Solubility of Naphthalene in Binary Aqueous Organic Cosolvent Mixtures: An Investigation of the Phenomenological Model

by

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Chapter 1 Introduction

1.1 Solubility Theories

Outwardly, solubility appears to be a simple property, yet paradoxically, many theories have been developed to describe it. Prior to discussing our phenomenological model, a review of other current solubility theories is warranted. I have limited my discussion to those theories which describe the dissolution of liquid and solid solutes, and are most frequently encountered in the pharmaceutical science literature. These theories were placed into three categories, namely regular and extended regular solution theories, specific interaction and contributional theories, and empirically related descriptions of solubility. These classifications are not intended to be rigorous, but only to serve as guidelines for the reader.

1.1.1 Regular Solution Theory and Extended Regular Solution Theories

Regular Solution Theory

Regular solution theory was developed by Hildebrand and Scott (1-4); in this theory solubility is described by the following equation,

$$\ln x_2 = \ln x_2^{ideal} - \frac{V_2\phi_1^2(\delta_1-\delta_2)^2}{RT} \qquad (1.1)$$

where x_2^{ideal} is the ideal solubility, x is the mole fraction, V denotes the molar volume, and ϕ represents the volume fraction. The symbol δ refers to the solubility parameter, the meaning of which will be discussed shortly. RT is the product of the gas constant and absolute temperature. The subscripts 1 and 2 refer to the solvent and solute, respectively. (These notations will be employed throughout the remainder of the chapter unless otherwise noted.) The second term on the right hand side of equation (1.1) represents the logarithm of the solute activity coefficient, and accounts for all nonidealities in the solution.

Solubility has been envisioned as a three-step process by Scatchard (5) and Hildebrand and Scott (1). The first step involves removal of a solute molecule from a crystal lattice; the second step entails formation of a cavity within the solvent, and the third step is the insertion of the solute into the solvent cavity. Assuming the pair potential interaction energies associated with each step are additive, we write the energy change associated with the entire process

$$\Delta \mu = \mu_{11} + \mu_{22} - 2(\mu_{11}\mu_{22})^{1/2}$$

or

$$\Delta \mu = \left(\mu_{11}^{1/2} - \mu_{22}^{1/2}\right)^2 \qquad (1.2)$$

Equation (1.2) assumes the solute-solvent interaction pair potential, μ_{12}, is equal to the geometric mean of the solvent-solvent, μ_{11} and solute-solute, μ_{22} interaction pair potentials. Provided the volume change of mixing is zero, we may write

$$\mu_{11} = \left(\frac{\Delta H_1^{vap}}{V_1}\right) = \delta_1^2 \quad \text{and} \quad \mu_{22} = \left(\frac{\Delta H_2^{vap}}{V_2}\right) = \delta_2^2$$

where ΔH^{vap} is the enthalpy of vaporization, and thus rewrite equation (1.2) as

$$\Delta\mu = \left(\delta_1 - \delta_2\right)^2 \qquad (1.3)$$

In addition to the geometric mean approximation and the absence of volume change upon mixing, regular solution theory also assumes the entropy of mixing is ideal. Given these assumptions, proper use of regular solution theory is restricted to solutions in which only dispersion interactions are prevalent, and the solute and solvent sizes are approximately equal. The theory has successfully described dissolution of nonpolar solutes in single nonpolar solvents, and can be extended to include cosolvent mixtures. Other authors have tried to extend this theory to describe solutions where dipole-dipole, hydrogen bonding, and non-random mixing predominate.

Extensions of Regular Solution Theory

Martin and coworkers (6-10) have used a modification of equation (1.1) to describe solubility in solutions regular solution theory is not expected to apply. Their solubility equation is written

$$\ln x_2 = \ln x_2^{ideal} - \frac{V_2 \phi_1^2 \left(\delta_1 + \delta_2 - 2W\right)^2}{RT} \qquad (1.4)$$

where W is an energy correction term for interactions other than dispersion interactions between the solute and solvent. This model has been shown to have some problems.

Richardson and coworkers (11) have demonstrated that the molar volume of solutes such as temazepam is often solvent dependent, and these changes in molar volume should be incorporated for correct application of this model. Grant and Higuchi (4) have stated that the W parameter is not always well correlated with solute polarities.

Hansen and Beerbower (12) partitioned the solubility parameter into dispersion (δ^d), polar (δ^p), and hydrogen bond (δ^h) components. They write the solubility parameter as

$$\delta^2 = (\delta^d)^2 + (\delta^p)^2 + (\delta^h)^2 \qquad (1.5)$$

Values for these parameters have been tabulated by Hoy and Martin (13). Beerbower et. al. (14) then partitioned the hydrogen bond solubility parameter into hydrogen bond acceptor and hydrogen bond donor terms, δ_b^h and δ_a^h, respectively, where $\delta^h = \delta_b^h \times \delta_a^h$. This approach combined with equation (1.1) results in

$$\ln x_2 = \ln x_2^{ideal} - \frac{D_0 V_2 \phi_1^2}{RT}$$

$$- \frac{V_2\phi_1^2\left(D_1\left(\delta_1^d\right)^2 + D_2\left(\delta_1^d\right) + D_3\left(\delta_1^p\right)^2 + D_4\left(\delta_1^p\right) + D_5\left(\delta_{1a}\delta_{1b}\right) + D_6\left(\delta_{1a}\right) + D_7\left(\delta_{1b}\right)\right)}{RT} \qquad (1.6)$$

where the D_i are adjustable parameters.

Beerbower (15) applied this model to solubility data of benzoic acid in 40 solvents of varying polarity. Sixty percent of the calculated solubility values were within 30% of the experimentally determined solubility values. Though both equations (1.4) and (1.5) were able to give reasonable solubility estimates for solutions outside the limits of regular solution theory, it is probably the increase in the number of adjustable parameters rather than any chemical or theoretical considerations which has provided this improvement.

Amidon, Yalkowsky, and coworkers (16-20) developed the Molecular Group Surface Area (MGSA) approach which expresses the energies of solute-solute, solvent-solvent, and solute-solvent interactions in terms of energies per unit area, as compared with the energies per unit volume which are used in regular solution theory. An analog to equation (1.3) is expressed by

$$\Delta\mu = \left(\gamma_1^{1/2} - \gamma_2^{1/2}\right)^2 = \gamma_{12} \qquad (1.7)$$

where γ_1 and γ_2 are the surface tensions of solvent and solute respectively, and γ_{12} is the solvent-solute interfacial tension. Equation (1.7) is an empirical relationship between interfacial tension and the surface tensions of pure substances known as Antonow's Rule (21). Using equation (1.7) we rewrite equation (1.1)

$$\log x_2 = \log x_2^{\text{ideal}} - \frac{C \times A_2 \times \gamma_{12}}{RT \times 2.303} \qquad (1.8)$$

Here, A_2 is the solute's molecular surface area, and it is multiplied by an empirical curvature correction factor, C. This factor is used to account for changes in macroscopic interfacial tension created by the sharp curvature of a molecular cavity.

In these studies, the value of C was between 0.33 and 0.57. The solute-solvent interfacial tension was estimated from measurements between tetradecane (to simulate a hydrophobic portion of a solute molecule) and the solvent or cosolvent mixture the solute was dissolved in.

The theory worked well when the interfacial tension between a solute and solvent was easily determined, but difficulties ensued in some studies (17,19-20) where solute molecules possessed both a hydrophobic and a hydrophilic group contribution to the solute-solvent interfacial tension. As indicated by Yalkowsky and Rubino (22), measuring interfacial tensions between hydrophilic components of the solute molecule and the solvent or cosolvent mixture was often difficult.

Huyskens and Haulait (23) developed the "mobile order" theory to account for non-ideal entropy changes within a solution, which are not included by regular solution theory. According to these workers, two factors contribute to the total entropy of a solution. One factor is based on the number of positions one molecule may occupy relative to another in a liquid mixture. This is similar to the entropy created by a defect in a crystal lattice. The second factor is attributable to the resultant expansion of the liquid system induced by addition of liquid solutes . The expansion increases the number of positions a molecule may populate within the system. This entropy is analogous to that caused by gaseous expansion. These authors were able to predict volume fraction solubility of nonpolar solutes in nonpolar liquids.

Recently, Ruelle and coworkers have attempted to extend this theory to include prediction of polar and nonpolar solutes in polar solvents (24-26). They introduce parameters to account for hydrogen bonding interactions, dispersion interactions, and positional effects created by hydrogen bonding between hydrogen bond acceptor sites on a solute molecule and donor sites on a solvent molecule. Though they show agreement between calculated and experimental values of solubility that is usually within an order of magnitude, the model is difficult to apply given all the specific interactions one must consider in order to achieve this agreement.

1.1.2 Specific Interaction and Contributional theories

Specific Solute-Solvent Interaction Theory

The specific solute-solvent interaction theory proposed by Fung and Higuchi (27-28) was developed from observations made on solubility data. In particular, much higher solubilities were achieved for chemicals such as salicylic acid, acetanilide, carbazole, picric acid, and phthalic anhydride when they were dissolved in interactive solvents (chloroform and diethyl ether) than in inert solvents (cyclohexane, *n*-heptane, decane, and other hydrocarbons). These workers assumed that some specific interaction was occurring between the solute and the solvent, which was increasing their solubilities in these solvents. An equilibrium reaction equation was written to describe the formation of a suspected solvate complex,

$$iA_o + jS \overset{K_{ij}}{\rightleftharpoons} A_iS_j \qquad (1.9)$$

where A_o is the uncomplexed solute species, S is the interactive solvent species, A_iS_j is the solvate complex, and K_{ij} is the solvate complex formation constant. The subscripts were included to account for the formation of 1:1, 1:2, and 1:3 solute:solvent complexes, though usually only 1:1 complexes were believed to exist. The stoichiometry was determined by the agreement of the calculated values with experimental data.

The observed solubility, C_{obs}, in an inert and interacting solvent mixture was written as

$$C_{obs} = C_o + \sum K_{ij}(C_o)^i S^j \qquad (1.10)$$

where C_o is the molar solubility in an inert cosolvent, and S is the molar concentration of the interactive solvent species.

The exchange constants determined from equation (1.10) were frequently in agreement with those obtained by N.M.R. spectrophotometric measurements, and were usually less than or close to 1 M^{-1} particularly when chloroform was the interacting solvent. This theory provided a description of solubility in inert and interacting cosolvent mixtures, but could not describe solubility in systems in which nonspecific interactions were dominant.

Acree (29) has criticized this model for its assumption that C_o is independent of solvent composition, as experimental evidence did not always support this claim (30). He also questioned the credibility of the solvate formation constant values, for he found that he needed $K_{1:1}$ and $K_{1:2}$ constants to properly describe benzil solubility in a binary solvent mixture containing carbon tetrachloride, and yet no experimental evidence has supported the existence of such complexes. Connors (31) has also questioned the validity of formation constant values of less than 1 M^{-1}.

Nearly Ideal Binary Solvent (NIBS) Model and Its Modifications

Burchfield and Bertrand (32) have suggested that any excess extensive property of a three-component system, ΔZ_{123}^{excess}, may be modeled by the following equation

$$\Delta Z_{123}^{excess} = \frac{n_1 n_2 \Gamma_1 \Gamma_2 A_{12} + n_1 n_3 \Gamma_1 \Gamma_3 A_{13} + n_2 n_3 \Gamma_2 \Gamma_3 A_{23}}{n_1 \Gamma_1 + n_2 \Gamma_2 + n_3 \Gamma_3} \tag{1.11}$$

where the subscripts 1, 2, and 3 refer to solvent component A, solvent component B, and the solute, respectively. The number of molecules is denoted by n; A_{ij} represents an interaction parameter between species i and j, and Γ_i is a weighting factor for each component. This model assumes that only nonspecific interactions are present throughout the three-component system.

Equation (1.11) has been used in three ways depending upon the assignment of weighting factors. In one form, all weighting factors are set equal to one. In another form all weighting factors are based on the molar volumes of solute and solvent molecules; and the third form incorporates a Flory-Huggins approach to account for changes in entropy attributable to extreme variations in the sizes of species within the solution.

Acree and coworkers (33-40) have explored the potential of this model to describe solubility data of semipolar solutes in nonpolar solvent mixtures. In one investigation (34) benzoic acid solubility was studied in various carbon tetrachloride and hydrocarbon solvent mixtures. Benzoic acid is known to exist as a dimer in these solutions. Acree found that by writing this model to account for the benzoic acid dimer, he could calculate reasonable estimates for the benzoic acid solubility.

In other studies (38-40), where existence of specific solute-solvent interactions was suspected, he extended the NIBS model by including equilibrium constants for the formation of solute-solvent complexes.

$$A + B \underset{}{\overset{K^{\phi}_{AB}}{\rightleftharpoons}} AB \tag{1.12}$$

Here A is the solute; B is the complexing component of the binary solvent mixture; and AB is the solute-solvent complex. The formation constant, K^{ϕ}_{AB}, expressed in terms of the volume fraction concentrations of each component, is given by

$$K^{\phi}_{AB} = \frac{\phi_{AB}}{\phi_A \phi_B} \tag{1.13}$$

When solute complexation with both solvent components was suspected, a competitive associated NIBS model was written to include the following equilibria:

$$A + B \underset{}{\overset{K^{\phi}_{AB}}{\rightleftharpoons}} AB \tag{1.12}$$

$$K^{\phi}_{AB} = \frac{\phi_{AB}}{\phi_A \phi_B} \tag{1.13}$$

and

$$A + C \underset{}{\overset{K^{\phi}_{AC}}{\rightleftharpoons}} AC \tag{1.14}$$

$$K^{\phi}_{AC} = \frac{\phi_{AC}}{\phi_A \phi_C} \qquad (1.15)$$

Despite these modifications, use of the NIBS model is still restricted to solutions containing solvents and solutes of primarily nonpolar character, and where only small changes (5 to 25 fold) in solubility occur.

Universal Quasi-Chemical (UNIQUAC) and Universal Quasi-Chemical Functional-Group Activity Coefficients (UNIFAC) Theories

In 1975, Abrams and Prausnitz (41) proposed the UNIQUAC theory as a method for the correlation and prediction of liquid-vapor and liquid-liquid equilibria. This theory partitions the activity coefficient of each component in a liquid mixture into two coefficients. A combinational coefficient reflects entropy contributions to nonideality based on size and geometric differences of molecules within the mixture, and a residual activity coefficient reflects the enthalpic contributions to nonideality due to intermolecular interactions. The combinational activity coefficient is expressed as a function of molecular volume fraction, mole fraction, the number of nearest neighbors, the van der Waals surface area, and the van der Waals volume of a given component in the mixture. The residual activity coefficient is expressed as a function of the molecular volume fraction of the given component in the mixture, and as a function of interaction parameters . The interaction parameters describe all possible intermolecular interactions for a given component with other components present in the mixture. For a binary system, two pairs of interaction parameters would be needed to completely describe the system, and a ternary system would require three pairs of interaction parameters . The interaction parameters are determined by a nonlinear regression analysis of an experimentally determined quantity such as the activity coefficient of a chemical in a liquid mixture . A second calculation is performed to estimate another experimental quantity such as the activity coefficient of the solute in a different liquid mixture.

The UNIFAC theory was developed, as an extension of UNIQUAC, by Fredenslund (42) in 1976. This theory treats a solution as a combination of functional groups rather than whole molecules. A two-step procedure, similar to the methods used in application of UNIQUAC, is needed to obtain estimates of solution behavior. Here, the interaction parameters characterize interaction energies between functional groups rather than whole molecules. Extensive collections of interaction parameters exist (43-46), and may be used to eliminate the first step in the process. The UNIFAC model has been used in both pharmaceutical (47) and environmental (48-49) sciences to predict solubilities in aqueous and binary aqueous organic cosolvent mixtures.

Excess Free Energy of Mixing Theory

Williams and Amidon (50-52) have developed a theory based on the ideas of Wohl (53), who expressed the excess free energies of mixtures in terms of increasing powers of volume fractions of the components in the solution. Using these ideas, Williams and Amidon expressed the mole fraction solubility of a solute in a binary solvent mixture as a function of the solute solubility in each pure solvent, and all solvent-solvent, solvent-solute, and solute-solute interactions. Their theory has not been used extensively, perhaps as a result of its intimidating appearance, and description of its founding principles.

Competitive Preferential Solvation (COPS) Theory

COPS theory was introduced in 1974 by Nagy and coworkers (54-59), and permitted the quantitation of solute-solvent interactions. The theory is founded on these five postulates.

Postulate #1 The solvent constituents compete to solvate the solute, and the solute interacts with the entire surrounding medium.

Postulate #2 The molecules in the solvation shell are incessantly alternating between solvating and complexing states. Complexation is a state of preferred orientation between a solute and solvent molecule, while solvation is a less ordered state.

Postulate #3 The solvation shell composition is controlled by affinity constants, $K_{i(j)}$, $K_{i(k)}$, $K_{i(l)}$...and the respective solvent constituent concentrations C_j, C_k, C_l...

Postulate #4 The solute is considered to be partitioned among all solvent components, hence the solvation shell is comprised of a weighted mixture of pure solvent components. Mathematically, we write

$$C_i = X_{i(j)} + X_{i(k)} + X_{i(l)} + \ldots \qquad (1.16)$$

where

$$X_{i(j)} = C_i \times \frac{K_{i(j)}}{K_{i(j)}C_j + K_{i(k)} + K_{i(l)}C_l + \ldots} = C_i P_{i(j)} \qquad (1.17)$$

Here, C_i represents the concentration of solute, and $K_{i(j)}$ and C_j represent the affinity constant and concentration of solvent component j. Their product is divided by the summation of all other solvent component concentrations and affinity constant products. $P_{i(j)}$ is a generalized partition factor.

Postulate #5 The solvent effects on any physicochemical property, T, are additive in the solvation shell so that

$$T = P_{i(j)}T_{i(j)} + P_{i(k)}T_{i(k)} + P_{i(l)}T_{i(l)} \cdots \qquad (1.18)$$

This model has successfully described both U.V. and N.M.R. spectrophotometric shift data (54,55,57,58), the transport of ionic sodium and potassium across binary liquid membranes (59), and solvent effects on chemical kinetic phenomena (54,56).

Acree and coworkers (60) have shown that the COPS model can be reduced to a form bearing resemblance to the NIBS model, but the model could not be altered to resemble the extended or competitive NIBS models which account for specific solute-solvent interactions. In the same paper, Acree also questions the validity of the affinity constants to accurately depict chemical reality. A study of carbazole solubility in dibutyl ether-*n*-alkane mixtures was analyzed with the COPS model, and the results surprisingly indicated that the *n*-alkanes preferentially solvated the carbazole, a chemically unreasonable event. To further diminish the credibility of the affinity constants, he cites a study conducted by Nagy and coworkers (58) in which the order of interacting power of the inert cosolvents was given as benzene > *n*-heptane > cyclohexane > chlorobenzene. This again seems chemically unreasonable. Perhaps the failures are attributable to the model's failure to account for solvent-solvent interactions.

