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Solubility of aromatic compounds in mixed solvents

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The University of Arizona, 1988

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**SOLUBILITY OF AROMATIC COMPOUNDS
IN MIXED SOLVENTS**

by

Kenneth Robert Morris

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PHARMACEUTICAL SCIENCES

**In partial Fulfillment of the Requirements
For the Degree of**

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

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THE UNIVERSITY OF ARIZONA
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SIGNED: Bennett D. Morris

DEDICATION

This work is dedicated to my wife, Maggie, who had faith in me and my abilities when I had none. Also to my family, Berk, Phyllis and Dave for their support, concern and patience over these 37 years.

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ABSTRACT

The solubilities of benzene, naphthalene and anthracene were measured in five binary solvent systems. These systems consisted of water and one of the following water miscible organic solvents: acetone, acetonitrile, methanol, ethanol, and isopropanol. The measurements were made at intervals of 0.1 volume fractions of the organic cosolvent. Solubility data were also collected for the above solutes in mixed solvent systems containing three and five cosolvents. In addition, the solubilities of six other aromatic solutes were measured in the binary solvent systems of methanol/water and acetone/water.

The data was used to test the log-linear solubility model of Yalkowsky (1981). The model predicts a linear relationship between the solubility of a solute in a binary solvent system (S_m) and the volume fraction of cosolvent present (f_c).

$$\log S_m = \sigma f_c + \log S_w$$

Where S_w is the solubility of the solute in water and σ is the proportionality constant and slope of the curve. The model is easily extended to multiple mixed solvents by combining the σ values from the binary solvent systems.

$$\log (S_m/S_w) = \sum_i (\sigma_i f_i)$$

A method was developed to estimate σ in a given binary solvent system from the octanol-water partition coefficient of the solute. Combining this method with the generalized solubility equation of Yalkowsky to estimate S_w , allows a priori estimates of solubility in mixed solvents.

Maximum deviations in the binary solvent systems studied were related to maxima in excess density. In the alcoholic binary solvent systems the minima were related to minima in the heats of mixing of the two cosolvents.

The herbicide atrazine deviated dramatically from the model. The system was examined for possible changes in the crystal structure of atrazine. It was found that some crystal modification occurred in the presence of mixed solvents. The rate of the change appears to be dependant on the concentration of the cosolvent. A change or modification in the crystal violates one of the basic assumptions of the log-linear model. The assumption is that the crystal contributes equally to the solubility behavior irrespective of the solvent system. It was determined that atrazine undergoes a polymorphic transition in the systems studied. It is postulated that this polymorphism is responsible for the anomolous solubility behavior observed for atrazine.

CHAPTER 1

INTRODUCTION

Estimating the solubility of hydrophobic organic compounds in mixed solvent systems has become increasingly important in recent years. This is a result of the increased awareness of the importance of solubility in many environmental fate processes. Because of the growing number of systems for which solubilities must be known, measuring every value is highly impractical if not impossible.

Existing theories address either water solubility or solubility in solvents with a low degree of self-association. These approaches are useful for extrapolation to mixed solvent systems only when the solvent and co-solvent are very similar. None of these approaches accurately predicts the solubility of a solute in water-cosolvent systems (Abramowitz 1986).

Yalkowsky et al. (1984) have demonstrated a log-linear trend in the solubility vs. volume fraction cosolvent. Although this relationship holds for a range of solvents and solutes, a degree of deviation was noted in some cases. This study was designed to further develop and test the generality of the log-linear model and develop a method of estimating mixed solvent solubility based on the model.

Environmental Significance

Pollutants in mixed solvent industrial effluent may remain in solution or may precipitate on contact with water. Our ability to predict a system's behavior is dependent on our ability to estimate the mixed solvent solubility. Similarly, predicting bio-concentration and toxicity in affected aqueous eco-systems requires an accurate assessment of the exposure concentration (i.e. solubility of the pollutant in the solution phase).

The sorption of organic pollutants from mixed solvent systems to sorbate is "driven" by the activity coefficient in the solution phase (Karickhoff 1984). Sorption and mixed solvent solubility are inversely related. Rao et al. (1985) have established the inverse relationship between the log of the sorption coefficient and the fraction cosolvent. This is important in modeling the movement of toxic wastes from landfills and in the development of cleanup procedures for spills and landfills.

The ability to estimate solution phase activity, and thus sorption, is vital considering the large number of pollutants and systems involved and the impracticality of collecting the necessary data on each pollutant in each system. In most cases, the error incurred with the log-linear model is far less than the error in the transport model that it services.

Sorption and Solubility

The solubility of a crystalline solute is an equilibrium process between two phases, the excess solute and the solution phase. The equilibrium constant (K) for such a process is the ratio of the mole fraction concentration of the solute in the solution phase (X_m) to that in the crystal (X_{cr}) so $K = X_m/X_{cr}$. If the crystal is not penetrated by the liquid phase, $X_{cr} = 1$ and $K = X_m$.

With these assumptions, mole fraction solubility (S) may be expressed in terms of the equilibrium constant.

$$S = K = X_m/X_{cr} \quad (1.1)$$

Analogously, the sorption coefficient (K_s) may be represented by

$$K_s = X_s/X_m \quad (1.2)$$

where X_s is the mole fraction concentration in the sorbed phase.

Recalling that activity is the activity coefficient (γ) times the concentration, and that at equilibrium all phases in contact have equal activities, K_s and S can be expressed in terms of their activity coefficients as

$$K_s = \gamma_m/\gamma_s \quad (1.3)$$

and

$$S = \gamma_{cr}/\gamma_m \quad (1.4).$$

Solving equations (1.3) and (1.4) for γ_m and equating them gives rise to

$$K_S = \frac{B}{S} \quad (1.5)$$

where B is a constant which is equal to (γ_{Cr}/γ_S) .

Equation (1.5) predicts an inverse relationship between solubility and sorption coefficient. Rao et al.(1985) have verified this inverse relationship for several pollutants using standard HPLC and soil columns. Rubino (1984) has demonstrated the log-linear relationship between solute solubility and fraction cosolvent. Combining the two models should allow the prediction of mixed solvent sorption from predicted mixed solvent solubilities. To test the models, both solubility and sorption data on the same systems are required.

Using a simple mass balance relationship, Karickhoff (1979) developed an expression relating the fraction of a compound remaining in solution when equilibrated with sediments. The equilibrium concentration of a solute distributed between a solution phase (C_S) and a sorbed phase (C_P) may be represented as

$$C_S \xrightleftharpoons{K} C_P \quad (1.6).$$

Where K is the equilibrium constant or partition coefficient and C is the concentration in the respective phase.

Defining total concentration (C_T) as the mass of solute per unit volume of suspension, ϕ as the volume of solution per unit volume of suspension, and π as the mass of sediment per unit volume of suspension, leads to the mass balance expression

$$C_T = \phi C_S + \pi C_P \quad (1.7).$$

Substituting for C_P from equation (1.6) gives

$$C_T = \phi C_S + \pi K C_S \quad (1.8)$$

or,

$$f_S = \frac{\phi C_S}{C_T} = \frac{1}{1 + \pi' K} \quad (1.9)$$

where $\pi' = \pi/\phi$ which is the sorbent/solution ratio, and f_S is the fraction of the total solute in the solution phase.

Starting with known values of C_T , K (which may be estimated), and π' , and using a prediction for solution phase concentration, equation (1.9) would allow comparison of estimated f_S values against observed values without measuring the sorbed phase.

Pharmaceutical Significance

Solubility of a drug is an important factor in defining dosage forms and routes of administration (Flynn, 1976). Sparsely soluble drugs may dissolve so slowly that the gastrointestinal residence time of an oral dosage form is too short for complete absorption. Drugs that degrade in

solution may be stable in the solid form and thus lend themselves to suspension type formulations (Flynn, 1976).

Many drugs must be formulated as parenteral solutions at some point in their development. The parenteral formulation may be the final product or the formulation needed in the preliminary animal studies. Pure aqueous formulations are desirable because water is a biologically 'safe' solvent. When a drug is sparsely soluble in water, an alternate solvent system may be chosen to increase its solubility.

There are several reasons to favor a predictive approach over the traditional trial and error means of finding an appropriate mixed solvent system. Due to the large number of drug candidates examined every year by a company, trial and error may be too costly or even impossible given time constraints. The ability to estimate a drug's solubility from semi-empirical relationships could greatly reduce time and expense involved in formulation development.

Work by Rubino and Yalkowsky (1984) points to the water-cosolvent interaction as the major contributor to deviation from log-linear solubility behavior. Because there are relatively few nontoxic cosolvents used in the industry, the characterization of the viable systems should be easy relative to the environmental systems. Drug molecules are often more complex than pollutant molecules.

Toxicity is a major concern to the pharmaceutical formulator. The log-linear relationship predicts that a linear increase in the volume fraction of cosolvent results in an exponential increase in solubility. This indicates that an increase in cosolvent presence might actually reduce the amount delivered and, thus, reduce any undesirable effects of the cosolvent. For example, if the required dose of a drug is 10 mg and its solubility in a mixed solvent system of 20% propylene glycol(PG) and 80% water is 1 mg/ml, 10 ml of the mixture would be required. This means 2 ml of PG would be injected with the drug. If increasing the percentage of PG to 40% results in a solubility of 10 mg/ml, only 1 ml of solution and, therefore, only 0.2 mls of the PG would be injected. Even though the percentage of PG was doubled the amount injected was reduced by a factor of 10.

CHAPTER 2

THEORETICAL BACKGROUND

Classical thermodynamics deals with quantifying the macroscopic manifestations of intermolecular forces. That is to say, the measurable parameters of thermodynamics (pressure, volume, temperature, etc.) reflect the degree to which the molecules are associated. Thermodynamics is successful in predicting the properties of near "ideal" (see below) liquids and mixtures of liquids (Prausnitz, 1986). It is far less useful in predicting properties of mixtures of non-ideal liquids. Extra-thermodynamic relationships are often employed in such systems (Leffler and Grunwald 1963). These "local" relationships between thermodynamic quantities are not part of the formal structure of thermodynamics but do share similar approaches (Leffler and Grunwald 1963). The similarity is that the macroscopic behavior is explained independent of microscopic rationale. Linear free energy relationships and quantitative structure activity relationships are of this type.

Intermolecular Forces

Intermolecular forces are ultimately based on Coulomb's Law of charge interaction (Moore, 1972).

$$F = \frac{e_i e_j}{r^2} \quad (2.1)$$

Where F is the force between two point charges with magnitudes of e_i and e_j , respectively, separated in vacuo by distance r . By this law, like charges repel and unlike attract each other, attractive forces are then negative. All electrostatic forces may be represented as the gradient of the potential energy. The potential energy (U) between two spherical molecules is a function of r , and is related to the force by

$$U = \int F(r) dr \quad (2.2).$$

The negative of the potential energy is the work required to separate the molecules from r to an infinite distance.

1) Ionic Interactions. For two ions the integrated form of equation (2.1) is

$$U_{ij} = \frac{e_i e_j}{r} + C \quad (2.3)$$

where C is a constant of integration that goes to zero at infinite separation. Since e is a multiple of the unit charge (ϵ) for ions, the potential can be expressed in terms of ionic valencies (z), dielectric constant of the medium (D), and ϵ which is $4.8024 \text{ E-}10 \text{ (erg cm)}^{1/2}$.

$$U_{ij} = \frac{z_i z_j \epsilon^2}{Dr} \quad (2.4)$$

D is a macroscopic parameter which reflects the medium's tendency to conduct electricity relative to a vacuum. D is only useful if r is large compared to molecular dimensions so the medium can be treated as uniform. If the potential is measured in a vacuum D = 1.

This is a long-range attraction since the force falls off with r^{-2} and the potential as r^{-1} . The longer the range of the attraction the less temperature sensitivity is expected. This is because the increase in kinetic energy experienced by a molecule is less likely to take it out of the range of interaction.

2) Dipolar Interaction. Molecules with no net electric charge may still give rise to electrostatic forces. In these molecules the center of charges of opposite sign and equal magnitude are separated by a distance (r'), giving rise to a dipole moment (μ).

$$\mu = er' \quad (2.5)$$

The potential energy between two such dipolar molecules is a function of the distance between the dipole centers and the orientation of the dipoles relative to each other. Temperature is included in the expression for U since the orientation is temperature sensitive. Keesom (1912) in a first attempt to explain van der Waals forces (forces

between uncharged molecules) derived equation (2.6) from statistical analysis.

$$U_{ij} = - \frac{2\mu_i^2 \mu_j^2}{3r^6 kT} \quad (2.6)$$

Where k is Boltzmann's constant and T is temperature.

Keesom found that orientations resulting in negative potential energies were the most probable. This did not fully explain van der Waals forces since nonpolar molecules also attract, but it did do well for interaction between permanent dipoles. The potential drops proportionally with r^{-6} but is still considered a long range force relative to those of repulsion (see below).

Equation (2.6) can be expressed as the square root of the product of the potentials produced in pure i and j .

$$U_{ij} = (U_{ii}U_{jj})^{1/2} \quad (2.6a)$$

Dipolar interactions are an example of a property whose energy of interaction follows this geometric mean "rule" that is often used in solubility theories (Prausnitz, 1985).

Some molecules have quadrupole in addition to dipole moments. These potentials vary as r^{-10} or more, however, and have far less effect on thermodynamic properties.

3) Induced Dipolar Interaction. Molecules with no permanent dipole moment may exhibit one when subjected to an electric field. The electron cloud is distorted from its usual shape causing a temporary or "induced" dipole. The

induced dipole moment (μ^i) is proportional to the field strength (E), and is related by a constant called the polarizability (α).

$$\mu^i = -\alpha E \quad (2.7)$$

The polarizability is a measure of how easily a molecule's electrons are displaced by an electric field.

When the electric field is created by a polar molecule, the resultant force is necessarily attractive (Prausnitz, 1986). Debye's equation for the average potential energy of induction is

$$U_{ij} = - \frac{\alpha_i \mu_j^2 + \alpha_j \mu_i^2}{r^6} \quad (2.8)$$

This general form of the equation takes into account the induction of a dipole in another polar molecule. The magnitude of an induced dipole is, however, much less than the permanent. The induced dipole effect is also small relative to observed potentials (Moore, 1972) and still does not explain attractive forces for inert gases. There is no dependence on temperature since a dipole may be induced in any direction if α is isotropic, and once again the potential is long-range varying with r^{-6} . If α is anisotropic appropriate corrections must be included. Equation (2.8) actually represents the sum of the interaction energies each species induces in the other.

That is, the sum of the interaction energy of the dipole of i on j and visa versa.

4) Dispersion Interactions. The attractive potential between nonpolar molecules was explained by London in 1930 . He developed a picture of nonpolar molecules as having some electronic orientation if viewed on a small enough time scale. This sets up an electric field that can, as seen above, induce a dipole. This was named the dispersion force because he derived it from the quantum mechanical consideration of dispersion of electromagnetic radiation in matter (Joos, 1932). It is also called the induced dipole-induced dipole force.

The potential may be expressed in terms of the characteristic electronic frequency of a molecule in its unexcited state (ν_0).

$$U_{ii} = - \frac{3h\nu_0\alpha_i^2}{4r^6} \quad (2.9)$$

Where h is Plank's constant. Since $\nu_0 \approx I/h$, where I is the first ionization potential of the molecule, equation (2.9) can be approximated in a more useful form.

$$U_{ii} = - \frac{3I_1\alpha_i^2}{4r^6} \quad (2.9a)$$

Equation (2.9a) says that the potential is independent of temperature and varies as r^{-6} . The equation also shows that the variation is proportional to the square of the

polarizability while only dependent upon the first power of ionization potential. Since ionization potentials do not vary greatly between compounds, equation (2.9) can be approximated for two single species (ii,jj) and a mixture of the two (ij).

$$U_{ii} = k \frac{\alpha_i^2}{r^6} \quad (2.10)$$

and

$$U_{jj} = k \frac{\alpha_j^2}{r^6} \quad (2.11)$$

and

$$U_{ij} = k \frac{\alpha_i \alpha_j}{r^6} \quad (2.12)$$

From above it follows that k should not vary greatly between compounds so the potential may be approximated as

$$U_{ij} = (U_{ii}U_{jj})^{1/2} \quad (2.13).$$

Equation (2.13) is another form of the geometric mean rule used in liquid solution theories such as regular solution theory (Hildebrand, 1962). In the absence of other van der Waals forces and hydrogen bonding, the equation describes the dispersive component of the interaction.

Dispersion forces contribute very significantly even to the energy of very polar molecules and mixtures. For example, 27% of the intermolecular force is dispersion in

pure acetone and 20% in a mixture of acetone and water. In the same systems induction accounts for only 6% and 5% respectively.

Dispersion, dipole-dipole and dipole-induced dipole are generally referred to as van der Waals forces. Of these, the two most important (dipolar and dispersion forces) obey the geometric mean rule.

5) Repulsion. Overlap of the electron densities of interacting molecules results in a repulsive force, unless the molecules can form a bond (Murrell, 1982). This may be seen qualitatively as electrons with the same spin trying to occupy the same space, which violates Pauli's exclusion principle. Quantum mechanics has produced expressions to quantify this overlap in terms of the overlap of the wave functions of the molecules. The expression predicts an exponential decay of the potential with intermolecular distance with fitted constants. It is usually more convenient to represent the repulsive energy as a simple inverse power law.

$$U = \frac{A}{r^n} \quad (2.14)$$

Where A is a constant and n ranges from 8 to 16.

Semi-empirical Potential Determination

The total potential energy may be represented as a sum of the attractive and repulsive energies.

$$U_{\text{total}} = U_{\text{repulsive}} + U_{\text{attractive}} \quad (2.15)$$

Mie (Murrell, 1982) proposed the following equation.

$$U = \frac{A}{r^n} - \frac{B}{r^m} \quad (2.16)$$

Where $n > m$ because the repulsive forces are much shorter range than the attractive. For non-polar spherically symmetrical isolated molecules, Lennard and Jones let $m=6$ since the van der Waals forces dominate the interaction. There is, however, no theoretical bases for n . They set $n=12$ to satisfy the relationship mentioned above between n and m and to facilitate calculations. Making these substitutions in equation (2.16) and rearranging assuming there is an r at which U is at a minimum gives

$$U = -4U_{\text{min}} \left[\frac{\sigma^{12}}{r} - \frac{\sigma^6}{r} \right] \quad (2.17)$$

where σ is the value of r when $U=0$. For a general Mie potential $\sigma = (6/n)^{1/(n-6)} r_{\text{min}}$. U_{min} , σ , and n can be obtained experimentally from properties of the system and the second virial coefficient (Prausnitz, 1986). Equation (2.17) is called the Lennard-Jones potential or the 6-12 potential and is one in the family of Mie potentials. This relationship works well for inert gases under normal conditions, but not for liquids.

There have been attempts to extend the Mie two body type potential to condensed phases. It must be assumed that pair wise interactions are additive and higher order interactions may be ignored. Representing number of nearest neighbors as z , the number of molecules as N and treating interaction with other than nearest neighbors with numerical constants s_1 results in equation (2.18).

$$U = 0.5Nz \left[\frac{s_n^A}{r^n} - \frac{s_m^B}{r^m} \right] \quad (2.18)$$

If the condensed phase is a crystal, the s terms can be determined from lattice geometry. Liquids have no set geometry and do not lend themselves to this type of analysis.

Hydrogen Bonding

When hydrogen is bonded to a sufficiently electronegative atom (A) a third electronegative atom (B) can form a hydrogen bond with hydrogen. This does not violate hydrogen's mono-valent state as the hydrogen bond is not a covalent bond. The hydrogen remains closer to the atom with which it is covalently bonded although the bond becomes more polar (Prausnitz, 1986). This may be represented schematically as



Hydrogen bonding may result in polymer type structures in liquids (Franks, 1966) or open crystals such as ice. Bond strength is the main difference between hydrogen bonds

and covalent bonds. Typical hydrogen bonds strengths are approximately an order of magnitude weaker than covalent bonds. The range is ≈ 8 to 40 kJ/mol for hydrogen bonds and ≈ 200 to 400 for covalent bonds.

It is the hydrogen bond's intermediate strength that makes it so important. Nowhere is this more evident than in liquids. Water's high dielectric constant, high boiling point, density maximum and its high solvating power are all due to hydrogen bonding. When it is present, hydrogen bonding is the most important factor controlling the solubility of non-electrolytes in water and organic solvents.

Classical Thermodynamic Treatments

Treating intermolecular forces at the level discussed above is useful in characterizing only very simple systems. The pair-wise potentials are typically coupled with statistical considerations to produce an expression for free energy. This is used to derive an equation of state and then physical properties. Predicting the physical properties of solutions further complicates the issue. It is not, however, the statistical treatment of liquids that causes problems.

The statistical treatment of liquids requires a model of its structure. Although many models have been proposed (Franks, 1966), none works for all liquids. Treating the

liquid as a lattice works if the liquid structure is dominated by van der Waals forces. Even properties of mixtures of different sizes of molecules (eg. ethylene in polyethylene), can be described by the Flory-Huggins relationship which is based on a lattice model. Such models fail when hydrogen bonding controls the structure and, therefore, the entropy of mixing. Radial distribution and interstitial models suffer equally frustrating limitations (Hildebrand, 1962).

Classical thermodynamics has been slightly more successful in addressing the problem. This is due to the semi-empirical nature of the thermodynamic approaches. When considering solubility, classical and extra thermodynamics are the only viable choices. As with gases, an "ideal" behavior is described and from this hypothetical reference point real relationships are inferred.

Ideal Solutions

In an ideal solution all the components experience uniform intermolecular forces. That is, in a mixture of molecules of A and B the intermolecular forces are the same between A and B as they are in pure A or pure B. This means that the heat of mixing is zero and the entropy of mixing is proportional only to the mole fraction of the components. The ideal solubility of both liquids and solids in liquids are discussed below.

Solubility of Liquids in Liquids. When both components of a binary solution follow Raoult's law, the mixture is said to be ideal. Raoult's law states that the mole fraction of a solute (X_1) in a solvent is equal to the ratio of its partial vapor pressure above the solution (P_i) to its pure vapor pressure (P_i^0).

$$X_1 = P_i/P_i^0 \quad (2.19)$$

Partial vapor pressure is a measure of the escaping tendency of the component. The escaping tendency is, in turn, a reflection of the degree of association of the solution. By studying the change of P_i with temperature and pressure, many physical properties of the solution may be determined (Moore, 1972).

Equilibrium between phases may be defined as the point of equal chemical potential between two phases. Chemical potential (u) is the partial molar Gibbs free energy (G) at constant temperature and pressure. Gibbs free energy may be defined as; $G = H - TS$.

$$u_1 = (\delta G/\delta n)_{PT} \quad (2.20)$$

By combining the the expression for chemical potential (u_1) of a component in an ideal solution with Raoult's law, the chemical potential may be expressed in terms of the mole fraction instead of the partial pressure.

$$u_1 = u_1^0 + RT \ln X_1 \quad (2.21)$$

Where u_i^0 is the chemical potential of pure liquid i in equilibrium with its vapor, R is the gas constant and T is the temperature in degrees Kelvin.

Ideal liquids are miscible in all proportions. In addition the volume change and the enthalpy of mixing are zero. The ideal entropy of mixing (ΔS_m) is given by

$$\Delta S_m = n_A \Delta S_A + n_B \Delta S_B \quad (2.22)$$

where n_A and n_B are the number of moles of A and B respectively. Expressing the amounts as mole fraction (X) and substituting $\Delta S_i = -R \ln X_i$ for each component gives the general equation.

$$\Delta S_m = -R \sum_i (X_i \ln X_i) \quad (2.23)$$

If the two components are of equal size and interactions are controlled entirely by dispersion forces, the solution will have near ideal behavior.

Solubility of Solids in Liquids. The ideal solubility of solids may be factored into the processes of melting the solid and cooling it to the temperature of interest, and then mixing the sub-cooled liquid (SCL) with the solvent (Flynn, 1979). The mixing of the two liquids then follows the relationships for ideal liquid solutions. The crystal energy of the solid is handled separately. Equilibrium occurs when the the free energy of the total process is at a minimum. The melting process is endothermic and contributes positively to ΔG , while the mixing is exothermic and tends

to decrease ΔG . At minimum ΔG these forces must balance.

The variation of the ideal mole fraction solubility with temperature is easily derived from first thermodynamic principles. Using the criteria for equilibrium above and equation (2.21), the chemical potential for a solid in equilibrium with a liquid is given by

$$u_i^s = u_i^l = u_i^{ol} + RT \ln X_i \quad (2.24).$$

Where u_i^s and u_i^l are the chemical potentials for the solid and liquid, respectively. This may be written as

$$\ln X_i = \frac{G_i^{os} - G_i^{ol}}{RT} \quad (2.25).$$

Maxwell's relations show that $(\delta G/\delta T)_p = -S$ and $\Delta G = \Delta H - T\Delta S$ is a definition Gibbs' free energy. From these a form of the Gibbs-Helmholtz equation arises.

$$\frac{\delta(\Delta G/T)}{\delta T} = -\frac{\Delta H}{T^2} \quad (2.26)$$

Differentiating equation (2.25) with respect to T and using the above definition for G gives the following.

$$\frac{d \ln X_i}{dT} = \frac{H_i^{os} - H_i^{ol}}{RT^2} = \frac{\Delta H_f}{RT^2} \quad (2.27)$$

Where ΔH_f is the enthalpy of fusion which is assumed to be independent of changes in temperature. A constant ΔH_f implies that the change in heat capacity between the solid

and the liquid is zero ($\Delta C_p^{S-1} = 0$). Integrating equation (2.27) from the melting point of the solid to the temperature of interest gives

$$\ln X_i = \Delta H_f \int_{T_m}^T RT^{-2} dT = \frac{\Delta H_f}{R} \left[\frac{1}{T_m} - \frac{1}{T} \right] \quad (2.28)$$

This is the expression for mole fraction solubility of a solid in an ideal solution. From this expression it follows that the solubility is independent of the solvent and depends only on the crystal energy. Using the relationship between entropy and enthalpy at constant pressure ($\Delta S = \Delta H/T$), equation (2.28) may be written

$$\ln X_i = \frac{\Delta S_f}{R} \left[\frac{T_m - T}{T} \right] \quad (2.29).$$

Equation (2.29) works moderately well for solutions of compounds such as naphthalene in benzene, or even in mixtures of nonpolar solvents. When the system is naphthalene in water or water and water miscible solvents (mixed solvents), the equation does not apply. If the relationship held for polar solvents, the solubility of naphthalene in water and in benzene should be equal.

Real Solutions of Non-Electrolytes

The concept of thermodynamic activity was introduced by Lewis in 1907 (Lewis and Randall, 1923). The purpose was to maintain the forms of the ideal equations (above) while accurately representing real behavior. The relative activity may be thought of as an effective or corrected pressure.

Using the Raoult's law standard state, the activity of a component in solution (a_i) may be represented by

$$a_i = \gamma_i X_i \quad (2.30)$$

where the proportionality constant γ_i is called the activity coefficient. Substituting this relationship in equation (2.24), gives the chemical potential in terms of the activity.

$$u_i^s = u_i^l = u_i^{ol} + RT \ln a_i \quad (2.31)$$

Following the same steps as above, equation (2.29) may now be written as

$$\ln X_i = \frac{\Delta S_f}{R} \left[\frac{T_m - T}{T} \right] - \ln \gamma_i \quad (2.32).$$

The history of solubility prediction might more accurately be called the history of activity coefficient prediction. This is in part due to the desire to retain expressions with similar form to ideal expressions. This lends a common reference point for studying solubility.

A point of practical importance is that for solids not completely miscible in solvents the activity coefficient of equation (2.32) must use Raoult's law standard state of the pure super-cooled liquid vapor pressure (Karickhoff, 1987). This is opposite of the normal convention of using a Henry's law standard state for ionic solutes. Henry's law was an attempt to explain deviation of dilute solutes from Raoult's law. The law says, $P_i = K_i X_i$, where K_i is the Henry's constant for solute i in a given solvent. An analogous expression to (2.32) may be derived using the infinite dilution standard state, however, there are practical reasons for using the pure SCL standard state.

The first reason is that a sparsely soluble solute reaches saturation long before $X_i=1$. This means that although it is present in small quantity it follows Raoult's law. Consider a solute i that reaches saturation at $X_i=0.1$. At that point the vapor pressure of the solute over the solution is equal to the pure SCL vapor pressure. The behavior is, therefore, best treated with the SCL standard state. The second reason is that the pure component vapor pressure can be measured for liquids or predicted for solids. When using literature activity coefficient data it is necessary to know the standard state used.

Mixed Solvent Solubility. The thermodynamic treatment of infinitely dilute solutions in a mixed solvent derives from the Duhem-Margules equations (Denbigh, 1983). For two miscible solvents (A and B) and a solute (C), a form of the equation is

$$X_A \left[\frac{\delta \ln a_A}{\delta X_C} \right] + X_B \left[\frac{\delta \ln a_B}{\delta X_C} \right] = -X_C \left[\frac{\delta \ln a_C}{\delta X_C} \right] \quad (2.33).$$

With the assumption that $d \ln a_C = d \ln X_C$, equation (2.33) can be rearranged to give equation (2.34).

$$-dX_C = X_A d \ln a_A + X_B d \ln a_B \quad (2.34)$$

This relationship gives the solubility in terms of mole fractions and activities. It does not, however, provide a theoretical means of determining the needed activities.

Classical Approaches for Predicting γ

The prediction of γ requires that models based upon simplifying assumptions of the dissolution process be constructed. These models are then tested and their limits determined. Many models build on earlier models refining and customizing the approach.

The van Laar Equations

Van Laar constructed a model of mixing based on the assumptions that there is no volume change on mixing and the

entropy of mixing is ideal. It follows then that the excess molar Gibbs free energy is equal to the excess internal energy. Van Laar calculated the energy of mixing by following a Hess's law path.

First, the pure liquids are vaporized isothermally by reducing the pressure. Next, the ideal vapors are mixed in the vapor phase and finally the vapors are condensed isothermally to their original pressure. Van Laar used the van der Waals equation of state to represent the volumetric properties of the pure fluids. Performing these calculations leads to the equation below.

$$g^e = \frac{n_1 n_2 b_1 b_2}{n_1 b_1 + n_2 b_2} \left[\frac{v a_1}{b_1} - \frac{v a_2}{b_2} \right]^2 \quad (2.35)$$

where g^e is the excess molar Gibbs free energy, and a and b are the constants from the van der Waals equation of state. The activity coefficients are obtained from a differential form of the expression. For a two component system the van Laar equations are

$$\ln \gamma_1 = A \left[1 + \frac{A n_1}{B n_2} \right]^{-2} \quad (2.36)$$

and

$$\ln \gamma_2 = B \left[1 + \frac{B n_2}{A n_1} \right]^{-2} \quad (2.37).$$

Where;

$$A = b_1/RT \left[\frac{va_1}{b_1} - \frac{va_2}{b_2} \right]^2 \quad (2.38)$$

and

$$B = b_2/RT \left[\frac{va_1}{b_1} - \frac{va_2}{b_2} \right]^2 \quad (2.39).$$

If A and B are used as adjustable parameters, the van Laar equations can describe the behavior of a range of nonpolar mixtures. The equations can also be extended to cover mixed solvents. The equations do not work for many systems if A and B are not allowed to vary. Also the theory has no success with systems of polar liquids.

Regular Solution Theory

Hildebrand used the same assumptions as van Laar to describe solutions. Both Hildebrand and Scatchard independently decided that using the van der Waals equation of state was a large source of error. Instead they defined a parameter called the cohesive energy density (c). This may be thought of as the energy required to remove a molecule from solution and is represented as

$$c = \Delta E^V/v \quad (2.40).$$

Where ΔE^V is the energy of total vaporization and v is the molar volume of the liquid. Expressing c for a general

binary mixture gives the following relationship for the energy of mixing E_m .

$$-E_m = (n_1v_1 + n_2v_2)(c_{11} \phi_1^2 + 2c_{12} \phi_1\phi_2 + c_{22} \phi_2^2) \quad (2.41)$$

Where ϕ are the volume fractions of the respective components. They obtained the excess energy of mixing from the combination of equations (2.41) and (2.40). It must be assumed that it is equal to the difference between the energy of mixing of the binary solution and the individual components.

$$\begin{aligned} E^e &= E_m - E_1n_1 - E_2n_2 \\ &= (n_1v_1 + n_2v_2)(c_{11} + c_{22} - 2c_{12})\phi_1\phi_2 \end{aligned} \quad (2.42)$$

At this point the geometric mean rule is invoked. This says that if the interactions between molecules are controlled by London's dispersion forces that

$$c_{12} = (c_{11}c_{22})^{1/2} \quad (2.43).$$

This also holds for Keesom forces, when present, and may be used as an approximation for all van der Waals forces. It does not, however, work for hydrogen bonding. Letting, $\sqrt{c_{11}} = \delta_1$ and $\sqrt{c_{22}} = \delta_2$ (where the δ terms are called solubility parameters) equation (2.42) may be written

$$E^e = (n_1v_1 + n_2v_2) \phi_1\phi_2 (\delta_1 - \delta_2)^2 \quad (2.43).$$

Recall that Hildebrand and Scatchard made the same assumptions that van Laar made, therefore $g^e = E^e$. The expressions for the activity coefficients follow from substitution into $g_i^e = RT \ln \gamma_i$.

$$RT \ln \gamma_1 = v_1 \phi_2^2 (\delta_1 - \delta_2)^2 \quad (2.44)$$

$$RT \ln \gamma_2 = v_2 \phi_1^2 (\delta_1 - \delta_2)^2 \quad (2.45)$$

These are called the regular solution equations. Extending the the regular solution approach to multiple solvents is very simple. A parallel derivation is carried out resulting in

$$RT \ln \gamma_i = v_i (\delta_i - \sum \phi_j \delta_j)^2 \quad (2.45)$$

Regular solution theory is very useful for prediction of γ in solutions of nonpolar components. By its nature, though, it can only predict positive deviations from ideality. This and the inability to handle hydrogen bonding (polar) solvents restrict its utility.

Many modifications have been proposed and tested for regular solution theory (Prausnitz, 1986). These include not using the geometric mean rule and using adjustable fitting parameters. The only real improvement is gained at the loss of the models a priori estimating ability.

Extrathermodynamic Relationships for γ

Leffler and Grunwald (1963) describe extrathermodynamic relationships in the following way.

When the explanation of substituent or medium effects is given in terms of similar effects in a model reaction the quantities compared are thermodynamic, usually free energies, enthalpies, or entropies. The simple relationships often found among such quantities are not, however, part of the formal structure of thermodynamics. Hence they are called extrathermodynamic relationships. Although the relationships themselves are outside of thermodynamics, the approach resembles that of thermodynamics in the sense that the detailed microscopic mechanisms need not be explicitly identified.

These relationships have long been used by kineticists looking at the change in ΔG of a reaction that occurs when substituents are added to the reactants. It may also be useful in physical processes that are not adequately characterized by classical equilibrium thermodynamics.

In some physical systems unique relationships between thermodynamic variables will arise. These relationships may only hold for these systems or may be more general but they are not predicted from first thermodynamic principles. These are often called linear free energy relationships (LFER).

In 1940 Hammett related the changes of rate and equilibrium constants to the addition of substituents.

$$\log K = \log K_0 + \sigma_1 \quad (2.46)$$

Where K and K_0 are either the rate or equilibrium constants

of the substituted and parent compounds respectively and σ_1 is the substituent effect of component 1. Writing equation (2.46) for rate and equilibrium constants and assuming that the σ 's are proportional gives

$$\log(k/k_0) = p \log(K/K_0) \quad (2.47).$$

Where p is the proportionality constant relating the ratio of the $\log K$ terms. By substituting equation (2.47) into the relationship $\Delta G = RT \ln K$ and using δ to denote a change in ΔG , an expression can be written linearly relating the effect of the same substituent on the free energy of the rate and equilibrium processes.

$$\delta_i \Delta G_k = p \delta_i \Delta G_K \quad (2.48)$$

Equation (2.48) is the the Hammett LFER.

The enthalpy-entropy compensation effect used in chromatography to elucidate mechanisms of adsorption is an extrathermodynamic relationship. The approach is based on the Gibbs equation (Tomlinson, 1982)

$$\Delta G = \Delta H - T \Delta S \quad (2.49).$$

Where ΔH and ΔS are the changes in enthalpy and entropy of a process. Since adding substituents may affect the enthalpy and/or entropy contribution to ΔG , the equation may be written to represent the change.

$$\delta \Delta G = \delta \Delta H - T \delta \Delta S \quad (2.50)$$

Where the δ represents the change in the variable upon the addition of the substituent. For many systems a Hammett type relationship exists. This implies either ΔH or ΔS is constant or they are linearly related. The latter case is found in most such systems (Leffler and Grunwald 1963).

$$\delta\Delta H = \beta\delta\Delta S \quad (2.51)$$

β is a proportionality constant with units of temperature and is commonly referred to as the compensation temperature. It is believed (Woodburn, 1987) that different adsorption mechanisms which follow equation (2.51) have different compensation temperatures and may be categorized based on β .

Solving equation (2.51) for ΔS , substituting it into (2.50) and rearranging allows β to be quantified.

$$\delta\Delta G = \delta\Delta H(1 - T/\beta) \quad (2.52)$$

If ΔH and equilibrium K 's are known, β can be determined from a plot of $\ln K$ vs. $-T$ which should be linear if the mechanisms of adsorption are the same for all the compounds studied.

MGSA (Molecular and Group Surface Areas)

MGSA has its basis in the cavity model of Herman (1969) and the approach was developed by Amidon and Yalkowsky (1974). The process of solubilization is factored into three parts.

First, the work of cavity creation can be expressed as the surface area created by the solvent cavity and the surface tension of the solvent molecules.

If w_{11} is the work of cohesion required to separate the solvent molecules and only $1/2$ the work is used because no molecule is removed,

$$1/2 w_{11} = A_2 \Gamma_1 \quad (2.53)$$

where A_2 is the surface area of the solute molecule and Γ_1 is the surface tension of the solvent.

Second, the work of removing a solute molecule from a group of other solute molecules can be expressed as

$$1/2 w_{22} = A_2 \Gamma_1 \quad (2.54)$$

where w_{22} is the work of cohesion in removing a solute molecule from the group ($1/2$ of which is regained when the cavity closes) and Γ_2 is the surface tension of the solute.

Third, the remaining work involved in inserting a solute molecule into the solvent cavity is expressed as

$$w_{12} = (\Gamma_1 + \Gamma_2 - \Gamma_{12}) A_2 \quad (2.55)$$

where w_{12} is the work of adhesion and Γ_{12} is the interfacial tension between the solute and solvent.

Combining the above equations gives the excess free energy of a solute in solution:

$$1/2 w_{11} + 1/2 w_{22} - w_{12} = \Gamma_{12} A_2 \quad (2.56).$$

Assuming that $g^e = RT \ln \gamma$ and substituting this for $\log \gamma$ in

the real single component solubility equation (2.32) gives

$$\log X = \frac{-\Delta H}{2.303RT} * \frac{(T_m - T)}{T_m} - \frac{\Gamma_{12} A_2}{2.303RT} \quad (2.57)$$

$$\log \gamma = \frac{\Gamma_{12} A_2}{2.303RT} \quad (2.58)$$

Equation (2.58) predicts γ of a solute given the enthalpy of fusion, solvent-solute inter-facial tension, and molecular surface area.

Writing equation (2.57) for water and another for a cosolvent gives expressions for solubility in water (X_w) and solubility in cosolvent (X_c). When these expressions are substituted into the log-linear equation for mixed solvent solubility (X_m) of Yalkowsky ($\log X_m = f_c \log X_c + f_w \log X_w$) we get

$$\log X_m = \log X_w - f_c \frac{\Delta \Gamma A_2}{2.303 RT} \quad (2.59)$$

where $\Delta \Gamma = \Gamma(\text{water-solute}) - \Gamma(\text{cosolvent-solute})$. Written in this form the interfacial tension term represents the ratio of the activity coefficient in water to that in a cosolvent.

$$\log \frac{\gamma_w}{\gamma_c} = \frac{\Delta \Gamma A_2}{2.303 RT} \quad (2.60)$$

The expression for the $\log \gamma$ of the solute may be factored into terms to represent the varying contributions

by different groups or substituents on the molecule. These group effects give this approach its extrathermodynamic or LFER character.

If Γ_i is the interfacial tension between the solvent and the i^{th} type group and A_i is the surface area of the group, then

$$\log \gamma = \frac{\sum_i (\Gamma_i A_i)}{2.303 RT} \quad (2.61).$$

If, for example, the solute is divided into polar and hydrocarbon components

$$\log \gamma = \frac{\Gamma_p A_p + \Gamma_h A_h}{2.303 RT} \quad (2.62).$$

For many organic molecules this reduces to

$$\log \gamma = \frac{\Gamma_h A_h}{2.303 RT} \quad (2.63)$$

because the polar portion does not contribute demonstrably to the solubilization of hydrophobic compounds (Yalkowsky 1975). Using the substitutions that led to (2.59) gives

$$\log X_m = \log X_w + f_c \frac{\Delta \Gamma_h A_h}{2.303 RT} \quad (2.64)$$

where $\Delta \Gamma_h$ is the interfacial tension between water and a reference hydrocarbon minus the interfacial tension between the cosolvent and a reference hydrocarbon.

Since $\Gamma(\text{water-hydrocarbon})$ and $\Gamma(\text{cosolvent-hydrocarbon})$ are constant for a given cosolvent, the only parameter needed for the calculations of the ratio of activity coefficients is A_h . MGSA works well for rigid polynuclear aromatic and alkane solutes. It has significant problems in dealing with compounds that have appreciable polar surface area. This is largely because it is difficult to accurately factor and quantify the different surface types in such molecules.

UNIFAC

The UNIFAC approach is a group contribution to γ based on the assumptions that γ can be factored into a residual (r), which is related to the interactions between functional groups and a combinatorial (c) portion, which considers the geometry of the molecules.

$$\gamma = \gamma^r + \gamma^c \quad (2.65)$$

Three types of group parameters are used to calculate the γ . These are volume, surface area, and energy of interaction parameters (Prausnitz, 1986).

The approach extrapolates to mixed solvents with considerable effort. Many solvent parameters and energy of interaction terms for between the solutes and solvents are required. The salient point for this discussion is that it is another example of an extrathermodynamic relationship.

That is, in the course of the calculation of γ^{\pm} it is assumed that there is an additive constitutive relationship for many volumetric and thermodynamic properties of interest.

The Log-Linear Relationship

The log-linear relationship will be discussed in some detail in chapter 3. The basic primacies upon which the approach is based are examples of extrathermodynamic relationships.

First it is assumed that the free energy of transfer of a solute into a mixed solvent (ΔG_m) is equal to the sum of the ΔG 's for the component solvents weighted by their respective volume fractions. For a solute in two cosolvents 1 & 2,

$$\Delta G_m = f_1 \Delta G_1 + f_2 \Delta G_2 \quad (2.66).$$

Following the arguments at the beginning of this section, the effect of substituents on the free energy would be given by equation (2.67).

$$\delta \Delta G_m = f_1 \delta \Delta G_1 + f_2 \delta \Delta G_2 \quad (2.67).$$

Use is made of this relationship when deriving semi-empirical relationships between the ratios of activity coefficients for different compounds.

Summary

The direct use of intermolecular potentials to predict macroscopic properties of systems is impractical even for relatively simple physical systems. Classical thermodynamic approaches are capable of describing systems that are primarily controlled by van der Waals interactions. They may be empirically extended to treat other types of systems that include more entropic contributions to the behavior (i.e., systems which have hydrogen bonding). Extrathermodynamic approaches can handle the widest variety of real systems with their highly empirical or correlational nature.

The trade-off in using extrathermodynamics over classical thermodynamics or intermolecular potentials is one of utility for molecular level rationale. Extrathermodynamic relationships may have a rationale at the molecular level, but it is not necessary to recognize this to use the approach. In fact, many such relationships are fortuitous and have no obvious rationale. Intermolecular potentials rely on describing a model of interaction which may be very accurate, but may also require solving many body problems to predict even the simplest properties.

With each approach, the limitation is how well the controlling interactions can be predicted at the level required by the approach. (Hydrogen bonding being the Gordian Knot for solution theories.) The best approach is

the one that best matches the level of complexity of the system of interest. For solubility estimation in mixed solvents extrathermodynamics represents the approach of 'least' complexity that is useful.

CHAPTER 3

LOG-LINEAR RELATIONSHIP

This approach is based on the assumption that the solubility of a solute in a mixed solvent may be expressed as the composition weighted linear combination of its log solubility in real single solvent systems. Multi-cosolvent systems are also easily treated with this semi-empirical model.

The goal is to estimate the solubility of nonpolar solutes in mixed solvent systems from easily obtainable physical properties of the components. This is accomplished by using semi-empirical relationships to estimate those physical properties that are needed in the log-linear model.

Derivation of the Log-Linear equation

For a real single solvent system the solubility of a crystalline solute may be represented by equation (3.1).

$$\log X = \frac{-\Delta H_f}{2.303 RT} * \frac{T_m - T}{T_m} - \log \gamma \quad (3.1)$$

where ΔH_f is the heat of fusion, γ is the activity coefficient of the solute, X is the mole fraction solubility, T_m is the melting point of the solute in $^{\circ}K$, T is the temperature of interest, and R is the universal gas constant.

Substituting $R = 1.987 \text{ cal/}^{\circ}\text{K mole}$, $T = 298^{\circ}\text{K}$ and $\Delta\dot{H}_f/T_m = \Delta S_f$ into (3.1) gives

$$\log X = \frac{-\Delta S_f (\text{MP}-25)}{1364} - \log \gamma \quad (3.2)$$

where MP is the melting point of the solute in degrees centigrade.

Yalkowsky and Roseman (1981) derived an equation expressing the log solubility of a solute in a mixed solvent system (S_m) in terms of its log solubility in pure cosolvent (S_c) and in pure water (S_w), each is weighted by its volume fraction in the mixture (f_c and f_w), i.e.

$$\log S_m = f_c \text{ Log } S_c + (1-f_c) \text{ Log } S_w \quad (3.3)$$

where f_w is replaced by $(1-f_c)$.

Equation (3.3) assumes that the volume of the solute is much less than the total volume and that the free energy is proportional to the logarithm of the solubility ($\Delta G \propto \log S$). It also assumes that the volume fraction is proportional to the fraction of a molecule in contact with a given solvent.

The volume fraction is thought to be proportional to the surface area of the molecule in contact with the particular cosolvent. Yalkowsky et al. (1976) have shown that the solutes' molecular surface area is proportional to the log solubility for a wide range of drugs. Since it is the surface area and not the molar concentration that

effects solubilization (Yalkowsky, 1976), volume fraction is the logical choice for an independent variable.

Assuming a constant ΔS_f and MP, and writing the solubility equation for the solute in water and in the cosolvent gives the following pair of equations.

$$\log S_w = \frac{\Delta S_f (MP-25)}{1364} - \log \gamma_w \quad (3.4)$$

and

$$\log S_c = \frac{\Delta S_f (MP-25)}{1364} - \log \gamma_c \quad (3.5).$$

where γ_w and γ_c are the activity coefficients in water and cosolvent, respectively. (The error of expressing the solubility in units other than mole fraction will be discussed in the experimental chapter). Substituting these equations into equation (3.3) gives

$$\log S_m = \log S_w + f_c(\log \gamma_w - \log \gamma_c) \quad (3.6).$$

For a given cosolvent-water system, the difference between the equilibrium activity coefficients in the pure solvents must be constant so that

$$\log \gamma_w - \log \gamma_c = \sigma \quad (3.7)$$

Thus equation (3.6) can be written as

$$\log S_m = \log S_w + f_c \sigma \quad (3.8).$$

Equation (3.8) predicts a linear relationship between $\log S_m$ and f_c with a slope equal to σ . This equation assumes the effect of the crystal on the solubility is the same in water, pure cosolvent, or any combination of the two. This does not hold, for instance, if the solute is hydrated in aqueous solutions but not in mixed solvents. The terminally based (i.e.: end to end) slope is the ratio of the solubility in pure cosolvent (S_c) to the water solubility (S_w). One or both of these numbers are usually available in the literature or through the predictive methods described below. A hypothetical $\log S_m$ vs. f_c plot is shown in Figure 3.1. This represents the reference or ideal situation for the purpose of this study.

Similarly, for multiple cosolvent systems, equation (3.8) becomes

$$\log (S_m/S_w) = \sum_i (f_i \sigma_i) \quad (3.9)$$

which predicts $\log S_m$ will vary linearly with f_i if all other concentrations are held constant. The above relationship was observed by Rubino (1984) for several drugs in mixed solvents and by Yalkowsky et al. for a range of pollutants in cosolvent-water systems (E.P.A. report #CR811852-01-0).

