SOLVENT EFFECTS ON THE SOLUBILITY AND COMPLEXATION OF NAPHTHALENE AND THEOPHYLLINE IN BINARY AQUEOUS-ORGANIC MIXTURES

by

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To my parents
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Approved:

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Table of contents

Page

I. **INTRODUCTION** 1

I. INTRODUCTION

1 HISTORICAL BACKGROUND OF SOLUBILITY

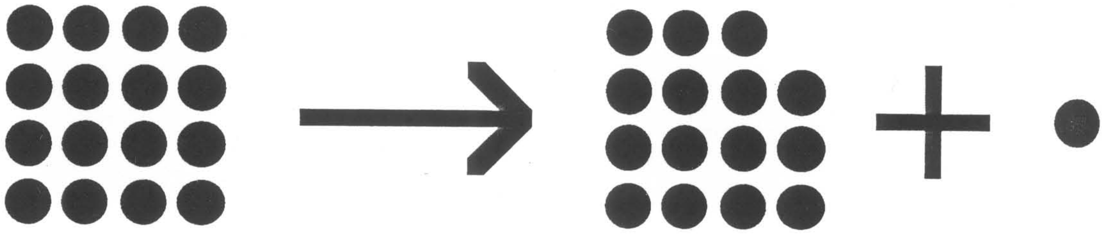
Various methods have been utilized to enhance the solubility of organic molecules. Organic cosolvents, complexation agents, and surfactants have been used to increase the solubility of poorly soluble drugs.[1] In the present study, drug solubility and drug complexation in the presence of mixed aqueous-organic solvents was pursued.

A. The Solubility Process

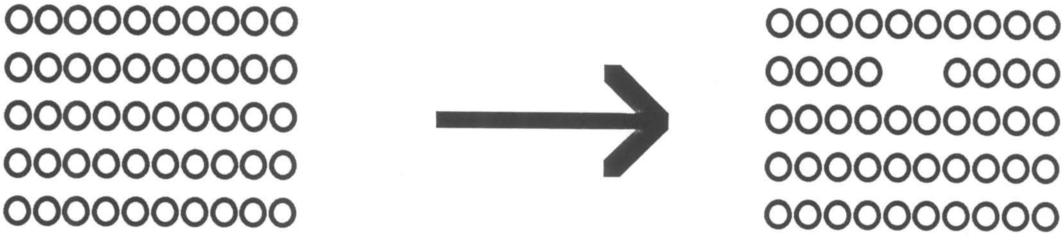
The solubility of a nonsolvated form of a crystalline organic molecule can be represented by the following equilibrium

$$\mathrm{D}\ (\text{solid}) \quad \overset{K_s}{\rightleftharpoons} \quad \mathrm{D}\ (\text{aqueous})$$

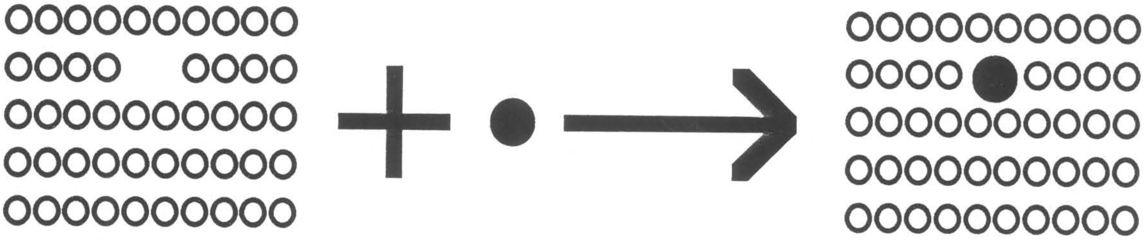
where K_s is the equilibrium constant associated with the solubility process. The solubility process has been divided into three steps by Hildebrand and Scott (1950) and by Scatchard (1931)[2] in order to illustrate the changes in the intermolecular interaction energies. (Scheme 1)



Step 1. Abstraction of one solute molecule from the crystal lattice.



Step 2. Creation of the cavity in the solvent.



Step 3. Insertion of the solute molecule in the cavity and the subsequent interaction between the solute and the solvent.

Scheme 1. The solubility process.

The first step in this scheme represents the removal of one solute molecule from the crystal lattice. The second step involves the creation of a cavity in the solvent large enough to allow the insertion of the solute molecule. The final step entails the insertion of the abstracted solute molecule from stage one into the cavity that was created in the second step, and the subsequent interaction of the solute molecule with the surrounding solvent molecules.

B. The Regular Solution Theory

The regular solution theory takes into account only the molecular pair potentials for the three forementioned steps, and represents the overall change in the pair-potential energy (ΔU) as

$$\Delta U = U_{AA} + U_{BB} - 2U_{AB} \qquad (1\text{-}1)$$

where U_{BB} represents the energy change that is associated with breaking the interaction between two solute (solute-solute) molecules in the crystal lattice (step 1), U_{AA} represents the energy change associated with breaking the solvent-solvent interactions required in creating the cavity (step 2), and U_{AB} represents the energy change associated with solute-solvent interactions (step 3). The positive signs for the first two terms in the above equation signify that the first two steps in this process require energy to break the solute-solute and solvent-solvent interactions, whereas the last step liberates energy (represented by the negative sign) through the formation of new interactions between the solute and the solvent molecule. It should be emphasized that this analysis is highly simplified, since the analysis involves only pair-wise molecular interactions. At this point a crucial assumption is made, namely,

$$U_{AB} = (U_{AA} U_{BB})^{1/2} \qquad (1-2)$$

This assumption, which is known as the geometric mean assumption, when incorporated into equation (1-1) leads to

$$\Delta U = (U_{AA}^{1/2} + U_{BB}^{1/2})^{2} \qquad (1-3)$$

Now, the solubility parameter is defined as

$$\delta_A = U_{AA}^{1/2} \qquad \delta_B = U_{BB}^{1/2} \qquad (1-4)$$

Substituting this definition into equation (1-3) gives the potential energy change in terms of the solubility parameters of the solute and the solvent, from which equation (1-5), the Hildebrand solubility equation, can be derived,

$$\ln x_{exp} = (\ln x_{ideal}) - (V_B \, \phi_A^{2} \, (\delta_A - \delta_B)^{2} / RT) \qquad (1-5)$$

where x_{ideal} is the ideal solubility of the solute, V_B is the molar volume of the solute, ϕ_A is the volume fraction of the solvent, and x_{exp} is the experimental solubility (mole fraction scale). Values of solubility parameters for the solvent and the solute molecules can be measured experimentally (from heats of vaporization), and have been tabulated. The solubility parameter for mixed aqueous cosolvent systems has been calculated via

$$\delta = \phi_A\delta_A + \phi_B\delta_B + \ldots \qquad (1\text{-}6)$$

where ϕ_A represents the volume fraction of cosolvent A and δ_A represents the solubility parameter associated with cosolvent A.

The ability of the Hildebrand equation to predict solubilities is good for nonpolar solutes in nonpolar solvents, where the intermolecular forces present are predominantly London dispersion forces. Solutions of nonpolar solutes in nonpolar solvents, where the size of the solute and solvent molecules do not differ appreciably, are referred to as regular solutions. The Hildebrand equation does not provide good estimates of solubilities in cases where either the solute or the solvent is polar, since the geometric mean rule is no longer valid in these situations. This is due to the presence of intermolecular forces other than the London dispersion forces, in particular dipole-dipole, dipole-induced dipole, charge transfer, and hydrogen bonding interactions. It should be noted that in cases of charge transfer and hydrogen bonding, specific molecular interactions occur and the entropy of mixing will no longer be ideal, which is another underlying assumption in the derivation of the regular solution theory.

Hildebrand and coworkers have discussed the above mentioned limitations of their regular solution theory; however many scientists still attempt to apply the regular solution theory to cosolvent systems consisting of water and/or alcohols or to polar solutes such as caffeine, theophylline, and theobromine.

C. Extended Regular Solution Theory

Martin and coworkers [3-5] realized that the major limitations of the regular solution theory arise from the geometric mean assumption (Equation 1-2). In order to alleviate this problem they replaced U_{AB} with an adjustable parameter W. Subsequently the value of W is calculated from the solubility data themselves. The value of W is then regressed in a third- or fourth-degree polynomial against the solubility parameter of the binary mixture prepared. At this stage the solubility is predicted for the binary solvent by calculating a W from the regressed polynomial, this value along with the solubility parameter then being used to calculate the solubility. This method yields errors in predicted mole fraction solubility of < 3%; however this should not be surprising since the solubility data themselves are used to calculate W, an adjustable parameter.

D. Two-Dimensional Analog of The Regular Solution Theory

Yalkowsky and coworkers[6] pursued a more theoretical approach to overcome the limitations of the regular solution theory caused by the geometric mean assumption. This approach is made possible by the fact that the potential energies in Eq (1-1) can be expressed either in terms of energy per unit volume of the solute molecule or in terms of energy per unit surface area of the solute molecule.[6] In the original Hildebrand regular solution theory the energies were expressed in terms of the molecular volume of the solute molecule. Yalkowsky and coworkers[7] expressed the potential energies in terms of energy per unit surface area. In this model the solubility parameters ($\delta_1, \delta_2, \delta_{12}$) are replaced by the surface and the interfacial tensions ($\gamma_1, \gamma_2, \gamma_{12}$), and the partial molal volume is replaced by the molar surface area. However, upon simplification only the interfacial tension will be needed.

The primary advantage of this model is that the quantity δ_{12} is replaced by γ_{12}, which can be determined experimentally. This model is complementary to the original regular solution theory because the interfacial tension (γ_{12}) is easier to measure for solute and solvents of different polarity where the regular solution theory fails. The interfacial tension term has to be modified, however, since the bulk macroscopic interfacial tension cannot be used owing to the presence of curvature at the interface surrounding the solute molecule. To correct for this a curvature correction factor was introduced; this was empirically determined from the data and was shown to be in good agreement with theoretical estimates. Another modification made use of the Langmuir principle of independent surface action, in which the hydrocarbon and polar groups are considered to make independent additive contributions to the surface and interfacial tensions. In subsequent work Amidon, Yalkowsky and Leung[8] indicate that this modification might not be necessary. In this study the solubility of aliphatic alcohols in water was correlated against the alcohols' total surface area, hydrocarbon surface area, and a combination of hydrocarbon surface area and hydroxyl group surface area. The correlation coefficients obtained were 0.974, 0.94, 0.978, respectively, indicating that the total surface area seems as good a parameter as the combination of the hydrocarbon and hydroxyl group surface areas, especially when the computational effort of calculating these parameters is considered. However, the authors decided to divide the total area into hydrophobic and polar contributions.

Subsequently, Yalkowsky and coworkers[9] represented the solubility of the drug in water as

$$-\mathbf{k}T \ln x_w = -\mathbf{k}T \ln x_i + \gamma_{wh}\ \mathrm{HSA} + \varepsilon_{wp}\ \mathrm{PSA} \qquad (1\text{-}7)$$

where x_i is the ideal mole fraction solubility, and γ_{wh} and ε_{wp} represent the microscopic surface energy density (free energy per unit area at the aqueous interface) with the hydrophobic and polar portions of the solute molecule, respectively HSA and PSA represent the hydrocarbon and polar surface area of the solute molecule. A similar equation was written for solubility of a solute in pure cosolvent. In order to predict the solubility of the solute in the mixed aqueous organic solvent it was assumed that the solvent properties of the mixed solvent are linear combinations of the properties of the pure solvents. The weighting factor chosen for this linear combination was the volume fraction of the solvent present. In this process the equation for each pure solvent is multiplied by its volume fraction, and the two equations are then added. With the assumption that the sum of volume fractions of water and cosolvent is unity (this might not be valid owing to presence of the solute), the following equation was obtained,

$$\mathbf{k}T \ln x_f = \mathbf{k}T \ln x_w + [\, \Delta\gamma \text{ HSA} + \Delta\varepsilon \text{ PSA}]\, f_c \qquad (1\text{-}8)$$

where x_f is the mole fraction solubility in the mixed aqueous organic solvent, x_w is the mole fraction solubility in pure water, $\Delta\gamma = \gamma_{wh} - \gamma_{ch}$ (γ_{ch} is the interfacial tension between the cosolvent and the hydrophobic portion of the solute), $\Delta\varepsilon = \varepsilon_{wp} - \varepsilon_{cp}$ (ε_{cp} is the interfacial tension between the cosolvent and the polar portion of the solute), and f_c is the volume fraction of the organic cosolvent present. The above equation may be rewritten in the form

$$\ln (x_f) = \ln (x_w) + \sigma f_c \qquad (1\text{-}9)$$

where is σ referred to as the solubilizing power of the cosolvent. Owing to its simplicity the above equation has been extensively tested [10-12]. It should also be mentioned that the solubilizing power has also been empirically related to the solute's octanol-water partition coefficient. However, the main approach taken is to determine the solubility of the drug as a function of the volume percent of cosolvent present, the data then being plotted in a semilogthermic fashion against the volume fraction of the cosolvent. Most points do not lie on the straight line that is predicted by this equation. The curves obtained are either concave downward at the higher composition of organic cosolvent or they are sigmodal. Occasionally extremum points are observed, where the solubility of the solute is greater in the binary mixture than in either of the pure solvents. The presence of the curvature that is apparent in many of the plots has been attributed to two different types of nonideality. The first type involves the solvent system itself; specifically, the assumption that the cosolvent can be represented as a linear combination of the two pure solvents ignores any specific solvent-solvent interactions that may be present. The second nonideality might arise from specific interactions between the solute molecule with itself or either (or both) of the kinds of solvent molecules that are present.

E. The UNIQUAC and UNIFAC Models

The UNIQUAC[13] (universal quasi-chemical equation or model) takes the above mentioned interactions into account. The approach involves two successive correlations. The first step entails the use of nonlinear regression analysis to determine the best estimates of the interaction parameters for an experimentally determined quantity. The number of interaction parameters is based upon the system under study; if the system is composed of solute in a mixed binary cosolvent system six interaction parameters would be required to describe the system. The second step utilizes the parameters obtained in the first step to estimate a second experimental quantity. The UNIQUAC approach is applied to the whole solute molecule, whereas the UNIFAC model (acronym for UNIQUAC functional-group activity coefficients) treats the solute molecule as a collection of different functional groups. This method also proceeds in two steps as mentioned previously. The calculations are very involved and time consuming. However, an extensive data base consisting of interaction parameters and computer programs has been developed. Williams and Amidon[14-16] have described a model that is similar in approach to the UNIQUAC model.

F. Specific Solute-Solvent Interaction Model

A very simplified approach with minimal computational effort was developed by Fung and Higuchi [17]. This approach takes into account only the solute-solvent interactions. It should be noted that owing to its simplicity it is only applicable to systems consisting of an inert solvent (saturated hydrocarbons) and an interacting solvent (usually chloroform, ether, or amides). The solubility of the solute is then described as the intrinsic solubility of the solute in the inert solvent plus the amount that is solubilized as a result of solvate complex formation with the interacting solvent. The solvate formation is represented by an equilibrium step

$$iA + jS \overset{Kij}{\rightleftharpoons} A_iS_j$$

where S represents the interacting solvent, A represents the solute, A_iS_j represents the solvate formed, and K_{ij} represents the formation constant. The solubility data can generally be modelled by one or two equilibrium steps. The limitation of this model arises from the fact that one of the solvents has to be non-interacting or inert and the other solvent interacting. The interactions between the interacting solvent and solute molecule are considered mainly to be due to hydrogen bonding or charge transfer interactions.

G. Nearly Ideal Binary Solvent Theory

Acree and coworkers argued that in the specific solute-solvent interaction model several equilibrium steps are required to describe the solubility data. The nearly ideal binary solvent model (NIBS) was developed to describe the data. This model is based entirely on non-specific interactions [18]. The model has achieved moderate success.

The model was later extended by Acree to include an equilibrium step describing specific interaction between the solute and the solvent [19]. It should be noted that the values of the equilibrium constant calculated via the NIBS and the specific interaction model will differ owing to the fact that the NIBS model incorporates nonspecific terms whereas the specific interaction model does not [20].

H. Uhlig's Gas Solubility Model

Acree's discussion suggests that the solubility process presented in scheme 1 can be broken down into different contributions and that the evaluation of these contributions are highly model dependent. Both Hildebrand's regular solution theory and Yalkowsky's two-dimensional analogy broke the solubility process into three contributions, and both models made approximations to simplify the solute-solvent interaction term. A model proposed in 1937 by Uhlig[21] and used later by Eley[22,23] to interpret gas solubilities in different solvents did not attempt to simplify the solute-solvent interaction term. In particular, Uhling divided the free energy for the process into a free energy contribution from the cavity formation (step 2) and a free energy change for solute-solvent interaction (step 3). The free energy for solute-solute (gas-gas) interaction was assumed to be negligible. The free energy change for cavity formation was taken as the work against the surface forces of the solvent, which was calculated by multiplying the surface area of the solute molecule by the solvent surface tension. The free energy for solute-solvent interaction was left as a parameter, which was later proved to be negligible for most gases. This method of modeling gas solubility was highly successful, and radii for various gas molecules, in good agreement with the values calculated by other means, could be obtained. For an extensive review of the solubility of gases in liquids the reader is referred to an article by Battino and Clever.[24]

I. Contributional Models

Roseman and Jencks[25] studied the solubility of uric acid and naphthalene in binary mixtures of aqueous-organic cosolvents. The free energy change of the solution process was modelled as a result of three different contributions, the first contribution arising from cavity formation, the second contribution arising from non-polar solute-solvent interactions (dispersion, dipole-induced dipole, and quadrupole forces), and the third contribution from polar interactions. This last term was primarily limited to solute-solvent hydrogen bonding. The overall free energy for the transfer of solute from gas phase to the solvent was described as

$$\Delta G_{tr} = \Delta G^{cav} + \Delta G^{int}_{nonpolar} + \Delta G^{int}_{polar} \qquad (1\text{-}10)$$

They further argued that the driving force for a favorable free energy transfer for both nonpolar and polar solute from pure water to water-cosolvent mixtures arises from a more favorable contribution from the first two terms in going from water to water-cosolvent mixtures. They also note that the third term does not contribute for nonpolar solutes, whereas for polar solutes this term can either be close to zero or can contribute unfavorably to the free energy of transfer.

Perez-Tejeda and coworkers[26], who also studied the transfer of naphthalene from water to mixed aqueous organic solvents, describe the transfer free energy for this process as consisting of a cavity and an interaction term. The cavity term is calculated based on the scaled particle theory, which will be discussed later.

2. THE PROPOSED SOLUBILITY MODEL

In our model the solubility process is composed of three terms as in scheme 1, however a different formalism is adopted. The overall free energy change is considered to be composed of a free energy associated with an abstraction of solute molecule from the crystal lattice (solute-solute interaction), a free energy term associated with the creation of the cavity (solvent-solvent interaction referred to as the general medium effect in our model), and a free energy term associated with the insertion and subsequent interaction of the solute with the solvent (solute-solvent interaction referred to as the solvation effect in our model).

$$\Delta G^{\circ}_{\text{total}} = \Delta G^{\circ}_{\text{lattice}} + \Delta G^{\circ}_{\text{gen.med.}} + \Delta G^{\circ}_{\text{solv.}} \qquad (2\text{-}1)$$

In our approach each contribution is treated independently and quantitative expressions for the general medium and the solvation effect are derived.

A. The Solvation Effect

The solvation effect in our model arises as a consequence of step-wise competitive equilibria of water (W) and organic cosolvent (M) molecules with the solute, R:

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

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

$$\vdots$$

$$\vdots$$

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

It should be obvious that this approach with many equilibrium steps may have practical disadvantages associated with it, in particular evaluation of several equilibrium steps is tedious and requires precise data. In our case, however we find that we only need the first two equilibrium steps in order to describe the data, thus we write

$$RW_2 + M \overset{K_1}{\rightleftharpoons} RWM + W \qquad (2\text{-}2)$$

$$RWM + M \overset{K_2}{\rightleftharpoons} RM_2 + W \qquad (2\text{-}3)$$

The solute (R) may exist as three different solvated species, namely RW_2,RWM, or RW_2. The contribution to the free energy from solvation is then postulated to be a weighted average of contributions from these three solvated species,

$$\Delta G^\circ_{solv} = \Delta G^\circ_{WW} F_{WW} + \Delta G^\circ_{WM} F_{WM} + \Delta G^\circ_{MM} F_{MM} \qquad (2\text{-}4)$$

where F_{WW}, F_{WM}, F_{MM} are the fractions of the solute present in each of the three species. Since $F_{WW} + F_{WM} + F_{MM} = 1$ the above equation can be simplified to

$$\Delta G^\circ_{solv} = (\Delta G^\circ_{WM} - \Delta G^\circ_{WW})\ F_{WM} + (\Delta G^\circ_{MM} - \Delta G^\circ_{WW})\ F_{MM} + \Delta G^\circ_{WW} \qquad (2\text{-}5)$$

The above equation can be rewritten as

$$\Delta G^\circ_{solv} = S_1\ F_{WM} + S_2\ F_{MM} + \Delta G^\circ_{WW} \qquad (2\text{-}6)$$

where the definitions of S_1 and S_2 are obvious. From the definition of the equilibrium constants (equations 2-2,2-3) the above fractions can be written as

$$F_{WM} = \frac{K_1 x_1 x_2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (2\text{-}7)$$

$$F_{MM} = \frac{K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (2\text{-}8)$$

where x_1 and x_2 are the mole fractions of water and the organic cosolvent, respectively. Substituting these in Eq 2-6 and simplifying, the following equation is obtained,

$$\Delta G^\circ_{solv} = \frac{S_1K_1x_1x_2 + S_2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + \Delta G^\circ_{WW} \qquad (2\text{-}9)$$

which can be transformed to

$$\Delta G^\circ_{solv} = \frac{S_1K_1x_2 + (S_2K_1K_2 - S_1K_1)x_2^2}{1 + (K_1-2)x_2 + (1- K_1+K_1K_2)x_2^2} + \Delta G^\circ_{WW} \qquad (2\text{-}10)$$

where we have used $x_1+x_2=1$, an approximation because of the presence of the solute. It is convenient to express the above equation as

$$\Delta G^\circ_{solv} = \frac{a_2x_2 + b_2x_2^2}{1 + m_2x_2 + n_2x_2^2} + \Delta G^\circ_{WW} \qquad (2\text{-}11)$$

where the definitions of the parameters are apparent by comparing the above two equations. The parameter subscripts indicate that two equilibrium steps have been utilized in the solvation model.

In the above model some interesting special cases of the solvation effect exists. For example if $S_1=0$ and $S_2=0$

then there is no net solvation effect. Furthermore if $K_1=2$ and $K_2=0.5$, then the solvation effect can be described as "ideal" or nonselective solvation, in which

$$\Delta G^\circ_{\text{ideal solv}} = \Delta G^\circ_{WW} x_1^2 + 2\,\Delta G^\circ_{WM}\, x_1 x_2 + \Delta G_{MM}^\circ x_2^2 \qquad (2\text{-}12)$$

In this case the distribution of the solvated species is statistically rather than chemically determined. This condition is characteristic of a binding process involving two identical, independent binding sites.[27] Furthermore if we let solvation stoichiometery be indicated RW_iM_j so that $i+j=k$, and define f_1 and f_2 as the mean fractional compositions of the solvation shell with respect to components 1 and 2, so that $f_1+f_2=1$, then

$$f_2 = (1/k) \sum j\, f_{ij} \qquad (2\text{-}13)$$

and we find that in the ideal solvation condition $f_1=x_1$ and $f_2=x_2$; the mean solvation shell composition is identical to the bulk composition in the special case of nonselective solvation.

In the above solvation model two equilibrium steps have been utilized. If only one equilibrium step is utilized (which is equivalent to setting $K_2=0$), the following solvation model is obtained:

$$\Delta G^\circ_{\text{solv}} = \frac{S_1 K_1 x_2}{1 + (K_1-1) x_2} + \Delta G^\circ_{WW} \qquad (2\text{-}14)$$

In this case the ideal solvation case arises when K_1=1.

B. The General Medium Effect

In our model the general medium effect is the free energy required to create the cavity in the solvent. Two methods are available for calculating the free energy change for the cavity formation. One of these is based on scaled particle theory (SPT), and the other is a semi-empirical model which treats cavity formation as the work done against the surface forces of the solvent (at the microscopic level). The scaled particle theory is based on statistical mechanical arguments, in which the general approach is to start with a cavity of zero radius, followed by a scaling up to a desired radius of the cavity. The solute molecule is treated as a hard sphere, and the solvent as hard cores whose volume and pressure at given temperature is determined by real intermolecular potentials.[28] The hard sphere diameter of the solute and the solvent is then used to calculate the energy of cavity formation, though a problem arises in that this calculated value is extremely sensitive to the hard sphere diameters of the solute and the solvent molecules. Therefore it has been pointed out that the application of the scaled particle theory is restricted to systems composed of nearly spherical and apolar molecules with no orientational molecular correlations.[29]

The second method is more promising since the free energy change for cavity formation is not as sensitive to the molecular parameters. This model, which was proposed by Uhlig[21], as described in section I-1-H, takes the free energy change for cavity formation as the work done against the surface forces of the solvent, which is calculated by multiplying the surface area of the solute molecule by the solvent surface tension.

$$\Delta G^{\circ}_{\text{gen med}} = A\gamma \tag{2-15}$$

There are two problems associated with this simple model, the first being that the microscopic surface tension is needed. The microscopic and bulk surface tensions are different owing to the presence of curvature at molecular dimensions. Many equations have been derived that relate the microscopic surface tension to the bulk surface tension, the most notable one being derived by Tolman in 1949 [30]. However, all these equations require a radius of curvature and another parameter referred to as the equimolecular dividing surface. Since these two parameters cannot be predicated by thermodynamics, nor can they be easily measured, the theoretical approach to this problem fails to lead to a practical solution.

The experimentalists have approached the problem by adding an adjustable curvature correction parameter. Yalkowsky[9] has shown experimentally that this factor is around 0.5 for interfacial tensions and that it remains constant, that is, the curvature correction factor does not change as a function of the solute molecule or the solvent, or the solvent composition in cases of mixed aqueous organic solvents. However, Moura-Ramos[31,32] argues that the curvature correction term is a function of the size and the shape of the cavity. Several equations have been derived based on the shape of the solute and the solvent molecules in relation to the reference cavity (defined as a cavity which has the same size and shape as that occupied by a single molecule in the pure liquid). This approach is of little value in mixed aqueous-organic solvents where three species (solute,water, cosolvent) contribute to the structure of the cavity. Therefore in our approach we admit this weakness and do not attempt to correct for the curvature dependence of surface tension, with the idea that the correction term remains constant as indicated by Yalkowsky.

The second problem that arises in calculating the free energy for the cavity formation with equation (2-15) is that the surface area for the cavity is not well defined.

In particular the surface area can be interpreted as either the van der Waals or contact surface area or the "solvent accessible surface area".[33-35] If the area is interpreted as the van der Waals surface area then it remains constant as a function of solvent composition; however if it is interpreted as the solvent accessible surface area the surface area will change as a function of the solvent composition. We have developed the following quantitative model for this dependence of the cavity surface area on the solvent composition.

We let A_1 be the solvent accessible surface area in pure solvent 1 (water) and A_2 the solvent accessible surface area in pure solvent 2 (cosolvent). Then postulate that A is an average of A_1 and A_2 weighted by the mean solvation shell composition or

$$A = A_1 f_1 + A_2 f_2 \qquad (2\text{-}16)$$

$$A = A_1 + (A_2 - A_1)\ f_2 \qquad (2\text{-}17)$$

Using equations 2-13, 2-7, and 2-8 in the above equation we can obtain

$$A = A_1 + A' \frac{K_1 x_2 + K_1(2K_2-1)x_2^2}{1+ m_2 x_2 + n_2 x_2^2} \qquad (2\text{-}18)$$

where $A' = (A_2 - A_1)/2$.Thus if the area is solvent independent, $A'=0$ and $A=A_1$, a constant area, but in general

Eq (2-18) provides an expression for a solvent-dependent surface area.