Qualitative Contributional Model

Roseman and Jencks (61) investigated the cosolvent effects of urea and ethanol on the solubilities of uric acid and naphthalene in water in an effort to understand the driving force of hydrophobic interactions. Their results led to the development of a qualitative description of the energetic contributions which regulate solubility phenomena. They hypothesize that the total free energy change of transfer of a gaseous molecule to a liquid state, $\Delta G_{g\rightarrow l}^{trans}$, is given by the sum of a cavity contribution, ΔG_{cavity}, a nonpolar interaction contribution, $\Delta G_{nonpolar}$, and a polar interaction contribution, ΔG_{polar}. They write

$$\Delta G_{g\rightarrow l}^{trans} = \Delta G_{cavity} + \Delta G_{nonpolar} + \Delta G_{polar} \tag{1.19}$$

They postulated that the addition of organic cosolvents to aqueous solutions of both polar and nonpolar solutes created a favorable energetic change in the ΔG_{cavity} and $\Delta G_{nonpolar}$ terms, thus increasing dissolution. They considered that the energetic contribution of ΔG_{polar} is zero for nonpolar solutes, and nearly zero for polar solutes when organic cosolvents which are capable of hydrogen bond formation are added. If a nonhydrogen bond forming cosolvent is added to an aqueous solution of a polar solute that is capable of hydrogen bonding, an unfavorable energetic contribution to solubility will ensue. Roseman and Jencks did not formulate a quantitative version of this model.

1.1.3 Empirical Methods

Kamlet and coworkers (62-65) have expressed solvent dependent properties, XYZ, using the following equation:

$$XYZ = XYZ_0 + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term(s)} \qquad (1.20)$$

The cavity term represents the endoergic process of disturbing solvent-solvent interactions to create a solute sized cavity in the solvent. The dipolar term represents the exoergic effects of dipole-dipole, dipole-induced dipole, and induced dipole-induced dipole interactions between solvent and solute molecules. The exoergic hydrogen bond term(s) account for specific hydrogen bonding interactions between solute and solvent molecules.

Applied specifically to solubility predictions of nonelectrolytes, they write the logarithm of solubility as

$$\log S = XYZ_o + \frac{mV_2}{100} + s\pi_2^* + a(\alpha_m)_2 + b(\beta_m)_2 \qquad (1.21)$$

The cavity term is represented by $\frac{mV_2}{100}$, where V_2 is the solute molar volume, and m is a constant. The dipolar term is equated to $s\pi_2^*$ where s is a constant, and π_2^* is a solvatochromic parameter of the solute. This parameter measures the ability of a compound to stabilize a neighboring charge or dipole by virtue of its dielectric effect. The hydrogen bond contribution is found in the $a(\alpha_m)_2$ and $b(\beta_m)_2$ terms, where a and b are constants and α_m and β_m are solvatochromic parameters that characterize the ability of compounds, in their monomeric states (where self association is possible), to donate or accept hydrogen bonds. The values of all the solvatochromic parameters are scaled between 0 and 1.

The equation has predicted the solubility of many aliphatic compounds in water (usually to within an order of magnitude) (64). Attempts to describe the solubility of aromatic compounds have not been successful (65). Specifically, the exoergic dipolar term gave a "wrong sign" when the data were analyzed. It was further noticed the term could be removed without significant effects on the predictive ability of the equation. To compensate for these discrepancies, Kamlet added parameters to the term according to a set of "ground rules". He attributes this deviation to stacking interactions among the aromatic compounds. Yalkowsky (66) has criticized this approach for several reasons. First, he states that ambiguities exist in the application of these ground rules to compounds, such as octyl benzene, which possess both aromatic and aliphatic characteristics. Second, the general applicability of these rules to many different aromatic compounds would imply that compound size or varying substitutions on an aromatic compound does not affect stacking interactions. He further adds that application of this model is hindered by the absence of extensive tables containing solvatochromic parameter values, whereas his empirical model (to be discussed next) requires only knowledge of octanol-water partition coefficient values, which have been collected into an extensive data base (67).

Log Linear Model

In the early 1980's (68-70) Yalkowsky and coworkers derived an equation relating the aqueous solubility of organic nonelectrolytes to their entropies of fusion and their octanol-water partition coefficients. The relationship was given by

$$\log S_w = \frac{-\Delta S_f(\mathrm{mp} - 25)}{2.303RT} - \log P + c \qquad (1.22)$$

where ΔS_f is the entropy of fusion, mp is the melting point of the solid, c is a constant and log P is the logarithm of the octanol-water partition coefficient. Log S_w is the logarithm of solubility . The same equation, without the entropy term, was also used to predict the aqueous solubilities of liquid, organic nonelectrolytes (69). The predicted solubilities were usually within an order of magnitude of experimental solubilities.

In later publications (22, 71-72), he extended the theory to predict solubilities of organic nonelectrolytes in cosolvent mixtures. The relationship was given by

$$\log S_m = \log S_W + f(\log S_c - \log S_W) \qquad (1.23)$$

Here, S_m is the solubility of the nonelectrolyte in an aqueous organic cosolvent mixture; S_w is the solubility in pure water; S_c is the solubility in pure cosolvent; and f is the volume fraction of organic cosolvent in the aqueous organic cosolvent mixture. Yalkowsky (22) does address the presence of curvature, which is often observed in plots of log (S_m/S_w) versus the volume fraction of cosolvent. He suggests that such deviations from the linear relationship of equation (1.23) may be caused by solvent-solvent interactions or specific solute-solute interactions that are unaccounted for in the equation.

1.2 Phenomenological Model

The phenomenological model, developed in this laboratory, has been shown to effectively describe the solvent effects on many chemical phenomena including complexation (73), surface tension (74) and solubility (75-77). This thesis examines its application to solvent effects on solubility. A detailed derivation has been previously published (76) and will not be repeated here; however, the important concepts will be discussed below.

1.2.1 General Concepts

The phenomenological model envisions solubility as the four-step process depicted in Scheme 1-1. The first step involves removal of a molecule from the crystal lattice and subsequent transformation to a liquid phase. The second step involves formation of a cavity, of surface phase composition f_2, within the bulk solvent. Here f_2 is the mean fractional organic composition of the solution immediately surrounding the cavity; in general its composition differs from that of the bulk solution. In the third step, the liquid solute molecule is inserted into the cavity (of surface phase composition f_2) resulting in an unsolvated solute within the cavity. The fourth step involves transformation of the unsolvated solute into a solvated solute.

Step 1.	Crystalline Solute	$\rightleftharpoons$	Liquid Solute
Step 2.	Bulk Solvent	$\rightleftharpoons$	Solvent with molecular cavity (surface phase composition f_2)
Step 3.	Solvent with molecular cavity (surface phase composition f_2) + Liquid solute	$\rightleftharpoons$	Unsolvated solute in the cavity (surface phase composition f_2)
Step 4.	Unsolvated solute in cavity (surface phase composition f_2)	$\rightleftharpoons$	Solvated solute in cavity (surface phase composition f_2)
Sum	Crystalline Solute + Bulk Solvent	$\rightleftharpoons$	Solvated solute

Scheme 1-1. The four step dissolution process.

Using Scheme 1-1, we write the total free energy change of dissolution as

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Intersolute} + \Delta G^{\circ}_{Gen.Med.} + \Delta G^{\circ}_{Insertion} + \Delta G^{\circ}_{Solvation} \qquad (1.24)$$

where $\Delta G^{\circ}_{Intersolute}$, the intersolute effect, is the free energy change created by solute-solute interactions in both solution and solid phase. The solute-solute interactions in the solution phase are considered negligible in dilute solutions, or in solutions in which the driving force for interaction is minimal. Solid phase solute-solute interactions are controlled by the crystal lattice energy of the solute molecule. $\Delta G^{\circ}_{Gen.Med.}$ is the general medium effect, and accounts for all solvent-solvent interactions within the system. This is the free energy change associated with the formation of a cavity of surface mean fractional composition f_2 (the subscript 2 refers to the organic cosolvent in our binary aqueous organic cosolvent mixtures) in the bulk solvent . $\Delta G^{\circ}_{Solvation}$, or the solvation effect, is the free energy change of molecular solute interactions with the surface phase cavity solution of mean fractional composition f_2; thus this term represents the solute-solvent interactions. $\Delta G^{\circ}_{Insertion}$ is the free energy change ascribed to the insertion of a solute molecule into a cavity of surface phase composition f_2. Since the solvation term accounts for interaction of the solid with the cavity surface phase, this term is included within the solvation effect and may be set equal to zero.

We now rewrite equation (1.24) as

$$\Delta G^{\circ}_{Total} = \Delta G^{\circ}_{Intersolute} + \Delta G^{\circ}_{Gen.Med.} + \Delta G^{\circ}_{Solvation} \qquad (1.25)$$

Expressions for the general medium and solvation effects are presented below. All solute-solute interactions are assumed to be independent of solvent composition, and through application of the Leffler-Grunwald delta operator, the intersolute effect is eliminated from the solubility equation, thus negating the need for development of a $\Delta G^{\circ}_{\mathrm{Intersolute}}$ expression.

1.2.2 The Solvation Effect

The solvation effect can be modeled as a stepwise, competitive, exchange equilibrium between water (W) and organic cosolvent (M) for a solute (R). We denote the equilibrium exchange constant as K_n where n refers to the n^{th} step in the process. This is illustrated in Scheme 1-2 for a two-step equilibrium process. The number of steps may be generalized if desired, but we will restrict ourselves to the two-step process because this has been shown to adequately describe dissolution. (75-77).

$$RW_2 + M \overset{K_1}{\rightleftharpoons} RWM + W \qquad (1.26)$$

$$RWM + M \overset{K_2}{\rightleftharpoons} RM_2 + W \qquad (1.27)$$

Scheme 1-2

Though the equilibria are depicted on an individual molecular exchange basis for mathematical convenience, a more general view is probably needed for greater chemical accuracy. With this view, the solute first moves from a fully hydrated state to a partially solvated state and then from a partially solvated to fully solvated state in the second step.

By expressing the total free energy change of solvation as the weighted average of each species we write,

$$\Delta G^{\circ}_{\text{Solvation}} = \Delta G^{\circ}_{RW_2} F_{RW_2} + \Delta G^{\circ}_{RWM} F_{RWM} + \Delta G^{\circ}_{RM_2} F_{RM_2} \qquad (1.28)$$

where F_{RW_2}, F_{RWM}, and F_{RM_2} are the fractions of solute in the fully hydrated, partially solvated, and fully solvated forms. Because the sum of these fractions is equal to one, we may rewrite equation (1.28) as

$$\Delta G^{\circ}_{\text{Solvation}} = \Delta G^{\circ}_{RW_2} + (S_1) F_{RWM} + (S_2) F_{RM_2} \qquad (1.29)$$

where

$$S_1 = \Delta G^{\circ}_{RWM} - \Delta G^{\circ}_{RW_2} \qquad (1.30)$$

and

$$S_2 = \Delta G^{\circ}_{RM_2} - \Delta G^{\circ}_{RW_2} \qquad (1.31)$$

The equilibrium constants, K_1 and K_2, depicted in Scheme 1-2 may be used in conjunction with the bulk mole fractions of water, x_1, and organic cosolvent, x_2, to obtain explicit expressions for F_{RWM} and F_{RM_2}.

$$F_{RWM} = \frac{K_1 x_1 x_2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \qquad (1.32)$$

$$F_{RM_2} = \frac{K_1K_2x_2^{2}}{x_1^{2} + K_1x_1x_2 + K_1K_2x_2^{2}} \qquad (1.33)$$

Combining equations (1.29, 1.32 and 1.33) gives

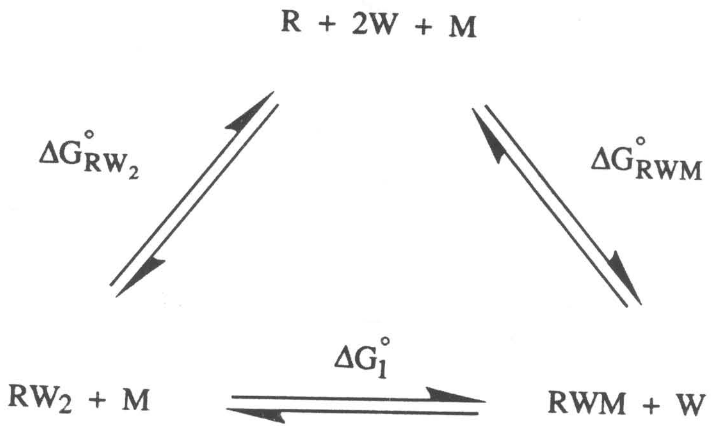
$$\Delta G^{\circ}_{solvation} = \frac{S_1K_1x_1x_2 + S_2K_1K_2x_2^{2}}{x_1^{2} + K_1x_1x_2 + K_1K_2x_2^{2}} + \Delta G^{\circ}_{RW_2} \quad (1.34)$$

Using the thermodynamic cycles given by Schemes 1-3 and 1-4 we obtain expressions for S_1 and S_2 in terms of the solvation exchange constants, and writing

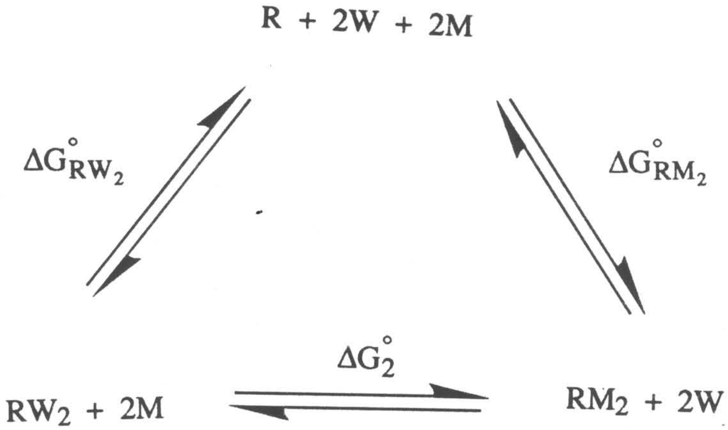
$$S_1 = \Delta G^{\circ}_{RWM} - \Delta G^{\circ}_{RW_2} = -kT \ln K_1 = \Delta G^{\circ}_1 \qquad (1.35)$$

and

$$S_2 = \Delta G^{\circ}_{RM_2} - \Delta G^{\circ}_{RW_2} = -kT \ln K_1K_2 = \Delta G^{\circ}_2 \qquad (1.36)$$



Scheme 1-3. Thermodynamic cycle which gives the relations for equation (1.35).



Scheme 1-4. The thermodynamic cycle which gives the relations for equation (1.36).

Substituting equations (1.35) and (1.36) into equation (1.34) we arrive at the expression for the free energy change of solvation.

$$\Delta G^{\circ}_{\text{solvation}} = \frac{(-kT \ln K_1)\, K_1 x_1 x_2 + (-kT \ln K_1 K_2)\, K_1 K_2 x_2{}^2}{x_1{}^2 + K_1 x_1 x_2 + K_1 K_2 x_2{}^2} + \Delta G^{\circ}_{RW_2} \quad (1.37)$$

1.2.3 *The General Medium Effect*

Using a modified version of Uhlig's gas solubility model (78), we express the general medium effect by equation (1.38)

$$\Delta G^{\circ}_{\text{Gen.Med.}} = gA\gamma \quad (1.38)$$

The general medium effect gives the energy change associated with the formation of a cavity within the bulk solvent, and its energetic contribution to the solubility process is unfavorable. Here, g represents an empirical curvature correction factor which corrects for deviations in the effective surface tension caused by curvature on the molecular level . The van der Waals surface contact area of the solute is given by A. This area is defined as the locus of all exterior points of the van der Waals surface of the solute molecule that could be in contact with the van der Waals surface of a solvent molecule. This area is treated as a composition independent term. The surface tension, γ, is that for a cavity of surface phase composition f_2. We define f_2 as the mean fractional composition of the solvation shell with respect to the organic cosolvent. We derive an expression for f_2 through use of the following summation.

$$f_2 = \frac{1}{k}\sum j\, F_{RW_i M_j} \qquad (1.39)$$

The solvation stoichiometry is denoted by RW_iM_j, and $k = i + j$ (k is also equal to the number of solvation steps). Analogous to the definition and derivation of f_2, we define f_1 as the mean fractional composition of the solvation shell with respect to water, given by

$$f_1 = \frac{1}{k}\sum i\, F_{RW_i M_j} \qquad (1.40)$$

The surface tension of the solvation shell is defined by equation (1.41),

$$\gamma = \gamma_1 f_1 + \gamma_2 f_2 = \gamma_1 + (\gamma_2 - \gamma_1) f_2 \qquad (1.41)$$

where γ_1 and γ_2 are the bulk surface tensions of pure water and organic cosolvent, respectively. Substituting (1.32), (1.33) and (1.39) into (1.41), we express the surface tension of the solvation shell as

$$\gamma = \gamma_1 + \gamma' \left(\frac{K_1 x_1 x_2 + \ 2K_1 K_2 x_2{}^2}{x_1{}^2 + K_1 x_1 x_2 + K_1 K_2 x_2{}^2} \right) \qquad (1.42)$$

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

Thus, the general medium effect is given by substitution of (1.42) into (1.38)

$$\Delta G^\circ_{\text{Gen.Med.}} = gA\gamma_1 + gA\gamma' \left(\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} \right) \quad (1.43)$$

The total energy of dissolution is given by substituting equations (1.37) and (1.43) into equation (1.25)

$$\Delta G^\circ_{\text{Total}} = gA\gamma_1 + \frac{(-kT \ln K_1 + gA\gamma')\, K_1x_1x_2 + (-kT \ln K_1K_2 + 2gA\gamma')\, K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + \Delta G^\circ_{\text{RW}_2} + \Delta G^\circ_{\text{Intersolute}} \quad (1.44)$$

In a completely aqueous medium ($x_2 = 0$) this equation reduces to

$$\Delta G^{\circ\, x_2=0}_{\text{Total}} = gA\gamma_1 + \Delta G^\circ_{\text{RW}_2} + \Delta G^\circ_{\text{Intersolute}} \quad (1.45)$$

Using the Leffler-Grunwald operator (79), the solvent effect is defined as

$$\delta_m \Delta G^\circ = \Delta G^\circ_{(x_2)} - \Delta G^\circ_{(x_2=0)} \quad (1.46)$$

Application of this operator to equation (1.44) eliminates the solvent independent terms, and allows it to be reduced and expressed as

$$\delta_m \Delta G^\circ = \frac{(-kT \ln K_1 + gA\gamma')\, K_1 x_1 x_2 + (-kT \ln K_1 K_2 + 2gA\gamma')\, K_1 K_2 x_2^2}{x_1^2 + K_1 x_1 x_2 + K_1 K_2 x_2^2} \tag{1.47}$$

This equation has three adjustable parameters, namely the solvation exchange constants K_1 and K_2, and the product gA of the surface area and the curvature correction factor. These parameters are obtained by fitting solubility data to the equation using Systat®, Version 5.2, a nonlinear regression software program.