Estimation of Water Solubility

Yalkowsky and Valvani (1980) developed a semi-empirical method of predicting the water solubility of nonelectrolytes based on melting point and the octanol-water partition coefficient of the solute at 25°C.

Octanol-Water Partition Coefficient. The octanol-water partition coefficient (P) of a solute is a measure of the distribution of the solute between an aqueous phase and an octanol phase. It is considered a polarity index (Yalkowsky, 1981) useful for estimating activity coefficients of nonpolar organic solutes.

At equilibrium the constant relating the distribution of a solute between two liquid phases, octanol (o) and water (w), may be represented by

$$P = X_o/X_w \quad (3.10).$$

If the Raoult's law standard state is chosen, the activity of the solute in a phase (a) = γX . Equation (3.10) becomes

$$P = \frac{a_o/\gamma_o}{a_w/\gamma_w} \quad (3.11).$$

But $a_o = a_w$ for this standard state so the equation is

$$P = \gamma_w/\gamma_o \quad (3.12).$$

P is often used as an estimate for γ_w because for most nonpolar solutes, $\gamma_o \approx 1$.

It is worth noting that the activity as defined by Henry's law will not lead directly to equation (3.12). This is because implicit in the activity is the Henry's constant which is solvent dependent (i.e., $a=H \cdot X$ where H is the Henry's constant). The activities in each of the two phases cannot, therefore, be equal and will not cancel. Some confusion may arise when comparing γ values from the literature. This is due to the common practice of using Henry's law for the solute. The equivalent expression can, of course, be gotten starting with Henry's law, but using literature values of activity or activity coefficients must be done with knowledge of the source of the values.

Nys and Rekker (1974) developed a group contribution approach for estimation of P . The approach treats molecules as a collection of groups or moieties. Each moiety is assumed to make the same contribution to the partition coefficient irrespective of its molecule of residence. By summing the contributions made to P by the groups in the molecule, the value for P is obtained. The approach is very accurate for a broad range of environmental compounds (Abramowitz, 1985) and becomes less accurate as the molecules become more complex. Table 3.1 lists some group contribution values of Nys and Rekker.

Water Solubility From Log P . The ideal γ_w of a solute is the reciprocal of its mole fraction solubility, $X = \gamma^{-1}$. From equation (3.12) it was estimated that for nonpolar

molecules that $P \approx \gamma_w$. Therefore, it was assumed that the water solubility was proportional to the reciprocal of the octanol-water partition coefficient ($X \propto P^{-1}$). It is customary to express the values as logarithms for ease of computation. Thus, $\log X = -\log P + \text{constant}$.

This proved to be a good assumption for 104 organic liquids (Yalkowsky, 1981). They regressed the $\log X$ of the liquids against their $\log P$ values and got a regression coefficient of 0.955. For solids there has to be a term to account for the crystal energy. They assumed the temperature of interest is 25°C and that $\Delta S_f \approx 13.5$ eu, Walden's rule. This leads to a simplified expression for the ideal solubility of a rigid solid nonpolar organic molecule.

$$\log X^1 = -0.01(MP - 25) \quad (3.13)$$

This relationship was added to that for the liquids to describe water solubility for solids and liquids in the same relationship. If a compound is a liquid its melting point is replaced by 25°C.

The most general expression was derived from regressing a broad range of compounds against their partition coefficients is given below.

$$\log S_w = -\log P - 0.01(MP - 25) + 0.8 \quad (3.14)$$

where P is the octanol-water partition coefficient, S is the

solubility (moles/ml), and MP is the melting point of the compound in degrees centigrade. Yalkowsky also developed equations specific for classes of compounds (eg; polycyclic aromatics), but the most general equation for nonelectrolytes is used here to severely test the model.

Log-Linear Equation with Log S_w Estimate. Substituting the semi-empirical relationship for $\log S_w$ into equation (3.8) results in a general equation for mixed solvent solubility.

$$\log S_m = \sigma f_c - \log P - 0.01(MP-25) + 0.8 \quad (3.15)$$

This equation allows prediction of mixed solvent solubility given σ , MP and $\log P$ values (MP is replaced by 25° for liquids). The estimation of σ is essential to the utility of the model.

Estimation of σ

It would be desirable to estimate σ for all systems of cosolvents with an analytic expression. Realistically, a semi-empirical approach is in order. The use of $\log P$ would be advantageous since it is available from the literature or by prediction. This would also mean that only one property would be required, along with fitting coefficients, for an a priori estimate of mixed solvent solubility.

The terminally based slope, σ , of the $\log S$ vs. fraction cosolvent curve may be represented as

$$\sigma = \log (S_C / S_W) \quad (3.16)$$

or,

$$\sigma = \log (\gamma_W / \gamma_C) \quad (3.17)$$

where γ_W and γ_C are the activity coefficients in the water and cosolvent, respectively.

Similarly, the log of the octanol-water partition coefficient of the solute (P) is

$$\log P = \log (\gamma_W / \gamma_O) \quad (3.18).$$

Assuming the log activity coefficient in a cosolvent is proportional to that in octanol, σ can be written as

$$\sigma = \log (\gamma_W/b'\gamma_O) = \log P + b \quad (3.19).$$

Where b is the proportionality constant between γ_C and γ_O . The assumption of proportionality between activity coefficients in cosolvent and octanol relies upon van der Waal's forces controlling the interactions between solute and cosolvent.

Within a given mixed solvent system, the change in σ with a change in solute is given by equation (3.19). This type of extrathermodynamic relationship was discussed in CHAPTER 2. Using 'a' as the proportionality constant

$$\delta\sigma = a \delta\log P + b \quad (3.20).$$

Where a and b are now the slope and intercept of the σ vs. $\log P$ curve.

Equation (3.20) predicts that within a solvent system

the terminally based slope of the log-linear solubility curve is proportional to the solutes' octanol-water partition coefficient. Yalkowsky (1984) found the relationship to hold well for a variety of solutes in propylene glycol.

Log-Linear Equation with Log S_w and σ Estimation.

Substituting equation (3.20) into (3.15) gives an equation of the following form.

$$\log S_m = f_c(a \log P + b) - \log P - 0.01(MP-25) + 0.8 \quad (3.21)$$

For a given cosolvent system, the mixed solvent solubility may be estimated from the melting point, the $\log P$ and the empirical constants a and b . The $\log P$ can be estimated from group contributions so the estimate may be done a priori. For multiple cosolvents the same substitutions would be made in equation (3.9).

Deviations from Ideality

Deviation from the predicted linear solubility behavior has been observed by several investigators (Rubino, 1984, Hagen, 1983, Flynn, 1979). The deviant curve may be sigmoidal or concave in higher cosolvent fractions (Yalkowsky et al). This project was designed with primarily rigid polynuclear aromatic hydrocarbons in an attempt to isolate deviation due to mixed solvent interaction as opposed to solute-mixed solvent interactions.

Excess Solubilities

Excess solubility is conceptually analogous to excess free energy. Excess free energy may be defined as the free energy not predicted by ideal treatment of a system.

Using the solubility of equation (3.8) as the ideal (S_i), the excess solubility is given by

$$\log (S_m/S_i) = \log S_{\text{exp}} - f_c \log S_c + (1-f_c)\log S_w \quad (3.22).$$

This assumes that the crystal form of the solute remains the same over all cosolvent-water compositions. It also assumes that no water or cosolvent is present in the crystalline solute. Equation (3.22) is a measure of interactions taking place in the solute-mixed solvent mixture not occurring in mixtures of the solute with the individual solvents (Rubino 1984).

Other excess properties are determined in the same manner, that is

$$\log (P_m/P_i) = \log P_{\text{exp}} - f_c \log P_c + (1-f_c)\log P_w \quad (3.23)$$

where P is now the property of interest. Comparison and correlation of excess solubilities with excess properties may suggest possible rationales for predicting solute solubility and elucidating the interactions causing the deviation.

Rubino and Yalkowsky (1984) found that the excess density maximum corresponds most closely to the excess

solubility maximum for several drug-cosolvent systems. They also inferred that the nonideality is largely due to the cosolvent-water interaction. These two observations are consistent since the solute concentration is thought too low to significantly affect how the solvent system is structured.

Equation (3.23) may be factored further into the contributions to the excess made by the interaction of water-cosolvent (P_{WC}) and the solute-mixed solvent (P_{MC}) assuming contributions by solute-cosolvent-water are negligible. This may be expressed as

$$\log (P_m/P_i) = \log P_{WC} + \log P_{MC} - f_C \log P_C + (1-f_C)\log P_W \quad (3.24).$$

By eliminating or minimizing the specific solute-cosolvent interactions, the contribution of the water-cosolvent interaction should be isolated. This was addressed by selecting primarily unsubstituted rigid aromatic compounds. Hydrophobic interaction between the solute and cosolvents will still occur. These interactions should be proportional to the size of the molecule and, therefore, be exposed by trends observed with different molecules in the same system of mixed solvents.

Form of the Deviation

If the deviation is dependent only on the size of the molecule (only hydrophobic interaction with the

solvents), then the shape of the deviation should be the same for hydrophobic solutes of different sizes in the same solvent system. APPENDIX A shows the solubility curves for all the solutes studied in each system respectively. The shapes of the curves are characteristic for the solvent systems studied.

The characteristic "sigmoidal" shape can be qualitatively explained by considering what is happening to the solvent structure.

At low cosolvent fractions the effect is entropic, the water is restructuring with some success about the cosolvent. These water-cosolvent interactions make the cosolvent a slightly poorer solvent. The cosolvents' solubilizing power is therefore decreased relative to that assumed by the model. $\log S_m$ is no longer proportional to the volume fraction of cosolvent and produces a lower solubility than predicted. This is not a large effect in the systems used in this study.

At high cosolvent fractions the system is more loosely structured and adherence to the model would be expected. Solubility should be controlled by the enthalpy of mixing. However, the water is now destructured more than is allowed for by equation (3.8). That is, the water is relatively free to interact with the solute due to the lack of interaction with other water molecules. The water is now

a better solvent for its association with the cosolvent than it is in the pure state. The solute is, therefore, more soluble than predicted. This effect is larger in the systems studied. This rational is consistent with finding density as the best predictor of excess solubility in similar systems.

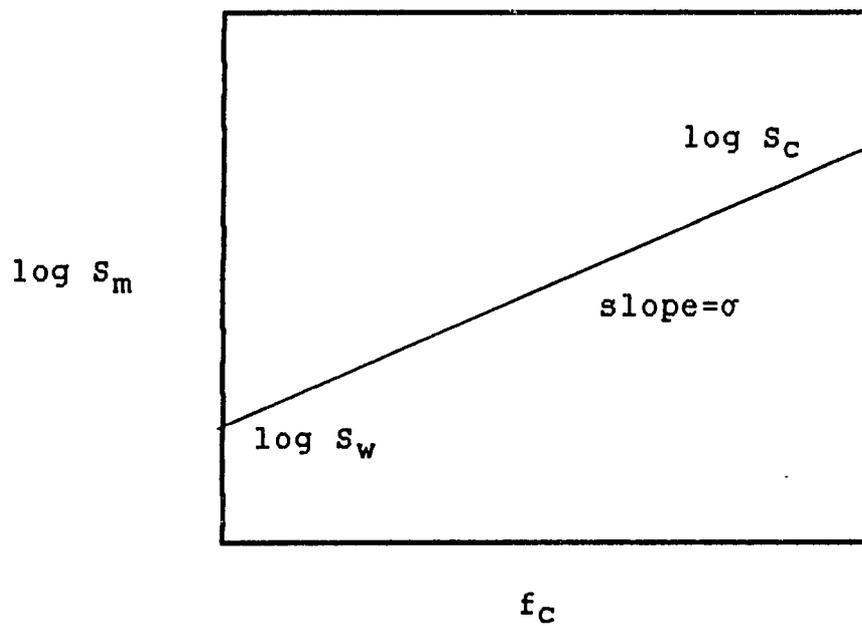


FIGURE 3.1: HYPOTHETICAL PLOT OF IDEALIZED SYSTEM
($\log S_m$ vs. f_c)

TABLE 3.1

GROUP CONTRIBUTIONS TO LOG PARTITION COEFFICIENTS

Substituent	Contribution
CH ₃	0.70
CH ₂	0.53
CH(unsaturated)	0.36
C(unsaturated)	0.16
C(bridgehead)	0.30
C ₆ H ₅	1.90
F(aromatic)	0.43
Cl(aromatic)	0.93
Br(aromatic)	1.17
I(aromatic)	1.46
OH(aromatic)	-0.37
OCH ₃ (aromatic)	0.24
COOH(aromatic)	0.00
NH ₂ (aromatic)	-0.91
NO ₂ (aromatic)	-0.09
CONH ₂ (aromatic)	-1.26
CN(aromatic)	-0.20

CHAPTER 4

SOLUBILITY MEASUREMENT IN COSOLVENT SYSTEMS

Thorough testing of the log-linear model required the collection of a considerable amount of data. The data set was intended to span as broad a range of solute solubilities as possible while staying within the confines described in CHAPTER 3. The water miscible cosolvents were selected to be representative of environmental and pharmaceutical concerns while possessing the properties needed for the study.

The solubilities of all the solutes were measured in the mixed solvent systems of acetone/water and methanol/water. In addition benzene, naphthalene and anthracene solubility data were collected in the ternary and quinary system described below. The systems studied are summarized in Table 4.1. The data were statistically evaluated and analyzed. Analytical problems that arose are discussed.

Experimental

Table 4.2 lists the solutes and cosolvents used along with their source and purity. The abbreviations listed are used throughout this work. The terms binary, ternary, and quinary solvent systems do not include the solute, i.e. they

refer to the number of cosolvents and water present. Because water is present in all the systems studied, it will be included explicitly in a description only when necessary for clarity. For example ANT/MOH corresponds to anthracene in methanol-water mixtures, and ANT/ACE/MOH corresponds to anthracene in acetone-methanol-water mixtures.

Solutes were selected to span a range of aromatic hydrocarbons differing in either the number of benzene rings, arrangement or substitution. Benzene, naphthalene and anthracene were chosen as reference solutes because of their detectability and environmental importance. These three solutes were measured in all the mixed solvent systems studied. Table 4.3 lists the structures and Table 4.4 lists some physical properties of the solutes used.

Solubility Measurement in Binary Solvent Systems

For each binary mixed solvent system studied a series of mixtures of cosolvent and water were made as follows: 10 ml, 20 ml... 90 ml of cosolvent were mixed with 90 ml, 80 ml were placed, in duplicate, in glass vials with teflon-lined caps. The size of the vials used varies with the characteristics of the system, as the solubility of some solutes is so low that the saturated solution has to be injected undiluted or concentrated into the HPLC. When this is the case the saturated solutions were prepared in 10 or 15

ml vials. For solute systems of relatively high solubility 3ml vials were used.

Liquid solutes were added dropwise with hand mixing to the vials containing the above described mixed solvents until a phase separation was obtained. In the case of solid solutes, small increments of solute were added stepwise to the mixed solvent contained in the vials until there is excess solid present. Care was taken to insure an excess of the solute present to achieve saturation even if there is loss to the glass, the cap liner or the head space.

All saturated solutions were equilibrated by rotating on a mechanical rotator (14 rpm) for 24 to 48 hrs. The time necessary to reach equilibrium was determined for anthracene in water. This was done by taking samples of a prepared vial at intervals and determining the concentration against a standard curve. When no change in concentration occurred between two intervals, equilibrium was assumed. This was approximately 36 hours. Anthracene was chosen because it has the lowest water solubility of the compounds studied, with the exception of chrysene which was handled separately due to analytical problems (see below). The time the other compounds took to reach equilibrium is, therefore, less than anthracene and much less in the mixed solvent systems. When degradation was a problem the rotation times were reduced.

After saturation was achieved, the saturated solutions were centrifuged at 3000 rpm for 10 minutes in a TJ-6 model

Beckman refrigerated centrifuge. Aliquots of the mixed solvent phase were analyzed by HPLC after appropriate dilution. Dilutions were made with a mixture of acetonitrile-water to prevent separation of phases upon mixing.

Solubility determinations in methanol-water and acetone-water mixtures were made for all solutes. Determinations in ethanol-water, acetonitrile-water, and isopropanol-water mixtures were also made for benzene, naphthalene, and anthracene. The solubility data and plots of the solubilities vs. fraction cosolvent were presented in APPENDIX A.

Solubility Measurement in Ternary Solvent Systems

A ternary mixed solvent system was prepared by mixing appropriate amounts of each of the three cosolvents in the manner described above. A complete system of mixtures was prepared, with an increment of 10% between the volume fraction of each solvent in the mixture. For example, the system of ANT/ACE/MOH (water is understood to be the third cosolvent) would start with 0% ACE, 0% MOH and 100% WATER. Next might be 0% ACE, 10% MOH and 90% WATER and so on until all 10% incremental combinations of the three cosolvents were studied.

After the solutions reach saturation they were analyzed in the same way as the binary systems.

The ternary mixed solvent systems were ANT/ACE/MOH, BEN/ACE/MOH, and NAP/MOH/ACN in WATER. These data were presented in APPENDIX B. Full data was not collected for benzene due to infinite miscibility at higher volume fractions of organic cosolvents.

Solubility Measurement in Quinary Solvent Systems

Solubility determinations on quinary mixed solvent systems were performed for benzene, naphthalene, and anthracene. In all cases the solvent system consists of mixtures of the following solvents: WATER, EOH, MOH, IPA, and ACE. The quinary solvent mixtures were prepared by mixing equal proportions of each cosolvent and water. For example, a quinary mixture containing a cosolvent fraction of 0.4 is made with 10% EOH, 10% MOH, 10% IPA, 10% ACE, and 60% water. The volume fraction of the water varied by 20%, from 0 to 100%.

The data were collected as above and the results were presented in APPENDIX C. Again full data were not collected for benzene in these systems due to infinite miscibility.

Analytical System

The HPLC system consists of two Beckman 110B solvent pumps, a U.V. detector set at 254 nm, and a Beckman analytical optical unit with a 8 ul cell. A Kratos 980 fluorescence detector was used for chrysene. The injection loop has a volume of 20 ul. Chromatograms were recorded and

integrated by a Hewlett-Packard 3390A integrator. The columns used were a 5um Alltech C18 column and a C8 250 mm in length and 4.6 mm i.d.

Chromatographic conditions were as follows: the mobile phase used was generally acetonitrile/water (70/30), the flow rate was 1.0 ml/min, the detector range was 0.08, and the integrator attenuation varied. Under these conditions the retention time for the solutes studied ranges from 3-15 minutes.

At least 3 standards of known concentration were used with each HPLC run. Each experiment consisted of two replicates of eleven samples. Every sample was analyzed at least twice resulting in a total of approximately 425 data points.

Data Analysis

All the raw data were entered into a 'DBASE III' database file. A DBASE program was written to transform the data into an ASCII file. The data were then sent to the DEC VAX mainframe and used as input for SAS (statistical analysis system). Terminally based slopes were calculated and linear regressions were then performed using the PROC REG program in the SAS statistical library.

Data from an earlier mixed solvent solubility project (EPA, 1986) were included in the analysis of σ . These data were collected by the same laboratory as described above.

Results and Discussion

All of the solubility data are presented in APPENDICES A-C. The practical problems of working with aromatic hydrocarbons include low water solubility, photosensitivity, and, in the case of benzene, partitioning of the organic cosolvent into a liquid solute. Problems that arose during this project were discussed below.

Analytical Problems

Low Water Solubility. None of the compounds studied have high water solubility (see Table 4.4). The detection of chrysene was particularly difficult since its water solubility is approximately 2 ppb and an HPLC-fluorescence assay had to be developed.

The fluorescence spectrum was determined on an American Instrument Company spectrophotofluorimeter. An excitation wavelength was chosen to be high enough to minimize any background absorption that would attenuate the absorption of the solute. It also had to be a wavelength where the solute absorbed sufficiently. The wavelength chosen was 427 nm and a band pass or cutoff filter of 370 was used on the emission side. This assay proved very sensitive for chrysene.

Photosensitivity. All of the mixtures in this study were equilibrated and assayed in the dark. Because an excess of the solute was present, there was always enough to saturate the solution phase.

Partitioning Problems. Benzene and α -naphthol were the only two liquid solutes in the study. Liquid solutes were added dropwise to a mixed solvent system until a phase separation occurs. This was to insure that an excess of the solute was present. In some mixed solvents, however, the volume of the new phase exceeded the volume of the liquid solute added. This was attributed to the organic cosolvent in the mixture partitioning preferentially into the solute.

The problem with this is that the fraction of cosolvent left in the original phase was changed. Any measurement made in this phase is meaningless since the composition of the phase determines the solubility. To guard against such errors it was decided that if the volume of the solute phase increased, the data would not be used. This varied with the different solutes and different fraction cosolvents. The system of α -naphthol in acetone/water was eliminated completely on this basis.

TABLE 4.1
SUMMARY OF SYSTEMS STUDIED

		C O S O L V E N T S							
		MOH	ACE	EOH	ACN	IPA	Ternary systems	Quinary systems	
S O L U T E S	BEN	*	*	*	*	*	*	*	
	NAP	*	*	*	*	*	*	*	
	ANT	*	*	*	*	*	*	*	
	BIP	*	*	*				
	PYR	*	*					
	CHR	*	*					
	NOL	*	O					
	ATR	*	*					
	DIU	*	*					
	PHN	*	*					

(*) Completed.

(O) This system presented the partitioning problem described.

TABLE 4.2

SOLVENTS AND SOLUTES: SOURCES AND ABBREVIATIONS

SOLUTES (purity 98% or >)		
Name	Abbreviation	Source
Anthracene	ANT	3
Atrazine	ATR	7
Benzene	BEZ	8
Biphenyl	BIP	1
Chrysene	CHR	1
Diuron	DIU	7
Naphthalene	NAP	2
α -Naphthol	NOL	1
Pyrene	PYR	1
Phenanthrene	PHN	1
COSOLVENTS		
Methanol	MOH	4
Ethanol	EOH	4
Isopropanol	IPA	5
Acetone	ACE	6
Acetonitrile	ACN	5
Glass-distilled deionized water was used in this project.		

- | | |
|---------------------------------|--------------------------|
| 1. Aldrich Chemical Co. | 5. Fisher Scientific Co. |
| 2. Alpha Products. | 6. Ashland Chemical Co. |
| 3. Sigma Chemical Co. | 7. Crescent Chemical Co. |
| 4. U.S. Industrial Chemical Co. | 8. E.M. Industries Inc. |

TABLE 4.3
STRUCTURE OF SOLUTES

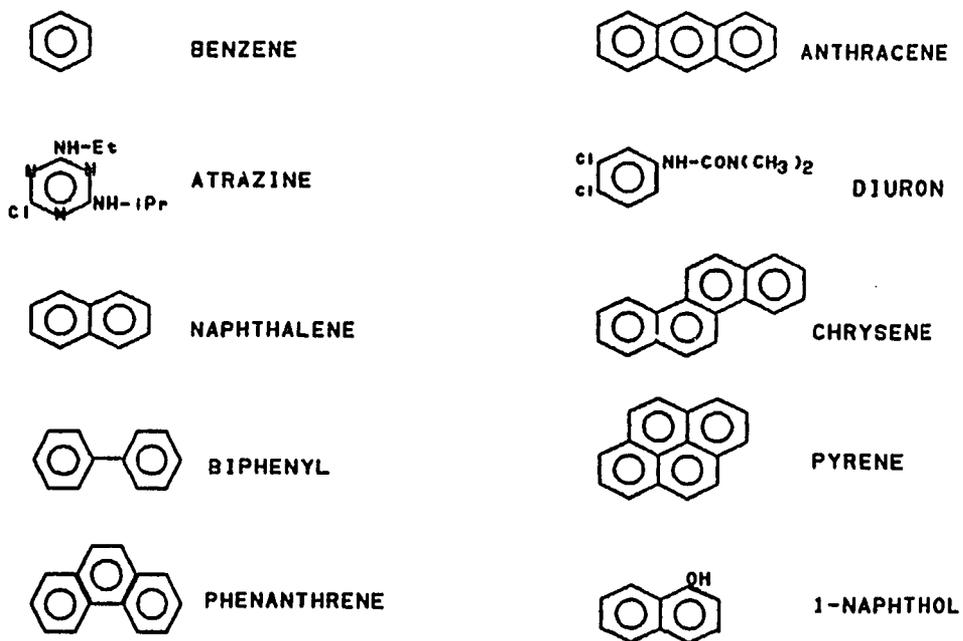


TABLE 4.4
PHYSICAL PROPERTIES OF SOLUTES

SOLUTE	MOL.WT.	MP(°C)	LOG P	H ₂ O SOL (ppm)
Benzene	78.12	5.5	2.13	1.78 E+3
Naphthalene	128.2	80.0	3.29	3.17 E+1
Anthracene	178.20	216.0	4.45	4.45 E-2
Phenanthrene	178.2	101.0	4.45	1.00 E 0
Pyrene	202.3	150.0	4.90	1.3 E-1
Chrysene	228.3	256.0	5.61	1.8 E-3
Biphenyl	154.21	69.0	3.84	6.8 E 0
Atrazine	215.68	277.0	0.81	7.26 E+1
Diuron	233.10	158.5	2.91	1.59 E+2

CHAPTER 5

RESULTS

The log-linear relationship between solubility in mixed solvents and the fraction cosolvent has been observed in a number of systems (Rubino, 1984). This study is a first attempt to determine the role of the cosolvent-water interaction in the behavior of the whole system. In this chapter the estimation of σ and mixed solvent solubility will be analyzed with respect to the log-linear model.

Solubility Behavior in Mixed Solvent Systems

Solubility measurements for the solutes described in Chapter 4 were made in mixed solvent systems. All of the solutes were studied in the binary solvent systems of acetone/water and methanol/water. Anthracene, naphthalene and benzene were studied in three additional binary systems as well as ternary and quinary systems.

Binary Solvent Systems

Solute solubility in the various cosolvent-water binary mixtures show a reasonable log linear relationship according to the following equation.

$$\log S_m = \sigma f_c + \log S_w \quad (5.1)$$

Where S_m is the solubility of the solute in the binary mixed

solvent system, f_c is the fraction cosolvent, σ is the slope of the line, and $\log S_w$ is the intercept. σ can be estimated from a knowledge of the solubility of the solute in the pure cosolvent and in water. Table 5.1 lists the terminally based (ie. end to end) slopes for all the binary systems. The data for these systems is tabulated and plotted by binary solvent system in APPENDIX A.

The solubility data is plotted for six solutes in the methanol/water system (Figure 5.1) and for naphthalene in six solvent systems (Figure 5.2). Since the endpoints of each curve are fixed, the only reasonable measure of agreement with the model is the deviation from the log-linear line. The average absolute deviation and average factor of deviation are presented for each 10% increase in cosolvent for the figures shown. Table 5.2 shows that the maximum average error did not exceed a factor of three for any of the twelve systems.

Of the binary solvent systems studied methanol/water usually shows the least deviation from the model for a given solute. Figure 5.2 shows naphthalene in all the binary systems including the systems of acetone/water and isopropanol/water which show the most deviation from the model. The average deviations presented are typical of the remaining systems studied. APPENDIX A contains the tabulated deviations point by point for all the systems studied. Possible reasons for the relative magnitude and

form of the deviations will be discussed at length in Chapter 6.

Ternary Solvent Systems

In a manner similar to the treatment of the binary solvent systems, the solubility in a ternary solvent mixture consisting of acetonitrile, methanol and water can be treated as the sum of the logarithmic solubilities in the individual volume fractions of the solvents.

$$\log S_m = \sigma_{ACN}f_{ACN} + \sigma_{MOH}f_{MOH} + \log S_w \quad (5.2)$$

Where f_{ACN} , f_{ACE} and f_{MOH} are the volume fractions of acetonitrile, acetone and methanol respectively in the ternary solvent systems. The values of σ were taken directly from Table 5.1 and the $\log S_w$ values are averaged for the individual binary mixed solvent systems.

Note that the estimation of solubility in ternary solvent systems requires only the σ value from the binary solvent systems and the solubility in water. This means no data from the ternary system is needed for the estimate.

The solubility (mg/ml) of benzene, naphthalene and anthracene in the ternary solvent systems studied can be described by the following equations respectively:

$$\log S_m = 1.94f_{ACN} + 2.06f_{MOH} - 0.19 \quad (5.3)$$

$$\log S_m = 5.22f_{ACE} + 4.21f_{MOH} - 4.26 \quad (5.4)$$

$$\log S_m = 3.86f_{ACE} + 3.39f_{MOH} - 1.59 \quad (5.5)$$

The data for these systems and deviations from the log-linear model are listed in Table 5.3 - 5.5.

The truncated data set for benzene in acetone, methanol and water is the result of the fact that it is completely miscible before $f_{BEN} = 1$. This requires using the density of benzene as its high endpoint in the calculation of σ . This contributes to the relatively larger error observed for benzene in the ternary system studied. Even with these problems the average error was a factor of 3.56 and the maximum error observed was a factor of 5.4. This would be adequate for many environmental applications or as a starting point in a formulation.

The other two ternary systems are anthracene and naphthalene in acetone, methanol and water and acetonitrile, methanol and water respectively. The data from these systems agree very well with the log-linear model predictions. The anthracene system deviated from the model by only a factor of 1.54 with maximum of 3.08. The naphthalene system averaged 1.39 with a maximum of 3.58 in a large data set.

The combination of cosolvents to form the multiple mixed solvent systems can be thought of as combining binary solvent systems. The observed deviation in the multiple mixed solvent systems actually decreased relative to most of

the binary systems studied. The binary system of ANT/ACE/H₂O exhibits a slightly greater deviation than the ternary solvent system above. The same is true for NAP/ACN/H₂O relative to the ternary solvent system. Both solutes in MOH/H₂O exhibit less deviation. This type of fortuitous canceling of errors may not be predictable, however, it was observed frequently when using common cosolvents of environmental interest.

Quinary Solvent System

The solubilities of naphthalene, benzene and anthracene in quinary mixed solvent systems consisting of equal amounts of acetonitrile, methanol, ethanol and isopropanol with varying amounts of water are given in Table 5.6.

In principle, the solubility of naphthalene, anthracene and benzene in these systems can be treated as the sum of the logarithmic solubilities in the individual volume fractions of the cosolvents (as above). The equations for estimating the solubility of benzene, naphthalene and anthracene respectively, then, follow directly from the results of Table 5.1.

$$\log S = 1.73f_{ACN} + 2.05f_{EOH} + 1.95f_{IPA} + 2.06f_{MOH} - 0.19 \quad (5.6)$$

$$\log S = 4.61f_{ACN} + 4.29f_{EOH} + 4.13f_{IPA} + 4.21f_{MOH} - 4.26 \quad (5.7)$$

$$\log S = 3.86f_{ACN} + 3.48f_{EOH} + 3.32f_{IPA} + 3.39f_{MOH} - 1.59 \quad (5.8)$$

where the solubilities are defined as above, f_{ACN} is the volume fraction of acetonitrile, f_{EOH} is the volume fraction of ethanol, f_{IPA} is the volume fraction of isopropanol and f_{MOH} is the volume fraction of methanol. The intercept is taken to be the average of the observed water solubilities for the respective binary systems in APPENDIX A .

Equations (5.6) - (5.8) can be reduced to a simpler form if the volume fraction of each cosolvent is the same. In this case, the results would be a linear sum of the coefficients from the above equations for benzene, naphthalene and anthracene respectively.

$$\log S = 8.00 (f_C) - 0.19 \quad (5.9)$$

$$\log S = 17.24(f_C) - 4.26 \quad (5.10)$$

$$\log S = 14.15(f_C) - 1.59 \quad (5.11)$$

A linear regression of the results from solubility measurements in the quinary cosolvent-water systems vs. fraction cosolvent yielded the following equations.

$$\log S = 12.9(f_C) - 0.09 \quad (5.12)$$

$$n = 5 \quad s = 0.984 \quad r = 0.970$$

$$\log S = 19.1(f_C) - 4.16 \quad (5.13)$$

$$n = 6 \quad s = 0.085 \quad r = 0.995$$

$$\log S = 14.9(f_C) - 1.67 \quad (5.14)$$

$$n = 6 \quad s = 0.138 \quad r = 0.996$$

The favorable comparison of these two sets of equations show that the solubility of benzene, naphthalene, and anthracene in these multicomponent systems can be treated as the weighted sum of their log solubility in the individual cosolvents. Coupling the σ values from the different binary solvent systems allows the estimation of solubility in any ternary or quinary system studied with reduced error. The larger disagreement for benzene in these systems is due to the experimental difficulties discussed in Chapter 3.

In addition, inspection of the deviation from the log-linear model presented in Table 5.6 shows deviations comparable to those observed for ternary mixed solvent systems. Naphthalene in this system shows a maximum deviation of a factor of 1.4 and the average deviation is zero. Anthracene does nearly as well and benzene does well considering the problems discussed. The canceling of errors when using multiple cosolvents seems, again, to be a factor. Unless the system is restricted to cosolvents with the same hydrogen bonding characteristics, it seems likely that some canceling of errors will occur.

Prediction of σ

In Chapter 3 a semi-empirical equation for estimating σ from the solute's octanol-water partition coefficient (P) was developed.

$$\sigma = a \log P + b \quad (5.15)$$

Where a and b are fitted parameters.

The terminally based slopes of all the solutes in a given solvent system were regressed against $\log P$ with the 'PROC REG' linear regression program contained in SAS. Binary solvent systems from Yalkowsky et al. (1986) are also included. The resulting values for a and b , as well as, the adjusted r -squared values are presented in Table 5.7.

The high degree of correlation over several orders of magnitude of $\log P$ make these equations useful for estimating σ . The low r^2 for the EG systems is due to the low slope of the curve and is, thus, artifactual. The σ values for chrysene and phenanthrene in acetone and methanol were predicted before they were measured. The experimental and predicted values for these systems are within a few percent of each other.

Substituting the proper a and b values from Table 5.7 into Equation (5.15) gives the equation for σ in the acetone-water systems

$$\sigma = 0.997 \log P + 0.484 \quad (5.16).$$

$$\text{adj. } r^2 = .927$$

The plots of σ vs. $\log P$ for all the systems studied as well as the raw data and regression statistics are presented in APPENDIX B. Atrazine was not included in the regressions because of its anomalous solubility behavior between 0 and 10% cosolvent. This will be discussed in Chapter 7.

When experimental values for solute solubility in the pure cosolvent are unavailable due to the complete miscibility of the solute, the density of the solute was substituted (eg; benzene).

Table 5.8 shows the deviation between the observed σ values and those calculated from equations like (5.15). As stated earlier atrazine will be discussed in the next chapter. For the remaining systems, the maximum deviation is ≈ 0.8 or a factor of ≈ 6 and a minimum of zero. This method provides a method for rapidly obtaining an estimate for σ with no laboratory effort.

The estimation of σ is potentially very useful. It should be noted, however, that what has been predicted is the end to end slope. This does not in anyway estimate the deviation from the model, only the "ideal" log-linear curve. For some systems, such as the binary methanol/water system, this seems to be sufficient to predict the actual solubility. For other systems such as isopropanol/water, the error is larger (\approx a factor of 7 at its worst). The deviation is the topic of Chapter 6.

Mixed Solvent Solubility Estimation

An equation to estimate the solubility of solutes in mixed solvent systems without any solubility data was also developed in Chapter 3. The equation (3.21) utilizes the a and b values derived above and the log P and MP (melting point) of the solute.

$$\log S_m = f_c(a \log P + b) - \log P - 0.01(MP-25) + 0.8 \quad (5.17)$$

Substituting the a , b , MP , and $\log P$ values into Equation (5.17) for the system of chrysene in acetone/water, produces the predictions listed in Table 5.9. Chrysene was not included in the regression for the a and b values used here ($a=1.02$, $b=0.5$). (In fact, the estimation was made in the lab in order to facilitate the development of the analytical method for chrysene. The dilutions to the equilibrated solutions and the standards for the HPLC run were calculated on the basis of the σ estimation.)

The model does a good job of predicting the solubility of chrysene between the end points with maximum deviation at the end points. The variation can be reduced by a factor of two to ten by using an equation which is specific for polynuclear aromatics (see Chapter 3). Even without the correction, an order of magnitude prediction is available in minutes. Considering the fact that the acetone/water system usually shows significant deviation, this represents a good test of the model.

Summary

The log-linear model predicts solubility behavior in the binary mixed solvent systems with reasonable accuracy. The accuracy varies with the particular system. It does a better job with the ternary and quinary mixed solvent

systems than with binary. The deviation is less than an order of magnitude at the maximum, usually considerably less.

Estimating σ from the solute's log P works well with a maximum deviation of approximately 0.8 in the systems studied. With a known log S_w , the σ estimation makes rapid calculation of the solubility in mixed solvent systems possible. Estimating log S_m from log P using the relationship for predicting log S_w and σ results in a greater error. However, this error can be reduced with the use of log S_w equations specific to the family of solutes in question.

The ability to estimate log S_m with the ease that this approach affords is a useful tool in preliminary investigation of solubility in mixed solvent systems. In environmental systems the accuracy of the method may be sufficient as it stands. Further characterization of the deviation is required and is discussed in the next chapter.

TABLE 5.1
 TERMINALLY BASED SLOPES IN BINARY SYSTEMS

C O S O L V E N T S						
		MOH	ACE	EOH	ACN	IPA
S O L U T E S	BEN	2.06	1.94	2.05	1.73	1.95
	NAP	3.39	4.17	3.48	3.86	3.32
	ANT	4.21	5.22	4.29	4.61	4.13
	BIP	3.97	4.80	4.09
	PYR	4.30	5.36
	CHR	4.96	6.11
	NOL	2.78
	ATR	2.40	2.63
	DIU	2.27	2.51
PHN	3.31	4.24	

TABLE 5.2
 AVERAGE ERROR IN 6 BINARY SOLVENT SYSTEMS

FRACTION COSOLVENT	AVERAGE ABSOLUTE DEV		AVERAGE FACTOR OF ERRS	
	MEO SYSTEMS	NAP SYSTEMS	MEO SYSTEMS	NAP SYSTEM
0	0	0	0.0	0.0
0.1	0.25	0.13	1.8	1.3
0.2	0.33	0.21	2.1	1.6
0.3	0.37	0.31	2.3	2.0
0.4	0.32	0.46	2.1	2.9
0.5	0.26	0.37	1.8	2.3
0.6	0.24	0.31	1.7	2.0
0.7	0.15	0.28	1.4	1.9
0.8	0.13	0.17	1.3	1.5
0.9	0.1	0.09	1.3	1.2
1	0	0	0.0	0.0

TABLE 5.3
TERNARY SOLVENT SYSTEM DATA

FRAC ACE	FRAC MOH	LOG S OBS	LOG S PRED	DEVIATION OBS-PRED	ANTI LOG DEVIATION
0.1	0.1	-3.29	-3.22	-0.07	0.85
0.1	0.3	-2.34	-2.38	0.04	1.08
0.1	0.4	-1.87	-1.95	0.08	1.21
0.1	0.5	-1.43	-1.53	0.10	1.27
0.1	0.6	-1.09	-1.11	0.02	1.05
0.1	0.8	-0.13	-0.27	0.14	1.38
0.2	0.2	-1.97	-2.27	0.30	2.01
0.2	0.3	-1.83	-1.85	0.02	1.05
0.2	0.4	-1.38	-1.43	0.05	1.13
0.2	0.5	-0.90	-1.01	0.11	1.29
0.2	0.6	-0.56	-0.59	0.03	1.07
0.3	0.1	-1.77	-2.17	0.40	2.53
0.3	0.2	-1.57	-1.75	0.18	1.52
0.3	0.3	-1.06	-1.33	0.27	1.87
0.3	0.4	-0.64	-0.91	0.27	1.86
0.3	0.5	-0.33	-0.49	0.16	1.44
0.3	0.6	-0.01	-0.07	0.06	1.14
0.4	0.1	-1.36	-1.65	0.29	1.95
0.4	0.2	-0.99	-1.23	0.24	1.74
0.4	0.3	-0.58	-0.81	0.23	1.69
0.4	0.4	-0.11	-0.39	0.28	1.90
0.4	0.5	-0.05	0.03	-0.08	0.83
0.5	0.1	-0.64	-1.13	0.49	3.08
0.5	0.2	-0.42	-0.71	0.29	1.94
0.5	0.3	-0.07	-0.29	0.22	1.65
0.5	0.4	0.19	0.13	0.06	1.14
0.6	0.1	-0.30	-0.61	0.31	2.03
0.6	0.2	0.12	-0.19	0.31	2.02
0.6	0.3	0.35	0.23	0.12	1.30
0.8	0.1	0.55	0.44	0.11	1.30
Averages:				0.17	1.54

TABLE 5.4
TERNARY SOLVENT SYSTEM DATA

FRAC MOH	FRAC ACN	LOG S OBS	LOG S PRED	DEVIATION OBS-PRED	ANTI LOG DEVIATION
0.0	0.0	-1.59	-1.59	0.00	1.00
0.0	0.1	-1.28	-1.20	-0.08	0.84
0.0	0.2	-0.66	-0.82	0.16	1.44
0.0	0.3	-0.08	-0.43	0.35	2.25
0.0	0.4	0.39	-0.05	0.44	2.73
0.0	0.5	0.76	0.34	0.42	2.63
0.0	0.6	1.28	0.73	0.55	3.58
0.0	0.7	1.57	1.11	0.46	2.87
0.0	0.8	1.78	1.50	0.28	1.91
0.0	0.9	2.01	1.88	0.13	1.34
0.0	1.0	2.26	2.27	-0.01	0.98
0.1	0.0	-1.35	-1.25	-0.10	0.80
0.1	0.1	-0.97	-0.87	-0.11	0.79
0.1	0.2	0.04	-0.48	0.52	3.30
0.1	0.3	0.11	-0.09	0.20	1.60
0.1	0.4	0.72	0.29	0.43	2.67
0.1	0.5	1.09	0.68	0.41	2.58
0.1	0.6	1.41	1.07	0.34	2.21
0.1	0.7	1.68	1.45	0.23	1.69
0.1	0.8	1.94	1.84	0.10	1.27
0.1	0.9	2.20	2.22	-0.02	0.95
0.2	0.0	-1.10	-0.91	-0.19	0.65
0.2	0.1	-0.62	-0.53	-0.09	0.81
0.2	0.2	-0.03	-0.14	0.11	1.29
0.2	0.3	0.57	0.25	0.32	2.11
0.2	0.4	0.82	0.63	0.19	1.54
0.2	0.5	1.25	1.02	0.23	1.71
0.2	0.6	1.59	1.40	0.19	1.53
0.2	0.7	1.86	1.79	0.07	1.17
0.2	0.8	2.21	2.18	0.03	1.08
0.3	0.0	-0.94	-0.57	-0.37	0.43
0.3	0.1	-0.30	-0.19	-0.11	0.77
0.3	0.2	0.37	0.20	0.17	1.48
0.3	0.3	0.80	0.59	0.22	1.64
0.3	0.4	1.21	0.97	0.24	1.73
0.3	0.5	1.53	1.36	0.17	1.49
0.3	0.6	1.86	1.74	0.12	1.31
0.3	0.7	2.13	2.13	0.00	1.00

TABLE 5.4 (con't)

FRAC MOH	FRAC ACN	LOG S OBS	LOG S PRED	DEVIATION OBS-PRED	ANTI LOG DEVIATION
0.4	0.0	-0.56	-0.23	-0.33	0.47
0.4	0.1	0.02	0.15	-0.13	0.74
0.4	0.2	0.67	0.54	0.13	1.36
0.4	0.3	1.12	0.92	0.20	1.57
0.4	0.4	1.46	1.31	0.15	1.41
0.4	0.5	1.82	1.70	0.12	1.33
0.4	0.6	2.12	2.08	0.04	1.09
0.5	0.0	-0.10	0.11	-0.21	0.62
0.5	0.1	0.42	0.49	-0.07	0.85
0.5	0.2	1.01	0.88	0.13	1.36
0.5	0.3	1.48	1.26	0.22	1.65
0.5	0.4	1.75	1.65	0.10	1.26
0.5	0.5	2.06	2.04	0.02	1.06
0.6	0.0	0.35	0.44	-0.09	0.81
0.6	0.1	0.84	0.83	0.01	1.02
0.6	0.2	1.30	1.22	0.08	1.21
0.6	0.3	1.65	1.60	0.05	1.12
0.6	0.4	2.05	1.99	0.06	1.15
0.7	0.0	0.72	0.78	-0.06	0.86
0.7	0.1	1.20	1.17	0.03	1.07
0.7	0.2	1.62	1.56	0.07	1.16
0.7	0.3	2.03	1.94	0.09	1.23
0.8	0.0	1.11	1.12	-0.01	0.97
0.8	0.1	1.53	1.51	0.02	1.05
0.8	0.2	1.93	1.89	0.04	1.09
0.9	0.0	1.45	1.46	-0.01	0.97
0.9	0.1	1.89	1.85	0.04	1.10
1.0	0.0	1.79	1.80	-0.01	0.98
				0.10	1.39

TABLE 5.5
TERNARY SOLVENT SYSTEM DATA

FRAC ACE	FRAC MOH	LOG S OBS	LOG S PRED	DEVIATION OBS-PRED	ANTI LOG DEVIATION
0.0	0.0	0.16	0.19	-0.03	0.93
0.4	0.4	2.27	1.79	0.48	3.02
0.4	0.5	2.72	2.00	0.72	5.30
0.5	0.1	1.27	1.37	-0.10	0.80
0.5	0.2	1.89	1.57	0.32	2.08
0.5	0.3	2.51	1.78	0.73	5.40
0.5	0.4	2.68	1.98	0.70	4.97
0.6	0.1	1.69	1.56	0.13	1.35
0.6	0.2	2.49	1.77	0.72	5.30
0.6	0.3	2.66	1.97	0.69	4.88
0.8	0.1	2.50	1.95	0.55	3.56
				0.45	3.42

TABLE 5.6
QUINARY SOLVENT SYSTEM DATA

FRAC	LOG S OBS	LOG S PRED	LOG DEV OBS-PRE	ANTILOG DEV
ANTHRACENE				
0.00	-4.32	-4.16	-0.16	0.69
0.00	-4.14	-4.16	0.02	1.05
0.00	-4.63	-4.16	-0.47	0.34
0.05	-3.10	-3.27	0.17	1.47
0.05	-3.42	-3.27	-0.15	0.70
0.05	-3.22	-3.27	0.05	1.12
0.10	-2.03	-2.38	0.35	2.21
0.10	-2.15	-2.38	0.23	1.68
0.10	-2.16	-2.38	0.21	1.64
0.15	-1.10	-1.48	0.38	2.41
0.15	-0.97	-1.48	0.51	3.25
0.15	-1.02	-1.48	0.46	2.90
0.20	-0.41	-0.59	0.18	1.51
0.20	-0.31	-0.59	0.28	1.91
0.20	-0.26	-0.59	0.33	2.14
0.25	0.25	0.30	-0.05	0.89
0.25	0.33	0.30	0.03	1.07
0.25	0.37	0.30	0.07	1.17
Averages			0.13	1.56

TABLE 5.6 (con't)

FRAC	LOG S OBS	LOG S PRED	LOG DEV OBS-PRE	ANTILOG DEV
BENZENE				
0.00	0.19	0.19	0.00	1.00
0.05	0.39	0.59	-0.20	0.63
0.10	0.90	0.99	-0.09	0.81
0.15	1.69	1.39	0.30	2.00
0.20	2.60	1.79	0.81	6.46
Averages			0.16	2.18
NAPHTHALENE				
0.00	-1.59	-1.59	0.00	1.00
0.05	-1.12	-0.87	-0.25	0.56
0.10	-0.14	-0.15	0.01	1.03
0.15	0.71	0.56	0.15	1.40
0.20	1.36	1.28	0.08	1.20
0.25	1.97	2.00	-0.03	0.93
Averages			-0.01	1.02

TABLE 5.7

 σ CORRELATIONS WITH LOG P

SUMMARY OF REGRESSIONS PARAMETERS FOR TERMINAL SLOPE (σ)
VS. LOG P IN EACH BINARY SOLVENT SYSTEM:

COSOLVENT/WATER SYSTEM	R SQUARED (adjusted)	n	(a)	(b)
ACETONE	0.93	14	1.00	0.48
ACETONITRILE	0.90	8	1.03	0.35
DIMETHYLACETAMIDE	0.95	7	0.86	0.89
DIMETHYLFORMAMIDE	0.94	7	0.87	0.87
DIMETHYLSULFOXIDE	0.95	7	0.89	0.87
ETHYLENE GLYCOL	0.75	7	0.36	1.04
ETHANOL	0.94	11	0.85	0.81
ISOPROPANOL	0.85	9	0.89	0.63
METHANOL	0.84	16	0.68	1.07
PROPYLENE GLYCOL	0.96	8	0.62	0.77