C. The Total Solvent Effect

The total solvent effect (Eq 2-1) is the sum of the solute-solute interaction, the general medium effect (Eq 2-15), and the specific solvation effect (equation 2-11). Substituting equations 2-18,2-15,2-11 in equation 2-1 the following equation is obtained

$$\Delta G^\circ = A_1\gamma + \frac{(a_2 + A'K_1\gamma)x_2 + [b_2 + A'K_1(2K_2-1)\gamma]x_2^2}{1 + m_2x_2 + n_2x_2^2} + \Delta G^\circ_{WW} + \Delta G^\circ_{lattice} \quad (2\text{-}19)$$

For fully aqueous medium, where $x_2=0$,

$$\Delta G^\circ_{(x2=0)} = A_1\gamma_1 + \Delta G^\circ_{WW} + \Delta G^\circ_{lattice} \quad (2\text{-}20)$$

where γ_1 is the surface tension of water. Defining the solvent effect relative to water by

$$\delta_m\Delta G^\circ = \Delta G^\circ - \Delta G^\circ_{(x_2=0)} \quad (2\text{-}21)$$

we obtain

$$\delta_m\Delta G^\circ = A_1(\gamma - \gamma_1) + \frac{(a_2 + A'K_1\gamma)x_2 + [b_2 + A'K_1(2K_2-1)\gamma]x_2^2}{1 + m_2x_2 + n_2x_2^2} \quad (2\text{-}22)$$

This equation has taken into account a solvent-dependent surface area for the general medium effect and two equilibrium steps for the solvation effect. It should be noted that the $\Delta G_{lattice}$ term, which corresponds to the solute-solute interaction, has been subtracted out. We have assumed that this interaction is not solvent dependent, which requires that the solubility be low and that the solid phase composition be solvent independent.

Equation 2-22 can be simplified if we assume A′=0; that is, that the surface area of the cavity is defined by the van der Waals area of the solute. Then

$$\delta_m \Delta G^\circ = A_1(\gamma - \gamma_1) + \frac{a_2 x_2 + b_2 x_2^2}{1 + m_2 x_2 + n_2 x_2^2} \qquad (2\text{-}23)$$

Equation 2-22 might also be simplified by assuming one equilibrium step for the solvation effect and retaining the solvent dependent surface area for the general medium effect, to give

$$\delta_m \Delta G^\circ = A_1(\gamma - \gamma_1) + \frac{(a_1 + A' K_1 \gamma)x_2}{1 + m_1 x_2} \qquad (2\text{-}24)$$

Finally, equation 2-22 can be presented in its simplest form when we assume only one equilibrium step for the solvation effect and define the area of the cavity as the van der Waals area, giving

$$\delta_m \Delta G^\circ = A_1(\gamma - \gamma_1) + \frac{a_1 x_2}{1 + m_1 x_2} \qquad (2\text{-}25)$$

3. HISTORICAL BACKGROUND OF COMPLEXATION

A. The Complexation Process

The complexation between two molecules S and L may be represented by

$$mS + nL \overset{K_{mn}}{\rightleftharpoons} S_mL_n$$

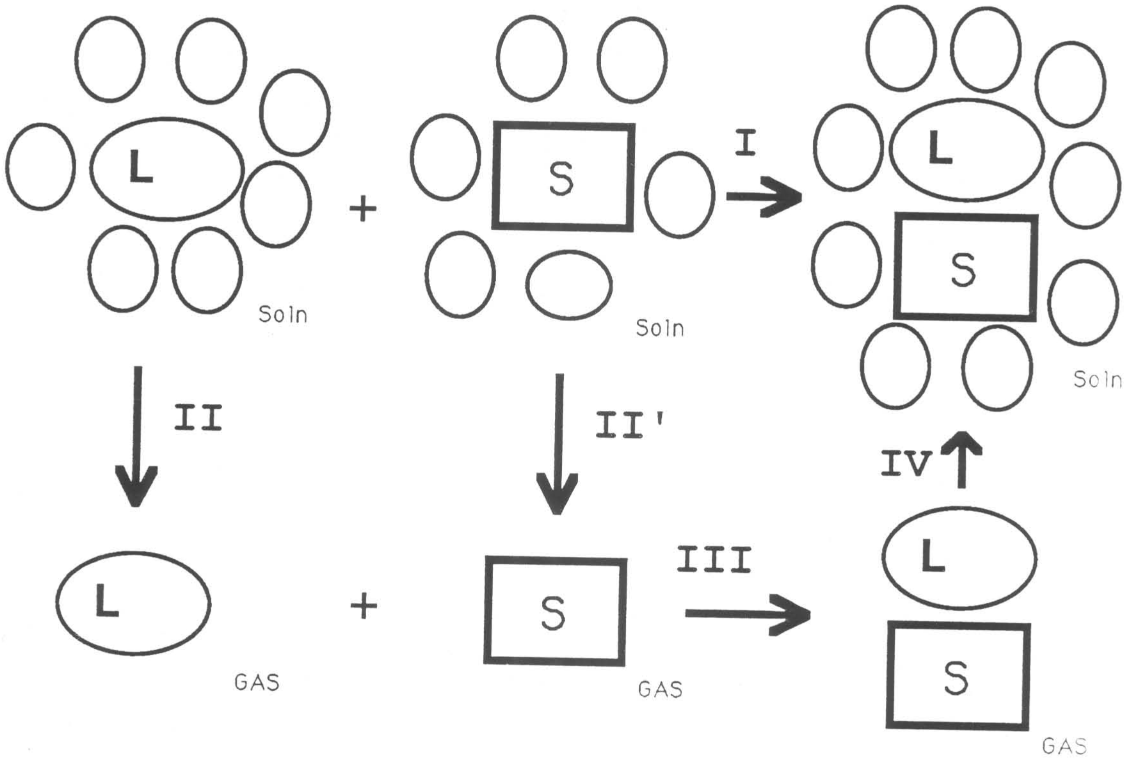
where S represents the substrate, and L represents the ligand. The equilibrium constant (also referred to as the complexation, stability, association, binding, or formation constant) can be defined as

$$K_{mn} = \frac{[S_mL_n]}{[S]^m\ [L]^n} \qquad (3\text{-}1)$$

where [S] is the free substrate concentration, [L] is the free ligand concentration, and $[S_mL_n]$ is the concentration of the complex formed. In one-to-one stoichometry between the substrate and the ligand the stability constant is expressed as

$$K_{11} = \frac{[SL]}{[S][L]} \qquad (3\text{-}2)$$

In further discussions regarding complexation, a one-to-one complexation is implied. The free energy change for complexation in solution has been broken down into three



Scheme 2. The complexation process.

ΔG_{I} = Free energy change for association in solution

$\Delta G_{II,II'}$ = Free energy change of removal of substrate and ligand from the solution to vacuum or gas.

ΔG_{III} = Free energy change of association in vacuum or gas

ΔG_{IV} = Free energy change in putting the complex into solution contributions by Sinanoglu (scheme 2),[36] where the free energy for complexation in solution is expressed as

$$\Delta G_{I} = \Delta G_{II,II'} + \Delta G_{III} + \Delta G_{IV} \qquad (3\text{-}3)$$

The first term arises from the removal of the substrate and the ligand from the solvent into vacuum or gas. The second term corresponds to the free energy for complexation in vacuum, and the third term arises from the free energy change in placing the complex into the solution. The solvent effect is then defined as

$$\Delta G_{solv\ eff} = \Delta G_{I} - \Delta G_{III} = \Delta G_{II,II'} + \Delta G_{IV} \qquad (3\text{-}4)$$

which is equivalent to

$$\Delta G_{solv\ eff} = G^{(AB)}{}_{solv\ eff} - G^{A}{}_{solv\ eff} - G^{B}{}_{solv\ eff} \qquad (3\text{-}5)$$

This equation illustrates the idea that binding is enhanced in solvents with weak selective solvation for the uncomplexed components and/or a strong selective solvation for the molecular complex. The solvent effect has also been expressed by Sinanoglu as

$$\Delta G_{solv\ eff} = \Delta G_{I} - \Delta G_{III} = \Delta G_{c} + \Delta G_{int} + \Delta G_{vf} + \Delta G_{red} + \Delta\Delta G_{mix} \qquad (3\text{-}6)$$

where ΔG_c is referred to as the cavity squeeze effect, which is due to the change in surface area exposed to the solvent. ΔG_{int} is the change in interaction energies between the solutes and the solvent, the ΔG_{vf} term is the positional entropy change in going from the molecular gas volume to a free volume (vf) in the cavity, and ΔG_{red} is the reduction in forces that hold the substrate and the ligand together in presence of the solvent. This term is the change in intrinsic free energy of the complex formation due to the presence of the solvent medium. The last term is due to mixing effects. The reader is referred to references 36, 37, 38, and 39 for further details on the evaluation of some of the above parameters.

Moser and Cassidy[40] have used a similar model to describe the extent of quinhydrone formation, where the free energy change for complexation in the solvent is broken into four contributions,

$$\Delta G^{\circ} = \Delta G_{vac} + \Delta G_{soln} + \Delta G_{solv} + \Delta G_{surface} \qquad (3\text{-}7)$$

where ΔG_{vac} is the free energy change for the complex formation in vacuum. The ΔG_{soln} is the reduction in free energy of quinhydrone complex by the surrounding medium. This term was considered negligible since any significant change in the interaction between the complex molecules would result in a shift in the wavelength of the charge transfer transition for the complex, and no such change was observed. The last two terms correspond to changes in interaction energies and the cavity squeeze effect (the first two terms in the previous model). The authors plot the free energy change for complexation in various aqueous-organic solvents versus the solvent surface tension of the solvent and attribute the curvature in such a plot to changes in solvation properties of the species in various solvents and/or to variations in the surface area change (ΔA) in each solvent.

Connors and Sun[41] viewed the free energy change for complexation as

$$\Delta G^\circ = \Delta G^\circ_{SL} + \Delta G^\circ_{solvent} \qquad (3\text{-}8)$$

where the first term on the right is due to substrate-ligand interaction and the second term corresponds to a cavity squeeze effect. Surprisingly, when the free energy change for complex formation between methyl cinnamate and theophylline was plotted versus the surface tension of the solvent a straight line was obtained. The solvents used were mixed aqueous organic solvents as well as salt solutions. (The presence of salt increases the surface tension of water). The free energy change was extrapolated to a surface tension of zero in order to obtain the intrinsic substrate-ligand interaction. Harrison and Eftink[42] later proposed that the extrapolation should be to a value of 23 dynes/cm, based on an average surface tension of several organic solvents. This surface tension is presumably the surface tension (γ_0) at which there is no longer a solvophobic driving force for complexation. Connors and coworkers have subsequently calculated the dispersion force contribution to the surface tension to be in the range of 20-30 dynes/cm for most solvents and have typically used the value of 25 dynes/cm for γ_0.

Connors and Pendergast[43] have expressed the free energy for complexation as

$$\Delta G^\circ = \Delta G^\circ_{MM} + \Delta G^\circ_{MS} + \Delta G^\circ_{SS} \qquad (3\text{-}9)$$

where ΔG°_{MM} is the contribution from the medium-medium interactions (which embodies the solvophobic effect), ΔG°_{MS} includes all the medium-solute interactions (which includes the solvation effect terms) and ΔG°_{SS} includes all solute-solute interactions.

Paulson and Connors[44] have studied the complexation constants for α-cyclodextrin and various substrates (mainly methyl orange) in mixed aqeous organic solvents. They have modelled the free energy change for complexation as a general medium contribution (cavity squeeze effect) and a selective solvation effect. Their model is further extended in the present thesis.

B. Other Correlative Approaches

The free energy change for complexation has been correlated with various measurements of solvent polarity, for example $E_{T(30)}$, dielectric constant, solvent polarizability, and the solubility parameter have been used. The following are just a few examples in which correlations between a solvent property and complexation constant were sought.

Chapman and Still[45] have studied molecular complexation in various pure organic solvents, finding no connection between the free energy change for complexation and solvent properties such as dielectric constant or dipole moment; however they found a correlation as a function of solvent surface area. In particular the complexation constant increased with the surface area of the solvent molecule. This has been attributed to a decrease in solute coordination number, which leads to decrease in extent of solvation, the main idea being that binding is favored by solvents which selectively provide weak solvation for the uncomplexed components or strong solvation for the molecular complex. They also obtained a correlation between the free energy change for complexation between their ligand and substrate (imidazole) and free energy change for ligand solvation (imidazole solubility).

Smithrud and Diederich[46] studied the complexation constants of inclusion complexes in water and 17 organic solvents covering the entire polarity range; they found that the empirical solvent polarity parameter $E_{T(30)}$ was very useful for correlating the complexation data. They also used molecular polarizability and the solubility parameter to correlate the complexation data, and although they did not obtain good correlations the general trend that binding is enhanced in solvents with low molecular polarizability and high solubility parameter (cohesive interactions) was observed.

Schneider and coworkers[47] measured various complexation constants in aqueous-organic solvent mixtures (mainly methanol) and observed linear correlation between the log of the complexation constant and solvophobicity parameter (S_p) that were better than solvent polarity parameters such as $E_{T(30)}$ or the Winstein-Grunwald Y "ionizing power". The solvophobicity parameter (S_p) is based on linearly correlated standard free energies of noble gases, alkanes, etc. for the transfer from gas to a given solvent, and have been used to correlate Diels-Alder reaction rates[48]. The solvophobic parameter is defined to be S_p=1.0 in water and

S_p=0 in _n_-hexane. The Sp values are found to be almost linear in volume percent of organic solvent in aqueous binary mixtures.

4. THE PROPOSED COMPLEXATION MODEL

Recall that for solubility (Eq 2-1) the free energy change was composed of three contributions.

$$\Delta G^\circ_{\text{Total}} = \Delta G^\circ_{\text{lattice}} + \Delta G^\circ_{\text{gen med}} + \Delta G^\circ_{\text{solv}} \qquad (4\text{-}1)$$

where the first term represents the solute-solute interactions, the second term represents the solvent-solvent interactions, and the third term represents the solute-solvent interactions. For complexation the above model can be modified so that

$$\Delta G^\circ_{\text{Total}} = \Delta G^\circ_{\text{SL}} + \Delta G^\circ_{\text{gen med}} + \Delta G^\circ_{\text{solv(SL)}} - \Delta G^\circ_{\text{solv(S)}} - \Delta G^\circ_{\text{solv(L)}} \qquad (4\text{-}2)$$

where $\Delta G^\circ_{\text{SL}}$ is the free energy change associated with the substrate-ligand interaction. This term is expected to change as a function of the cosolvent present; however, this change is not appreciable for complexation in which either the ligand or the substrate is nonpolar. The $\Delta G^\circ_{\text{gen med}}$ term arises as the result of the cavity squeeze effect; in particular there is a change in surface area exposed to the solvent as the separate cavities containing the substrate and the ligand molecules coalesce into a single cavity containing the complex. Therefore the general medium effect for complexation can be expressed as

$$\Delta G^\circ_{\text{gen med}} = \Delta A(\gamma - \gamma_o) \qquad (4\text{-}3)$$

where ΔA is the change in surface area, γ is the solvent surface tension, and γ_0 is the surface tension at which there is no net solvophobic driving force for association. This has been approximated to be 20-30 dynes/cm as mentioned previously. ΔA may be variable if solvent accessible surface area is chosen to calculate the change in the surface area; however if van der Waals surface area is chosen ΔA remains constant.

The last three terms in equation 4-2 reflect the solvation effect for the complex, substrate, and ligand respectively. The solvation effect for the substrate and ligand have been described previously and the solvation effect for the complex can be modeled via the same equation. If we assume that the surface area does not change as a function of solvent composition, we define D^i as (recall this is part of the solvation effect derived previously, Eq 2-11)

$$D^i = \frac{a_2^i x_2 + b_2^i x_2^2}{1 + m_2^i x_2 + n_2^i x_2^2} \qquad (4\text{-}4)$$

where the superscript (i) denotes the solvation effect for the species i. The total solvent effect on complexation can be expressed as

$$\Delta G^{\circ}{}_{com} = \Delta G^{\circ}{}_{SL} + \Delta A(\gamma-\gamma_{o}) + D^{SL} - D^{S} - D^{L} + \Delta G_{WW}^{SL} - \Delta G_{WW}^{S} - \Delta G_{WW}^{L} \qquad (4\text{-}5)$$

For fully aqueous medium where $x_2=0$,

$$\Delta G^{\circ}{}_{com(x2=0)} = \Delta G^{\circ}{}_{SL} + \Delta A\ (\gamma_1-\gamma_0) + \Delta G_{WW}^{SL} - \Delta G_{WW}^{S} - \Delta G_{WW}^{L} \qquad (4\text{-}6)$$

where γ_1 is the surface tension of pure water. Defining the solvent effect relative to water as

$$\delta_m \Delta G^{\circ}{}_{com} = \Delta G^{\circ} - \Delta G^{\circ}{}_{(x_2=0)} \qquad (4\text{-}7)$$

we obtain

$$\delta_m \Delta G^{\circ}{}_{com} = \Delta A(\gamma-\gamma_1) + D^{SL} - D^{S} - D^{L} \qquad (4\text{-}8)$$

Since the last two terms have been evaluated via the solubility studies, the solvation effect for the complex can be evaluated.

A. The Simplified Approach

An approximation can be made in which the solubility process is viewed as a net gain of one solvation effect, whereas complexation is viewed as a net loss of one solvation effect. In this treatment where we have assumed this partial cancellation of the solvation effect, the solvation effect in equation 4-8 can be represented as

$$\delta_m \Delta G^{\circ}{}_{com} = \Delta A(\gamma-\gamma_1) - D \qquad (4\text{-}9)$$

where D represents a composite solvation effect. This equation can be expressed as

$$\delta_m \Delta G^{\circ}{}_{com} = \Delta A(\gamma-\gamma_1) + D \qquad (4\text{-}10)$$

with the understanding that the values of S_1 and S_2 obtained via Eq. 4-10 will have different signs as the S_1 and S_2 obtained in the solubility case.

B. The Rigorous Approach

An alternative approach to using Eq. 4-8 to evaluate the solvation effect for complexation would involve the definition of ΔA, where

$$\Delta A = A^{SL} - A^{S} - A^{L} \qquad (4-11)$$

Substituting this equation into equation 4-8 we obtain,

$$\delta_m \Delta G^\circ{}_{com} = A^{SL}(\gamma-\gamma_1) - A^{S}(\gamma-\gamma_1) - A^{L}(\gamma-\gamma_1) + D^{SL} - D^{S} - D^{L} \qquad (4-12)$$

Upon rearrangement the following equation is obtained,

$$\delta_m \Delta G^\circ{}_{com} = [A^{SL}(\gamma-\gamma_1) + D^{SL}] - [A^{S}(\gamma-\gamma_1) + D^{S}] - [A^{L}(\gamma-\gamma_1) + D^{L}] \qquad (4-13)$$

comparing the second and the third term in the brackets with equations 4-4 and 2-23 the following expression is obtained

$$\delta_m \Delta G^\circ{}_{com} = [A^{SL}(\gamma-\gamma_1) + D^{SL}] - \delta_m \Delta G^\circ{}_{sub} - \delta_m \Delta G^\circ{}_{lig} \qquad (4-14)$$

where the second and third term on the right hand side are the free energy change for the solubility of naphthalene and theophylline, and the left hand side is the free energy change for the complexation of the two.

This approach in evaluating the solvation effect for the complex is superior to equation 4-8, since Eq. 4-8 requires a surface area for the substrate, ligand, and the change in the area upon complex formation ΔA; whereas equation 4-14 requires only an area estimate for the complex. Furthermore, the uncertainty associated with ΔA is relatively high since this value is obtained by subtracting the surface area of the substrate and the ligand from the surface area of the complex.

II. Experimental

A. Materials

Naphthalene (Mallinckrodt, Purified) was used without further purification. The experimentally determined melting point was equal to the literature value [49] of 80.3°C.

Theophylline (Sigma Chemical Co.) was recrystalized from water. The recrystallized crystals were dried at 105°C for 12 hours, subsequently the crystals were triturated in a mortar, and dried at 105°C for another 24 hours. Differential scanning calorimetry experiments indicated the anhydrous form was present with a melting point of 271-273°C. (Literature value 271°C [50])

4-Butylbenzoic acid (99%) obtained from Aldrich Chemical Company was used as the internal standard in the HPLC assay.

Acetonitrile (HPLC grade) was obtained from EM Science. Methanol (HPLC grade) and ethylene glycol (Reagent grade) were obtained from J. T. Baker. Glacial acetic acid (99.7+%,A.C.S. reagent) was obtained from Aldrich Chemical Company. Distilled water was purified via the Sybron/Barnstead PCS water purification system consisting of prefilter, organic, ion-exchange, and microfilter (.2μ) cartridges (Barnstead Company, Dubuque, IA).

Borosilicate glass ampules were obtained from Wheaton Scientific (Millville, NJ).

B. Apparatus

The solubilities and complexation constants for naphthalene and theophylline were determined at 25.00 ± 0.05°C. The temperature was maintained in a large water bath equipped with a relay and a mercury column thermoregulator (Brownell Scientific Co.). The water bath was also equipped with a rotating shaft which allowed ampules to be rotated end over end at 32 revolutions per minute.

Theophylline solubility was measured spectrophotometrically. The spectra were obtained on a Cary 14 spectrophotometer modified by OLIS (On-Line Instrument System, Inc., Jefferson, GA) or on a Beckman DU 65 spectrophotometer.

Naphthalene concentrations were determined using a Waters HPLC System (Millipore Corporation, Milford, MA). The system consisted of a model 501 solvent delivery system and a model 484 variable wavelength UV/Vis detector. The columns used were Econosphere C-18 5μ (4.6 x 250 mm) and

Econosphere C-8 5μ (4.6 x 150 mm) obtained from Alltech Associates, Inc., (Deerfield, Il) and Zorbax® C-8 5μ (4.6 x 150 mm) obtained from Dupont Chromatography Products (Chadds Ford, PA). Dynamax® HPLC method manager program version 1.1 from Rainin instrument Co., Inc., (Woburn, MA) along with a Macintosh SE-20MB (Apple computers, Inc., Cupertino, CA) was used for data acquisition and analysis.

The melting points for theophylline and naphthalene were determined using a Mettler TA 3000 thermal analysis system consisting of TC 10A TA processor and a DSC 20 standard cell (Mettler Instrument Co., Highstown, NJ).

Corey-Pauling-Koltun (CPK) space-filling models were obtained from the Ealing Corporation (South Natick, MA).

C. Solubility Measurements for Naphthalene and Theophylline

The solubilities of naphthalene and theophylline in mixed aqueous organic cosolvents were determined as follows, the mixed aqueous organic cosolvents were prepared by volumetric measurements of the organic solvent and water. About 10 milliliters of this was then added to a 10 ml ampule containing an excess amount of the solute. The ampules were chilled in dry ice-acetone bath prior to sealing to minimize the evaporation of the organic portion of the cosolvent during the sealing process. The sealed ampules were then placed in the water bath for at least 48 hours. The water bath was equipped with a rotating shaft, allowing the ampules to be rotated end over end. This agitation was important especially in the case of theophylline because it had a tendency to cake at the bottom of the ampule. The temperature of the water bath was maintained at 25.00 ± 0.05°C. After 48 hours the ampules were removed from the water bath and filtered through a 0.22 µm Teflon® membrane filter (Gelman Sciences, Inc., Ann Arbor, Michigan). The filtrate was then diluted appropriately. The wavelength used (λ_{max}) was 271.5 nm for theophylline. At this wavelength the ε_{max} was 1.01×10^4.

D. Binding Constant Determinations via the Solubility Method.

The binding constant between theophylline and naphthalene in mixtures of aqueous organic cosolvents was determined as follows. The cosolvents were prepared as mentioned previously. Subsequently the cosolvent was used to prepare a 3×10^{-2} M solution of theophylline. Excess solid naphthalene was placed into 15 ampules. The first ten ampules were numbered 1 through 10, subsequently 1 through 10 milliliters of the $3x10^{-2}$ M theophylline solution was delivered into each ampule utilizing a buret. Then additional cosolvent was buretted so a total of 10 milliliters was delivered into each ampule. The remaining five ampules contained only the cosolvent and were used to obtain naphthalene's solubility. The ampules were sealed, taking the precautions mentioned previously, and were placed in the water bath. After at least 48 hours the ampules were removed and filtered through a 0.22 µm Teflon® membrane filter. The filtrate was then diluted appropriately with mobile phase and the concentration of naphthalene present in each ampule was determined using High Performance Liquid Chromatography. Due to instrument availability and optimization of the assay method, the mobile phases and columns used for each of the three cosolvent systems were different. For the aqueous methanol cosolvents the mobile phase consisted of methanol/water/glacial acetic acid (70/29/1 v/v), the column was Econosphere C-8 5µ (4.6 x 250 mm), and the flow rate was 1.0 ml/min. For the aqueous acetonitrile system the mobile phase consisted of acetonitrile/water/glacial acetic acid (50/49/1 v/v), the column was Zorbax® C-8 5µ (4.6 x 150 mm), and the flow rate was 1.3 ml/min. For the aqueous ethylene glycol cosolvent systems the mobile phase used was (65/34/1 v/v), the column was Econosphere C-18 5µ (4.6 x 150 mm), and the flow rate was 1.5 ml/min. Typical chromatographs appear in Appendix A.

The internal standard used for all the three cosolvent systems was 4-butylbenzoic acid. Standards were prepared for each cosolvent to contain the same organic composition as the samples being analyzed. For example, for the 62.56% (w/w) ethylene glycol/water cosolvent system, the samples were prepared by pipetting five milliliters of the filtrate into a 25 milliliter volumetric flask; subsequently five milliliters of internal standard (4-butylbenzoic acid dissolved in mobile phase) was added. This was then diluted to the mark with the mobile phase. The naphthalene standards were prepared by pipetting five milliliters of the 62.56% (w/w) ethylene glycol/water cosolvent mixture into a 25 milliliter volumetric flask, and subsequently five milliliters of the internal standard was added. An appropriate volume of naphthalene stock solution (dissolved in mobile phase) was pipetted, and the solution was then diluted to the mark with the mobile phase. The wavelength selected was usually 275 nm, which corresponds to λ_{max} for naphthalene; however in some of the experiments 254 nm was chosen.

E. Density Measurements

Densities of the saturated naphthalene and theophylline solutions were determined for each mixed aqueous organic cosolvent prepared. The procedure to determine solubility of naphthalene and theophylline was followed to obtain the saturated filtrate with respect to either naphthalene or theophylline. Seven milliliters of this saturated filtrate was then pipetted and weighed to determine the density of the saturated cosolvent.

F. Surface Area Determinations.

A simple non-computational method was developed to estimate the molecular surface area. A Corey-Pauling-Koltun (CPK) space-filling model was constructed. The CPK model was then wrapped in aluminum foil in such manner that the minimum amount of foil was used to completely enclose the model. To achieve this the aluminum foil was not forced into the crevices; rather a smooth, snug contour of the CPK model was obtained. This piece of aluminum foil was then removed and weighed. This weight was then converted to surface area by cutting various size squares of aluminum foil. The surface areas of the squares were calculated by measuring their linear dimensions; these pieces were weighed. From this information the weight of aluminum foil necessary to cover the CPK model was then converted into surface area taking into account the scaling factor for the CPK model (1.25 cm = 1.0 Å).