1.3 Statement of the Problem

Khossravi (76), examined the solvent effects on the solubility of biphenyl and substituted biphenyls, specifically 4-hydroxybiphenyl, 4,4' - dihydroxybiphenyl, and 4-bromobiphenyl, in water-methanol binary cosolvent systems. His primary goal was to establish whether A represents the total molecular surface area, or only the hydrophobic portion of the surface area, as had been postulated earlier. He found that the gA parameter values obtained from his data analyses were well correlated with the hydrophobic surface areas of the solutes. He also found the curvature correction factor values were constant and approximately equal to 0.37 for every system he studied. He postulated that the value of g would remain relatively constant for a given solute in different cosolvent systems.

The objective of this work was to test his hypothesis concerning the solvent dependency of g. The solubility of naphthalene was examined in six different binary aqueous organic cosolvent systems. The organic cosolvents were acetone, dimethylsulfoxide (DMSO), ethanol, methanol, 2-propanol, and 1,2-propanediol, and they were chosen to obtain a broad range of surface tension values and chemical types. Naphthalene was selected on the basis of its solubility properties, stability, and unambiguous hydrophobic nature. The results of these studies are presented and discussed in the following chapters in terms of the phenomenological model.

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Chapter 2 Experimental

2.1 *Materials*

The organic solvents, acetone, dimethylsulfoxide (DMSO), ethanol, methanol, 2-propanol and 1,2-propanediol used in our solubility studies were of HPLC grade and were obtained from EM Science (Gibbstown, NJ). Reagent grade acetone from Mallinkrodt (Paris, KY) was employed for solute recrystallizations.

Distilled, deionized water was obtained from an in-house Sybron/Barnstead PCS water purification system which consisted of prefilter, organic, ion-exchange, and microfilter (0.2 μm) cartridges (Barnstead Co., Dubuque, IA).

Naphthalene, purchased from Mallinkrodt (Paris, KY) and Aldrich Chemical Co. (Milwaukee, WI), and 1,4-diphenylbenzene (Aldrich Chemical Co.) were both recrystallized from acetone. Following recrystallization, naphthalene melted sharply at 80.0 °C (literature value 80.3 °C [1]), and 1,4-diphenylbenzene melted sharply at 213.0 °C (literature value 213 °C [2]).

Sample solutions were filtered through Teflon®, 25 mm, 0.2 μm filter membranes obtained from Alltech Associates, Inc. (Deerfield, IL) and Whatman (Maidstone, England).

Borosilicate glass 10 and 20 ml ampoules were acquired from Wheaton Scientific (Millville, NJ).

2.2 *Apparatus*

Naphthalene solubilities in methanol-water cosolvent systems were determined with a Beckman DU-65 spectrophotometer (Fullerton, CA). A Hitachi U-3000 spectrophotometer (San Jose, CA) was used for naphthalene solubility determinations in 2-propanol-water cosolvent systems and 1,4-diphenylbenzene solubility determinations in methanol-water cosolvent systems. Hellma, 1.00 cm and 10.00 cm, quartz cuvettes were used throughout the spectrophotometric analyses.

All remaining solutions were analyzed by high performance liquid chromatography (HPLC). Our system consisted of a Waters (Millipore Corp., Millford, PA) model 501 solvent delivery system, a Waters model 484 variable wavelength UV-Vis detector, and an Econosphere, C-8, 5 μm, (150 X 4.6 mm) cartridge column acquired from Alltech Associates, Inc.(Deerfield, IL). Samples were introduced with a Rheodyne model 7125 manual injector (Rheodyne, Inc., Cotati, CA) fitted with a 50-μl sample loop and Rheodyne position sensing switch. Data acquisition and analysis were executed by a Macintosh SE- 20 MB (Apple Computers, Inc., Cupertino, CA) and Dynamax® HPLC method manager software program version 1.1 from Rainin Instrument Co., Inc., (Woburn, MA). Samples were sealed in glass ampoules and rotated end over end at 32 revolutions per minute in a large water bath. The bath temperature was maintained at 25.00 ± 0.05 °C by a relay and mercury column thermoregulator (Brownell Scientific Co.). Melting point determinations were made with a Thomas Hoover capillary melting point apparatus (Arthur H. Thomas Co., Philadelphia, PA). Solutions and solutes were weighed on a Mettler AE 200 analytical balance (Mettler Instrument Corp., Hightstown, NJ) or a Ohaus GT 4100 electronic balance (Ohaus Corp., Florham Park, NJ).

Corey-Pauling-Koltun (CPK) space-filling molecular models were purchased from Ealing Corp. (South Natick, MA) and used for molecular surface area determinations.

2.3 *Procedures*

2.3.1 Solute Recrystallization

An excess of solute was added to a 500-ml round bottom flask containing 100 ml of acetone. Boiling chips were added, and the acetone was heated to boiling with a steam bath. A water-cooled reflux column was used to condense the acetone vapor generated from the heating. The solvent was boiled until all or nearly all solute had dissolved, and then the hot solution was filtered through a warmed buchner funnel. After equilibration to ambient temperature, the crystals were collected via a second filtration and washed with acetone that had been chilled in dry ice. The crystals were dried in a dessicator, under vacuum for 36 to 48 hours.

2.3.2 Binary Aqueous Organic Cosolvent Preparation

Typically 12 to 15 binary aqueous-organic cosolvent solutions were prepared for each complete solubility study; the solvent compositions of the solutions were varied from 0 to 1 mole fraction organic, and the volumes from 100 to 1000 ml. A particular mole fraction organic concentration was selected, and the weights of water and organic cosolvent required to prepare this concentration were calculated. Water and organic cosolvent were then poured into a tared volumetric flask until the necessary weights were reached. The solution was well mixed.

2.3.3 Sample Preparation

An excess of recrystallized solute was placed into ampoules, and then cosolvent solution was added to the ampoules with a syringe. The ampoules were transferred to a dry ice-acetone bath and chilled for one to two minutes prior to sealing with a torch. After sealing, the ampoules were transferred to a water bath where they were rotated end over end and equilibrated to 25.00 ± 0.05 °C for at least 48 hours. Usually six samples were prepared for each cosolvent composition that was studied; one sample was dedicated to a solubility estimation analysis to properly determine the dilution required to analyze the five remaining samples.

The saturated solutions were filtered through Teflon® 22 µm filter membranes, and an appropriate volume of the filtrate was pipetted into a tared volumetric flask. The weight of the filtrate was recorded for use in a density calculation at a later time. For spectrophotometric analyses, samples were appropriately diluted with their respective cosolvent solution, and for chromatographic analyses, dilutions were made with mobile phase.

2.3.4 Analytical Methods

Spectrophotometric analyses of naphthalene solutions were conducted at 275 nm and analyses of 1,4-diphenylbenzene were performed at 280 nm. Both spectra revealed very broad bands near these wavelengths. The molar absorptivity for naphthalene was 5.4×10^3 L mole^{-1} cm^{-1}, and that for 1,4-diphenylbenzene was 3.1×10^4 L mole^{-1} cm^{-1}. Both these values were relatively insensitive to changes in the composition of the solvent.

HPLC analyses were performed on naphthalene solutions only and were conducted at a wavelength of 275 nm. A methanol/water (1.5/1 v/v premixed) mobile phase was pumped through an Econosphere, C-8, 5 µm, (150 X 4.6 mm) cartridge column at 1.0 ml / min. Naphthalene was used as an external standard. A sample chromatogram is displayed in Appendix A.

2.3.5 Surface Area Determination

A simple, inexpensive method was developed to determine molecular surface area (3). A molecular model was constructed using a Corey-Pauling-Koltun (CPK) space-filling model kit. The model was wrapped with tautly stretched aluminum foil, ignoring fine features so that the wrapped model resembled a smooth shell. The aluminum foil was removed and weighed; this weight was converted to an area via a standard curve relating surface areas (based on linear dimensions) of aluminum foil squares to the squares' respective weights.

2.4 Calculations

Solute molar concentrations were converted to solute mole fraction concentrations so the unitary standard free energy change of dissolution could be calculated. The conversion was accomplished by the following treatment of the experimental data.

The density of a saturated solution was multiplied by 1000 to express the weight of solution on a 1000 ml basis. We will denote this weight by the letter A.

$$\rho_{\text{saturated solution}} \times 1000 = \text{A} \qquad (2.1)$$

The weight of solute in the saturated solution was calculated by multiplying its molar concentration, M, by its formula weight, FW. We denote this weight as B.

$$\text{M} \times \text{FW} = \text{B} \qquad (2.2)$$

The total solvent weight is determined by subtracting B from A. We will use the letter C to designate this weight.

$$A - B = C \tag{2.3}$$

To determine the weight of organic cosolvent in the total solvent, we multiply the total solvent weight, C, by the weight to weight percent of organic in the original cosolvent. We denote the weight of organic cosolvent as D.

$$C \times ({}^{\mathrm{w}}\!/\!_{\mathrm{w}}\,\%) = D \tag{2.4}$$

The weight of water is calculated by subtracting D from C, and is designated as E.

$$C - D = E \tag{2.5}$$

Dividing the weights of organic cosolvent and water, D and E respectively, by their formula weights will give the number of moles of each, designated D' and E'. Since all quantities were based on 1000 ml, the mole fraction concentration of solute, x_3, could be calculated from the number of moles of water, E', organic solvent, D', and the molar concentration of solute, M, using equation (2.6).

$$x_3 = \frac{M}{M + D' + E'} \tag{2.6}$$

The unitary standard free energy change for dissolution on a molecular basis was calculated by multiplying the Boltzman constant, k , the absolute temperature, T , and the natural logarithm of the solute mole fraction concentration by -1 as shown in equation (2.7)

$$\Delta G_u^\circ = -kT \times \ln x_3 \qquad (2.7)$$

2.5 References

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Chapter 3 Results

In this chapter, results from the naphthalene solubility experiments are presented. Section 3.1 describes naphthalene solubilities and related information. Section 3.2 contains the parameter values obtained by fitting the solubility data to the phenomenological model (equation 1.47). Section 3.3 gives plots of the data and curve fits generated from these models.

3.1 Solubility Data

In this section, results from the naphthalene solubility studies in six binary aqueous organic cosolvent systems are presented. All studies were conducted at 25.0 ± 0.05 ° C. Two tables are used to present the data for each cosolvent study: in the first table the weight of the solution components and the solution densities are reported; in the second table, concentration related information is presented.

Table 3.1 a. Solubility Data for Naphthalene in Binary Water-Acetone Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of Acetone in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.996 (0.001)
933.95	53.90	0.053 (0.0024)	0.988 (.0021)
812.21	154.33	0.204 (0.0030)	0.967 (0.0062)
719.44	231.34	0.60 (0.015)	0.951 (0.0044)
623.93	310.89	1.99 (0.017)	0.937 (0.0016)
534.48	382.24	2.80 (0.066)	0.920 (0.0020)
459.14	432.53	12.2 (0.18)	0.904 (0.0020)
384.18	479.31	25.1 (0.72)	0.889 (0.0064)
275.38	533.48	64 (1.1)	0.873 (0.0023)
212.85	550.91	100.2 (0.73)	0.864 (0.0026)
154.88	556.15	142 (1.3)	0.853 (0.0026)
92.64	551.15	209 (4.8)	0.853 (0.0046)
71.71	542.64	237 (3.1)	0.852 (0.0037)
37.72	524.38	291 (1.5)	0.854 (0.0015)
-	490.78	371 (1.5)	0.861 (0.0050)

---

[a] Numbers in parentheses are standard deviations.

Table 3.1 b. Solubility Data for Naphthalene in Binary Water-Acetone Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG_u° [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.01759	0.07771	4.1 (0.18)	4.838
0.05566	0.3337	15.9 (0.23)	4.239
0.0907	1.070	47 (1.1)	3.760
0.13387	3.882	155 (1.3)	3.230
0.18156	6.018	218 (5.2)	3.050
0.22613	28.84	950 (14)	2.405
0.27902	65.79	1960 (56)	2.066
0.37536	200.2	5000 (85)	1.608
0.44533	354.1	7820 (57)	1.374
0.52694	575.8	11100 (100)	1.174
0.64856	1002	16300 (370)	0.9463
0.70125	1222	18500 (250)	0.8645
0.81176	1697	22700 (120)	0.7293
1.0	2549	28900 (120)	0.5621

---

[a] Numbers in parentheses are standard deviations.
[b] Unitary standard free energy change for dissolution

Table 3.2 a. Solubility Data for Naphthalene in Binary Water-Dimethylsulfoxide Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of DMSO in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.996 (0.001)
938.47	59.44	0.042 (0.0018)	0.998 (0.0052)
900.02	101.82	0.059 (0.0025)	1.002 (0.0029)
812.82	207.17	0.124 (0.0029)	1.020 (0.002)
758.62	259.92	0.157 (0.0046)	1.02 (0.015)
682.51	348.84	0.289 (0.0075)	1.032 (0.0088)
639.90	392.61	0.396 (0.0054)	1.033 (0.0094)
558.26	480.48	0.76 (0.010)	1.040 (0.0089)
493.58	562.68	1.42 (0.010)	1.058 (0.0085)
444.64	609.36	2.17 (0.012)	1.056 (0.0046)
363.41	704.93	5.23 (0.032)	1.074 (0.0082)
274.96	787.34	13.63 (0.087)	1.076 (0.0042)
188.05	854.39	35.1 (0.31)	1.078 (0.0035)
127.17	883.47	67.7 (0.55)	1.078 (0.0053)
60.09	870.64	141 (4.2)	1.072 (0.0036)
-	820.37	246 (1.3)	1.067 (0.0039)

---

[a] Numbers in parentheses are standard deviations.

Table 3.2 b. Solubility Data for Naphthalene in Binary Water-Dimethylsulfoxide Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG_u° [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.01439	0.06138	3.2 (0.14)	4.935
0.02542	0.09744	4.6 (0.20)	4.745
0.05550	0.2029	9.7 (0.23)	4.444
0.073213	0.2707	12.3 (0.36)	4.325
0.10542	0.5318	22.5 (0.58)	4.047
0.12393	0.7615	30.8 (0.42)	3.900
0.16558	1.601	59.4 (0.80)	3.594
0.20813	3.196	110.6 (0.79)	3.310
0.24011	5.221	169.6 (0.95)	3.108
0.30923	13.97	408 (2.5)	2.703
0.39767	41.78	1063 (6.8)	2.253
0.51161	126.4	2740 (24)	1.798
0.61564	279.5	5280 (4.3)	1.471
0.7696	706.2	11000 (320)	1.090
1.0	1548	19200 (99)	0.7673

---

[a] Numbers in parentheses are standard deviations.

[b] Unitary standard free energy change for dissolution

Table 3.3 a. Solubility Data for Naphthalene in Binary Water-Ethanol Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of Ethanol in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.996 (0.001)
879.07	102.85	0.051 (0.0023)	0.982 (0.0076)
815.42	150.30	0.078 (0.0021)	0.9658 (0.00065)
738.93	215.53	0.164 (0.0022)	0.955 (0.0028)
681.61	262.35	0.327 (0.0028)	0.944 (0.0023)
593.09	338.76	1.076 (0.0053)	0.933 (0.0053)
544.60	370.31	1.80 (0.052)	0.917 (0.0045)
447.81	447.01	4.56 (0.033)	0.899 (0.0039)
358.71	513.09	9.13 (0.075)	0.881 (0.0044)
297.94	554.54	13.7 (0.15)	0.866 (0.0045)
231.85	598.01	21.1 (0.52)	0.851 (0.0039)
126.43	662.62	38.3 (0.28)	0.827 (0.0066)
93.28	678.63	47.5 (0.36)	0.819 (0.0034)
28.40	703.56	71.4 (0.55)	0.803 (0.0018)
-	713.66	86.5 (0.51)	0.800 (0.0051)

---

[a] Numbers in parentheses are standard deviations.

Table 3.3 b. Solubility Data for Naphthalene in Binary Water-Ethanol Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG_u° [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.04375	0.07758	4.0 (0.18)	4.839
0.06723	0.1247	6.0 (0.16)	4.644
0.10239	0.2806	12.8 (0.17)	4.310
0.13083	0.5866	25.5 (0.22)	4.007
0.18258	2.084	83.9 (0.41)	3.486
0.21005	3.660	140 (4.1)	3.254
0.28076	10.28	356 (2.6)	2.829
0.35871	22.90	713 (5.9)	2.500
0.42125	37.17	1070 (11)	2.301
0.50215	63.27	1650 (41)	2.082
0.67208	137.7	2990 (22)	1.762
0.73992	182.6	3700 (28)	1.646
0.90643	319.9	5570 (43)	1.416
1.0	417.3	6750 (40)	1.306

---

[a] Numbers in parentheses are standard deviations.

[b] Unitary standard free energy change for dissolution

Table 3.4 a. Solubility Data for Naphthalene in Binary Water-2- Propanol Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of 2-Propanol in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.996 (0.001)
887.47	92.20	0.052 (0.0014)	0.9797 (0.00049)
737.32	219.99	.324 (0.0029)	0.958 (0.0035)
682.57	259.77	0.813 (0.0073)	0.943 (0.0030)
558.50	354.91	4.05 (0.034)	0.917 (0.0016)
469.27	421.78	6.93 (0.019)	0.898 (0.0017)
375.64	494.84	12.57 (0.045)	0.883 (0.0032)
311.28	536.04	17.3 (0.13)	0.865 (0.0039)
235.49	587.92	24.1 (0.40)	0.847 (0.0059)
150.25	641.65	36.0 (0.16)	0.828 (0.0035)
64.63	686.30	50 (1.8)	0.801 (0.0013)
-	720.27	65.5 (0.48)	0.786 (0.0022)

---

[a] Numbers in parentheses are standard deviations.

Table 3.4 b. Solubility Data for Naphthalene in Binary Water-2-Propanol Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG_u° [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.03021	0.07949	4.0 (0.11)	4.831
0.08211	0.5670	25.3 (0.23)	4.023
0.10242	1.503	63.5 (0.57)	3.622
0.16003	8.557	316 (2.7)	2.906
0.21227	16.33	540.7 (1.5)	2.640
0.28313	33.61	981 (3.5)	2.343
0.34050	51.20	1348 (9.9)	2.17
0.42808	81.48	1880 (31)	1.979
0.56147	145.5	2810 (12)	1.740
0.76097	254.2	3900 (140)	1.511
1.0	409.1	5110 (37)	1.316

---

[a] Numbers in parentheses are standard deviations.

[b] Unitary standard free energy change for dissolution

Table 3.5 a. Solubility Data for Naphthalene in Binary Water-Methanol Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of Methanol in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.996 (0.001)
912.89	69.55	0.044 (0.0022)	0.982 (0.0014)
816.97	148.31	0.0738 (0.00063)	0.965 (0.0018)
727.72	225.37	0.145 (0.0072)	0.953 (0.0021)
634.87	303.52	0.319 (0.0023)	0.939 (0.0024)
526.95	391.53	0.899 (0.0090)	0.919 (0.0021)
371.50	513.98	3.59 (0.050)	0.889 (0.0033)
320.06	553.88	5.66 (0.040)	0.880 (0.0013)
212.95	628.01	13.4 (0.11)	0.854 (0.0033)
116.11	685.08	28.5 (0.40)	0.8297 (0.00084)
86.19	696.54	36.6 (0.38)	0.8194 (0.00079)
58.91	710.83	45.7 (0.72)	0.815 (0.0034)
33.39	718.53	56.10 (0.063)	0.808 (0.0014)
-	729.98	73.3 (0.58)	0.8033 (0.0044)

---

[a] Numbers in parentheses are standard deviations.

