyclodextrin	Cosolvent	K_1	$-g\Delta A/Å^2$ molecule^{-1}
Methyl Orange	methanol	4.94(0.57)	55.9(3.8)
Methyl Orange	DMSO	6.4(1.2)	92.0(9.0)
Methyl Orange	ethylene glycol	7.73(2.04)	93.(13)
Methyl Orange	acetonitrile	40.3(5.7)	47.9(3.5)
Methyl Orange	isopropanol	43.0(4.3)	41.3(2.6)
Methyl Orange	dioxane	30.6(3.8)	73.7(4.5)
Methyl Orange	acetone	45.7(6.1)	35.2(2.3)
4-nitroaniline	methanol	2.907(0.006)	75.81(0.12)
4-nitroaniline	DMSO	0.508(0.003)	697(4)
4-nitroaniline	ethylene glycol	0.743(0.025)	494(15)
4-nitroaniline	isopropanol	52.27(0.67)	32.02(0.20)
4-nitroaniline	acetonitrile	46.58(0)	37.01(0)
4-nitroaniline	ethanol	25.41(0.28)	37.77(0.20)
4-nitroaniline	acetone	7.55(0)	94.23(0)

Table 7.3. Comparison of the Solvation Exchange Constant Values for the Various Cosolvent Systems Generated by the Original and Modified Solvent Effect Models

Cosolvent System	K_1 Values for the Methyl Orange Complexation Studies		K_1 Values for the 4-Nitroaniline Complexation Studies		K_1 Values for the 4-Nitroaniline Solubility Studies		K_2 Values for the 4-Nitroaniline Solubility Studies	
	Original Model	Modified Model	Original Model	Modified Model	Original Model	Modified Model	Original Model	Modified Model
methanol	4.9	4.9	2.9	2.9	2.7	3.0	1.5	1.6
DMSO	6.4	6.4	0.5	0.5	4.0	3.9	3.7	3.9
ethylene glycol	7.7	7.7	0.74	0.74	3.9	5.4	0.65	0.96
acetonitrile	40.3	40.3	46.6	46.6	8.1	8.4	5.6	5.8
isopropanol	43	43	52.3	52.3	5.9	5.5	10.6	10.4
ethanol	-	-	25.4	25.4	4.2	4.2	5.1	5.0
acetone	46	46	7.6	7.6	9.5	10.6	3.5	3.9
dioxane	31	31	-	-	-	-	-	-

Table 7.4. Comparison of the Curvature Correction Factor Values for the Various Cosolvent Systems Generated by the Original and Modified Solvent Effect Models Based on Hydrophobic Surface Areas

Cosolvent System	g Values for the Methyl Orange Complexation Studies - Calculated Using the Hydrophobic Surface Area of the Cyclodextrin Interior		g Values for the 4-Nitroaniline Complexation Studies -Calculated Using the Hydrophobic Surface Area of the Cyclodextrin Interior		g Values for the 4-Nitroaniline Solubility Studies - Calculated Using the Solute Hydrophobic Surface Area		g Values for the Napthalene Solubility Studies	
	Original Model	Modified Model	Original Model	Modified Model	Original Model	Modified Model	Original Model	Modified Model
methanol	0.41	0.53	0.64	0.72	0.52	0.69	0.37	0.45
DMSO	0.63	0.88	6.7	6.6	1.26	1.8	-	-
ethylene glycol	0.55	0.89	4.8	4.7	1.24	1.47	0.68	0.83
acetonitrile	0.12	0.46	0.006	0.36	0.43	0.96	0.39	0.59
isopropanol	0.10	0.39	0.002	0.31	0.16	0.65	-	-
ethanol	-	-	0.11	0.36	0.31	0.68	-	-
acetone	0.03	0.34	0.74	0.90	0.54	0.97	-	-
dioxane	0.36	0.70	-	-	-	-	-	-

modified model also produces g values for the alcohols in the 4-nitroaniline solubility systems that are virtually identical. The inference from this observation is that closely related cosolvents yield similar g values for a given solubility process. Therefore we might be able to predict the g value for a solubility solvent effect process based solely on cosolvent chemical similarity.

We will now discuss the g values generated by the modified model for 4-nitroaniline solubility in the ethylene glycol and DMSO solubility systems. We argued in Chapter Five that the g term for these cosolvent systems reflected the total solute surface area. Part of this postulate was based on the comparison of the g values generated by the original model for 4-nitroaniline solubility with that of napthalene, a completely hydrophobic molecule, in the ethylene glycol cosolvent system. We showed that a better agreement between the g values of these two systems was obtained when the total surface area of 4-nitroaniline was used to calculate g. We see in Table 7.5 that the similarity of the g values calculated from the total solute surface area of 4-nitroaniline with that of the napthalene g value is not only confined to the ethylene glycol cosolvent system when the modified model is used. The same trend is also seen with the methanol and acetonitrile cosolvent systems.

Table 7.5. Comparison of the Curvature Correction Factor Values for Selected Solubility Systems Generated by the Modified Solvent Effect Model

Solute	g Values Based on the Original Model for the Methanol System		g Values Based on the Original Model for the Ethylene Glycol System		g Values Based on the Original Model for the Acetonitrile System	
	Based on the Hydro-phobic Surface Area	Based on the Total Surface Area	Based on the Hydro-phobic Surface Area	Based on the Total Surface Area	Based on the Hydro-phobic Surface Area	Based on the Total Surface Area
napthalene	0.45	0.45	0.83	0.83	0.59	0.59
4-nitroaniline	0.69	0.32	1.47	0.68	0.96	0.45

Therefore we cannot conclude from these analyses that the g term is a reflection of the total solute surface area. However, Table 7.4 indicates that the largest g values are always associated with the ethylene glycol and DMSO cosolvent systems. This trend is observed in each of the complexation and solubility studies and is seen in both models. Solubility studies, conducted in the cosolvent systems used in our studies, for solutes which range from being completely hydrophobic to completely hydrophilic, may help elucidate the association between g and the hydrophobic and hydrophilic surface areas of the solute.

Next we will discuss the α-cyclodextrin - 4-nitroaniline complexation studies conducted in the ethylene glycol and DMSO cosolvent systems. Both the original and modified models are incapable of generating physically reasonable $g\Delta A$ values for these systems. We pointed out in Chapter Four that, due to the scatter associated with the profiles for the α-cyclodextrin - 4-nitroaniline complexation studies in all of the cosolvent systems, analyses of these systems were based on points taken from a hand-drawn line which best described the experimental data for each cosolvent system. The shape of this line is somewhat arbitrary for the ethylene glycol cosolvent system. We originally used a straight line to describe this system. However, a convex upward shaped line can describe

the experimental data just as accurately. Reanalysing the ethylene glycol system with points taken from this line shape with the modified complexation model yields K_1 and $g\Delta A$ values of 2.00(17) and 214.9(14.6) $Å^2$ $molecule^{-1}$. The curve fit is shown in Figure 7.1. Although the $g\Delta A$ value from this analysis is still larger than the values obtained for the other cosolvent systems, it is now physically reasonable and approaches 217(7) $Å^2$ $molecule^{-1}$, the value of the total surface area of the interior of the cyclodextrin cavity. This analysis suggests that parameter values generated for these systems are suspect and may be due to insufficient characterisation of these profiles. More experimental data points are needed for these systems in order to clearly define their profile shapes and generate meaningful parameter values.