The surface area change for complexation was determined by measuring the surface area of the complex formed and subtracting the surface area of naphthalene and theophylline obtained. The surface area of complex was calculated by maximizing the area overlap between the naphthalene and theophylline by placing the two models plane to plane. The two models were then attached together with rubber bands and the surface area determined as mentioned previously.

G. Calculation of the Binding Constant

The complexation constant for the naphthalene and theophylline was determined by the solubility method.[51] The solubility method takes advantage of the fact that the solubility of the substrate (naphthalene) is increased as a consequence of the complex formed with the ligand (theophylline). The total solubility of the substrate (S_t) is then the sum of the solubility of the substrate in absence of the ligand (s_o) and the amount of substrate that is solubilized by the presence of the ligand. If we assume that only the 1:1 complex is formed then

$$S_t = s_o + [SL] \qquad (5\text{-}1)$$

Combining the above equation with the mass balance equation for the ligand and the definition of the stability constant (K_{11}), the following equation can be obtained[27],

$$S_t = s_o + K_{11}s_oL_t/(1 + K_{11}s_o) \qquad (5\text{-}2)$$

where L_t is the total ligand concentration. A plot of S_t versus L_t reveals a straight line with the slope of $K_{11}s_o/(1+K_{11}s_o)$ and the intercept s_o. The stability constant is obtained via

$$K_{11} = \text{SLOPE} / (1\text{-SLOPE})\ \text{INTERCEPT} \qquad (5\text{-}3)$$

The slope and the intercept were calculated using the unweighted least squares method. The propagation of errors treatment[52] was applied to the above equation to obtain the standard deviation for the binding constant (K_{11}):

$$\sigma^2_{K_{11}} = K^2_{11}\left[\frac{\sigma^2_s}{(\text{slope})^2} + \frac{\sigma^2_{int}}{(\text{int})^2} + \frac{\sigma^2_{slope}}{(1\text{-slope})^2}\right] \qquad (5\text{-}4)$$

where $\sigma_{K_{11}}$ is the standard deviation of the binding constant.

σ_s is the standard deviation of the slope obtained via the least squares method.

σ_{int} is the standard deviation of the intercept obtained via the least squares method.

G Calculation of the Unitary Standard Free Energy Change for the Binding Constant.

The binding constant (K_{11}) as determined above is on the molar concentration basis. However, it appears that the mole fraction concentration scale is more appropriate because the purely configurational (mixing) contribution is excluded[53]. To convert the binding constant obtained on the molar scale (K_c) to the one on the mole fraction scale (K_x) the following equation is used,

$$K_x = K_c M^* \rho \qquad (5\text{-}5)$$

where ρ is the density of the saturated naphthalene solution in g/ml, K_c is the binding constant with the units of M^{-1}, and M^* is the total number of moles of solvent per 1 Kg of solvent. The density and binding constant were measured. M^* was calculated, for example for 62.56% (w/w) ethylene glycol/water,

$$M^* = (625.6/62.07) + (374.4/18.01) \qquad (5\text{-}6)$$

where 62.07 is the molecular weight of ethylene glycol and 18.01 is the molecular weight of water.

Then

$$\Delta G^o{}_U = -\mathbf{k}T \ln K_x = -\mathbf{k}T \ln (K_c M^* \rho) \qquad (5\text{-}7)$$

The propagation of error treatment is applied to obtain the standard deviation for the free energy,

$$\sigma^2_{\Delta G^o_U} = (-\mathbf{k}T)^2 \left[\frac{\sigma^2_{K_c}}{K_c^2} + \frac{\sigma^2_{M^*}}{M^{*2}} + \frac{\sigma^2_\rho}{(\rho)^2} \right] \qquad (5\text{-}8)$$

where σ_{K_C} is the standard deviation calculated for the binding constant (denoted $\sigma_{K_{11}}$ in the previous treatment), σ_{M^*} is the standard deviation of the total number of moles present in 1 Kg of solvent, and σ_ρ is the standard deviation of the density of the saturated naphthalene cosolvent. In this treatment the contribution of error from the temperature was neglected, for this was calculated to be negligible. It was further assumed that the second term in the parentheses does not contribute significantly to the standard deviation of the change in the free energy compared to the other two terms.

I. Calculation of Unitary Standard Free Energy Change for the Solubility.

The solubility data were converted from the molar scale (K_C) to the mole fraction scale (K_X) as follows. From the density of the saturated solution the weight of one liter of solution was determined (Note that one liter of the saturated solution is used as the basis of this analysis). Subsequently the weight of the solute present in that one liter of saturated solution was subtracted to obtain the weight of the cosolvent. (Note the solute weight is a negligible quantity) From w/w % and the weight of cosolvent the weight of water and organic solvent were determined. From the weights and molecular weights of water and organic solvent the moles of water and organic solvent were calculated. The moles of naphthalene present in that one liter of solution was then divided by the sum of the moles of water, moles of organic, and moles of naphthalene itself to obtain the solubility of naphthalene on a mole fraction basis.

III. Results

The complexation constant for naphthalene (S) and theophylline (L) was determined by the solubility method. The total solubility of naphthalene in the presence of different concentrations of theophylline appears in Appendix B. Table B-I contains the data for the ethylene glycol-water mixtures, Table B-II for the acetonitrile-water mixtures, and Table B-III for the methanol-water mixtures. The plots of solubility of naphthalene versus the total theophylline concentrations added, with the least squares lines superimposed, appear in Figures B.1 through B.13. From the slope and the intercept of the least squares line the complexation constant for each cosolvent was calculated via equation (5-3).

The calculated complexation constants (K_{11}) along with their standard deviations calculated via the propagations of errors treatment (equation 5-4) appear in Appendix C. Appendix C also contains the concentrations in %volume/volume (before mixing), %w/w, x_2, and the calculated surface tensions for the solvent mixtures prepared. (The surface tensions were calculated by an equation developed by Connors and Wright.[54]) In addition it contains the density of the saturated naphthalene solution, and total moles of solvent present in 1 kg. of solvent (equation 5-6). The density and total moles present along with the complexation constant was then used to calculate the unitary free energy changes for the complexation of naphthalene and theophylline (Eq 5-7). The complexation constants for naphthalene and theophylline in methanol-water mixtures have been determined by Sun[55] and the values obtained in this study are consistent with Sun's results.

The molar solubility of naphthalene and theophylline along with the density of their saturated solutions for each solvent mixture appears in Appendix D. The unitary free energy changes for naphthalene and theophylline solubility also appear in Appendix D.

Table I-III contains the %w/w and mole fraction of the solvent mixtures along with $(\gamma-\gamma_1)$, the relative surface tension of the cosolvent with respect to water. The quantity $(\gamma-\gamma_1)$ is simply the surface tension of water (71.8 dynes/cm) subtracted from the surface tension of the solvent. It should be mentioned that throughout this study water is chosen as the reference solvent. The above tables also contain the unitary free energy changes with respect to water $(\delta_m \Delta G^\circ_U)$ for the complexation of naphthalene and theophylline, the solubility of naphthalene, and the solubility of theophylline. The quantity $(\delta_m \Delta G^\circ_U)$ is the change in the unitary free energy in going from water as the solvent to the solvent of interest. Henceforth, this quantity ($\delta_m \Delta G°_U$) is referred to as the medium effect on the unitary free energy change or simply as the medium effect.

Figures 1 through 3 are plots of the medium effect on unitary free energy change for the complexation of naphthalene and theophylline, the solubility of naphthalene, and the solubility of theophylline plotted versus the relative surface tension ($\gamma-\gamma_1$). Figures 4 to 6 are the plots of the medium effect on the three above mentioned processes with respect to the mole fraction (x_2) of the organic solvent present. Finally Figures 7 through 9 are the plots for the three processes versus the percent weight/weight organic solvent present.

From the above figures it is observed that the free energy change for the complexation of naphthalene and theophylline becomes more positive with respect to water as more organic cosolvent is added, indicating that the formation of the complex becomes unfavorable by addition of organic cosolvent. The free energy change for the solubility of naphthalene becomes more negative with respect to water as more organic cosolvent is added, indicating that the solubility of naphthalene is enhanced by the addition of organic cosolvent. The free energy change for the solubility of theophylline is not significant in going from water to pure organic cosolvent, furthermore the free energy change goes through a minimum in acetonitrile-water and methanol-water mixtures. In these two mixtures the solubility of theophylline is enhanced by addition of organic cosolvent until a minimum is observed; then the solubility becomes increasingly disfavored as pure organic concentrations are reached.

The values obtained for the surface area of naphthalene, theophylline, and the complex appear in Table IV. These values were determined using the non-computational method which has been described previously. The change in area for complex formation is calculated by subtracting the surface area for theophylline and naphthalene from the surface area determined for the complex. For naphthalene the van der Waals surface area has been calculated to be 156.76 Å^2/molecule by Pearlman.[56] An estimate for water-accessible surface area was obtained by treating the solute,the complex, and the water molecules as being spherical. An effective radius was calculated for the solute and the complex, which along with the radius of water (1.5Å), defined a larger sphere whose surface area corresponds to the water-accessible surface area.

Table I. Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the ethylene glycol-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$ [a] dynes/cm	$\delta_m\Delta G^\circ_U$ [b] 10^{-20} J/molecule (1)	$\delta_m\Delta G^\circ_U$ [c] 10^{-20} J/molecule (2)	$\delta_m\Delta G^\circ_U$ [d] 10^{-20} J/molecule (3)
0.00	0.0000	0.0	----	----	0.001
2.85	0.0084	-1.0	0.032 (0.032)[e]	-0.037	-0.020
5.54	0.0167	-1.9	0.072 (0.033)	-0.083	-0.045
8.33	0.0257	-2.8	0.086 (0.032)	-0.128	-0.041
11.01	0.0347	-3.6	0.136 (0.031)	-0.180	-0.052
13.80	0.0444	-4.5	0.166 (0.032)	-0.232	-0.068
16.43	0.0540	-5.3	0.222 (0.032)	-0.272	-0.103
21.78	0.0748	-6.9	0.261 (0.031)	-0.369	-0.105
27.08	0.0973	-8.3	0.341 (0.032)	-0.479	-0.142

[a] γ_1 = 71.8 dynes/cm.

[b] For the reference solvent (water) ΔG°_U = -3.430(.031).

[c] For the reference solvent (water) ΔG°_U = 5.156(.017).

[d] For the reference solvent (water) ΔG°_U = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table I. *(continued)* Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the ethylene glycol-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$[a] dynes/cm	$\delta_m\Delta G^\circ_U$[b] 10^{-20} J/molecule (1)	$\delta_m\Delta G^\circ_U$[c] 10^{-20} J/molecule (2)	$\delta_m\Delta G^\circ_U$[d] 10^{-20} J/molecule (3)
32.31	0.1217	-9.8	0.427 (0.031)[e]	-0.612	-0.193
37.49	0.1483	-11.1	0.498 (0.031)	-0.737	-0.223
42.62	0.1773	-12.4	0.601 (0.031)	-0.879	-0.267
52.70	0.2443	-14.8	0.789 (0.031)	-1.181	-0.359
62.56	0.3266	-17.0	1.000 (0.032)	-1.515	-0.493
72.22	0.4300	-18.9	1.177 (0.032)	-1.850	-0.536
81.67	0.5640	-20.7	1.472 (0.037)	-2.219	-0.577
83.20	0.5897	-21.0	1.532 (0.035)	-2.300	----
100.00	1.0000	-23.7	1.835 (0.043)	-2.961	-0.665

[a] γ_1 = 71.8 dynes/cm.

[b] For the reference solvent (water) ΔG°_U = -3.430(.031).

[c] For the reference solvent (water) ΔG°_U = 5.156(.017).

[d] For the reference solvent (water) ΔG°_U = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table II. Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the acetonitrile-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$[a] dynes/cm	$\delta_m\Delta G°_U$[b] 10^{-20}J/molecule (1)	$\delta_m\Delta G°_U$[c] 10^{-20}J/molecule (2)	$\delta_m\Delta G°_U$[d] 10^{-20}J/molecule (3)
0.00	0.0000	0.0	0.012 (0.032)[e]	-0.012	----
0.00	0.0000	0.0	0.020 (0.032)	-0.017	-0.003
2.17	0.0096	-7.9	0.087 (0.031)	-0.105	-0.059
5.05	0.0228	-15.1	0.186 (0.032)	-0.243	-0.149
7.21	0.0330	-19.0	0.288 (0.032)	-0.368	-0.226
10.09	0.0469	-23.0	0.381 (0.032)	-0.511	-0.317
12.57	0.0594	-25.7	0.505 (0.031)	-0.709	----
15.27	0.0733	-28.0	0.614 (0.031)	-0.852	-0.462
16.26	0.0785	-28.7	----	----	-0.515
18.16	0.0887	-30.0	0.738 (0.032)	-1.051	-0.556

[a] γ_1= 71.8 dynes/cm.

[b] For the reference solvent (water) $\Delta G°_U$ = -3.430(.031).

[c] For the reference solvent (water) $\Delta G°_U$ = 5.156(.017).

[d] For the reference solvent (water) $\Delta G°_U$ = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table II. *(continued)* Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the acetonitrile-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$[a] dynes/cm	$\delta_m\Delta G°_U$[b] 10^{-20}J/molecule	$\delta_m\Delta G°_U$[c] 10^{-20}J/molecule	$\delta_m\Delta G°_U$[d] 10^{-20}J/molecule
			(1)	(2)	(3)
22.40	0.1125	-32.3	0.952 (0.034)[e]	-1.398	-0.653
25.66	0.1316	-33.7	1.102 (0.033)	-1.556	-0.699
34.81	0.1898	-36.6	1.495 (0.057)	-2.145	----
40.23	0.2280	-37.9	1.582 (0.052)	-2.424	-0.858
56.41	0.3623	-40.4	----	----	-0.882
69.97	0.5056	-41.6	----	----	-0.826
84.46	0.7047	-42.6	----	----	-0.633
93.65	0.8662	-43.1	----	----	-0.385
96.88	0.9317	-43.2	----	----	-0.192
100.00	1.0000	-43.3	----	----	0.151

[a] γ_1= 71.8 dynes/cm.

[b] For the reference solvent (water) $\Delta G°_U$ = -3.430(.031).

[c] For the reference solvent (water) $\Delta G°_U$ = 5.156(.017).

[d] For the reference solvent (water) $\Delta G°_U$ = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table III. Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the methanol-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$[a] dynes/cm	$\delta_m\Delta G^\circ_U$[b] 10^{-20} J/molecule (1)	$\delta_m\Delta G^\circ_U$[c] 10^{-20} J/molecule (2)	$\delta_m\Delta G^\circ_U$[d] 10^{-20} J/molecule (3)
0.00	0.0000	0.0	0.013 (0.034)[e]	0.008	0.001
0.00	0.0000	0.0	-0.046 (0.032)	0.020	----
2.38	0.0135	-5.2	-0.007 (0.034)	-0.032	----
5.11	0.0294	-10.0	0.061 (0.032)	-0.131	-0.048
5.11	0.0294	-10.0	0.066 (0.031)	-0.121	----
7.44	0.0432	-13.5	0.108 (0.034)	-0.176	----
7.44	0.0432	-13.5	0.150 (0.032)	-0.203	----
9.85	0.0579	-16.5	0.133 (0.032)	-0.259	-0.087
14.95	0.0900	-21.7	0.265 (0.031)	-0.415	-0.137
20.05	0.1236	-25.7	0.365 (0.032)	-0.591	----

[a] γ_1= 71.8 dynes/cm.

[b] For the reference solvent (water) ΔG°_U = -3.430(.031).

[c] For the reference solvent (water) ΔG°_U = 5.156(.017).

[d] For the reference solvent (water) ΔG°_U = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table III. *(continued)* Summary of the unitary free energy changes with respect to water for the complexation of naphthalene and theophylline (1), solubility of naphthalene (2), and the solubility of theophylline (3) for the methanol-water cosolvents at 25.0 °C.

%w/w organic	x_2	$\gamma-\gamma_1$[a] dynes/cm	$\delta_m \Delta G°_U$[b] 10^{-20} J/molecule (1)	$\delta_m \Delta G°_U$[c] 10^{-20} J/molecule (2)	$\delta_m \Delta G°_U$[d] 10^{-20} J/molecule (3)
29.92	0.1936	-31.3	0.581 (0.032)[e]	-0.992	-0.311
40.07	0.2732	-35.4	0.857 (0.038)	-1.435	-0.444
49.91	0.3591	-38.5	1.069 (0.032)	-1.870	-0.542
60.12	0.4588	-41.2	1.235 (0.035)	-2.277	-0.617
65.10	0.5119	-42.3	----	----	-0.620
75.04	0.6283	-44.4	----	----	-0.579
84.99	0.7610	-46.4	----	----	-0.501
95.25	0.9186	-48.4	----	----	-0.373
100.00	1.0000	-49.3	----	----	-0.323

[a] γ_1= 71.8 dynes/cm.

[b] For the reference solvent (water) $\Delta G°_U$ = -3.430(.031).

[c] For the reference solvent (water) $\Delta G°_U$ = 5.156(.017).

[d] For the reference solvent (water) $\Delta G°_U$ = 3.043(.002).

[e] Standard deviations appear in parentheses.

Table IV. The van der Waals and water-accessible surface area determined for naphthalene, theophylline and the complex.

	Naphthalene	Theophylline	Complex	ΔA
	Å^2/ molecule	Å^2/ molecule	Å^2/ molecule	Å^2/ molecule
van der Waals surface area	150 (3)	180 (4)	290 (9)	-40
Water accessible surface area	300	360	500	-160

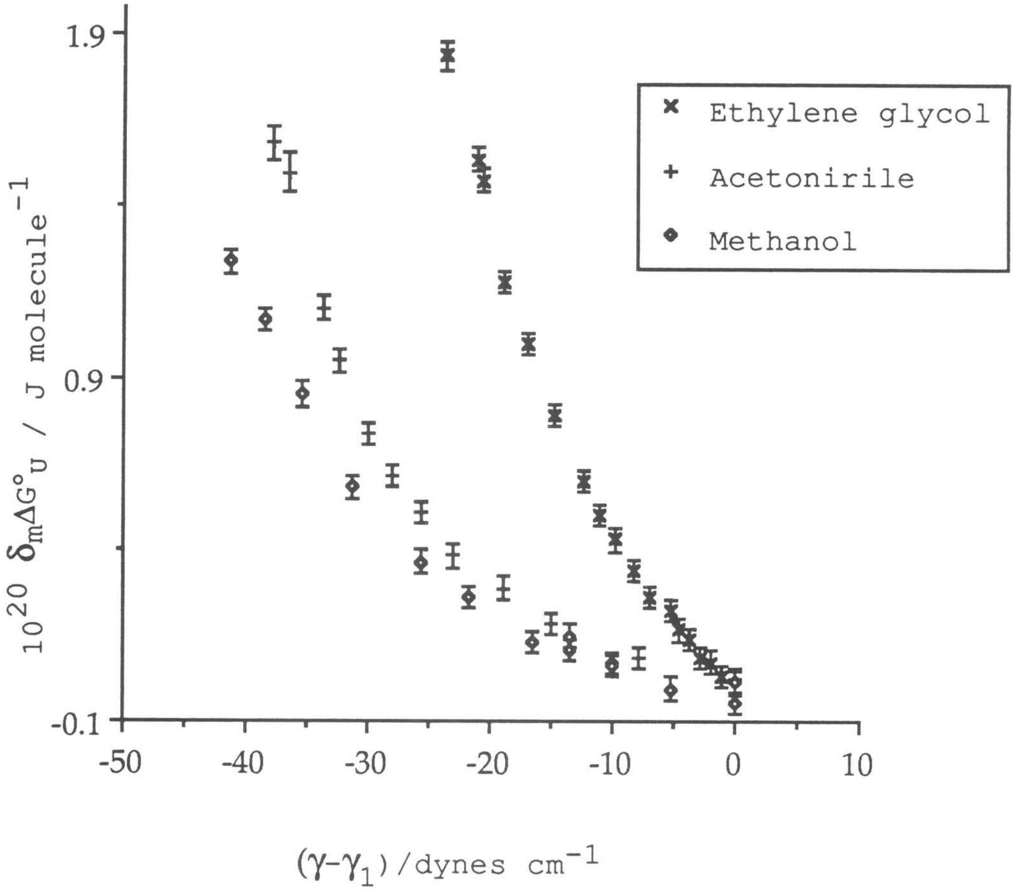


Figure 1. The medium effect on the unitary free energy change for the complexation of naphthalene and theophylline plotted versus the relative surface tension of the cosolvents prepared.

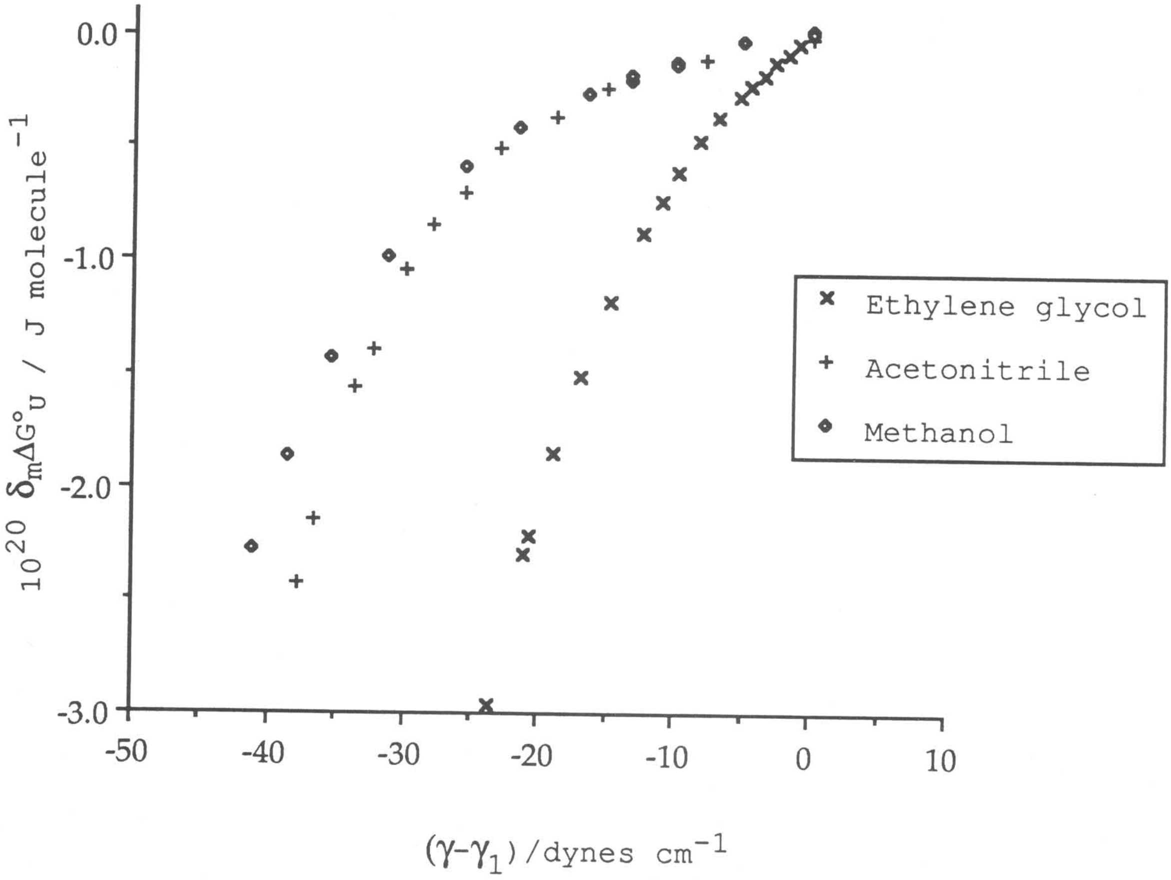


Figure 2. The medium effect on the unitary free energy change for the solubility of naphthalene plotted versus the relative surface tension of the cosolvents prepared.

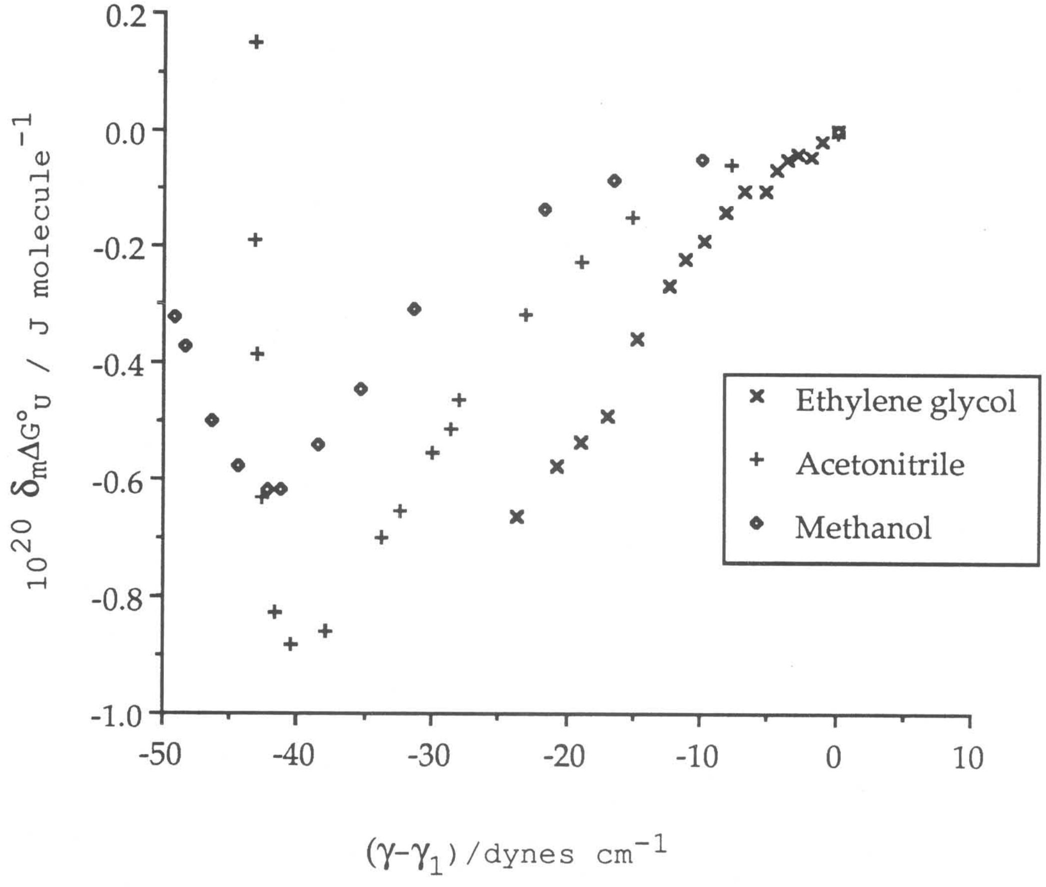


Figure 3. The medium effect on the unitary free energy change for the solubility of theophylline plotted versus the relative surface tension of the cosolvents prepared.