Table 3.5 b. Solubility Data for Naphthalene in Binary Water-Methanol Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG°_{u} [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.04108	0.06527	3.4 (0.17)	4.915
0.09262	0.1152	5.76 (0.049)	4.681
0.14831	0.2382	11.3 (0.56)	4.382
0.21275	0.5566	24.9 (0.18)	4.033
0.29468	1.691	70.1 (0.70)	3.575
0.43756	7.624	280 (3.9)	2.955
0.49318	12.58	442 (3.1)	2.749
0.62381	33.27	1049 (8.3)	2.349
0.76840	79.21	2220 (31)	1.992
0.81963	106.6	2860 (30)	1.869
0.87154	138.2	3570 (56)	1.762
0.92366	177.1	4378 (4.9)	1.660
1.0	245.0	5720 (45)	1.527

---

[a] Numbers in parentheses are standard deviations.

[b] Unitary standard free energy change for dissolution

Table 3.6 a. Solubility Data for Naphthalene in Binary Water-1,2-Propanediol Cosolvent Mixtures

Weight of Water in 1000 ml of Solution / g	Weight of 1,2-Propanediol in 1000 ml of Solution / g	Weight of Naphthalene in 1000 ml of Solution / g	Solution Densities / g ml^{-1}
995.50	-	.02736 (0.000088)[a]	0.966 (0.0011)
934.00	55.78	0.0333 (0.00066)	0.99 (0.015)
847.77	155.79	0.051 (0.0016)	1.004 (0.0018)
790.77	216.30	0.066 (0.0033)	1.007 (0.0016)
673.84	336.24	0.132 (0.0034)	1.010 (0.0012)
612.94	405.53	0.214 (0.0018)	1.019 (0.0042)
533.93	478.74	0.389 (0.0035)	1.013 (0.0029)
487.81	526.98	0.567 (0.0057)	1.02 (0.064)
416.42	606.40	1.076 (0.0060)	1.024 (0.0059)
309.12	706.91	2.49 (0.025)	1.02 (0.010)
260.47	758.85	3.72 (0.055)	1.023 (0.0089)
149.95	856.49	8.10 (0.085)	1.015 (0.0078)
117.22	884.90	10.46 (0.083)	1.013 (0.0049)
55.72	930.59	15.6 (0.39)	1.00 (0.013)
-	988.46	23.6 (0.13)	1.012 (0.0058)

---

[a] Numbers in parentheses are standard deviations.

Table 3.6 b. Solubility Data for Naphthalene in Binary Water-1,2-Propanediol Cosolvent Mixtures

Mole Fraction Organic (x_2)	Mole Fraction Naphthalene (x_3) / 10^{-4}	Molar Concentration of Naphthalene / 10^{-4} M	ΔG_u° [b] / 10^{-20} J molecule^{-1}
0	0.03864	2.135 (0.0069)[a]	5.131
0.01394	0.04938	2.60 (0.051)	5.025
0.04170	0.08030	3.9 (0.13)	4.825
0.06878	0.1102	5.1 (0.23)	4.695
0.10566	0.2459	10.3 (0.27)	4.365
0.13544	0.4251	16.7 (0.14)	4.139
0.17512	0.8446	30.3 (0.27)	3.857
0.20368	1.300	44.2 (0.45)	3.680
0.25639	2.701	83.9 (0.47)	3.379
0.35126	7.349	195 (2.0)	2.967
0.40822	11.87	290 (4.3)	2.770
0.57490	32.19	632 (6.6)	2.360
0.64125	44.98	816 (6.5)	2.224
0.79816	78.66	1215 (31)	1.993
1.0	139.3	1840 (10)	1.757

---

[a] Numbers in parentheses are standard deviations.

[b] Unitary standard free energy change for dissolution

3.2 *Curve Fit Parameters*

The solubility data from each cosolvent study were used in combination with equation (1.47) and Systat ® version 5.2, a nonlinear regression curve fitting program to estimate values for the solvation exchange constants K_1, K_2, and the gA term. The values for these parameters are furnished in Table 3.7.

Table 3.7. Solubility Parameters for Naphthalene in Various Cosolvent Systems

Cosolvent	K_1	K_2	gA / Å^2 molecule^{-1}	Goodness of Fit Criterion[a] / %
Acetone	6.5 (0.48)[b]	2.9 (0.37)	69 (1.6)	1.5
DMSO	4.8 (0.15)	1.3 (0.10)	127 (2.2)	0.64
Ethanol	3.6 (0.35)	3.5 (0.55)	54 (1.5)	1.5
2-Propanol	7 (1.1)	6 (1.5)	43 (2.3)	2.1
Methanol	2.52 (0.071)	1.19 (0.085)	63.2 (0.80)	0.15
1,2-Propanediol	4.0 (0.14)	2.2 (0.17)	71 (1.3)	0.31

---

[a] Curve Fit Criterion = 100 (standard deviation of points about the fitted line divided by the largest absolute value of the ordinate values).

[b] Numbers in parentheses are standard deviations.

3.3 Solubility Plots

Plots of the unitary standard free energy of dissolution as a function of the mole fraction organic cosolvent are presented in this section. The solid line in these plots represents the curve fits to the phenomenological model. The curve fits indicate that the solubility model effectively describes the experimental data.

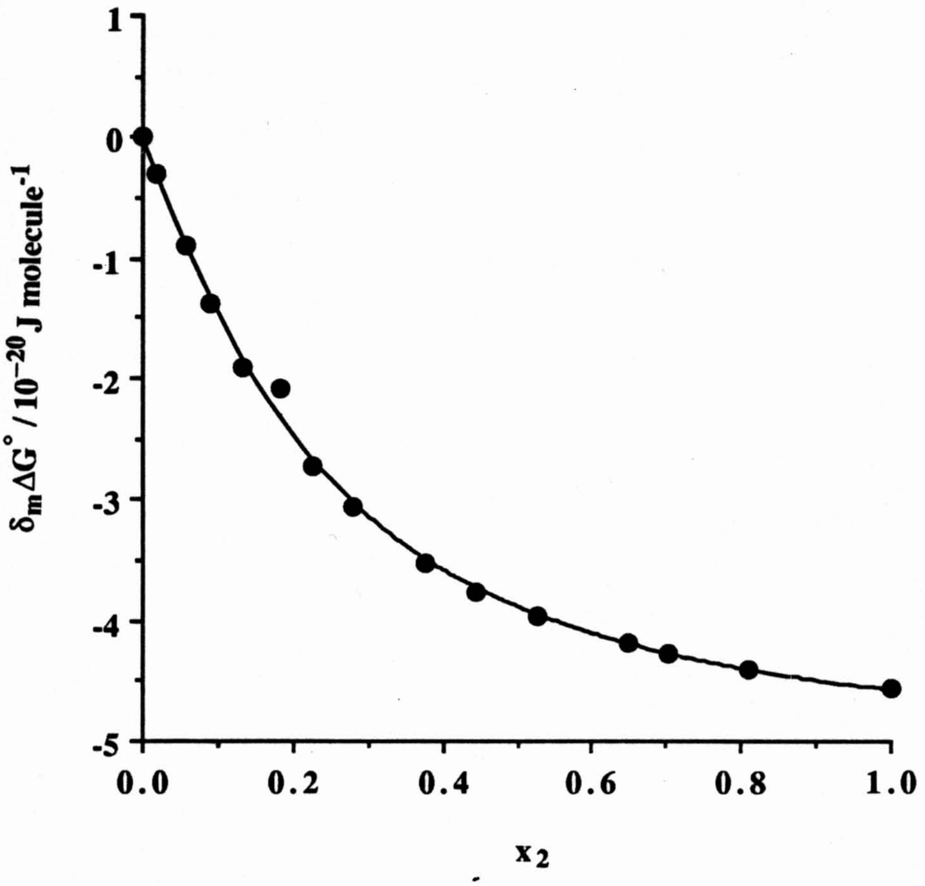

Figure 3.1. Solvent effect on the solubility of naphthalene in the water-acetone binary cosolvent system showing the experimental data points and the fitted curve.

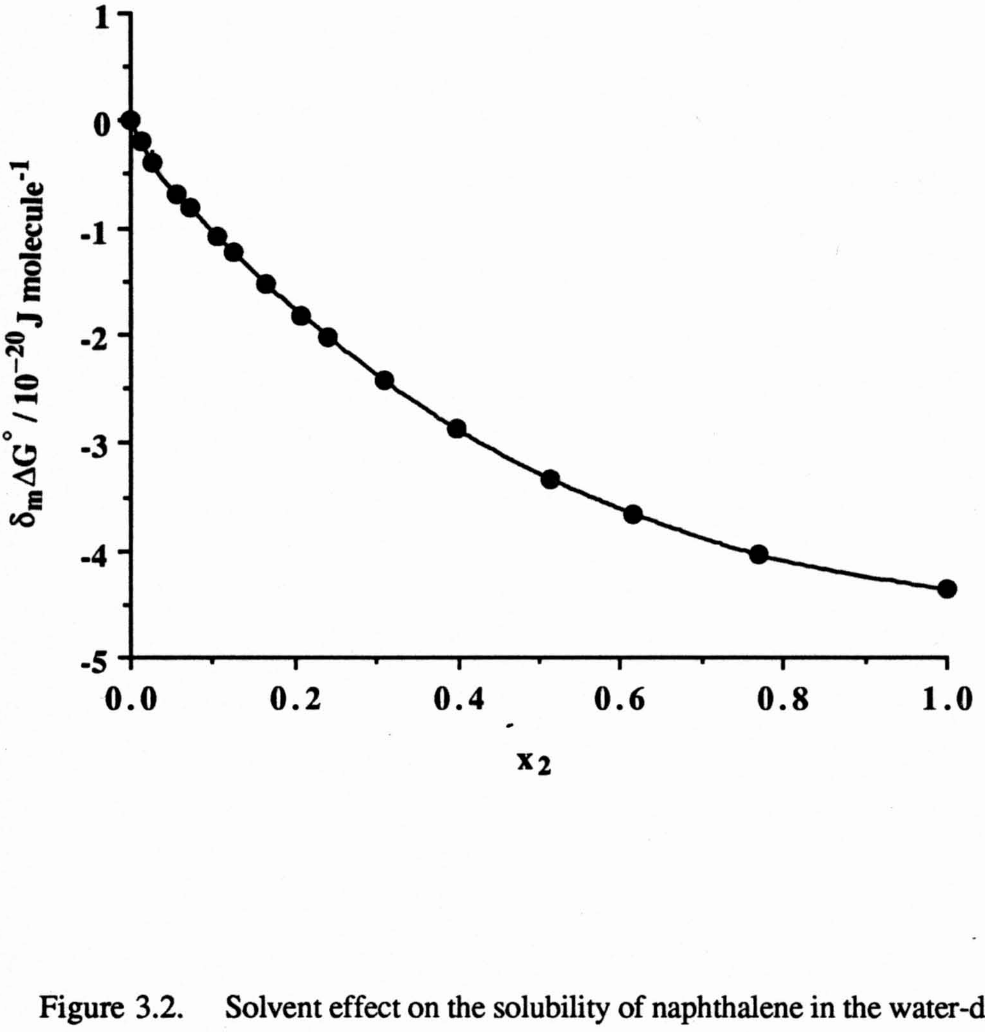

Figure 3.2. Solvent effect on the solubility of naphthalene in the water-dimethyl sulfoxide binary cosolvent system showing the experimental data points and the fitted curve.

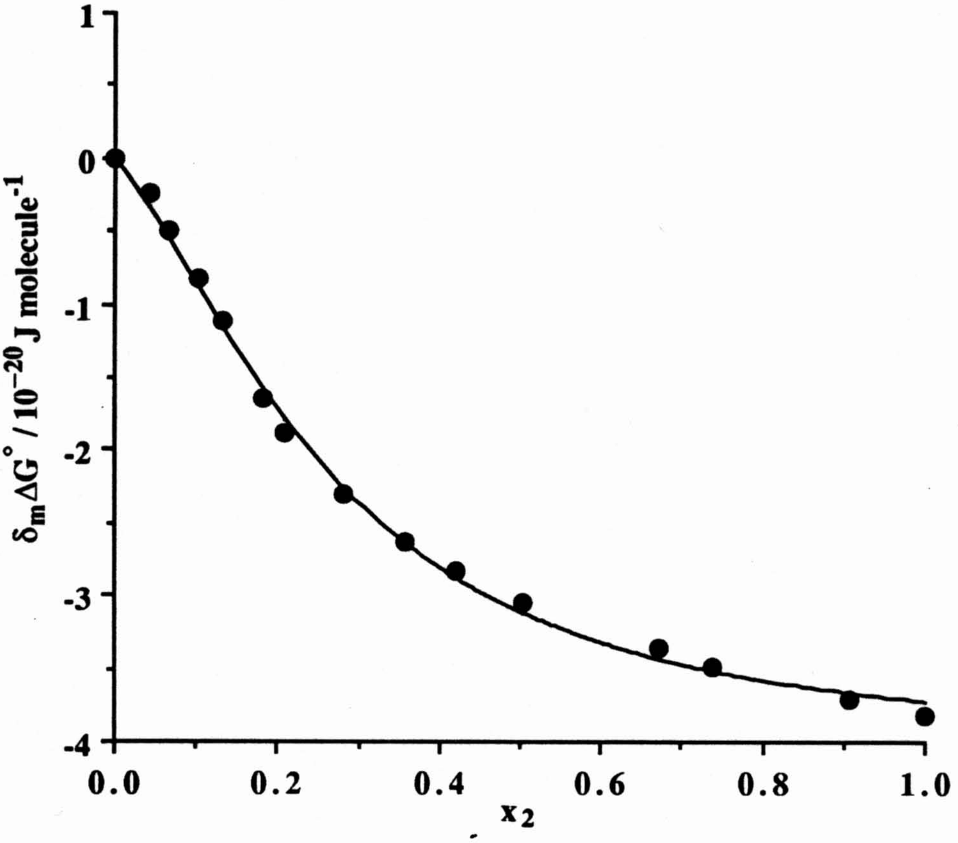

Figure 3.3. Solvent effect on the solubility of naphthalene in the water-ethanol binary cosolvent system showing the experimental data points and the fitted curve.

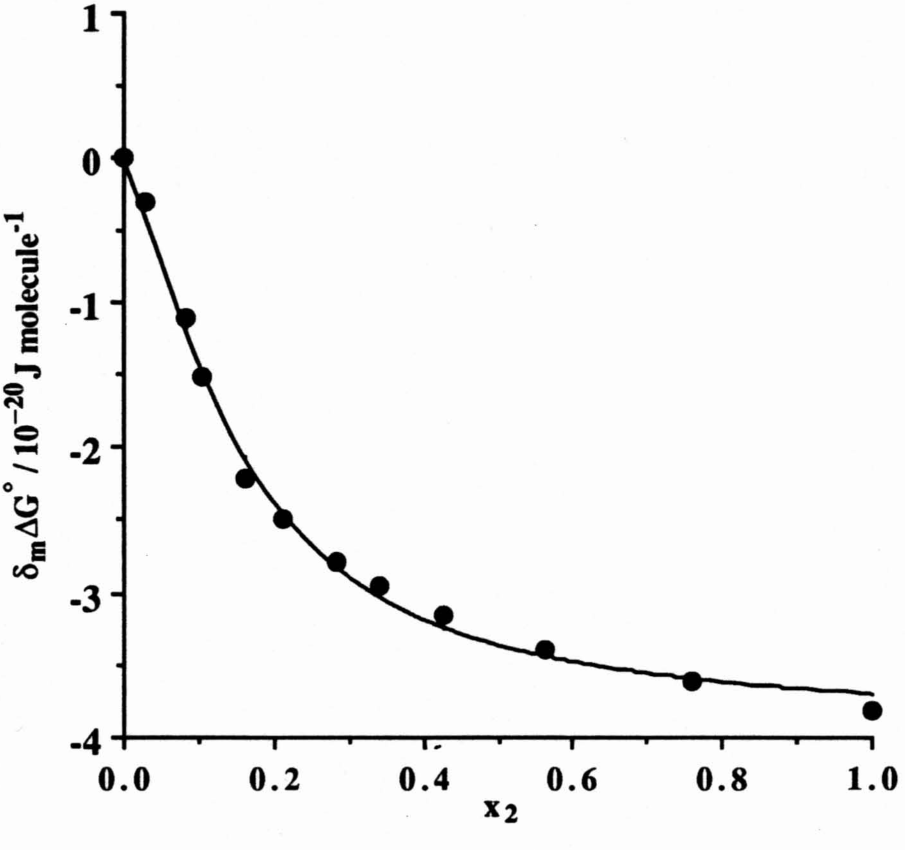

Figure 3.4. Solvent effect on the solubility of naphthalene in the water-2-propanol binary cosolvent system showing the experimental data points and the fitted curve.

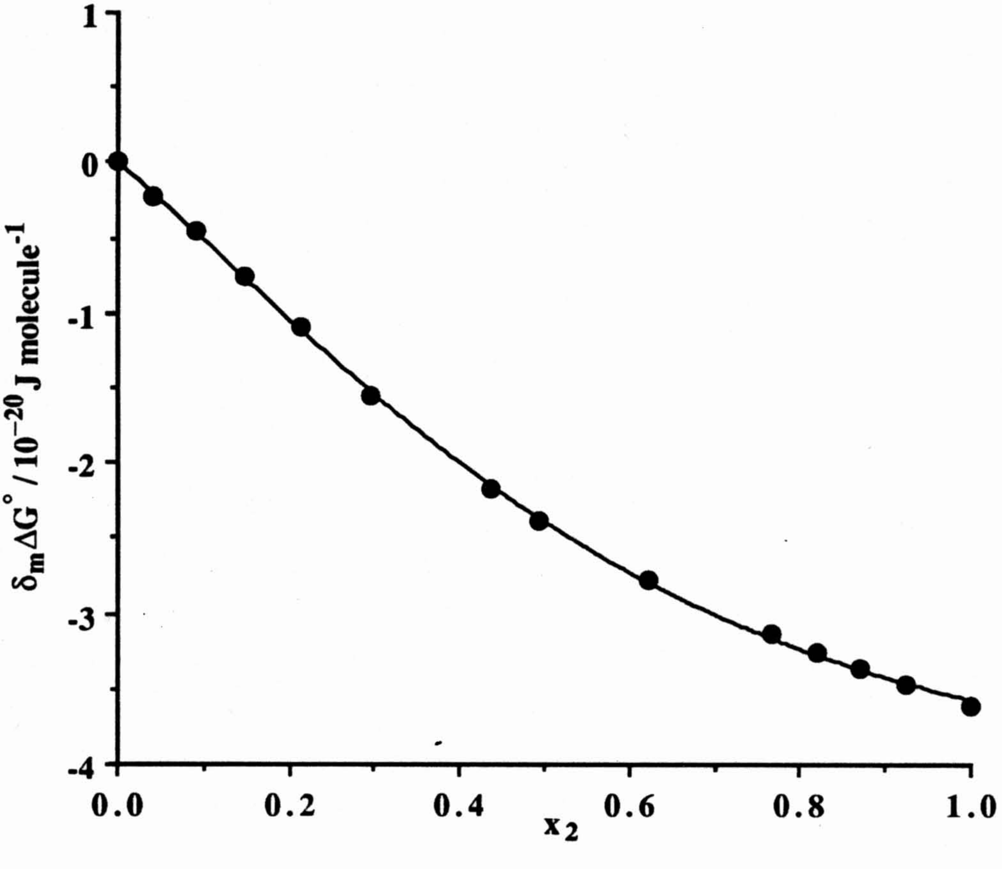

Figure 3.5. Solvent effect on the solubility of naphthalene in the water-methanol binary cosolvent system showing the experimental data points and the fitted curve.