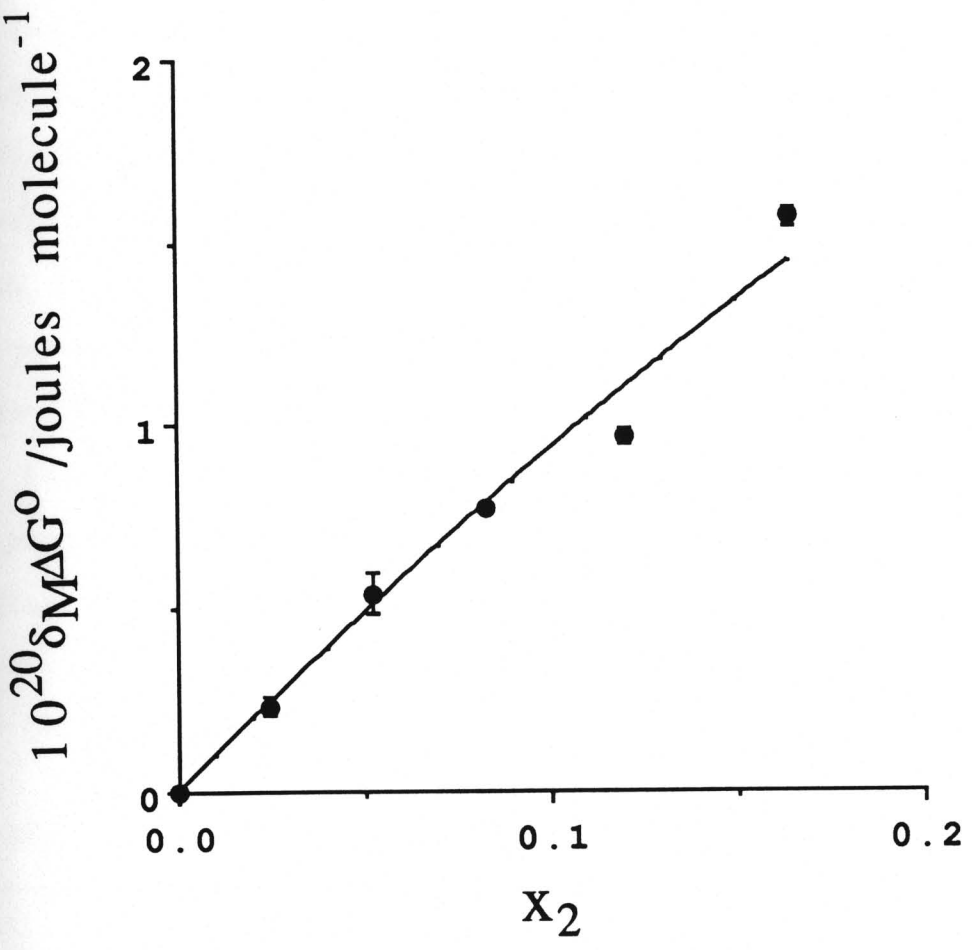

Figure 7.1. Solvent effect profile based on the reanalysis of α-cyclodextrin-4-nitroaniline complexation in the ethylene glycol system using points taken from a convex upward shaped line showing the experimental data points and the fitted curve.

We have shown that the modified model reduces the large variability in the $g\Delta A$ terms observed in the various cosolvent systems. Although this is encouraging, it does not prove the modified model's validity nor disprove the validity of the original model equations. The crux of the development of the modified models is the claim that the solvation term should be dropped because it is implicitly taken into account in the general medium effect term. We now present two cases which may provide an experimental basis for testing this argument and discriminating between the two models. We will then compare the solubility expressions for the two models under these conditions. Our original solubility model equation is

$$\delta_m \Delta G^\circ_{OM} =$$

$$\frac{(-\mathbf{k}T \ln K_1 + gA\gamma')\, K_1 x_1 x_2 + (-\mathbf{k}T \ln K_1 K_2 + 2gA\gamma')\, K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (1.22)$$

and the modified form of the solubility equation is

$$\delta_m\Delta G^\circ_{MM} = \frac{gA\gamma' K_1 x_1 x_2 + 2gA\gamma' K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (7.2)$$

where the subscripts OM and MM on the free energy term refer to the original and modified solvent effect models. The first case involves systems where A=0. Applying this condition to our original and modified model equations yields

$$\delta_m\Delta G^\circ_{OM} = \frac{-\mathbf{k}T \ln(K_1) K_1 x_1 x_2 - \mathbf{k}T \ln(K_1 K_2) K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (7.4)$$

and

$$\delta_m\Delta G^\circ_{MM} = 0 \qquad (7.5)$$

In other words, the modified solubility model would predict that there will be no solvent effects on solubility for such a solute system. If A is a reflection of the hydrophobic surface area, such solute systems could be

found in completely hydrophilic molecules such as sugars. The only justification that can be used for the application of the modified solubility model in these systems, provided a solvent effect exists, would be to argue that A is not solely composed of the hydrophobic surface area. A second case, which also leads to equations 7.4 and 7.5, is for systems where $\gamma' = 0$. Once again we see that this form of the modified solubility model predicts the lack of a solvent effect. In order to see if Equation 7.4 can successfully model this type of system, solubility studies would have to be carried out in binary systems composed of solvents that have similar surface tensions. The organic solvents acetone and methanol, which have surface tensions of 22.9 $dynescm^{-1}$ and 22.4 $dynescm^{-1}$ at 25°C (2), are potential candidates for these types of studies.

We have seen that there are limitations associated with the modified models and that the original models appear to be more universal in their application. Nevertheless, the modified models seem to be more useful in predicting complexation and solubility profiles than the original models. We have shown that the modified model of the solvent effect process on complexation produces $g\Delta A$ values for the various cosolvent systems that approach the hydrophobic surface area of the cyclodextrin interior. We also noticed a similarity in the g terms generated by the

modified model for the alcohol series in the 4-nitroaniline solubility studies. Lastly, for most of the cosolvent systems, a significant decrease in the variation of the g term was observed when we compared the g values for different solvent effect processes conducted in the same cosolvent system. These observations are all indications that the modified model equations possess a greater potential for predictability than the original model equations.