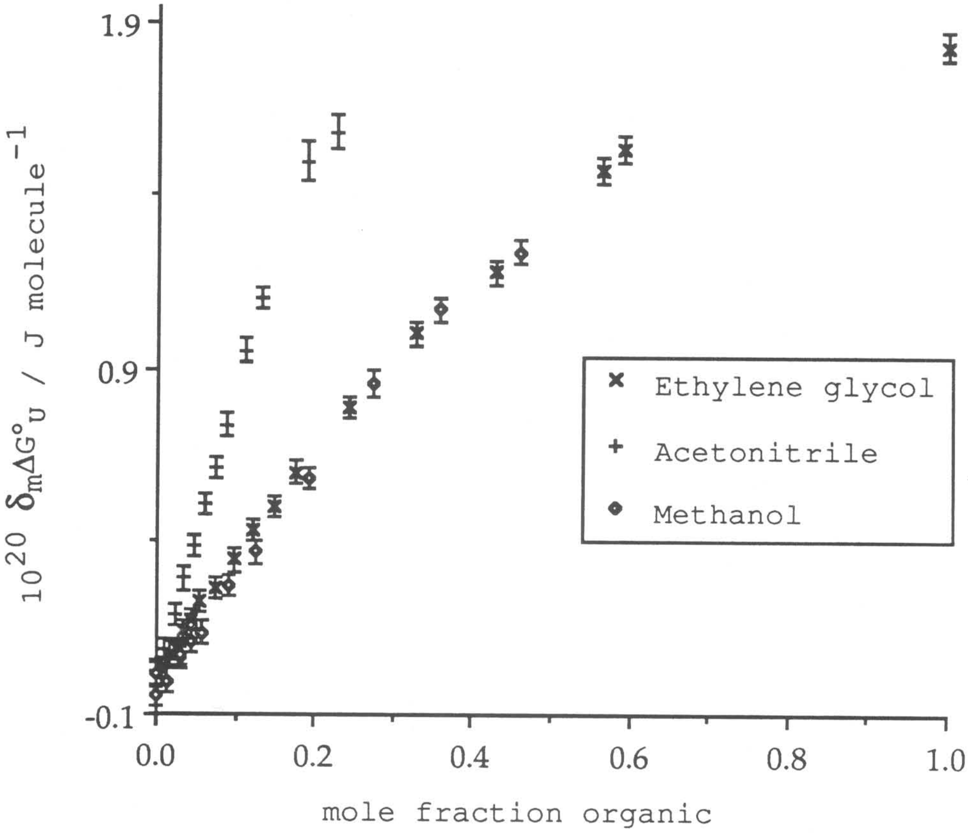


Figure 4. The medium effect on the unitary free energy change for the complexation of naphthalene and theophylline plotted versus the mole fraction of the organic solvent present.

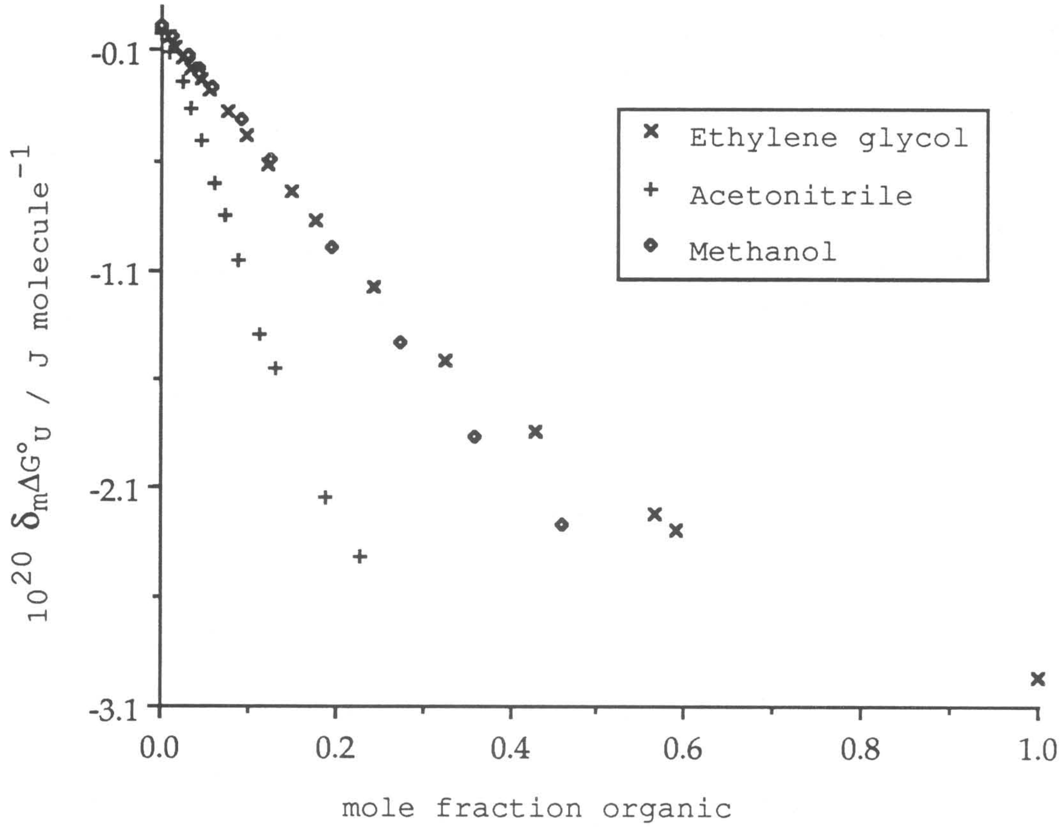


Figure 5. The medium effect on the unitary free energy change for the solubility of naphthalene plotted versus the mole fraction of the organic solvent present.

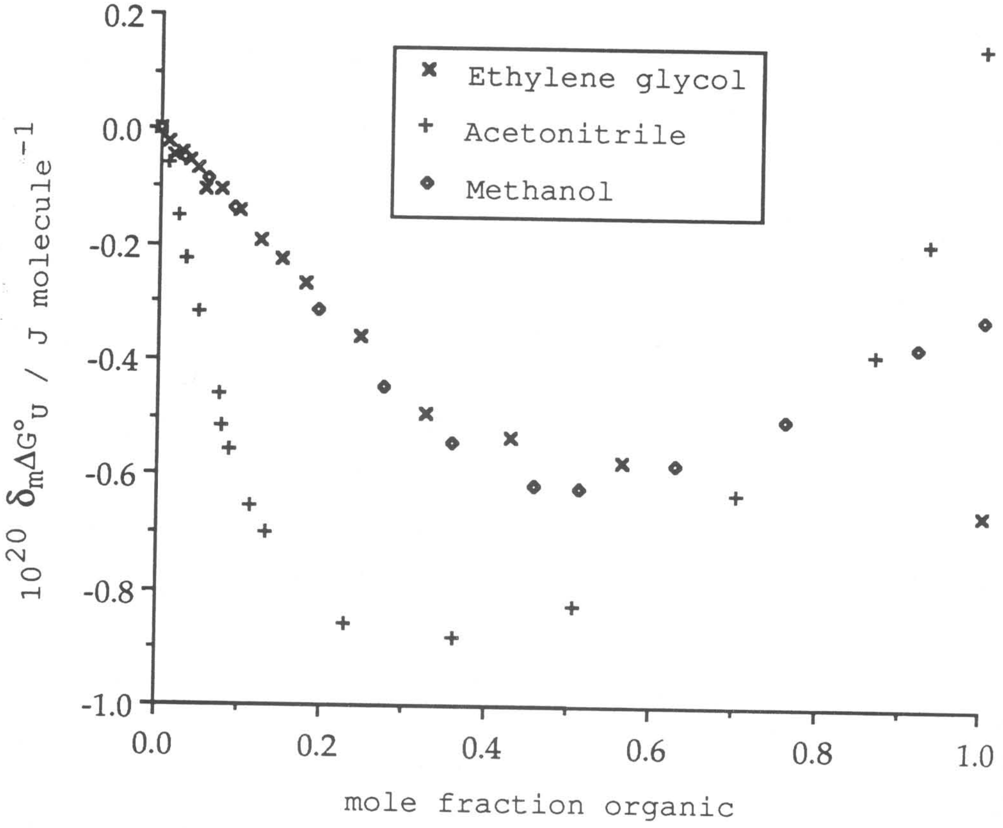


Figure 6. The medium effect on the unitary free energy change for the solubility of theophylline plotted versus the.mole fraction of the organic solvent present.

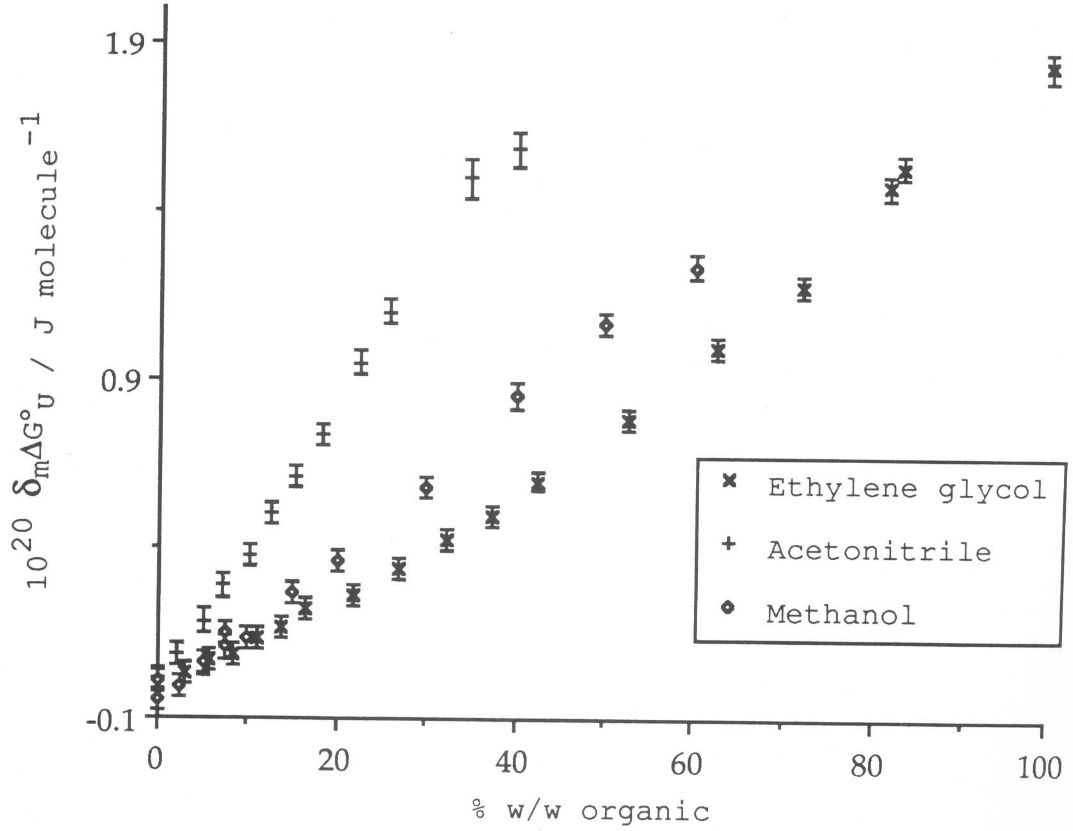


Figure 7. The medium effect on the unitary free energy change for the complexation of naphthalene and theophylline plotted versus the percent weight/weight of the organic solvent present.

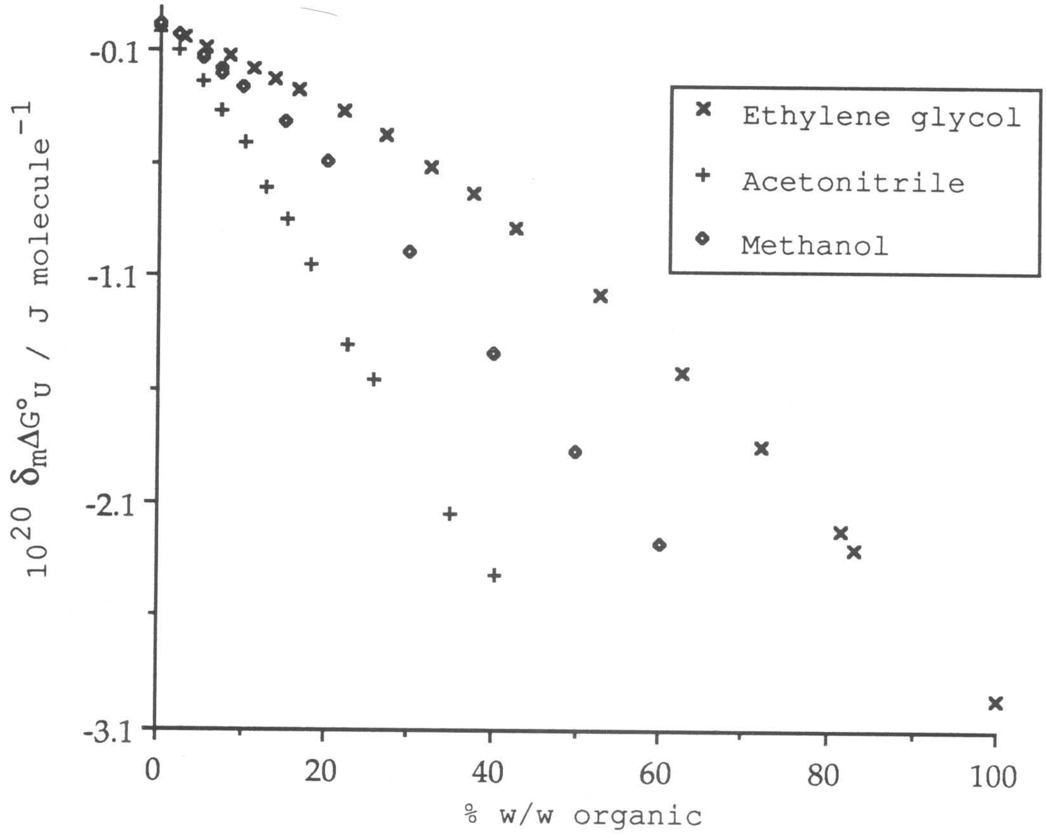


Figure 8. The medium effect on the unitary free energy change for the solubility of naphthalene plotted versus the percent weight/weight of the organic solvent present.

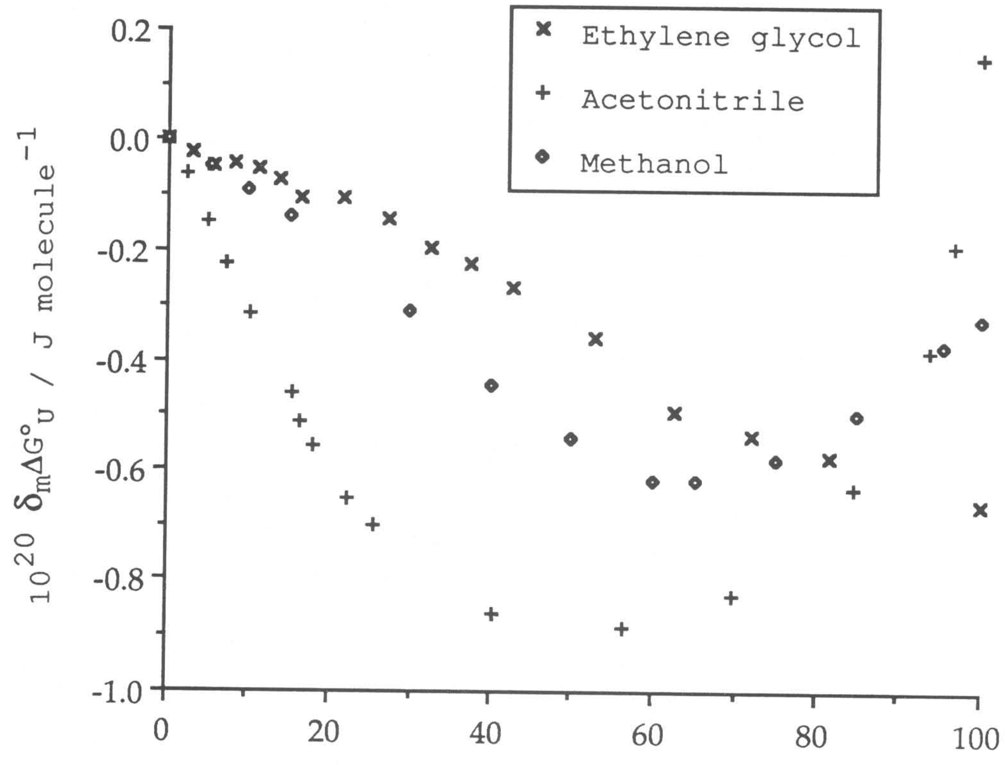


Figure 9. The medium effect on the unitary free energy change for the solubility of theophylline plotted versus the percent weight/weight of the organic solvent present.

IV. DISCUSSION

A. Parameter Evaluation

The solubility data were analyzed using equation 2-23,

$$\delta_m \Delta G^\circ = A_1(\gamma - \gamma_1) + \frac{a_2 x_2 + b_2 x_2^2}{1 + m_2 x_2 + n_2 x_2^2}$$

and the complexation data were analyzed via 4-10,

$$\delta_m \Delta G^\circ_{com} = \Delta A(\gamma - \gamma_1) + D$$

where we have assumed that the surface area of the cavity is independent of cosolvent identity and the cosolvent composition. In order to determine the dependence of the parameters obtained on the surface area of the solute (A in Eq. 2-23) and the change in the surface area for the complex (ΔA in Eq.4-10), the parameters were evaluated twice using two sets of areas. The first set of areas correspond to the van der Waals surface area, whereas the second set correspond to the water-accessible surface area (Table IV). By choosing an area the first term on the right hand side could be evaluated, where we have used the bulk surface tension of the solvents. The left hand sides ($\delta m \Delta G^\circ$) are the experimentally determined values and correspond to the change in the unitary free energy change in going from water as the reference solvent to the solvent of interest. The parameters (S_1, K_1, S_2, K_2) were then determined by a non-linear regression program developed by SYSTAT, Inc.[57] These parameters are listed in Tables V and VI.

B. Applicability of The Model

In the application of the model various assumptions were made which contribute to certain limitations of the model. One of the assumptions made is that the solute-solute interaction is solvent independent. This requires that the solubility of solute be low enough to avoid the presence of solute-solute interactions in solution. Another implication of this assumption is that the crystal lattice energy for the solute is solvent independent. In the case of theophylline this second assumption may not be valid due to a change in the crystal lattice structure[58,59]; in particular theophylline monohydrate is present in water-rich solutions and anhydrous theophylline is present in cosolvent-rich solutions. Despite the above mentioned limitations the model is capable of quantitatively describing the data (Figures 10 through 18).

C. Dependence of Solvation Effect on Surface Area

As mentioned previously, the parameters calculated and hence the solvation effect is dependent on the value of surface area chosen. However, the value of area chosen does not affect the quality of the curve fits obtained. Figures 19 through 21 illustrate the effect of area value on the general medium effect and the solvation effect for methanol-water mixtures. The general medium effect for solubility becomes favorable as more organic cosolvent is added, whereas the solvation effect becomes unfavorable. Recall that the experimental values are the sum of a general medium effect contribution and a solvation effect contribution. For complexation the general medium effect becomes unfavorable as more organic cosolvent is added, whereas the solvation effect becomes favorable.

The dependence of the model parameters (S_1, K_1, S_2, K_2) on the surface area chosen appears in Tables V and VI, where in Table V the van der Waals area was used and in Table VI the water-accessible area was used. The values of K_1 and K_2 remain fairly constant as a function of area chosen. Furthermore, the K_1 and K_2 values obtained are consistent with the equilibrium constants expected for an exchange process, the expected range for such a process being roughly 0.01 to 100. The values obtained for S_1 and

S_2 are also consistent with the expected values. Since S_1 and S_2 are differences in noncovalent interaction energies, their values are expected to be no higher than 10-20 kcal/mole[60], which corresponds to values of 7-14 x 10^{-20} joules/molecule.

D. Concluding Remarks

The values of K_1 appear to be fairly constant for each cosolvent; for example, K_1 values for naphthalene solubility, theophylline solubility, and the complexation between naphthalene and theophylline in methanol-water mixtures are 11.6(0.3), 11.7(0.4),and 10.8(3) respectively if the van der Waals surface area is chosen. This indicates that K_1 is dependent on the identity of the cosolvent and not the identity of the solute molecule. On the other hand, the values of K_2 appear to be independent of the cosolvent identity and dependent on the solute identity. For example, the K_2 values obtained for naphthalene solubility are 2.9(0.6), 6.3(1.5), and 2.3(0.1) in methanol, acetonitrile, and ethylene glycol, respectively. The constancy of K_1, if borne out by subsequent studies on other processes, could lead to predictability of this parameter. This is the type of observation that can be of considerable practical interest.

It is interesting, and unexpected, that the relative contribution to the solvation effect, expressed in S_1, should be unfavorable relative to fully aqueous solution, even though K_1 is greater than unity. That is, the relative affinities (K_1) of the cosolvent and water for the solute do not appear to reflect their relative contributions to the solvation energy (S_1). These are independent factors.

E. Future Work

The complexation data obtained were analyzed by the simplified model (Eq. 4-10), where we have assumed a partial cancellation of the solvation effect. In future work, the solvation effect for complexation will be evaluated via Eq 4-14, where we do not make this assumption. This analysis will shed light on the validity and application of this approximation in present work and future work preformed by our group.

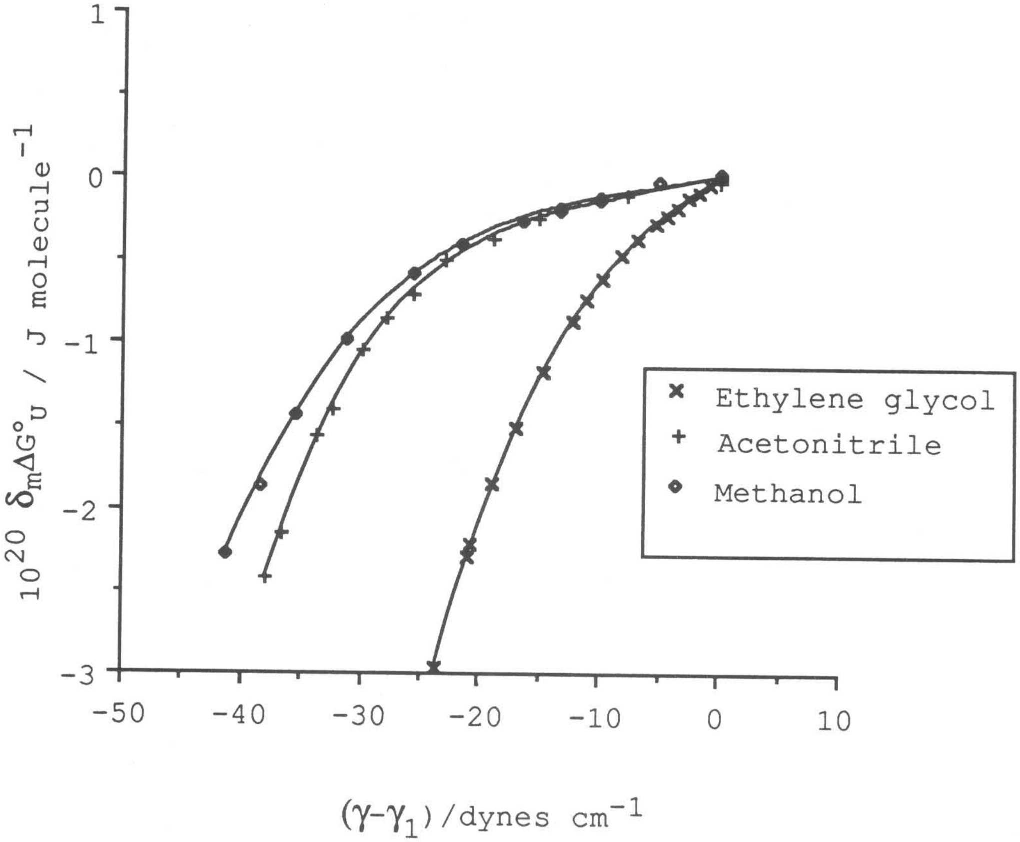


Figure 10. The medium effect on the unitary free energy change for the solubility of naphthalene plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

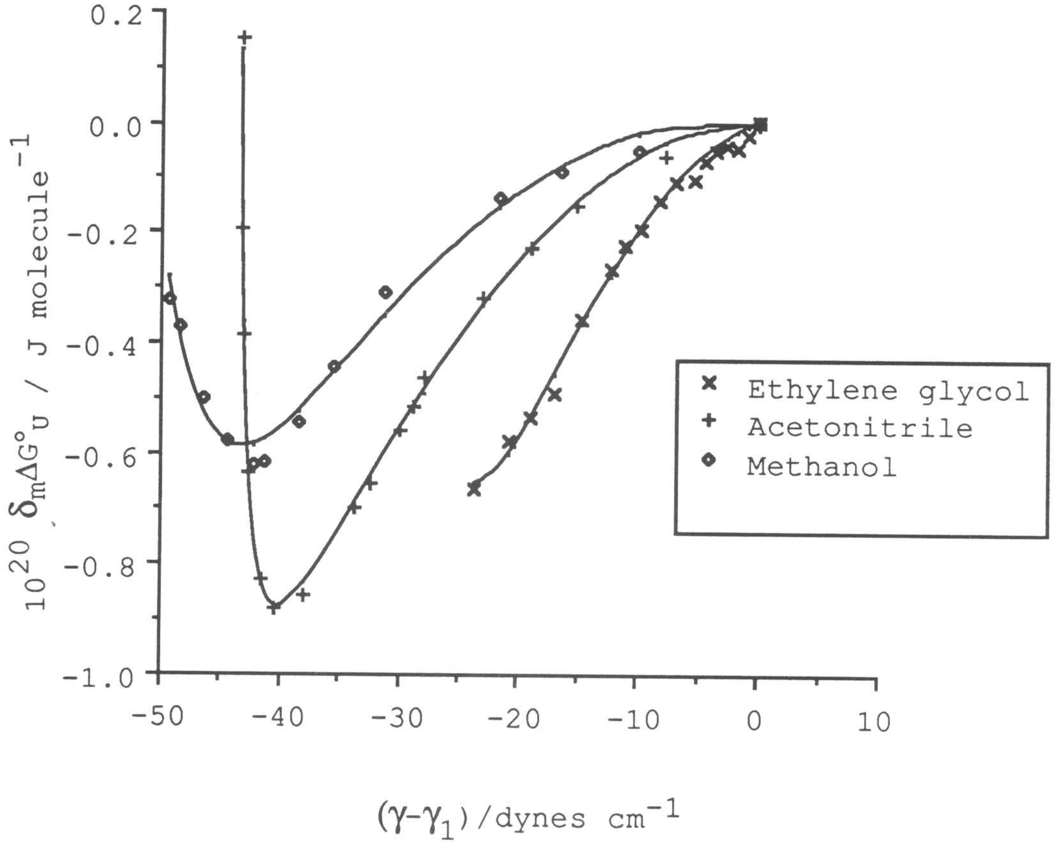


Figure 11. The medium effect on the unitary free energy change for the solubility of theophylline plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