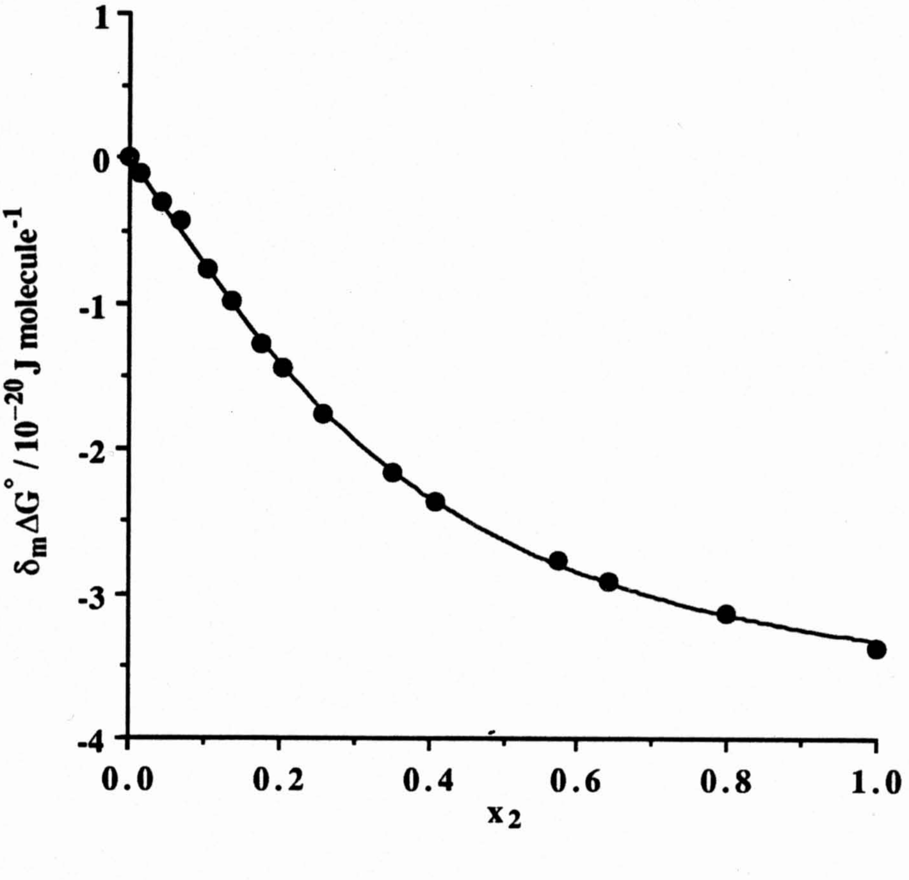

Figure 3.6. Solvent effect on the solubility of naphthalene in the water-1,2-propanediol binary cosolvent system showing the experimental data points and the fitted curve.

Chapter 4 Discussion

Though the principal objective of this work was to explore the solvent dependency of the g term, we have gained valuable information related to the exchange constants, K_1 and K_2. This information will be discussed in Section 4.1. The solvent dependency of the g term will be considered in Section 4.2. Before beginning these discussions, a brief comment on the ability of the model to describe solubility data is merited. As demonstrated by the goodness of fit criterion values in Table 3.7 and the fits to naphthalene solubility data shown in Figures 3.1 through 3.6, the model effectively describes these data. Moreover, in other investigations (1-4), the phenomenological model provided equally excellent fits to solubility data for both semipolar and nonpolar solutes. From the purely empirical point of view, therefore, equation (1.47) appears to be a versatile and effective function for describing solvent effects in binary solvent systems.

4.1 Solvation Exchange Constants

A partial collection of solvation exchange constants is provided in Table 4.1. The parameters were generated from this and other studies (1-4), and the list is restricted to simple aromatic compounds.

Table 4.1. Solvation Exchange Constant Parameters.

Solute	Cosolvent	Reference	K_1	K_2
Naphthalene	Acetonitrile	1	4.81 (0.14)[a]	5.4 (0.6)
4-Nitroaniline	Acetonitrile	2	8.31 (0.90)	5.6 (1.0)
Naphthalene	Acetone	This Work	6.5 (0.48)	2.9 (0.32)
4-Nitroaniline	Acetone	2	9.5 (1.8)	3.5 (1.3)
Naphthalene	DMSO	This Work	4.8 (0.15)	1.3 (0.10)
4-Nitroaniline	DMSO	2	4.0 (0.53)	3.7 (0.76)
Naphthalene	Ethanol	This Work	3.6 (0.35)	3.5 (0.55)
4-Nitroaniline	Ethanol	2	4.2 (0.34)	5.1 (0.62)
4-MCB[b]	Ethanol	3	3.99	3.22
Naphthalene	Ethylene Glycol	1	3.04 (0.03)	1.21 (0.04)
4-Nitroaniline	Ethylene Glycol	2	3.9 (0.24)	0.7 (0.21)
Naphthalene	2-Propanol	This Work	7 (1.1)	6 (1.5)
4-Nitroaniline	2-Propanol	2	5.9 (0.51)	10.6 (1.2)
Naphthalene	Methanol	This Work	2.52 (0.071)	1.19 (0.085)
4-Nitroaniline	Methanol	2	2.7 (0.35)	1.5 (0.49)
4-MCB	Methanol	3	2.49	1.30
2,4,6-TCB[c]	Methanol	3	2.78	1.27

---

[a] Numbers in parentheses are standard deviations.

[b] 4-Monochlorobiphenyl

[c] 2,4,6-Trichlorobiphenyl

Table 4.1 continued. Solvation Exchange Constant Parameters.

Solute	Cosolvent	Reference	K_1	K_2
HCB[d]	Methanol	3	3.76	1.21
Biphenyl	Methanol	4	2.45 (0.07)	1.28 (0.07)
4-HB[e]	Methanol	4	2.33 (0.04)	1.61 (0.05)
4,4'-DHB[f]	Methanol	4	2.62 (0.08)	2.2 (0.11)
4-BB[g]	Methanol	4	2.6 (0.13)	1.4 (0.16)

Some general observations may be made from the data in this table. The exchange constants appear to be physically reasonable values, and all are between 0.5 and 11. Comparisons of 4-nitroaniline and naphthalene K_1 and K_2 values reveal that they follow similar trends in terms of increasing and decreasing values relative to each other. For example, in the acetonitrile, acetone, DMSO, and methanol systems K_1 is usually larger than K_2. The same relationship was established for solvation exchange constant values obtained from analysis of surface tension data (5). To demonstrate that both exchange constant values, K_1 and K_2, are influenced by the solvent used in the study, I have used the following analysis.

---

[d] 2,2',4,4',6,6'-Hexachlorobiphenyl
[e] 4-Hydroxybiphenyl
[f] 4,4'-Dihydroxybiphenyl
[g] 4-Bromobiphenyl

If we add equations 1.26 and 1.27 in Scheme 1-2, we obtain equation (4.1).

$$RW_2 + 2\,M \overset{\beta_2}{\rightleftharpoons} RM_2 + 2\,W \qquad (4.1)$$

Here, two organic cosolvent molecules, 2 M, displace two water molecules, 2 W, from a fully hydrated solute, RW_2, to give a fully solvated solute, RM_2. The exchange constant , denoted as β_2, may be expressed as

$$\beta_2 = K_1K_2 \qquad (4.2)$$

where K_1 and K_2 are defined in chemical equations 1.26 and 1.27. By plotting ln β_2 exchange constant, against the logarithm of the octanol-water partition coefficients (log P) (6) for the cosolvents used in any study, we might expect to see a correlation between the solvation of the (nonpolar) solute and the nonpolarity of the organic cosolvent. It is expected that increasingly nonpolar solvents will preferentially solvate a nonpolar or mostly nonpolar solute. To test this postulate I examined data collected from the previously mentioned surface tension investigation.

In this study, conducted by Khossravi and Connors (5), the phenomenological model was used to describe surface tensions of aqueous organic cosolvent mixtures. Here the air-solution interface represented the solvation shell, and air was the "solute". When surface tension data collected from this study are treated as previously described, the plot shown in Figure 4.1 ensues.

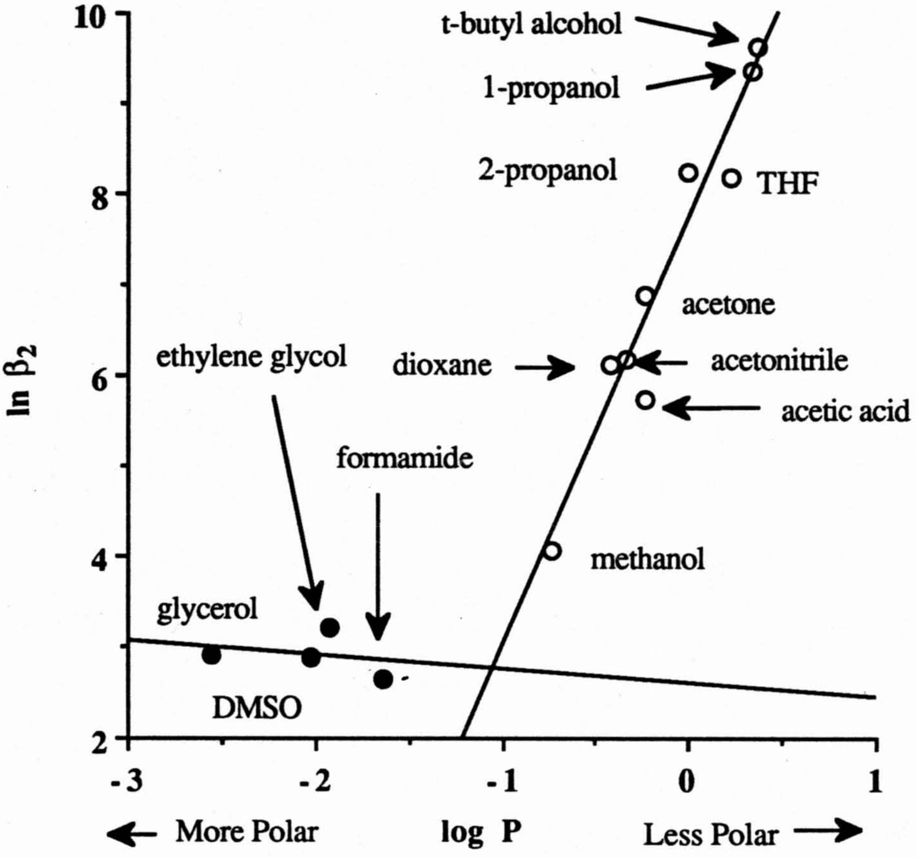

Figure 4.1. Plot of ln β_2 from the surface tension analysis against the log P of the cosolvents.

Figure 4.1 seems to indicate the existence of two classes of cosolvents. The first class possesses larger ln β_2 values and larger log P values. The second class contains smaller ln β_2 and log P values . These classifications seem to support our hypothesis concerning the occurrence of greater solvation of a nonpolar solute (air in this case) with increasing nonpolarity of the cosolvents (or a larger log P values), for the first class. This argument is speculative. When the same treatment is applied to data generated from the naphthalene and 4-nitroaniline solubility studies as shown in Figures 4.2 and 4.3, a less compelling, but still consistent, trend is seen, with an indication of two types of cosolvent behavior: in the less polar class, β_2 increases as log P increases, whereas in the more polar class, β_2 increases as log P decreases. Khossravi and Connors (7) have discussed similar behavior in terms of independent hydrophobic and hydrophilic contributions in the solute molecule; here I suggest that independent hydrophobic and hydrophilic contributions from the solvent may also require consideration.

Figures 4.2 and 4.3 display a vague existence of two cosolvent classes; however, the coupling of high solvation constants with larger log P values is not always observed as it is with the surface tension data. The methanol and ethanol points, despite their high log P values relative to DMSO, 1,2-propanediol, and ethylene glycol, exhibit relatively low solvation constant values (given by ln β_2). In to order to determine the soundness of this argument, and better understand the relevancy of the exchange constant values, more solubility studies are required. The organic cosolvents used in these studies should be selected on the basis of their log P values in an effort to better characterize the rough correlations which are shown in Figures 4.2 and 4.3.

Previously, plots of ln K_1 as a function of log P were made using the surface tension (5) and 4-nitroaniline data (2). They are included along with a similar plot using the data generated from this investigation. The plots are shown in Figures 4.4 to 4.6. The ethanol and methanol points again seem to show small ln K_1 values despite their relatively high log P values. It is also observed that the classes are not as well defined as they are in Figures 4.1 to 4.3, especially for the solubility data analyses.

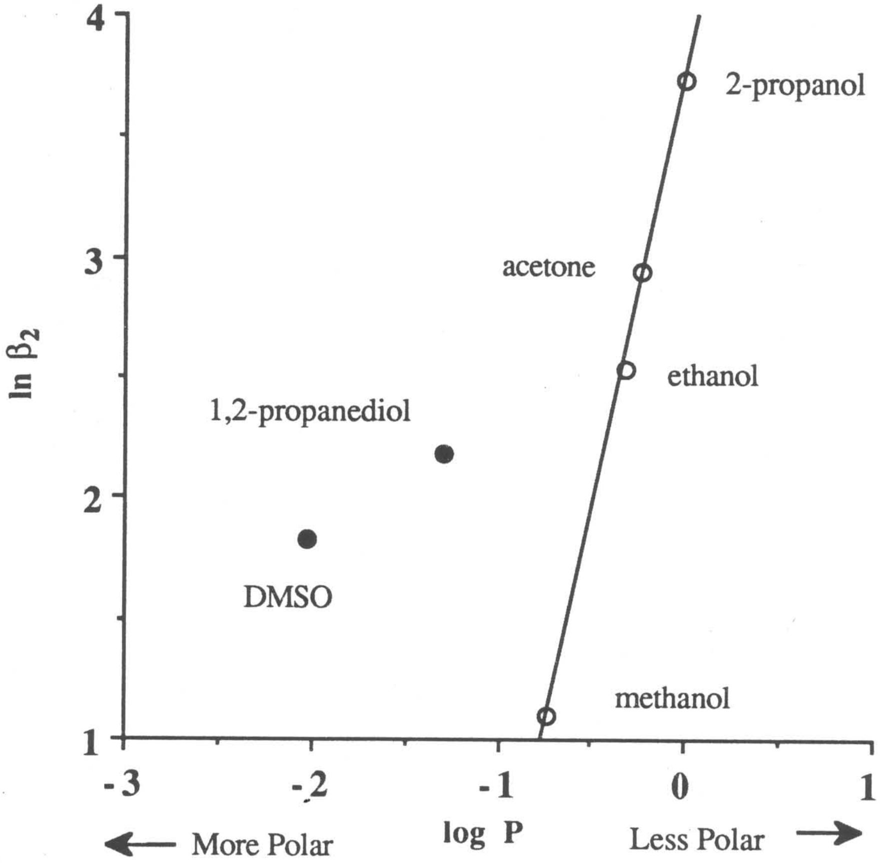

Figure 4.2. Plot of ln β_2 from the naphthalene solubility studies against the log P of the cosolvents.

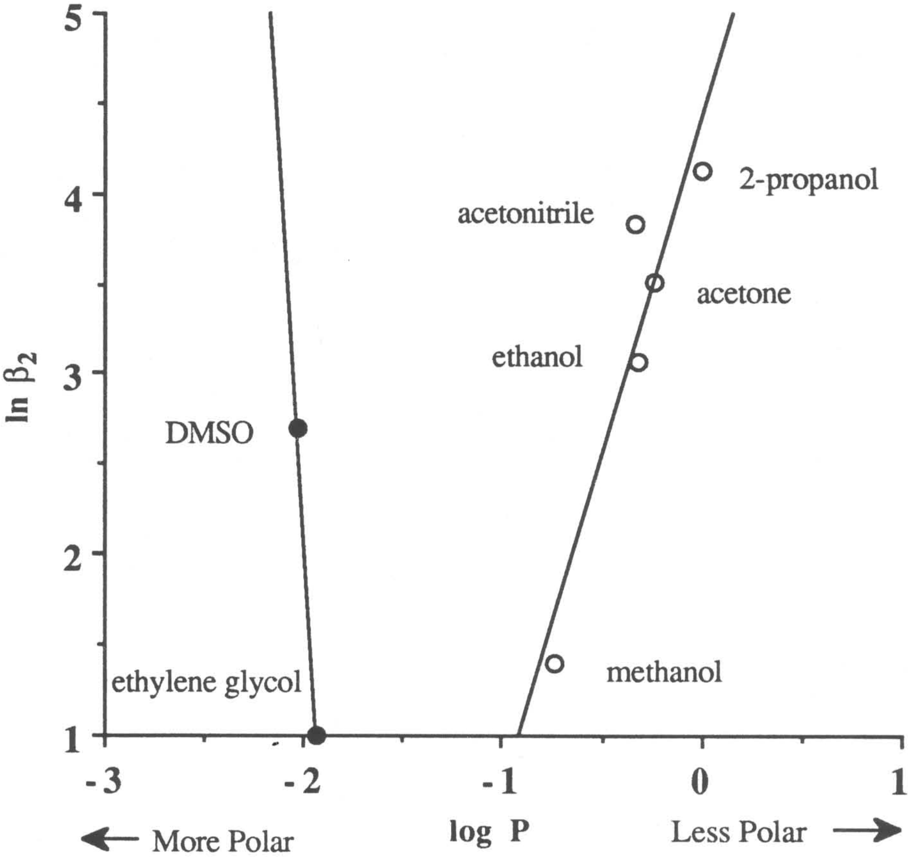

Figure 4.3. Plot of ln β_2 from the 4-nitroaniline solubility studies against the log P of the cosolvents.