We complete this chapter by investigating our postulate that the solvation exchange constant for the complexation studies reflects the ability of the cosolvent to partition into the interior of the cyclodextrin cavity. If this postulate is correct, then a model containing the the solvation exchange constants for the 4-nitroaniline solubility studies should be incapable of describing the complexation profiles. In this analysis we fit the complexation data for each of the cosolvent systems to Equation 7.6,

$$\delta_m \Delta G^\circ = \frac{g\Delta A\gamma' K_1 x_1 x_2 + 2g\Delta A\gamma' K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (7.6)$$

using as fixed parameter values the solvation exchange constants for the 4-nitroanilne solubility studies. Equation 7.6 is simply a modified 2-step solvation exchange complexation model equation. The result of the analyses is that with the exceptions of the α-cyclodextrin-4-nitroaniline acetone and methanol cosolvent systems, the curve fits are poor. The inability of the solvation exchange constants obtained from 4-nitroaniline solubility studies to accurately describe most of these cosolvent systems, suggests that a phenomenon is occurring in these complexation studies which is not being taken into account by these solvation exchange constants. This supports our postulate that the complexation solvation exchange constants are unique in that they are associated with the partitioning of the cosolvent into the cyclodextrin cavity. Comparison of the solvation exchange constants of the 4-nitroaniline solubility and α-cyclodextrin-4-nitroaniline complexation studies for the methanol systems in Table 7.3 reveals that their K_1 values are almost identical. Similar

K_1 values are also found for these solvent effect processes in the acetone cosolvent system. Therefore it is not surprising that such good curve fits are obtained for these systems with Equation 7.6. We will now speculate on the significance of the trends observed in the fit of Equation 7.6 to the complexation data of the various cosolvent systems. A possible explanation for these observed trends is that there are two mechanisms associated with the solvation exchange constant. The first is associated with competitive complexation, defined by

$$SLW + M \rightleftharpoons MLW + S \qquad (7.7)$$

in which the substrate competes with the cosolvent for the cyclodextrin cavity. This mechanism appears to be the predominant mechanism in our complexation studies. The second mechanism is associated with the solvation of the complex, defined by

$$SLW + M \rightleftharpoons SLM + W \qquad (7.8)$$

which is simply our definition of the one step solvation exchange constant. This appears to be the predominant mechanism for α-cyclodextrin-4-nitroaniline complexation

in the acetone and methanol cosolvent systems. The predominant mechanism for K_1 in a particular cosolvent system therefore seems to be dependent on both the cosolvent and substrate.

C. CONCLUSION

We have presented two different models for solvent effects on solubility and complexation. One, the original model, is based on a separate solvation and general medium effect terms and a second, the modified model, combines the two effects in a single term. While both models are capable of adequately describing the solubility and complexation systems and produce similar exchange constant values, the modified model is the only one that is capable of generating reasonable $g\Delta A$ values that approach the hydrophobic surface area of the cyclodextrin interior for most of the cosolvent systems. Although the modified models are less universal than the original models, they appear to have a greater potential for predicting solvent effect complexation and solubility profiles. The solvation exchange constants for the solubility studies appear to be dependent on the cosolvent and seem to be unaffected by the identity of the solute. Lastly, there are indications that the discontinuity associated with plots of ln K_1 against

cosolvent polarity for the various complexation cosolvent systems arise from the partitioning of the cosolvent into the cyclodextrin cavity.

REFERENCES

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APPENDIX A

α-CYCLODEXTRIN - METHYL ORANGE COMPLEXATION DATA

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water[a]	1664.05
organic	314.82

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.0666\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.425,1.429,1.429
64.52	0.998
93.68	0.878
124.91	0.778
132.24	0.762
156.13	0.706
165.30	0.686
218.58	0.602

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.09658	0.9686	51.411	4.48(0.01)	71(1)	3.363(0.005)

[a] The water weight includes the contribution from concentrated HCl.

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1558.09
organic	387.68

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.1583\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.492,1.486,1.494
81.93	1.110
122.89	0.962
163.46	0.892
163.86	0.892
204.32	0.820
204.82	0.826
286.74	0.705

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.12327	0.9653	48.830	4.28(0.02)	49(1)	3.200(0.007)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1455.77
organic	470.49

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.7082\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.816,1.813,1.816
76.29	1.497
114.43	1.391
152.58	1.296
166.76	1.243
190.72	1.200
208.44	1.170
267.01	1.060

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.15443	0.9540	49.366	4.420(0.003)	31(2)	3.00(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1376.19
organic	537.14

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.9611\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.922,1.928,1.922
79.77	1.645
122.41	1.518
159.53	1.444
163.33	1.429
199.41	1.370
204.02	1.356
285.63	1.223

x_2	ρ_o g/ml	M* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.18070	0.9526	48.489	4.27(0.09)	25(0.1)	2.90(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1226.35
organic	773.68

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.9336\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.756,1.751,1.756
67.93	1.446
101.90	1.324
121.69	1.300
135.87	1.235
152.11	1.226
169.84	1.170
237.77	1.037

x_2	ρ_o g/ml	M^* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.12753	1.0472	38.817	3.70(0.03)	40(2)	3.05(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1037.32
organic	961.84

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.7137\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.536, 1.532, 1.533
76.30	1.359
114.46	1.284
129.33	1.235
152.61	1.226
161.67	1.182
190.76	1.164
267.06	1.062

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.17685	1.060	34.816	4.4(0.2)	16(4)	2.6(0.1)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1133.96
organic	873.27

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.9153\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.448,1.452,1.457
96.68	1.305
128.82	1.265
145.03	1.251
161.03	1.225
193.37	1.199
241.71	1.151
338.40	1.058

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.23128	1.071	31.259	2.8(0.1)	16(2)	2.59(0.04)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1978.24
organic	22.30

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.8842\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	0.958, 0.942, 0.948
32.50	0.370
48.75	0.324
54.85	0.267
64.99	0.262
68.56	0.231
81.24	0.243
113.74	0.207

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00328	0.9973	54.800	2.20(0.03)	659(83)	4.32(0.05)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1955.39
organic	45.17

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.9151\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.347,1.362,1.357
51.37	0.493
77.06	0.377
86.14	0.356
102.74	0.308
107.68	0.311
128.43	0.263
179.80	0.199

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00669	0.9990	54.349	3.40(0.02)	362(9)	4.07(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1448.20
organic	552.21

Absorbance as a Function of Cyclodextrin Concentration $S_t=4.0876\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.500,1.513
62.78	1.114
94.17	1.024
119.14	0.972
125.56	0.932
148.92	0.857
156.95	0.854
219.73	0.742

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.10009	1.0290	44.433	2.90(0.01)	78(3)	3.37(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1334.40
organic	665.31

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.8933\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.380,1.389,1.388
65.08	1.119
97.61	1.028
115.08	0.988
130.15	0.958
143.85	0.916
162.69	0.899
227.77	0.789