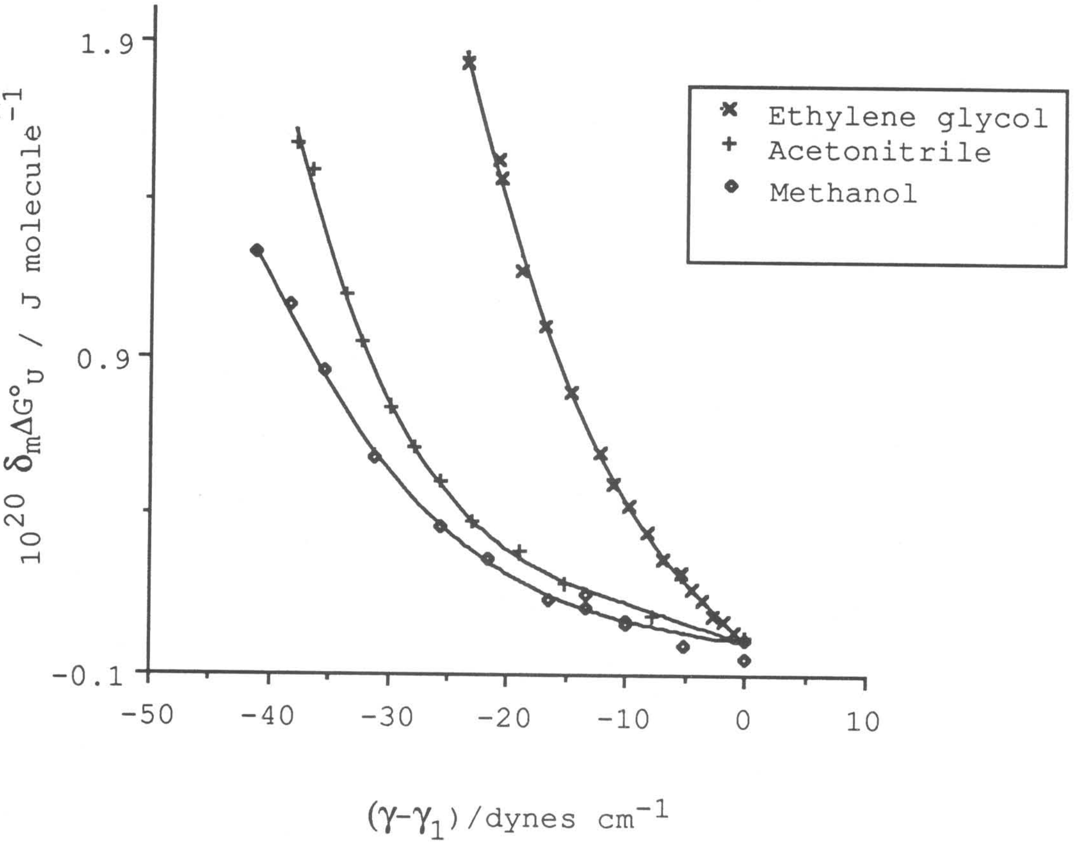


Figure 12. The medium effect on the unitary free energy change for the complexation of naphthalene and theophylline plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

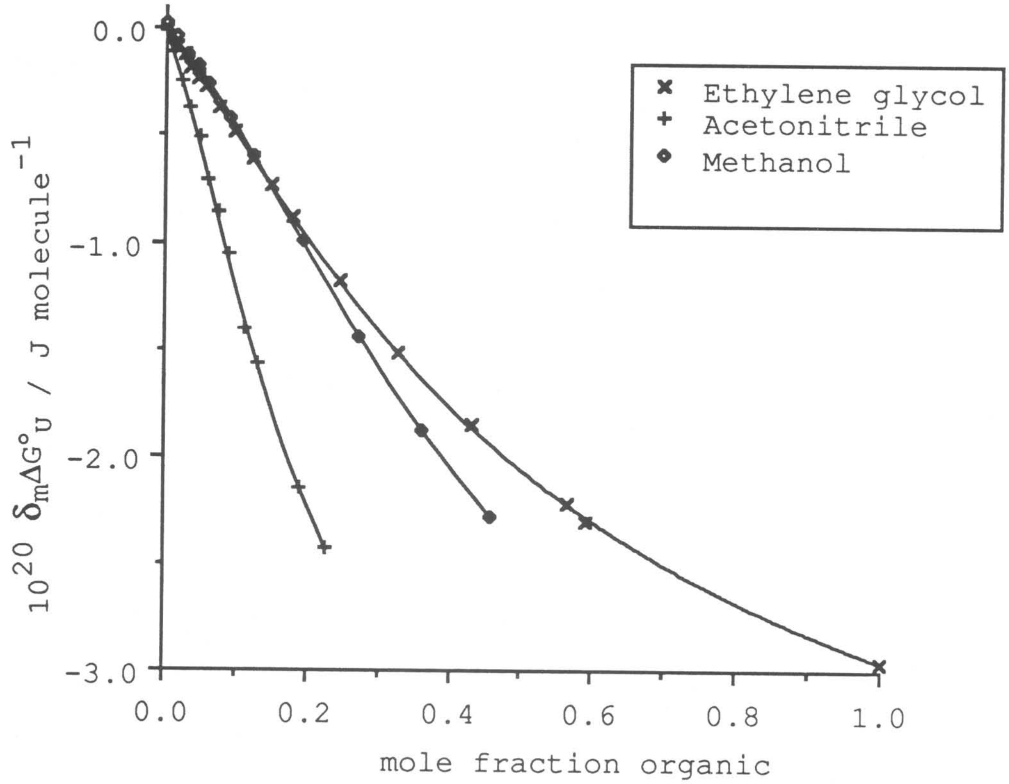


Figure 13. The medium effect on the unitary free energy change for the solubility of naphthalene plotted versus the mole fraction of organic cosolvent present along with the fitted curves obtained.

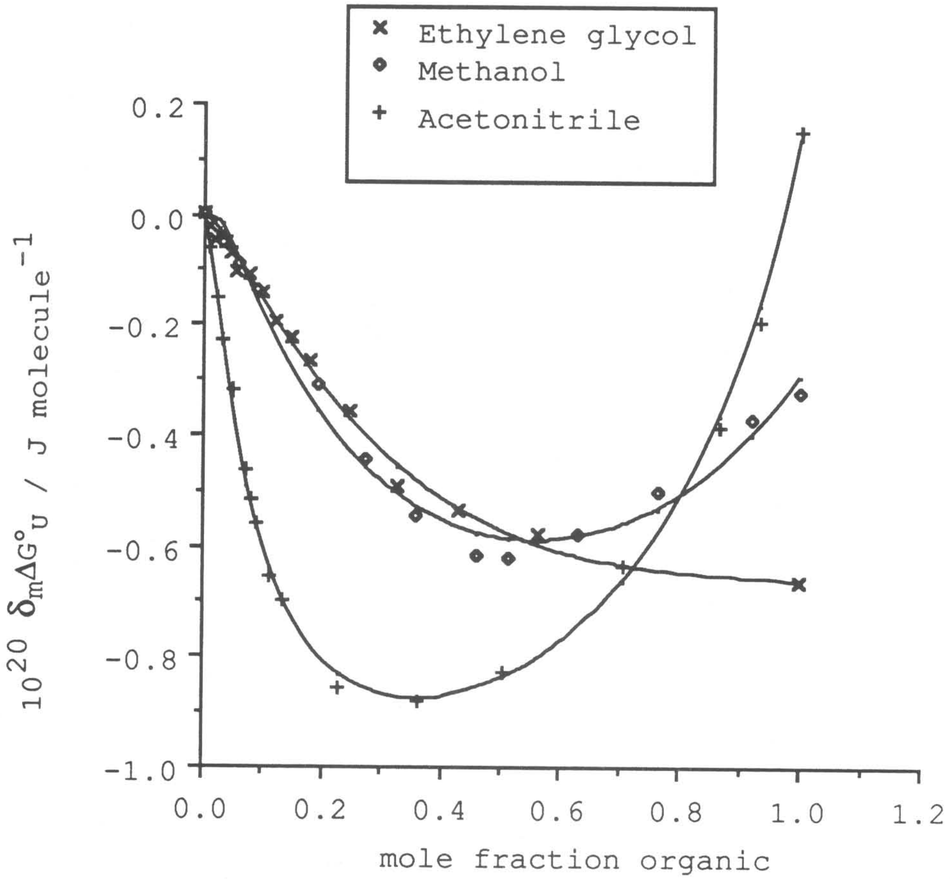


Figure 14. The medium effect on the unitary free energy change for the solubility of theophylline plotted versus the mole fraction of organic cosolvent present along with the fitted curves obtained.

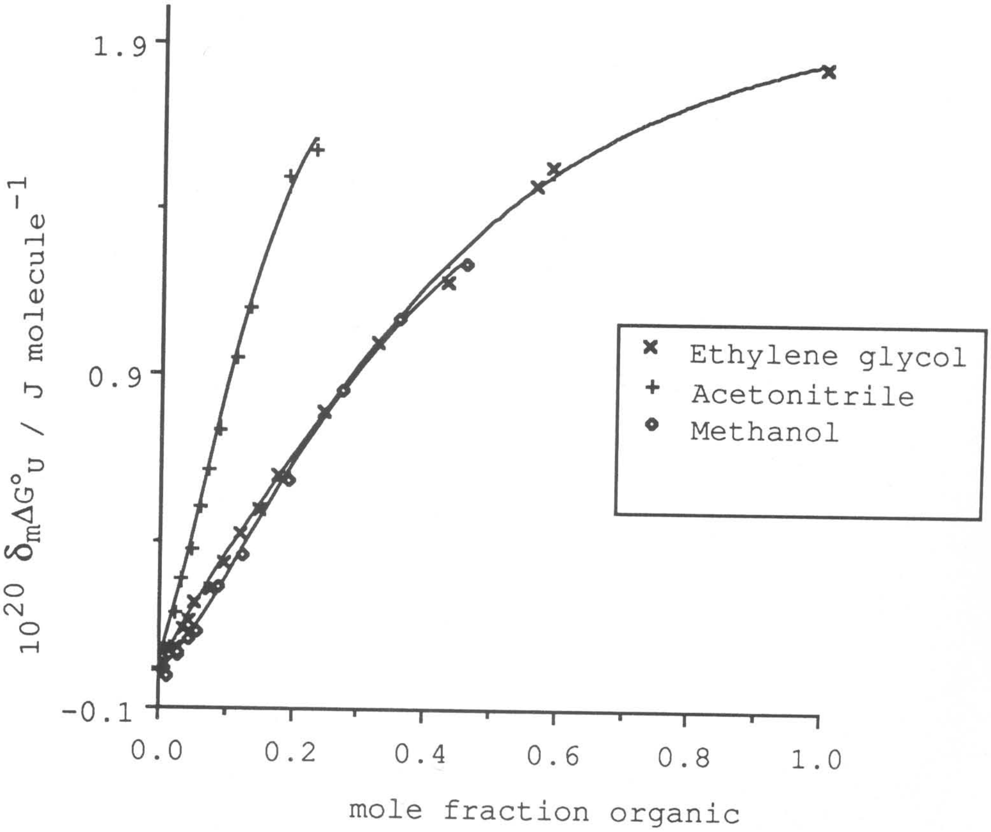


Figure 15. The medium effect on the unitary free energy change for the complexation of naphthalene and theophylline plotted versus the mole fraction of organic cosolvent present along with the fitted curves obtained.

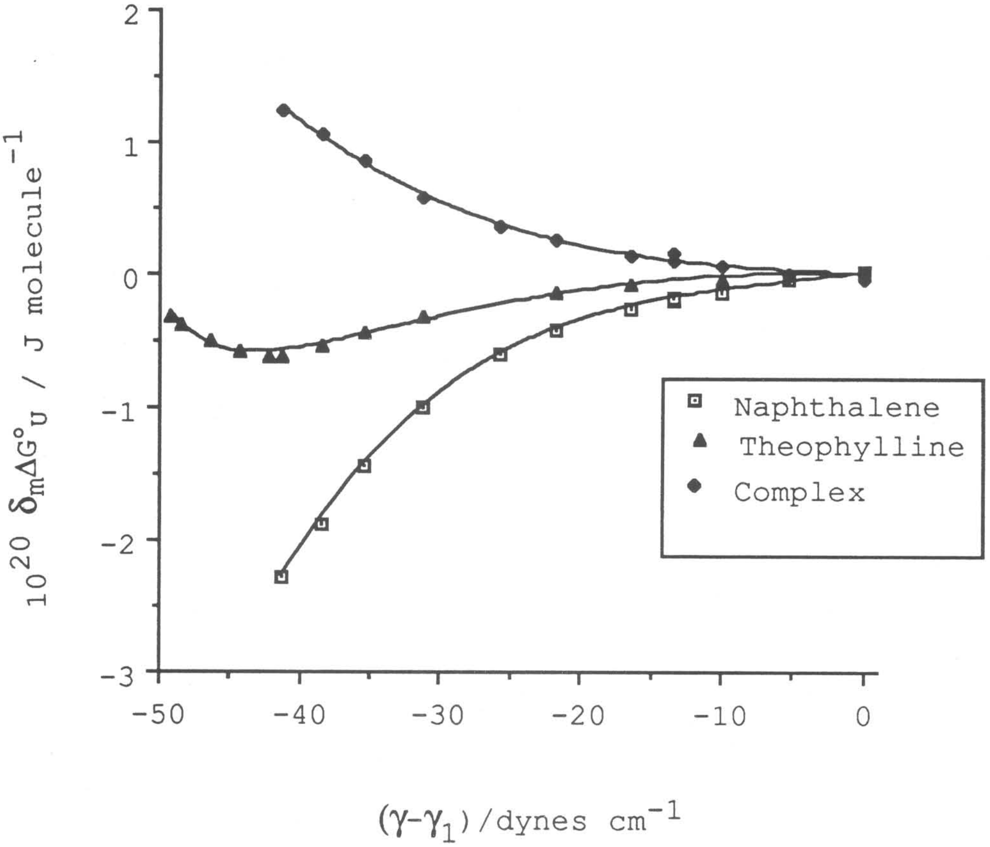


Figure 16. The medium effect on the unitary free energy change for the solubility of naphthalene, solubility of theophylline, and the complexation of naphthalene and theophylline in methanol-water mixtures plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

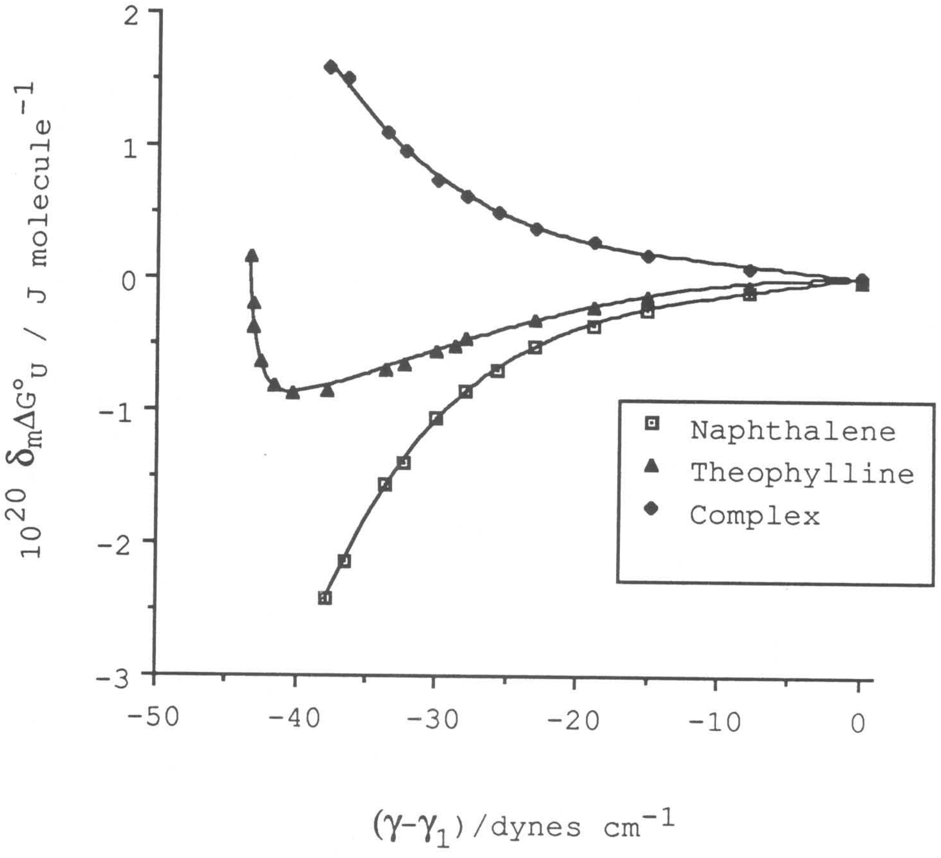


Figure 17. The medium effect on the unitary free energy change for the solubility of naphthalene, solubility of theophylline, and the complexation of naphthalene and theophylline in acetonitrile-water mixtures plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

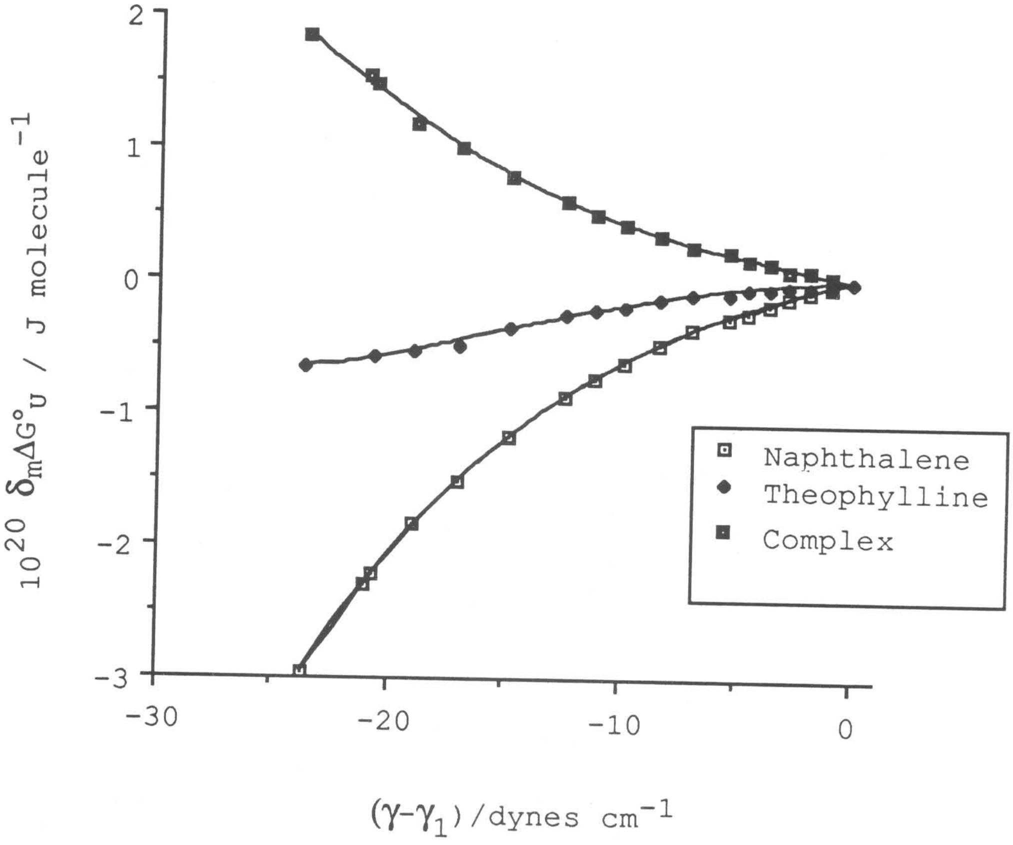


Figure 18. The medium effect on the unitary free energy change for the solubility of naphthalene, solubility of theophylline, and the complexation of naphthalene and theophylline in ethylene glycol-water mixtures plotted versus the relative surface tension of the solvent prepared along with the fitted curves obtained.

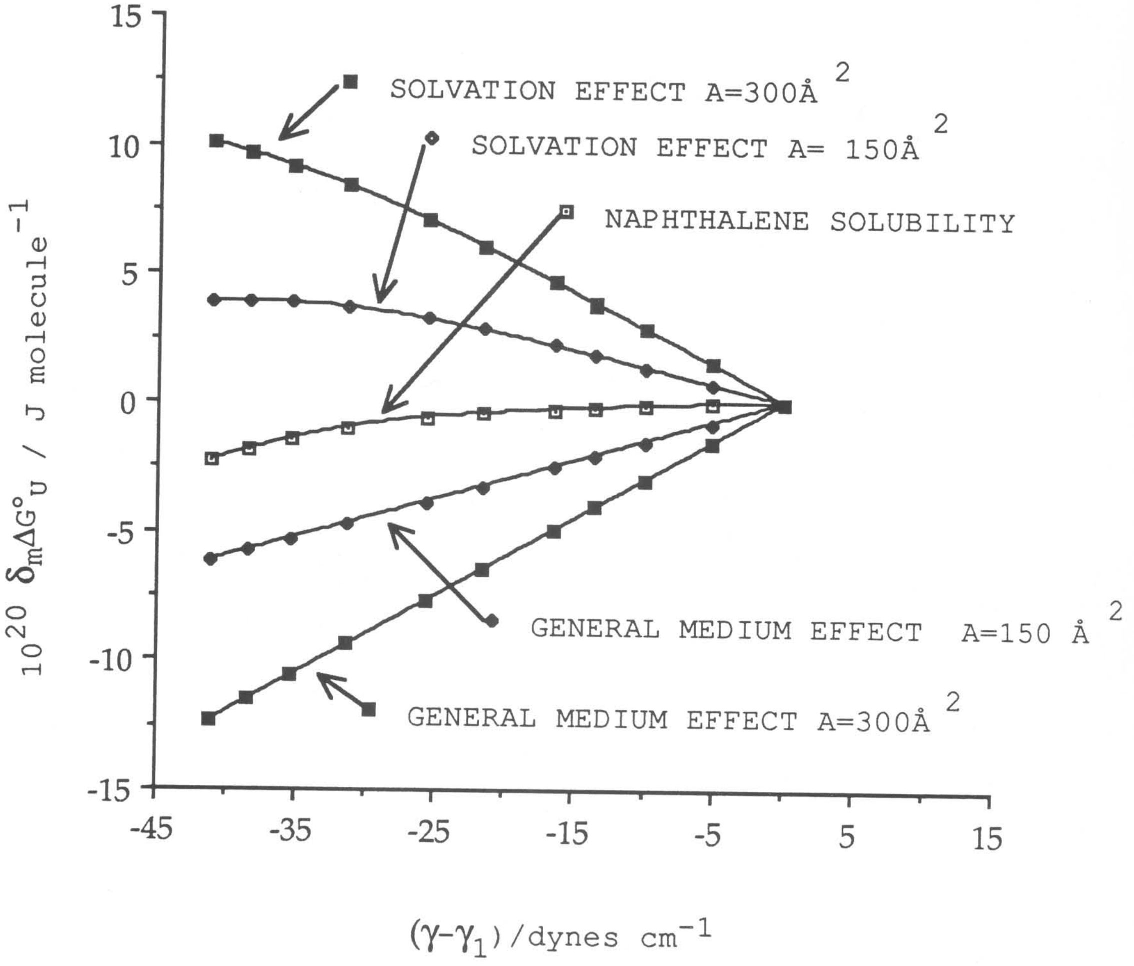


Figure 19. The general medium and solvation effect contribution to the solubility of naphthalene in methanol-water mixtures based on the surface area of naphthalene chosen.

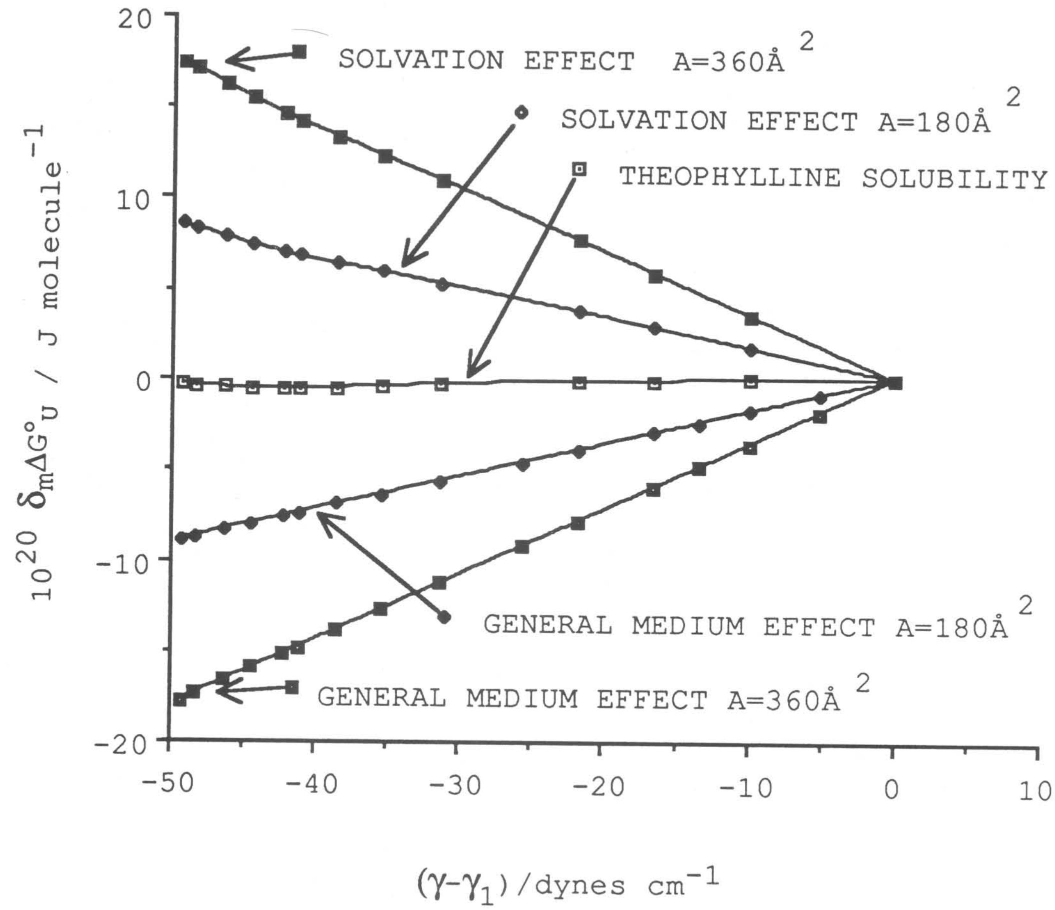


Figure 20. The general medium and solvation effect contribution to the solubility of theophylline in methanol-water mixtures based on the surface area of theophylline chosen.

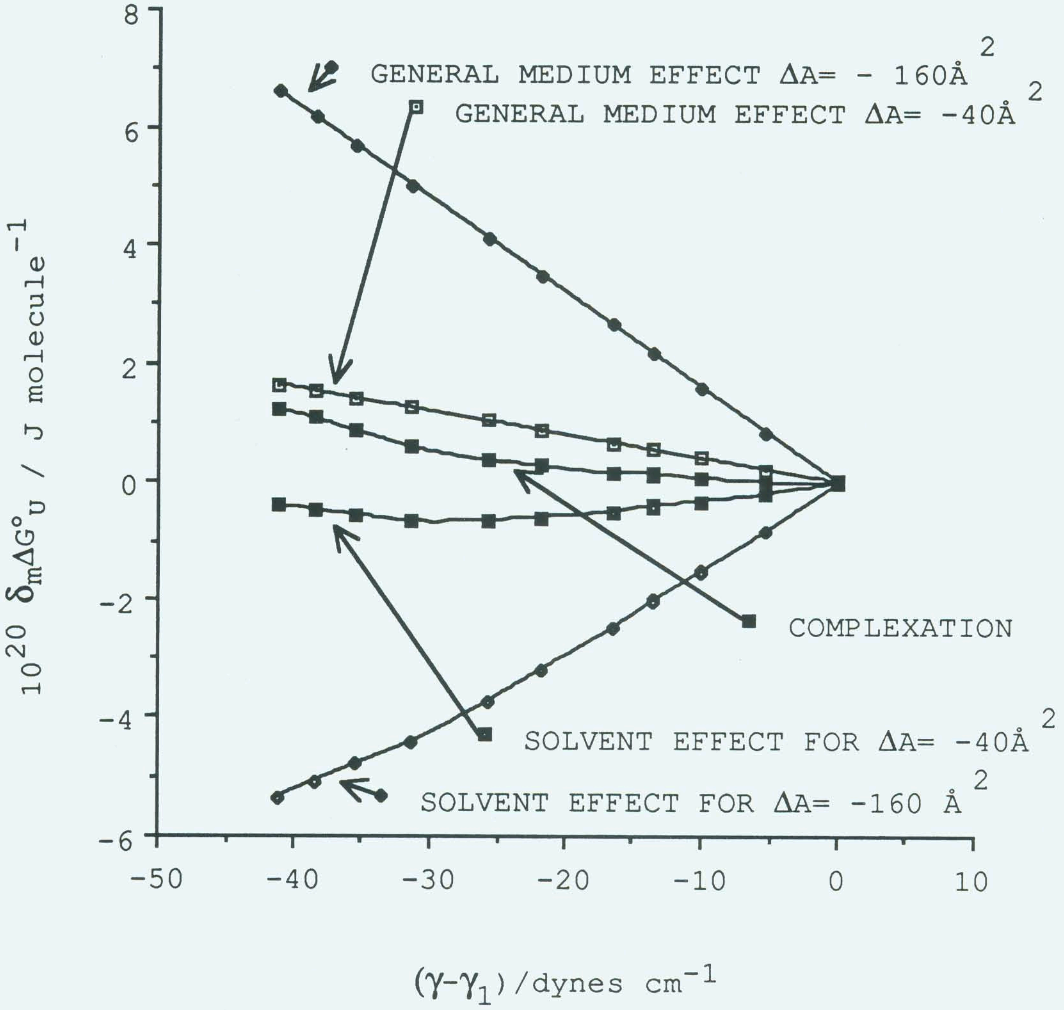


Figure 21. The general medium and solvation effect contribution to the complexation of naphthalene and theophylline in methanol-water mixtures based on the change in the surface area chosen.