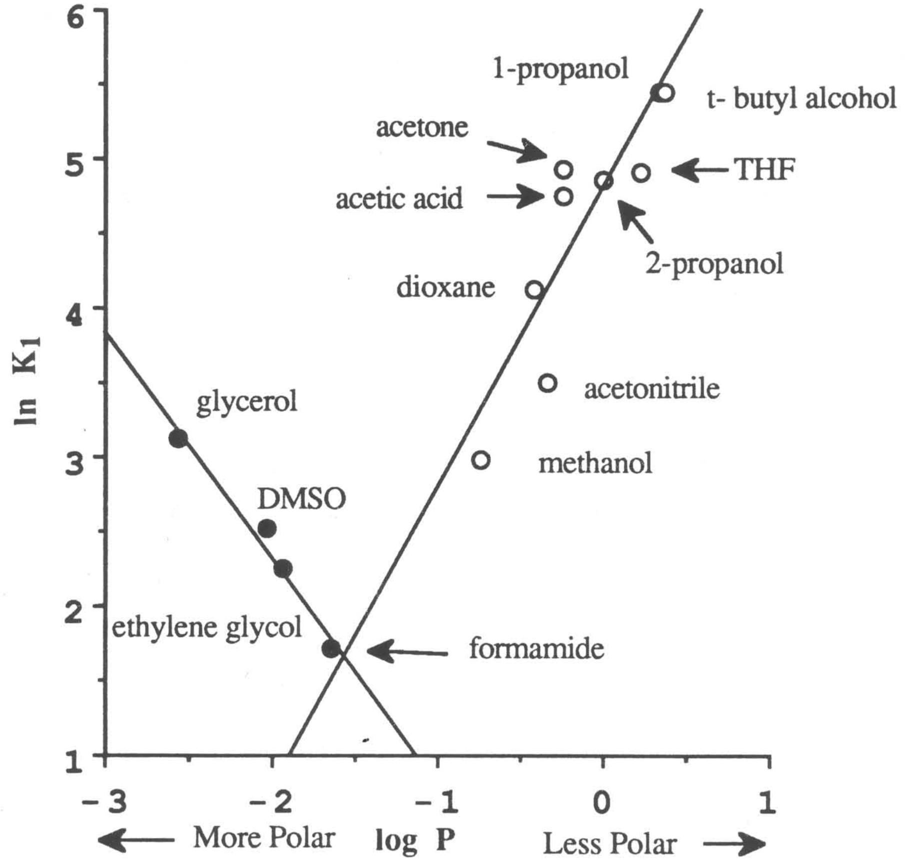

Figure 4.4. Plot of ln K_1 from the surface tension analysis against the log P of the cosolvents.

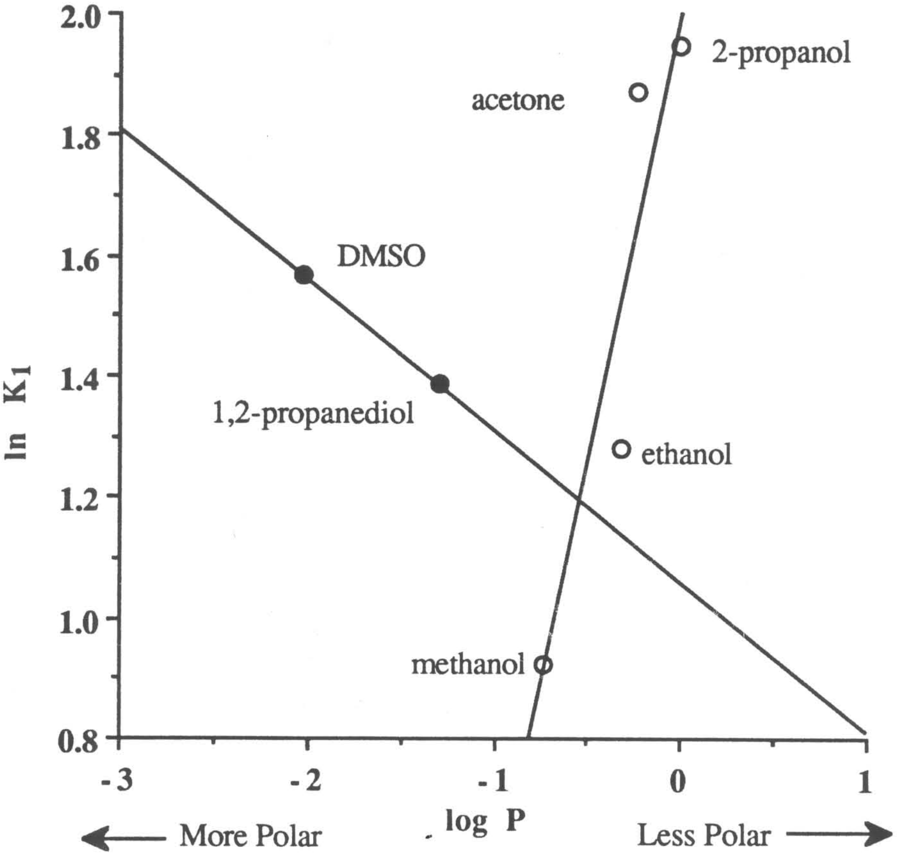

Figure 4.5. Plot of ln K_1 from the naphthalene solubility studies against the log P of the cosolvents.

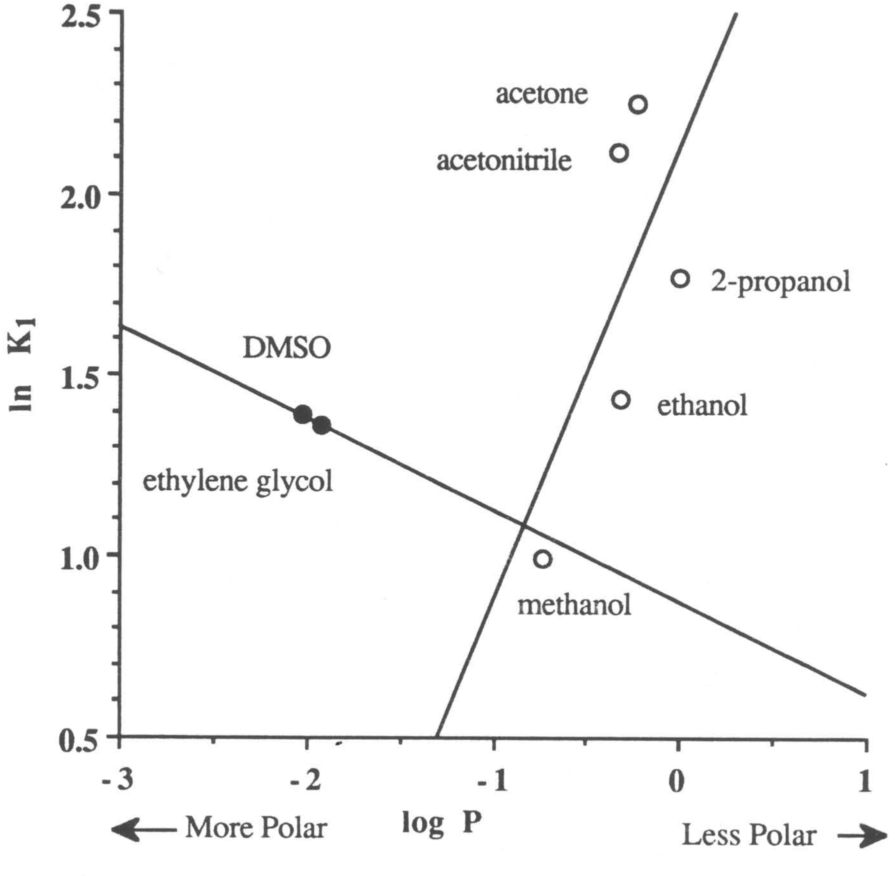

Figure 4.6. Plot of ln K_1 from the 4-nitroaniline solubility studies against the log P of the cosolvents.

4.2 gA Parameter Values

The gA parameter values and the curvature correction factors obtained from the naphthalene solubility studies are presented in Table 4.2. The curvature correction values were calculated by dividing the gA parameter values by the area of the naphthalene molecule, estimated through our aluminum foil wrapping technique to be 147 ± 3 Å^2.

Table 4.2. gA Parameter Values and Calculated Curvature Correction Values from Naphthalene Solubility Studies.

Cosolvent	gA / Å^2 molecule^{-1}	g
Acetone	69 (1.6)	0.47 (0.016)
DMSO	127 (2.2)	0.86 (0.025)
Ethanol	54 (1.5)	0.37 (0.014)
2-Propanol	43 (2.3)	0.29 (0.017)
Methanol	63.2 (0.80)	0.43 (0.012)
1,2-Propanediol	71 (1.3)	0.48 (0.014)

The gA, and thus the g, parameters vary from 0.29 to 0.86. This variation constitutes a fundamental problem within the phenomenological model. The expression for $\Delta G^{\circ}_{\text{Total}}$ in pure water was given by equation (1.45) in Chapter 1:

$$\Delta G_{\mathrm{Total}}^{\circ\, x_2=0} = gA\gamma_1 + \Delta G_{\mathrm{RW}_2}^{\circ} + \Delta G_{\mathrm{Intersolute}}^{\circ} \qquad (1.45)$$

Here, $\Delta G_{\mathrm{Total}}^{\circ\, x_2=0}$, $\Delta G_{\mathrm{RW}_2}^{\circ}$, and $\Delta G_{\mathrm{Intersolute}}^{\circ}$ are all constants in water. The product of gA and γ_1, the surface tension of water, must also be constant, for all the cosolvent systems; that is, the model assumes that gA is independent of x_2, so it follows that it should have a single value in all cosolvent systems, since it must become a single value in pure water (the reference solvent). Clearly the variation in the gA parameter creates a mathematical inconsistency in the model. In the succeeding sections, an explanation for the variation in gA will be offered, and a new model which incorporates this variation without any mathematical inconsistencies will be derived and tested.

4.2.1 Explanation for the Variation in the gA Parameter

The variation of the gA parameter may be partly attributable to an incomplete separation of the general medium and the solvation effects. The general medium effect, which was intended to account for solvent-solvent interactions, does contain solvation exchange constants, which function to describe solute-solvent interactions. Perhaps this coupling of solute-solvent and solvent-solvent interactions leads to the transfer of some cavity formation energy (the general medium effect) into the solvation terms (the solvation effect). Thus the gA values may reflect the net energy of cavity formation rather than the total energy of cavity formation within the solvent. This postulated redistribution of energy may occur upon solvation of the solute when equilibrium is achieved. The amount of energy distributed to the solvation term should be dependent upon the solution's ability to solvate the solute molecule. Therefore as we change the organic cosolvents we might expect to observe changes in the gA parameter. The direction of the effect (based on this concept of redistribution of energy from the gA term to the solvation term) may be anticipated as follows: the greater the solvation of the solute, the smaller the gA factor that will be observed. Thus for nonpolar solutes, gA should be smaller in less polar solvents. This trend has been observed by Connors and coworkers (4). To further investigate this postulated correlation, the gA parameters acquired from the naphthalene and 4-nitroaniline (2) solubility studies were plotted against log P. In Figure 4.7 parameter values from the naphthalene studies are used, and in Figure 4.8, parameter values from the 4-nitroaniline studies are used.

A definite trend is observed in both plots, though the 4-nitroaniline data provides a stronger relation. These plots support this idea, but further solubility investigations incorporating cosolvents with log P values ranging from -1 to -2 would help to determine the validity of these interrelations, and support the aforementioned argument. Ideally, a similar relationship should be observed for various solutes in a single cosolvent system. A solute of greater nonpolarity would be expected to have a larger gA term in a polar solvent system. As solutes of increasingly polarity are studied, the gA term should decrease, reflecting greater solvation. This could not be tested owing to the lack of sufficient log P values for the solutes that have been studied in single binary aqueous organic cosolvent systems.

The original objective was to determine the solvent dependency of g (A was assumed to be constant); however, such separation of the gA term into its components is difficult because it is impossible to determine where the change in the total gA parameter occurs. Both variables may be changing simultaneously, or only one may change while the other is constant. With this argument, I conclude that this term should not be separated into distinct contributions of g and A, but should be treated as a single variable until we can be certain the area term or the curvature correction factor is constant in all cosolvents.

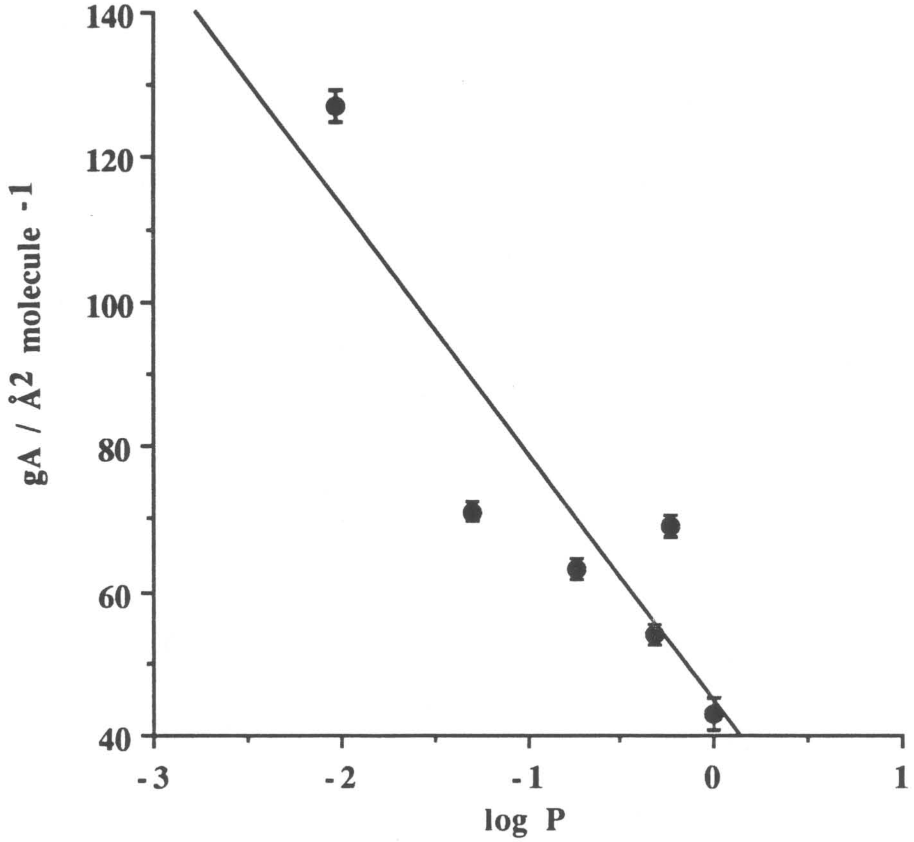

Figure 4.7. gA parameter values from naphthalene solubility against log P.

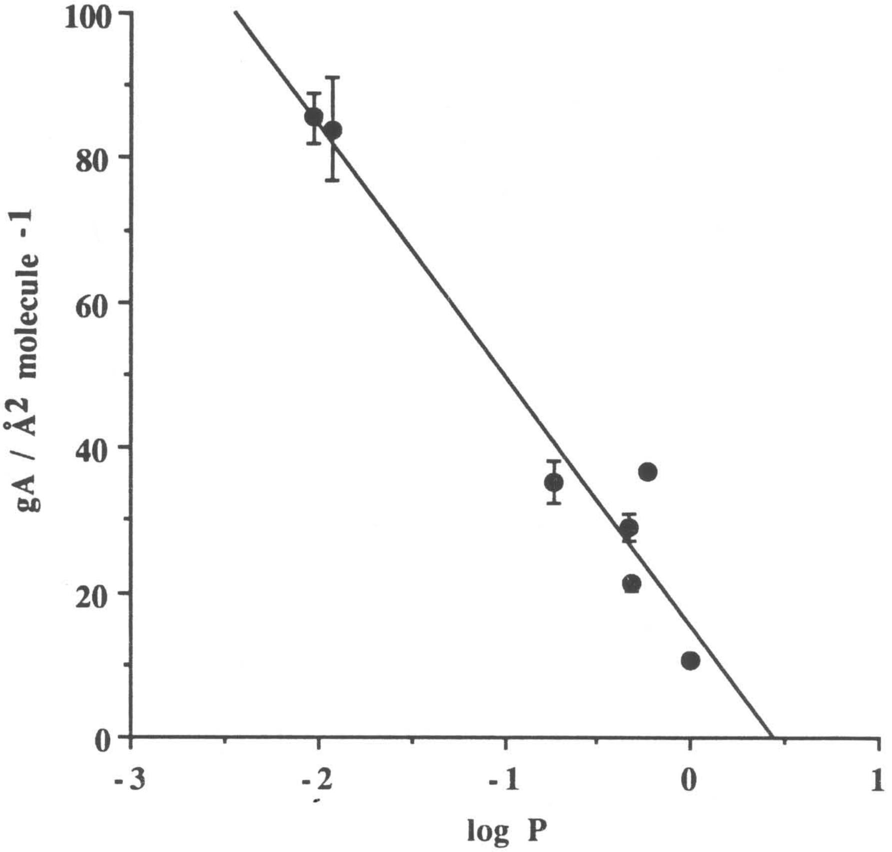

Figure 4.8. gA parameter values form the 4-nitroaniline solubility studies against log P.

4.2.2 Modification of the Phenomenological Model

Several other approaches were explored in an attempt to circumvent the mathematical inconsistency created by the variation of the gA parameter. The most successful of these, proposes that gA depends upon solvent identity, and therefore is a function of solvent composition. In this approach, we express the gA parameter as a function of the cosolvent composition. This is accomplished by treating this variable in a manner analogous to the solvation shell interfacial tension (equation 1.41), writing

$$gA = gA_1f_1 + gA_2f_2 \qquad (4.3)$$

Treatment as before gives

$$gA = gA_1 + gA'\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} \qquad (4.4)$$

where gA_1 is the value of the gA variable in a pure aqueous environment, and $gA' = (gA_2 - gA_1) / 2$ where gA_2 refers to the gA variable in a pure organic cosolvent. All other terms have already been defined.

Multiplying equation (4.4) by equation (1.42) leads to a new expression for the general medium effect:

$$\Delta G^{\circ}_{Gen.Med.} = gA_1\gamma_1 + gA'\gamma_1\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}$$

$$+ gA_1\gamma'\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + gA'\gamma'\left(\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}\right)^2 \qquad (4.5)$$

Substituting equations (4.5) and (1.37) into equation (1.25), we obtain the following expression for the total free energy change of dissolution in an aqueous organic binary cosolvent mixture.

$$\begin{aligned}\Delta G^{\circ}_{\mathrm{Total}} &= \Delta G^{\circ}_{\mathrm{RW}_2} + \Delta G^{\circ}_{\mathrm{Intersolute}} + gA_1\gamma_1 \\ &+ \frac{(gA_1\gamma' - kT\ln K_1)K_1x_1x_2 + (2gA_1\gamma' - kT\ln K_1K_2)K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} \\ &+ gA'\gamma_1\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + gA'\gamma'\left(\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}\right)^2 \qquad (4.6)\end{aligned}$$

In water, where $x_2 = 0$, we write equation (4.6) as

$$\Delta G^{\circ\, x_2=0}_{\mathrm{Total}} = \Delta G^{\circ}_{\mathrm{RW}_2} + \Delta G^{\circ}_{\mathrm{Intersolute}} + gA_1\gamma_1 \qquad (4.7)$$

All the terms on the right hand side of equation (4.7) are constant. In Section 4.3, the method used to calculate the value of gA_1, the gA term in pure water, will be described in detail.