For a given solute:

$$\sigma = (a) \cdot \log P + (b)$$

where: σ is the terminally based slope of the log S_m vs. fraction cosolvent curve and $\log P$ is the octanol-water partition coefficient of the solute

TABLE 5.8
 DEVIATION OF σ FROM LOG P PREDICTION

		C O S O L V E N T S				
		MOH	ACE	EOH	ACN	IPA
	BEN	-0.24	-0.35	-0.30	-0.48	-0.29
S	NAP	0.06	0.37	-0.15	0.09	-0.26
O	ANT	0.11	0.29	-0.30	-0.32	-0.46
L	BIP	0.29	0.48	0.02
U	PYR	-0.09	0.00
T	CRY	0.08	0.02
E	ATR	0.78	1.34
S	DIU	-0.78	-0.88
	PHN	-0.79	-0.70

TABLE 5.9
CHRYSENE SOLUBILITY ESTIMATES IN ACE/WATER

FRACTION COSOLVENT	LOG S observed	LOG S predicted	DEVIATION (obs-pred)
0.00	-5.68	-4.75	-0.93
0.20	-3.53	-3.51	-0.02
0.40	-2.68	-2.26	-0.42
0.60	-1.19	-1.02	-0.17
0.80	-0.30	0.23	-0.53
1.00	0.43	1.47	-1.04

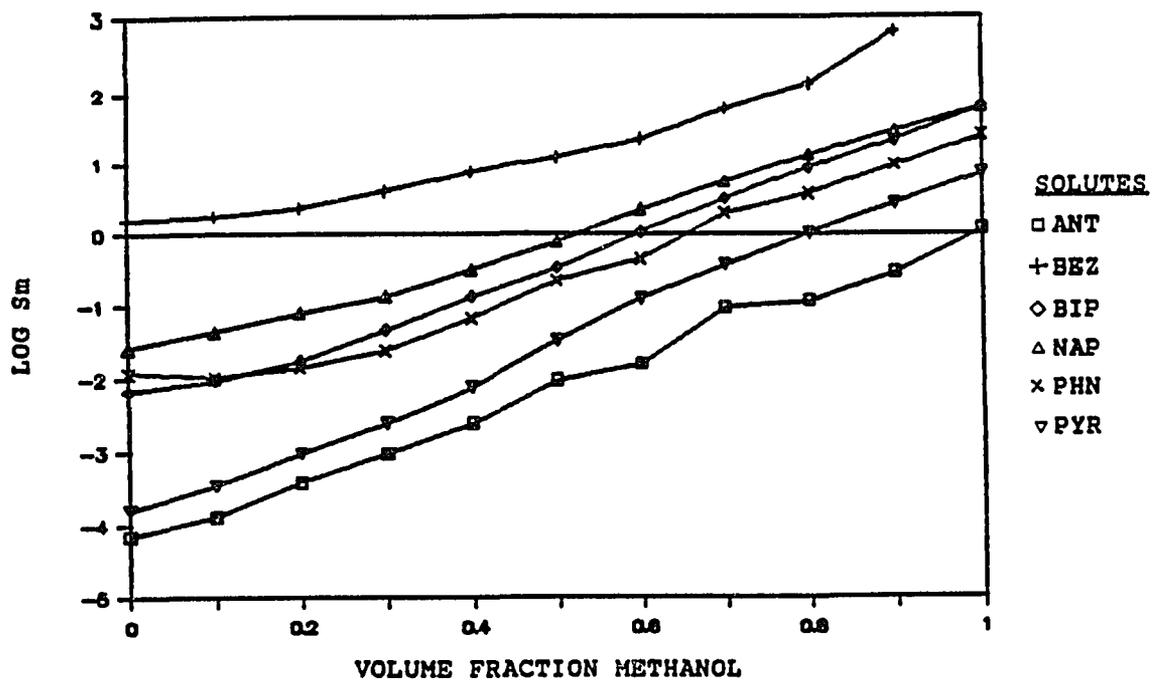


FIGURE 5.1
SIX SOLUTES IN MOH/WATER

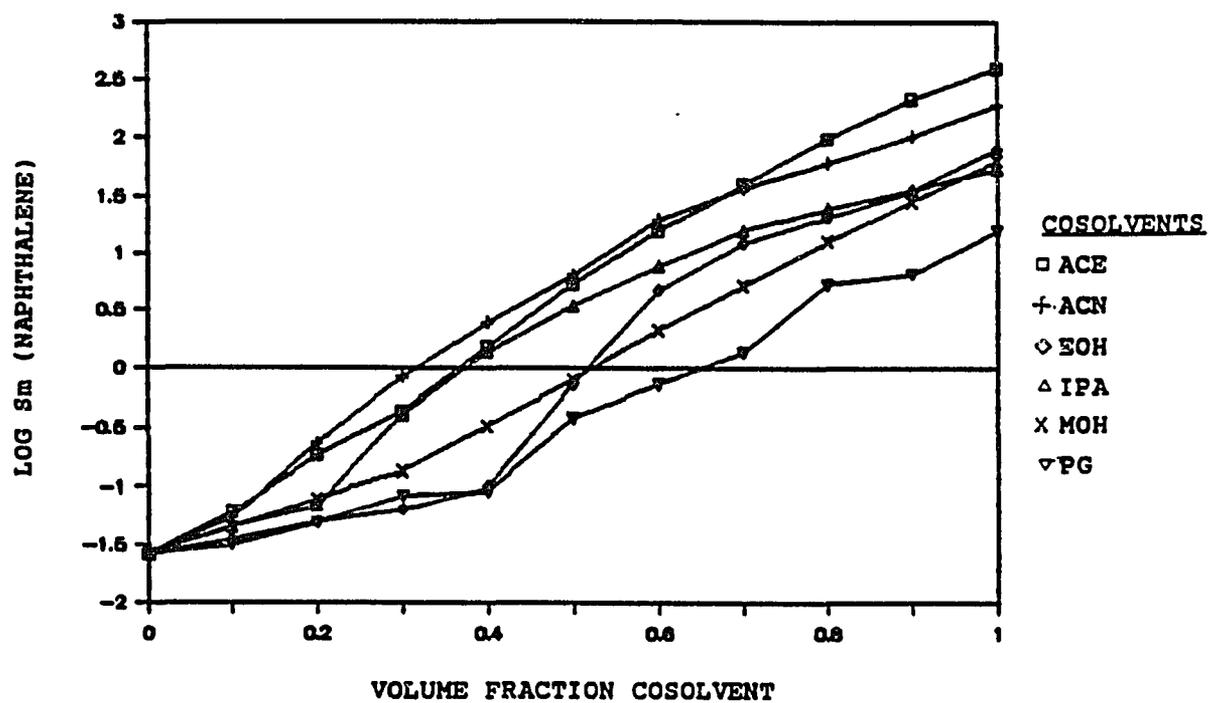


FIGURE 5.2
NAPHTHALENE IN SIX BINARY SOLVENT SYSTEMS

CHAPTER 6

DEVIATIONS FROM THE LOG-LINEAR MODEL

Deviation from the log-linear model may occur for several reasons. The cosolvents might interact with water to make cavity creation either more or less difficult than the model predicts. The solute might have a 'specific' interaction with the cosolvent or the water increasing its solubility compared to the model's prediction. Additionally, any changes in the crystal structure of solid solutes when in contact with the mixed solvent system can effect the observed solubility.

If deviation from the model is controlled largely by the interaction of water with the cosolvent, the excess solubilities for different solutes in the same mixed solvent system should be similar. The excess solubility is defined here as the difference between the observed solubility and that predicted by the log-linear model. This assumes specific interactions between the solute and the cosolvent and/or water are negligible.

The majority of the solutes chosen for this study are unsubstituted aromatic hydrocarbons (see Table 4.3). These solutes should have no specific interactions with the mixed solvent system. They interact through van der Waals forces

only. Atrazine and diuron are two herbicides that were included because of their environmental significance. Both of these are capable of hydrogen bonding with the solvents. Diuron is discussed separately in this chapter and atrazine is the subject of Chapter 7.

Description of Excess Solubility Curves

Excess solubilities were described in Chapter 3. Briefly, excess solubility is the difference between the solubility observed and that predicted by the log-linear model. The excess solubility data for all the binary solvent systems studied are tabulated in APPENDIX A. The plots of excess solubility vs. volume fraction cosolvent are presented in Figures 6.1-6.6.

Alcohol-Water Binary Mixed Solvent Systems

The basic shape of the excess solubility curves for all of the unsubstituted solutes in the alcohol-water systems is sigmoidal. This is common for excess solubility in mixed solvent systems (Hagen, 1983). The average maximum negative deviations occur at volume fractions of approximately 0.40, 0.33 and 0.13 for the methanol, ethanol and isopropanol systems, respectively. The average maximum positive deviations occur at volume fractions of 0.58, 0.63 and 0.57 for the same systems respectively.

Methanol/Water Systems. All of the solutes were studied in this system (see Figure 6.1 and 6.6). In the

methanol/water systems the maximum negative deviation is larger than the maximum positive deviation. All of the deviation is negative for naphthalene, biphenyl and phenanthrene. None of the curves cross the agreement line before a volume fraction of approximately 0.5. This is consistent with the observations of Rubino (1984) for drugs in the same system. Except for chrysene, all of the excess curves begin with a negative slope and have an inflection point around the average maximum negative deviation. Chrysene is the only unsubstituted compound studied that has the opposite behavior. Excess solubility of diuron fits the general profile described above, but has a much larger maximum negative deviation (a factor of 16). It is possible that hydrogen bonding between the carbonyl group and the solvents or the hydrogen on the α nitrogen of diuron changes solubility behavior.

The estimation of the solubility of unsubstituted aromatics in the methanol/water mixed solvent system with the log-linear model can be improved with the above observations. The positive deviation tends to be small and is probably not a great source of error. The maximum negative deviation is usually around a factor of five and occurs near a volume fraction of 0.25. The deviation is typically minimal (less than a factor of 1.5) above a volume fraction of ≈ 0.5 .

Ethanol/Water Systems. The average maximum positive deviation in the ethanol/water system occurs at 0.63 volume fraction cosolvent and the average maximum negative at 0.33 (see Figure 6.2). All three solutes studied, anthracene, biphenyl and naphthalene exhibit a sigmoidal curve with a maximum positive and negative deviation. Anthracene crosses the agreement line at a volume fraction of approximately 0.28 and biphenyl and naphthalene at approximately 0.5. The trend of the larger molecule having relatively greater positive and smaller negative deviation observed for the methanol/water system is also observed here.

For compounds of the type studied, the maximum positive deviation can be expected at approximately 0.63 at a maximum factor of approximately three. The maximum negative should be around 0.3 volume fraction ethanol at a maximum factor of around seven.

Isopropanol/Water Systems. Anthracene, naphthalene and benzene in isopropanol/water all exhibit sigmoidal curves with both negative and positive deviation (see Figure 6.3). The average maximum positive and negative deviations occur at volume fractions of 0.56 and 0.13 respectively. The negative deviation is relatively small at a factor of approximately two and the maximum positive is approximately a factor of nine. The trend for naphthalene and anthracene as the cosolvent goes from methanol to ethanol to isopropanol is toward greater positive deviation. While the

factor of two maximum negative deviation may not be negligible, the dominant deviation is the positive. The larger the molecule the larger the positive deviation, so for most molecules of this class (larger than two rings) the maximum positive deviation is indicated.

Acetone and Acetonitrile Binary Mixed Solvent Systems

Both of these cosolvents can act as a hydrogen bond acceptor but neither can donate a proton. The effect this has on the structure of the mixed solvent system is unknown. The excess solubility behavior the compounds studied exhibit in these systems is quite different than that in the alcohol/water systems. The curves are not generally sigmoidal and negative deviation is minimal. The positive deviation is quite large and is not as localized to a given volume fraction as it was with the alcohol systems.

Acetone/Water Systems. All the solutes were studied in this system (see Figures 6.4 and 6.6). The deviation is predominantly positive with a maximum of a factor of approximately nine. The volume fraction at which this deviation is likely to occur, however, is not predictable. For the data set in this study, it would be more accurate to assume a slight positive deviation diminishing toward the end points. The fact that the deviation is primarily positive is useful. Interestingly, the excess solubility of

diuron is quite low.

Acetonitrile/Water Systems. Anthracene and naphthalene were the only solutes studied in this system (see Figure 6.5). The deviation is virtually all positive with a maximum at a volume fraction of 0.5 for anthracene and 0.6 for naphthalene. The maxima are a factor of 8 and 3.5 respectively. The curves are nearly bell shaped with the smaller naphthalene exhibiting less positive deviation than the larger anthracene as was observed in the alcohol systems.

Cosolvent-Water Interaction and Excess Solubility

As stated in Chapter 5, one goal of this study is to determine the role of the cosolvent-water interaction to the solubility behavior of the various solutes. This will be explored using the excess solubility data from above and APPENDIX A. The best case would allow predictions of the solubility behavior of the solute from properties of the mixed solvent system and the log-linear model. The log-linear model would supply the "ideal" line and the mixed solvent properties would provide estimates of the position and magnitude of the deviation. The approach used here is to discuss the observed excess solubility behavior with respect to what is known thermodynamically and structurally about the mixed solvent systems.

Alcohol/Water Solvent Systems

It has been observed by Franks (1969) that the alcohols above have a minimum in their heats of mixing with water at a volume fraction of 0.48 for methanol and ethanol and 0.34 for isopropanol. These systems also display a maximum in excess density at similar volume fractions of 0.56, 0.51 and 0.50 respectively. In each alcohol/water system, the maximum in excess density correlates well with the average maximum positive deviation. The minimum in ΔH_m corresponds to the maximum for ethanol and methanol but not isopropanol. These relationships may be conceptually explained by considering the structure of the solvents and the interaction of the solvents with the solutes.

Each water molecule can participate in four approximately tetrahedrally oriented hydrogen bonds. These bonds are ≈ 4.5 kcal/mole in strength and $\approx 1.77\text{\AA}$ in length (Pauling, 1960). According to Franks (1966) "the formation of the bonds is an essentially co-operative process because the mutual polarization of the participating water molecules is of a kind strongly to facilitate further bonding." Thus when a fluctuation leads to the formation of one bond, many form simultaneously and a cluster appears. These remain until a high energy fluctuation destabilizes them. This process may be somewhat analogous to dispersion interactions. The short lived clusters have been called flickering clusters.

While there is much debate over the effect these clusters have of the thermodynamics of water, the existence of the clusters is born out spectroscopically. These clusters have a lifetime 2-3 orders of magnitude greater than the period of a molecular vibration. They have an open structure which Eley (1939) hypothesized may account for 9 cm³ of empty space per mole of water or approximately 50% of the space occupied by one mole of water. The water not involved in clusters is thought to be in a dense non-hydrogen bonded state. Others (Samoilov, 1946) find evidence for the occupation of some cavities by non-hydrogen bonded water molecules (which is the basis for the interstitial model).

The alcohols also form hydrogen bonds in the pure state. Although each molecule is capable of forming three such bonds, it can form only two in a repeating pattern. Each oxygen acting as a proton donor and a proton acceptor.

X-Ray radial distribution curves indicate that alcohols do not form the three dimensional structures present in water. Instead, linear polymers from 5-7 molecules long seem to be the predominant structure in lower alcohols (Franks, 1966). The life times of the polymers is less than that of the water clusters and the associated hydrogen bonds have an energy of ≈ 5.8 kcal/mole (cf. 4.5 kcal/mol for water). Combining what is known about the structure of alcohols and water does not define the structure of a

mixture of the two solvents. Although hydrogen bonding in water and alcohols is similar in character it gives rise to very different structures.

Minimum in Heat of Mixing. The minimum in ΔH_m of alcohols and water at low volume fraction alcohol is a reflection of the breaking of the alcohol's structure and the attempt on the part of water to incorporate alcohol into its structure.

The breaking of the alcohol-alcohol hydrogen bonds is endothermic. Since the mixing is very exothermic, the water is either forming more hydrogen bonds with other water molecules to accommodate the alcohol or it is forming strong hydrogen bonds with the alcohol. It is probable that both possibilities occur to some degree. In either case, the alcohol interacts with the water to create the negative ΔH_m .

Maximum in Density. At some point in mixing alcohols and water, the structure of the water and the alcohol are maximally disrupted. This is because, as explained above, the structure of the pure solvents is very different and cannot be maintained simultaneously. Figure 6.7 shows a two dimensional schematic representation of the structures of water, alcohol, and the mixture of the two. When the solvent system has minimum structure it should display maximum excess density. This is accepted as the reason

water at 4°C has a higher density than ice, for example. This density maximum occurs at or slightly above the 50:50 mark for the systems studied, which is approximately where the structure would be expected to be minimal if the cosolvents were of approximately equal size.

An unsubstituted aromatic solute introduced into such an environment would interact with water much differently than the log-linear model assumes. The model (which is based on a weighted combination of the composition) assumes that the water interacts the same with the solute at any concentration of water. The contribution water makes to solubilizing the solute is assumed to be proportional only to the volume fraction of water present. However, water that is no longer part of a hydrogen bonded lattice and is less able to exclude or "squeeze" a nonpolar solute out of solution. In fact it may be able to interact more through van der Waals forces with the nonpolar aromatics. In this case, water is acting like a "better" solvent than is predicted by the model. This is consistent with the maximum in excess solubility associated with the same volume fraction cosolvent as the maximum excess density. The fact that for ethanol and methanol that this occurs with the large exothermic heat of mixing (minimum ΔH_m) suggests that water is forming strong hydrogen bonds with the alcohols.

Acetone and Acetonitrile/Water Solvent Systems

ΔH_m in Acetone and Acetonitrile. Since neither acetone or acetonitrile are capable of hydrogen bonding in the pure state, there is no reason to expect an endothermic contribution to ΔH_m from the breaking of hydrogen bonds in the pure solvents.

Acetone does have negative a ΔH_m at most volume fractions, this is probably due to the formation of hydrogen bonds in water. Acetonitrile displays only positive ΔH_m . It is possible that acetonitrile does not form strong hydrogen bonds with water and/or is accommodated less by water causing hydrogen bond breaking. Solutes in these systems display very little negative excess solubility

Maximum in Density. The same argument that was presented to explain the maximum in excess solubility and excess density for the alcohols applies here. The structure of the water would have to break down at some point with the addition of cosolvent. At high cosolvent/low water concentrations in the acetone and acetonitrile systems, the hydrogen bonding is out weighed by the van der Waals interactions. This rationale works well for the acetonitrile systems. The excess density maximum for the system occurs at a volume fraction of approximately 0.50 which is close the 0.55 value observed for anthracene and naphthalene in the system. Acetone, however, shows neither a distinct excess density or excess solubility maximum.

Solute Self Association

A solute may self associate in solution making it appear as if it has a larger solubility than the unassociated solute actually has. Since the unsubstituted polynuclear aromatic solutes used in this study are incapable of hydrogen bonding, the self association would be through van der Waals interactions.

In water, the tendency to associate should be the greatest since the solutes are being excluded from the water structure. As the fraction cosolvent increases, however, the solute should find less incentive to self associate. This would result in the excess solubility being greatest at the water rich end of the excess solubility curve. The excess solubility figures presented show almost exactly the opposite behavior. This implies self association was, at least, not a large source of error in this study.

Conclusions

The environment presented to a nonpolar molecule by the mixed solvents will be determined by a combination of the hydrogen bonding in the mixed solvent (structure) and the inherent van der Waals forces involved. The log-linear model assumes that the solute "sees" the cosolvent and water proportionately to their volume fraction. Over the range of cosolvent concentrations, this assumption is violated to a

greater or lesser degree in all real mixed solvent systems.

The excess solubility curves for the solutes studied are similar in shape for each given solvent system. The point of maximum excess can be estimated in the alcohol/water systems studied with a knowledge of the ΔH_m minimum (not for IPA) or the excess density maximum for the two solvents involved. The magnitude of the deviations appears to follow the size of the solute. An estimate for the magnitude was given in the description of the excess solubility curves. The point of maximum excess solubility in acetonitrile/water systems can also be estimated from the maximum in excess density. Acetone/water did not appear to follow the same trends, although it does display a relatively constant positive excess density and excess solubility. The ranges were also described.

The utility of the model lies in its simplicity. The only requirements are a knowledge of the structure of the compound to calculate $\log P$, the a and b constants for the calculation of σ , the excess density maximum for ethanol/water and an estimate for the magnitude of the deviation in the same mixed solvent system.

Note that the first of the four parameters is characteristic of the solute while the later three are characteristic of the cosolvent. Once a cosolvent system is characterized, only a single parameter is required to estimate its solubility behavior.

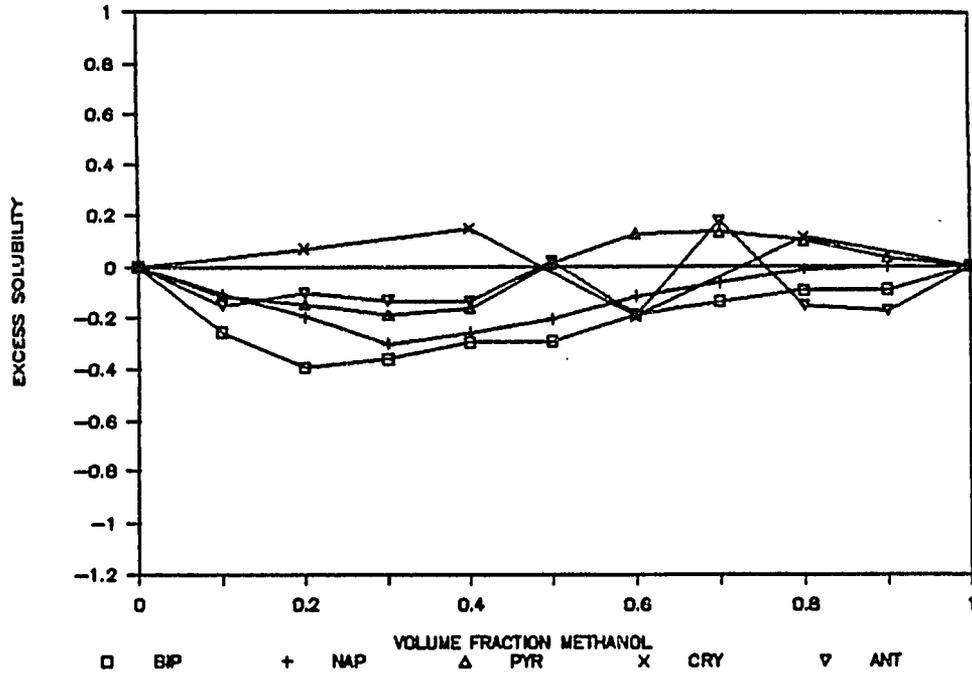


FIGURE 6.1

EXCESS SOLUBILITY: SOLUTES IN MOH/WATER

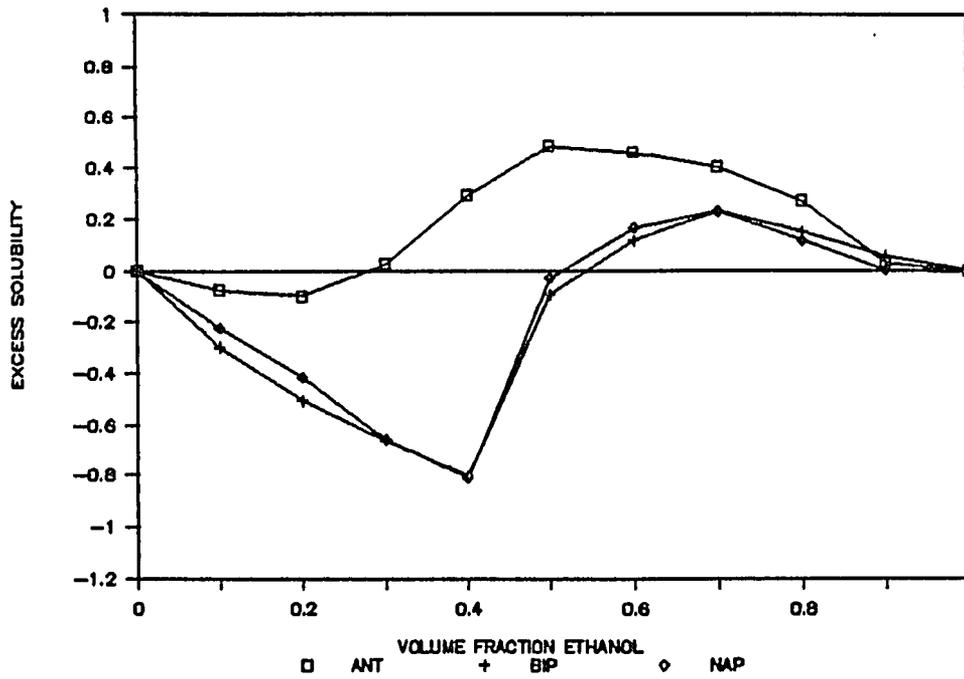


FIGURE 6.2

EXCESS SOLUBILITY: SOLUTES IN EOH/WATER

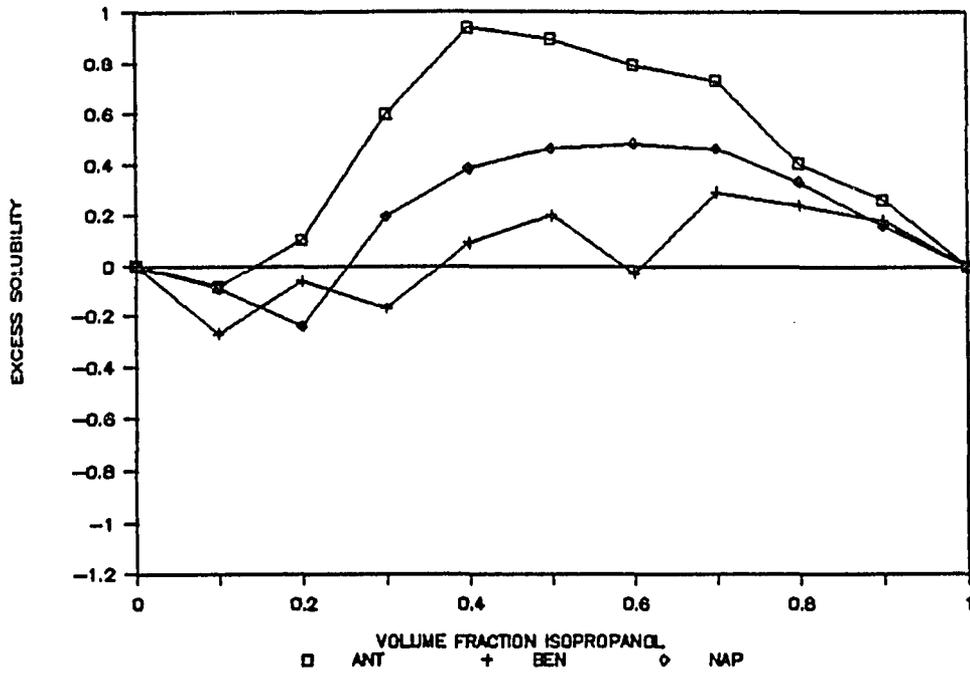


FIGURE 6.3

EXCESS SOLUBILITY: SOLUTES IN IPA/WATER

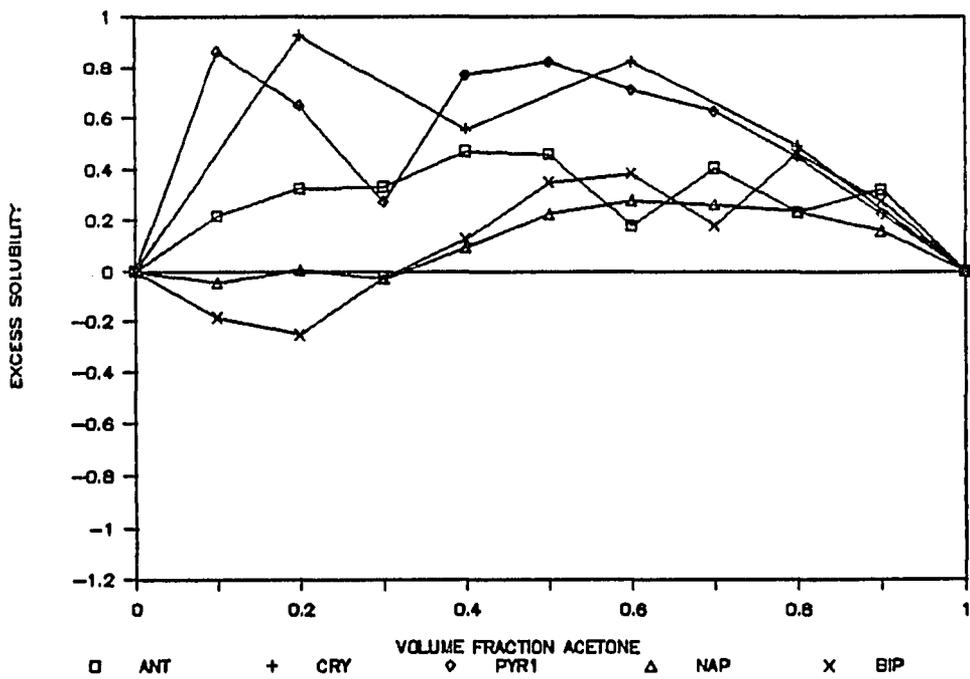


FIGURE 6.4

EXCESS SOLUBILITY: SOLUTES IN ACE/WATER

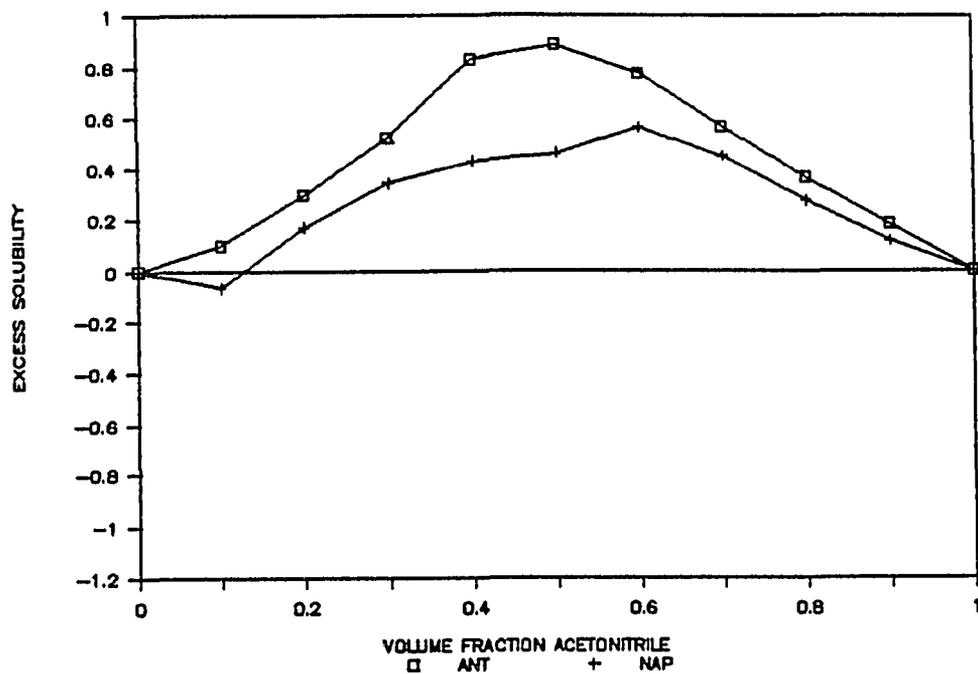


FIGURE 6.5

EXCESS SOLUBILITY: SOLUTES IN ACN/WATER

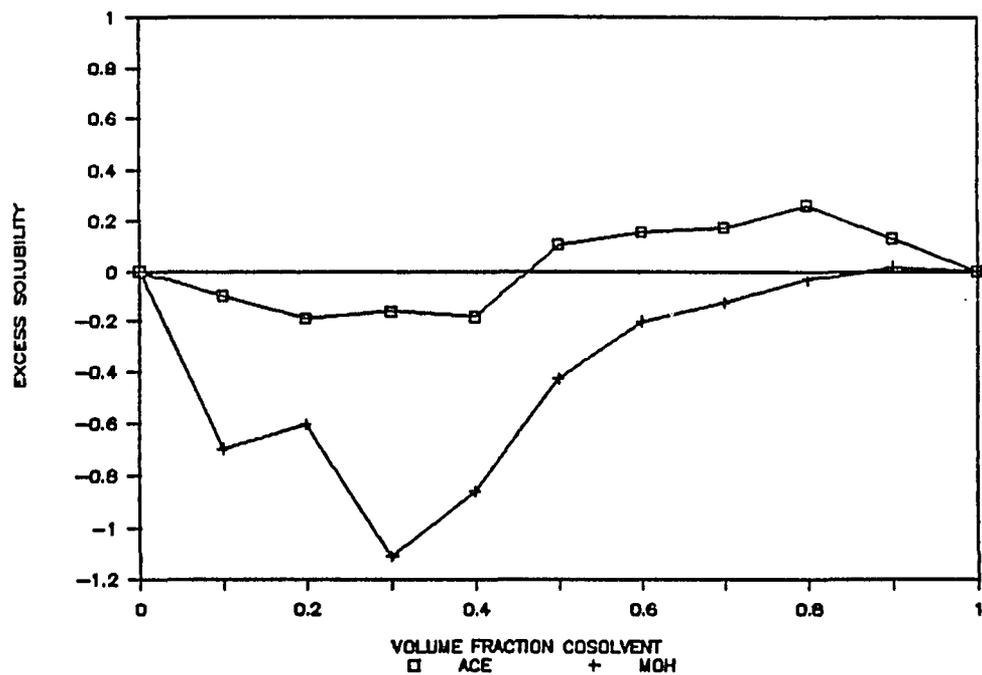


FIGURE 6.6

EXCESS SOLUBILITY: DIURON IN ACE/WATER AND MOH/WATER

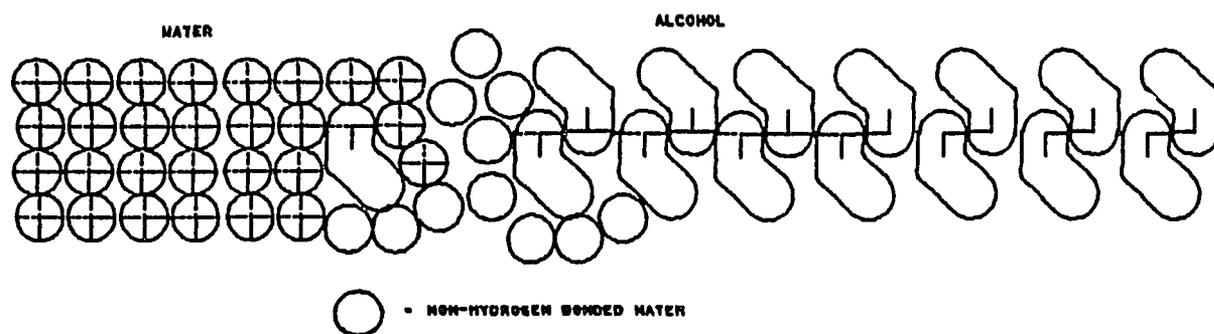


FIGURE 6.7

TWO DIMENSIONAL SCHEMATIC OF WATER AND ALCOHOL STRUCTURE

CHAPTER 7

CRYSTAL CHANGES IN ATRAZINE IN MIXED SOLVENTS

Atrazine in the binary solvent systems of acetone/water and methanol/water, deviates drastically from the log-linear model between zero and 0.1 volume fraction cosolvent (APPENDIX A). While investigating crystal structure changes as a possible cause for the deviation, two DSC (differential scanning calorimeter) peaks were discovered (at ≈ 178 and 182°C). There is a shoulder present in the DSC of the pure starting material but the relative areas seem to change with exposure to solvents.

It is known that crystals in the presence of solvents may undergo degradation, solvation or solvent mediated polymorphic transitions (Haleblaian and McCrone 1969). Any of these changes may effect the solubility behavior of the crystal. Experiments were conducted to determine whether the additional peak represents degradation, solvation or polymorphism.

Polymorphic Systems

Haleblaian (1969) defines polymorphism as "the ability of any element or compound to crystallize as more than one distinct crystal species." Haleblaian also points out that "The polymorphs of a compound can be as different in

structure and properties as the crystals of two different compounds." If a compound that has two polymorphic forms, α and β , is heated, the temperature at which α (the more stable form by convention) transforms to β is called the transition temperature. Polymorphs are classified on the basis of the location of the transition temperature relative to the melting points of the polymorphs involved. Figures 7.1 (a) and (b) show the Gibbs' free energy vs. temperature plots for the simplest case of the two types of polymorphic systems. The dotted curve represents the free energy of the liquid (the melt). The point where the liquid curve intersects the α and β curves gives the respective melting points of the polymorphs.

Figure 7.1(a) represents an enantiotropic system. In this system the transition temperature occurs before either of the two polymorphs reach their melting point. Figure 7.1(b) shows the monotropic system in which the polymorphs melt before the transition temperature is reached. These free energy (ΔG) vs. temperature (T) plots (ΔG -T plots) are particularly useful in conceptually analyzing stability characteristics of a system. At any temperature the form with the lowest ΔG will be the most stable, have the highest melting point and the lowest solubility. The change in stability on passing the transition temperature is easily recognized on these plots. The isobaric change of ΔG with T is equal to the negative of the entropy (S).

$$-S = \frac{\delta \Delta G}{\delta T} \quad (7.1)$$

So the slope of the curves gives a measure of the entropy of the polymorphs. If the slope of the β (when it is least stable) curve is greater than that of the α , the relative stabilities will eventually reverse.

Enantiotropic systems are sometimes referred to as reversible and monotropic as irreversible systems. This is because in enantiotropic systems each polymorph is the stable form at some point below its melting point. Therefore, the transform can occur in either direction in the solid phase. In the monotropic systems the stable form (α) must melt before it can transform into the meta-stable form (β). Many organic crystals exhibit monotropic behavior (Kitaigorodsky, 1973), but enantiotropic behavior is not uncommon (Rowe, 1984).

At a given temperature on the ΔG -T plot, the greater the difference in free energy (ΔG) between two polymorphs the more the conversion from the metastable to the stable form is favored. A difference in stability does not always mean the transformation will take place. Even if a transition is thermodynamically favored it may be prohibited kinetically. Diamond is a relatively unstable arrangement for carbon, thermodynamically, yet it is very stable at normal temperatures and pressures. In some cases the energy

barrier to transformation may be circumvented through a solvent mediated transition. If an excess of a meta-stable polymorph is placed in solvent, it may transform by dissolving and then precipitating in the more stable form.

Characterization of Polymorphic Systems

To characterize a system of polymorphs it is desirable to know several parameters. Knowledge of the transition temperature and melting points combined will determine whether the system is enantiotropic or monotropic. While melting points are often readily available, transition temperature is more difficult to obtain. The variation of the solubility of the polymorphs with temperature can yield an estimate of the transition temperature. The problem is getting sufficient quantities of the pure forms and getting accurate measurements of the solubility of the meta-stable form. The unstable form may convert to the stable form much faster in solution than in the solid phase (Haleblian, 1969). This may necessitate other techniques to determine the solubility of the meta-stable form.

If the heat of transition is available (ΔH_t), the heat of transition rule can be used. The rule according to Burger (1979) is;

If an endothermal transition is observed at some temperature it may be assumed that there is a transition point below it, i.e. the two forms are related enantiotropically

If an exothermal transition is observed at some temperature it may be assumed that there is no transition point below it, i.e. the two forms are either related monotropically or the transition temperature is higher

The problem is that the ΔH_t may be very small and difficult to observe with a DSC (differential scanning calorimeter). In that case the heat of fusion rule may be a better choice. The heat of fusion rule according to Burger (1979) is; "If the higher melting form has the lower heat of fusion the two forms are usually enantiotropic, otherwise they are monotropic." Heats of fusion are commonly available from DSC analysis.

Verification of Polymorphism

In practice, a major problem is deciding if a system really exhibits polymorphism. Impurities in compounds, solvate formation in solvents and degradation can all cause behavior similar to that of a polymorphic system. Each of these possibilities must be eliminated or shown as minor factors in the behavior of a system before polymorphism can be established. Standard analytical methods including, HPLC, IR, DSC, TGA, and microscopy are used to establish or rule out the presence of the mentioned possibilities.

Solubility and Crystal Studies

Before discussing the results of the experiments to characterize crystal structure, we will consider briefly

the possibilities of degradation and solvation in atrazine in the presence of mixed solvents.

Atrazine does degrade in strong mineral acids. The chlorine is hydrolyzed (see Table 4.3) to give the hydroxy-derivative. If the atrazine in the mixed solvents is degrading, the derivative would have to have the same detectability as the parent to give the relative increases observed. The other possibility is that it degrades more rapidly in pure water than in the mixed solvents. Neither of these possibilities is very likely.

Solvates (hydrate or methanolate) in s-triazine compounds, of which atrazine is a member, typically form at the ring nitrogens. In the case of atrazine, there is also the possibility of solvate formation at the amine positions. In either case the steric hindrance makes solvation unlikely (Karickhoff, 1987). The presence of a solvate could, however, explain the observed solubility behavior.

Analytical Methods and Results

Since it is difficult to determine crystal modification by a single method or experiment, a combination of differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), HPLC-UV, infrared spectrophotometry and hot stage microscopy were used. The results of these experiments were combined to help form an inductive conclusion about the system.

DSC Analysis. When excess atrazine that had been equilibrated in the presence of the mixed solvent system of methanol and water for 48 hours was analyzed, two overlapping endothermic peaks, or a peak with a large shoulder, were observed. A sample was analyzed wet and dry to make sure the peaks were present in both cases.

Atrazine was then recrystallized from two solvents by two methods. In the first method, water was supersaturated with atrazine by heating and then cooled over a period of three days to precipitate the atrazine. The second recrystallization used a saturated solution of atrazine in methanol to which water was added to reduce the solubility and precipitate atrazine. When a DSC was run on each sample, the single peak found corresponded to the lowest melting point peak (177°C) on the original DSC curve.

Concurrently, samples of atrazine that were equilibrated with methanol/water systems were analyzed. The fraction cosolvent went from 0%-100% in 25% increments. These samples were also followed with time. It appears that exposure to the mixed solvent system is accompanied by a relative increase in the area of the low melting point peak. IR and TGA studies to be discussed imply that the extra peak could not be explained by the formation of a solvate.

As stated above, the main route of degradation of atrazine is through acid catalyzed hydrolysis of the chlorine to yield the hydroxy-derivative. This takes fairly

severe conditions, i.e. a mineral acid at high concentration. To insure the extra peak was not the derivative, a sample was exposed to 1M HCl and H₂SO₄ for one and three hours, respectively. The remaining solid was analyzed on the DSC and no corresponding peak was observed. This was verified by HPLC and IR spectroscopy.

There does appear to be a change in the relative peak areas between the shoulder that appears in the stock crystal and that equilibrated in mixed solvent systems. Also for the 10% MOH/water system, the lower melting peak seems to increase in area relative to the higher. Unfortunately, this could not be followed any longer due to the DSC failure.

HPLC Analysis. A 0.1 mg/ml solution was made for the original atrazine sample and the recrystallized sample in acetonitrile. Both of these samples were injected on the HPLC system described in the Chapter 4. Both samples had a retention time of approximately 3.9 minutes and their average peak areas were equal to within approximately 3 percent. This is further evidence to rule out a degradation product as the extra peak. It is very unlikely that the hydroxy derivative would have the same retention time and intensity as the parent compound. The fact that there is mass balance and equal retention time in the HPLC analysis implies that all of the compound is atrazine.

TGA Analysis. The pure sample (predominately the 182°C peak) and the recrystallized sample (178°C) were both analyzed by TGA. The traces show no characteristic weight loss prior to fusion and no difference. This would normally be enough evidence to rule out the presence of a solvate of some type. Atrazine, unfortunately, sublimes before it melts so it can only be said that the evidence does not imply that a solvate is present. It does not eliminate the possibility. The IR study was used to further elucidated the matter.

IR Analysis. IR spectroscopy was used for two reasons; 1) to compare the spectra from the original compound and the recrystallized with the Sadtler library's atrazine spectrum. and 2) to see if there is significant hydrogen bonding characteristic of a solvate (in this case a hydrate or methanolate) present.

The spectra for the original atrazine, the recrystallized (from methanol and water) atrazine and the Sadtler reference atrazine are presented in APPENDIX B. The spectra of both samples correspond well to the library spectrum. (Note that the Sadtler spectrum is linear with respect to wavelength while the spectra produced in this study are linear with respect to wave number). This indicates that the compound is atrazine. It also suggests that the recrystallized sample is not a methanolate or hydrate. If it were either solvate there should be

significant changes due to hydrogen bonding. There should be a large broad peak due to O-H stretching and the N-H stretching frequencies should be lowered because the hydrogen bond weakens the N-H bond slightly. The peaks should be, relatively, broader than the corresponding peak in the library spectra. The bending frequencies should increase, but this shift is typically less pronounced than the stretching changes (Silverstein and Bassler, 1974).

Hot Stage Microscopy. The hot stage allows the observation of crystals under the microscope while the temperature is increased. The instrument used in this work is a Mettler P-80 with a Zeise polarizing microscope.

Crystals of the original atrazine, the recrystallized atrazine and atrazine that had been equilibrated with mixed solvents were observed with hot stage microscopy. The crystals of the original sample appear much larger (≈ 5 times) than the recrystallized sample. The equilibrated sample's crystals appear intermediate in size. The crystals are long cylinders and needles in the original sample and small needles in the recrystallized. It is not clear if the crystals are really different. Even if the habit is different the crystal structure could still be the same. (The habit refers to the external appearance of the crystal.)

Because the melting points of the two forms are so close together, accurate determination of melting point is difficult. This is also complicated by the tendency of the sample to sublime. When the original sample is melted (at $5^{\circ}\text{C}/\text{min}$) and allowed to cool the crystals are reduced in size. When the sample is re-heated the melting point is slightly lower, however, this may be due to the smaller size.

The recrystallized sample was heated at $1^{\circ}\text{C}/\text{min}$ from a temperature of 160 to 190°C . If the higher melting form (II) was the metastable form of atrazine, a transition might occur. First the lower melting form (I) should melt, then the melt should recrystallize, and finally II should melt. This was not observed. At 176.1°C a sharp melting of most of the sample occurred and a group of crystals remained. These remaining crystals melted by $\approx 178.3^{\circ}\text{C}$ and looked like the crystals that had already melted. It is not clear if the crystals present after the first melt were there before. It is possible that the melting points are too close together to observe the recrystallization or that the melting point of the first crystals simply span the range observed. When the heating rate is cut to $0.5^{\circ}\text{C}/\text{min}$ the same behavior is observed. It takes a relatively large amount of the sample to avoid loss to sublimation even under a coverslip. This does tend to obscure the observation.

When observed under silicone oil the melting point seems to broaden significantly, but no recrystallization is observed. The original purpose for observation under oil was to look for 'bubbles' of solvent escaping upon melting. None were observed.

Discussion and Summary

It is certain that a crystal with a different melting point than that of the original compound can be recrystallized from the starting material. The relationship of the two forms to each other is less certain. The above results may be organized to analyze atrazine's crystal structure with respect to possible explanation of its behavior.

Table 7.1 summarizes the above experimental results. The table is organized to show which possible crystal modification is supported by which analytical result. The level of certainty associated with each technique is ranked by a number between -2 and +2. A rank of +2 means the method strongly supports the possibility of the given modification and +1 means moderate support. A rank of 0 implies the method was inconclusive, -1 means moderate evidence against a modification and -2 represents strong evidence against the modification's presence.

The DSC studies give some support to the possibility of a polymorph and some reason to exclude solvates or

decomposition product. The TGA work suggests the extra peak is not a solvate but says nothing about the other possibilities. The hot stage supports the possibility of a polymorph but not a solvate. IR and HPLC both yield some evidence against decomposition or solvation and say nothing about polymorphism.

Evidence Pertaining to Degradation/Impurity. The IR study shows that the recrystallized compound (form I) is predominately atrazine. The HPLC study implies, through mass balance, that form I is all atrazine. Acid hydrolysis of the original compound (form II) did not yield the form I DSC peak suggesting that the peak is not a degradation product. Also, degradation in a sample typically produces broad DSC peaks, while the peaks in APPENDIX C are sharp. The above evidence taken together argue strongly against form I being a degradation product or impurity.