TABLE V. The model parameters (S_1,K_1,S_2,K_2) calculated based on the van der Waals surface area.

	S_1 10^{-20}J/ molecule	K_1	S_2 10^{-20}J/ molecule	K_2
METHANOL				
Naphthalene solubility	5.11 (0.09)[a]	11.59 (0.25)	3.56 (0.10)	2.95 (0.59)
Theophylline solubility	6.72 (0.13)	11.74 (0.38)	8.58 (0.03)	0.54 (0.08)
Complexation of naphthalene and theophylline	-1.38 (0.28)	10.81 (3.3)	-0.10 (0.13)	3.69 (2.3)
ACETONITRILE				
Naphthalene solubility	5.68 (0.15)	23.57 (1.3)	2.2 (0.23)	6.29 (1.5)
Theophylline solubility	6.59 (0.05)	27.26 (0.48)	7.93 (0.02)	0.23 (0.03)
Complexation of naphthalene and theophylline	-2.49 (0.96)	10.26 (4.9)	0.73 (0.18)	14.11 (8.8)
ETHYLENE GLYCOL				
Naphthalene solubility	1.83 (0.02)	6.98 (0.12)	0.59 (0.01)	2.28 (0.08)
Theophylline solubility	2.89 (0.52)	7.13 (1.4)	3.60 (0.01)	0.95 (0.77)
Complexation of naphthalene and theophylline	-0.24 (0.12)	1.26 (0.65)	0.90 (0.02)	3.79 (1.0)

[a] Standard deviations appear in parentheses.

TABLE VI. The model parameters (S_1, K_1, S_2, K_2) calculated based on the water-accessible surface area.

	S_1 10^{-20}J/ molecule	K_1	S_2 10^{-20}J/ molecule	K_2
METHANOL				
Naphthalene solubility	8.55 (0.89)[a]	14.4 (1.4)	10.76 (0.08)	3.97 (1.04)
Theophylline solubility	14.0 (0.18)	11.11 (0.21)	17.46 (0.03)	0.643 (0.06)
Complexation of naphthalene and theophylline	-3.79 (1.7)	17.60 (7.5)	-5.77 (0.08)	5.00 (3.52)
ACETONITRILE				
Naphthalene solubility	10.46 (0.30)	26.93 (0.64)	8.71 (0.21)	6.31 (1.38)
Theophylline solubility	14.34 (0.02)	24.91 (0.1)	15.73 (0.02)	0.23 (0.01)
Complexation of naphthalene and theophylline	-5.32 (0.30)	26.96 (1.3)	-4.32 (0.16)	9.19 (3.4)
ETHYLENE GLYCOL				
Naphthalene solubility	3.96 (0.06)	7.77 (0.11)	4.15 (0.01)	2.09 (0.17)
Theophylline solubility	5.86 (2.8)	7.14 (3.4)	7.87 (0.01)	1.32 (1.9)
Complexation of naphthalene and theophylline	-1.70 (0.21)	8.48 (0.81)	-1.93 (0.02)	3.83 (1.3)

[a] Standard deviations appear in parentheses.

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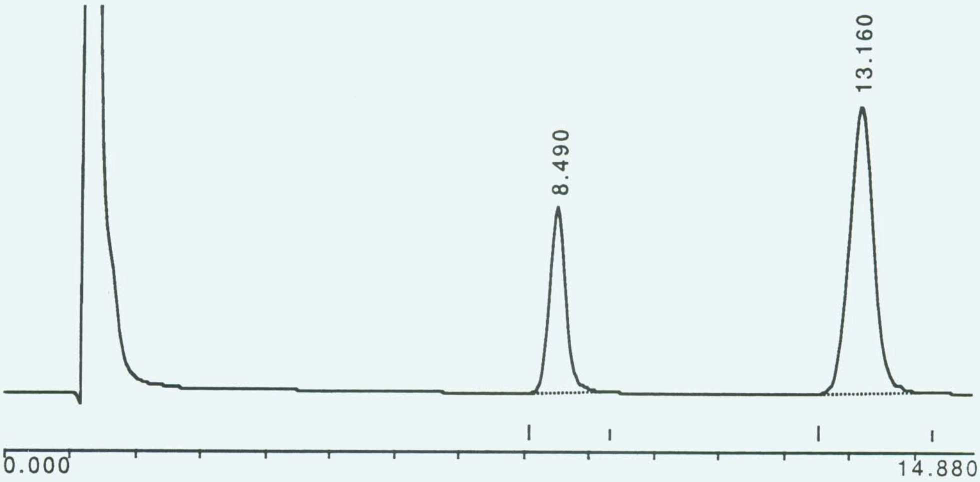
Appendix A

High Pressure Liquid Chromatograms

Date: Tue, Jul 31, 1990 12:33 PM
Data: dk-31JAN90-017

Sample: Mobile Phase: MeCN/Water/HoAc (50/49/1)
Wavelength: 254nm; 0.25 AUFS
Injection Volume: 100 µl; Flow rate 1.3 ml/min
Column: Zorbax® C-8, 5µ (4.6 x 150 mm)
Sample: Ampule #6 for the 12.57% (w/w) Acetonitrile/Water Cosolvent System

Method: dk
Sampling Int: 0.3 Seconds
Chromatogram:



Analysis: Channel A

Peak No.	Time	Type	Height(µV)	Area(µV-sec)	Area%
1	8.490	N	97644	1727759	30.667
2	13.160	N	150385	3906039	69.332
Total Area				5633798	99.999

Peak No.	Time	Asymmetry	Efficiency (N per column)
1	8.490	1.234	5907
2	13.160	1.096	6308

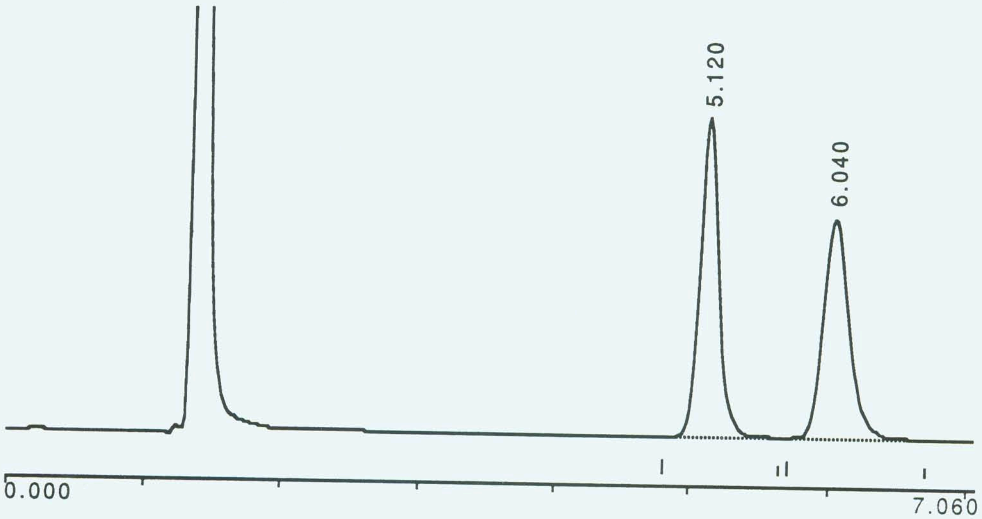
Figure A.1. High performance liquid chromatogram. The unlabeled peak corresponds to theophylline, peak number one corresponds to 4-Butyl benzoic acid, and peak number two corresponds to naphthalene.

Date: Tue, Jul 31, 1990 12:38 PM
Data: dk-28MAY90-013

Sample: Mobile Phase: MeOH/Water/HoAC (65/34/1)
Wavelength: 275 nm ; 0.35 AUFS
Injection Volume: 10 µl; Flow rate: 1.5 ml/min
Column: Econosphere C-18 5µ (4.6 mm x150 mm)
Sample: Ampule #7 for the 62.56% (w/w) Ethylene Glycol/Water Cosolvent System

Method: dk
Sampling Int: 0.3 Seconds

Chromatogram:



Analysis: Channel A

Peak No.	Time	Type	Height(µV)	Area(µV-sec)	Area%
1	5.120	N	358612	3462573	51.389
2	6.040	N	247733	3275372	48.611
Total Area				6737945	100.000

Peak No.	Time	Asymmetry	Efficiency (N per column)
1	5.120	1.375	7410
2	6.040	1.437	5053

Figure A.2. High performance liquid chromatogram. The unlabeled peak corresponds to theophylline, peak number number one corresponds to naphthalene, and peak number two corresponds to 4-Butyl benzoic acid.

Appendix B

Solubility of Naphthalene in Presence of Various Concentrations of Theophylline in Mixed Aqueous-Organic Cosolvents

Table B-I. Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol

2.85% w/w		5.54% w/w		8.33% w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	2.187	0.000	2.486	0.000	2.625
0.000	2.193	0.000	2.303	0.000	2.667
0.000	2.094	0.000	2.403	0.000	2.608
0.000	2.152	0.000	2.326	0.000	2.519
0.000	2.176	----	----	0.000	2.633
0.300	2.594	----	----	0.304	3.171
0.600	2.915	0.598	3.181	0.607	3.510
0.900	3.359	0.897	3.599	0.911	4.000
1.200	3.806	----	----	1.215	4.564
1.500	4.342	1.495	4.320	1.519	4.933
1.800	4.716	1.794	5.013	1.822	5.609
2.100	5.117	2.093	5.450	2.126	6.000
2.400	5.656	2.392	5.935	2.430	6.485
2.701	6.256	2.691	6.398	2.733	7.111
----	----	2.990	6.907	3.037	7.662

Table B-I. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol					
11.01% w/w		13.80% w/w		16.43% w/w	
$10^2\ L_t/M$	$10^4\ S_t/M$	$10^2\ L_t/M$	$10^4\ S_t/M$	$10^2\ L_t/M$	$10^4\ S_t/M$
0.000	2.889	0.000	3.345	0.000	3.518
0.000	2.889	0.000	3.158	0.000	3.498
0.000	2.928	0.000	3.152	0.000	3.487
0.000	2.904	0.000	3.276	0.000	3.561
0.000	2.944	0.000	3.269	0.000	3.455
0.299	3.360	0.297	3.716	0.299	4.018
0.598	3.808	0.593	4.209	0.598	4.543
0.896	4.254	----	----	0.897	5.331
1.195	4.703	1.186	5.212	1.196	5.609
1.494	5.324	1.483	5.592	1.495	5.960
1.793	5.734	1.780	6.110	1.794	6.499
2.092	6.321	2.076	6.756	2.093	6.837
2.391	6.751	2.373	7.300	2.392	7.369
2.689	7.236	2.669	7.882	2.692	8.041
2.988	7.871	2.966	8.454	2.991	8.705

Table B-I. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol					
21.78% w/w		27.08% w/w		32.31% w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	4.401	0.000	5.504	0.000	7.084
0.000	4.211	0.000	5.153	0.000	7.194
0.000	4.322	0.000	5.401	0.000	7.139
0.000	4.288	0.000	5.466	0.000	7.068
0.000	4.182	----	----	----	----
0.295	4.880	0.299	6.031	0.299	7.765
0.591	5.378	0.598	6.664	0.597	8.497
0.886	5.971	0.897	7.139	----	----
1.181	6.458	1.196	7.840	1.195	9.880
1.477	6.986	1.496	8.506	----	----
1.772	7.644	1.795	9.130	1.792	11.122
2.067	8.220	2.094	9.617	2.091	12.011
2.363	8.781	----	----	2.390	12.715
2.658	9.487	2.692	10.879	2.688	13.352
2.953	9.938	2.991	11.661	2.987	13.930

Table B-I. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol					
37.49% w/w		42.62% w/w		52.70% w/w	
10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M
0.000	0.926	0.000	1.264	0.000	2.383
0.000	0.922	0.000	1.252	0.000	2.376
0.000	0.935	0.000	1.251	0.000	2.368
0.000	0.922	0.000	1.223	0.000	2.351
0.000	0.918	0.000	1.246	0.000	2.339
0.303	1.012	0.304	1.317	0.298	2.463
0.605	1.090	0.609	1.415	0.596	2.591
0.908	1.159	0.913	1.514	0.894	2.713
1.210	1.248	1.217	1.605	1.192	2.823
1.513	1.299	1.521	1.682	1.491	2.957
1.815	1.385	1.826	1.760	1.789	3.048
2.118	1.482	2.130	1.855	2.087	3.154
2.420	1.561	2.434	1.934	2.385	3.253
2.723	1.643	2.738	2.046	2.683	3.361
3.026	1.727	3.043	2.118	2.981	3.495

Table B-I. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol					
62.56% w/w		72.22% w/w		81.67% w/w	
10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^2 S_t/M	10^2 L_t/M	10^2 S_t/M
0.000	4.788	0.000	0.961	0.000	2.019
0.000	4.760	0.000	0.949	0.000	2.020
0.000	4.745	0.000	0.945	0.000	2.013
0.000	4.718	0.000	0.943	0.000	2.022
0.300	4.841	0.299	0.982	0.299	2.048
0.599	4.963	0.599	0.988	0.597	2.104
0.899	5.149	0.898	1.010	0.896	2.114
1.198	5.317	1.198	1.033	----	----
1.498	5.528	----	----	1.493	2.155
1.797	5.589	1.796	1.079	1.792	2.158
2.097	5.816	2.096	1.095	2.090	2.229
2.396	5.988	2.395	1.120	2.389	2.216
2.696	6.038	2.695	1.147	2.687	2.238
2.995	6.211	2.994	1.168	2.986	2.286

Table B-I. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in ethylene glycol-water cosolvents at 25°C.

weight percent ethylene glycol			
83.20% w/w		100% w/w	
10^2 L_t/M	10^2 S_t/M	10^2 L_t/M	10^2 S_t/M
0.000	2.378	0.000	8.515
0.000	2.407	0.000	8.541
0.000	2.409	0.000	8.444
----	----	0.000	8.514
0.301	2.435	0.301	8.533
0.603	2.457	----	----
0.904	2.480	0.903	8.595
1.205	2.528	----	----
1.507	2.552	1.504	8.843
1.808	2.580	----	----
2.109	2.594	----	----
----	----	2.708	8.954
3.013	2.655	3.009	9.093

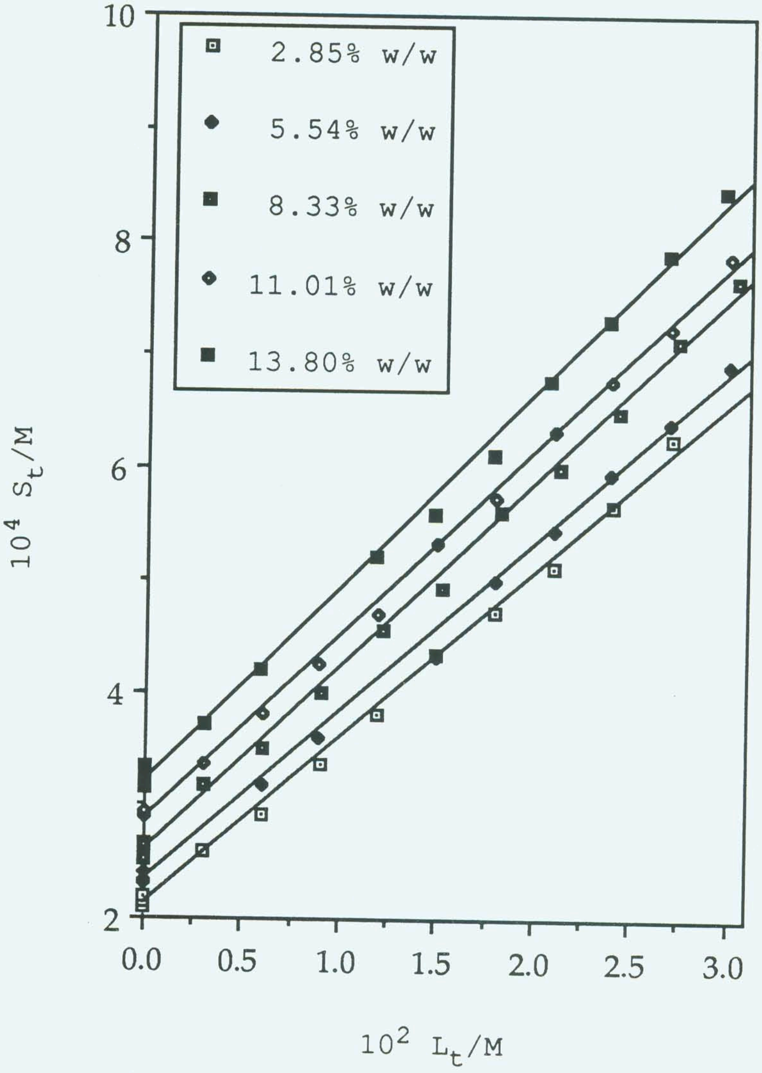


Figure B.1. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for ethylene glycol/water cosolvents at 25°C. The data appear in Table B-I.

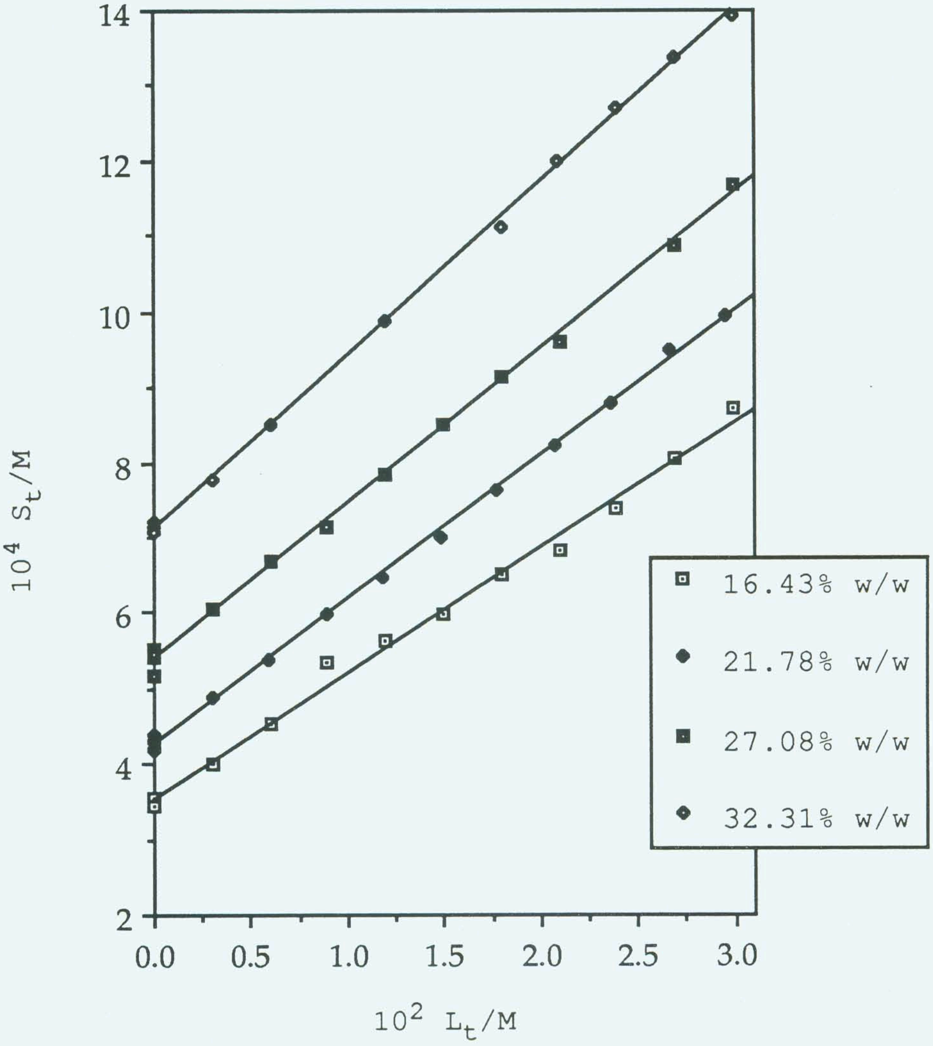


Figure B.2. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for ethylene glycol/water cosolvents at 25°C. The data appear in Table B-I.

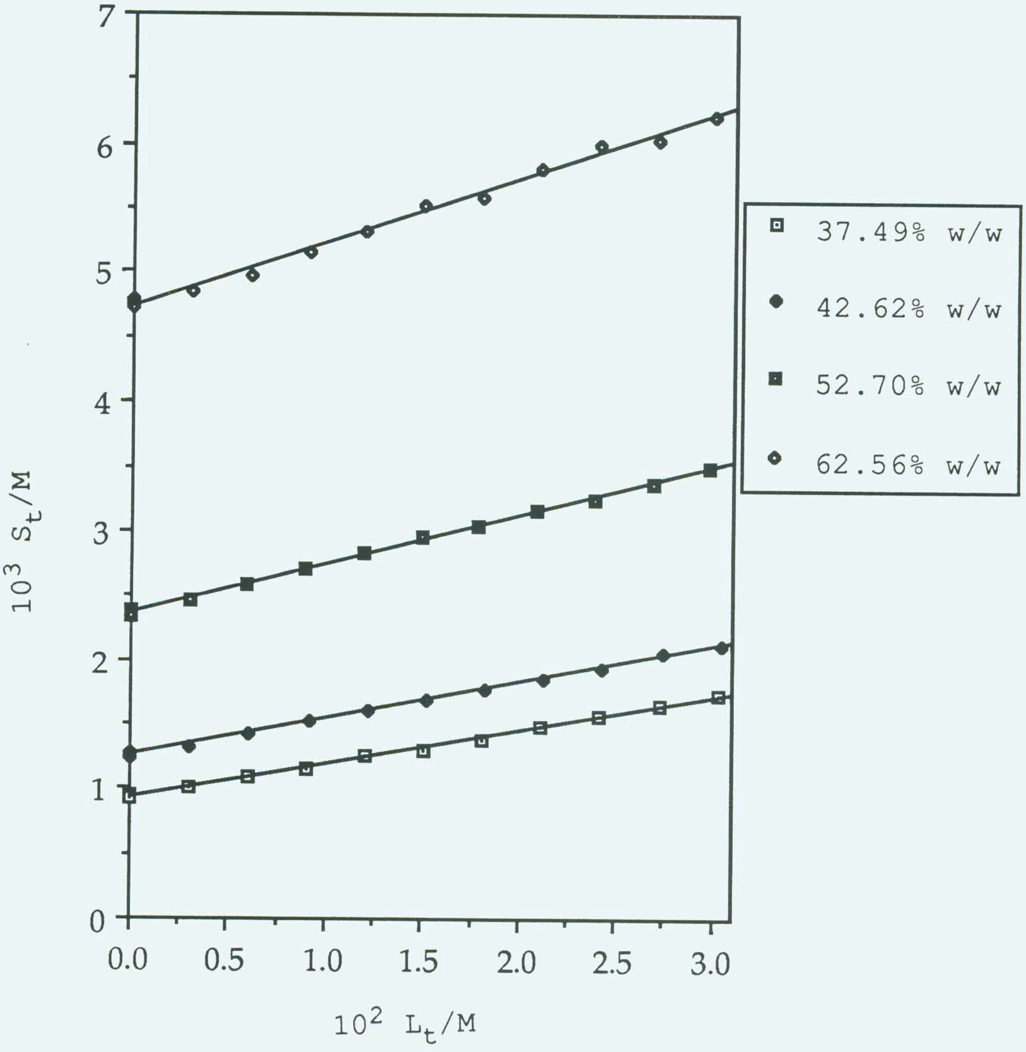


Figure B.3. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for ethylene glycol/water cosolvents at 25°C. The data appear in Table B-I.

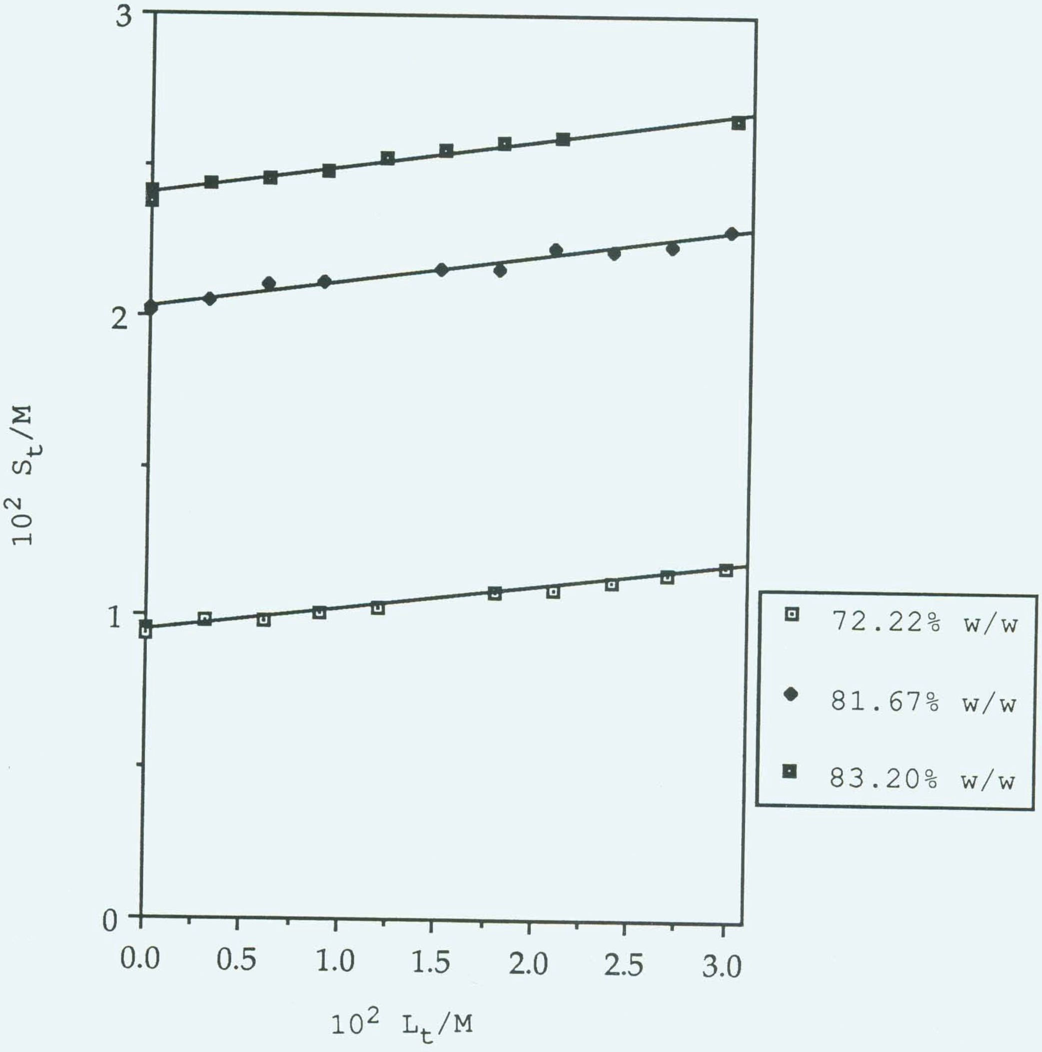


Figure B.4. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for ethylene glycol/water cosolvents at 25°C. The data appear in Table B-I.