After applying the Leffler-Grunwald delta operator as demonstrated in equation (1.46), we obtain this expression for a two-step solvation process with a composition dependent gA term.

$$\delta_m \Delta G^\circ = \frac{(gA_1\gamma' - kT \ln K_1)K_1x_1x_2 + (2gA_1\gamma' - kT \ln K_1K_2)K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2}$$

$$+ gA'\gamma_1 \frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} + gA'\gamma' \left(\frac{K_1x_1x_2 + 2K_1K_2x_2^2}{x_1^2 + K_1x_1x_2 + K_1K_2x_2^2} \right)^2 \quad (4.9)$$

Provided we have an independent estimate of gA_1, this equation still has only three adjustable parameters, namely the exchange constants, K_1 and K_2, and the new cavity parameter, gA'. Notice that when $gA' = 0$, equation (4.9) is reduced to equation (1.47), our original phenomenological model.

The parameters generated by fitting the naphthalene solubility data to equation (4.9) are presented in Table 4.3, and the curve fits are shown in Figures 4.9 to 4.14. The figures demonstrate the ability of equation (4.9) to adequately fit the naphthalene solubility data. The parameters seem to be within reasonable physical limits, although K_1 for 2-propanol is somewhat higher than expected. Comparisons of the exchange constant values obtained from the original phenomenological model (equation (1.47)) and equation (4.9) can be made by inspecting Table 4.4.

Table 4.3. Solubility Parameters Obtained from Naphthalene Solubility Data and Equation (4.9)

Cosolvent	K_1	K_2	gA'^{a} / Å^2 molecule^{-1}	gA_2^{d} / Å^2 molecule^{-1}	Goodness[b] of Fit Criterion/%
Acetone	5.8 (0.41)[c]	2.5 (0.48)	-6 (2.7)	53	1.5
DMSO	3.7 (0.10)	0.84 (0.088)	-24.0 (8.9)	17	0.58
Ethanol	6.3 (0.56)	4.6 (0.50)	21 (2.0)	107	1.0
2-Propanol	26 (3.7)	9 (0.91)	44 (2.5)	153	0.95
Methanol	2.75 (0.083)	1.31 (0.090)	4 (1.0)	73	0.14
1,2-Propanediol	3.8 (0.12)	2.0 (0.19)	-3.2 (0.76)	59	0.32

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[a] $gA' = (gA_2 - gA_1) / 2$

[b] Curve Fit Criterion = 100 (standard deviation of points about the fitted line divided by the largest absolute value of the ordinate values).

[c] Numbers in parentheses are standard deviations.

[d] $gA_2 = 2gA' + gA_1$

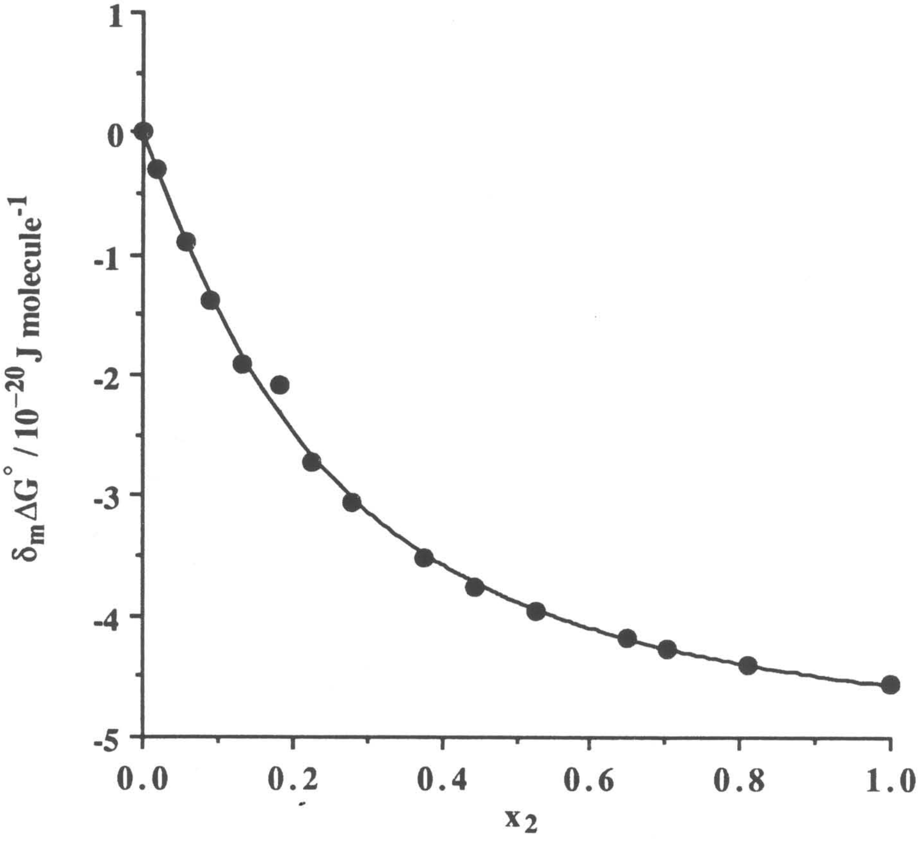

Figure 4.9. Solvent effect on the solubility of naphthalene in water-acetone binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

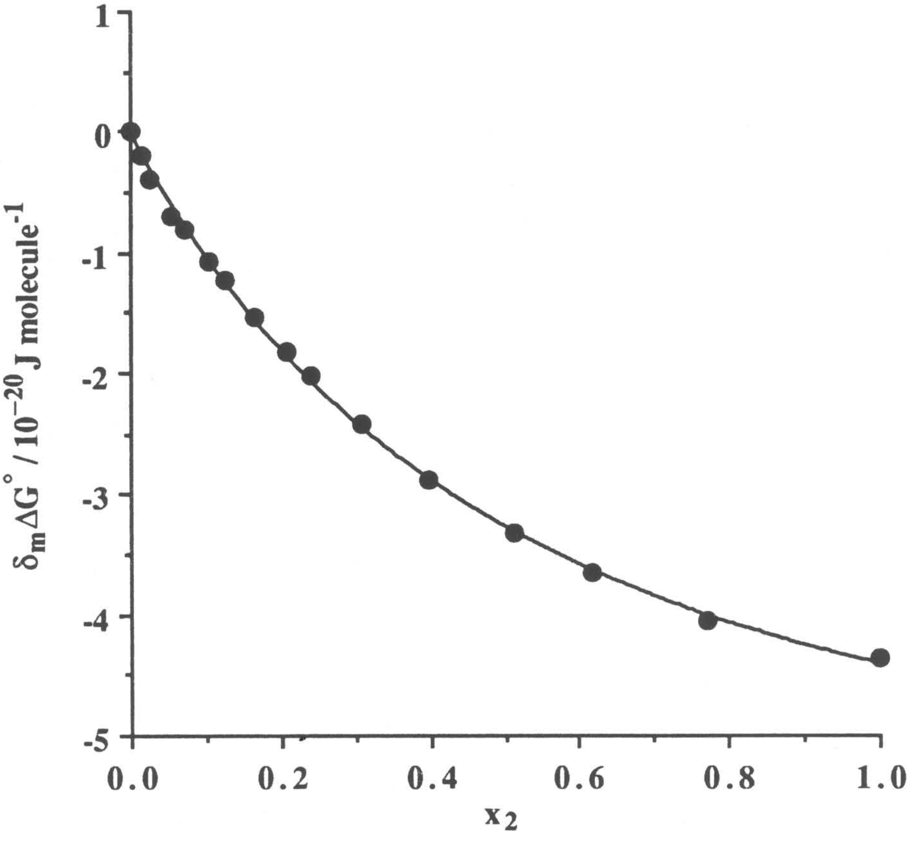

Figure 4.10. Solvent effect on the solubility of naphthalene in water-DMSO binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

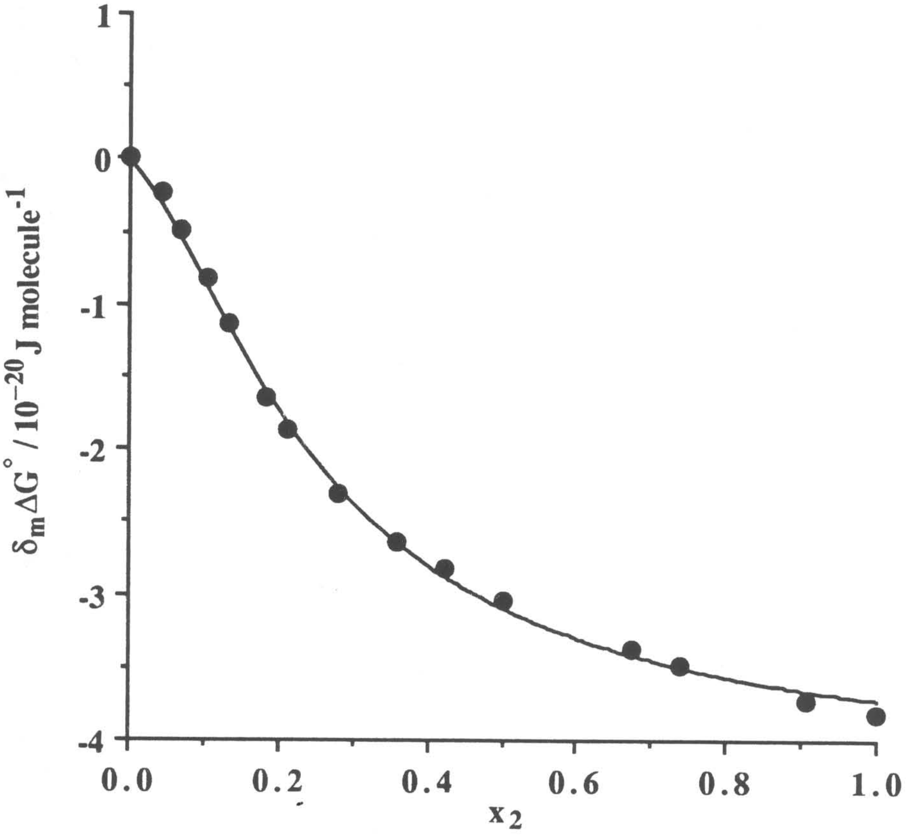

Figure 4.11. Solvent effect on the solubility of naphthalene in water-ethanol binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

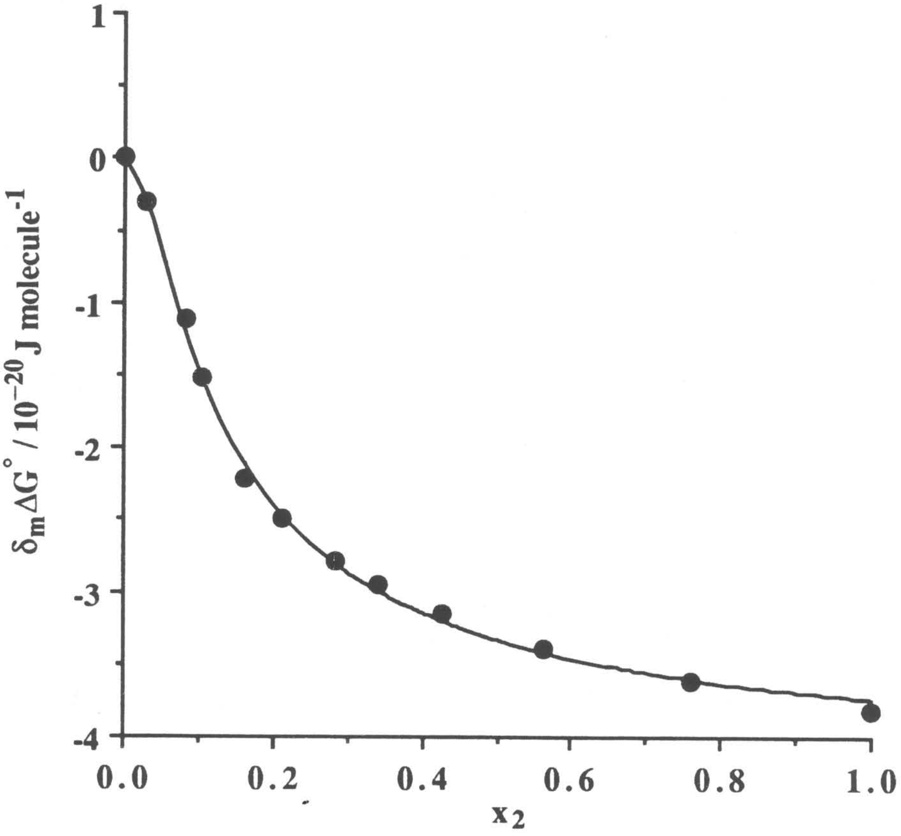

Figure 4.12. Solvent effect on the solubility of naphthalene in water-2-propanol binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

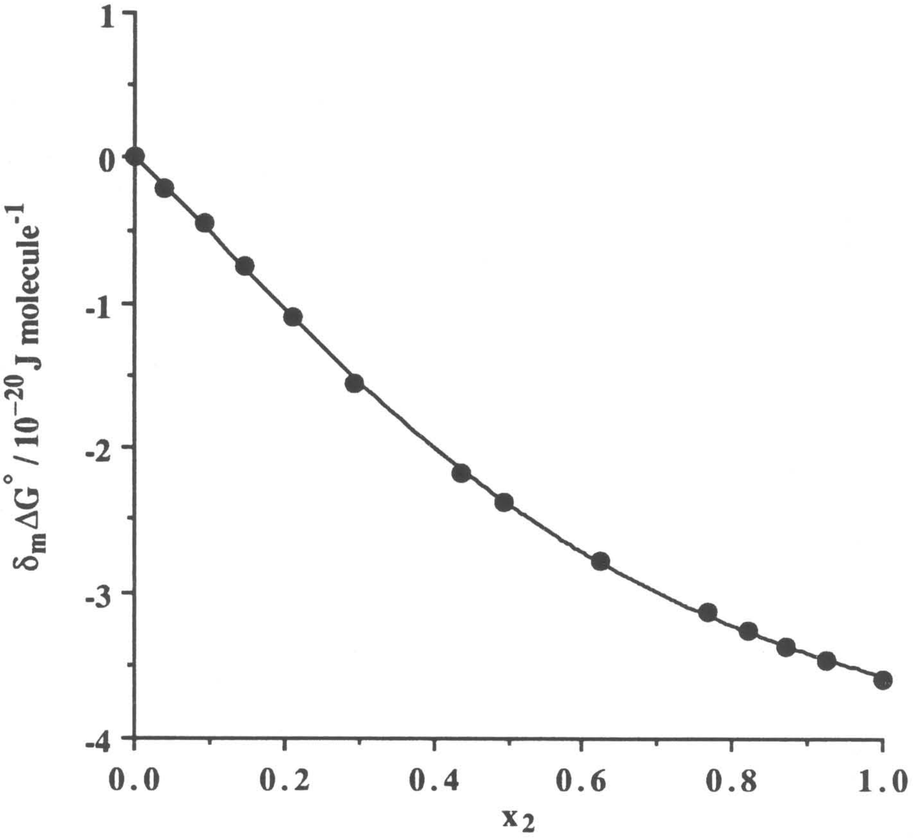

Figure 4.13. Solvent effect on the solubility of naphthalene in water-methanol binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

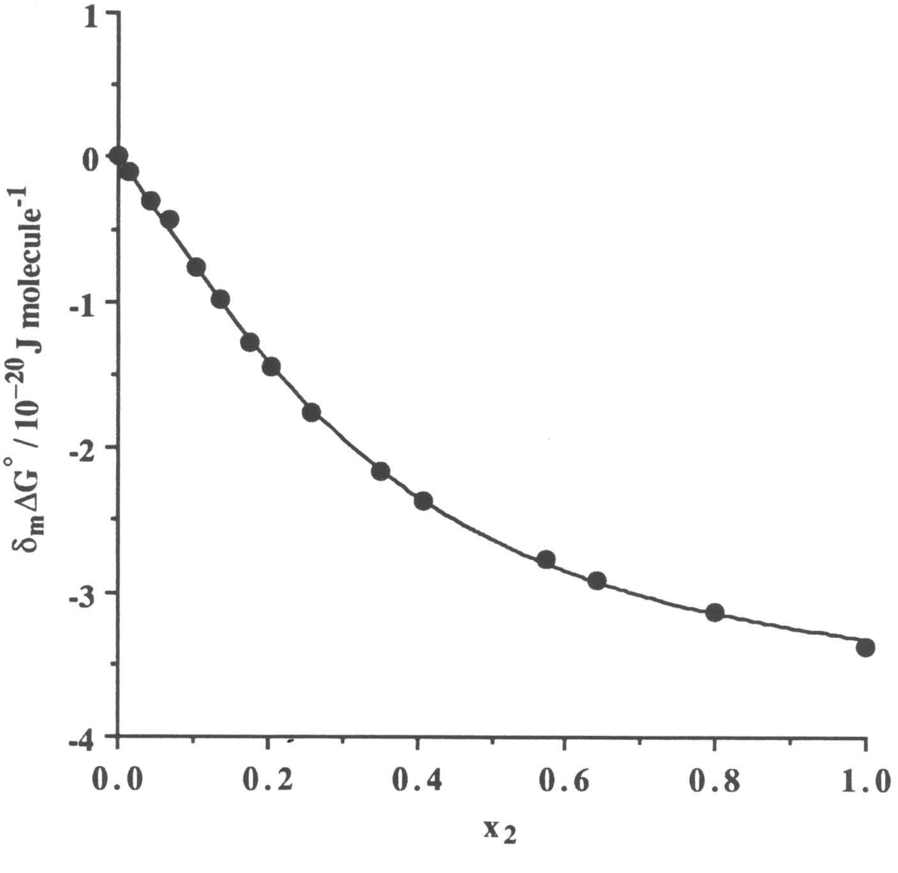

Figure 4.14. Solvent effect on the solubility of naphthalene in water-1,2-propanediol binary cosolvent system showing the experimental data points and the fitted curve. Data were fit to Equation (4.9).

Table 4.4. Comparison of Exchange Constants Obtained from Naphthalene Solubility Studies and Equation (1.47) and Equation (4.9)

Cosolvent	K_1 (equation 1.47)	K_2 (equation 1.47)	K_1 (equation 4.9)	K_2 (equation 4.9)
Acetone	6.5 (0.48)[a]	2.9 (0.37)	5.8 (0.41)	2.5 (0.48)
DMSO	4.8 (0.15)	1.3 (0.10)	3.7 (0.10)	0.84 (0.088)
Ethanol	3.6 (0.35)	3.5 (0.55)	6.3 (0.56)	4.6 (0.05)
2-Propanol	7 (1.1)	6 (1.5)	26 (3.7)	9 (0.91)
Methanol	2.52 (0.071)	1.19 (0.085)	2.75 (0.083)	1.31 (0.090)
1,2-Propanediol	4.0 (0.14)	2.2 (0.17)	3.8 (0.12)	2.0 (0.19)

The gA_2 parameter is calculated by rearranging the definition of gA':

$$gA_2 = gA_1 + 2gA' \qquad (4.10)$$

Hence, the value of gA_2 (and, indeed, all the parameter estimates) is subject to the validity of our estimate of gA_1, presented in Section 4.3. A plot of gA_2 against log P, similar to the plots given in Figures 4.7 and 4.8, is shown in Figure 4.15. A trend may exist, but more data points would be needed to substantiate this. If this is a true correlation between gA_2 and log P, we can infer that gA_2 increases with the

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[a] Numbers in parentheses are standard deviations.

nonpolarity of the cosolvent. The physical significance of gA_2 has yet to be established.