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.12697	1.0358	42.217	3.00(0.05)	46(2)	3.13(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Dioxane System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1980.75
organic	39.30

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.8430\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.3255,1.3254,1.3298,1.3264
49.96	0.5855
74.93	0.4621
77.90	0.4491
97.38	0.3899
99.90	0.3858
124.88	0.3336
174.83	0.2602

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00406	0.9966	54.379	4.436(0.006)	293(1)	3.981(0.001)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Dioxane System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1970.37
organic	50.02

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.8687\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.2108,1.2037,1.2012,1.1960
51.18	0.5878
76.76	0.4644
81.45	0.4574
101.81	0.3968
102.36	0.3862
127.94	0.3443
179.12	0.2774

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00519	0.9969	54.146	4.08(0.01)	219(3)	3.860(0.006)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Dioxane System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1919.97
organic	100.01

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.7953\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.3153,1.3109,1.3129,1.3114
24.59	1.0185
36.89	0.9188
49.19	0.8392
61.49	0.7674
86.08	0.6634
122.97	0.5952

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01059	0.9982	53.06	4.20(0.01)	134(2)	3.651(0.005)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Dioxane System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1700.27
organic	319.70

Absorbance as a Function of Cyclodextrin Concentration
$S_t = 2.8632 \times 10^{-5}$ M

$10^4 L_t$/M	Absorbance at 508nm
0	1.3613, 1.3529, 1.3553, 1.3572
13.02	1.3398
26.03	1.3051
50.86	1.2383
76.28	1.1888
101.70	1.1409
104.14	1.1352
127.13	1.0967
130.17	1.0950
177.98	1.0154

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03720	1.0076	48.287	4.4(0.6)	20(3)	2.83(0.06)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Dioxane System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1699.76
organic	320.50

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.8283\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.3393,1.340,1.3440,1.3382
53.34	1.2208
80.02	1.1785
82.19	1.1586
102.73	1.1179
106.70	1.1183
133.37	1.0736
186.72	0.9905

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03730	1.0073	48.271	5.8(0.4)	15(2)	2.70(0.05)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1965.96
organic	33.75

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.2591\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	0.716,0.722,0.712
64.66	0.268
96.99	0.229
129.32	0.182
145.84	0.169
161.65	0.163
182.30	0.154
226.30	0.116

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00515	0.9954	54.581	2.06(0.01)	300(23)	3.99(0.03)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1965.57
organic	35.32

Absorbance as a Function of Cyclodextrin Concentration $S_t=4.1334\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.773,1.773,1.772
64.53	1.062
96.79	1.212
129.06	1.318
130.81	1.311
161.32	1.375
163.51	1.369
225.86	1.451

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00538	0.9920	54.551	4.120(0.007)	258(8)	3.93(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1956.99
organic	42.26

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.7723\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.172,1.158,1.171
63.69	0.514
95.54	0.417
95.68	0.430
119.60	0.393
127.39	0.365
159.24	0.300
222.93	0.238

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00646	0.9922	54.417	2.88(0.02)	228(29)	3.88(0.05)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1942.46
organic	67.8

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.8640\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.767,1.767,1.767
62.43	0.896
93.66	0.727
124.87	0.621
137.61	0.578
156.09	0.541
172.01	0.494
218.52	0.431

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00901	0.9901	54.102	4.40(0.07)	169(4)	3.749(0.009)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1945.84
organic	74.27

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.7687\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.042,1.054,1.076
64.52	0.581
96.78	0.545
122.84	0.428
129.05	0.450
153.56	0.400
161.31	0.375
225.83	0.293

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01137	0.9895	53.813	2.6(0.3)	141(23)	3.67(0.07)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1910.86
organic	89.38

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.9640\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.878,1.872,1.874
65.04	1.125
71.25	1.087
97.56	0.942
130.88	0.804
142.49	0.766
178.12	0.678
227.63	0.575

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01390	0.9880	53.508	6.222(0.002)	105(1)	3.550(0.003)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1897.65
organic	102.63

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.8347\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.799,1.797,1.797
66.56	1.221
99.84	1.069
133.12	0.942
134.36	0.923
166.41	0.852
167.95	0.827

x_2	ρ_o / q/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01603	0.9811	53.252	4.46(0.02)	76(2)	3.41(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1871.86
organic	108.04

Absorbance as a Function of Cyclodextrin Concentration $S_t=4.0748\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.655, 1.655, 1.653
75.23	1.031
112.85	0.871
133.13	0.805
150.47	0.747
166.41	0.704
188.08	0.683
263.32	0.556

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01709	0.9990	53.127	3.92(0.01)	86(3)	3.46(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1856.42
organic	144.62

Absorbance as a Function of Cyclodextrin Concentration $S_t=4.2324\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.170, 1.180, 1.168
75.05	0.879
87.50	0.848
100.07	0.813
116.67	0.801
125.08	0.734
145.84	0.741
204.17	0.638

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02293	0.9827	52.443	2.35(0.04)	56(9)	3.28(0.07)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1990.28
organic	10.3065

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.3114\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.1017
12.39	0.7516
24.77	0.5686
49.54	0.3925
74.31	0.2984
99.08	0.2467
123.86	0.2014
173.40	0.1626

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00228	0.9950	55.074	4.68(0.08)	390(3)	4.10(0.003)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	3960
organic	39.85

Absorbance as a Function of Cyclodextrin Concentration $S_t=4.3870\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.2706
12.21	0.9541
24.42	0.7711
48.84	0.5624
97.68	0.3532
122.10	0.3099
170.94	0.2472

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00442	0.9930	54.925	2.81(0.01)	285(4)	3.972(0.005)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1970.75
organic	30.1816

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.5377\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.6021
12.51	1.2875
25.03	1.0807
50.06	0.8172
75.08	0.6591
100.11	0.5628
125.13	0.4898
175.19	0.3789

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00671	0.9920	54.767	4.34(0.03)	216(6)	3.86(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1960.09
organic	40.0228

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.4416\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.1610
11.85	0.9742
23.70	0.8280
47.41	0.6568
71.11	0.5427
94.81	0.4612
118.52	0.3985
165.92	0.3264

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00893	1.0100	54.615	4.73(0.02)	164(3)	3.751(0.007)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1939.44
organic	58.652

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.9438\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.2226
10.09	1.1025
20.17	0.9935
40.35	0.8424
60.52	0.7255
80.70	0.6411
100.87	0.5782
141.22	0.4748

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01316	0.9910	54.327	4.41(0.03)	102(2)	3.54(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1930.84
organic	74.845