Table B-II. Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in acetonitrile-water cosolvents at 25°C.

weight percent acetonitrile					
0.0 % w/w		0.0 % w/w		2.17% w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	2.137	0.000	2.033	0.000	2.524
0.000	2.099	0.000	2.078	0.000	2.553
0.000	2.088	0.000	2.100	0.000	2.527
0.000	2.048	----	----	0.000	2.587
0.299	2.476	0.299	2.432	0.299	3.005
0.597	2.907	0.599	2.813	0.598	3.400
0.896	3.305	0.898	3.258	0.897	3.829
----	----	----	----	1.197	4.299
1.493	4.149	1.497	4.121	1.496	4.735
1.792	4.607	1.796	4.557	1.795	5.230
2.091	5.066	2.096	5.000	2.094	5.693
2.389	5.558	2.395	5.439	2.393	6.236
2.688	5.969	2.694	5.974	2.692	6.690
2.987	6.478	2.994	6.444	2.992	7.180

Table B-II. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in acetonitrile-water cosolvents at 25°C.

weight percent acetonitrile					
5.05 % w/w		7.21 % w/w		10.09 % w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	3.529	0.000	4.709	0.000	6.672
0.000	3.459	0.000	4.654	0.000	6.591
----	----	0.000	4.623	0.000	6.245
----	----	----	----	0.000	6.301
0.299	3.882	0.300	5.124	0.300	7.065
0.598	4.363	0.600	5.714	0.599	7.607
0.897	4.853	0.900	6.065	0.899	8.184
1.197	5.301	1.201	6.739	1.198	8.775
1.496	5.805	1.501	7.275	1.498	9.516
----	----	1.801	7.802	1.798	9.969
2.094	6.850	2.101	8.258	2.097	10.645
2.393	7.444	2.401	8.841	2.397	11.279
2.692	7.877	2.701	9.469	2.696	11.902
2.991	8.452	3.001	10.081	2.996	12.562

Table B-II. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in acetonitrile-water cosolvents at 25°C.

weight percent acetonitrile					
12.57 % w/w		15.27 % w/w		18.16 % w/w	
10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M
0.000	1.020	0.000	1.409	0.000	2.242
0.000	1.037	0.000	1.420	0.000	2.252
0.000	1.009	0.000	1.425	0.000	2.239
0.000	1.027	0.000	1.415	----	----
0.299	1.100	0.299	1.485	0.300	2.360
0.597	1.175	0.597	1.580	0.601	2.487
0.896	1.228	0.896	1.651	0.901	2.524
1.194	1.303	1.194	1.719	1.201	2.637
1.493	1.376	1.493	1.796	1.501	2.708
1.791	1.458	1.791	1.879	1.802	2.832
2.090	1.531	2.090	1.950	2.102	2.934
2.388	1.598	2.389	2.029	2.402	2.984
2.687	1.677	2.687	2.137	2.702	3.110
2.985	1.746	2.986	2.198	----	----

Table B-II. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in acetonitrile-water cosolvents at 25°C.

weight percent acetonitrile					
22.40 % w/w		25.66 % w/w		34.81 % w/w	
10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^2 S_t/M
0.000	5.018	0.000	7.134	0.000	2.883
0.000	4.983	0.000	7.103	0.000	2.815
0.000	5.067	0.000	7.192	0.000	2.822
----	----	0.000	7.181	----	----
0.300	5.171	0.300	7.332	0.300	2.858
0.600	5.274	----	----	0.600	2.882
0.900	5.317	0.899	7.602	0.899	2.919
1.200	5.503	1.198	7.661	1.199	3.010
1.500	5.583	1.498	7.822	1.499	2.941
1.800	5.705	1.797	7.961	1.799	2.976
2.100	5.829	----	----	2.098	2.999
2.400	6.021	2.397	8.248	2.398	2.986
2.699	6.202	2.696	8.386	2.698	3.055
2.999	6.354	2.996	8.395	2.998	3.057

Table B-II. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in acetonitrile-water cosolvents at 25°C.

weight percent acetonitrile

40.23 % w/w	
$10^2\ L_t/M$	$10^2\ S_t/M$
0.000	5.106
0.000	5.149
0.000	5.092
0.300	5.152
0.601	5.223
0.901	5.166
1.502	5.212
1.802	5.277
2.103	5.282
2.403	5.378
2.704	5.443
3.004	5.436

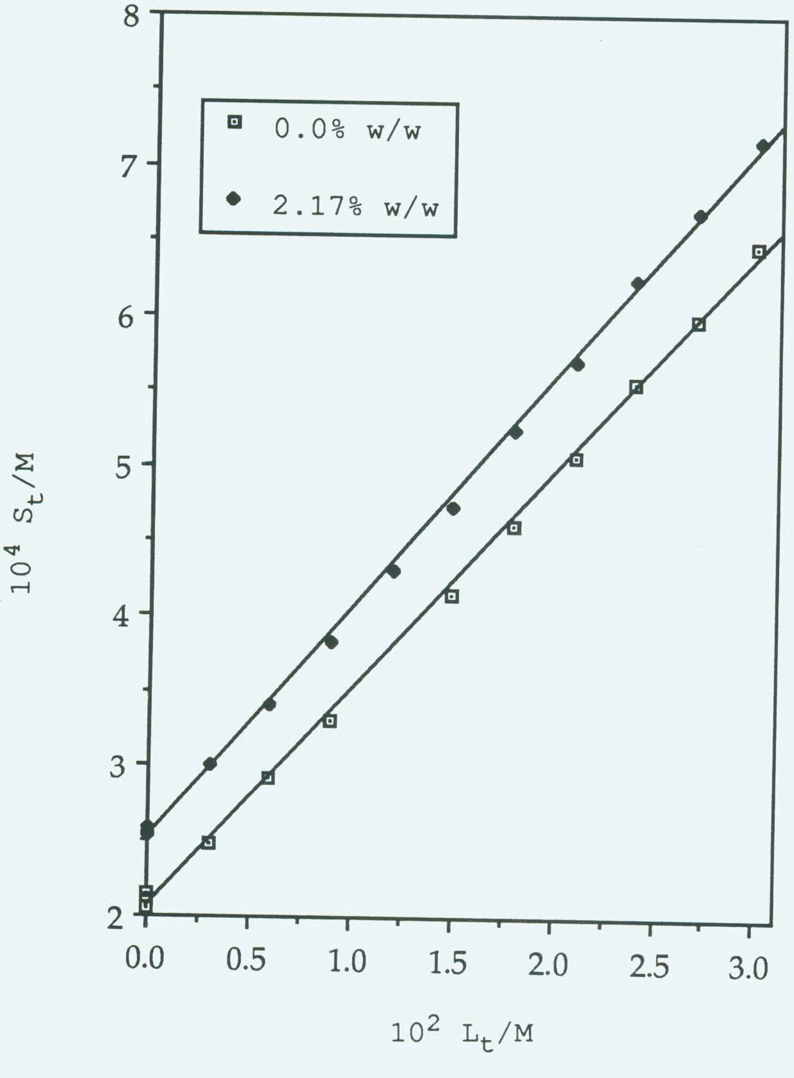


Figure B.5. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for acetonitrile/water cosolvents at 25°C. The data appear in Table B.II.

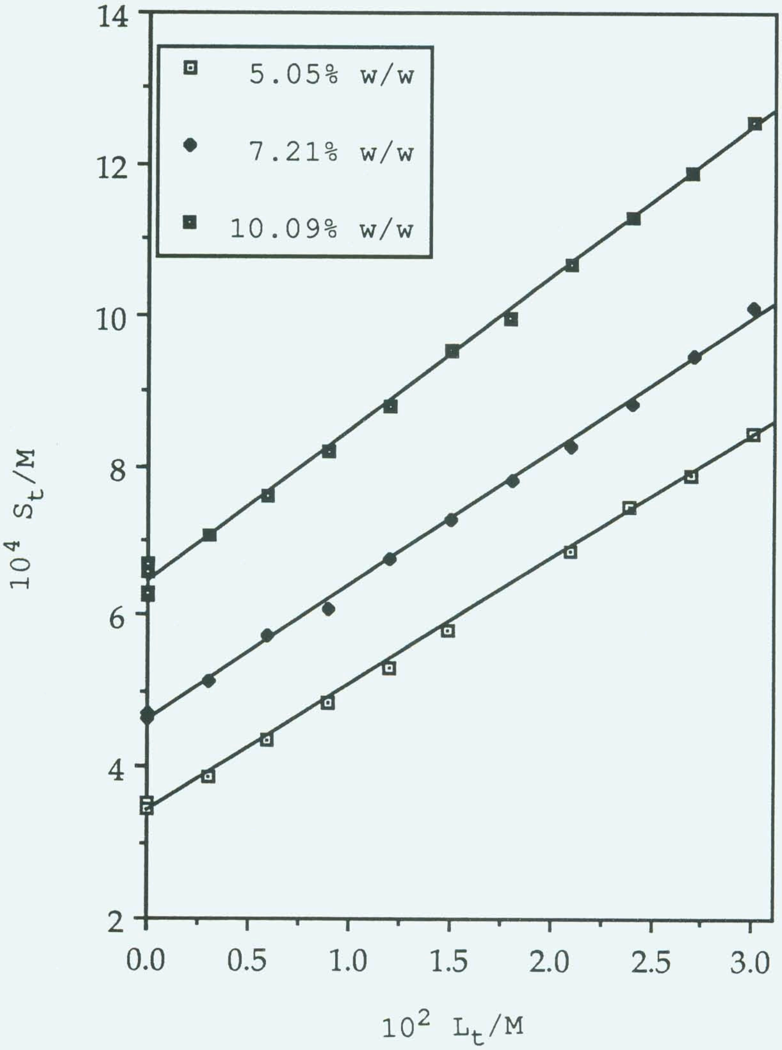


Figure B.6. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for acetonitrile/water cosolvents at 25°C. The data appear in Table B.II.

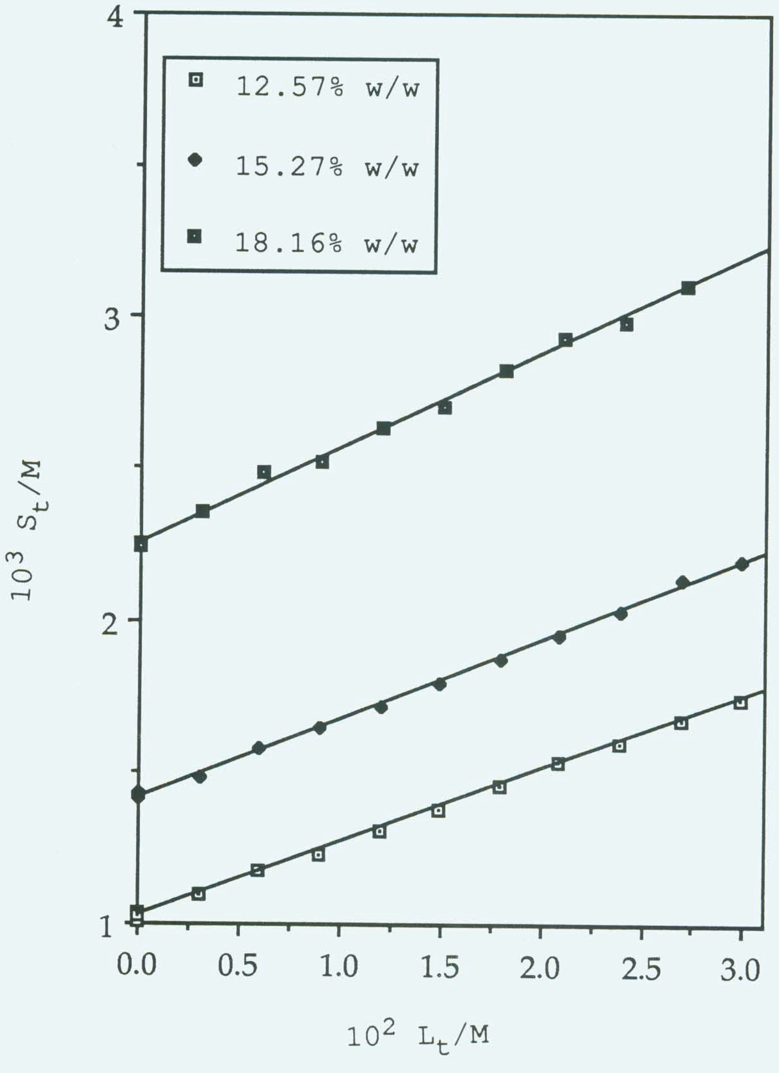


Figure B.7. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for acetonitrile/water cosolvents at 25°C. The data appear in Table B.II.

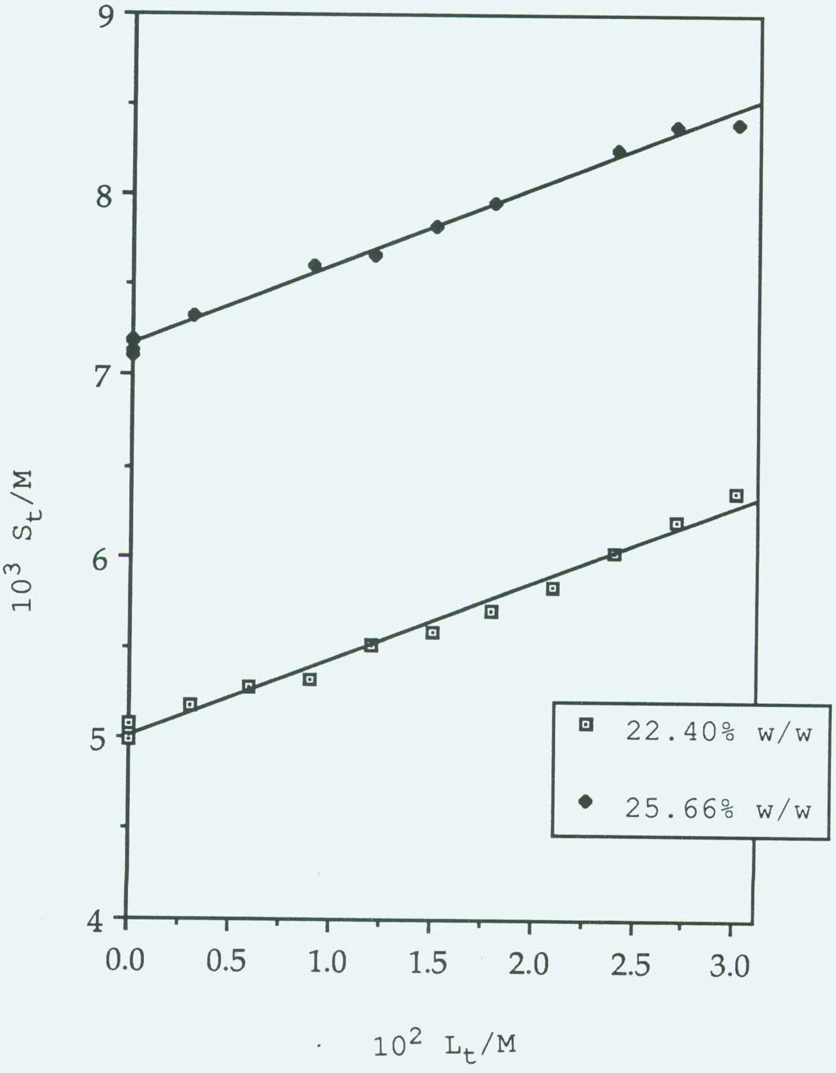


Figure B.8. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for acetonitrile/water cosolvents at 25°C. The data appear in Table B.II.

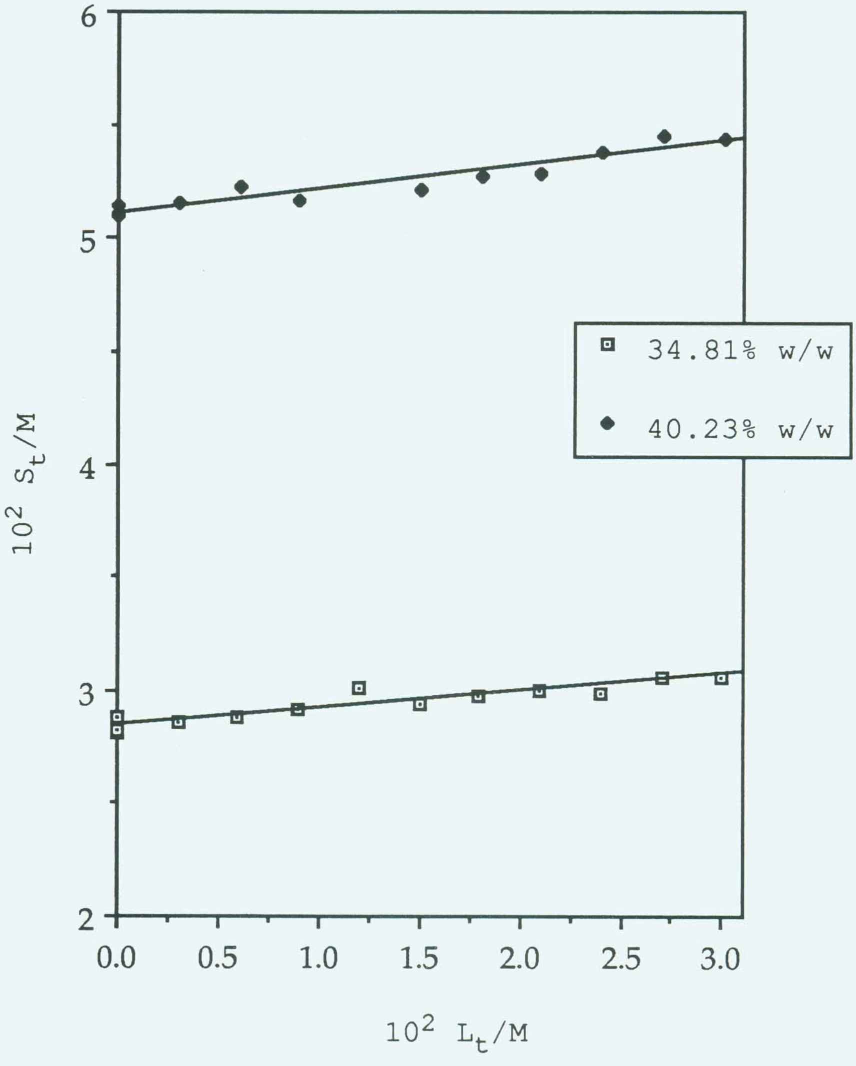


Figure B.9. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for acetonitrile/water cosolvents at 25°C. The data appear in Table B.II.

Table B-III. Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in methanol-water cosolvents at 25°C.

weight percent methanol					
0.0 % w/w		0.0 % w/w		2.38 % w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	1.985	0.000	1.918	0.000	2.088
0.000	1.954	0.000	1.913	0.000	2.015
----	----	----	----	0.000	2.336
----	----	----	----	0.000	2.126
0.301	2.360	0.300	2.324	0.299	2.644
0.602	2.741	0.600	2.800	0.598	3.055
0.903	3.142	----	----	0.897	3.435
1.204	3.405	1.199	3.651	1.196	3.920
1.505	3.847	1.499	4.112	1.496	4.466
1.806	4.258	1.799	4.548	1.795	4.855
2.107	4.762	2.098	5.073	----	----
2.408	5.146	2.398	5.556	2.393	5.840
2.709	5.650	2.698	6.073	2.692	6.411
3.011	6.187	2.998	6.567	2.991	7.130

Table B-III. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in methanol-water cosolvents at 25°C.

weight percent methanol					
5.11 % w/w		5.11 % w/w		7.44 % w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	2.698	0.000	2.626	0.000	2.951
0.000	2.557	0.000	2.596	0.000	2.835
----	----	----	----	0.000	2.639
----	----	----	----	0.000	2.999
0.299	3.057	0.299	3.010	0.301	3.016
0.598	3.532	0.598	3.575	0.602	3.630
0.897	4.049	0.897	4.119	0.903	3.851
1.195	4.530	1.196	4.549	1.204	4.990
1.494	4.955	1.495	5.034	----	----
1.793	5.542	1.793	5.594	1.805	5.709
2.092	6.055	2.092	6.050	2.106	6.401
2.391	6.685	2.391	6.481	2.407	6.852
2.690	7.158	2.690	7.110	2.708	7.638
----	----	2.989	7.643	3.009	8.153

Table B-III. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in methanol-water cosolvents at 25°C.

weight percent methanol					
7.44% w/w		9.85 % w/w		14.95 % w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^4 S_t/M
0.000	3.367	0.000	3.541	0.000	5.080
0.000	3.081	----	----	0.000	5.036
0.000	3.070	----	----	----	----
0.000	3.033	----	----	----	----
0.300	3.539	0.300	3.898	0.299	5.595
0.600	4.030	0.600	4.460	0.599	6.211
0.901	4.479	0.900	5.115	0.898	6.884
1.201	5.052	1.200	5.626	1.197	7.486
1.501	5.525	1.501	6.218	1.496	8.057
1.801	5.977	1.801	6.775	1.796	8.725
2.102	6.594	2.101	7.378	2.095	9.441
2.402	6.996	2.401	7.983	2.394	10.106
2.702	7.671	2.701	8.655	2.693	10.697
3.002	8.142	3.001	9.144	2.993	11.321

Table B-III. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in methanol-water cosolvents at 25°C.

weight percent methanol					
20.05 % w/w		29.92 % w/w		40.07% w/w	
10^2 L_t/M	10^4 S_t/M	10^2 L_t/M	10^3 S_t/M	10^2 L_t/M	10^3 S_t/M
0.000	7.414	0.000	1.848	0.000	5.043
0.000	7.500	0.000	1.827	0.000	5.022
0.000	7.518	0.000	1.845	0.000	5.028
0.000	7.332	0.000	1.869	----	----
0.000	7.469	----	----	----	----
----	----	0.299	1.901	0.299	5.151
0.589	8.575	0.598	2.036	0.598	5.377
0.884	9.546	0.897	2.155	0.897	5.493
1.179	10.297	1.196	2.272	1.196	5.682
1.474	10.970	1.495	2.382	1.495	5.886
1.768	11.668	1.794	2.503	1.794	6.247
2.063	12.581	2.093	2.615	2.093	6.067
2.358	13.345	2.392	2.762	----	----
2.652	14.141	2.691	2.914	2.691	6.596
2.947	14.953	2.990	3.013	----	----

Table B-III. (*continued*) Concentration variables in the solubility study of naphthalene (S) : theophylline (L) in methanol-water cosolvents at 25°C.

weight percent methanol			
49.91 % w/w		60.12% w/w	
10^2 L_t/M	10^2 S_t/M	10^2 L_t/M	10^2 S_t/M
0.000	1.350	0.000	3.304
0.000	1.326	0.000	3.319
0.000	1.341	0.000	3.342
0.000	1.346	----	----
0.000	1.354	----	----
0.300	1.376	0.299	3.368
0.600	1.398	0.597	3.395
0.900	1.419	----	----
1.200	1.450	1.195	3.502
1.500	1.473	1.493	3.522
1.799	1.515	1.792	3.553
2.099	1.541	2.091	3.634
2.399	1.572	2.389	3.710
2.699	1.610	2.688	3.756
2.999	1.628	2.987	3.807

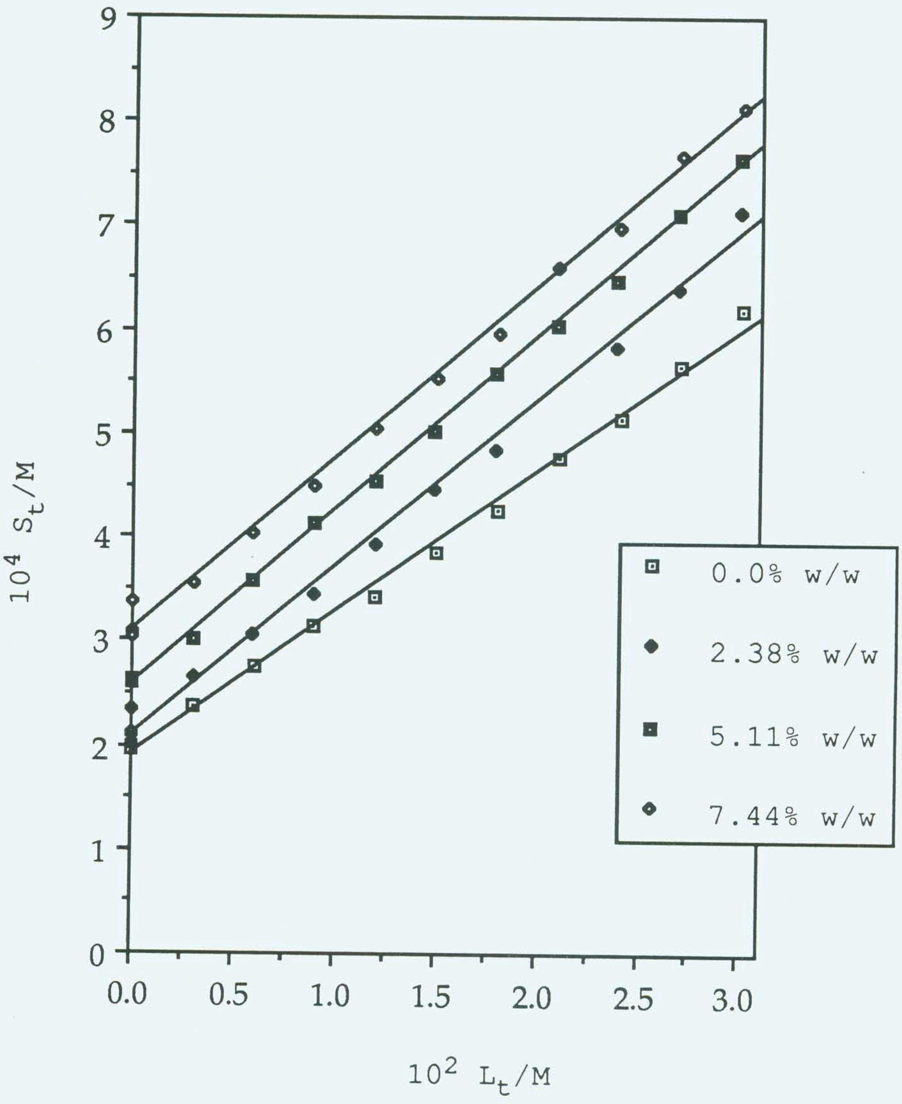


Figure B.10. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for methanol/water cosolvents at 25°C. The data appear in Table B.III.