The two-step composition dependent gA parameter model possesses an advantage over the original phenomenological model in that it eliminates the mathematical inconsistency inherent with the cosolvent composition independency of the gA term present in the original model. This model also effectively describes the naphthalene solubility data. The model possesses some disadvantages as well. The actual validity of the parameters is subject to speculation; they may be relegated to the roles of empirical curve fitting parameters. The model also relies on the calculation of the gA_1 constant, and some inaccuracies may be present in this calculation.

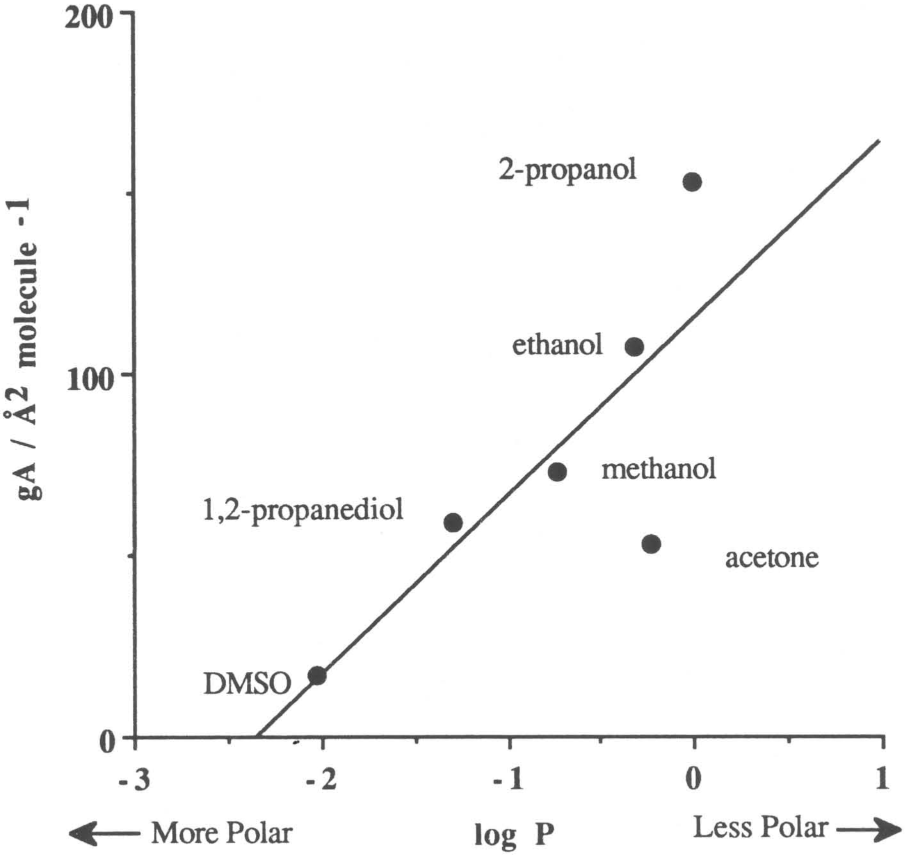

Figure 4.15. gA_2 parameter values from naphthalene solubility against log P. Fits were obtained from equation (4.9).

4.3 *Calculation of a Fixed gA Term in Pure Water (8)*

To obtain an estimate of gA_1, which is needed in equation (4.9), we proceed as follows. The solution free energy change in pure water is written

$$\Delta G^{\circ}_{\text{Total}} = \Delta G^{\circ}_{\text{Intersolute}} + \Delta G^{\circ}_{\text{Gen. Med.}} + \Delta G^{\circ}_{\text{Solvation}} \quad (4.10)$$

We make a key assumption that for naphthalene in pure water, the solvation contribution to $\Delta G^{\circ}_{\text{Total}}$ is negligible relative to the general medium and intersolute contribution to the energy, because naphthalene is very nonpolar and water is highly polar. Thus equation (4.10) becomes,

$$\Delta G^{\circ}_{\text{Total}} = \Delta G^{\circ}_{\text{Intersolute}} + \Delta G^{\circ}_{\text{Gen. Med.}} \quad (4.11)$$

The general medium effect is set equal to $gA\gamma_1$, where γ_1 is the surface tension of water. An estimate of $\Delta G^{\circ}_{\text{Intersolute}}$ is made using the following method. We assume that $\Delta G^{\circ}_{\text{Intersolute}}$ is the energy required to convert the solid crystalline solute to the liquid solute, at the temperature of interest, which is equivalent to assuming that a solute behaves like a liquid (9) . The calculation is from classical thermodynamics (10). At the melting point of the solid, the equilibrium between solid and melt can be described by

$$\Delta G^{\circ}_{\text{Intersolute}} = \Delta H^{\circ}_{\text{fusion}} - T_m \Delta S^{\circ}_{\text{fusion}} = 0 \quad (4.12)$$

If $\Delta H^{\circ}_{fusion}$ and Tm (the melting point) are known, then $\Delta S^{\circ}_{fusion}$ can be calculated. The $\Delta G^{\circ}_{Intersolute}$ at the experimental temperature T is calculated by equation (4.13).

$$\Delta G^{\circ}_{Intersolute} = \Delta H^{\circ}_{fusion} - T\Delta S^{\circ}_{fusion} \qquad (4.13)$$

where the essential approximation is that the heat capacities of the solid and liquid phases are equal. Combining these expressions gives equation (4.14)

$$gA_1 = \frac{\Delta G^{\circ}_{Total} - \left(\Delta H^{\circ}_{fusion} - T\Delta S^{\circ}_{fusion}\right)}{\gamma_1} \qquad (4.14)$$

Table 4.5 contains the enthalpies and entropies of fusion, melting temperatures and the aqueous solubilities of naphthalene, biphenyl, and substituted benzenes. Using the data presented in Table 4.5 and equation (4.14) gA_1 values were calculated and are given in Table 4.6, along with the estimated areas and calculated g values.

The product of molecular-surface area and the curvature correction factor for naphthalene in water was calculated to be 64.6 Å^2 molecule^{-1}; a value of 65 Å^2 molecule^{-1} was used for gA_1 in equation (4.9) The average of the curvature correction factor values is 0.41± (0.03). The essential constancy of g suggests that this calculation is valid. These results encourage further studies to test this equation using available literature data.

Table 4.5. Thermodynamic Values and Aqueous Solubilities of Selected Compounds

Compound	$\Delta H^{\circ}_{fusion}$/ cal mole^{-1}	$\Delta S^{\circ}_{fusion}$/ cal mole^{-1}	Melting Temperature/ K	ΔG°_{Total}/ 10^{-20} J molecule^{-1}
Naphthalene	4536 (11)[a]	12.8 (11)	353.4 (11)	5.131
Biphenyl	4440 (12)	9.10 (12)	488 (12)	5.824 (4)
1,4-DCB[b]	4370 (13)	13.4 (13)	326.1 (13)	4.87 (14)
1,4-DBB[c]	4870 (13)	13.5 (13)	360.3 (13)	5.65 (14)
1,4-DIB[d]	5340 (15)	13.22 (15-16)	404 (16)	6.87 (14)

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[a] Numbers in parentheses indicate the reference source of the data.

[b] 1,4-Dichlorobenzene

[c] 1,4-Dibromobenzene

[d] 1,4-Diiodobenzene

Table 4.6. gA_1 Values for Selected Compounds

Compound	Total Area / Å^2 molecule^{-1}	gA_1 / Å^2 molecule^{-1}	g
Naphthalene	147 (3)[a]	64.6	0.44
Biphenyl	179 (3)[b]	64.4	0.36
1,4-DCB	152 (7)	64.3	0.42
1,4-DBB	172 (3)	70.5	0.41
1,4-DIB	192 (4)	82.2	0.43

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[a] Numbers in parentheses indicate standard deviations.

[b] Reference (4)

4.4 Conclusions

In this investigation, the solubility of naphthalene in six binary aqueous organic cosolvents was examined, and the data were analyzed with the phenomenological model developed in this laboratory. The model effectively described all the solubility data. Greater understanding of the variable parameters in the model was obtained; these parameters are the solvation exchange constants, K_1 and K_2, and the cavity parameter, gA. The exchange constants seem to correlate with the ability of the solution to solvate a naphthalene solute molecule. The correlations were demonstrated by plotting the sum of the natural logarithm of the exchange constants against the logarithm of the oil-water partition coefficients of the cosolvents used in the study. Our principal objective was to investigate the potential cosolvent dependency of the curvature correction factor, the g of the gA parameter. The gA parameter demonstrated a substantial solvent dependency factor. An equilibrium transfer of energy from the gA term to the exchange constants was offered as a possible explanation for this variation, and a correlation between gA and cosolvent polarity seemed to support this idea. As a result of this analysis, a modification of the model was developed to describe the solvent composition dependency gA, and this equation gave good fits to the data. gA values were estimated for individual solvents.

4.5 References

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Appendix A

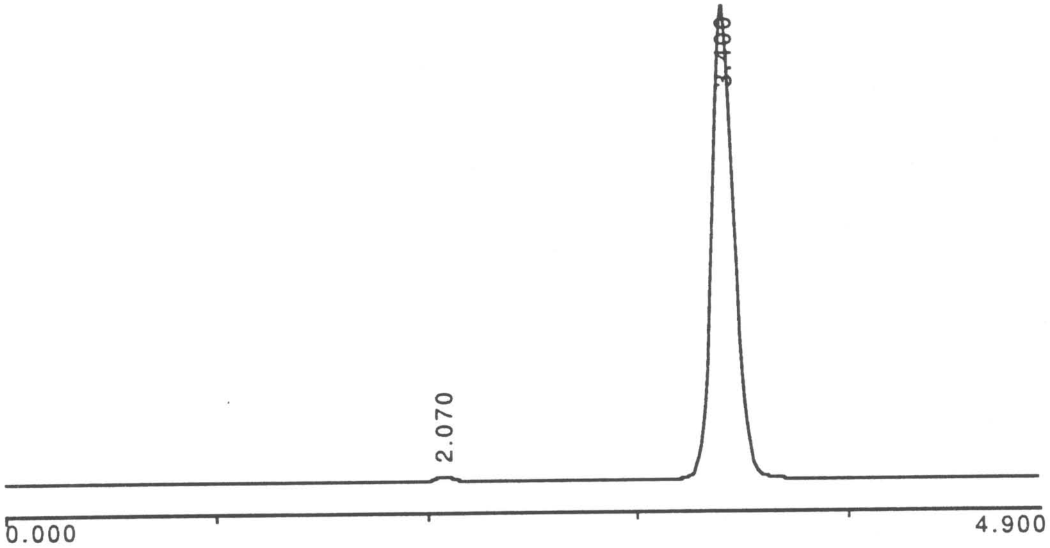
High Performance Liquid Chromatogram

Date: Mon, Jul 12, 1993 12:46
Data: JAY TRIAL-09JUN93-001

Sample: Econosphere, C-8, (150 X 4.6 mm) Cartridge Column
FLOW RATE: 1.0 ml/min
Moblie Phase: MeOH/Water(1.5/1 v/v)Pre-mixed
Injection Volume: 50 microliters
34c-14-14 #2

Method: JAY TRIAL
Inject Vol: 50
Sampling Int: 0.3 Seconds

Chromatogram:



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	2.070	N	5473	29412	1.072
2	3.400	N	368590	2712077	98.928
Total Area				2741489	100.000

Peak No.	Time	Asymmetry	Efficiency (N per column)
1	2.070	1.462	3709
2	3.400	1.263	5293

Figure Appendix A.1. High performance liquid chromatogram. The first peak corresponds to acetone, and the second peak corresponds to naphthalene.

Appendix B

The Solubility of Sucrose in Water-Ethanol Binary Cosolvent Solutions

The ability of the phenomenological model to describe the solubility of polar substances in binary aqueous organic cosolvent solutions was explored. In Table Appendix B.1, literature data from an investigation of sucrose solubility in water-ethanol mixtures are given (1); these data were analyzed with the original phenomenological model, equation (1.47).

Table Appendix B.1 The Solubility of Sucrose in Binary Water-Ethanol Cosolvent Mixtures

Weight of Sucrose / g	Weight of Water / g	Weight of Ethanol / g	Mole Fraction Ethanol (x_2)	ΔG°_{u} / 10^{-20}J molecule^{-1}
87.50	45.10	0	0	0.9422
81.50	44.82	3.91	0.0330	0.9777
74.50	43.83	8.52	0.0745	1.0167
67.90	41.87	13.74	0.1092	1.0514
58.00	40.38	20.24	0.1639	1.1179
47.10	38.02	28.13	0.2244	1.2015
33.90	34.47	37.64	0.2992	1.3277
18.80	29.57	49.28	0.3946	1.5522
6.60	21.94	61.15	0.5215	1.9369
0.90	12.83	71.18	0.6845	2.6759
0.36	3.28	77.39	0.9022	2.9623

The resultant parameter values from the fit to this data are given in Table Appendix B.2.

Table Appendix B.2. Parameter Values from Sucrose Solubility Studies in Water-Ethanol Mixtures.

K_1	K_2	gA / $Å^2$ $molecule^{-1}$	Goodness of Fit Criterion[a] / %
0.3 (0.12)	3.0 (1.2)	-0.0401 (0.00083)	1.2

The fit to the data is displayed in Figure Appendix B.1. The fit to the experimental data is quite good, and the K_1 and K_2 values seem reasonable. The negative gA term may be indicating that this quantity is merely an empirical curve fitting parameter, but more studies are required before any definitive conclusions can be drawn.

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[a] Curve Fit Criterion = 100 (Standard deviation of points about the fitted line divided by the largest absolute value of the ordinate values)

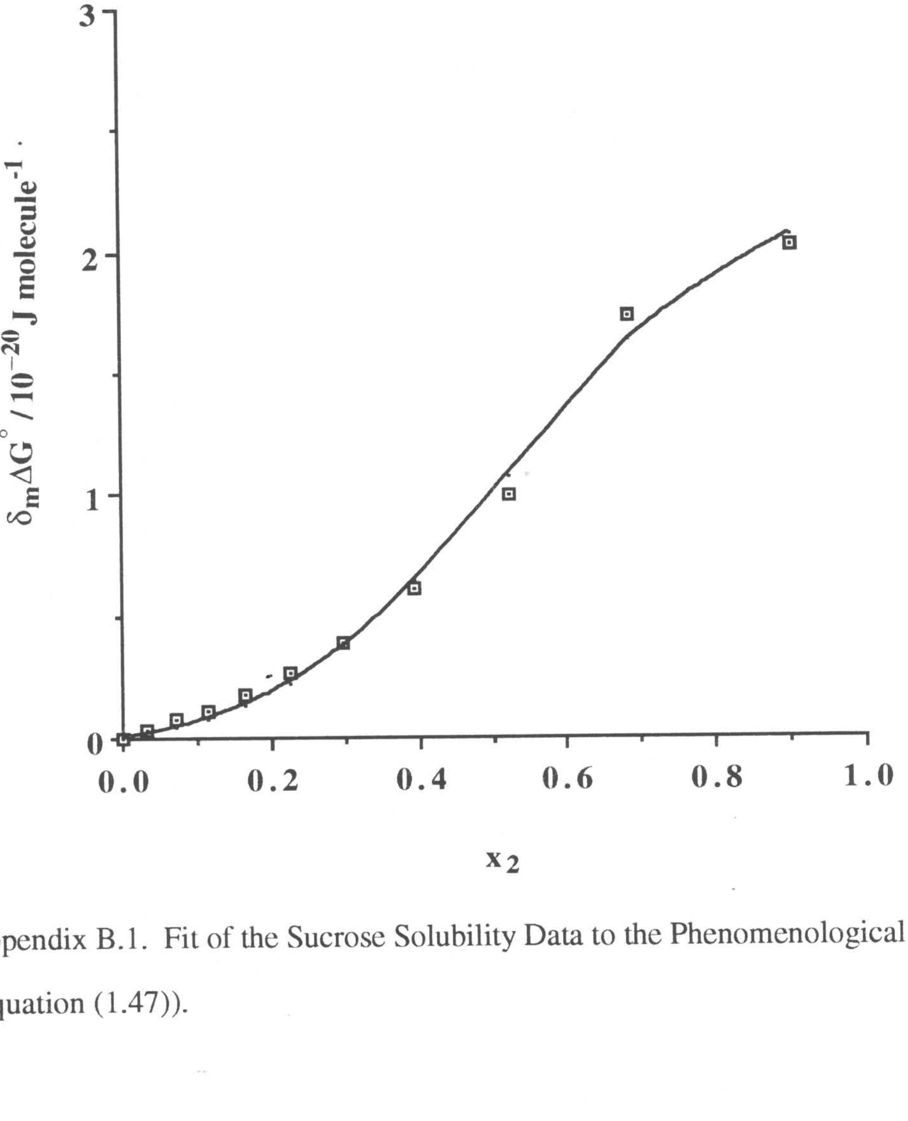

Figure Appendix B.1. Fit of the Sucrose Solubility Data to the Phenomenological Model (equation (1.47)).

Appendix B Reference

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Appendix C

Solubility of 1,4-Diphenylbenzene in Water-Methanol Cosolvent Mixtures

A solubility study of 1,4-diphenylbenzene in mixed methanol-water cosolvent systems was conducted. The solubility in solutions of organic mole fraction concentrations below 0.2112 could not be determined owing to the very low solubility. Since the solubility in water was not measured, the data were not analyzed. The solubility data from these studies is presented in Table Appendix C.1.

Table Appendix C.1. Solubility Data for 1,4-Diphenylbenzene in Water -Methanol Cosolvent Mixtures

Mole Fraction Methanol (x_2)	1,4-diphenylbenzene Concentration / M 10^{-5}	Density of Solution / g ml^{-1}	Mole fraction 1,4-diphenylbenzene (x_3) / 10^{-9}
0.2112	0.02 (0.011)[a]	0.9411 (0.00073)	5.2
0.2417	0.049 (0.0091)	0.933 (0.0014)	11.3
0.2728	0.14 (0.016)	0.926 (0.0020)	33.1
0.4382	1.63 (0.014)	0.8906 (0.00092)	443
0.5046	3.3 (0.12)	0.871 (0.0016)	948
0.6131	9.94 (0.086)	0.850 (0.0021)	3110
0.7384	27.8 (0.74)	0.825 (0.0011)	9550
0.8705	66 (1.4)	0.8043 (0.00094)	24700
0.9229	86.9 (0.41)	0.795 (0.0017)	33800
1.0	124 (3.6)	0.772 (0.0051)	51400

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[a] Numbers in parentheses are standard deviations.