Evidence Pertaining to Solvates. The IR spectrum of form I shows none of the differences from the reference spectrum that would be expected in the case of a hydrate or methanolate. It is possible that the magnitude of the shifts or the intensity of the expected peaks is too small to notice. The TGA, however, shows no weight loss at temperatures below the melting point. This points to the lack of solvate formation. It is true that the sample sublimes before it completely melts, however, Ashok Shah (personal communication, 1987) believes the weight loss

should have been observed if the compound were solvated. Observation of form I and II under silicone oil with hotstage microscopy showed no desolvating. In the HPLC studies, the presence of a solvate should have changed the relative peak areas of the two forms, unless the solvate has exactly the same retention time as the anhydrous form. The evidence does not completely eliminate the possibility of a solvate but does minimize the likelihood.

Evidence Pertaining to Polymorphism. Assuming that form I is not a degradation product, impurity or a solvate in conjunction with the DSC observation that in the presence of mixed solvent systems form I seems to increase with time, it is possible that atrazine exhibits polymorphism.

The DSC data suggests that form II (MP $\approx 182^{\circ}\text{C}$) is converting to form I (MP $\approx 177^{\circ}\text{C}$). Consider the possible systems of two polymorphs below their melting points. The form with the highest melting point can convert spontaneously to the low melting form only in an enantiotropic system (see Figure 7.1(a)). That is, the form with the highest melting point is the meta-stable form so the transition is thermodynamically favored.

In a monotropic system, any point below the melting point is also below the transition temperature (Figure 7.1(b)). In other words, the meta-stable form would have the lowest melting point. So to convert from a higher

melting form to a lower melting form in a monotropic system would require converting from the stable form to the meta-stable form. This is thermodynamically unfavored. This suggests that if the system is polymorphic it is most likely enantiotropic.

For the above situation to be true in the case of atrazine, it would mean that the original crystal purchased (form II) is the unstable polymorph. This corresponds to the β form in the figures presented. The occurrence of two stable polymorphs at room temperature is common and easily explained. Once a meta-stable polymorph is formed, its transition may be inhibited by the kinetics of diffusion in the solid state. Also, the free energy of transition (ΔG_t) between the two forms may be small at room temperature. The larger the magnitude of ΔG_t the more likely the change is to occur. When the original atrazine was sublimed, the resulting crystal displayed the lower melting point suggesting the transition does occur when possible.

Conclusions

Explaining the observed solubility behavior of atrazine in the binary solvent systems studied is tentative with the available data. It is known that solution phase transformation of polymorphs can occur and that the change will be much faster than in the solid phase (Halebian, 1969). If the rate is dependent on the amount of cosolvent

present, then it is possible that the transformation of form II to form I occurs faster in water. This would explain the relatively high solubility in the mixed solvent systems with the higher fractions of cosolvent. The problem is that the transformation rate is typically proportional to the solubility of the compound. This would give results opposite to those observed. However, it is possible that the preferred form is dependent on the solvent.

This study did not result in complete characterization of the atrazine system. It does point out some changes apparent in the behavior of the atrazine crystal not found in the literature search conducted. This is sufficient to suspect that atrazine violates a basic assumption of the log-linear model. The assumption is that the crystal contribution to the solubility is ideal. This means that the contribution remains the same irrespective of the solvent system in question. It seems likely that crystalline atrazine does not behave the same in different solvent systems.

TABLE 7.1
SUMMARY OF CRYSTAL STUDY EVIDENCE

METHOD	CRYSTAL MODIFICATION		
	DEGREDDATION	SOLVATION	POLYMORPHISM
DSC	-1	-1	+1
TGA	0	-1	0
HOT STAGE	-1	-1	+1
IR	-2	-2	0
HPLC	-2	-1	0

The scale: -2 (strong evidence against)
 -1 (weak evidence against)
 0 (inconclusive)
 +1 (weak evidence for)
 +2 (strong evidence for)

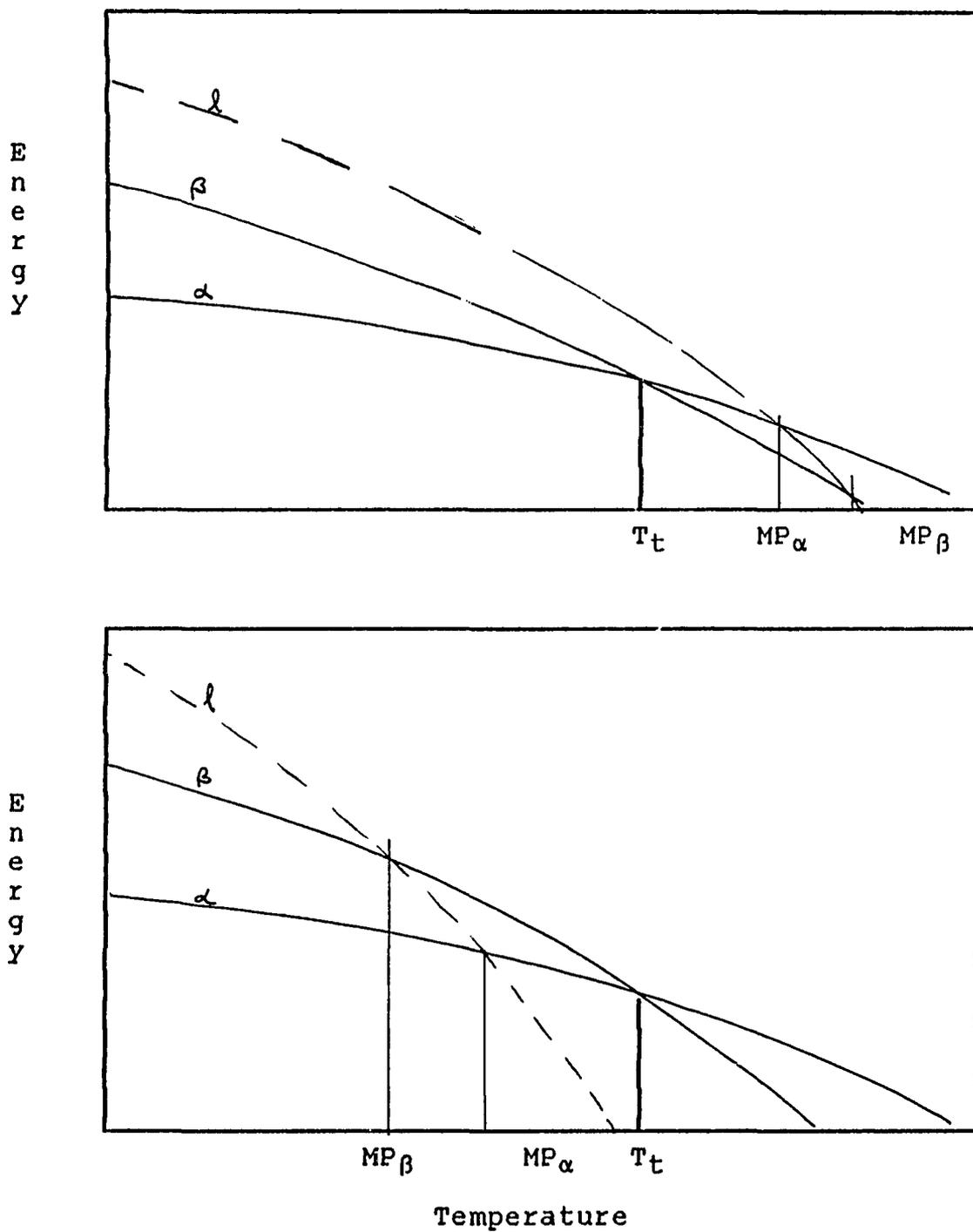


FIGURE 7.1: (a) enantiotropic system (top)
(b) monotropic system (bottom)

APPENDIX A.

BINARY SOLVENT SYSTEM DATA

BINARY SOLUBILITY DATA

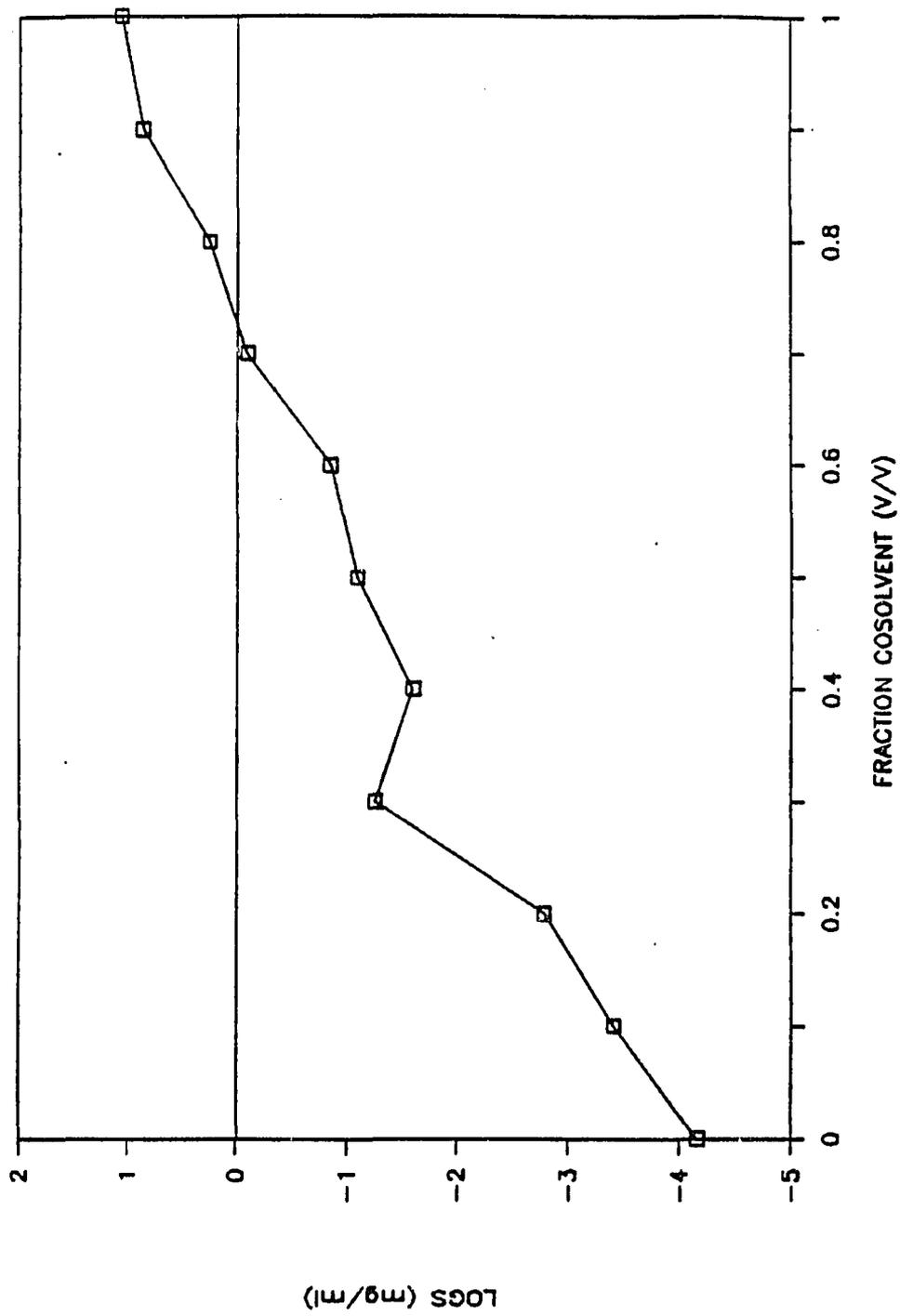
SYSTEM NAME: ANTHRACENE/ACETONE

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT     (mg/ml)        obs        pred        obs-pred
=====
0.0           7.010E-05      -4.15      -4.16      0.01
0.0           6.880E-05      -4.16      -4.16      -0.00
0.1           3.880E-04      -3.41      -3.64      0.23
0.1           3.720E-04      -3.43      -3.64      0.21
0.2           1.500E-03      -2.82      -3.12      0.29
0.2           1.780E-03      -2.75      -3.12      0.37
0.3           5.730E-03      -2.24      -2.59      0.35
0.3           5.190E-03      -2.28      -2.59      0.31
0.4           2.580E-02      -1.59      -2.07      0.48
0.4           2.410E-02      -1.62      -2.07      0.45
0.5           9.280E-02      -1.03      -1.55      0.52
0.5           6.860E-02      -1.16      -1.55      0.39
0.6           1.370E-01      -0.86      -1.03      0.16
0.6           1.470E-01      -0.83      -1.03      0.20
0.7           7.670E-01      -0.12      -0.51      0.39
0.7           8.050E-01      -0.09      -0.51      0.41
0.8           1.760E+00      0.25      0.02      0.23
0.8           1.780E+00      0.25      0.02      0.23
0.9           7.150E+00      0.85      0.54      0.32
0.9           7.490E+00      0.87      0.54      0.34
1.0           1.150E+01      1.06      1.06      0.00
1.0           1.130E+01      1.05      1.06      -0.01
=====

```

SYSTEM NAME: ANT/ACE



BINARY SOLUBILITY DATA

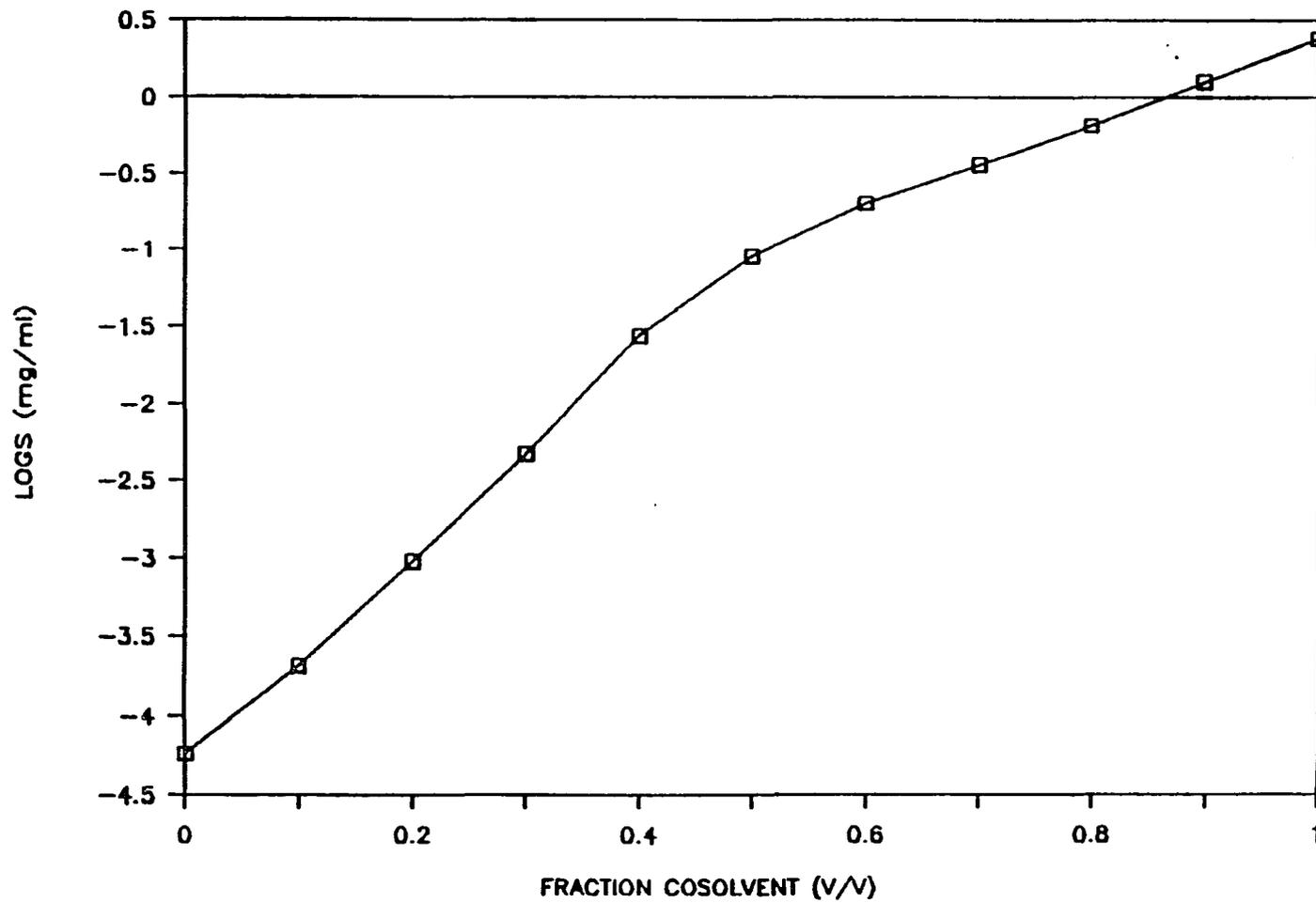
SYSTEM NAME: ANTHRACENE/ACETONITRILE

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=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	5.790E-05	-4.24	-4.24	0.00
0.0	5.760E-05	-4.24	-4.24	0.00
0.1	2.040E-04	-3.69	-3.78	0.09
0.1	2.140E-04	-3.67	-3.78	0.11
0.2	9.420E-04	-3.03	-3.32	0.29
0.2	9.480E-04	-3.02	-3.32	0.29
0.3	4.470E-03	-2.35	-2.86	0.51
0.3	4.840E-03	-2.32	-2.86	0.54
0.4	2.800E-02	-1.55	-2.40	0.84
0.4	2.650E-02	-1.58	-2.40	0.82
0.5	9.250E-02	-1.03	-1.94	0.90
0.5	8.860E-02	-1.05	-1.94	0.88
0.6	2.010E-01	-0.70	-1.47	0.78
0.6	2.030E-01	-0.69	-1.47	0.78
0.7	3.570E-01	-0.45	-1.01	0.57
0.7	3.670E-01	-0.44	-1.01	0.58
0.8	6.840E-01	-0.16	-0.55	0.39
0.8	6.500E-01	-0.19	-0.55	0.36
0.9	1.280E+00	0.11	-0.09	0.20
0.9	1.240E+00	0.09	-0.09	0.18
1.0	2.350E+00	0.37	0.37	0.00
1.0	2.400E+00	0.38	0.37	0.01

```
=====
```

SYSTEM NAME: ANT/ACN



BINARY SOLUBILITY DATA

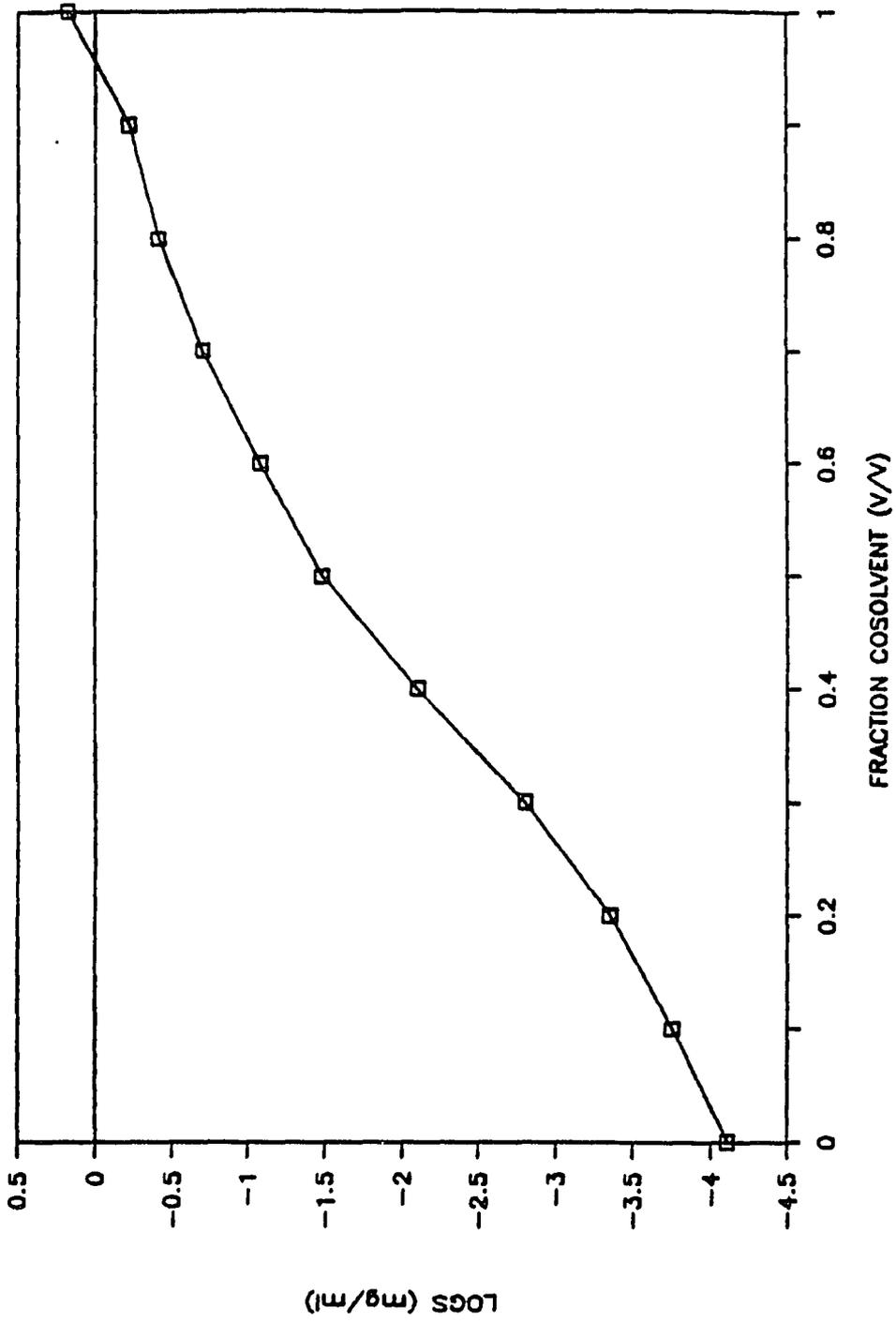
SYSTEM NAME: ANTHRACENE/ETHANOL

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            7.910E-05      -4.10      -4.11      0.01
0.0            7.500E-05      -4.12      -4.11      -0.01
0.1            1.730E-04      -3.76      -3.68      -0.08
0.1            1.860E-04      -3.73      -3.68      -0.05
0.2            4.400E-04      -3.36      -3.25      -0.10
0.2            4.460E-04      -3.35      -3.25      -0.10
0.3            1.650E-03      -2.78      -2.82      0.04
0.3            1.530E-03      -2.82      -2.82      0.01
0.4            8.020E-03      -2.10      -2.39      0.30
0.4            7.700E-03      -2.11      -2.39      0.28
0.5            3.060E-02      -1.51      -1.97      0.45
0.5            3.570E-02      -1.45      -1.97      0.52
0.6            8.430E-02      -1.07      -1.54      0.46
0.6            8.310E-02      -1.08      -1.54      0.46
0.7            2.030E-01      -0.69      -1.11      0.41
0.7            1.940E-01      -0.71      -1.11      0.39
0.8            4.100E-01      -0.39      -0.68      0.29
0.8            3.760E-01      -0.42      -0.68      0.25
0.9            5.860E-01      -0.23      -0.25      0.02
0.9            6.200E-01      -0.21      -0.25      0.04
1.0            1.330E+00      0.12       0.18      -0.06
1.0            1.690E+00      0.23       0.18      0.05
=====

```

SYSTEM NAME: ANT/EOH



BINARY SOLUBILITY DATA

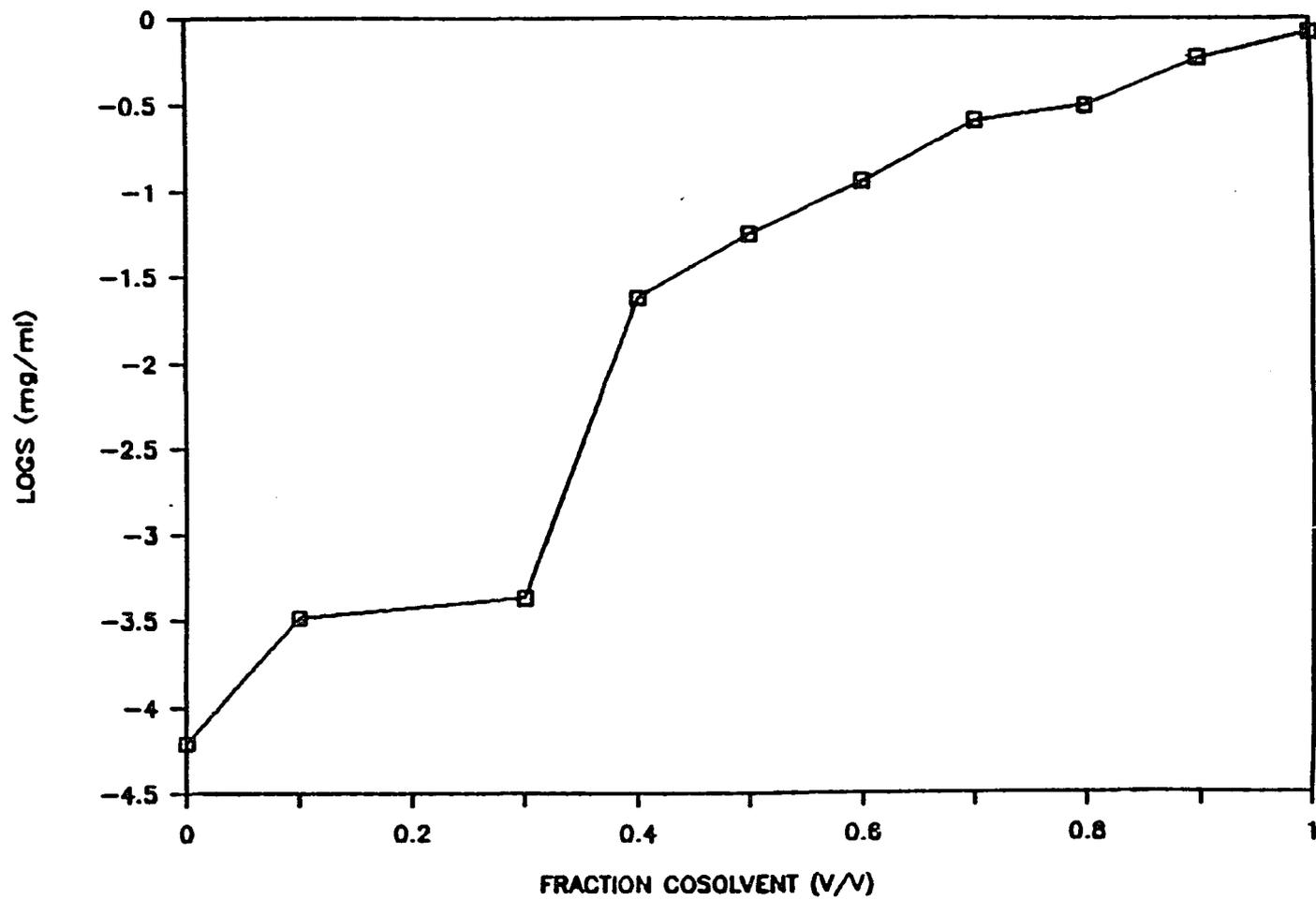
SYSTEM NAME: ANTHRACENE/ISOPROPANOL

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=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	6.330E-05	-4.20	-4.21	0.01
0.0	6.010E-05	-4.22	-4.21	-0.01
0.1	1.350E-04	-3.87	-3.80	-0.07
0.1	1.300E-04	-3.89	-3.80	-0.09
0.2	5.120E-04	-3.29	-3.38	0.09
0.2	5.420E-04	-3.27	-3.38	0.12
0.3	4.250E-03	-2.37	-2.97	0.60
0.3	4.380E-03	-2.36	-2.97	0.61
0.4	2.310E-02	-1.64	-2.56	0.92
0.4	2.520E-02	-1.60	-2.56	0.96
0.5	5.760E-02	-1.24	-2.15	0.91
0.5	5.420E-02	-1.27	-2.15	0.88
0.6	1.140E-01	-0.94	-1.73	0.79
0.6	1.160E-01	-0.94	-1.73	0.80
0.7	2.670E-01	-0.57	-1.32	0.75
0.7	2.520E-01	-0.60	-1.32	0.72
0.8	3.230E-01	-0.49	-0.91	0.42
0.8	3.060E-01	-0.51	-0.91	0.39
0.9	5.960E-01	-0.22	-0.49	0.27
0.9	5.700E-01	-0.24	-0.49	0.25
1.0	8.450E-01	-0.07	-0.08	0.01
1.0	8.110E-01	-0.09	-0.08	-0.01

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=====
```

SYSTEM NAME: ANT/IPA



BINARY SOLUBILITY DATA

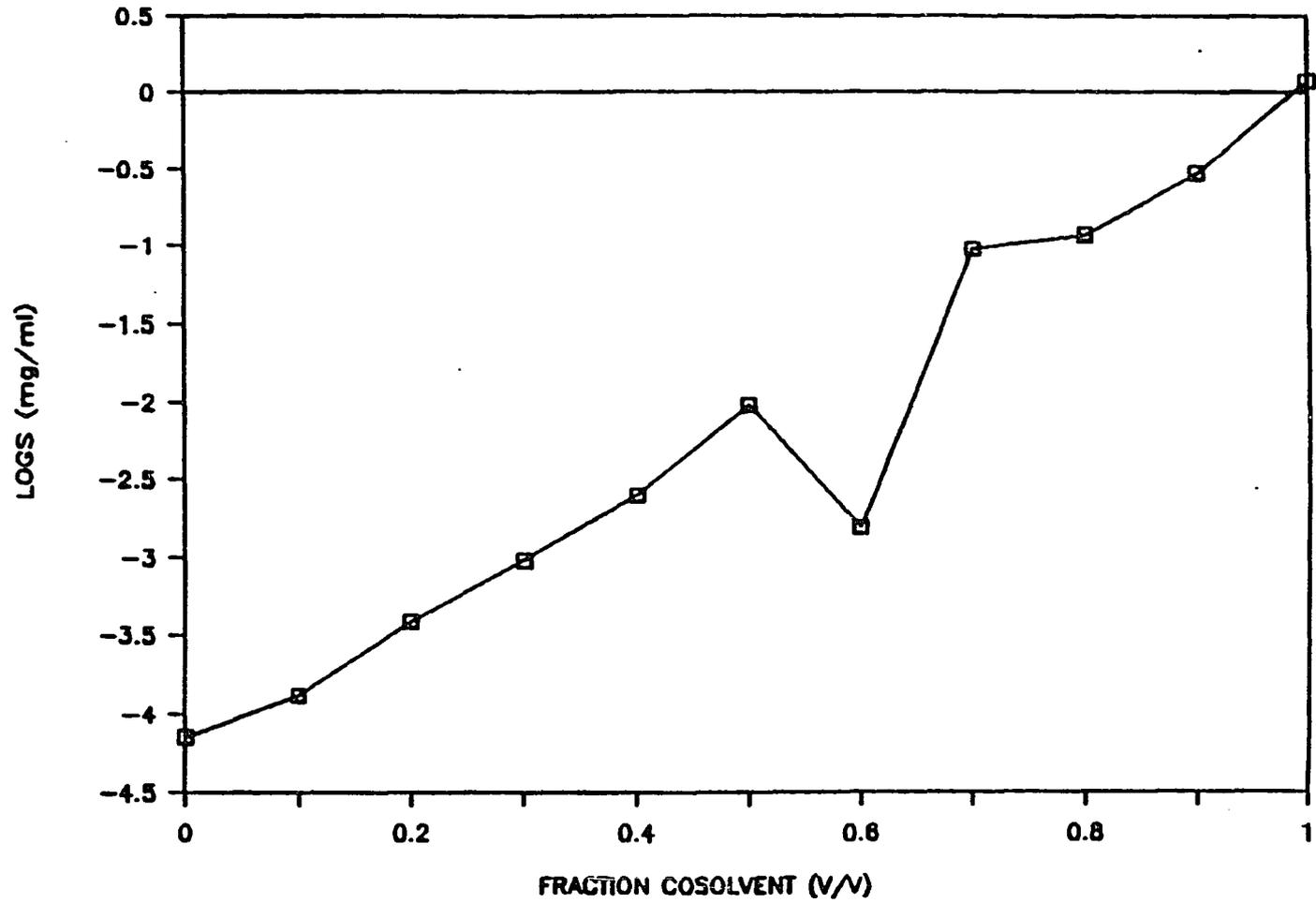
SYSTEM NAME: ANTHRACENE/METHANOL

```
=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	7.440E-05	-4.13	-4.15	0.02
0.0	6.790E-05	-4.17	-4.15	-0.02
0.1	1.330E-04	-3.88	-3.73	-0.15
0.1	1.300E-04	-3.89	-3.73	-0.16
0.2	3.940E-04	-3.40	-3.31	-0.10
0.2	3.850E-04	-3.41	-3.31	-0.11
0.3	9.830E-04	-3.01	-2.89	-0.12
0.3	9.240E-04	-3.03	-2.89	-0.15
0.4	2.630E-03	-2.58	-2.47	-0.11
0.4	2.420E-03	-2.62	-2.47	-0.15
0.5	9.400E-03	-2.03	-2.05	0.02
0.5	9.510E-03	-2.02	-2.05	0.02
0.6	1.480E-02	-1.83	-1.62	-0.21
0.6	1.590E-02	-1.80	-1.62	-0.17
0.7	9.230E-02	-1.03	-1.20	0.17
0.7	9.730E-02	-1.01	-1.20	0.19
0.8	1.120E-01	-0.95	-0.78	-0.17
0.8	1.210E-01	-0.92	-0.78	-0.14
0.9	3.140E-01	-0.50	-0.36	-0.14
0.9	2.780E-01	-0.56	-0.36	-0.19
1.0	1.140E+00	0.06	0.06	-0.00
1.0	1.190E+00	0.08	0.06	0.02

```
=====
```

SYSTEM NAME: ANT/MOH



BINARY SOLUBILITY DATA

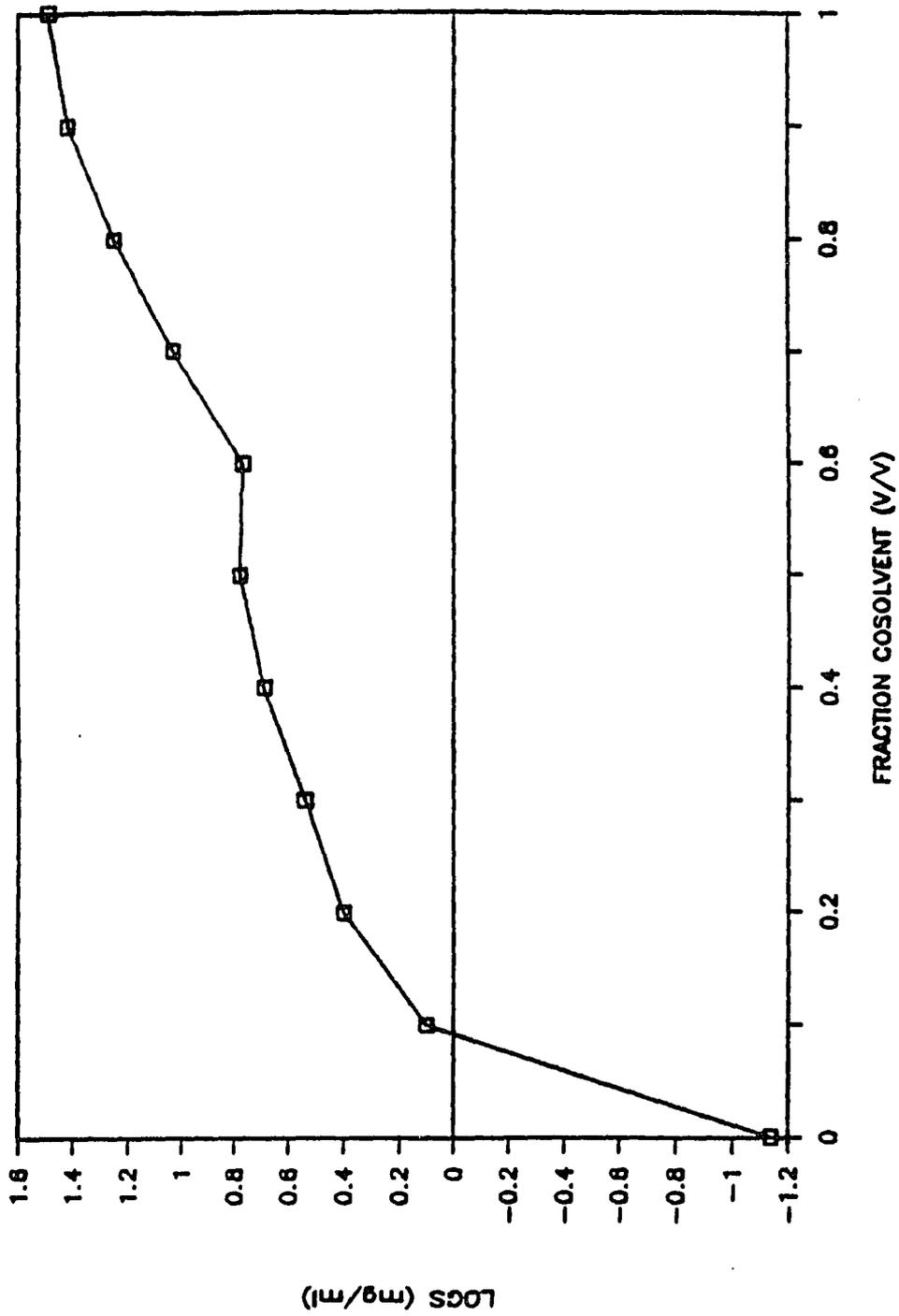
SYSTEM NAME: ATRAZINE/ACETONE

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=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	6.760E-02	-1.17	-1.14	-0.03
0.0	7.770E-02	-1.11	-1.14	0.03
0.1	1.263E+00	0.10	-0.88	0.98
0.1	1.262E+00	0.10	-0.88	0.98
0.2	2.751E+00	0.44	-0.61	1.05
0.2	2.290E+00	0.36	-0.61	0.97
0.3	3.691E+00	0.57	-0.35	0.92
0.3	3.176E+00	0.50	-0.35	0.85
0.4	5.390E+00	0.73	-0.09	0.82
0.4	4.509E+00	0.65	-0.09	0.74
0.5	5.814E+00	0.76	0.18	0.59
0.5	6.114E+00	0.79	0.18	0.61
0.6	6.438E+00	0.81	0.44	0.37
0.6	5.442E+00	0.74	0.44	0.30
0.7	1.103E+01	1.04	0.70	0.34
0.7	1.030E+01	1.01	0.70	0.31
0.8	1.801E+01	1.26	0.96	0.29
0.8	1.738E+01	1.24	0.96	0.28
0.9	2.725E+01	1.44	1.23	0.21
0.9	2.583E+01	1.41	1.23	0.19
1.0	3.189E+01	1.50	1.49	0.01
1.0	2.957E+01	1.47	1.49	-0.02

```
=====
```

SYSTEM NAME: ATR/ACE



BINARY SOLUBILITY DATA

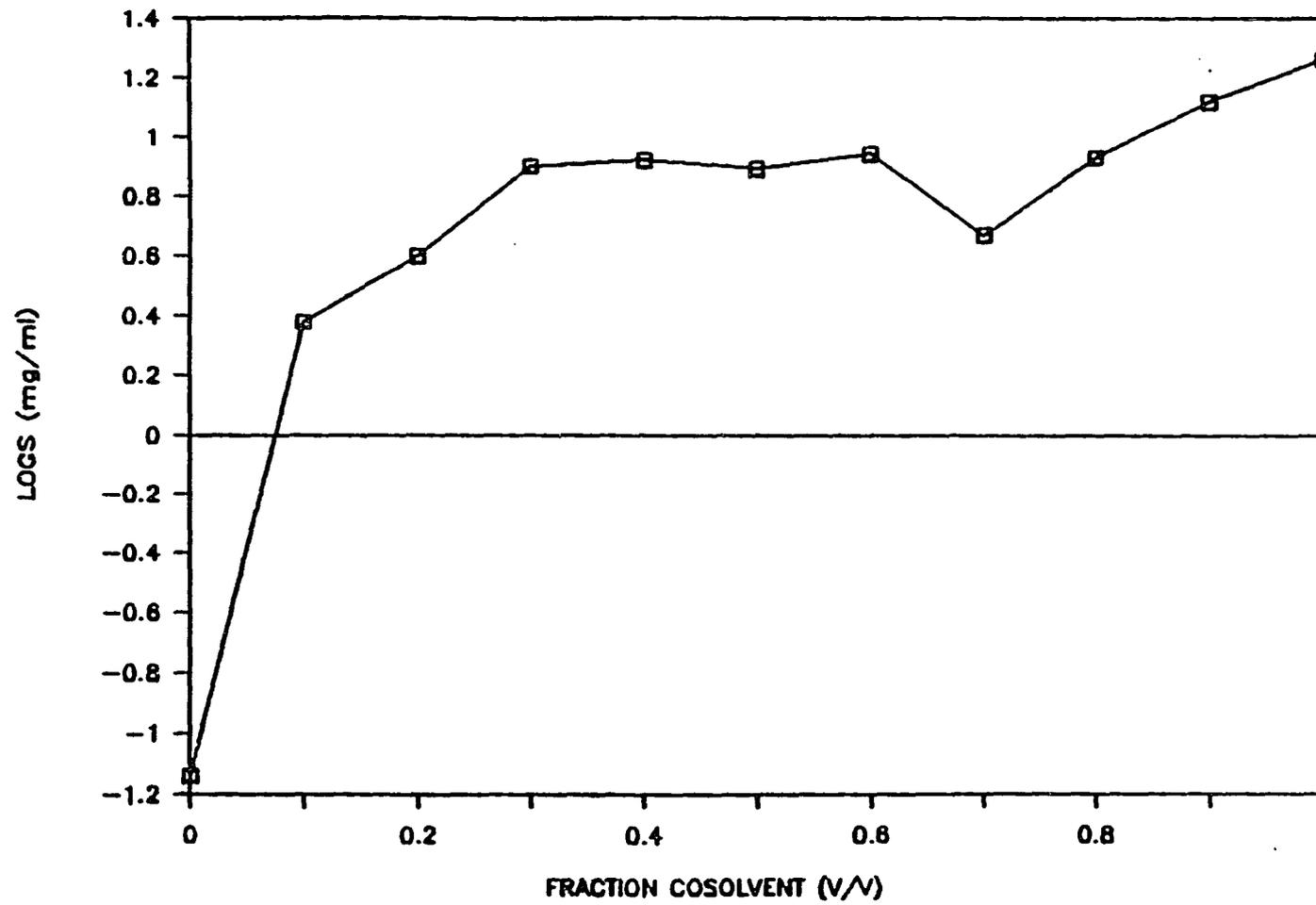
SYSTEM NAME: ATRAZINE/METHANOL

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            6.760E-02      -1.17      -1.14      -0.03
0.0            7.770E-02      -1.11      -1.14      0.03
0.1            2.758E+00      0.44       -0.90      1.34
0.1            2.093E+00      0.32       -0.90      1.22
0.2            4.050E+00      0.61       -0.66      1.27
0.2            3.929E+00      0.59       -0.66      1.25
0.3            7.634E+00      0.88       -0.42      1.30
0.3            8.085E+00      0.91       -0.42      1.33
0.4            8.758E+00      0.94       -0.18      1.12
0.4            7.859E+00      0.90       -0.18      1.08
0.5            8.399E+00      0.92        0.06      0.86
0.5            7.281E+00      0.86        0.06      0.80
0.6            8.578E+00      0.93        0.30      0.63
0.6            8.918E+00      0.95        0.30      0.65
0.7            4.588E+00      0.66        0.54      0.12
0.7            4.673E+00      0.67        0.54      0.13
0.8            8.688E+00      0.94        0.78      0.16
0.8            8.376E+00      0.92        0.78      0.14
0.9            1.268E+01      1.10        1.02      0.08
0.9            1.376E+01      1.14        1.02      0.12
1.0            1.827E+01      1.26        1.26      0.00
1.0            1.810E+01      1.26        1.26     -0.00
=====

```

SYSTEM NAME: ATR/MOH



BINARY SOLUBILITY DATA

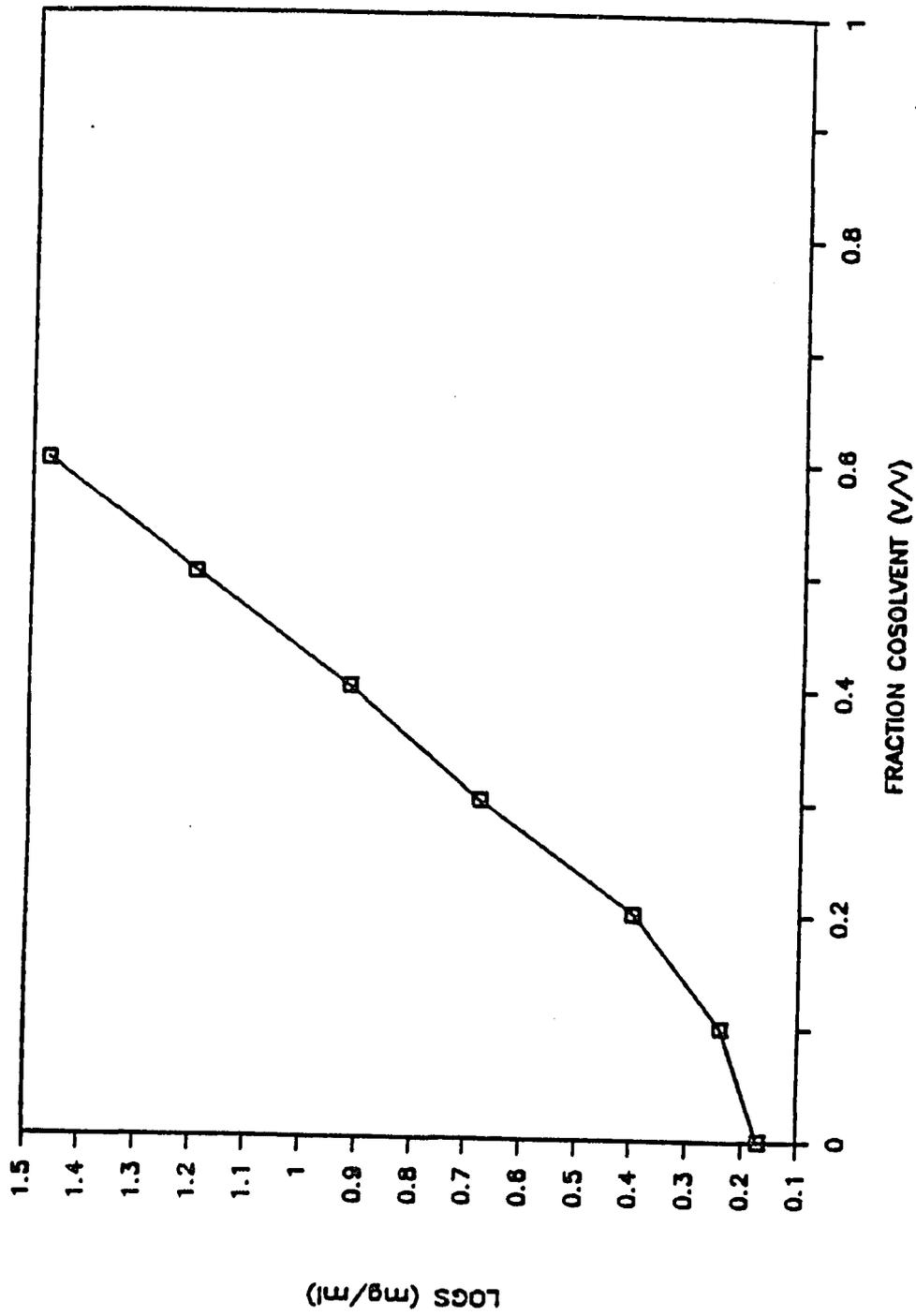
SYSTEM NAME: BENZENE/ACETONE

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=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	1.430E+00	0.16	0.17	-0.01
0.0	1.530E+00	0.18	0.17	0.01
0.1	1.770E+00	0.25	0.45	-0.20
0.1	1.700E+00	0.23	0.45	-0.22
0.2	2.560E+00	0.41	0.72	-0.32
0.2	2.510E+00	0.40	0.72	-0.32
0.3	4.850E+00	0.69	1.00	-0.32
0.3	4.740E+00	0.68	1.00	-0.33
0.4	8.280E+00	0.92	1.28	-0.36
0.4	8.180E+00	0.91	1.28	-0.37
0.5	1.699E+01	1.23	1.56	-0.32
0.5	1.477E+01	1.17	1.56	-0.39
0.6	2.936E+01	1.47	1.83	-0.36
0.6	2.958E+01	1.47	1.83	-0.36

