THERMODYNAMICS OF MOBILE ORDER THEORY:

SOLUBILITY AND PARTITION ASPECTS

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The purpose of this thesis is to analyze the thermochemical properties of solutes in nonelectrolyte pure solvents and to develop mathematical expressions with the ability to describe and predict solution behavior using Mobile Order Theory. Solubilities of pesticides (monuron, diuron, and hexachlorobenzene), polycyclic aromatic hydrocarbons (biphenyl, acenaphthene, and phenanthrene), and the organometallic ferrocene were studied in a wide array of solvents. Mobile Order Theory predictive equations were derived and percent average absolute deviations between experimental and calculated mole fraction solubilities for each solute were as follows: monuron in 21 non-alcoholic solvents (48.4%), diuron in 28 non-alcoholic solvents (60.1%), hexachlorobenzene (210%), biphenyl (13.0%), acenaphthene (37.8%), phenanthrene (41.3%), and ferrocene (107.8%).

Solute descriptors using the Abraham Solvation Model were also calculated for monuron and diuron. Coefficients in the general solvation equation were known for all the solvents and solute descriptors calculated using multilinear regression techniques.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

The need to understand the distribution of chemical, or their solubility, has not only led to the development of various analytical techniques such as high performance liquid chromatography (HPLC), micellar chromatography, and solid phase extractions but also to the understanding of these chemicals effects on the environment, wildlife and the human body. Partition coefficients are calculated as the ratio of the activity of the solute in phase A divided by the activity of the solute in phase B. Thermodynamic activities will be discussed in detail later, but for now it will suffice to state that at very high dilution the activity of the solute can be approximated by the solute's concentration, expressed in units of either mole fraction or molarity.   Phases A and B may be liquid, solid, supercritical fluid or gas phase or a combination thereof.

Many chemical reactions occur in liquid solutions, and at least one of the phases (often both phases) is liquid. That does not mean that the other types of phases should be ignored. Gas phases are important in gas-liquid chromatographic separations, anesthesiology and drug delivery formations in the form of nasal sprays, and the transport of volatile chemicals through the environment. Solid phases are encountered as stationary phases in many practical analytical methods involving gas-solid and high-performance liquid chromatography, though there is some disagreement in the published chemical literature regarding whether or not bonded-stationary phases should be treated in terms of a solute partitioning between the liquid mobile phase and a "liquid-like" stationary phase, or whether the process involves the absorption of the

solute onto a solid stationary phase. Solid phases are also encountered in water and

air purification processes involving charcoal and activated carbon, ion-exchange resins,

heterogeneous catalysis on metal surfaces, and absorption of pollutants onto soil from

aqueous solution. Supercritical fluids are used as the mobile phase in supercritical fluid

chromatographic separations, and as solvents in many industrial extraction processes.

Needless-to-say, any comprehensive thermodynamic treatment of solubility and

partitioning must contain provisions for all of the types of phases that might be

encountered.

As stated previously, water is the most studied solvent as far as solubility studies

are concerned. Part of the reason for the enormous interest in aqueous solutions

results from the fact that water has a large dielectric constant and very good solvating

capabilities. Inorganic salts dissolve in water through ionization. The respective cations

and anions are solvated by water molecules, which prevent the positively-charged and

negatively-charged ions from coming together to reform the crystalline salt. The

solubility of ionic salts is governed by the ionization processes, which mathematically

described in terms of a solubility product. For example, silver chloride, AgCl ionizes in

water to form the solvated Ag^+ and Cl^- ions

$$AgCl_{(solid)} \leftrightarrow Ag^+_{(aq)} + Cl^-_{(aq)}$$
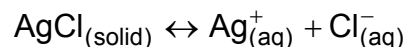
The "aq" subscript is used to denote that the ion is in an "aqueous" solution, solvated by

water molecules. The solubility product that corresponds to the ionization processes is

$$K_{(sp)} = a_{Ag^+} \cdot a_{Cl^-} = [Ag^+] \cdot [Cl^-]$$
(1.1)

the product of the activity of the silver ion, a_{Ag^+}, and activity of the chloride ion, a_{Cl^-}. In

eqn. 1.1 the activities have been approximated by the molar concentrations of the two

ions. The molar solubility of silver chloride in distilled water is the molar concentration

of the silver ion plus the intrinsic solubility of silver chloride. Intrinsic solubility is amount

of silver chloride that dissolves in water in the form of molecular AgCl. For many

inorganic salts the intrinsic solubility is extremely small, and often neglected in solubility

calculations.