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.5102\times10^{-5}$M	
$10^4 L_t/M$	Absorbance at 508nm
0	1.5470
6.96	1.4770
13.92	1.3917
27.84	1.2469
41.76	1.1509
55.68	1.0527
69.61	1.0024
97.45	0.8704

x_2	ρ_o g/ml	M* moles kg^{-1}	$-\Delta\varepsilon_{11}$ 10^{-4} $M^{-1}cm^{-1}$	K_{11} M^{-1}	$-\Delta G_u^0$ 10^{-20} joules molec.$^{-1}$
0.01681	0.988	54.081	4.8(0.1)	76(8)	3.42(0.04)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1920.23
organic	79.6763

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.6642\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.7021
6.36	1.6274
12.72	1.5331
25.44	1.4136
38.16	1.2964
50.87	1.218
63.59	1.1263
89.03	1.0003

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01797	0.988	54.003	3.75(0.04)	110(4)	3.57(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1918.64
organic	81.61

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.2161\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.019,1.011,1.016
17.61	0.887
28.14	0.838
42.21	0.761
44.03	0.759
56.29	0.707
70.36	0.658
98.50	0.578

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01842	0.9876	53.973	4.0(0.2)	96(8)	3.52(0.03)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1881.09
organic	120.2107

Absorbance as a Function of Cyclodextrin Concentration $S_t=5.4917\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.8775
6.34	1.8252
12.68	1.7714
25.36	1.6778
38.04	1.5917
50.72	1.5160
63.40	1.4858
88.76	1.3349

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02741	0.9827	53.378	2.88(0.04)	57(2)	3.29(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1883.22
organic	121.36

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.0300\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.391,1.390,1.399
72.42	1.053
108.63	0.939
144.84	0.864
157.39	0.821
181.06	0.783
196.74	0.752
253.48	0.660

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02764	0.9836	53.364	4.36(0.03)	49(1)	3.23(0.01)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1879.98
organic	125.89

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.0135\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.395,1.388,1.392
71.08	1.064
106.62	0.958
127.94	0.900
142.16	0.869
159.93	0.824
177.70	0.810
248.78	0.691

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02869	0.9826	53.295	4.25(0.02)	48(1)	3.226(0.003)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1839.67
organic	163.41

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.9640\times10^{-5}$M	
$10^4 L_t/M$	Absorbance at 508nm
0	1.348,1.348,1.347
75.48	1.120
113.23	1.033
150.97	0.961
156.86	0.949
188.71	0.907
196.07	0.890
264.20	0.792

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03770	0.98015	52.714	4.25(0.02)	29(1) [225]	3.01(0.01)

225

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1894.28
organic	107.38

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.9695\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.311,1.308,1.306
51.54	0.857
76.73	0.739
102.31	0.654
117.24	0.608
127.88	0.583
146.55	0.541
179.04	0.484

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01736	0.9879	53.193	4.12(0.55)	114(1)	3.582(0.004)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1890.00
organic	118.38

Absorbance as a Function of Cyclodextrin Concentration $S_t=2.7165\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.288,1.289,1.290
66.84	0.815
71.86	0.809
73.33	0.785
89.76	0.747
97.77	0.697
122.21	0.624
171.10	0.525

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01915	0.9873	52.992	4.72(0.04)	86(7)	3.46(0.04)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1840.37
organic	140.68

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.0206\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.264,1.269,1.266
50.74	0.912
76.12	0.811
88.74	0.765
101.49	0.746
110.92	0.717
126.86	0.669
177.60	0.564

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02327	0.9816	52.533	3.620(0.005)	94(1)	3.492(0.005)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1843.94
organic	164.67

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.2701\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 508nm
0	1.378,1.364,1.366
60.13	0.996
90.19	0.889
108.73	0.834
120.25	0.803
135.91	0.767
150.31	0.750
204.38	0.625

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02708	0.9827	52.117	3.72(0.02)	75(3)	3.34(0.02)

Complexation Data for Methyl Orange with
α-Cyclodextrin in the Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	1843.94
organic	164.67

Absorbance as a Function of Cyclodextrin Concentration $S_t=3.1656\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 508nm
0	1.472,1.471,1.469
71.67	1.093
107.51	0.975
129.27	0.909
143.34	0.885
160.91	0.844
179.18	0.808
250.85	0.689

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$-\Delta\varepsilon_{11}$ / 10^{-4} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03026	0.9812	51.774	4.258(0.007)	54(1)	3.262(0.003)

APPENDIX B

α-CYCLODEXTRIN - 4-NITROANILINE COMPLEXATION DATA

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in
0.01M pH 10 Carbonate Buffer

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4823\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 410nm
0	0.813,0.813,0.816
98.50	1.103
131.34	1.111
164.17	1.123
197.00	1.130
229.84	1.132
295.5	1.144
328.34	1.148

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0	0.9934(0.002)	55.509	4.73(0.02)	431(39)	4.15(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in
0.01M pH 10 Carbonate Buffer

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4823\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 410nm
0	0.813,0.807,0.813
96.08	1.098
128.11	1.107
160.14	1.117
192.16	1.126
224.19	1.132
288.24	1.132
320.27	1.140

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0	0.9934(0.002)	55.509	4.65(0.02)	475(36)	4.19(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in
0.01M pH 10 Carbonate Buffer

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2449\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 410nm
0	0.780,0.780,0.781
96.29	1.057
128.38	1.067
160.48	1.082
192.57	1.085
224.67	1.095
288.86	1.101
320.95	1.097

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0	0.9934(0.002)	55.509	4.14(0.04)	418(40)	4.14(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water[a]	950.78
organic	44.48

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2970\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.791,0.806,0.786
77.26	1.020
103.02	1.044
128.77	1.054
154.53	1.068
180.28	1.084
231.79	1.101
257.54	1.111

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02563	0.9853(0.0006)	55.424	5.09(0.03)	197(21)	3.81(0.04)

[a] The water weight includes the contribution from the carbonate buffer.

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	905.26
organic	83.06

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3795\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 410nm
0	0.824,0.825,0.824
95.13	1.023
126.85	1.043
158.56	1.065
190.27	1.080
221.98	1.090
285.40	1.112
317.11	1.21

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.04906	0.9769(0.004)	53.467	4.90(0.02)	126(7)	3.62(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	850.61
organic	132.17

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1928\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.813,0.812,0.815
100.18	0.972
133.58	0.993
166.97	1.014
200.37	1.031
233.76	1.048
300.55	1.069
333.95	1.098

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.08035	0.9720(0.0001)	52.242	5.42(0.07)	66(7)	3.34(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	800.30
organic	165.31

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1855\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.819,0.818,0.820
98.72	0.953
131.63	0.971
164.54	0.990
197.44	1.010
230.35	1.018
296.16	1.048
329.07	1.053

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.10406	0.9594(0.003)	51.349	4.76(0.04)	68(5)	3.34(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	800.81
organic	170.63