```
=====
```

SYSTEM NAME: BEN/ACE



BINARY SOLUBILITY DATA

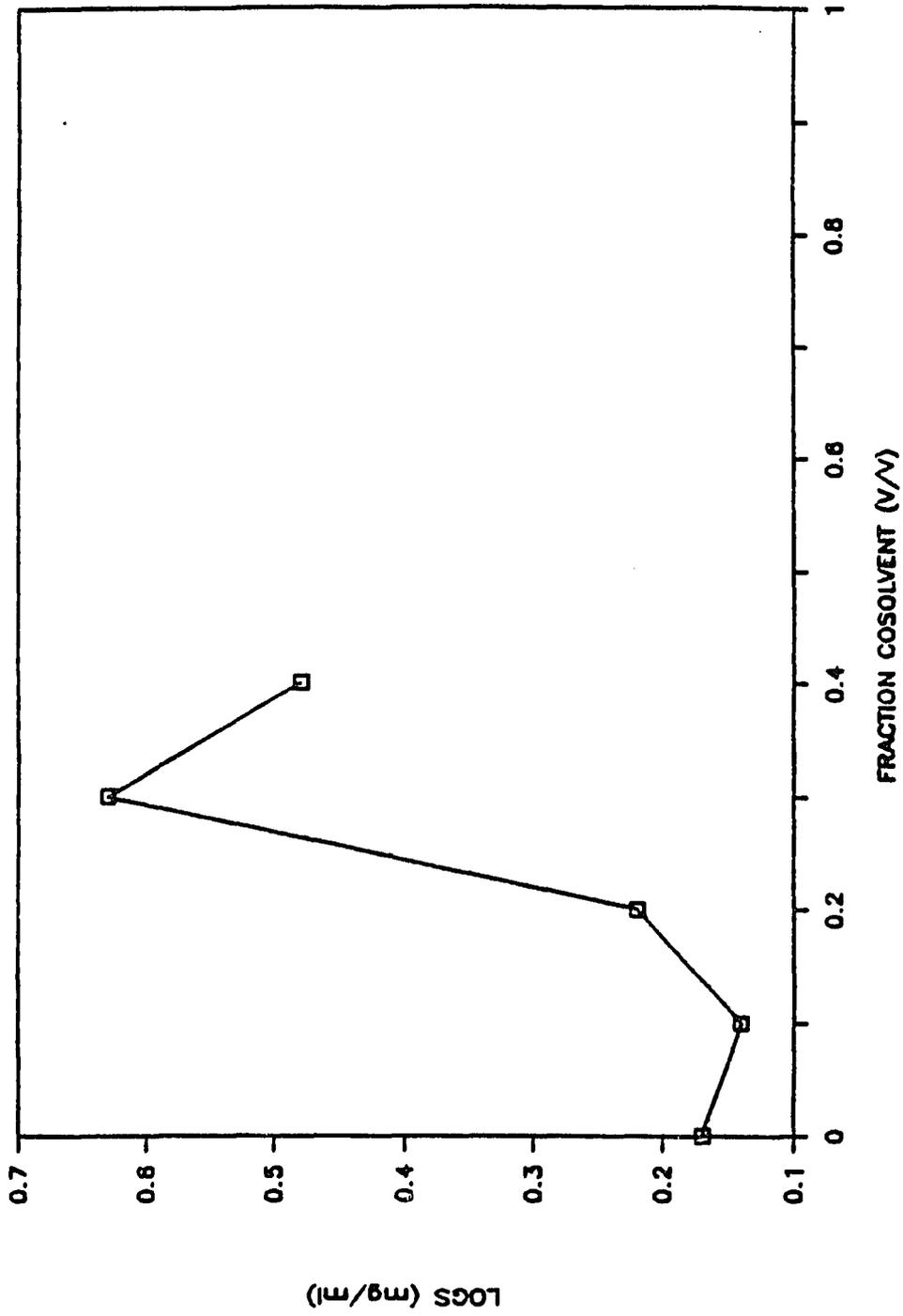
SYSTEM NAME: BENZENE/ACETONITRILE

```
=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	1.430E+00	0.16	0.17	-0.01
0.0	1.530E+00	0.18	0.17	0.01
0.1	1.480E+00	0.17	0.45	-0.28
0.1	1.250E+00	0.10	0.45	-0.35
0.2	1.780E+00	0.25	0.72	-0.47
0.2	1.510E+00	0.18	0.72	-0.55
0.3	4.270E+00	0.63	1.00	-0.37
0.3	4.300E+00	0.63	1.00	-0.37
0.4	2.940E+00	0.47	1.28	-0.81
0.4	3.090E+00	0.49	1.28	-0.79

```
=====
```

SYSTEM NAME: BEN/ACN



BINARY SOLUBILITY DATA

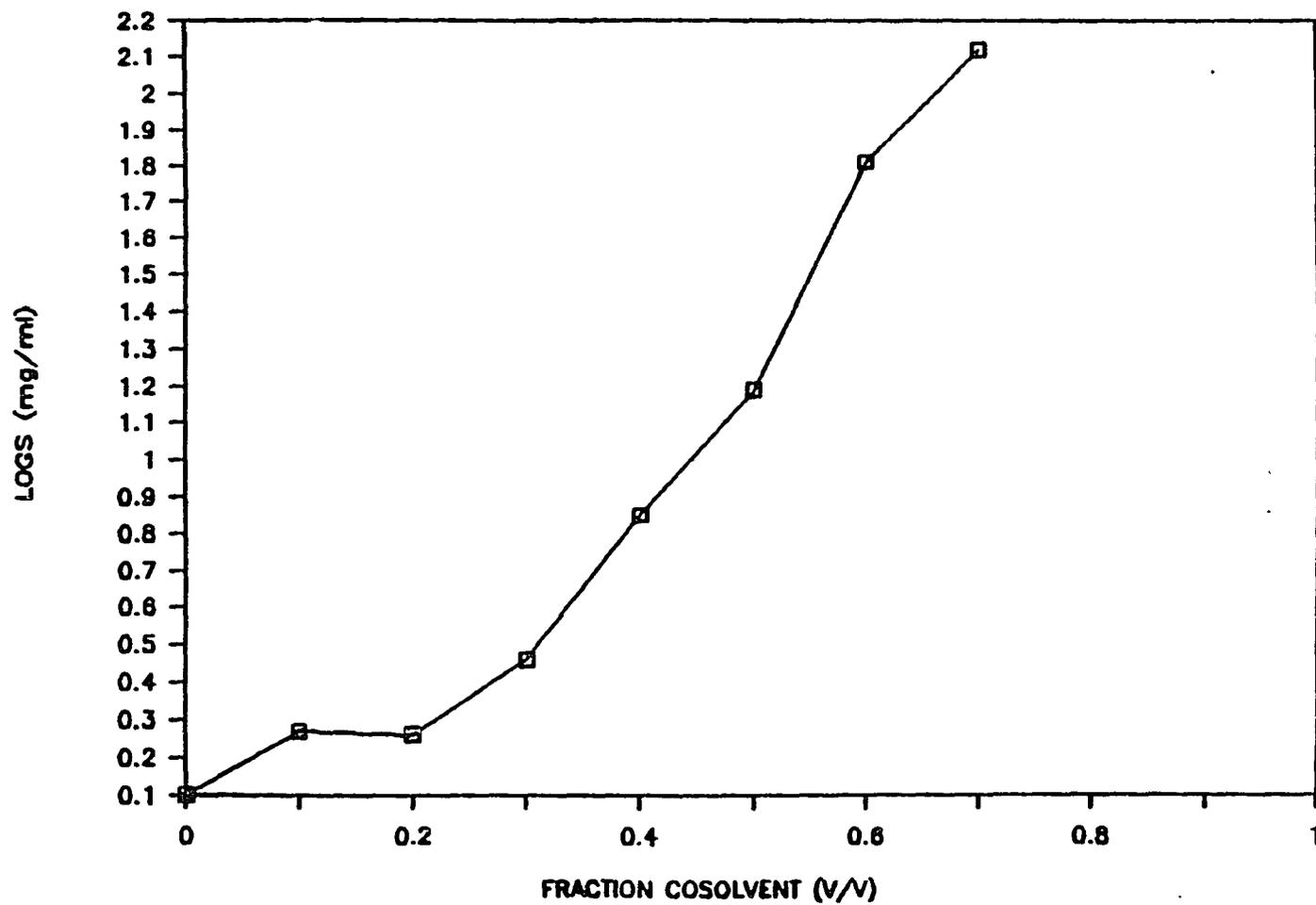
SYSTEM NAME: BENZENE/ETHANOL

```
=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	1.250E+00	0.10	0.10	-0.00
0.0	1.250E+00	0.10	0.10	-0.00
0.1	1.890E+00	0.28	0.39	-0.11
0.1	1.800E+00	0.26	0.39	-0.13
0.2	1.820E+00	0.26	0.67	-0.41
0.2	1.860E+00	0.27	0.67	-0.40
0.3	2.710E+00	0.43	0.96	-0.52
0.3	3.070E+00	0.49	0.96	-0.47
0.4	6.940E+00	0.84	1.24	-0.40
0.4	7.180E+00	0.86	1.24	-0.38
0.5	1.458E+01	1.16	1.53	-0.36
0.5	1.653E+01	1.22	1.53	-0.31
0.6	6.542E+01	1.82	1.81	0.01
0.6	6.498E+01	1.81	1.81	0.00
0.7	1.305E+02	2.12	2.09	0.02
0.7	1.322E+02	2.12	2.09	0.03

```
=====
```

SYSTEM NAME: BEN/EOH



BINARY SOLUBILITY DATA

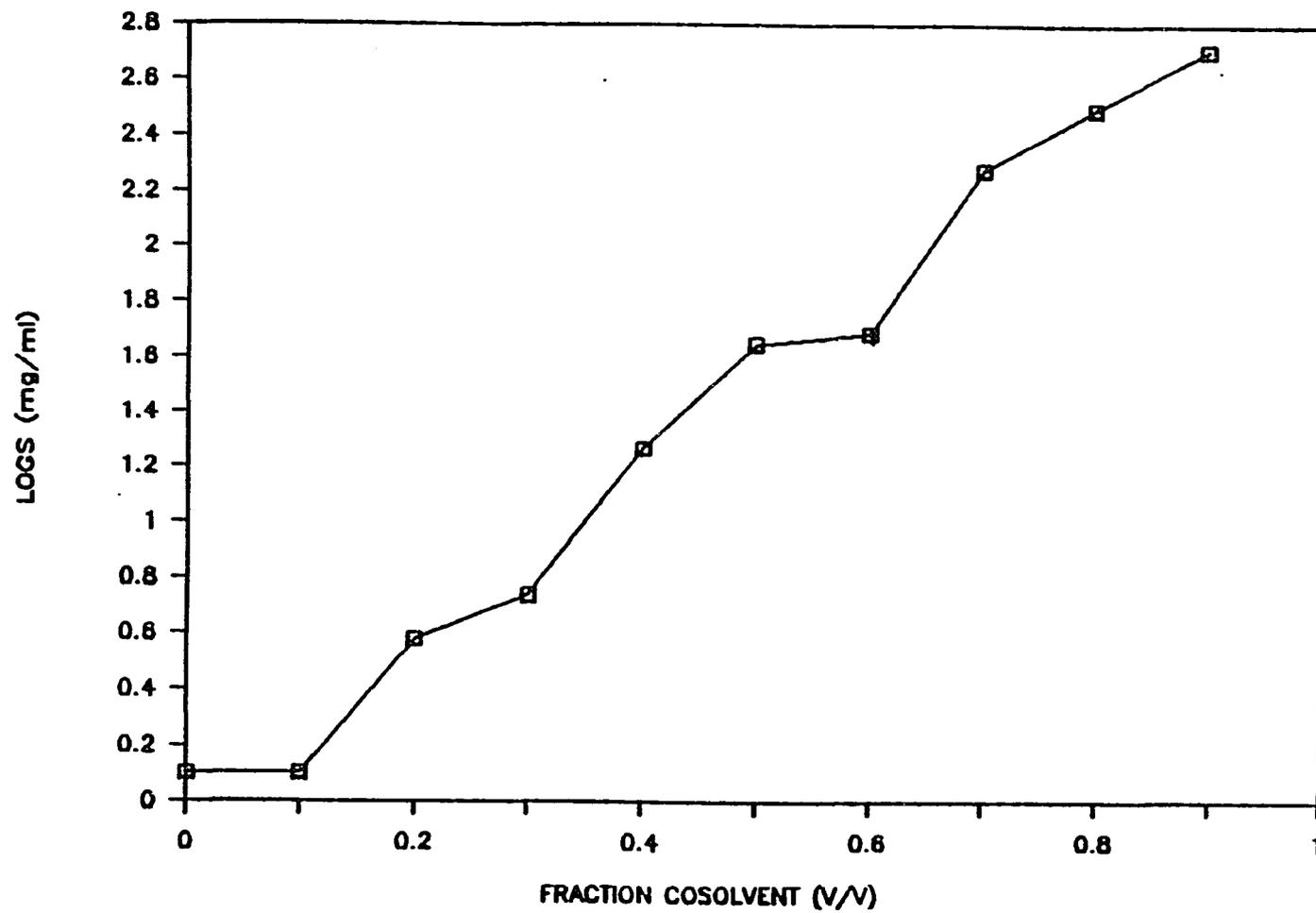
SYSTEM NAME: BENZENE/ISOPROPNOL

```
=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	1.260E+00	0.10	0.10	0.00
0.0	1.260E+00	0.10	0.10	0.00
0.1	1.350E+00	0.13	0.38	-0.25
0.1	1.190E+00	0.08	0.38	-0.31
0.2	4.100E+00	0.61	0.67	-0.06
0.2	3.560E+00	0.55	0.67	-0.12
0.3	5.670E+00	0.75	0.95	-0.20
0.3	5.330E+00	0.73	0.95	-0.23
0.4	1.880E+01	1.27	1.24	0.04
0.4	1.850E+01	1.27	1.24	0.03
0.5	4.260E+01	1.63	1.52	0.11
0.5	5.080E+01	1.71	1.52	0.19
0.5	4.170E+01	1.62	1.52	0.10
0.5	4.210E+01	1.62	1.52	0.10
0.6	4.430E+01	1.65	1.80	-0.16
0.6	4.320E+01	1.64	1.80	-0.17
0.6	5.520E+01	1.74	1.80	-0.06
0.6	5.450E+01	1.74	1.80	-0.07
0.7	1.950E+02	2.29	2.09	0.20
0.7	2.450E+02	2.39	2.09	0.30
0.7	1.638E+02	2.21	2.09	0.13
0.7	1.597E+02	2.20	2.09	0.12
0.8	3.080E+02	2.49	2.37	0.12
0.8	3.280E+02	2.52	2.37	0.14
0.9	4.940E+02	2.69	2.66	0.04
0.9	5.340E+02	2.73	2.66	0.07

```
=====
```

SYSTEM NAME: BEN/IPA



BINARY SOLUBILITY DATA

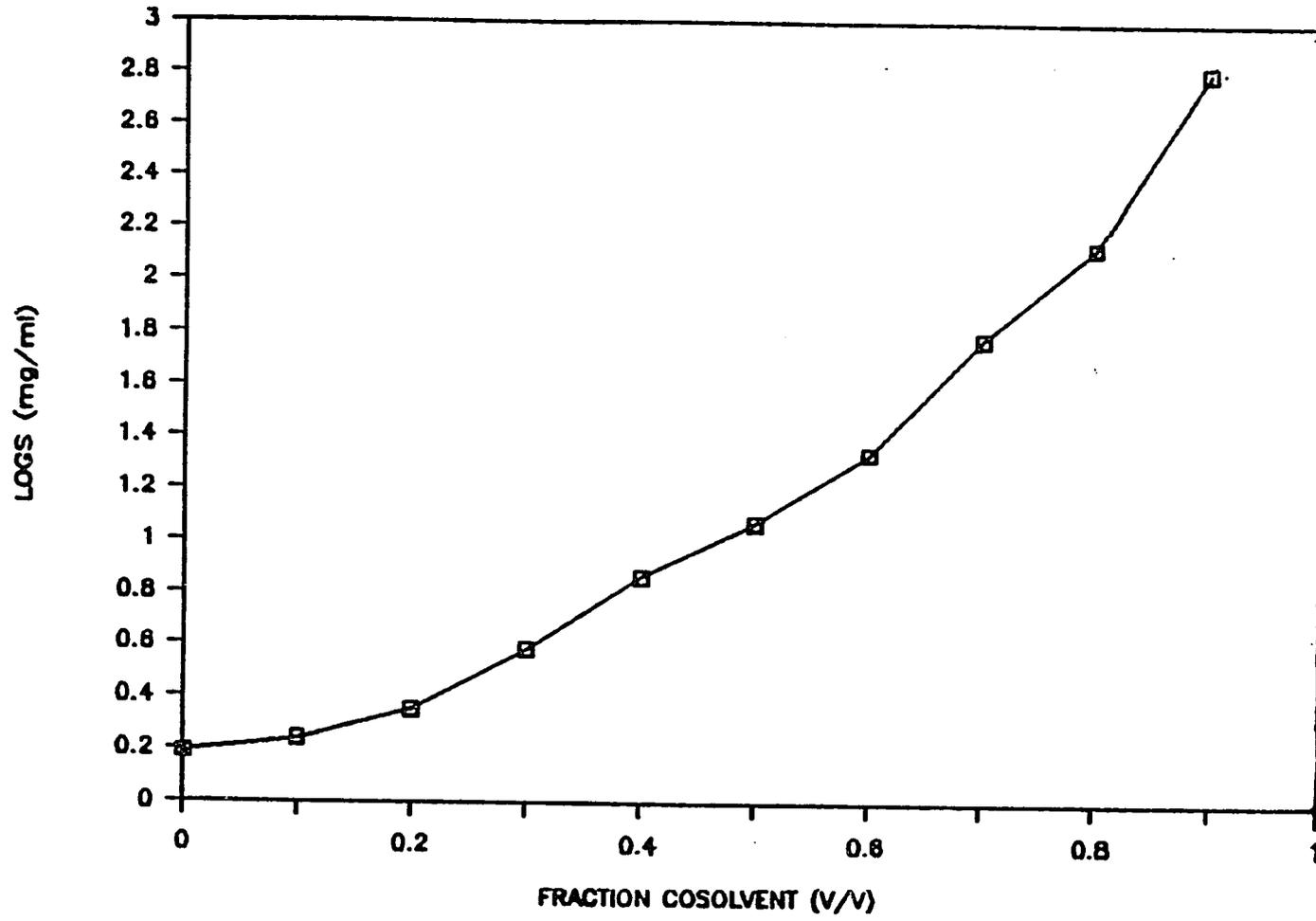
SYSTEM NAME: BENZENE/METHANOL

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            1.560E+00      0.19       0.19       0.00
0.0            1.570E+00      0.20       0.19       0.01
0.1            1.790E+00      0.25       0.47       -0.21
0.1            1.710E+00      0.23       0.47       -0.23
0.2            2.310E+00      0.36       0.74       -0.38
0.2            2.200E+00      0.34       0.74       -0.40
0.3            3.680E+00      0.57       1.02       -0.45
0.3            3.960E+00      0.60       1.02       -0.42
0.4            7.060E+00      0.85       1.29       -0.44
0.4            7.360E+00      0.87       1.29       -0.42
0.5            1.184E+01      1.07       1.57       -0.49
0.5            1.173E+01      1.07       1.57       -0.50
0.6            2.240E+01      1.35       1.84       -0.49
0.6            2.140E+01      1.33       1.84       -0.51
0.7            5.969E+01      1.78       2.12       -0.34
0.7            6.184E+01      1.79       2.12       -0.32
0.8            1.377E+02      2.14       2.39       -0.25
0.8            1.300E+02      2.11       2.39       -0.28
0.9            6.547E+02      2.82       2.67       0.15
0.9            6.425E+02      2.81       2.67       0.14
=====

```

SYSTEM NAME: BEN/MOH



BINARY SOLUBILITY DATA

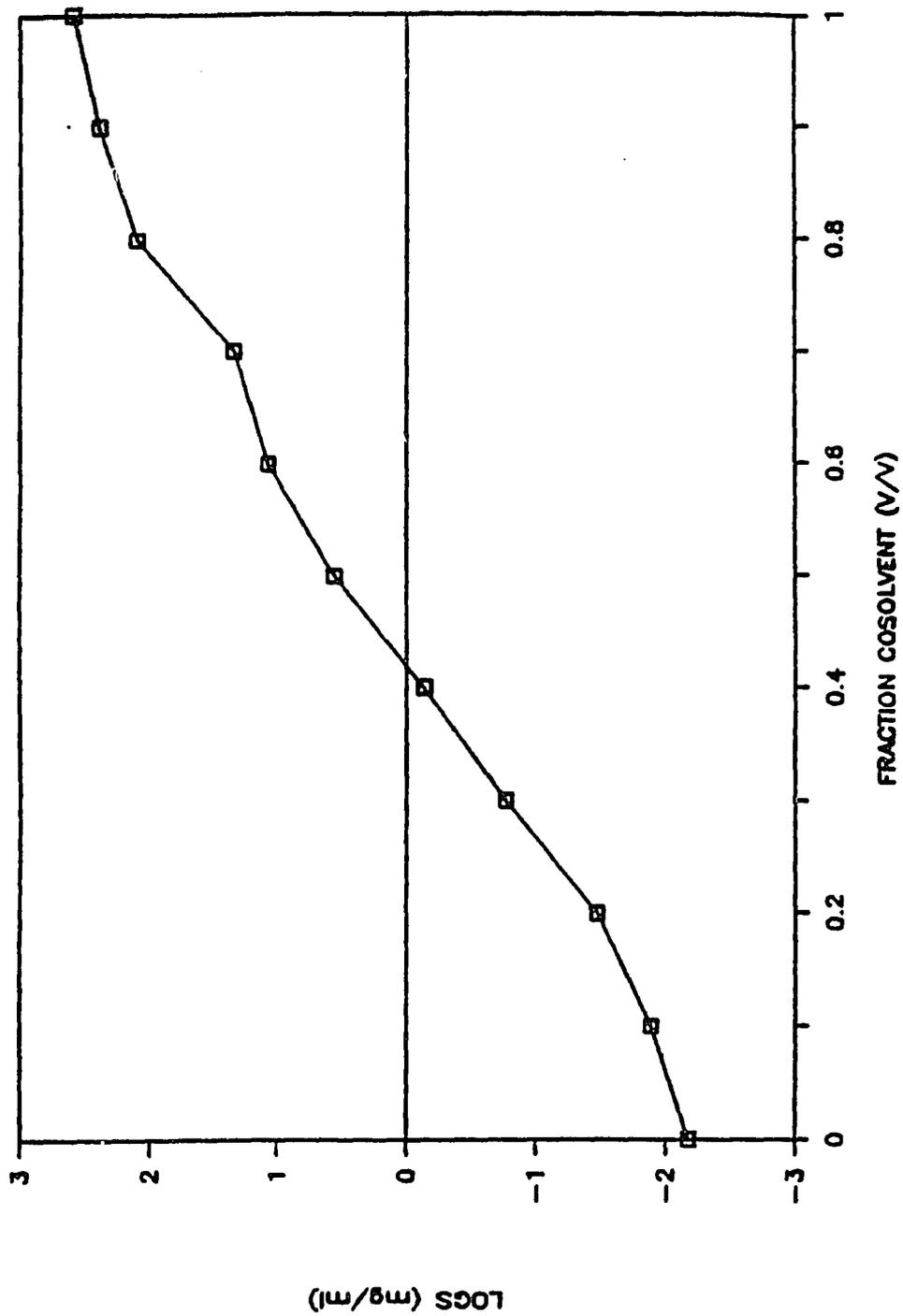
SYSTEM NAME: BIPHENYL/ACETONE

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=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	6.820E-03	-2.17	-2.16	-0.01
0.0	6.960E-03	-2.16	-2.16	0.00
0.1	2.000E-02	-1.70	-1.68	-0.02
0.1	1.964E-02	-1.71	-1.68	-0.03
0.2	1.880E-02	-1.73	-1.20	-0.53
0.2	1.766E-02	-1.75	-1.20	-0.55
0.3	1.460E-01	-0.84	-0.72	-0.12
0.3	1.470E-01	-0.83	-0.72	-0.11
0.4	9.500E-01	-0.02	-0.24	0.22
0.4	9.590E-01	-0.02	-0.24	0.22
0.5	4.320E+00	0.64	0.24	0.40
0.5	4.010E+00	0.60	0.24	0.36
0.6	1.339E+01	1.13	0.72	0.41
0.6	1.248E+01	1.10	0.72	0.38
0.7	4.974E+01	1.70	1.20	0.50
0.7	5.217E+01	1.72	1.20	0.52
0.8	2.391E+02	2.38	1.68	0.70
0.8	1.903E+02	2.28	1.68	0.60
0.9	2.730E+02	2.44	2.16	0.28
0.9	2.530E+02	2.40	2.16	0.24
1.0	4.325E+02	2.64	2.64	-0.00
1.0	4.407E+02	2.64	2.64	0.00

```
=====
```

SYSTEM NAME: BIP/ACE



BINARY SOLUBILITY DATA

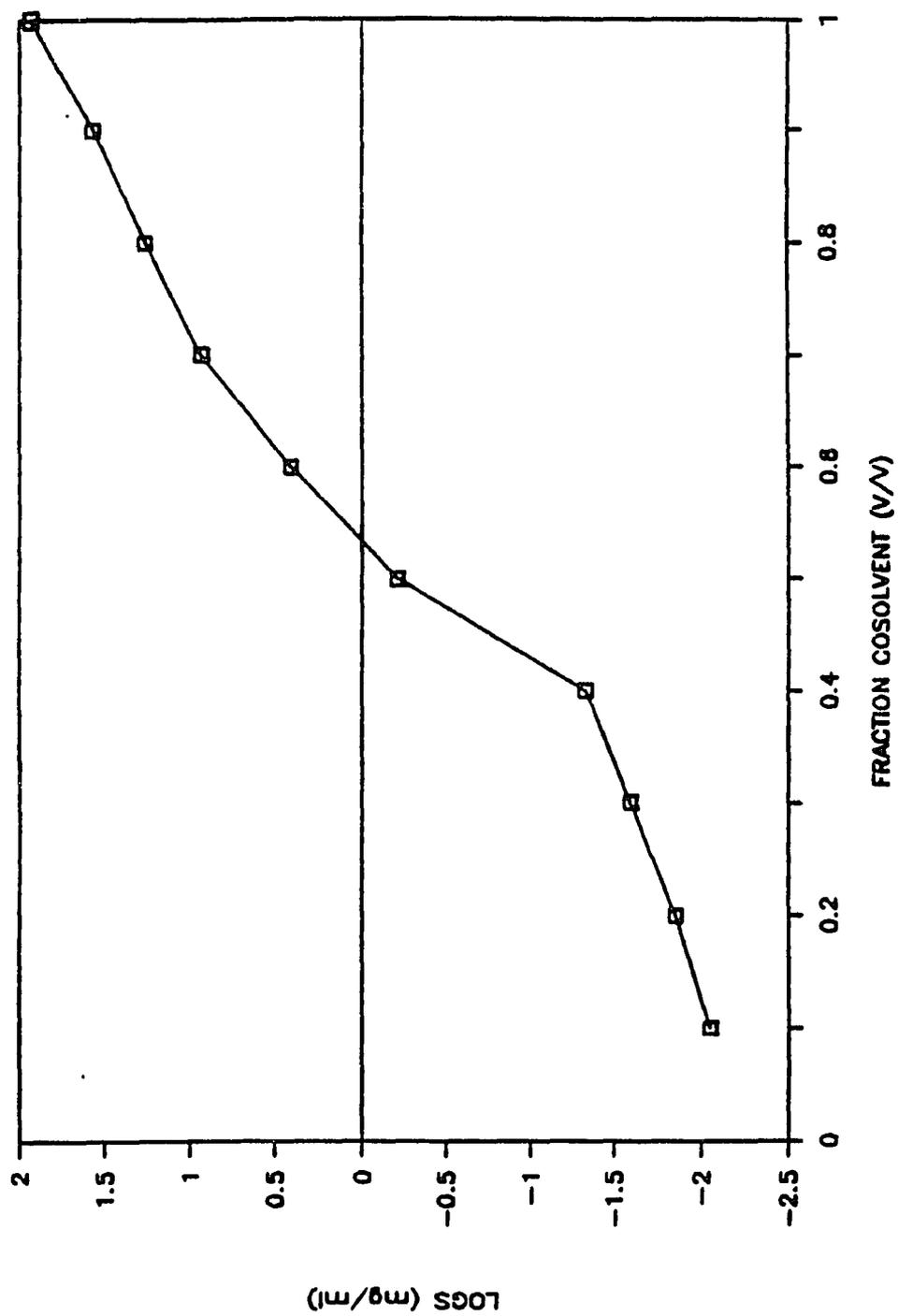
SYSTEM NAME: BIPHENYL/ETHANOL

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            6.750E-03      -2.17      -2.16      -0.01
0.0            7.130E-03      -2.15      -2.16      0.01
0.1            9.200E-03      -2.04      -1.75      -0.29
0.1            8.700E-03      -2.06      -1.75      -0.31
0.2            1.370E-02      -1.86      -1.34      -0.52
0.2            1.470E-02      -1.83      -1.34      -0.49
0.3            2.630E-02      -1.58      -0.93      -0.65
0.3            2.510E-02      -1.60      -0.93      -0.67
0.4            4.780E-02      -1.32      -0.52      -0.80
0.4            4.600E-02      -1.34      -0.52      -0.81
0.5            5.890E-01      -0.23      -0.12      -0.11
0.5            6.320E-01      -0.20      -0.12      -0.08
0.6            2.470E+00      0.39       0.29      0.10
0.6            2.650E+00      0.42       0.29      0.13
0.7            8.690E+00      0.94       0.70      0.24
0.7            8.400E+00      0.92       0.70      0.22
0.8            2.034E+01      1.31       1.11      0.20
0.8            1.619E+01      1.21       1.11      0.10
0.9            3.875E+01      1.59       1.52      0.07
0.9            3.631E+01      1.56       1.52      0.04
1.0            8.815E+01      1.95       1.93      0.02
1.0            8.115E+01      1.91       1.93     -0.02
=====

```

SYSTEM NAME: BIP/EOH



BINARY SOLUBILITY DATA

SYSTEM NAME: BIPHENYL/METHANOL

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```

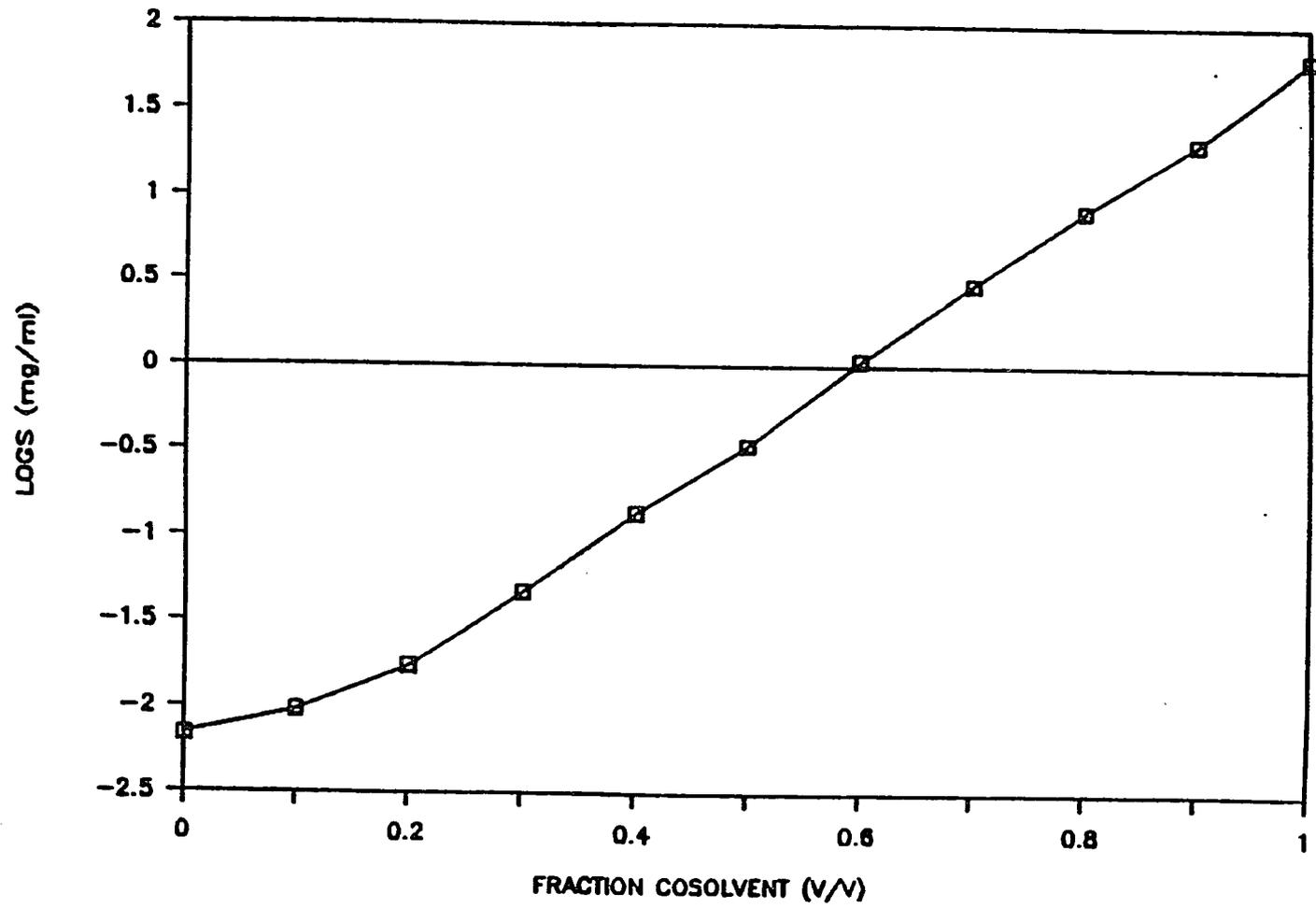
FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	7.130E-03	-2.15	-2.16	0.01
0.0	6.750E-03	-2.17	-2.16	-0.01
0.1	9.020E-03	-2.04	-1.76	-0.28
0.1	1.000E-02	-2.00	-1.76	-0.24
0.2	1.600E-02	-1.80	-1.37	-0.43
0.2	1.840E-02	-1.74	-1.37	-0.37
0.3	4.220E-02	-1.37	-0.97	-0.41
0.3	5.160E-02	-1.29	-0.97	-0.32
0.4	1.260E-01	-0.90	-0.57	-0.33
0.4	1.430E-01	-0.84	-0.57	-0.27
0.5	2.920E-01	-0.53	-0.18	-0.36
0.5	3.930E-01	-0.41	-0.18	-0.23
0.6	1.082E+00	0.03	0.22	-0.19
0.6	1.047E+00	0.02	0.22	-0.20
0.7	3.024E+00	0.48	0.62	-0.14
0.7	3.076E+00	0.49	0.62	-0.13
0.8	8.280E+00	0.92	1.02	-0.10
0.8	8.330E+00	0.92	1.02	-0.10
0.9	2.049E+01	1.31	1.41	-0.10
0.9	2.104E+01	1.32	1.41	-0.09
1.0	6.505E+01	1.81	1.81	0.00
1.0	6.419E+01	1.81	1.81	-0.00

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=====

```

SYSTEM NAME: BIP/MOH



BINARY SOLUBILITY DATA

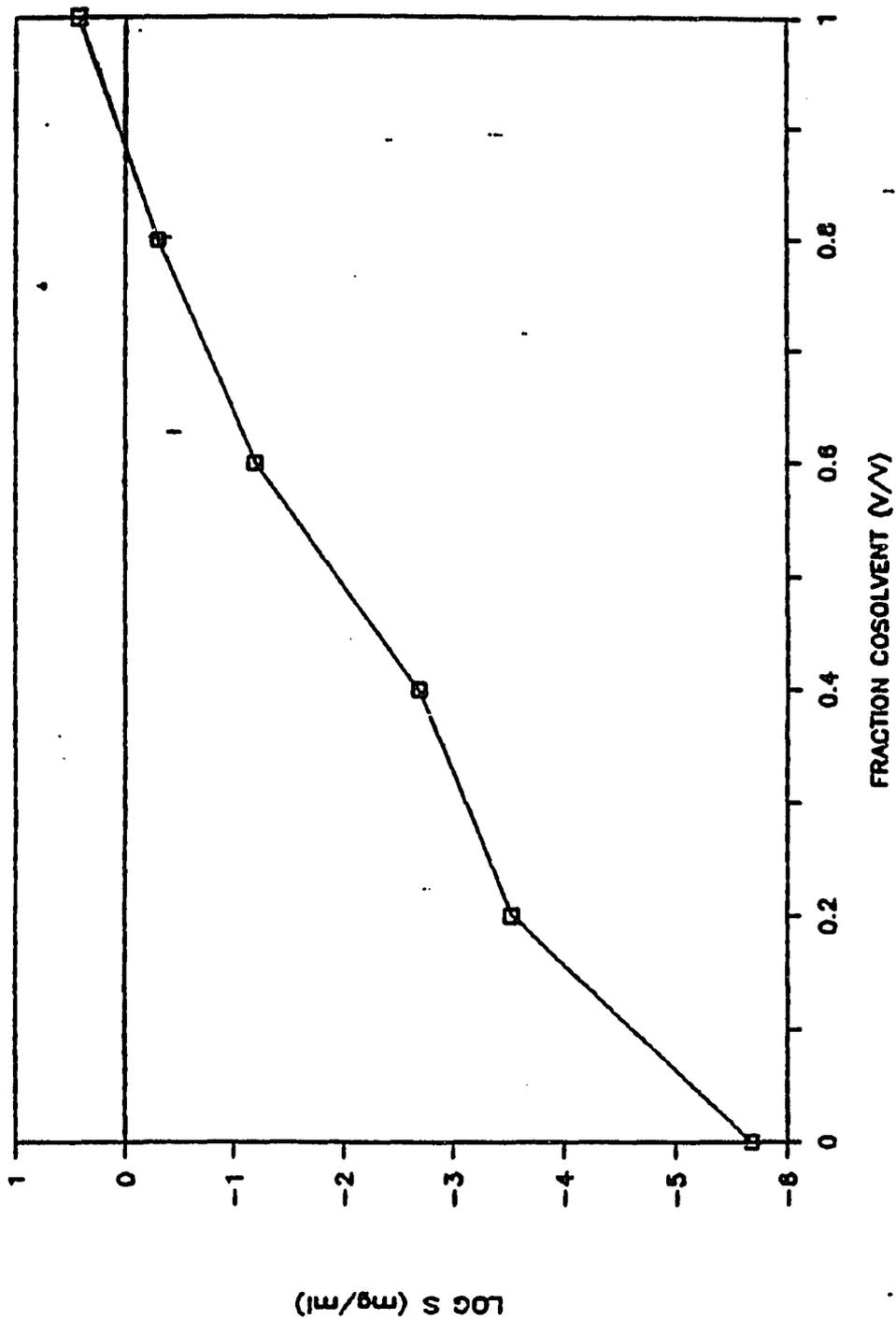
SYSTEM NAME: CRYSENE/ACETONE

```
=====
```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	2.090E-06	-5.68	-5.68	0.00
0.2	3.020E-04	-3.52	-4.46	0.94
0.2	2.920E-04	-3.53	-4.46	0.92
0.4	2.320E-03	-2.63	-3.24	0.60
0.4	1.880E-03	-2.73	-3.24	0.51
0.6	6.300E-02	-1.20	-2.01	0.81
0.6	6.600E-02	-1.18	-2.01	0.83
0.8	5.275E-01	-0.28	-0.79	0.51
0.8	4.663E-01	-0.33	-0.79	0.46
1.0	2.650E+00	0.42	0.43	-0.01
1.0	2.687E+00	0.43	0.43	-0.00

```
=====
```

SYSTEM NAME: CRY/ACE



BINARY SOLUBILITY DATA

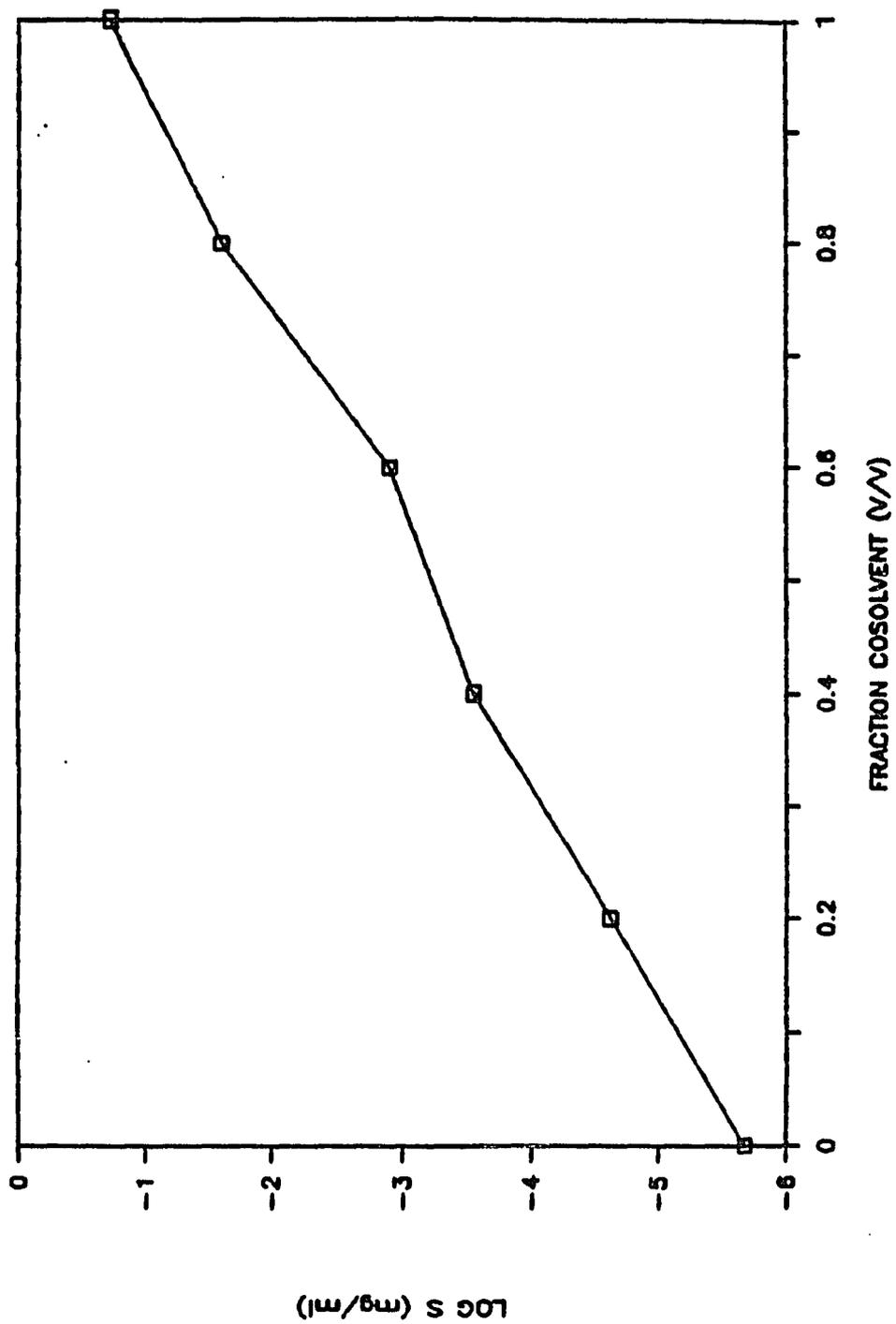
SYSTEM NAME: CRYSENE/METHANOL

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```

FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	2.090E-06	-5.68	-5.68	0.00
0.2	2.700E-05	-4.57	-4.69	0.12
0.2	2.150E-05	-4.67	-4.69	0.02
0.4	2.770E-04	-3.56	-3.70	0.14
0.4	2.850E-04	-3.55	-3.70	0.15
0.6	1.500E-03	-2.82	-2.70	-0.12
0.6	1.000E-03	-3.00	-2.70	-0.30
0.8	2.530E-02	-1.60	-1.71	0.12
1.0	1.910E-01	-0.72	-0.72	0.00

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```

SYSTEM NAME: CRY/MEO



BINARY SOLUBILITY DATA

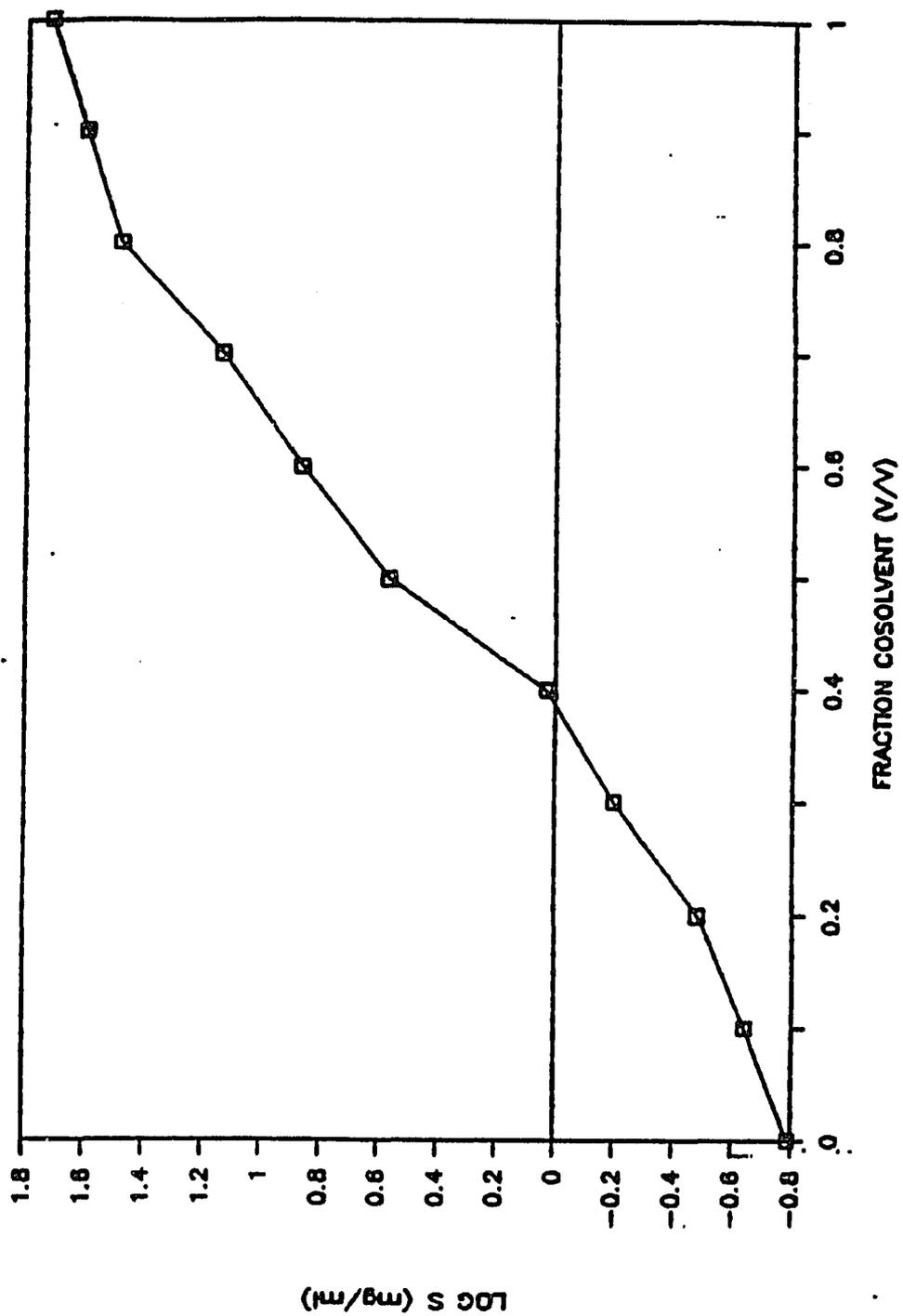
SYSTEM NAME: DIURON/ACETONE

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT     (mg/ml)        obs        pred        obs-pred
=====
0.0            1.380E-01      -0.86      -0.79      -0.07
0.0            1.890E-01      -0.72      -0.79       0.07
0.1            2.260E-01      -0.65      -0.54      -0.11
0.1            2.350E-01      -0.63      -0.54      -0.09
0.2            3.190E-01      -0.50      -0.29      -0.21
0.2            3.420E-01      -0.47      -0.29      -0.18
0.3            6.150E-01      -0.21      -0.04      -0.17
0.3            6.430E-01      -0.19      -0.04      -0.15
0.4            1.041E+00       0.02       0.21      -0.20
0.4            1.112E+00       0.05       0.21      -0.17
0.5            3.641E+00       0.56       0.47       0.10
0.5            3.855E+00       0.59       0.47       0.12
0.6            6.925E+00       0.84       0.72       0.12
0.6            7.894E+00       0.90       0.72       0.18
0.7            1.395E+01       1.14       0.97       0.18
0.7            1.391E+01       1.14       0.97       0.18
0.8            3.012E+01       1.48       1.22       0.26
0.8            3.008E+01       1.48       1.22       0.26
0.9            4.010E+01       1.60       1.47       0.13
0.9            3.984E+01       1.60       1.47       0.13
1.0            5.237E+01       1.72       1.72      -0.00
1.0            5.272E+01       1.72       1.72       0.00
=====