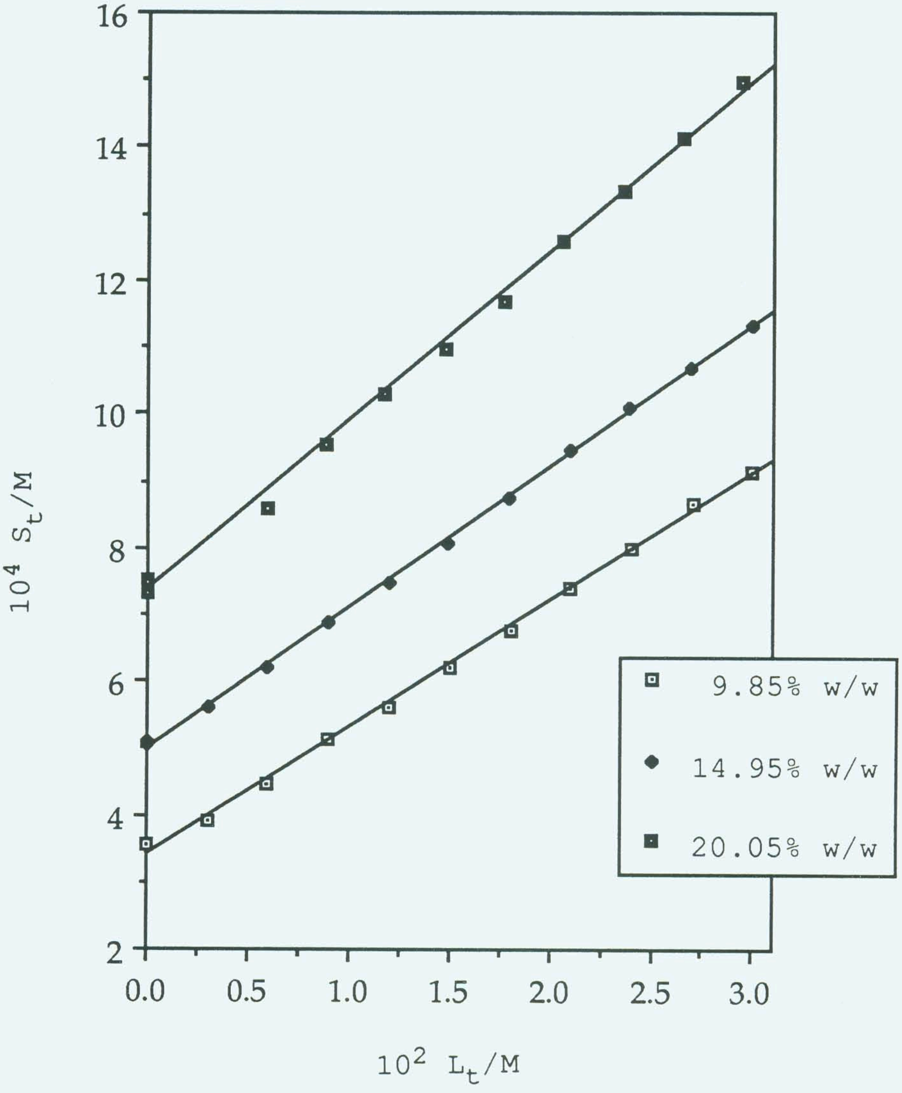


Figure B.11. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for methanol/water cosolvents at 25°C. The data appear in Table B.III.

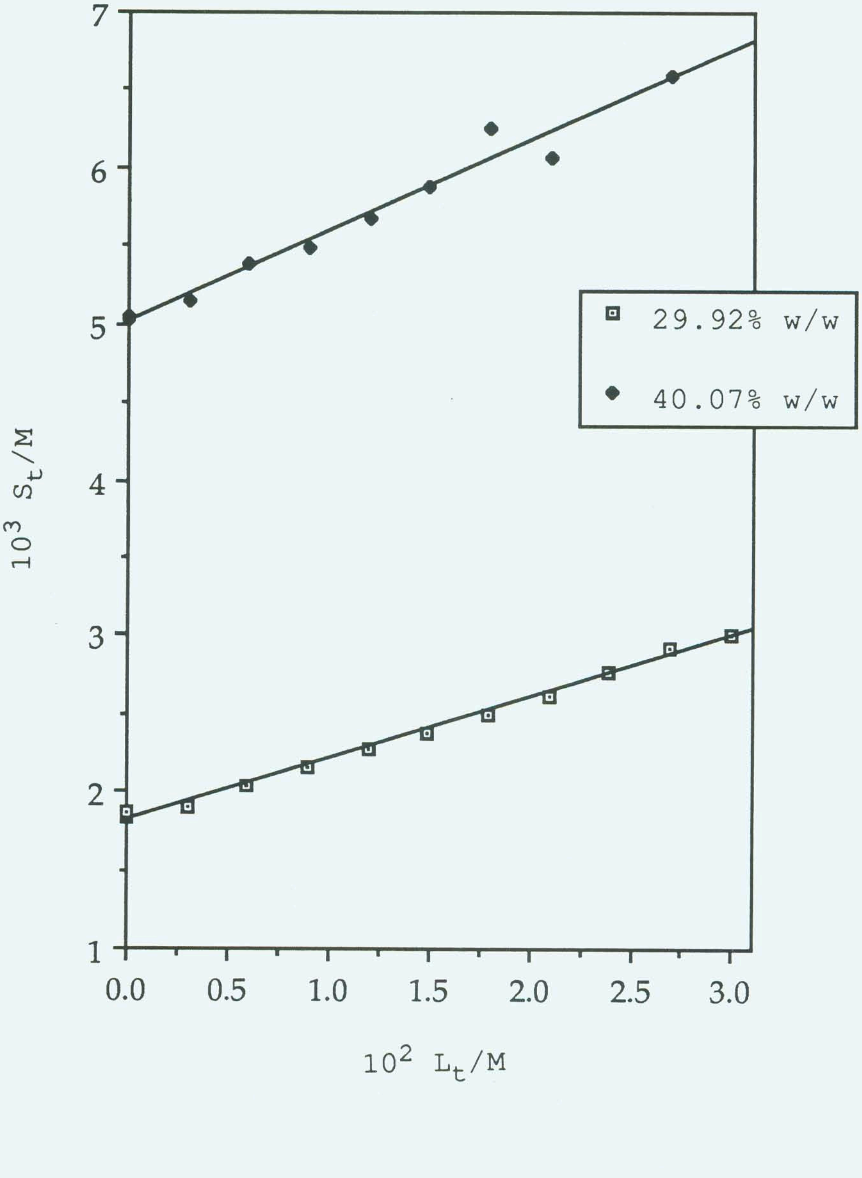


Figure B.12. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for methanol/water cosolvents at 25°C. The data appear in Table B.III.

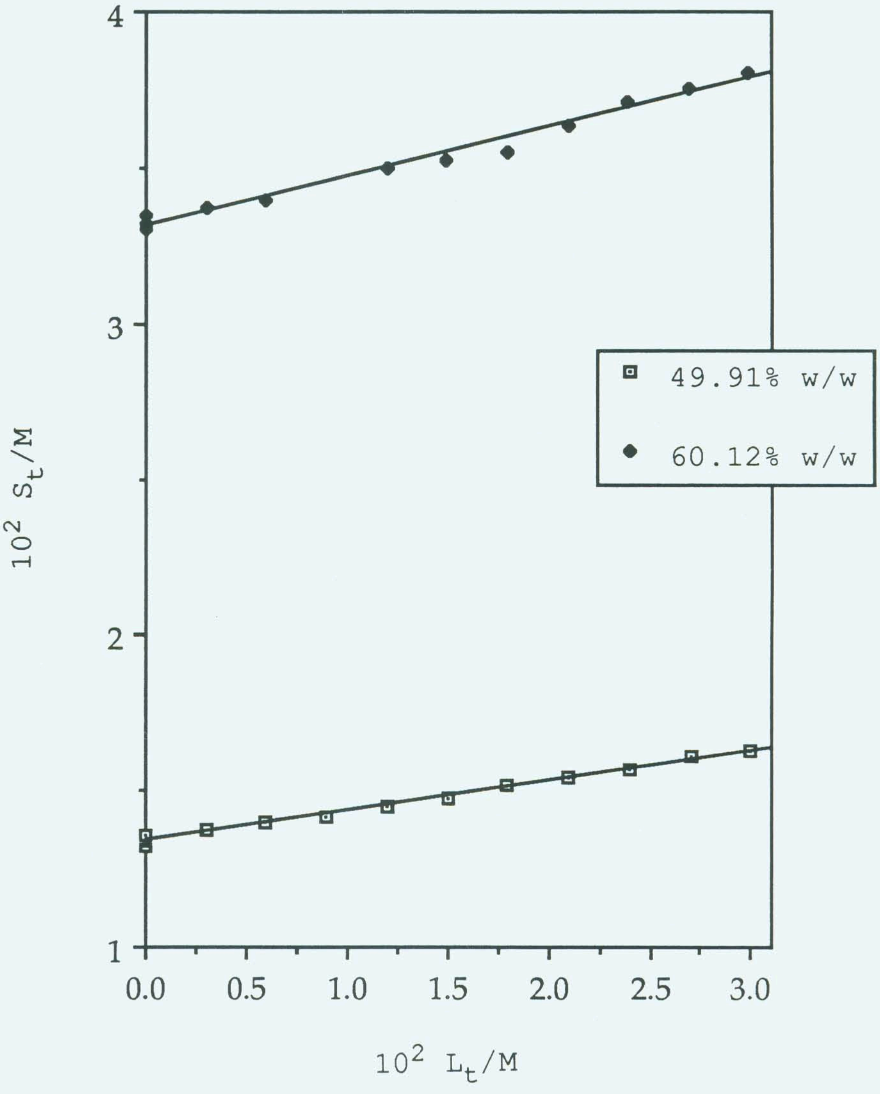


Figure B.13. Solubility diagram for the system naphthalene (S_t) : theophylline (L_t) for methanol/water cosolvents at 25°C. The data appear in Table B.III.

Appendix C

Complexation Constants and Unitary Free Energy Changes for Naphthalene and Theophylline in Mixed Aqueous-Organic Cosolvents

Table C-I. Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in ethylene glycol-water cosolvents at 25.0 °C.

%v/v[a] organic	%w/w	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M^* mol/kg	ΔG°_U 10^{-20} J/molecule
0.00	0.00	0.0000	71.8	----	----	----	----
2.56	2.85	0.0084	70.8	0.9990 (0.0006)	70.9 (1.4)[b]	54.38	-3.398 (0.008)
5.00	5.54	0.0167	69.9	1.0040 (0.0003)	65.3 (1.8)	53.32	-3.358 (0.011)
7.54	8.33	0.0257	69.0	1.0082 (0.0004)	64.1 (1.0)	52.22	-3.344 (0.007)
10.00	11.01	0.0347	68.2	1.0108 (0.0001)	57.8 (0.7)	51.17	-3.294 (0.005)
12.56	13.80	0.0444	67.3	1.0143 (0.0003)	54.7 (1.0)	50.07	-3.264 (0.008)
15.00	16.43	0.0540	66.5	1.0165 (0.0009)	48.6 (1.0)	49.03	-3.208 (0.009)
20.00	21.78	0.0748	64.9	1.0243 (0.0004)	45.9 (0.5)	46.92	-3.169 (0.004)
25.00	27.08	0.0973	63.5	1.0314 (0.0007)	39.2 (0.6)	44.84	-3.089 (0.006)

[a] %vol/vol before mixing

[b] Standard deviations appear in parentheses.

Table C-I. (*continued*) Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in ethylene glycol-water cosolvents at 25.0 °C.

%v/v[a] organic	%w/w	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M* mol/kg	ΔG°_U 10^{-20} J/molecule
30.00	32.31	0.1217	62.0	1.0380 (0.0005)	33.2 (0.3)[b]	42.77	-3.003 (0.004)
35.00	37.49	0.1483	60.7	1.0440 (0.0004)	29.1 (0.3)	40.73	-2.932 (0.004)
40.00	42.62	0.1773	59.4	1.0502 (0.0006)	23.8 (0.3)	38.71	-2.829 (0.004)
50.00	52.70	0.2443	57.0	1.0622 (0.0008)	16.6 (0.2)	34.74	-2.641 (0.004)
60.00	62.56	0.3266	54.8	1.0707 (0.0004)	11.1 (0.3)	30.85	-2.430 (0.009)
70.00	72.22	0.4300	52.9	1.0803 (0.0005)	8.2 (0.2)	27.04	-2.253 (0.008)
80.00	81.67	0.5640	51.1	1.0881 (0.0006)	4.6 (0.2)	23.30	-1.958 (0.020)
81.63	83.20	0.5897	50.8	1.0885 (0.0001)	4.1 (0.2)	22.69	-1.898 (0.017)
100	100	1.00	48.1	1.0992 (0.0030)	2.7 (0.2)	16.04	-1.595 (0.030)

[a] %vol/vol before mixing.

[b] Standard deviations appear in parentheses.

Table C-II. Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in acetonitrile-water cosolvents at 25.0 °C.

%v/v^a organic	%w/w	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M^* mol/kg	ΔG°_U 10^{-20} J/molecule
0.00	0.00	0.0000	71.8	0.9975 (0.0003)	72.9 (1.4)^b	55.50	-3.418 (0.008)
0.00	0.00	0.0000	71.8	0.9975 (0.0003)	71.5 (1.0)	55.50	-3.410 (0.006)
2.78	2.17	0.0096	63.9	0.9931 (0.0005)	61.9 (0.8)	54.83	-3.343 (0.005)
6.40	5.05	0.0228	56.7	0.9895 (0.0004)	49.6 (0.8)	53.93	-3.244 (0.007)
9.09	7.21	0.0330	52.8	0.9861 (0.0008)	39.3 (0.5)	53.26	-3.142 (0.006)
12.62	10.09	0.0469	48.8	0.9807 (0.0004)	32.1 (0.5)	52.36	-3.049 (0.007)
15.63	12.57	0.0594	46.1	0.9759 (0.0005)	24.2 (0.2)	51.58	-2.925 (0.004)
18.84	15.27	0.0733	43.8	0.9710 (0.0004)	19.0 (0.2)	50.74	-2.816 (0.004)
20.00	16.26	0.0785	43.1	----	----	----	----
22.22	18.16	0.0887	41.8	0.9647 (0.0003)	14.4 (0.3)	49.84	-2.692 (0.009)

[a] %vol/vol before mixing.

[b] Standard deviations appear in parentheses.

Table C-II. (*continued*) Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in acetonitrile-water cosolvents at 25.0 °C.

%v/v[a] organic	%w/w	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M* mol/kg	ΔG°_U 10^{-20} J/molecule
27.10	22.40	0.1125	39.5	0.9552 (0.0010)	8.9 (0.3)[b]	48.50	-2.478 (0.014)
30.77	25.66	0.1316	38.1	0.9479 (0.0003)	6.4 (0.2)	47.48	-2.328 (0.011)
40.74	34.81	0.1898	35.2	0.9262 (0.0003)	2.7 (0.3)	44.52	-1.935 (0.048)
46.43	40.23	0.2280	33.9	0.9137 (0.0007)	2.3 (0.2)	42.72	-1.848 (0.042)
62.50	56.41	0.3623	31.4	----	----	----	----
75.00	69.97	0.5056	30.2	----	----	----	----
87.50	84.46	0.7047	29.2	----	----	----	----
95.00	93.65	0.8662	28.7	----	----	----	----
97.56	96.88	0.9317	28.6	----	----	----	----
100	100	1.00	28.5	----	----	----	----

[a] %vol/vol before mixing.

[b] Standard deviations appear in parentheses.

Table C-III. Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in methanol-water cosolvents at 25.0 °C.

%v/v[a] organic	%w/w	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M* mol/kg	$\Delta G°_U$ 10^{-20} J/molecule
0.00	0.00	0.0000	71.8	0.9975 (0.0003)	72.8 (2.3)[b]	55.51	-3.417 (0.013)
0.00	0.00	0.0000	71.8	0.9975 (0.0003)	83.9 (1.7)	55.51	-3.476 (0.008)
3.00	2.38	0.0135	66.6	0.9932 (0.0002)	77.5 (2.4)	54.93	-3.437 (0.013)
6.40	5.11	0.0294	61.8	0.9879 (0.0005)	66.9 (1.5)	54.26	-3.369 (0.009)
6.40	5.11	0.0294	61.8	0.9879 (0.0005)	66.1 (0.9)	54.26	-3.364 (0.006)
9.27	7.44	0.0432	58.3	0.9835 (0.0002)	60.6 (2.2)	53.70	-3.322 (0.015)
9.27	7.44	0.0432	58.3	0.9835 (0.0002)	54.8 (1.2)	53.70	-3.280 (0.009)
12.20	9.85	0.0579	55.3	0.9799 (0.0002)	57.9 (1.0)	53.11	-3.297 (0.007)
18.27	14.95	0.0900	50.1	0.9713 (0.0002)	43.4 (0.4)	51.87	-3.165 (0.004)
24.17	20.05	0.1236	46.1	0.9629 (0.0005)	35.2 (0.5)	50.63	-3.065 (0.006)

[a] %vol/vol before mixing

[b] Standard deviations appear in parentheses.

Table C-III. (*continued*) Complexation constants and unitary free energy changes for naphthalene (S) and theophylline (L) in methanol-water cosolvents at 25.0 °C.

%v/v[a] organic	%w/w organic	x_2	γ dynes/cm	ρ g/ml	K_{11} M^{-1}	M* mol/kg	$\Delta G°_U$ 10^{-20} J/molecule
35.19	29.92	0.1936	40.5	0.9467 (0.0006)	22.2 (0.4)[b]	48.23	-2.849 (0.008)
45.95	40.07	0.2732	36.4	0.9283 (0.0006)	12.2 (0.6)	45.74	-2.573 (0.022)
55.88	49.91	0.3591	33.3	0.9090 (0.0005)	7.9 (0.2)	43.31	-2.361 (0.009)
65.71	60.12	0.4588	30.6	0.8881 (0.0008)	5.7 (0.2)	40.74	-2.195 (0.016)
70.34	65.10	0.5119	29.5	----	----	----	----
79.26	75.04	0.6283	27.4	----	----	----	----
87.80	84.99	0.7610	25.4	----	----	----	----
96.23	95.25	0.9186	23.4	----	----	----	----
100	100	1.00	22.5	----	----	----	----

[a] %vol/vol before mixing

[b] Standard deviations appear in parentheses.

Appendix D

Solubility and Unitary Free Energy Changes of Naphthalene and Theophylline in Mixed Aqueous-Organic Cosolvents

Table D-I. Solubility and unitary free energy changes for naphthalene and theophylline in ethylene glycol-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/ liter	ρ^a g/ ml	$\Delta G°_U$ 10^{-20} J/ molecule	K_c 10^{-2} mol/ liter	ρ^b g/ ml	$\Delta G°_U$ 10^{-20} J/ molecule
	Naphthalene			Theophylline		
0.00	----	----	----	3.39 (0.02)[c]	0.9997 (0.0008)	3.044
2.85	2.16 (0.04)	0.9990 (0.0006)	5.119	3.50 (0.03)	1.0026 (0.0023)	3.023
5.54	2.38 (0.08)	1.0040 (0.0003)	5.073	3.66 (0.06)	1.0068 (0.0002)	2.998
8.33	2.61 (0.06)	1.0082 (0.0004)	5.028	3.56 (0.04)	1.0094 (0.0003)	3.002
11.01	2.91 (0.03)	1.0108 (0.0001)	4.976	3.60 (0.05)	1.0125 (0.0003)	2.991
13.80	3.24 (0.08)	1.0143 (0.0003)	4.924	3.67 (0.03)	1.0159 (0.0006)	2.975
16.43	3.50 (0.04)	1.0165 (0.0009)	4.884	3.93 (0.08)	1.0197 (0.0002)	2.940
21.78	4.28 (0.09)	1.0243 (0.0004)	4.787	3.81 (0.04)	1.0263 (0.0002)	2.938
27.08	5.38 (0.16)	1.0314 (0.0007)	4.677	4.01 (0.05)	1.0329 (0.0002)	2.901

[a] Density of saturated naphthalene solution.

[b] Density of saturated theophylline solution.

[c] Standard deviations appear in parentheses.

Table D-I. (*continued*) Solubility and unitary free energy changes for naphthalene and theophylline in ethylene glycol-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/ liter	ρ^a g/ ml	$\Delta G°_U$ 10^{-20} J/ molecule	K_c 10^{-2} mol/ liter	ρ^b g/ ml	$\Delta G°_U$ 10^{-20} J/ molecule
	Naphthalene			Theophylline		
32.31	7.12 (0.06)[c]	1.0380 (0.0005)	4.544	4.34 (0.04)	1.0395 (0.0006)	2.850
37.49	9.25 (0.06)	1.0440 (0.0004)	4.419	4.47 (0.01)	1.0451 (0.0008)	2.820
42.62	12.47 (0.15)	1.0502 (0.0006)	4.277	4.76 (0.03)	1.0525 (0.0005)	2.776
52.70	23.64 (0.19)	1.0622 (0.0008)	3.975	5.40 (0.04)	1.0633 (0.0007)	2.684
62.56	47.53 (0.30)	1.0707 (0.0004)	3.641	6.69 (0.02)	1.0735 (0.0007)	2.550
72.22	94.95 (0.70)	1.0803 (0.0005)	3.306	6.58 (0.03)	1.0823 (0.0009)	2.507
81.67	201.85 (0.40)	1.0881 (0.0006)	2.937	6.32 (0.04)	1.0902 (0.0006)	2.466
83.20	239.77 (1.70)	1.0885 (0.0001)	2.856	----	----	----
100.00	850.36 (4.20)	1.0992 (0.0030)	2.195	5.47 (0.05)	1.1017 (0.0018)	2.378

[a] Density of saturated naphthalene solution.

[b] Density of saturated theophylline solution.

[c] Standard deviations appear in parentheses.

Table D-II. Solubility and unitary free energy changes for naphthalene and theophylline in acetonitrile-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/liter	ρ^a g/ml	ΔG°_U 10^{-20} J/molecule	K_c 10^{-2} mol/liter	ρ^b g/ml	ΔG°_U 10^{-20} J/molecule
	Naphthalene			Theophylline		
0.00	2.07 (0.03)[c]	0.9975 (0.0003)	5.144	----	----	----
0.00	2.09 (0.04)	0.9975 (0.0003)	5.139	3.42 (0.04)	0.9989 (0.0005)	3.040
2.17	2.55 (0.03)	0.9931 (0.0005)	5.051	3.86 (0.04)	0.9960 (0.0010)	2.984
5.05	3.49 (0.05)	0.9895 (0.0004)	4.913	4.69 (0.03)	0.9919 (0.0011)	2.894
7.21	4.66 (0.04)	0.9861 (0.0008)	4.788	5.56 (0.05)	0.9889 (0.0014)	2.817
10.09	6.45 (0.21)	0.9807 (0.0004)	4.645	6.78 (0.02)	0.9849 (0.0007)	2.726
12.57	10.23 (0.12)	0.9759 (0.0005)	4.447	----	----	----
15.27	14.17 (0.07)	0.9710 (0.0004)	4.304	9.23 (0.16)	0.9766 (0.0006)	2.581
16.26	----	----	----	10.40 (0.04)	0.9739 (0.0006)	2.528
18.16	22.44 (0.07)	0.9647 (0.0003)	4.105	11.30 (0.16)	0.9717 (0.0007)	2.487

[a] Density of saturated naphthalene solution.

[b] Density of saturated theophylline solution.

[c] Standard deviations appear in parentheses.

Table D-II. (*continued*) Solubility and unitary free energy changes for naphthalene and theophylline in acetonitrile-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/liter	ρ^a g/ml	$\Delta G°_U$ 10^{-20} J/molecule	K_c 10^{-2} mol/liter	ρ^b g/ml	$\Delta G°_U$ 10^{-20} J/molecule
	Naphthalene			Theophylline		
22.40	50.23 (0.42)[c]	0.9552 (0.0010)	3.758	13.75 (0.23)	0.9643 (0.0011)	2.390
25.66	71.64 (0.50)	0.9479 (0.0003)	3.600	14.94 (0.20)	0.9586 (0.0007)	2.344
34.81	274.49 (3.50)	0.9262 (0.0003)	3.011	----	----	----
40.23	511.59 (3.00)	0.9137 (0.0007)	2.732	19.08 (0.14)	0.9255 (0.0021)	2.185
56.41	----	----	----	17.16 (0.13)	0.8881 (0.0014)	2.161
69.97	----	----	----	12.91 (0.14)	0.8544 (0.0007)	2.217
84.46	----	----	----	6.75 (0.06)	0.8176 (0.0003)	2.410
93.65	----	----	----	3.26 (0.03)	0.7929 (0.0004)	2.658
96.88	----	----	----	1.95 (0.01)	0.7857 (0.0009)	2.851
100.00	----	----	----	0.81 (0.02)	0.7781 (0.0012)	3.194

[a] Density of saturated naphthalene solution.

[b] Density of saturated theophylline solution.

[c] Standard deviations appear in parentheses.

Table D-III. Solubility and unitary free energy changes for naphthalene and theophylline in methanol-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/liter	ρ^a g/ml	ΔG°_U 10^{-20} J/molecule	K_c 10^{-2} mol/liter	ρ^b g/ml	ΔG°_U 10^{-20} J/molecule
	Naphthalene			Theophylline		
0.00	1.97 (0.02)[c]	0.9975 (0.0003)	5.164	3.39 (0.02)	0.9989 (0.0005)	3.044
0.00	1.92 (0.00)	0.9975 (0.0003)	5.176	----	----	----
2.38	2.14 (0.14)	0.9932 (0.0002)	5.124	----	----	----
5.11	2.68 (0.05)	0.9879 (0.0005)	5.025	3.70 (0.02)	0.9902 (0.0007)	2.995
5.11	2.61 (0.02)	0.9879 (0.0005)	5.035	----	----	----
7.44	2.94 (0.09)	0.9835 (0.0002)	4.980	----	----	----
7.44	3.14 (0.15)	0.9835 (0.0002)	4.953	----	----	----
9.85	3.54 (0.00)	0.9799 (0.0002)	4.897	3.94 (0.05)	0.9827 (0.0004)	2.956
14.95	5.02 (0.03)	0.9713 (0.0002)	4.741	4.31 (0.04)	0.9743 (0.0009)	2.906
20.05	7.45 (0.08)	0.9629 (0.0005)	4.565	----	----	----

[a] Density of saturated naphthalene solution.

[b] Density of saturated theophylline solution.

[c] Standard deviations appear in parentheses.

Table D-III. (*continued*) Solubility and unitary free energy changes for naphthalene and theophylline in methanol-water cosolvents at 25.0 °C.

%w/w organic	K_c 10^{-4} mol/liter	ρ^a g/ml	$\Delta G°_U$ 10^{-20} J/molecule	K_c 10^{-2} mol/liter	ρ^b g/ml	$\Delta G°_U$ 10^{-20} J/molecule
	Naphthalene			Theophylline		
29.92	18.47 (1.70)[c]	0.9467 (0.0006)	4.164	5.95 (0.05)	0.9516 (0.0005)	2.732
40.07	50.31 (0.10)	0.9283 (0.0006)	3.721	7.63 (0.05)	0.9337 (0.0006)	2.599
49.91	134.34 (10.00)	0.9090 (0.0005)	3.286	8.99 (0.06)	0.9162 (0.0004)	2.501
60.12	332.16 (1.90)	0.8881 (0.0008)	2.879	9.92 (0.08)	0.8965 (0.0007)	2.426
65.10	----	----	----	9.58 (0.10)	0.8851 (0.0006)	2.423
75.04	----	----	----	7.94 (0.07)	0.8598 (0.0009)	2.464
84.99	----	----	----	5.98 (0.03)	0.8344 (0.0006)	2.542
95.25	----	----	----	3.96 (0.02)	0.8084 (0.0068)	2.670
100.00	----	----	----	3.32 (0.01)	0.7916 (0.0008)	2.720

[a] Density of saturated naphthalene solution.
[b] Density of saturated theophylline solution.
[c] Standard deviations appear in parentheses.