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4982\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.855,0.855,0.855
98.80	0.984
131.73	1.006
164.66	1.019
197.60	1.036
230.53	1.049
296.39	1.091
329.33	1.100

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.10699	0.9610(0.003)	51.241	4.87(0.08)	54(7)	3.24(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	777.51
organic	194.93

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5243\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.868,0.865,0.869
98.96	0.945
131.94	0.965
164.93	0.983
197.92	1.002
230.90	1.022
296.87	1.030
329.86	1.041

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.12355	0.9512(0.002)	50.639	5.41(0.08)	24(2)	2.90(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Methanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	749.88
organic	200.59

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.0900\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.868,0.865,0.869
93.96	0.919
125.28	0.937
156.60	0.963
187.92	0.975
219.24	0.999
281.88	1.020
313.20	1.037

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.13074	0.9549(0.0006)	50.381	6.28(0.59)	28(1)	2.97(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	953.41
organic	46.41

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.6054\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.851,0.851,0.851
100.52	1.119
134.03	1.136
167.54	1.151
201.05	1.160
234.56	1.162
301.57	1.177
335.08	1.185

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.0110	1.003(0.0020)	53.527	4.81(0.02)	269(23)	3.94(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	950.02
organic	50.69

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3795\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.828, 0.828, 0.830
100.98	1.082
134.64	1.095
168.3	1.107
201.96	1.116
235.62	1.129
302.94	1.137
336.59	1.144

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01215	0.9932(0.007)	53.346	4.71(0.02)	256(28)	3.92(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	900.08
organic	99.99

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3853\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.848,0.853,0.857
98.47	1.078
131.29	1.086
164.11	1.108
196.93	1.118
229.76	1.111
295.40	1.124
328.22	1.120

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02497	1.0039(0.001)	51.239	4.09(0.04)	296(57)	3.96(0.08)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	801.77
organic	198.49

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5851\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.919,0.918,0.918
98.47	1.069
131.29	1.089
164.11	1.103
196.93	1.118
229.76	1.125
295.40	1.137
328.22	1.142

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.05399	1.020(0.001)	47.034	3.75(0.01)	115(4)	3.55(0.01)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	700.15
organic	300.17

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4751\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.973,0.972,0.976
98.88	1.069
131.84	1.087
164.80	1.102
197.76	1.112
230.72	1.118
296.64	1.140
329.60	1.152

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.08955	1.0337(0.0009)	42.693	3.53(0.03)	57(4)	3.22(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
DMSO System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	600.36
organic	400.09

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5258\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	1.036,1.036,1.036
100.7	1.084
134.27	1.099
167.83	1.111
201.40	1.125
234.97	1.128
302.10	1.146
335.67	1.160

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.13318	1.0402(0.004)	38.428	4.61(0.06)	16(1)	2.66(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	920.76
organic	79.59

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5243\times10^{-5}$M	
$10^4 L_t/M$	Absorbance at 410nm
0	0.828,0.832,0.830
97.48	1.069
129.97	1.086
162.47	1.096
194.96	1.106
227.45	1.116
292.44	1.124
324.93	1.130

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02447	1.0020(0.0004)	52.375	4.43(0.01)	256(16)	3.91(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	841.48
organic	159.20

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4751\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.843,0.845,0.848
97.76	1.027
130.35	1.037
162.94	1.057
195.52	1.071
228.11	1.082
293.28	1.101
325.87	1.107

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.05205	1.0131(0.0005)	49.241	4.26(0.04)	128(17)	3.61(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	762.19
organic	237.78

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5938\times10^{-5}$M	
$10^4 L_t/M$	Absorbance at 410nm
0	0.866,0.868,0.864
100.48	0.996
133.97	1.017
167.46	1.036
200.95	1.045
234.44	1.056
301.43	1.073
334.92	1.082

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.08303	1.0214(0.001)	46.141	3.90(0.01)	78(3)	3.38(0.01)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	681.39
organic	319.19

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1652\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.862,0.869,0.869
100.09	0.957
133.45	0.972
166.81	0.988
200.17	0.998
233.53	1.005
300.26	1.024
333.62	1.035

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.11969	1.0318(0.001)	42.941	3.18(0.02)	51(3)	3.18(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethylene Glycol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	600.58
organic	407.74

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4331\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.923,0.917,0.917
99.32	0.968
132.43	0.980
165.54	0.999
198.65	1.011
231.75	1.022
297.97	1.036
331.08	1.041

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.16461	1.0394(0.0009)	39.578	5.85(0.1)	13(1)	2.58(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	990.17
organic	11.17

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4287\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.816,0.812,0.814
97.62	1.060
130.16	1.076
162.70	1.089
195.24	1.100
227.78	1.105
292.86	1.120
325.40	1.121

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules $molec.^{-1}$
0.00449	0.9875(0.005)	55.138	4.63(0.01)	254(15)	3.92(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	969.78
organic	29.03

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1204\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.780,0.771,0.776
103.04	0.969
137.39	0.990
171.73	0.998
206.08	1.011
240.43	1.026
309.12	1.050
343.47	1.048

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01183	0.9722(0.003)	54.541	4.61(0.04)	135(19)	3.65(0.06)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	949.82
organic	47.29

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.6068\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.848, 0.845, 0.852
95.87	1.002
127.82	1.017
159.78	1.040
191.73	1.049
223.69	1.061
287.60	1.080
319.56	1.085

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01952	0.9782(0.0006)	53.929	4.04(0.03)	102(7)	3.54(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	926.13
organic	65.76

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3737\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.822,0.823,0.825
99.48	0.950
132.64	0.967
165.80	0.985
198.96	1.002
232.12	1.012
298.44	1.034
331.60	1.045

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02760	0.9766(0.005)	53.300	4.29(0.03)	66(4)	3.35(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	899.93
organic	98.01

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2637\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.823,0.829,0.829
96.29	0.904
128.39	0.916
160.49	0.928
192.58	0.940
224.68	0.949
288.87	0.966
320.97	0.971

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.04172	0.9753(0.0003)	52.237	2.98(0.02)	52(3)	3.24(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	875.56
organic	122.18

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4461\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.854,0.857,0.862
101.67	0.918
135.56	0.928
169.45	0.943
203.34	0.955
237.23	0.964
305.01	0.976
338.90	0.985

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.05284	0.9661(0.01)	51.429	3.32(0.03)	31(1)	3.02(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Ethanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	850.83
organic	135.56

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.8819\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.927,0.924,0.925
101.19	0.973
134.92	0.986
168.65	0.995
202.39	1.006
236.12	1.013
303.58	1.028
337.31	1.035

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.05988	0.9713(0.0004)	50.931	3.07(0.01)	24.4(0.5)	2.92(0.01)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	990.98
organic	10.08

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4070\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.804,0.804,0.804
96.63	1.006
128.85	1.023
161.06	1.040
193.27	1.052
225.48	1.060
289.90	1.078
322.11	1.082