```

SYSTEM NAME: DIU/ACE



BINARY SOLUBILITY DATA

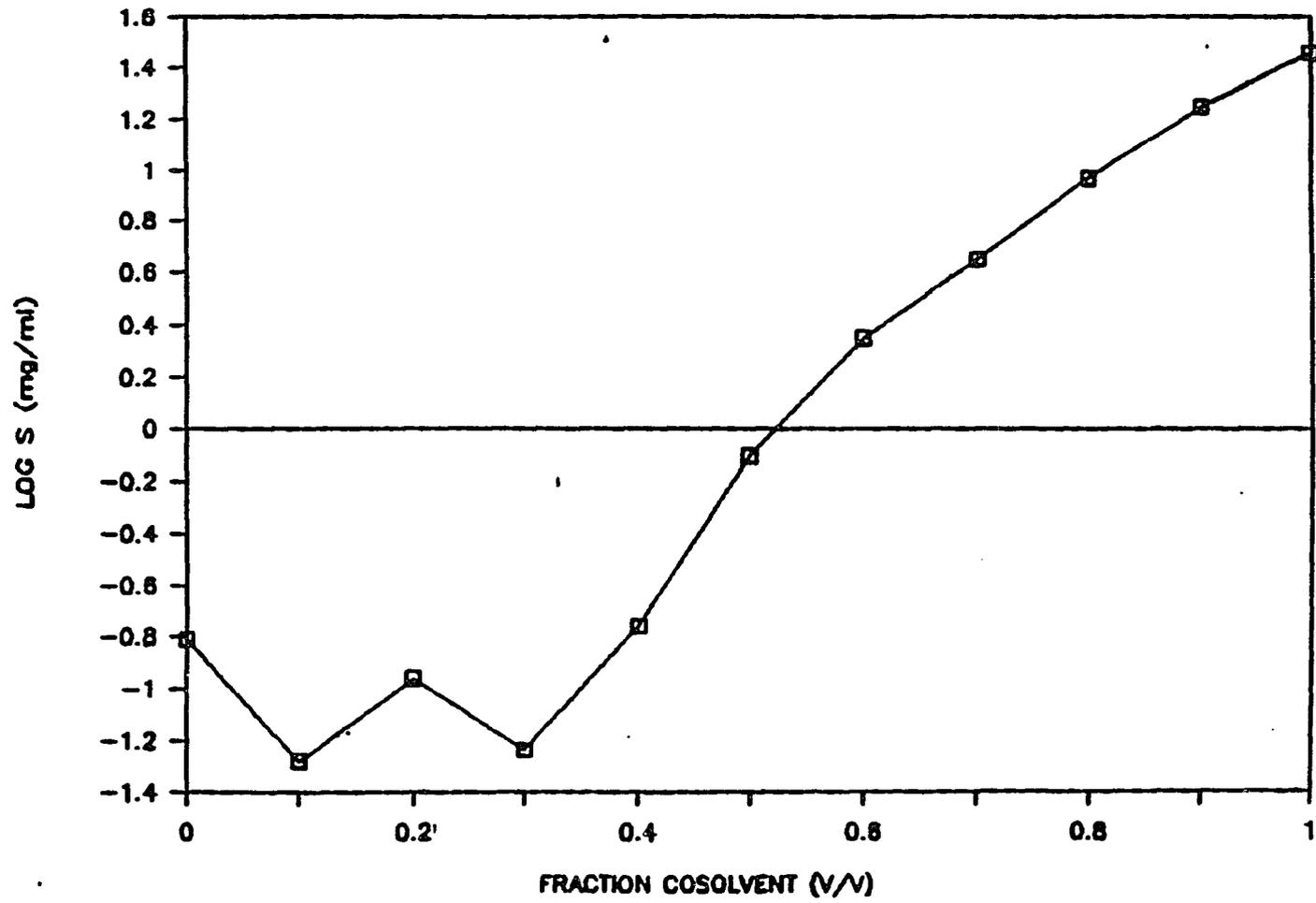
SYSTEM NAME: DIURON/METHANOL

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=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            1.390E-01      -0.86      -0.81      -0.05
0.0            1.690E-01      -0.77      -0.81       0.04
0.1            4.300E-02      -1.37      -0.58      -0.78
0.1            6.100E-02      -1.21      -0.58      -0.63
0.2            1.210E-01      -0.92      -0.36      -0.56
0.2            9.600E-02      -1.02      -0.36      -0.66
0.3            5.700E-02      -1.24      -0.13      -1.12
0.3            5.900E-02      -1.23      -0.13      -1.10
0.4            1.690E-01      -0.77       0.10      -0.87
0.4            1.800E-01      -0.74       0.10      -0.84
0.5            7.990E-01      -0.10       0.33      -0.42
0.5            7.840E-01      -0.11       0.33      -0.43
0.6            1.976E+00       0.30       0.55      -0.26
0.6            2.519E+00       0.40       0.55      -0.15
0.7            4.648E+00       0.67       0.78      -0.11
0.7            4.298E+00       0.63       0.78      -0.15
0.8            9.630E+00       0.98       1.01      -0.02
0.8            9.130E+00       0.96       1.01      -0.05
0.9            1.807E+01       1.26       1.23       0.02
0.9            1.728E+01       1.24       1.23       0.00
1.0            2.929E+01       1.47       1.46       0.01
1.0            2.778E+01       1.44       1.46      -0.02
=====

```

SYSTEM NAME: DIU/MEO



BINARY SOLUBILITY DATA

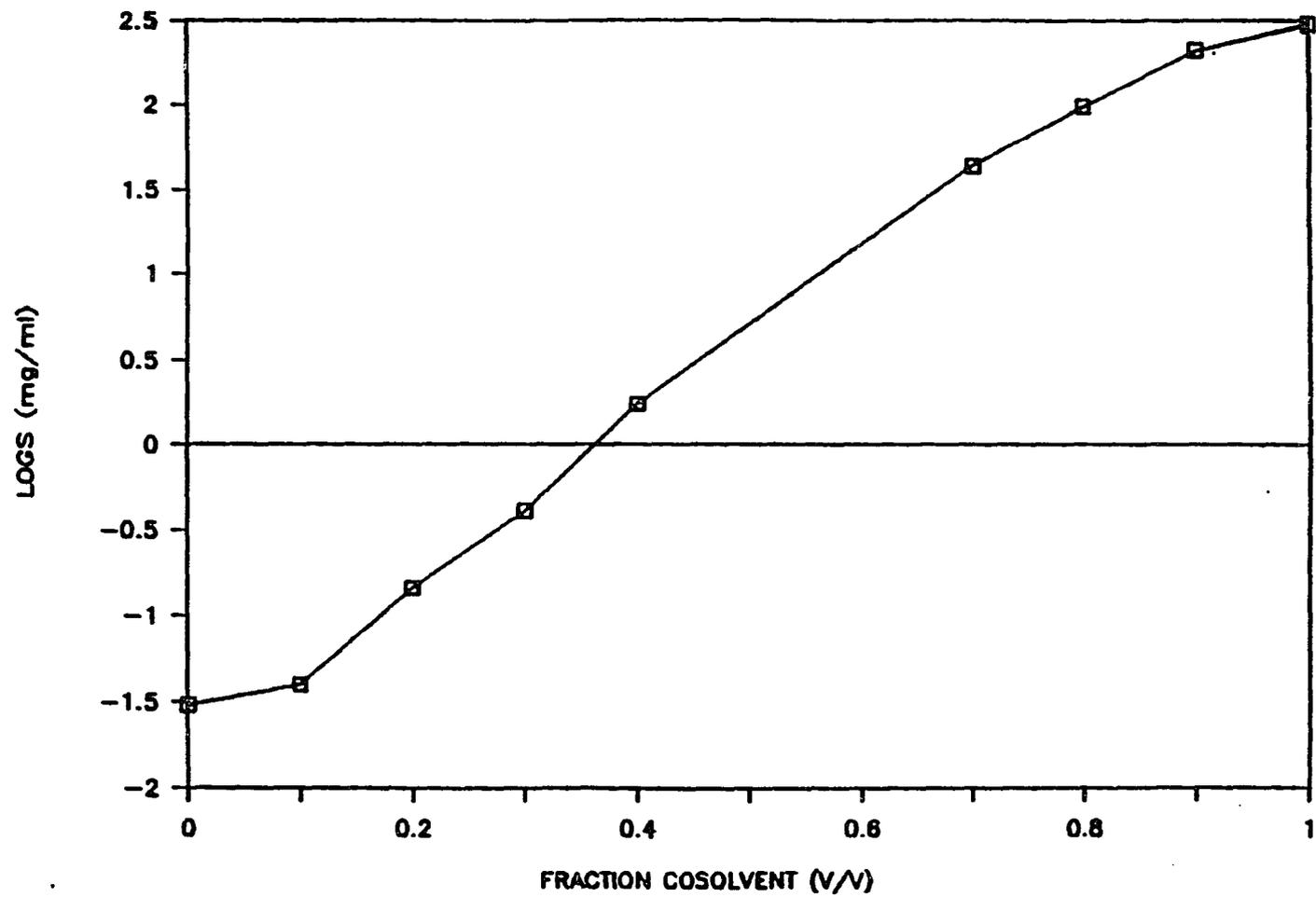
SYSTEM NAME: NAPHTHALENE/ACETONE

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=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            2.575E-02      -1.59      -1.58      -0.01
0.0            2.644E-02      -1.58      -1.58      0.00
0.1            6.700E-02      -1.17      -1.16      -0.01
0.1            5.500E-02      -1.26      -1.16      -0.10
0.2            1.460E-01      -0.84      -0.75      -0.09
0.2            2.140E-01      -0.67      -0.75      0.08
0.3            4.200E-01      -0.38      -0.33      -0.05
0.3            4.480E-01      -0.35      -0.33      -0.02
0.4            1.400E+00      0.15      0.09      0.06
0.4            1.620E+00      0.21      0.09      0.12
0.5            5.660E+00      0.75      0.51      0.25
0.5            5.120E+00      0.71      0.51      0.20
0.6            1.501E+01      1.18      0.92      0.25
0.6            1.677E+01      1.22      0.92      0.30
0.7            3.698E+01      1.57      1.34      0.23
0.7            4.354E+01      1.64      1.34      0.30
0.8            1.087E+02      2.04      1.76      0.28
0.8            8.520E+01      1.93      1.76      0.17
0.9            2.225E+02      2.35      2.17      0.17
0.9            2.003E+02      2.30      2.17      0.13
1.0            3.625E+02      2.56      2.59      -0.03
1.0            4.135E+02      2.62      2.59      0.03
=====

```

SYSTEM NAME: NAP/ACE



BINARY SOLUBILITY DATA

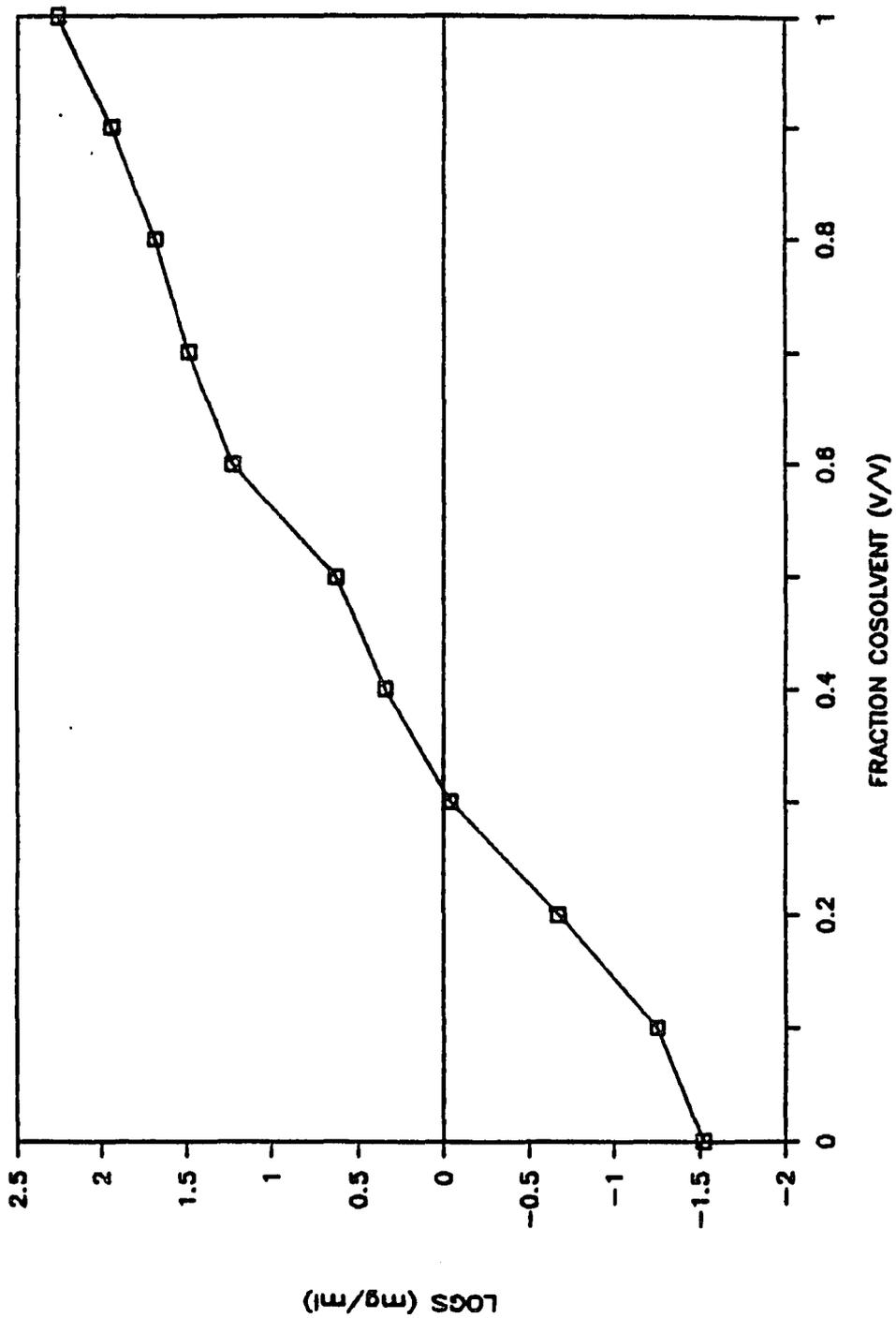
SYSTEM NAME: NAPHTHALENE/ACETONITRILE

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            2.575E-02      -1.59      -1.58      -0.01
0.0            2.644E-02      -1.58      -1.58      0.00
0.1            5.130E-02      -1.29      -1.19      -0.10
0.1            5.770E-02      -1.24      -1.19      -0.04
0.2            2.240E-01      -0.65      -0.81      0.16
0.2            2.300E-01      -0.64      -0.81      0.17
0.3            7.610E-01      -0.12      -0.42      0.30
0.3            9.200E-01      -0.04      -0.42      0.39
0.4            2.560E+00      0.41       -0.04      0.44
0.4            2.368E+00      0.37       -0.04      0.41
0.5            7.610E+00      0.88       0.35      0.53
0.5            5.200E+00      0.72       0.35      0.37
0.6            2.050E+01      1.31       0.74      0.58
0.6            1.910E+01      1.28       0.74      0.55
0.7            3.560E+01      1.55       1.12      0.43
0.7            3.840E+01      1.58       1.12      0.46
0.8            5.660E+01      1.75       1.51      0.24
0.8            6.260E+01      1.80       1.51      0.29
0.9            9.730E+01      1.99       1.89      0.09
0.9            1.067E+02      2.03       1.89      0.13
1.0            1.780E+02      2.25       2.28      -0.03
1.0            2.020E+02      2.31       2.28      0.03
=====

```

SYSTEM NAME: NAP/ACN



BINARY SOLUBILITY DATA

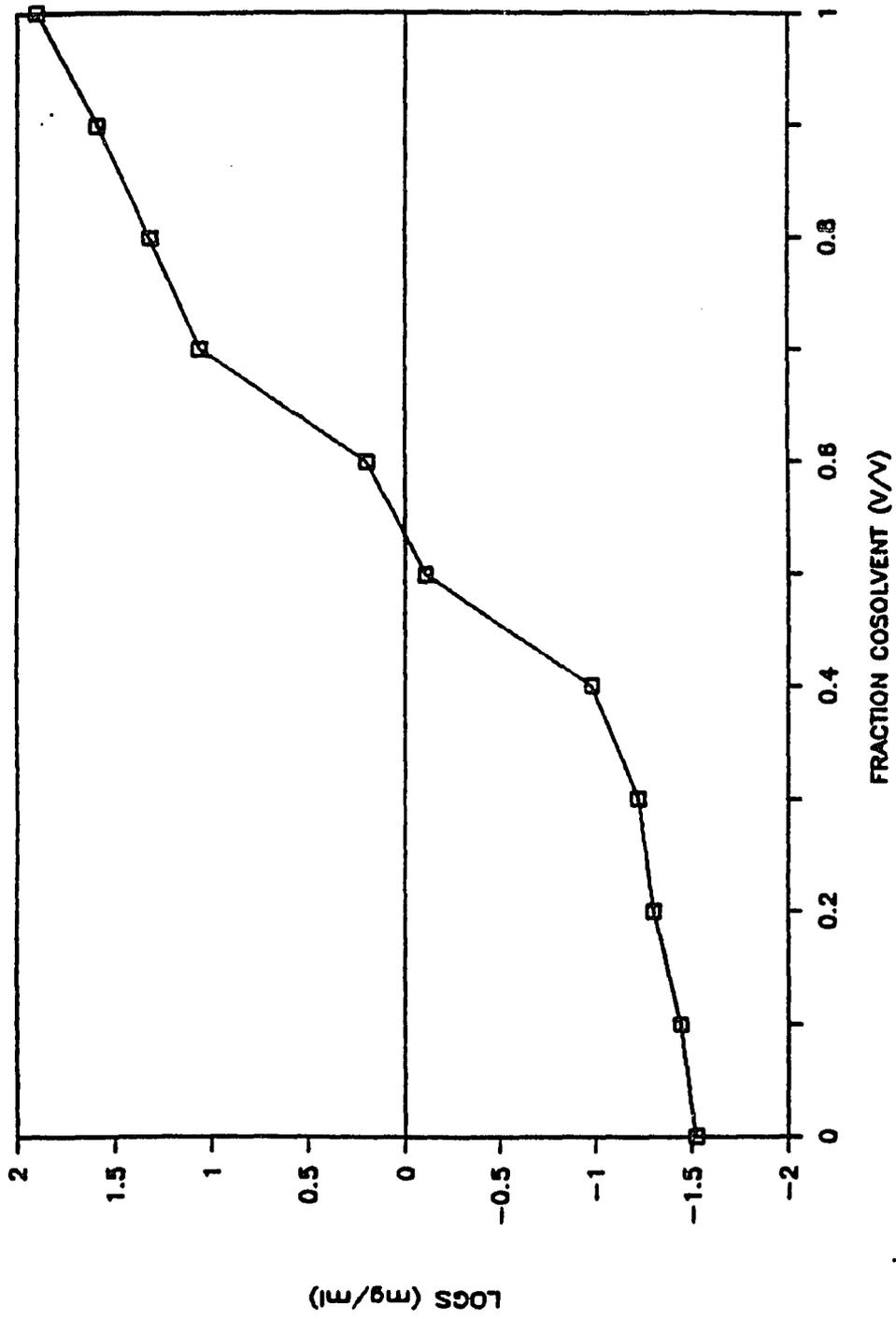
SYSTEM NAME: NAPHTHALENE/ETHANOL

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FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	2.575E-02	-1.59	-1.58	-0.01
0.0	2.644E-02	-1.58	-1.58	0.00
0.1	3.890E-02	-1.41	-1.23	-0.18
0.1	3.150E-02	-1.50	-1.23	-0.27
0.2	5.238E-02	-1.28	-0.88	-0.40
0.2	4.840E-02	-1.32	-0.88	-0.43
0.3	6.960E-02	-1.16	-0.54	-0.62
0.3	6.000E-02	-1.22	-0.54	-0.69
0.4	1.040E-01	-0.98	-0.19	-0.79
0.4	9.560E-02	-1.02	-0.19	-0.83
0.5	1.360E+00	0.13	0.16	-0.03
0.5	7.800E-02	-1.11	0.16	-1.27
0.6	5.810E+00	0.76	0.51	0.26
0.6	3.810E+00	0.58	0.51	0.07
0.7	1.359E+01	1.13	0.86	0.28
0.7	1.099E+01	1.04	0.86	0.18
0.8	2.132E+01	1.33	1.20	0.12
0.8	2.082E+01	1.32	1.20	0.11
0.9	3.348E+01	1.52	1.55	-0.03
0.9	3.792E+01	1.58	1.55	0.03
1.0	8.080E+01	1.91	1.90	0.01
1.0	7.670E+01	1.88	1.90	-0.02

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SYSTEM NAME: NAP/EOH



BINARY SOLUBILITY DATA

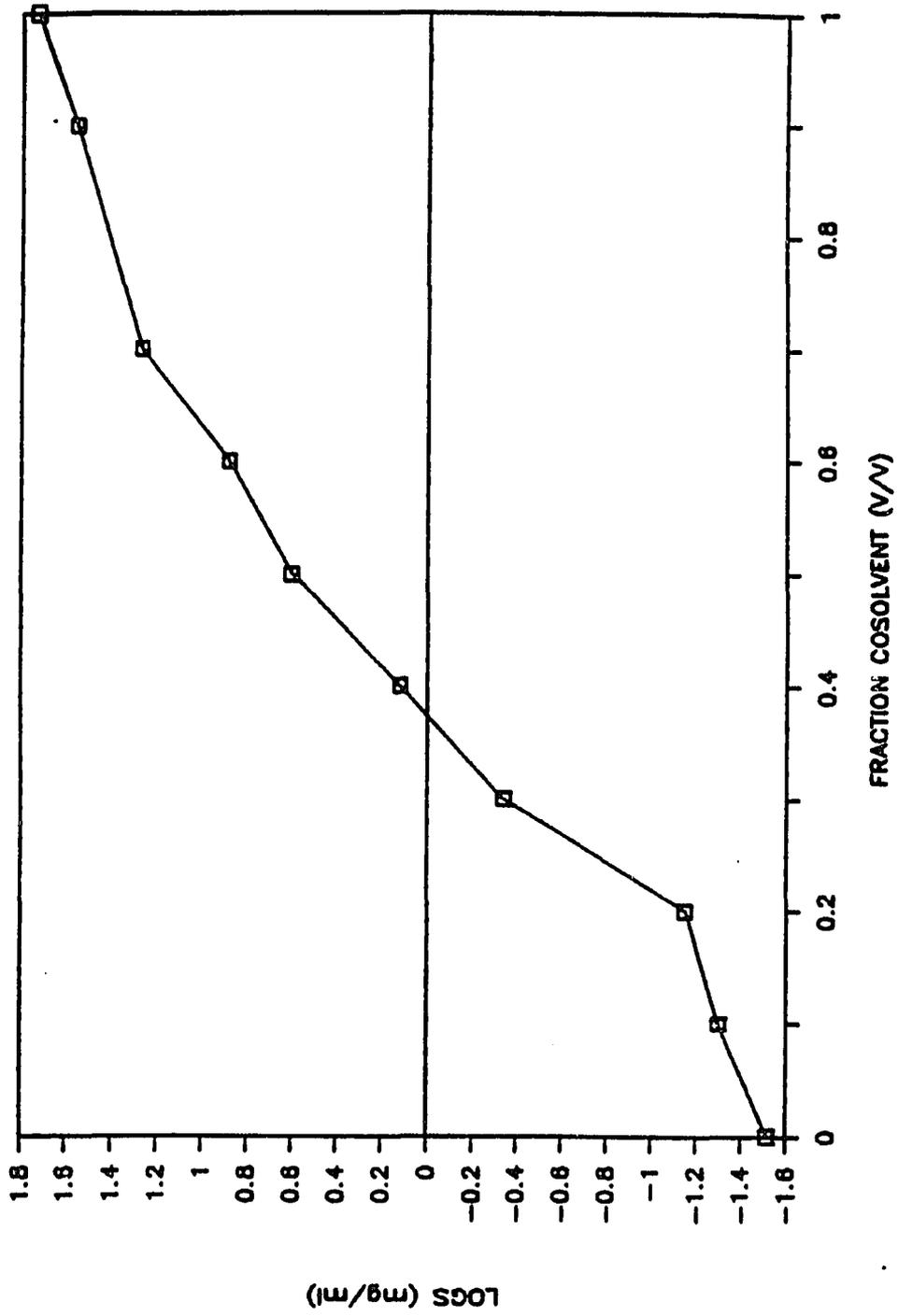
SYSTEM NAME: NAPHTHALENE/ISOPROPANOL

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=====
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FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	2.575E-02	-1.59	-1.58	-0.01
0.0	2.644E-02	-1.58	-1.58	0.00
0.1	4.280E-02	-1.37	-1.25	-0.12
0.1	4.830E-02	-1.32	-1.25	-0.07
0.2	7.000E-02	-1.15	-0.92	-0.24
0.2	6.720E-02	-1.17	-0.92	-0.26
0.3	3.810E-01	-0.42	-0.58	0.16
0.3	4.310E-01	-0.37	-0.58	0.22
0.4	1.400E+00	0.15	-0.25	0.40
0.4	1.320E+00	0.12	-0.25	0.37
0.5	3.620E+00	0.56	0.08	0.48
0.5	3.280E+00	0.52	0.08	0.44
0.6	7.950E+00	0.90	0.41	0.49
0.6	7.610E+00	0.88	0.41	0.47
0.7	1.469E+01	1.17	0.74	0.42
0.7	1.705E+01	1.23	0.74	0.49
0.8	2.491E+01	1.40	1.08	0.32
0.8	2.561E+01	1.41	1.08	0.33
0.9	3.698E+01	1.57	1.41	0.16
0.9	3.560E+01	1.55	1.41	0.14
1.0	5.466E+01	1.74	1.74	-0.00
1.0	5.370E+01	1.73	1.74	-0.01

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```

SYSTEM NAME: NAP/IPA



BINARY SOLUBILITY DATA

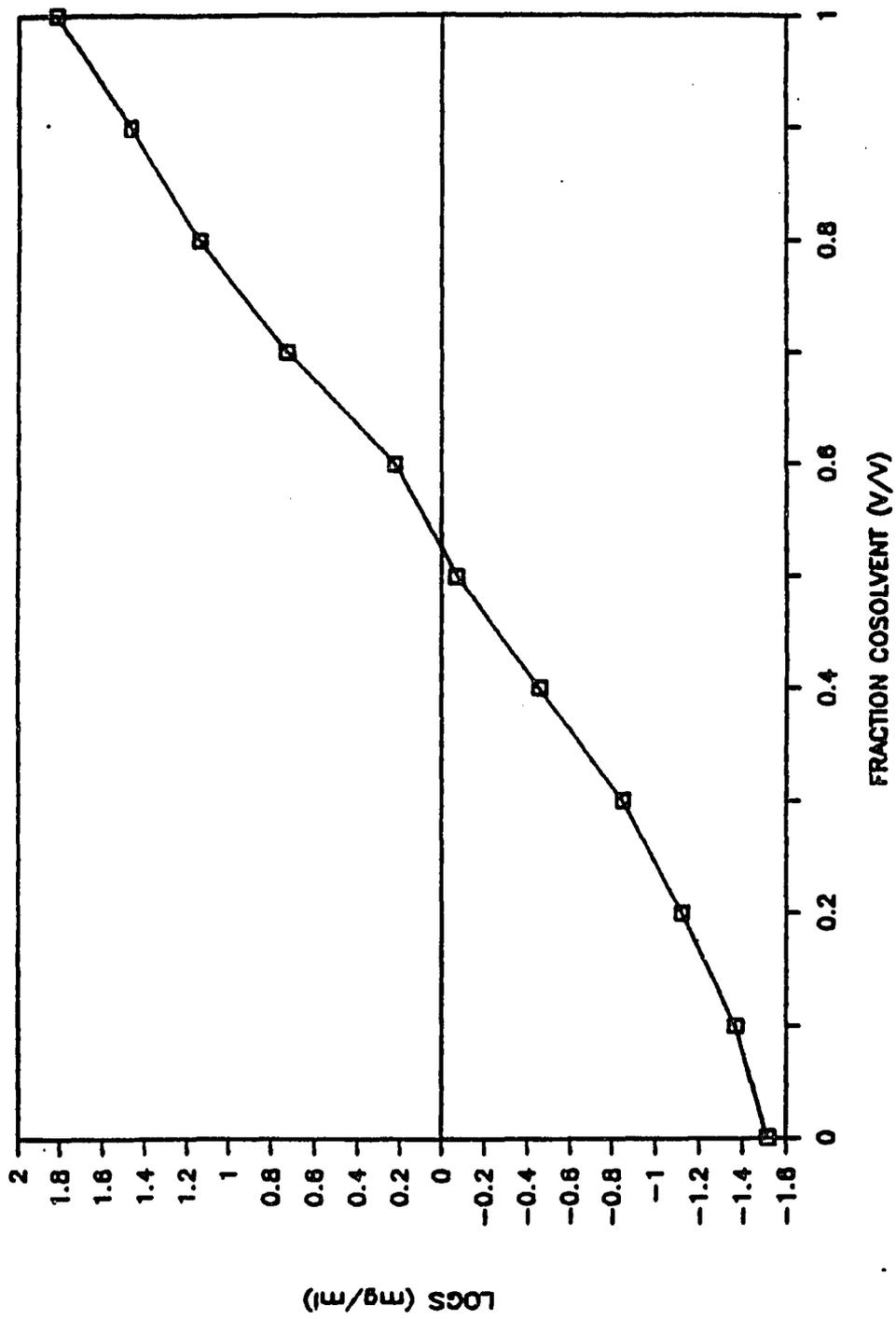
SYSTEM NAME: NAPHTHALENE/METHANOL

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            2.575E-02      -1.59      -1.58      -0.01
0.0            2.644E-02      -1.58      -1.58      0.00
0.1            4.120E-02      -1.39      -1.24      -0.14
0.1            4.820E-02      -1.32      -1.24      -0.08
0.2            6.700E-02      -1.17      -0.90      -0.27
0.2            9.100E-02      -1.04      -0.90      -0.14
0.3            1.270E-01      -0.90      -0.56      -0.33
0.3            1.410E-01      -0.85      -0.56      -0.29
0.4            3.035E-01      -0.52      -0.22      -0.29
0.4            3.460E-01      -0.46      -0.22      -0.24
0.5            8.330E-01      -0.08      0.12      -0.19
0.5            7.410E-01      -0.13      0.12      -0.25
0.6            2.025E+00      0.31      0.45      -0.15
0.6            2.295E+00      0.36      0.45      -0.09
0.7            5.030E+00      0.70      0.79      -0.09
0.7            5.510E+00      0.74      0.79      -0.05
0.8            1.222E+01      1.09      1.13      -0.04
0.8            1.374E+01      1.14      1.13      0.01
0.9            2.567E+01      1.41      1.47      -0.06
0.9            3.213E+01      1.51      1.47      0.04
1.0            6.618E+01      1.82      1.81      0.01
1.0            6.102E+01      1.79      1.81      -0.02
=====

```

SYSTEM NAME: NAP/MOH

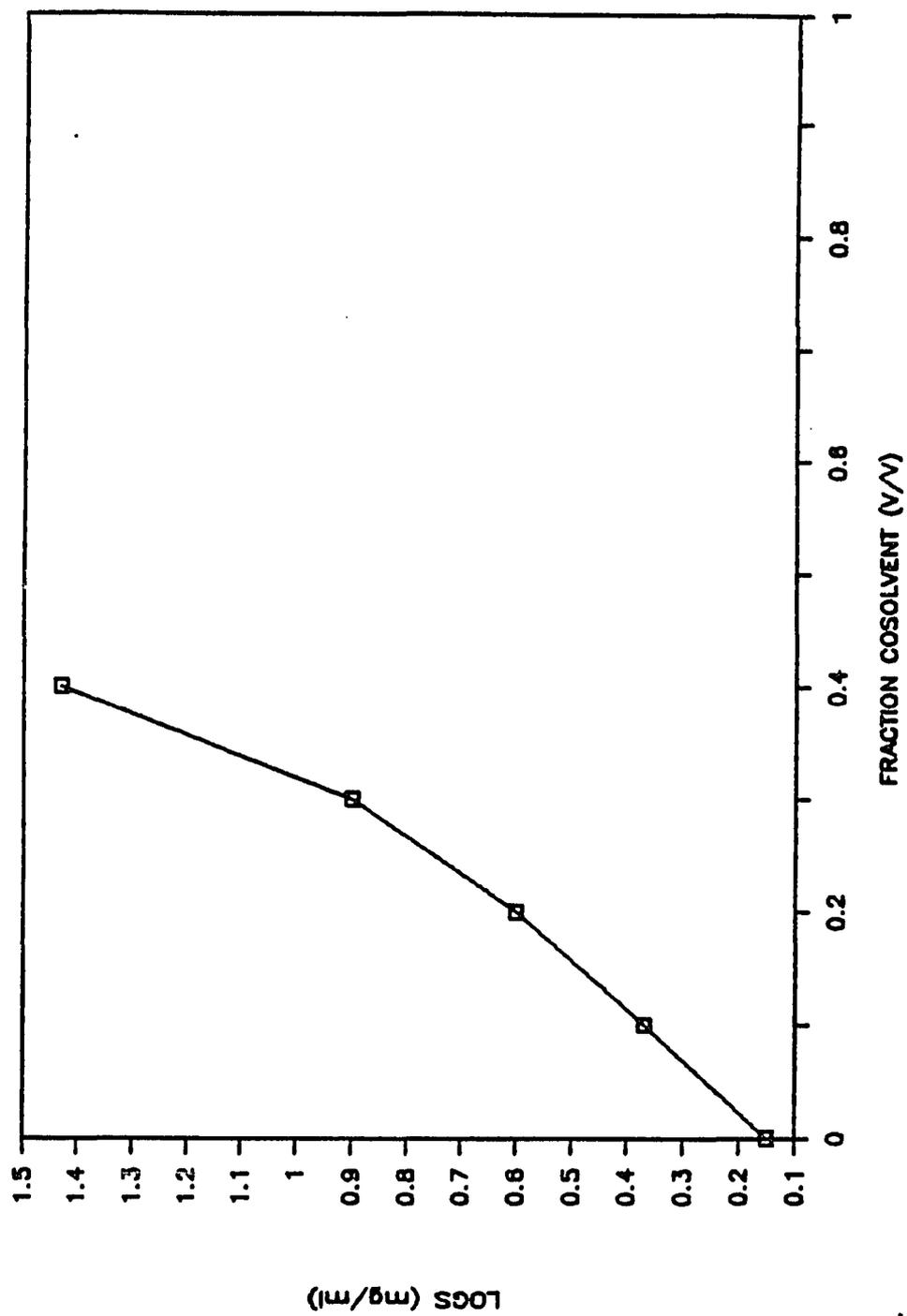


BINARY SOLUBILITY DATA

SYSTEM NAME: NAPTHOL/METHANOL

```
=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT     (mg/ml)        obs        pred        obs-pred
=====
0.0           1.407E+00      0.15       0.15       -0.00
0.0           1.417E+00      0.15       0.15       0.00
0.1           2.481E+00      0.39       0.43       -0.03
0.1           2.253E+00      0.35       0.43       -0.08
0.2           3.941E+00      0.60       0.71       -0.11
0.2           3.978E+00      0.60       0.71       -0.11
0.3           7.823E+00      0.89       0.99       -0.09
0.3           8.101E+00      0.91       0.99       -0.08
0.4           2.647E+01      1.42       1.27       0.16
0.4           2.682E+01      1.43       1.27       0.16
=====
```

SYSTEM NAME: NOL/MOH



BINARY SOLUBILITY DATA

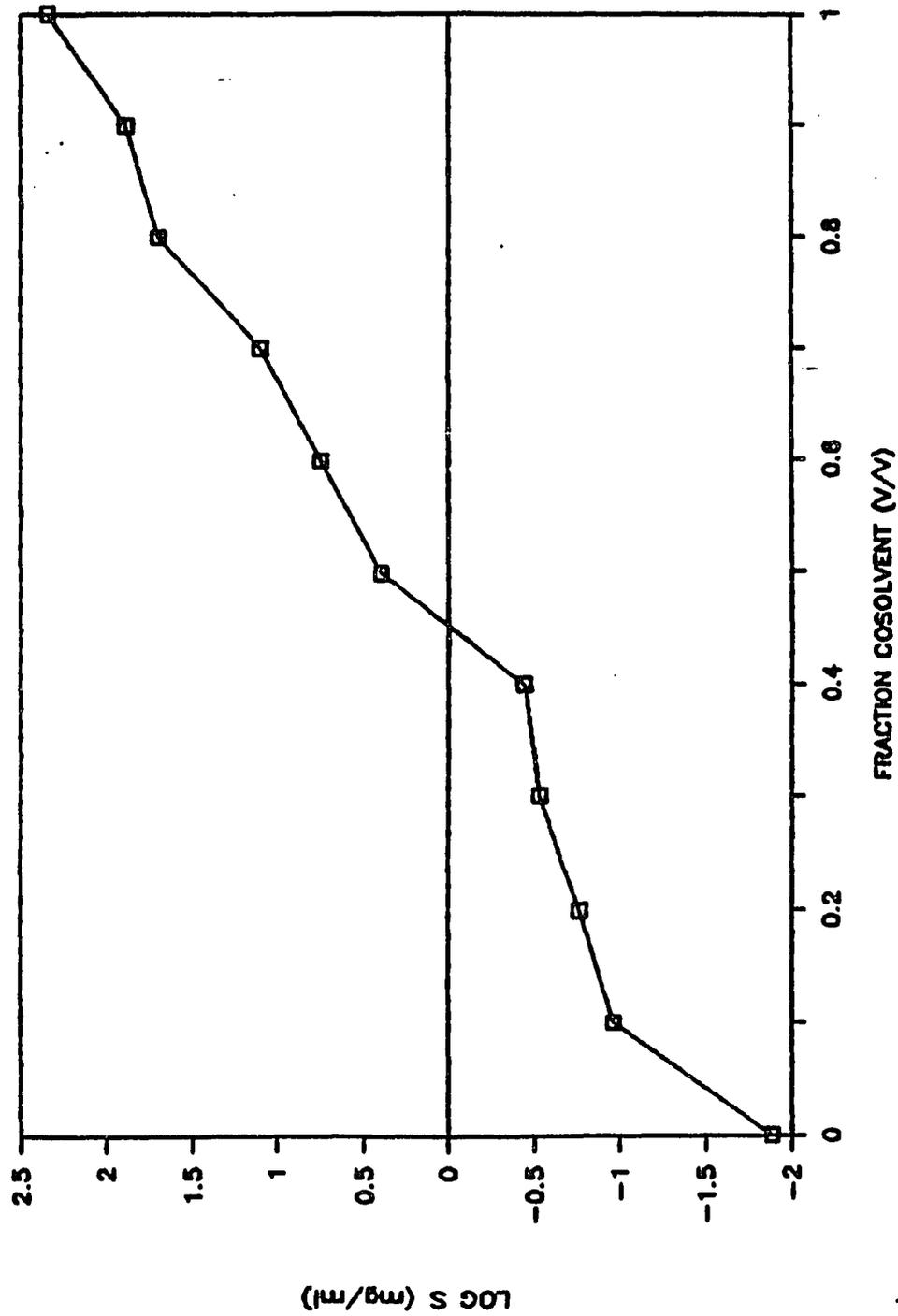
SYSTEM NAME: PHENANTHRENE/ACETONE

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT      (mg/ml)        obs        pred        obs-pred
=====
0.0            9.000E-03      -2.05      -1.91      -0.14
0.0            1.700E-02      -1.77      -1.91      0.14
0.1            1.060E-01      -0.97      -1.49      0.51
0.1            1.140E-01      -0.94      -1.49      0.54
0.2            1.750E-01      -0.76      -1.06      0.31
0.2            1.720E-01      -0.76      -1.06      0.30
0.3            2.970E-01      -0.53      -0.64      0.11
0.3            2.970E-01      -0.53      -0.64      0.11
0.4            3.500E-01      -0.46      -0.21      -0.24
0.4            3.800E-01      -0.42      -0.21      -0.21
0.5            2.550E+00      0.41       0.21      0.20
0.5            2.500E+00      0.40       0.21      0.19
0.6            5.650E+00      0.75       0.63      0.12
0.7            1.250E+01      1.10       1.06      0.04
0.7            1.260E+01      1.10       1.06      0.04
0.8            4.500E+01      1.65       1.48      0.17
0.8            5.563E+01      1.75       1.48      0.26
0.9            7.850E+01      1.89       1.91      -0.01
0.9            7.850E+01      1.89       1.91      -0.01
1.0            2.300E+02      2.36       2.33      0.03
1.0            2.040E+02      2.31       2.33      -0.02
=====

```

SYSTEM NAME: PHN/ACE



BINARY SOLUBILITY DATA

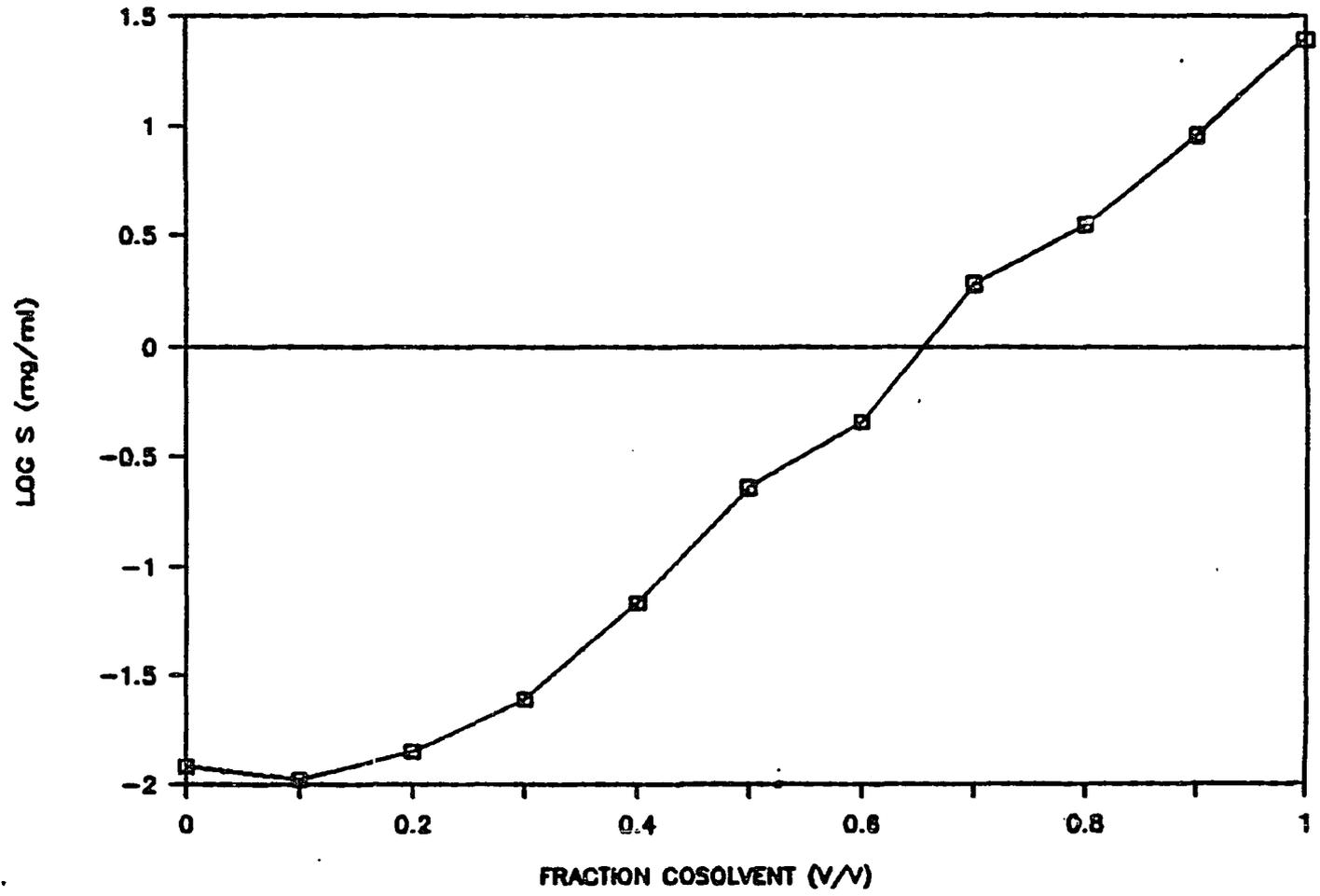
SYSTEM NAME: PHENANTHRENE/METHANOL

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FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	1.200E-02	-1.92	-1.92	-0.00
0.0	1.200E-02	-1.92	-1.92	-0.00
0.1	1.000E-02	-2.00	-1.59	-0.41
0.1	1.100E-02	-1.96	-1.59	-0.37
0.2	1.300E-02	-1.89	-1.26	-0.63
0.2	1.500E-02	-1.82	-1.26	-0.57
0.3	2.400E-02	-1.62	-0.93	-0.69
0.3	2.500E-02	-1.60	-0.93	-0.68
0.4	7.100E-02	-1.15	-0.60	-0.55
0.4	6.300E-02	-1.20	-0.60	-0.60
0.5	2.370E-01	-0.63	-0.27	-0.36
0.5	2.220E-01	-0.65	-0.27	-0.39
0.6	4.500E-01	-0.35	0.07	-0.41
0.6	4.600E-01	-0.34	0.07	-0.40
0.7	1.900E+00	0.28	0.40	-0.12
0.7	1.900E+00	0.28	0.40	-0.12
0.8	3.650E+00	0.56	0.73	-0.17
0.8	3.500E+00	0.54	0.73	-0.18
0.9	9.200E+00	0.96	1.06	-0.10
0.9	9.100E+00	0.96	1.06	-0.10
1.0	2.475E+01	1.39	1.39	0.00
1.0	2.475E+01	1.39	1.39	0.00

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=====
```