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00304	0.9848(0.0008)	55.118	4.43(0.03)	355(15)	4.06(0.06)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	980.60
organic	20.33

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.6879\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.820,0.822
98.11	1.050
130.82	1.067
163.52	1.087
196.23	1.103
228.93	1.113
294.34	1.129
327.05	1.138

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00618	0.9894(0.0008)	54.720	4.88(0.02)	154(12)	3.72(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	970.69
organic	29.47

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4070\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.815,0.809,0.815
96.63	1.006
128.85	1.023
161.06	1.040
193.27	1.052
225.48	1.060
289.90	1.078
322.11	1.082

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00902	0.9848(0.0008)	54.364	4.35(0.02)	151(9)	3.70(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	960.41
organic	39.90

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2405\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.807,0.807,0.803
97.67	0.978
130.23	1.000
162.78	1.027
195.34	1.042
227.90	1.060
293.01	1.083
325.57	1.090

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01230	0.9931(0.0007)	53.959	5.48(0.03)	77(3)	3.43(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	951.12
organic	49.14

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2941\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.809,0.815,0.810
96.80	0.961
129.06	0.980
161.33	0.995
193.59	1.008
225.86	1.025
290.39	1.048
322.66	1.071

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01525	0.9749(0.0008)	53.600	4.64(0.07)	79(11)	3.43(0.06)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	941.01
organic	59.96

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4041\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.828,0.820,0.824
97.71	0.964
130.28	0.982
162.85	1.007
195.42	1.023
227.99	1.044
293.13	1.076
325.70	1.090

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01874	0.9823(0.0003)	53.181	5.55(0.07)	61(6)	3.32(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	919.71
organic	78.14

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1435\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.814,0.815,0.817
98.99	0.914
131.99	0.923
164.98	0.940
197.98	0.948
230.98	0.965
296.97	0.982
329.97	0.988

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02483	0.9817(0.0004)	52.465	3.49(0.05)	63(7)	3.33(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Isopropanol System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	900.13
organic	95.64

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4374\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.814,0.815,0.817
95.98	0.924
127.98	0.934
159.97	0.943
191.97	0.960
223.96	0.969
287.95	1.004
319.94	0.996

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03087	0.9674(0.0008)	51.776	3.46(0.08)	42(6)	3.15(0.06)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	990.66
organic	10.09

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2738\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.789,0.797,0.792
99.11	1.035
132.14	1.047
165.18	1.061
198.21	1.070
231.25	1.087
297.32	1.094
330.35	1.100

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00445	0.9931(0.0004)	55.195	4.74(0.03)	228(30)	3.88(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	980.02
organic	20.15

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4418\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.816,0.820,816
94.66	1.012
126.21	1.028
157.76	1.048
189.32	1.062
220.87	1.073
283.97	1.089
315.53	1.093

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01143	0.9936(0.002)	55.020	4.53(0.02)	140(9)	3.68(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	960.29
organic	39.63

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2333\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.825, 0.823, 0.823
97.10	0.960
129.46	0.982
161.83	1.001
194.19	1.015
226.56	1.027
291.29	1.049
323.65	1.055

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01779	0.9822(0.009)	54.275	4.55(0.01)	73(2)	3.40(0.01)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	940.6
organic	58.99

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2767\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.830,0.827,0.830
97.07	0.926
129.43	0.942
161.79	0.958
194.15	0.976
226.50	0.994
291.22	1.009
323.58	1.016

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02679	0.9855(0.0005)	53.671	4.40(0.04)	44(3)	3.19(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	923.02
organic	78.43

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2956\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.812, 0.816, 0.817
96.93	0.887
129.24	0.902
161.55	0.923
193.86	0.937
226.17	0.961
290.79	0.993
323.10	1.002

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03595	0.9849(0.005)	53.070	4.40(0.04)	44(3)	3.19(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetonitrile System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	900.42
organic	94.64

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.2825\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.845,0.842,0.838
97.03	0.898
129.38	0.905
161.72	0.916
194.07	0.928
226.41	0.938
291.10	0.954
323.45	0.969

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.05580	0.9784(0.001)	53.198	3.25(0.06)	30(3)	3.03(0.05)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	990.45
organic	9.80

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3650\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.810, 0.815, 0.816
94.06	1.066
125.42	1.079
156.77	1.088
188.13	1.099
219.48	1.106
282.19	1.112
313.54	1.110

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00306	0.9911(0.0007)	55.134	4.43(0.01)	360(28)	4.07(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	982.78
organic	17.42

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.5721\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.831,0.835,828
97.62	1.071
130.15	1.086
162.69	1.099
195.23	1.108
227.77	1.112
292.85	1.126
325.39	1.128

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.00547	0.9925(0.002)	54.842	4.38(0.01)	270(15)	3.95(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	960.53
organic	37.51

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.1739\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.810,0.809,0.807
107.22	0.998
142.96	1.008
178.70	1.021
214.43	1.027
250.17	1.037
321.65	1.049
357.39	1.058

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01197	0.9843(0.0006)	54.070	3.90(0.03)	188(28)	3.79(0.06)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	939.52
organic	60.48

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.3288\times10^{-5}M$	
$10^4 L_t/M$	Absorbance at 410nm
0	0.841,0.842,0.842
97.10	0.986
129.47	1.001
161.83	1.015
194.20	1.027
226.57	1.040
291.30	1.053
323.67	1.064

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.01958	0.9758(0.001)	53.193	3.81(0.03)	107(9)	3.55(0.04)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	921.67
organic	71.92

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4215\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.857,0.857,0.857
97.87	0.981
130.49	0.999
163.11	1.016
195.74	1.028
228.36	1.040
293.60	1.058
326.23	1.066

x_2	ρ_o / g/ml	M^* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.02363	0.9795(0.002)	52.738	3.92(0.02)	75(3)	3.40(0.02)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the
Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	900.19
organic	99.60

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.6807\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.911,0.909,0.911
99.45	0.998
132.60	1.015
165.75	1.027
198.90	1.043
232.05	1.056
298.35	1.069
331.50	1.090

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03318	0.9779(0.0008)	51.695	3.77(0.04)	43(3)	3.16(0.03)

Complexation Data for 4-Nitroaniline with
α-Cyclodextrin in the

Acetone System

Weight Contributions of Water and Organic to Solvent Mixture/g	
water	880.02
organic	113.69

Absorbance as a Function of Cyclodextrin Concentration $S_t=7.4693\times10^{-5}$M	
$10^4 L_t$/M	Absorbance at 410nm
0	0.890, 0.892, 0.898
97.97	0.965
130.63	0.976
163.29	0.990
195.94	1.006
228.60	1.019
293.91	1.027
326.57	1.039

x_2	ρ_o / g/ml	M* / moles kg^{-1}	$\Delta\varepsilon_{11}$ / 10^{-3} $M^{-1}cm^{-1}$	K_{11} / M^{-1}	$-\Delta G_u^0$ / 10^{-20} joules molec.$^{-1}$
0.03853	0.9765(0.0005)	51.128	3.49(0.04)	38(3)	3.10(0.03)

APPENDIX C

CURVATURE CORRECTION FACTOR VALUES GENERATED BY THE ORIGINAL AND MODIFIED SOLVENT EFFECT MODELS

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated[a] Using the Hydrophobic Surface Area	g Calculated[b] Using the Total Surface Area
biphenyl solubility	methanol	0.415(0.008)	0.415(0.008)
napthalene solubility	methanol	0.367(0.015)	0.367(0.015)
4-nitroaniline solubility	methanol	0.518(0.054)	0.240(0.021)
α-cyclodextrin-Methyl Orange complexation	methanol	0.410(0.041)	0.198(0.002)
α-cyclodextrin-4-nitroaniline complexation	methanol	0.693(0.021)	0.308(0.011)

[a] The curvature correction factor values for the complexation studies were calculated using the hydrophobic surface area of the cavity interior of α-cyclodextrin for ΔA, which was 105(3) $Å^2 molecule^{-1}$. The hydrophobic surface area of 4-nitroaniline used to calculate g for the 4-nitroaniline solubility studies was 68(4) $Å^2 molecule^{-1}$. The solute surface areas used to calculate g for the napthalene and biphenyl solubility studies were 150(3)$Å^2 molecule^{-1}$ and 179(3)$Å^2 molecule^{-1}$ and were obtained from reference 1.

[b] The curvature correction factor values for the complexation studies were calculated using the total surface area of the cavity interior of α-cyclodextrin for ΔA, which was 217(7) $Å^2 molecule^{-1}$. The total surface area of 4-nitroaniline used to calculate g for the 4-nitroaniline solubility studies was 147(4) $Å^2 molecule^{-1}$.

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
4-nitroaniline solubility	DMSO	1.257(0.094)	0.583(0.029)
α-cyclodextrin-Methyl Orange complexation	DMSO	0.63(0.12)	0.304(0.056)
α-cyclodextrin-4-nitroaniline complexation	DMSO	6.73(0.23)	3.25(0.11)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
napthalene solubility	ethylene glycol	0.68(0.02)	0.68(0.02)
4-nitroaniline solubility	ethylene glycol	1.24(0.12)	0.573(0.051)
α-cyclodextrin-Methyl Orange complexation	ethylene glycol	0.55(0.14)	0.27(0.07)
α-cyclodextrin-4-nitroaniline complexation	ethylene glycol	4.76(0.22)	2.30(0.11)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
4-nitroaniline solubility	isopropanol	0.156(0.012)	0.073(0.004)
α-cyclodextrin-Methyl Orange complexation	isopropanol	0.105(0.029)	0.051(0.014)
α-cyclodextrin-4-nitroaniline complexation	isopropanol	0.002(0.003)	0.001(0.001)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
napthalene solubility	acetonitrile	0.387(0.028)	0.387(0.028)
4-nitroaniline solubility	acetonitrile	0.429(0.037)	0.199(0.013)
α-cyclodextrin-Methyl Orange complexation	acetonitrile	0.124(0.048)	0.060(0.023)
α-cyclodextrin-4-nitroaniline complexation	acetonitrile	0.006(0)	0.003(0)
4-nitroaniline solubility	ethanol	0.312(0.022)	0.145(0.0074)
α-cyclodextrin-4-nitroaniline complexation	ethanol	0.107(0.005)	0.052(0.002)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Original Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
α-cyclodextrin-Methyl Orange complexation	dioxane	0.362(0.040)	0.175(0.019)
4-nitroaniline solubility	acetone	0.541(0.066)	0.251(0.028)
α-cyclodextrin-Methyl Orange complexation	acetone	0.029(0.019)	0.014(0.009)
α-cyclodextrin-4-nitroaniline complexation	acetone	0.737(0.024)	0.355(0.012)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
biphenyl solubility	methanol	0.467(0.008)	0.467(0.008)
napthalene solubility	methanol	0.449(0.013)	0.449(0.013)
4-nitroaniline solubility	methanol	0.693(0.044)	0.321(0.012)
α-cyclodextrin-Methyl Orange complexation	methanol	0.533(0.040)	0.257(0.020)
α-cyclodextrin-4-nitroaniline complexation	methanol	0.723(0.020)	0.349(0.012)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
4-nitroaniline solubility	DMSO	1.815(0.112)	0.842(0.027)
α-cyclodextrin-Methyl Orange complexation	DMSO	0.877(0.09)	0.423(0.044)
α-cyclodextrin-4-nitroaniline complexation	DMSO	6.65(0.22)	3.20(0.11)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
napthalene solubility	ethylene glycol	0.826(0.017)	0.826(0.017)
4-nitroaniline solubility	ethylene glycol	1.469(0.092)	0.681(0.023)
α-cyclodextrin-Methyl Orange complexation	ethylene glycol	0.89(0.13)	0.428(0.061)
α-cyclodextrin-4-nitroaniline complexation	ethylene glycol	4.71(0.21)	2.27(0.10)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
4-nitroaniline solubility	isopropanol	0.645(0.038)	0.299(0.008)
α-cyclodextrin-Methyl Orange complexation	isopropanol	0.394(0.028)	0.190(0.014)
α-cyclodextrin-4-nitroaniline complexation	isopropanol	0.305(0.010)	0.147(0.005)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
napthalene solubility	acetonitrile	0.594(0.029)	0.594(0.029)
4-nitroaniline solubility	acetonitrile	0.960(0.058)	0.445(0.013)
α-cyclodextrin-Methyl Orange complexation	acetonitrile	0.457(0.036)	0.220(0.018)
α-cyclodextrin-4-nitroaniline complexation	acetonitrile	0.353(0.012)	0.170(0.006)
4-nitroaniline solubility	ethanol	0.681(0.04)	0.316(0.009)
α-cyclodextrin-4-nitroaniline complexation	ethanol	0.360(0.012)	0.174(0.006)

Curvature Correction Factor Values in the Various Cosolvent Systems Generated by the Modified Complexation and Solubility Models

System	Cosolvent	g Calculated Using the Hydrophobic Surface Area	g Calculated Using the Total Surface Area
α-cyclodextrin-Methyl Orange complexation	dioxane	0.702(0.048)	0.339(0.024)
4-nitroaniline solubility	acetone	0.974(0.064)	0.452(0.018)
α-cyclodextrin-Methyl Orange complexation	acetone	0.336(0.025)	0.162(0.012)
α-cyclodextrin-4-nitroaniline complexation	acetone	0.899(0.030)	0.433(0.015)