SYSTEM NAME: PHN/MEO



BINARY SOLUBILITY DATA

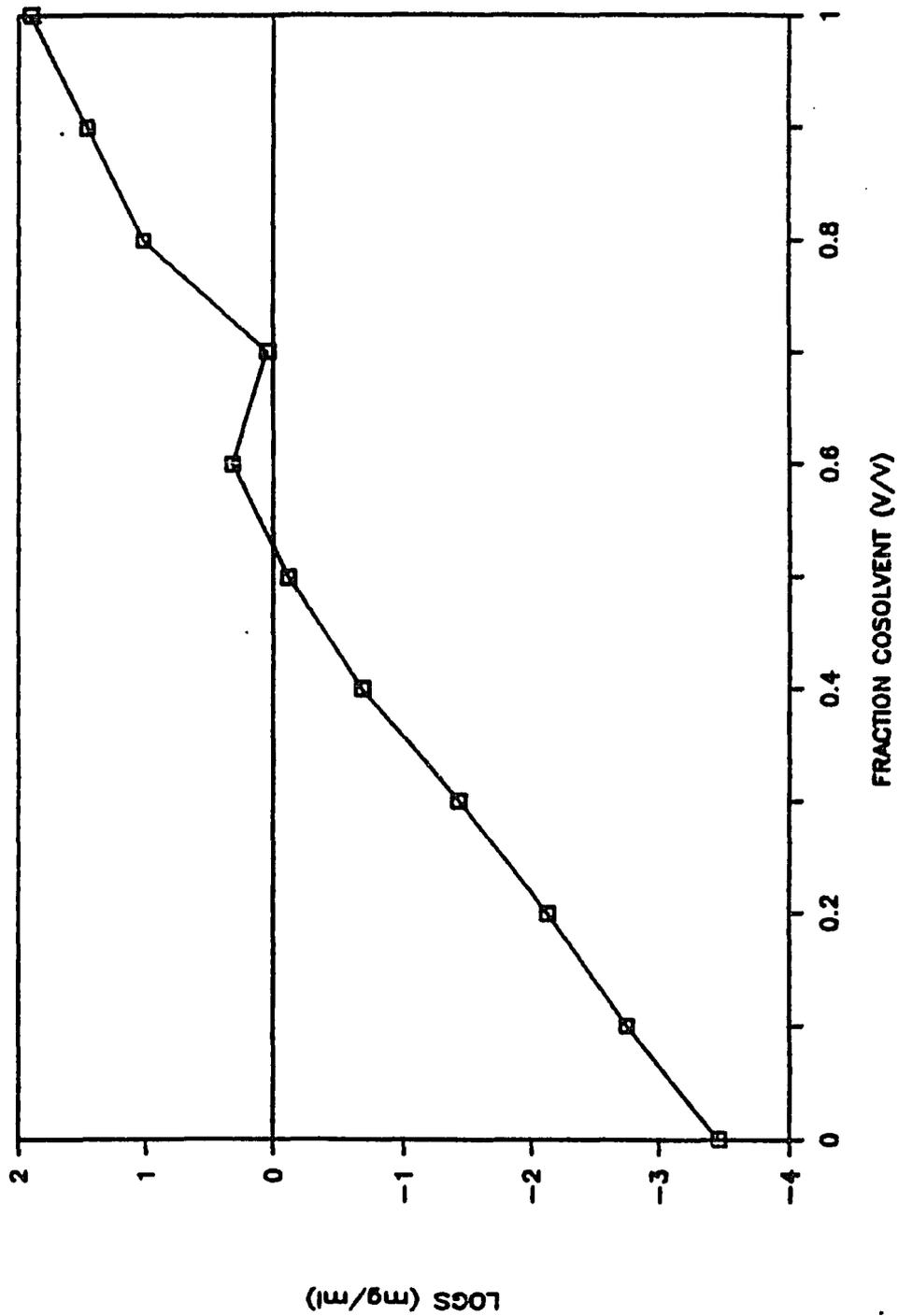
SYSTEM NAME: PYRENE/ACETONE

```

=====
FRACTION      SOLUBILITY      LOG S      LOG S      DEVIATION
COSOLVENT     (mg/ml)        obs        pred        obs-pred
=====
0.0           3.450E-04      -3.46      -3.46      -0.00
0.1           1.683E-03      -2.77      -2.92      0.15
0.1           1.880E-03      -2.73      -2.92      0.20
0.2           7.132E-03      -2.15      -2.39      0.24
0.2           7.638E-03      -2.12      -2.39      0.27
0.3           3.692E-02      -1.43      -1.85      0.42
0.3           3.806E-02      -1.42      -1.85      0.43
0.4           2.077E-01      -0.68      -1.32      0.63
0.4           2.060E-01      -0.69      -1.32      0.63
0.5           7.795E-01      -0.11      -0.78      0.67
0.5           7.711E-01      -0.11      -0.78      0.67
0.6           2.082E+00      0.32       -0.24      0.56
0.6           2.095E+00      0.32       -0.24      0.57
0.7           1.141E+00      0.06       0.29      -0.23
0.7           1.101E+00      0.04       0.29      -0.25
0.8           1.045E+01      1.02       0.83      0.19
0.8           1.036E+01      1.02       0.83      0.19
0.9           2.873E+01      1.46       1.36      0.09
0.9           2.960E+01      1.47       1.36      0.11
1.0           7.876E+01      1.90       1.90      -0.00
1.0           7.977E+01      1.90       1.90      0.00
=====

```

SYSTEM NAME: PYR/ACE



BINARY SOLUBILITY DATA

SYSTEM NAME: PYRENE/METHANOL

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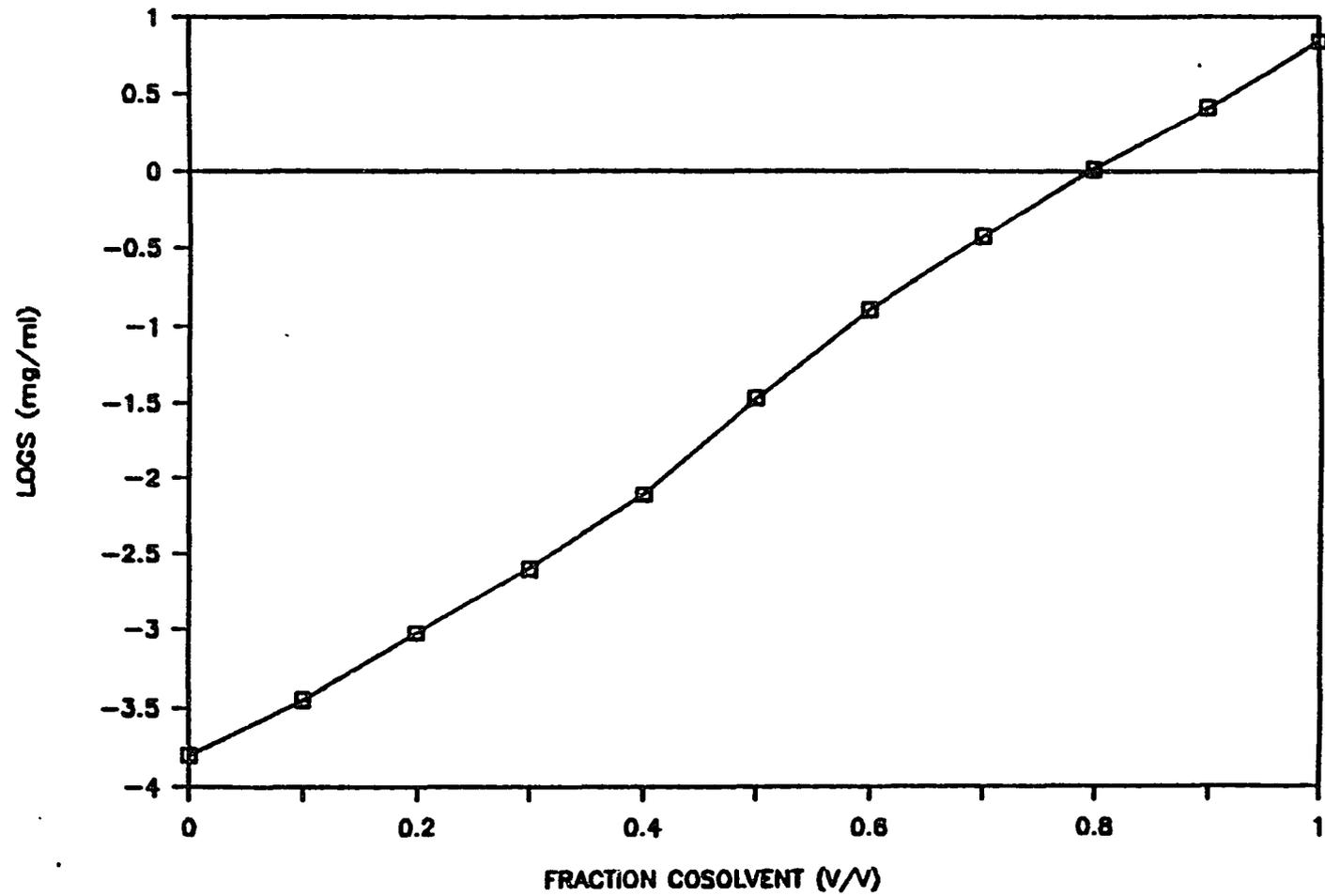
FRACTION COSOLVENT	SOLUBILITY (mg/ml)	LOG S obs	LOG S pred	DEVIATION obs-pred
0.0	3.450E-04	-3.46	-3.46	-0.00
0.1	5.290E-04	-3.28	-3.03	-0.25
0.1	3.455E-04	-3.46	-3.03	-0.43
0.2	1.270E-03	-2.90	-2.60	-0.30
0.2	1.303E-03	-2.89	-2.60	-0.29
0.3	3.595E-03	-2.44	-2.17	-0.27
0.3	3.602E-03	-2.44	-2.17	-0.27
0.4	1.126E-02	-1.95	-1.74	-0.21
0.4	1.003E-02	-2.00	-1.74	-0.26
0.5	3.560E-02	-1.45	-1.31	-0.14
0.5	3.500E-02	-1.46	-1.31	-0.15
0.6	1.422E-01	-0.85	-0.88	0.03
0.6	1.429E-01	-0.85	-0.88	0.03
0.7	4.270E-01	-0.37	-0.45	0.08
0.7	4.295E-01	-0.37	-0.45	0.08
0.8	1.115E+00	0.05	-0.02	0.07
0.8	1.188E+00	0.07	-0.02	0.09
0.9	2.476E+00	0.39	0.41	-0.02
0.9	2.250E+00	0.35	0.41	-0.06
1.0	6.979E+00	0.84	0.84	0.00
1.0	6.905E+00	0.84	0.84	-0.00

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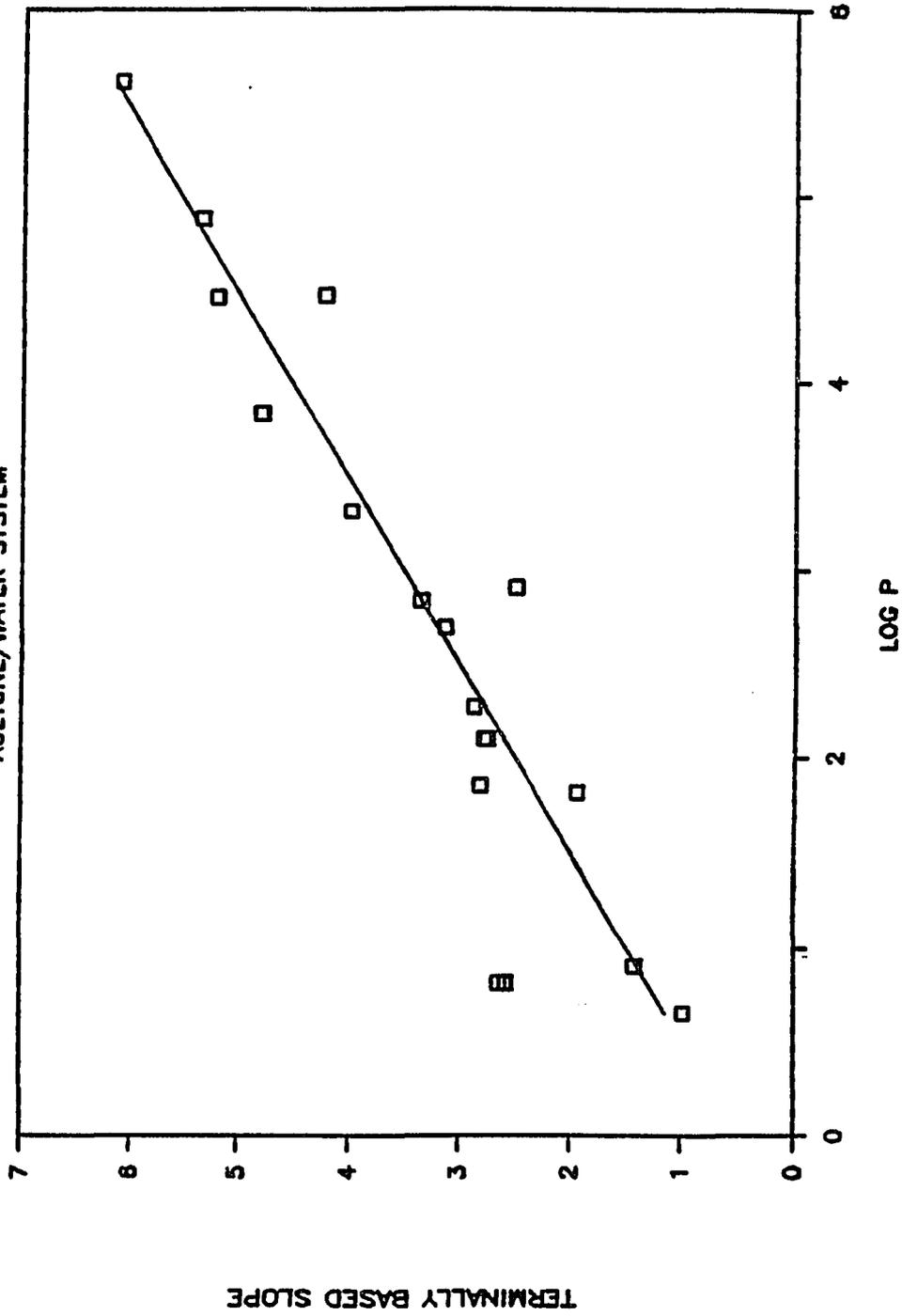
SYSTEM NAME: PYR/MOH



APPENDIX B.
DATA, PLOTS AND STATISTICS
FOR σ ESTIMATION

TERMINALLY BASED SLOPE VS LOG P

ACETONE/WATER SYSTEM



SOLVENT=ACETONE/WATER
(excluding atrazine)

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	29.36364	29.36364	178.566	0.0001
ERROR	13	2.137735	0.1644412		
C TOTAL	14	31.50137			
ROOT MSE		0.4055135	R-SQUARE	0.9321	
DEP MEAN		3.448667	ADJ R-SQ	0.9269	
C.V.		11.75856			

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.4843694	0.2452992	1.975	0.0699
LPS	1	0.9974082	0.07464028	13.363	0.0001

=====

SOLVENT=ACETONE/WATER
(including atrazine)

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	28.53116	28.53116	111.000	0.0001
ERROR	14	3.598536	0.2570383		
C TOTAL	15	32.1297			
ROOT MSE		0.5069894	R-SQUARE	0.8880	
DEP MEAN		3.3975	ADJ R-SQ	0.8800	
C.V.		14.92243			

PARAMETER ESTIMATES

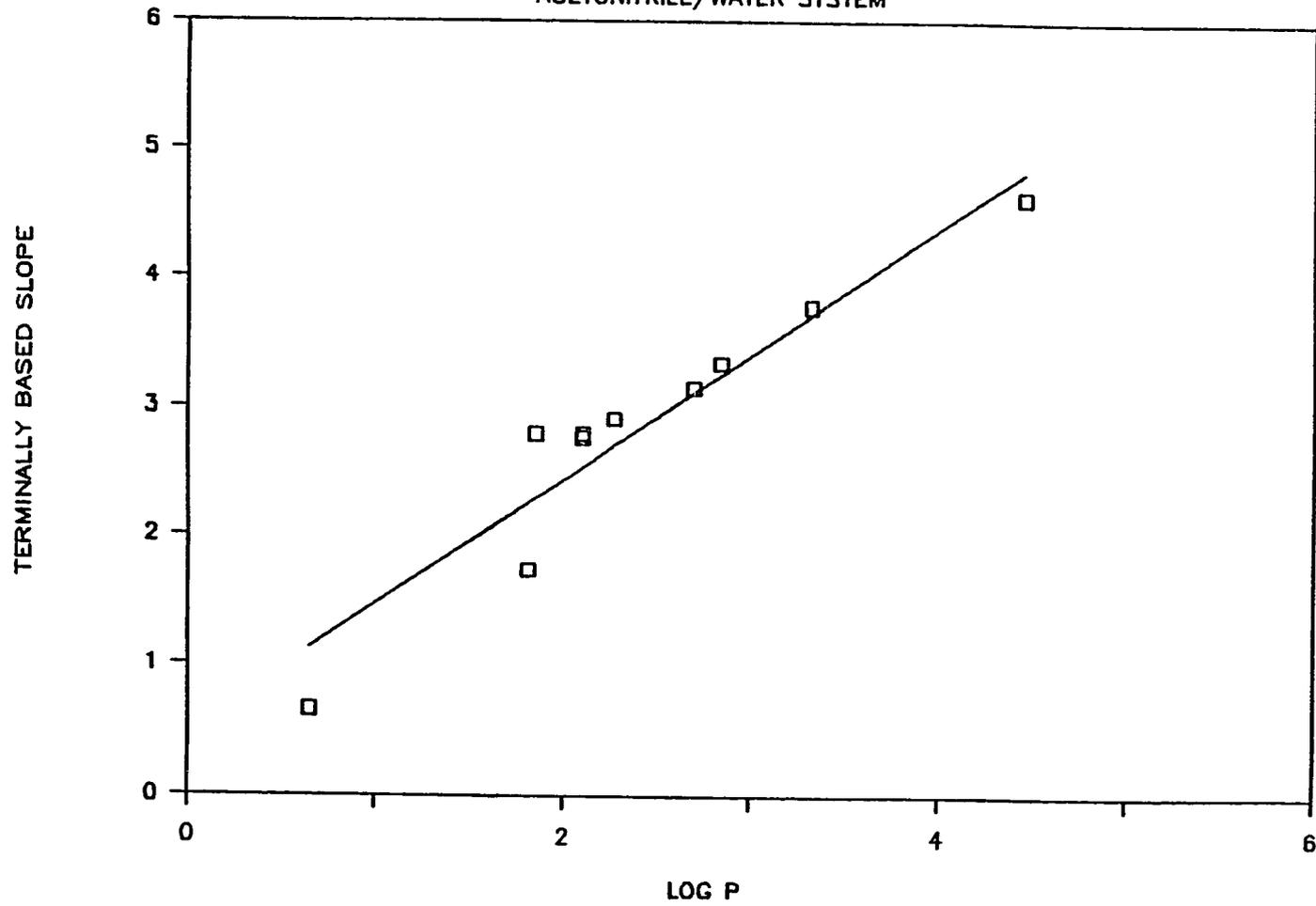
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.794888	0.277648	2.863	0.0125
LPS	1	0.9174222	0.08707799	10.536	0.0001

ACETONE/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
ATRAZINE	2.58	0.81
ATRAZINE	2.64	0.81
BENZAMIDE	0.98	0.65
ANALINE	1.42	0.90
BENZINE	1.94	1.81
NITROBENZENE	2.82	1.85
BENZOIC ACID	2.79	2.10
BENZOIC ACID	2.76	2.10
FLUOROBENZENE	2.88	2.27
TOLUENE	3.15	2.70
CHLOROBENZENE	3.37	2.84
DIURON	2.51	2.91
NAPHTHALINE	4.00	3.32
BIPHENYL	4.81	3.84
BIPHENYL	4.80	3.84
ANTHRACENE	5.21	4.45
ANTHRACENE	5.22	4.45
PHENANTHRENE	4.24	4.46
PYRINE	5.36	4.88
CRYSENE	6.11	5.61

TERMINALLY BASED SLOPE VS LOG P

ACETONITRILE/WATER SYSTEM



SOLVENT=ACETONITRILE/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	9.670612	9.670612	76.544	0.0001
ERROR	7	0.8843883	0.1263412		
C TOTAL	8	10.555			
ROOT MSE		0.355445	R-SQUARE	0.9162	
DEP MEAN		2.866667	ADJ R-SQ	0.9042	
C.V.		12.39925			

PARAMETER ESTIMATES

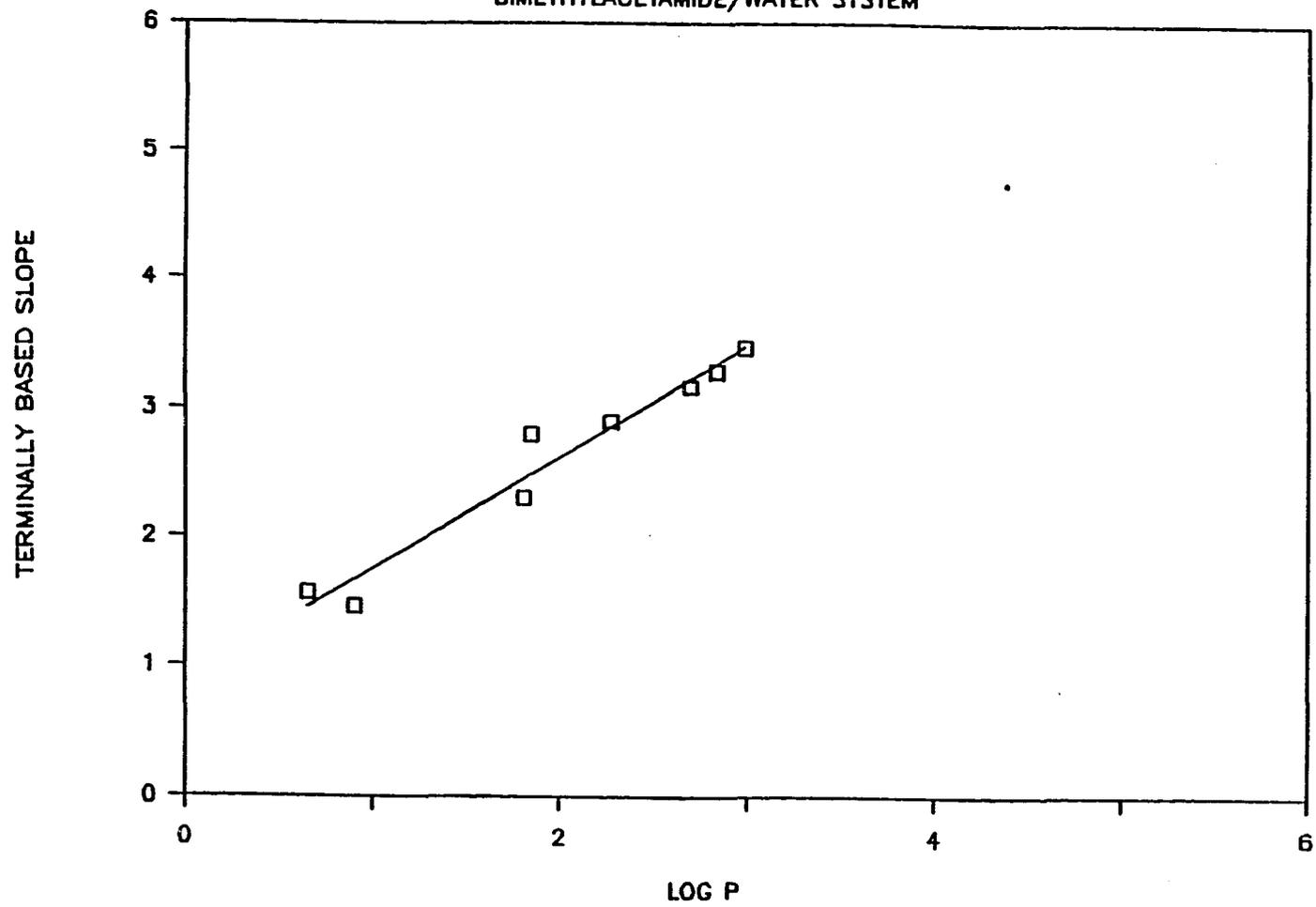
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.3528063	0.3108031	1.135	0.2937
LPS	1	1.028865	0.1175991	8.749	0.0001

ACETONITRILE/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	0.65	0.65
BENZINE	1.73	1.81
NITROBENZENE	2.79	1.85
BENZOIC ACID	2.79	2.10
BENZOIC ACID	2.76	2.10
FLUOROBENZENE	2.91	2.27
TOLUENE	3.15	2.70
CHLOROBENZENE	3.34	2.84
NAPHTHALINE	3.78	3.32
ANTHRACENE	4.62	4.45
ANTHRACENE	4.62	4.45

TERMINALLY BASED SLOPE VS LOG P

DIMETHYLACETAMIDE/WATER SYSTEM



SOLVENT=DIMETHYLACETAMIDE/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	3.972627	3.972627	129.782	0.0001
ERROR	6	0.1836603	0.03061006		
C TOTAL	7	4.156287			
ROOT MSE		0.1749573	R-SQUARE	0.9558	
DEP MEAN		2.61875	ADJ R-SQ	0.9484	
C.V.		6.680947			

PARAMETER ESTIMATES

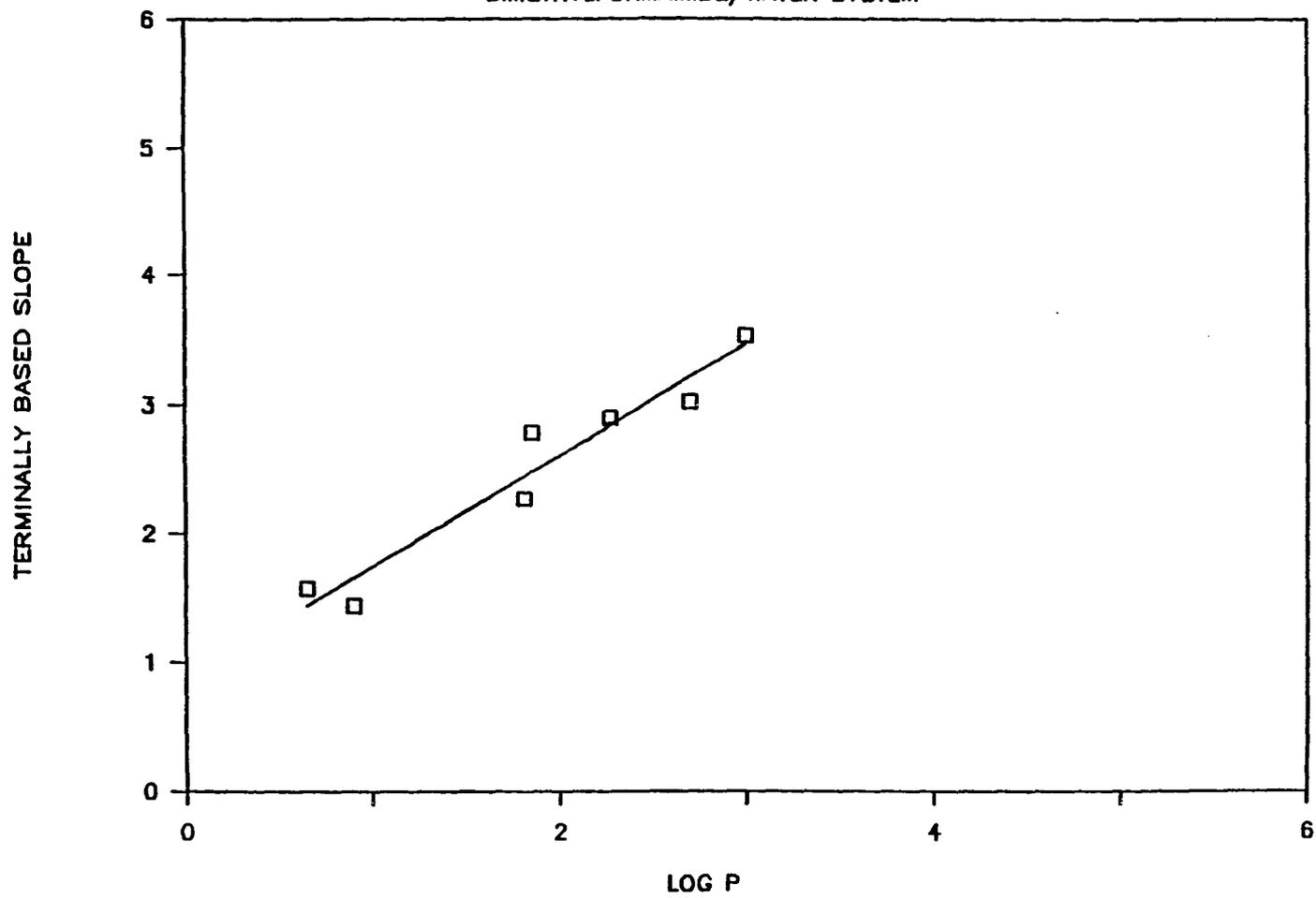
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.8925849	0.1636617	5.454	0.0016
LPS	1	0.8625435	0.07571364	11.392	0.0001

DIMETHYLACETAMIDE/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.56	0.65
ANALINE	1.46	0.90
BENZINE	2.30	1.81
NITROBENZENE	2.80	1.85
FLUOROBENZENE	2.90	2.27
TOLUENE	3.17	2.70
CHLOROBENZENE	3.29	2.84
BROMOBENZENE	3.47	2.99

TERMINALLY BASED SLOPE VS LOG P

DIMETHYLFORMAMIDE/WATER SYSTEM



SOLVENT=DIMETHYLFORMAMIDE/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	4.013465	4.013465	104.028	0.0001
ERROR	6	0.2314848	0.038581		
C TOTAL	7	4.24495			
ROOT MSE		0.19642	R-SQUARE	0.9455	
DEP MEAN		2.6075	ADJ R-SQ	0.9364	
C.V.		7.532884			

PARAMETER ESTIMATES

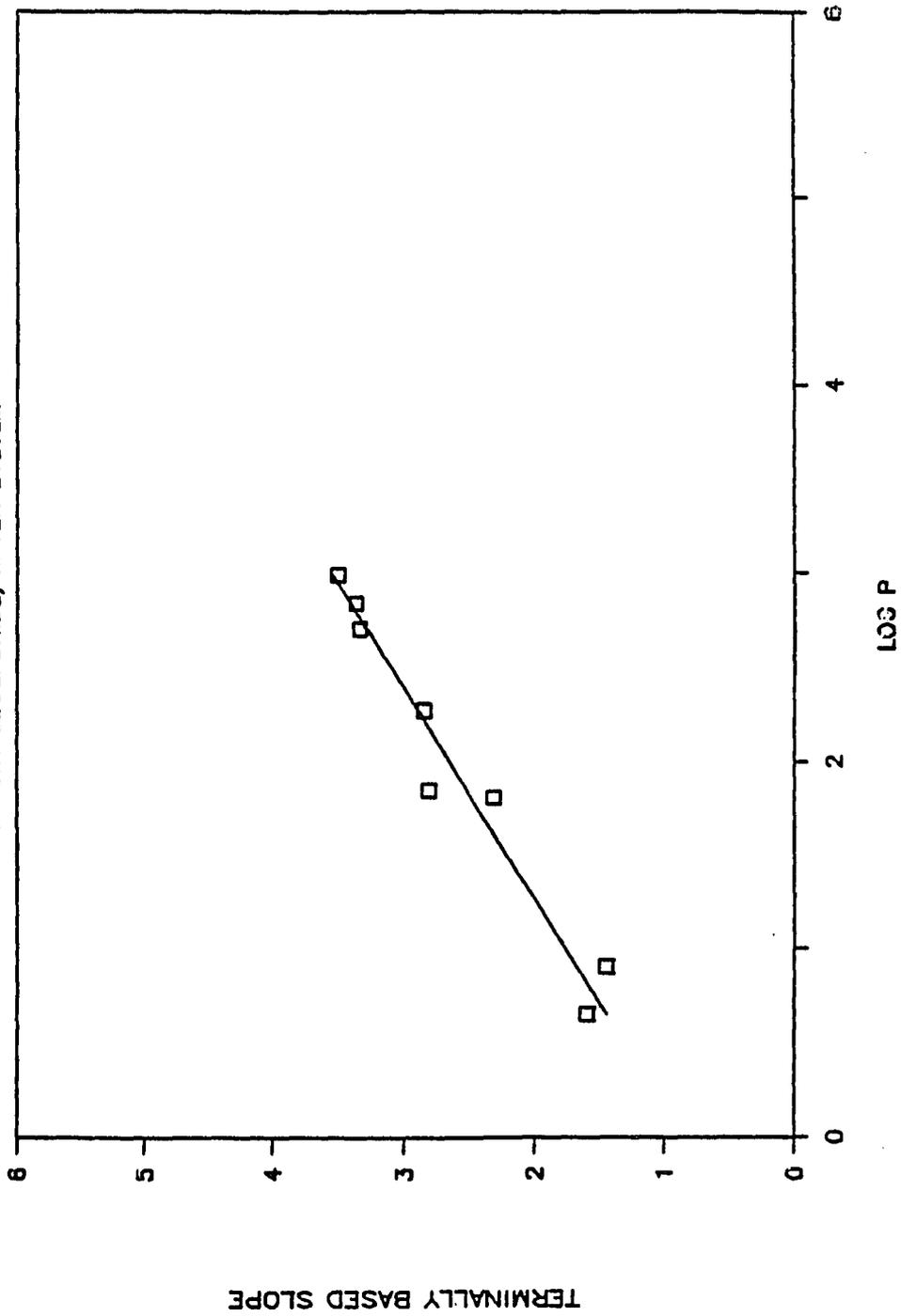
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.8724852	0.1837387	4.749	0.0032
LPS	1	0.8669655	0.08500172	10.199	0.0001

DIMETHYLFORMAMIDE/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.57	0.65
ANALINE	1.44	0.90
BENZINE	2.27	1.81
NITROBENZENE	2.78	1.85
FLUOROBENZENE	2.90	2.27
TOLUENE	3.02	2.70
BROMOBENZENE	3.54	2.99

TERMINALLY BASED SLOPE VS LOG P

DIMETHYLSULFOXIDE/WATER SYSTEM



SOLVENT=DIMETHYLSULFOXIDE/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	4.263326	4.263326	131.669	0.0001
ERROR	6	0.1942744	0.03237906		
C TOTAL	7	4.4576			
ROOT MSE		0.1799418	R-SQUARE	0.9564	
DEP MEAN		2.655	ADJ R-SQ	0.9492	
C.V.		6.77747			

PARAMETER ESTIMATES

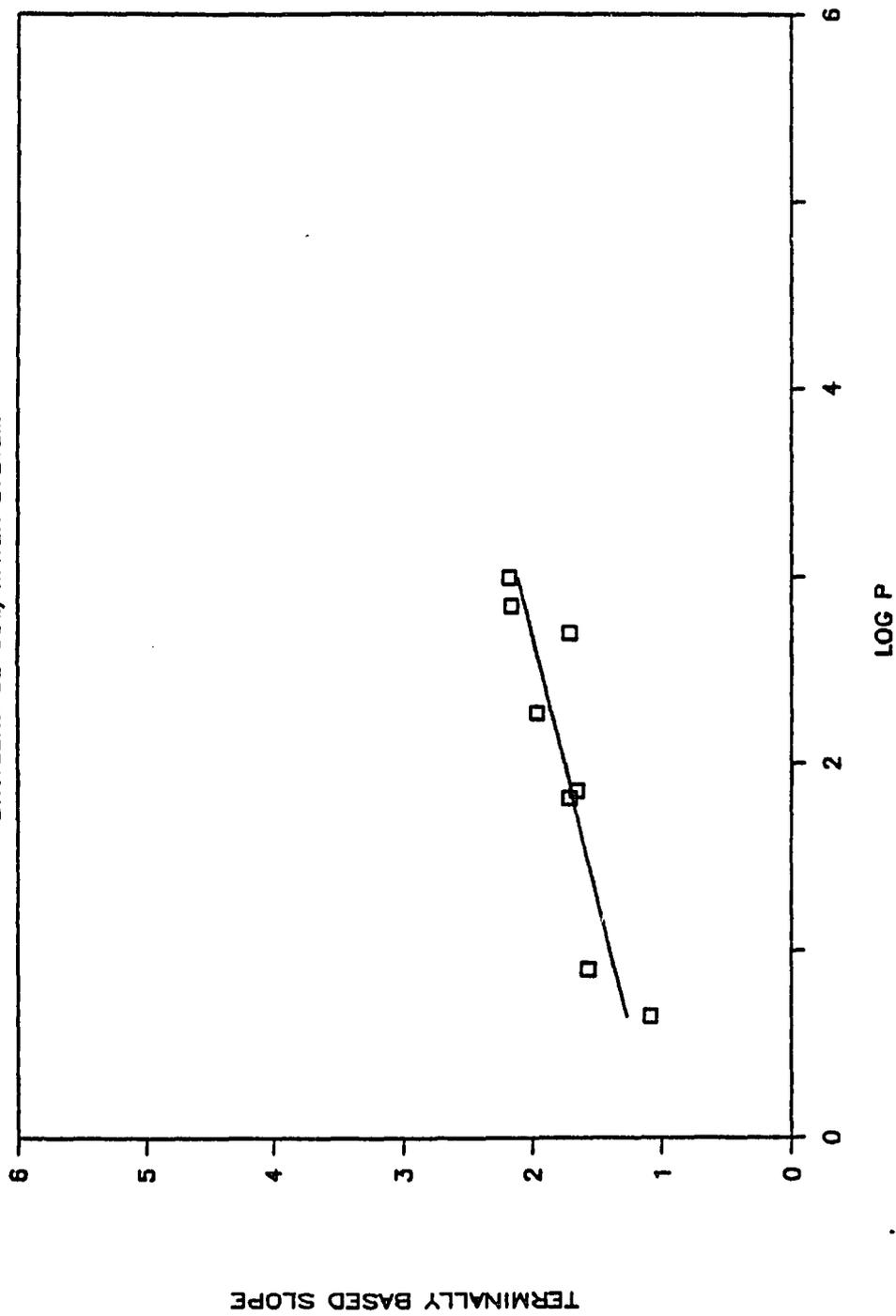
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.8667935	0.1683244	5.150	0.0021
LPS	1	0.8935448	0.07787072	11.475	0.0001

DIMETHYLSULFOXIDE/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.60	0.65
ANALINE	1.45	0.90
BENZINE	2.31	1.81
NITROBENZENE	2.81	1.85
FLUOROBENZENE	2.85	2.27
TOLUENE	3.34	2.70
CHLOROBENZENE	3.37	2.84
BROMOBENZENE	3.51	2.99

TERMINALLY BASED SLOPE VS LOG P

ETHYLENE GLYCOL/WATER SYSTEM



SOLVENT=ETHYLENE GLYCOL/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	0.6879435	0.6879435	21.640	0.0035
ERROR	6	0.190744	0.03179066		
C TOTAL	7	0.8786875			
ROOT MSE		0.1782994	R-SQUARE	0.7829	
DEP MEAN		1.75875	ADJ R-SQ	0.7467	
C.V.		10.13785			

PARAMETER ESTIMATES

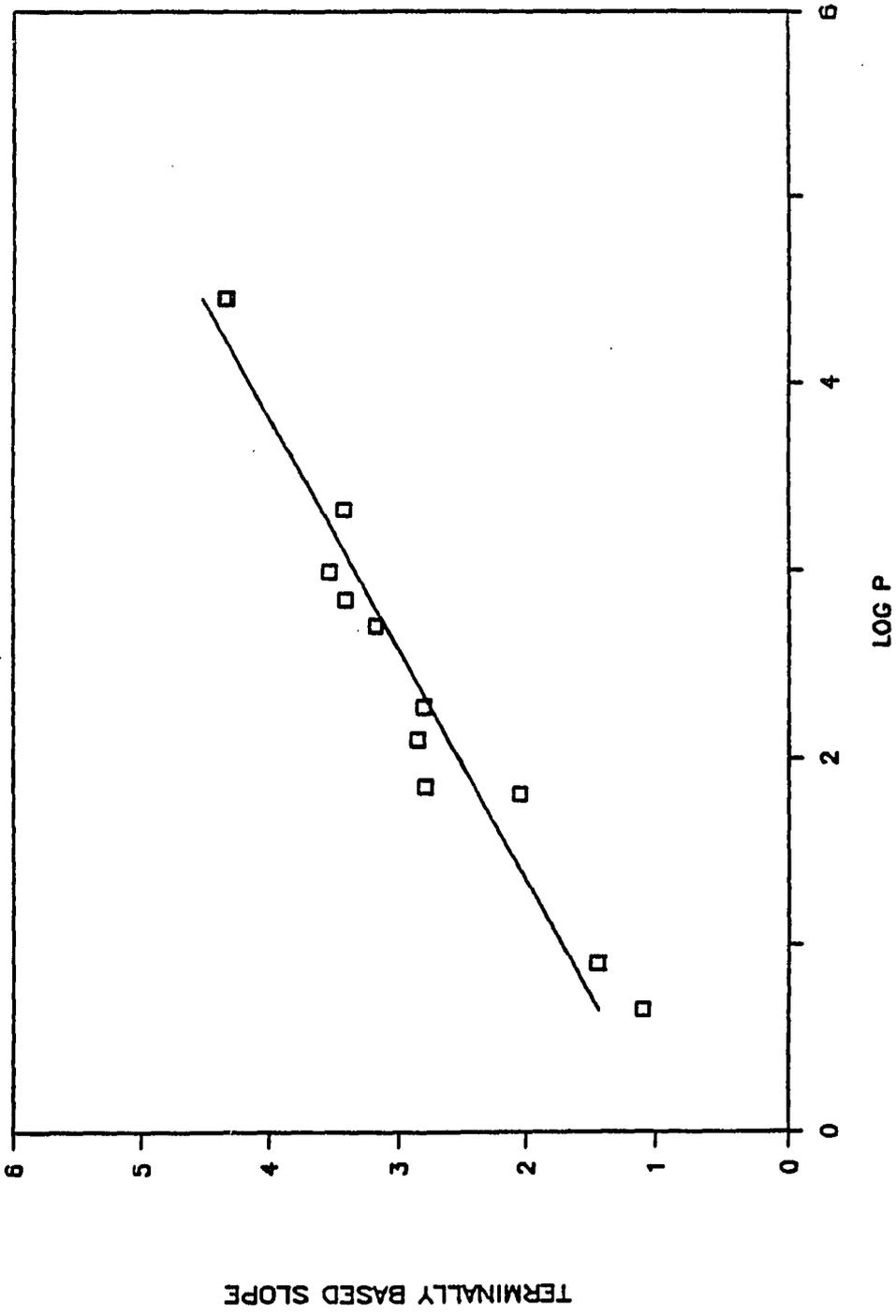
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	1.040427	0.166788	6.238	0.0008
LPS	1	0.3589372	0.07715994	4.652	0.0035

ETHYLENE GLYCOL/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.09	0.65
ANALINE	1.57	0.90
BENZINE	1.72	1.81
NITROBENZENE	1.66	1.85
FLUOROBENZENE	1.97	2.27
TOLUENE	1.72	2.70
CHLOROBENZENE	2.16	2.84
BROMOBENZENE	2.18	2.99

TERMINALLY BASED SLOPE VS LOG P

ETHANOL/WATER SYSTEM



SOLVENT=ETHANOL/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	9.925496	9.925496	167.132	0.0001
ERROR	10	0.5938708	0.05938708		
C TOTAL	11	10.51937			
ROOT MSE		0.2436946	R-SQUARE	0.9435	
DEP MEAN		2.918333	ADJ R-SQ	0.9379	
C.V.		8.350473			

PARAMETER ESTIMATES

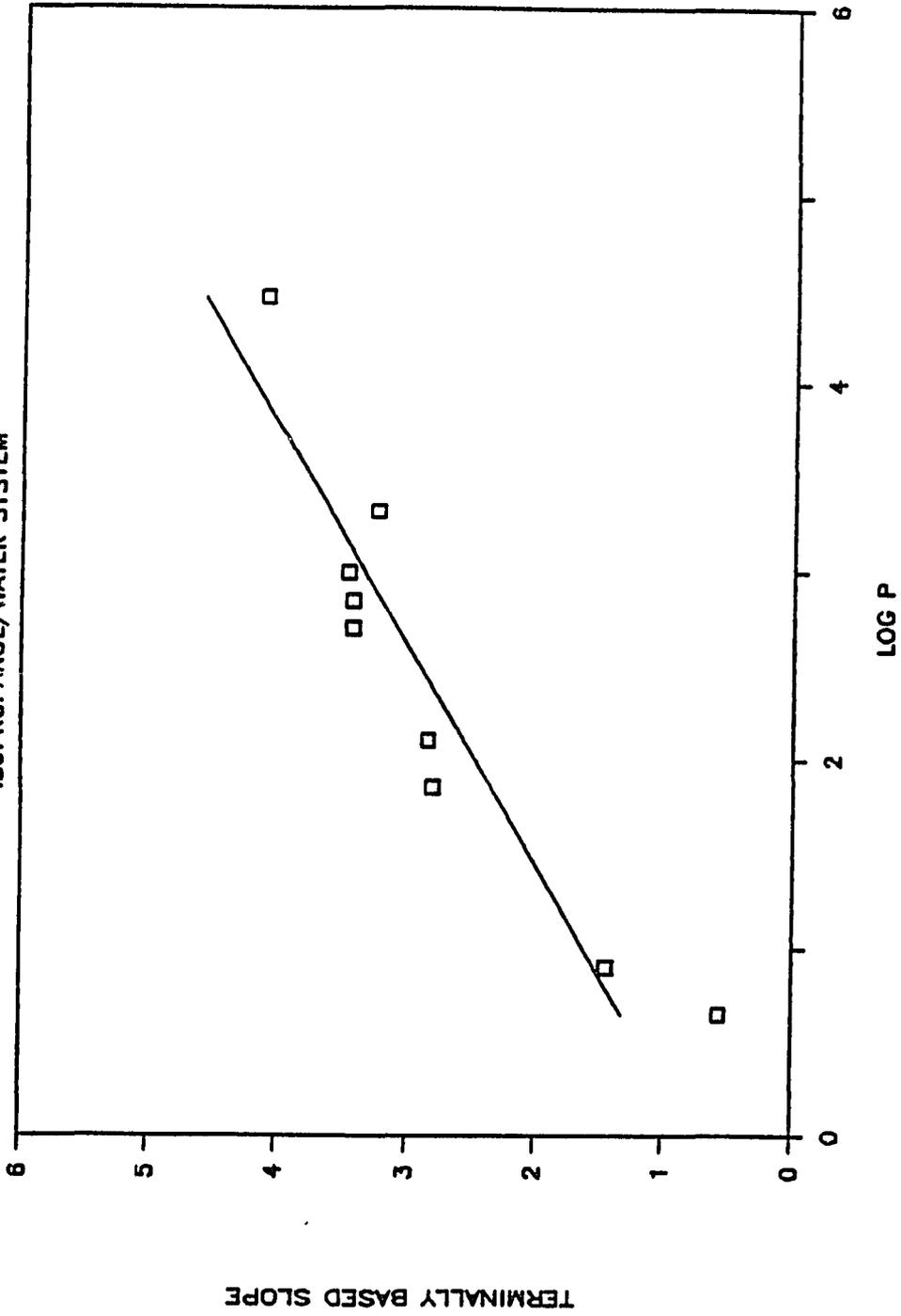
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.8143882	0.1772976	4.593	0.0010
LPS	1	0.8495068	0.0657108	12.928	0.0001

ETHANOL/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.10	0.65
ANALINE	1.45	0.90
BENZINE	2.05	1.81
NITROBENZENE	2.79	1.85
BENZOIC ACID	2.85	2.10
BENZOIC ACID	2.85	2.10
FLUOROBENZENE	2.80	2.27
TOLUENE	3.18	2.70
CHLOROBENZENE	3.41	2.84
BROMOBENZENE	3.54	2.99
NAPHTHALINE	3.42	3.32
ANTHRACENE	4.33	4.45
ANTHRACENE	4.35	4.45

TERMINALLY BASED SLOPE VS LOG P

ISOPROPANOL/WATER SYSTEM



SOLVENT=ISOPROPANOL/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	9.362067	9.362067	51.828	0.0001
ERROR	8	1.445093	0.1806367		
C TOTAL	9	10.80716			
ROOT MSE		0.4250137	R-SQUARE	0.8663	
DEP MEAN		2.738	ADJ R-SQ	0.8496	
C.V.		15.52278			

PARAMETER ESTIMATES

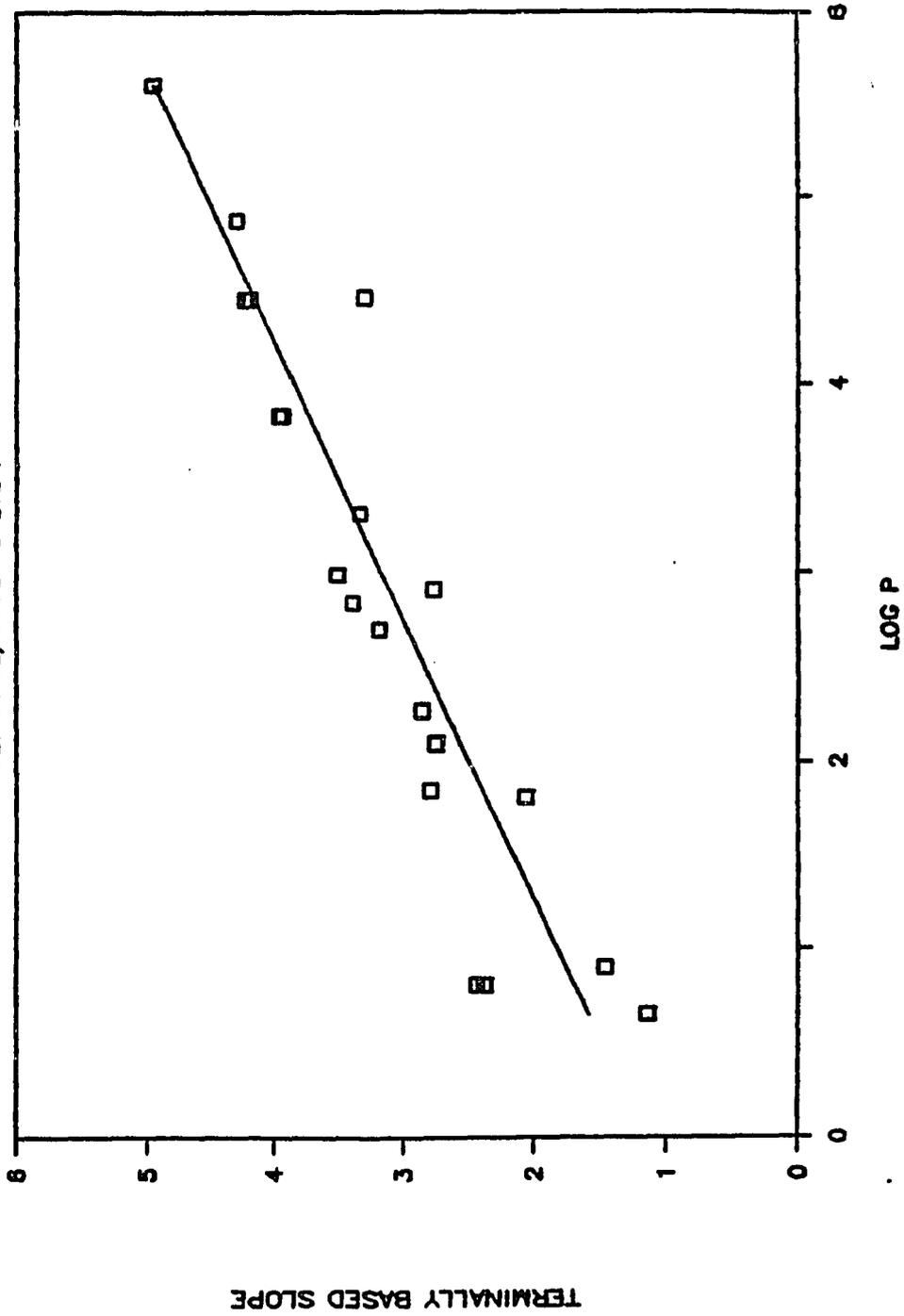
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.6276911	0.3224748	1.946	0.0875
LPS	1	0.8938199	0.1241558	7.199	0.0001

ISOPROPANOL/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	0.56	0.65
ANILINE	1.45	0.90
NITROBENZENE	2.81	1.85
BENZOIC ACID	2.84	2.10
BENZOIC ACID	2.84	2.10
TOLUENE	3.43	2.70
CHLOROBENZENE	3.43	2.84
BROMOBENZENE	3.47	2.99
NAPHTHALINE	3.25	3.32
ANTHRACENE	4.11	4.45

TERMINALLY BASED SLOPE VS LOG P

METHANOL/WATER SYSTEM



SOLVENT=METHANOL/WATER
(excluding atrazine)

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	13.54421	13.54421	83.700	0.0001
ERROR	15	2.427289	0.1618193		
C TOTAL	16	15.97149			
ROOT MSE		0.4022676	R-SQUARE	0.8480	
DEP MEAN		3.079412	ADJ R-SQ	0.8379	
C.V.		13.06313			

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	1.065157	0.2408161	4.423	0.0005
LPS	1	0.6773954	0.07404241	9.149	0.0001

SOLVENT=METHANOL/WATER
(including atrazine)

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	13.47249	13.47249	73.446	0.0001
ERROR	16	2.934955	0.1834347		
C TOTAL	17	16.40745			
ROOT MSE		0.4282928	R-SQUARE	0.8211	
DEP MEAN		3.041667	ADJ R-SQ	0.8099	
C.V.		14.08086			

PARAMETER ESTIMATES

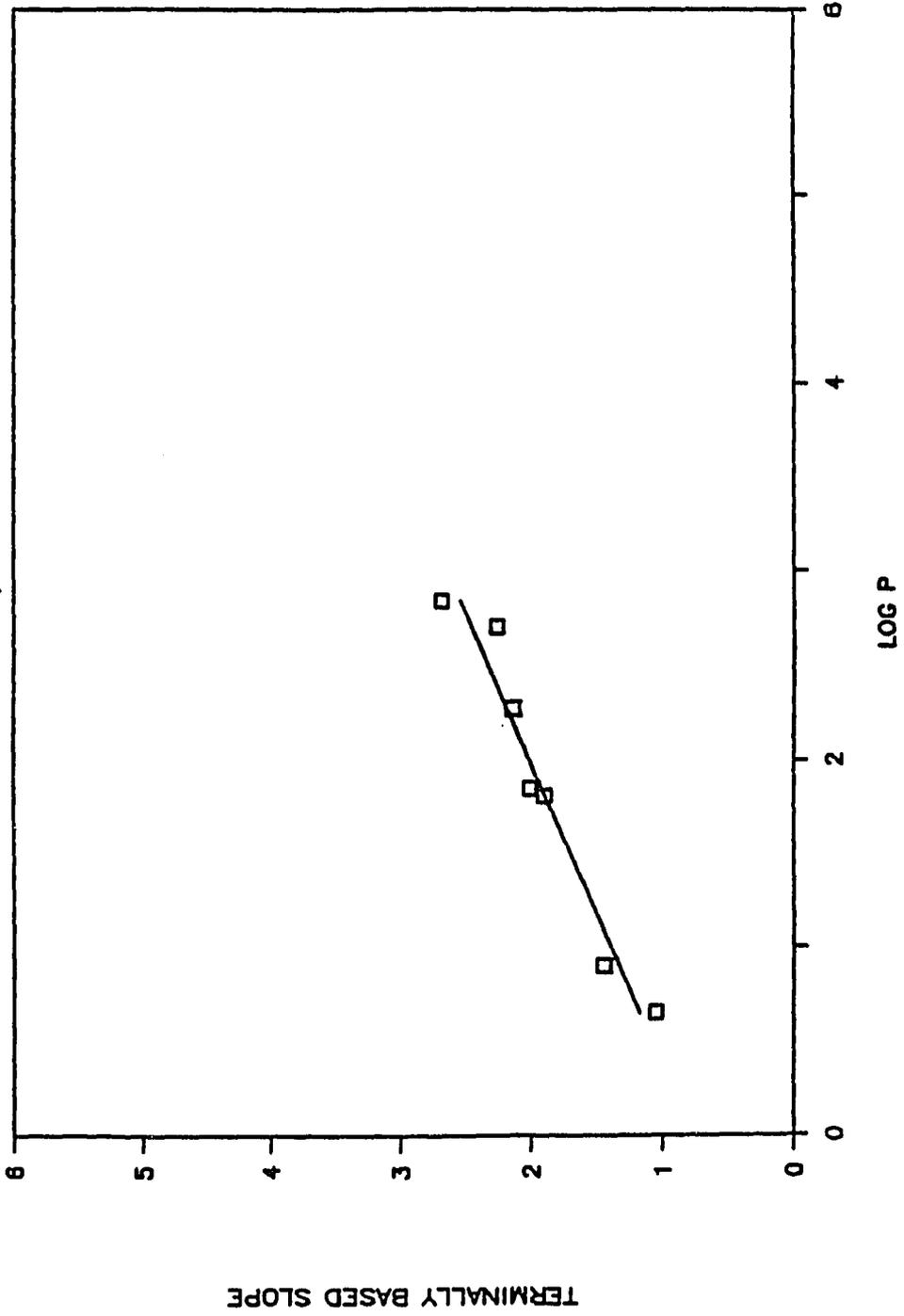
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	1.243889	0.2328007	5.343	0.0001
LPS	1	0.6300622	0.0735191	8.570	0.0001

METHANOL/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
ATRAZINE	2.37	0.81
ATRAZINE	2.43	0.81
BENZAMIDE	1.14	0.65
ANALINE	1.46	0.90
BENZINE	2.06	1.81
NITROBENZENE	2.79	1.85
BENZOIC ACID	2.75	2.10
BENZOIC ACID	2.75	2.10
FLUOROBENZENE	2.86	2.27
TOLUENE	3.19	2.70
CHLOROBENZENE	3.40	2.84
DIURON	2.77	2.91
BROMOBENZENE	3.52	2.99
NAPHTHALINE	3.34	3.32
BIPHENYL	3.95	3.84
BIPHENYL	3.97	3.84
ANTHRACENE	4.24	4.45
ANTHRACENE	4.20	4.45
PHENANTHRENE	3.31	4.46
PYRINE	4.30	4.88
CRYSENE	4.96	5.61

TERMINALLY BASED SLOPE VS LOG P

PROPYLENE GLYCOL/WATER SYSTEM



SOLVENT=PROPYLENE GLYCOL/WATER

DEP VARIABLE: SLOPE
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	2.669092	2.669092	181.399	0.0001
ERROR	7	0.1029973	0.0147139		
C TOTAL	8	2.772089			
ROOT MSE		0.1213009	R-SQUARE	0.9628	
DEP MEAN		2.108889	ADJ R-SQ	0.9575	
C.V.		5.751885			

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	0.7716728	0.1072026	7.198	0.0002
LPS	1	0.6226045	0.04622686	13.468	0.0001

PROPYLENE GLYCOL/WATER SYSTEM

SOLUTE	TERMINAL SLOPE	LOG P
BENZAMIDE	1.05	0.65
ANALINE	1.45	0.90
BENZINE	1.90	1.81
NITROBENZENE	2.01	1.85
FLUOROBENZENE	2.14	2.27
TOLUENE	2.26	2.70
CHLOROBENZENE	2.68	2.84

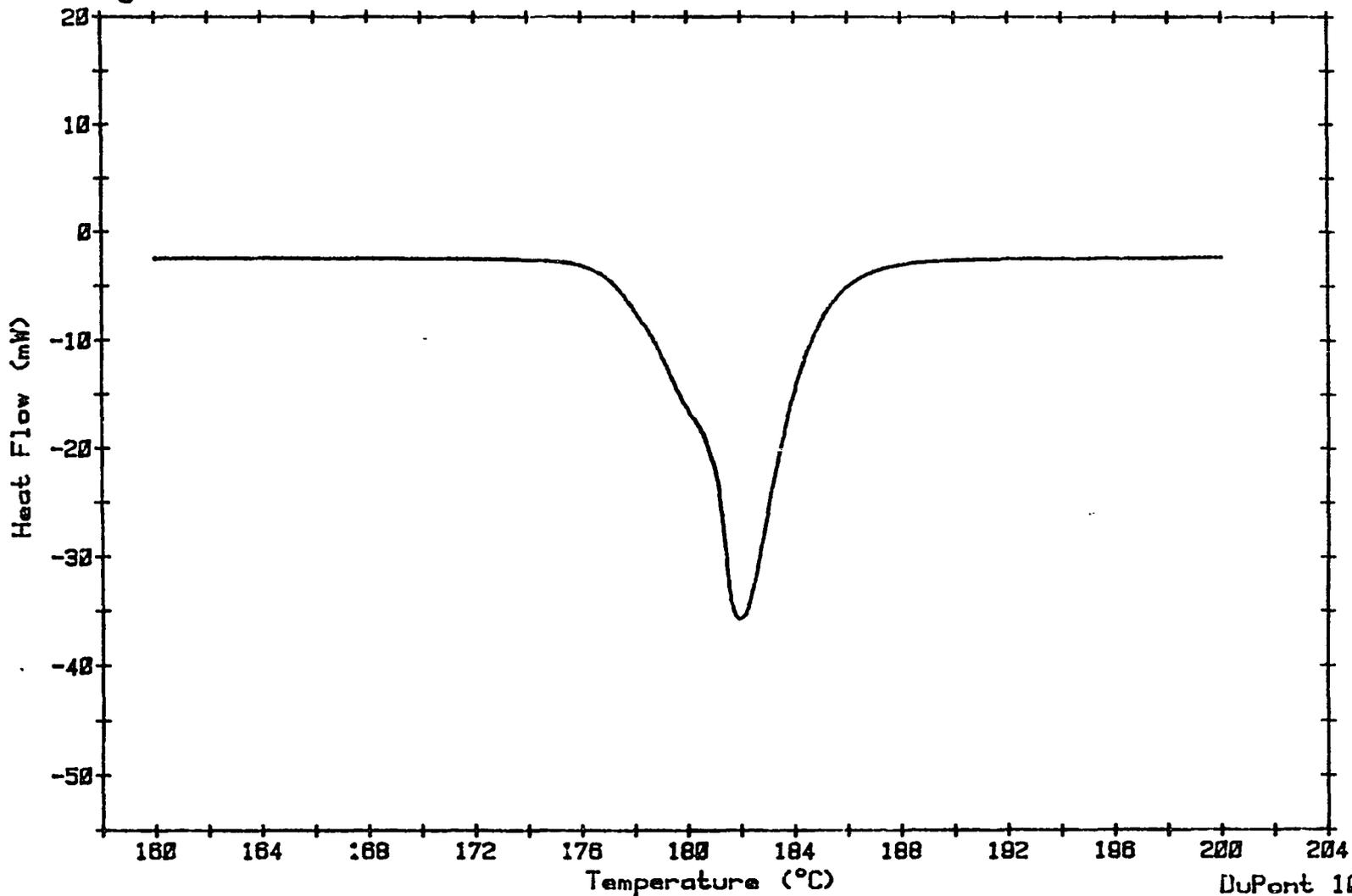
APPENDIX C.

DSC AND IR ANALYSIS
OF ATRAZINE

Sampler: ATR / SOLID
Size: LG
Rate: 10 DPM
Program: Interactive DSC V3.0

DSC

Date: 7-Oct-87 Time: 16:31:29
File: ATR.01 MORRIS ATRAZINE
Operator: SRN/KM
Plotted: 7-Oct-87 17:09:50

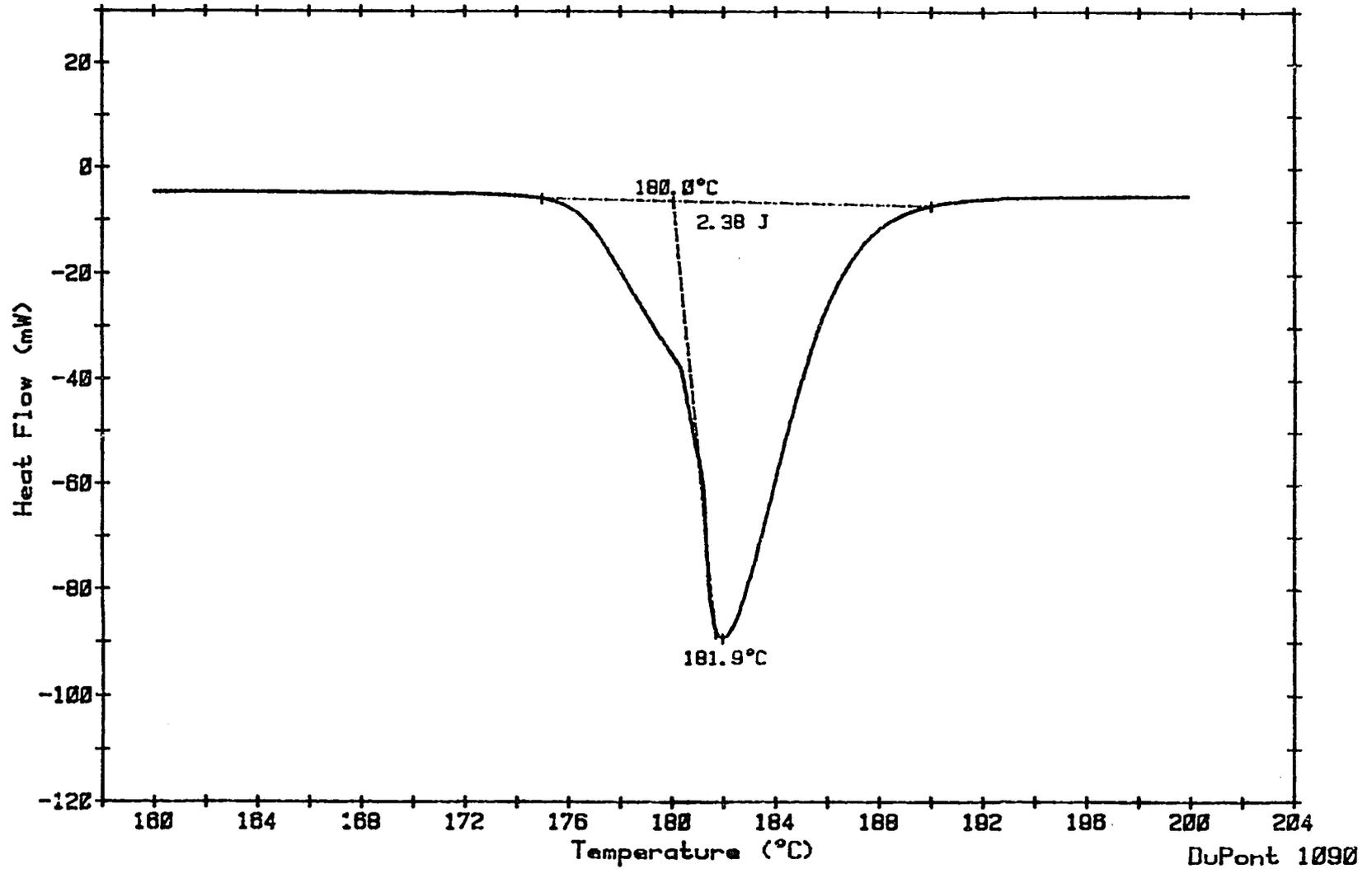


DuPont 1090

Sample: ATR /10% MOH /WET
Size: LG
Rate: 10 DPM
Program: Interactive DSC V3.0

DSC

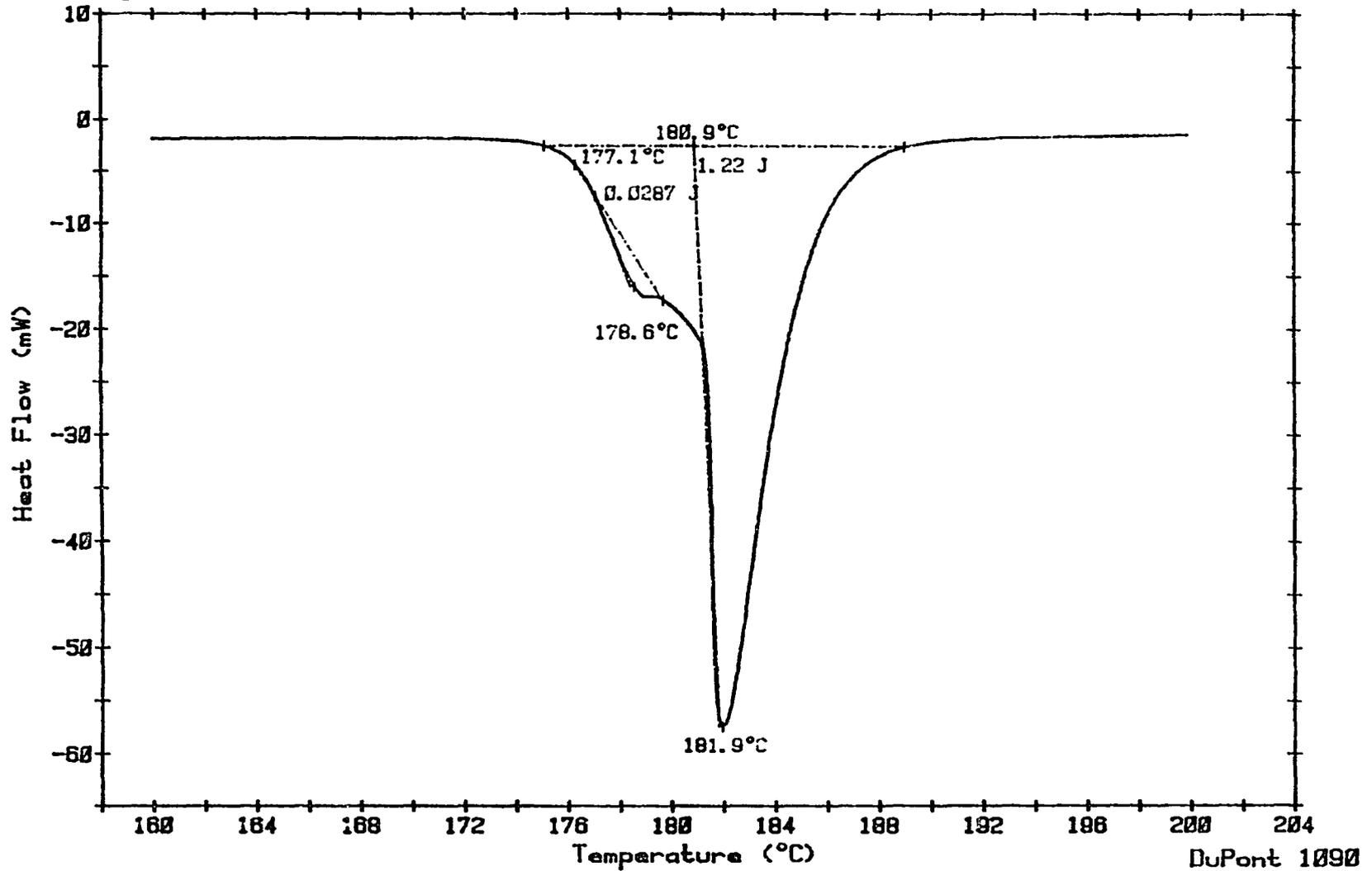
Date: 7-Oct-87 Time: 14:50:23
File: ATR10W.01 MORRIS ATRAZINE
Operator: SRN/KM
Plotted: 7-Oct-87 15:29:30



Sample: ATR 10%WET 4DAYS
Size: LG
Rate: 10
Program: Interactive DSC V3.0

DSC

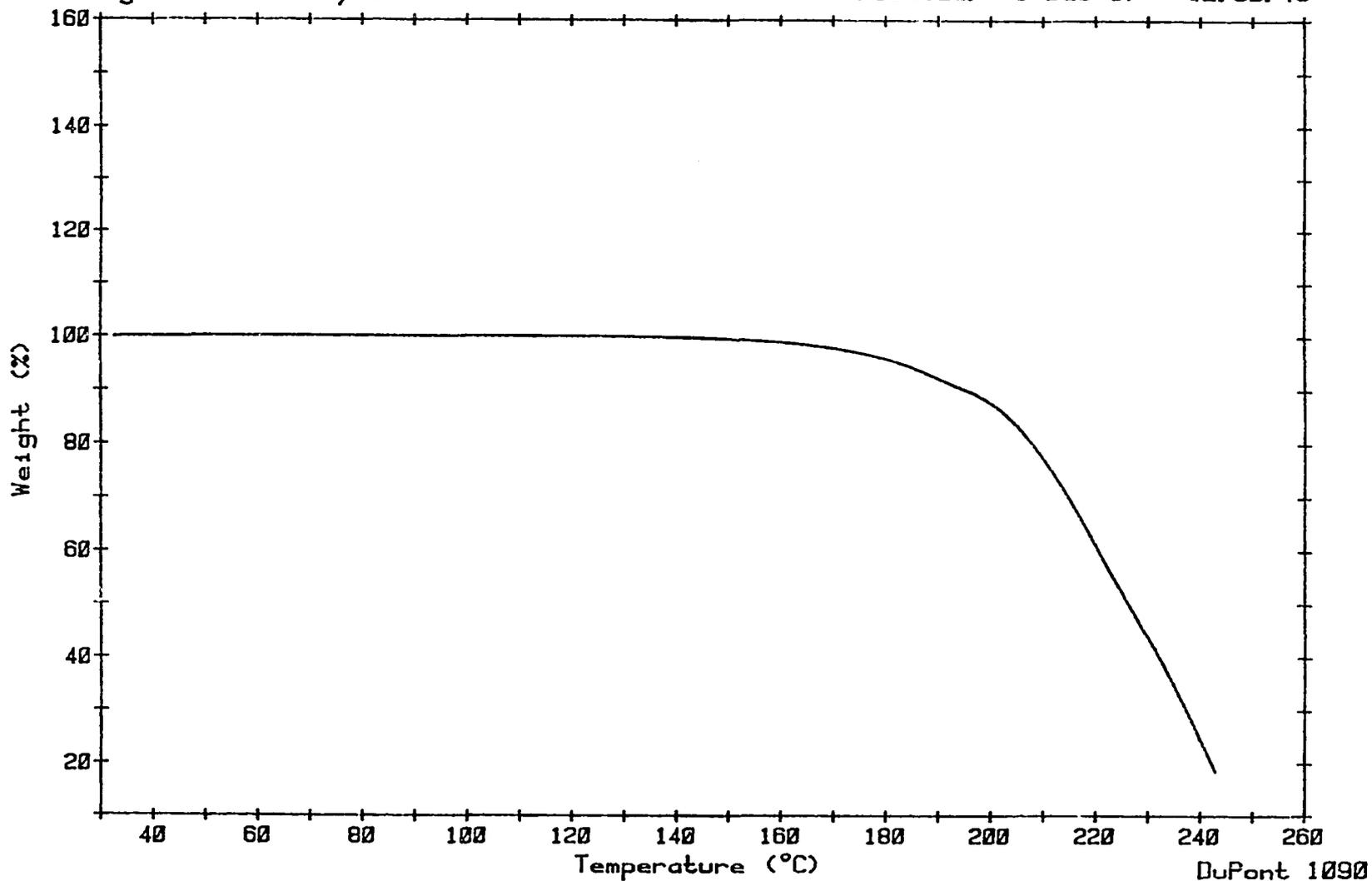
Date: 9-Oct-87 Time: 12:35:16
File: ATR10WET.02 MORRIS ATRAZIN
Operator: KM
Plotted: 9-Oct-87 14:07:42



Sample: ATR/REXTAL/MOH
Size: 13.15 mg
Rate: 10 DPM
Program: TGA Analysis V2.0

TGA

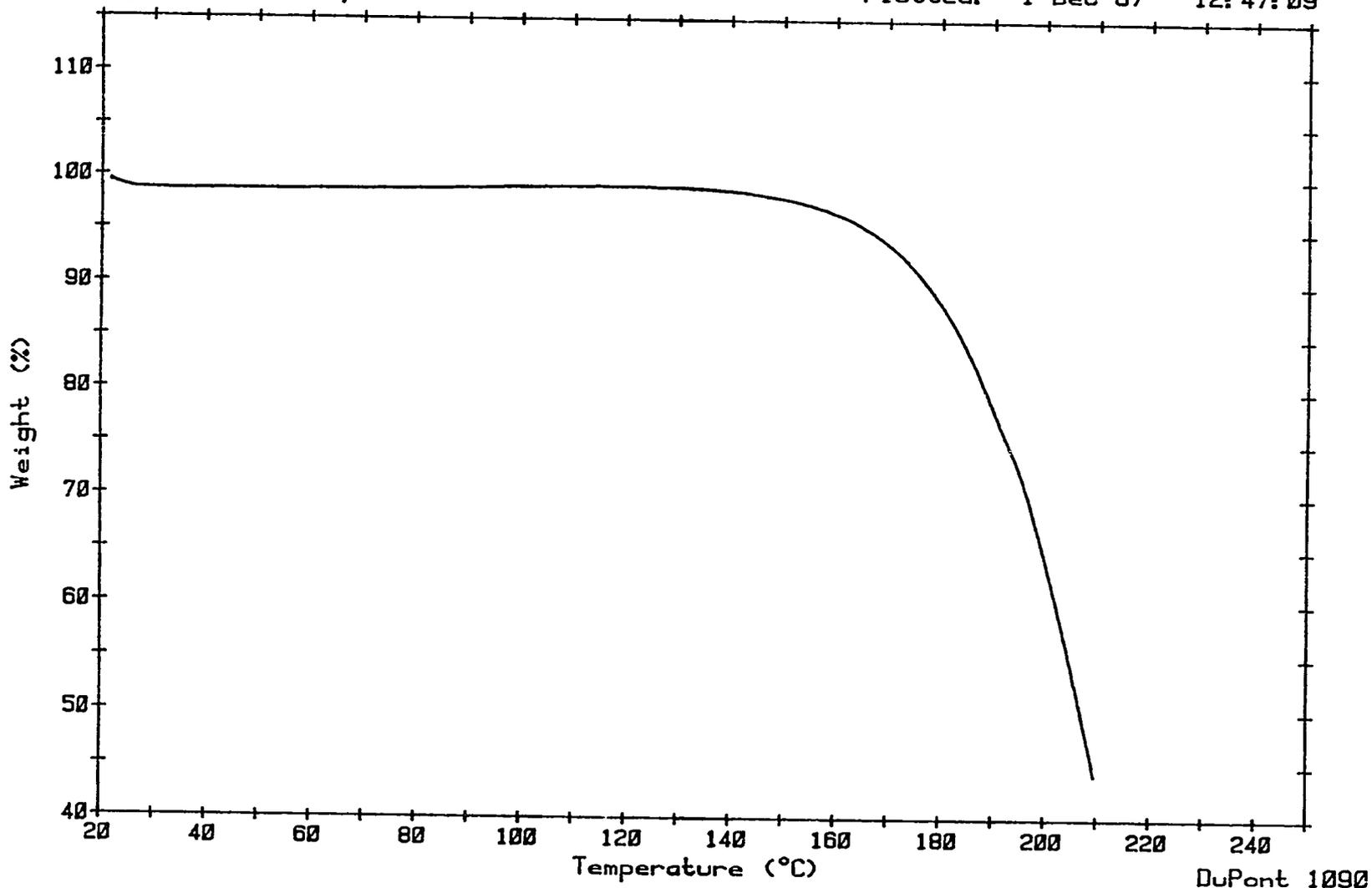
Date: 29-Oct-87 Time: 14:55:42
File: ATR/XTAL.01 MORRIS ATRAZINE
Operator: SRN
Plotted: 1-Dec-87 12:50:48



Sample: ATR/REXTAL/MOH
Size: 3.16 mg
Rate: 10 DPM
Program: TGA Analysis V2.0

TGA

Date: 29-Oct-87 Time: 13:38:57
File: ATR/REXTAL.01 MORRIS ATRAZI
Operator: SRN
Plotted: 1-Dec-87 12:47:09



DuPont 1090

Sample: ATR H2O XTAL

Size: SM

Rate: 10

Program: Interactive DSC V3.0

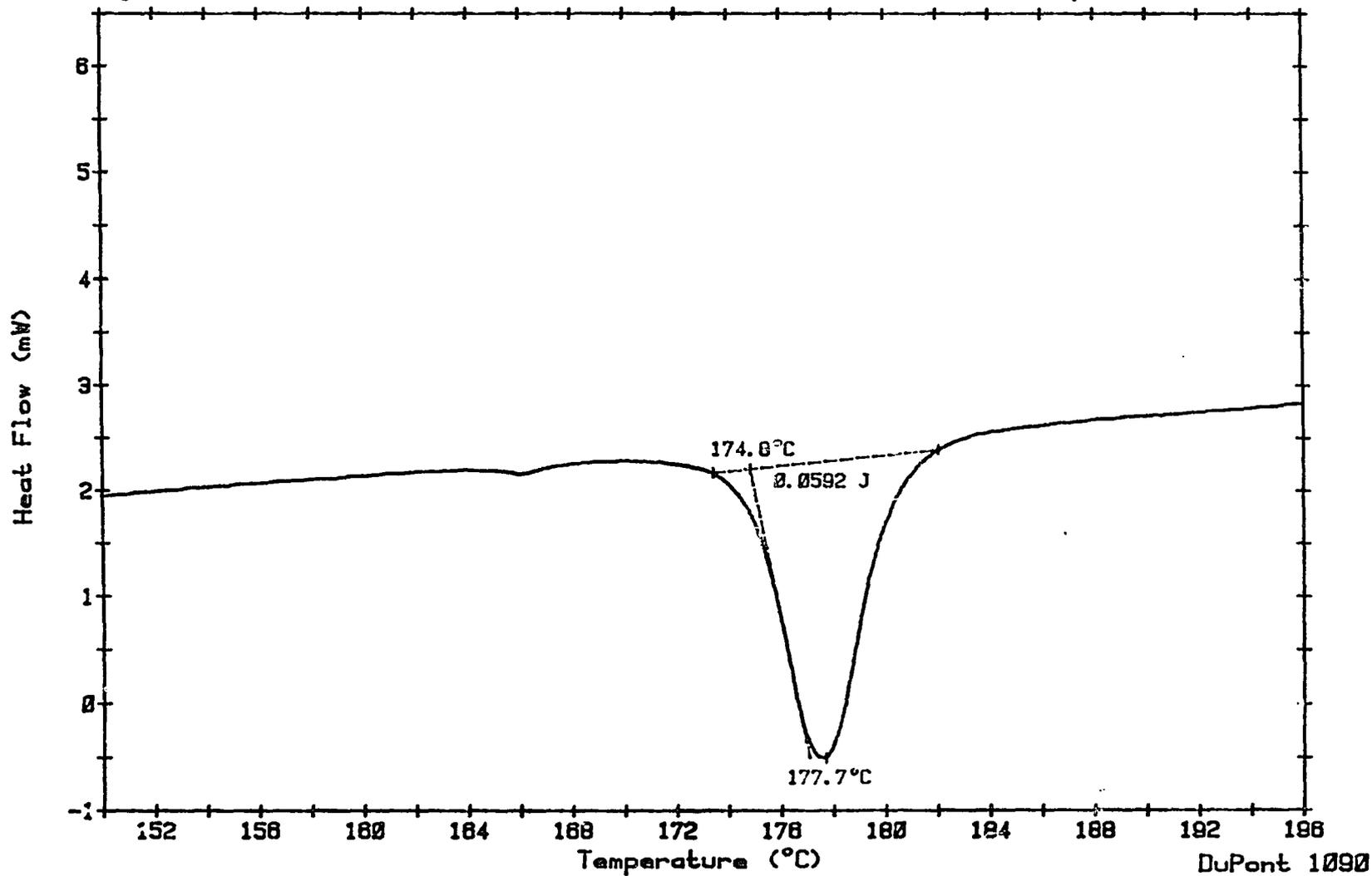
DSC

Date: 30-Sep-87 Time: 11:02:38

File: DATA.01 SREE

Operator: KM

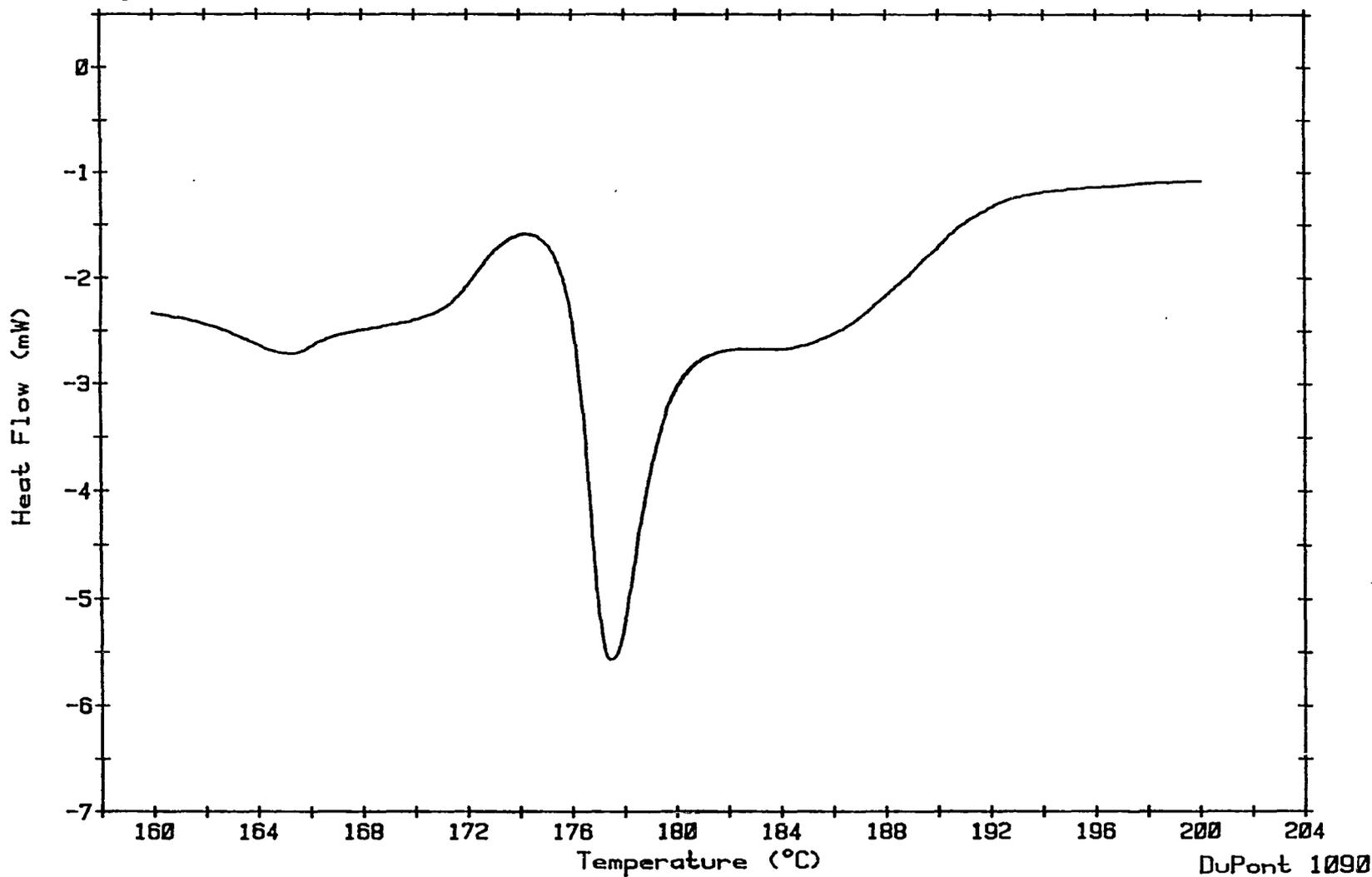
Plotted: 30-Sep-87 13:23:07



Sample: ATR/MOH/REXTAL
Size:
Rate: 10 DPM
Program: Interactive DSC V3.0

DSC

Date: 23-Oct-87 Time: 17:41:59
File: ATR/MOH/RC.01 MORRIS ATRAZI
Operator: SRN
Plotted: 18-Nov-87 5:38:36



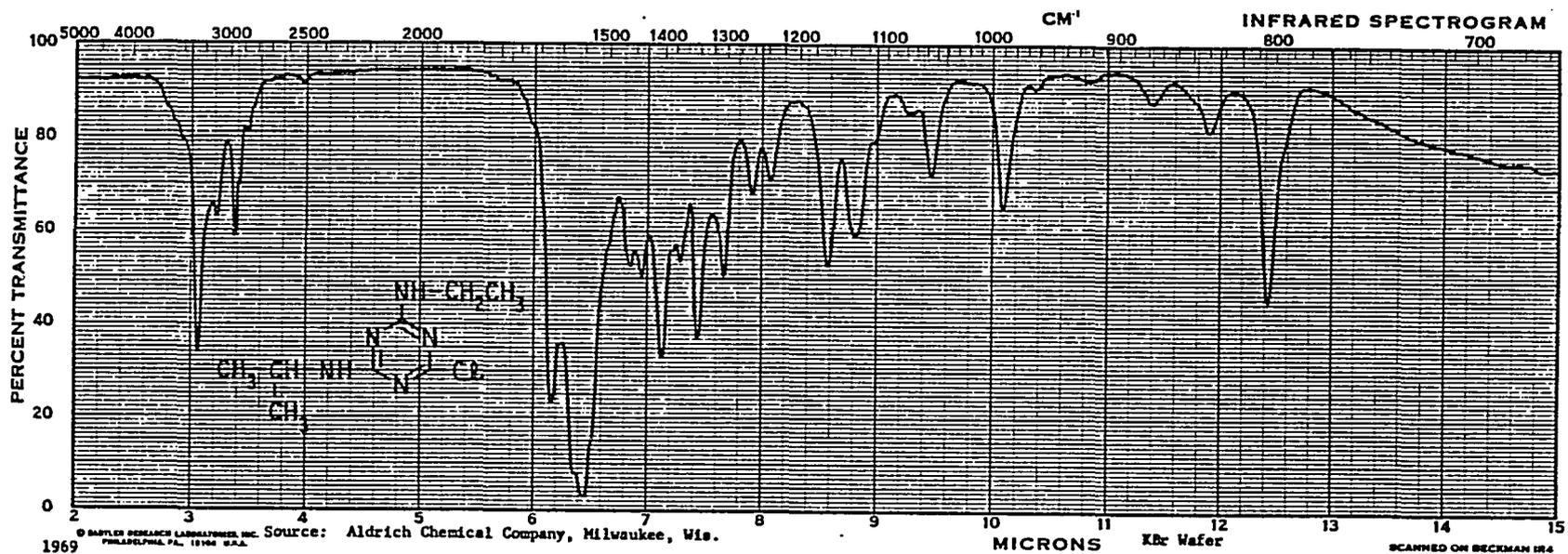
2-CHLORO-4-(ETHYLAMINO)-6-(ISOPROPYLAMINO)-s-TRIAZINE

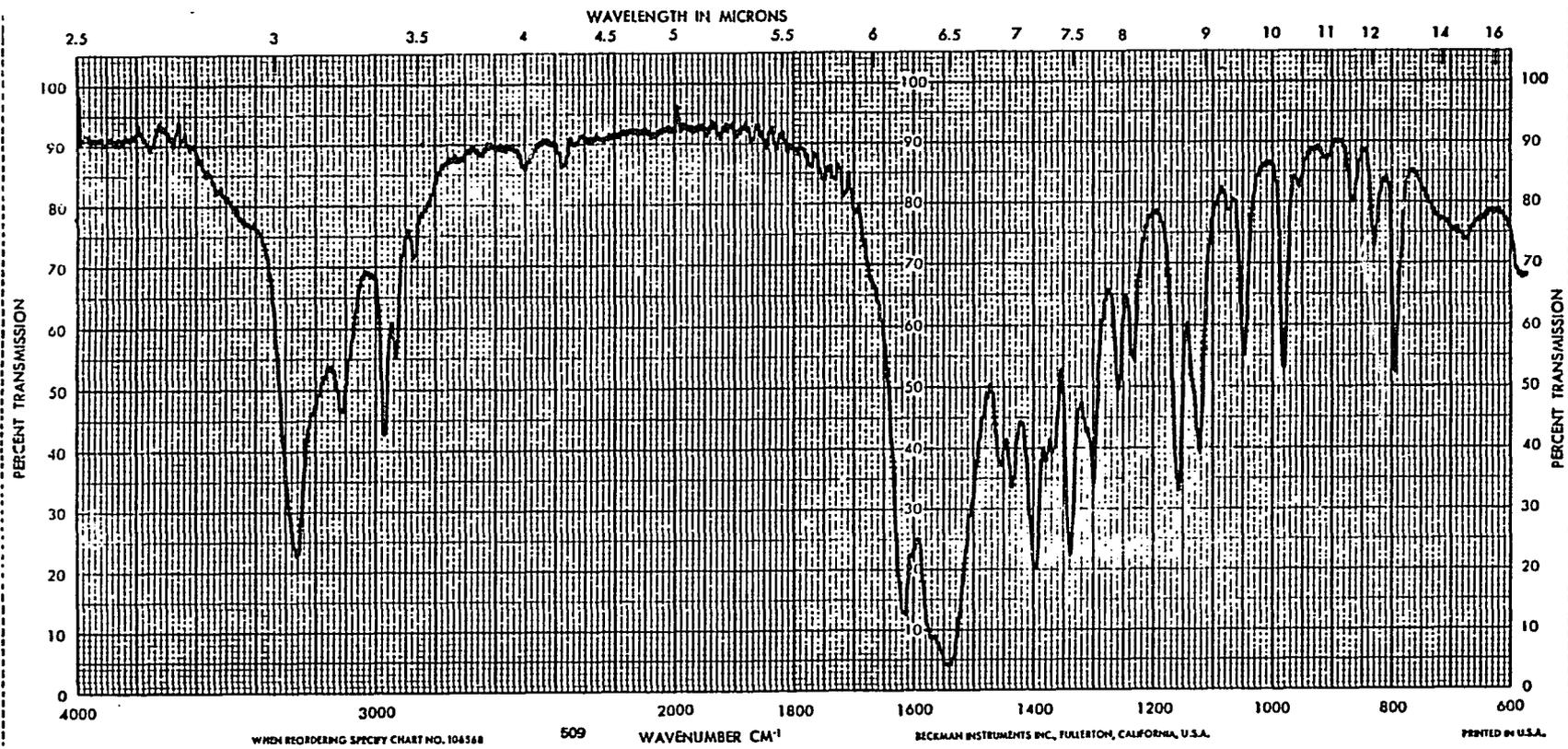
$C_8H_{14}ClN_5$

Mol. Wt. 215.69

M. P. 172-174.5°C

35712





WHEN REORDERING SPECIFY CHART NO. 104568

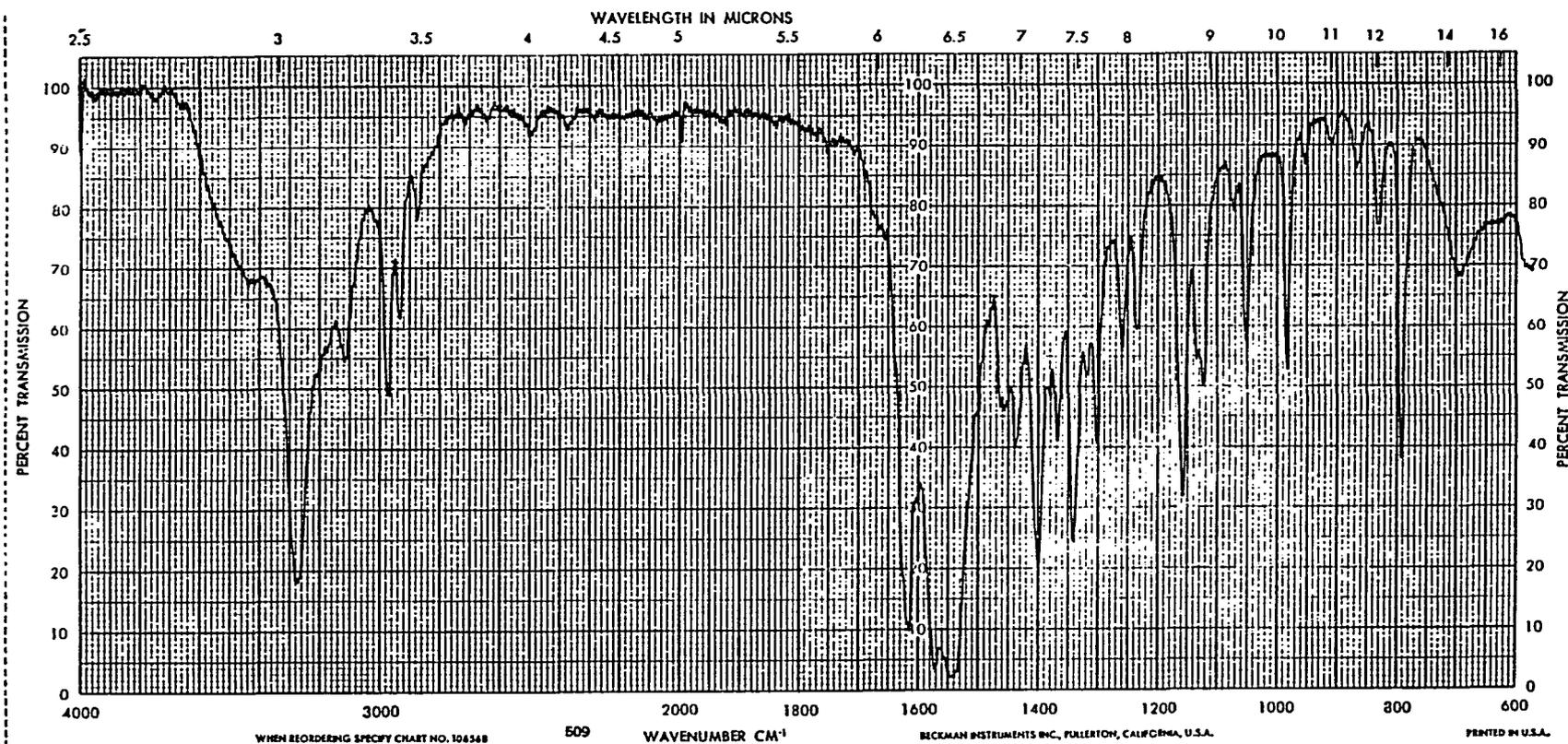
509

WAVENUMBER CM⁻¹

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ORIGINAL SAMPLE



RECRYSTALIZED FROM MOH/WATER

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