Water dissolves polar organic molecules through dipole-dipole solute-water type

molecular interactions. Dipole-dipole interactions represent a fairly strong attraction

between two polar molecules. Dipole-dipole forces are effective only when the polar

molecules are in close proximity to one another. Unequal sharing of bonding electrons

between two bonded atoms leads to the formation of a polar covalent bond. In water,

there are two oxygen-hydrogen covalent bonds. The oxygen atom exerts a greater

attraction for the bonding electrons than the hydrogen atom, as reflected by the oxygen

atom's much larger electronegativity, X_O = 3.5 versus X_H = 2.1. If one were able to

take a snapshot of the electron distribution around the oxygen atom, it would appear

that oxygen had nine electrons (rather than eight electrons) a significant portion of the

time. Similarly, it would appear that hydrogen had no electron a significant portion of

the time. The unequal sharing of the bonding electrons would thus give the oxygen

atom extra electron distribution, and give the hydrogen atom an electron deficiency.

The oxygen atom would be the negative end of the polar covalent bond, whereas the

hydrogen atom would be the positive end of the polar covalent bond. Bond polarity and

molecular shape determine whether or not a molecule is polar or nonpolar. For a

molecule to be polar it must have both a positive and negative end. Some molecules may contain polar covalent bonds, but because of the molecule's shape, the molecule as a whole does not have a positive and negative end. A molecule does not have to be polar in order for dipole-dipole molecules to form. Dipole-dipole interactions can exist between a polar molecule and polar functional group, and between two polar functional groups. Water also has the ability to form hydrogen bonds, which involves the attraction of the hydrogen atom to the electron pairs on oxygen atoms (or nitrogen or fluorine atoms) of neighboring molecules. Hydrogen-bonds are generally much stronger than dipole-dipole interactions.

There can be no dipole-dipole forces between nonpolar molecules, yet some type of attractive force must be operable in order to keep the molecules together in liquid state. To understand such attractions, one must remember that electrons are constantly in motion. In a collection of helium atoms, the average distribution of the electrons around each nucleus would be spherically symmetrical. Helium atoms are nonpolar and possess no permanent dipole moment. The instantaneous distribution of electrons, however, can be quite different between the "average" distribution. If one could take a snapshot of the electron distribution around a helium atom at any given instant, one might find both electrons on one side of the nucleus. At this instant, the electron distribution would not be symmetrical and the atom would have an instantaneous dipole. It is possible to create instantaneous dipoles in nonpolar molecules by having a polar molecule in very close proximity. Electrons repeal each other, and the presence and motions of electrons on one molecule may influence the electron distribution on an adjacent molecule. The ease with which the charge

distribution in a molecule can be distorted by an external electric field is called polarizability. The greater the polarizability of a molecule, the easier it is to distort it's electron cloud to give a momentary dipole. In both polar and nonpolar molecules there will also be very weak attractive forces between the electrons in one molecule and the nuclei in an adjacent molecule. Weak interactions involving induced dipole – induced dipole attractions, and involving electrons in one molecule and nuclei in an adjacent molecule are often lumped together under the broad umbrella of London-dispersion forces, dispersion forces or van der Waals type attractions. Such interactions are very weak, and often not an important consideration in solublizing polar molecules in water. Much stronger interactions dominate. In nonpolar solvents dispersion forces play a major role in the solubilization process.

One may now be able to understand why nonpolar molecules are not very soluble in water. The dissolution of a crystalline substance may be considered to arise from three, and in some cases four, contributions:

i.   The breaking of solute-solute interactions in the crystalline lattice;

ii.   the breaking of solvent-solvent interactions, referred to in many thermodynamic treatments as cavity formation;

iii.   the formation of solute-solvent interactions; and

iv.   the perturbation of solvent-solvent interactions in the immediate vicinity of the solute, as in solvent structuring.

Each of these four contributions may be further divided in specific chemical (i.e., complexation) and nonspecific physical (simple dispersion) interactions as discussed above. Specific interactions are characterized by a specific geometric orientation of one

5

molecule with respect to an adjacent molecule and arise from strong dipole-dipole interactions, hydrogen-bonding and complexation. Dipole-dipole interactions require the alignment of the positive end of molecule and the negative end of an adjacent molecule, which involves a specific geometric orientation of molecules. Whereas nonspecific interactions are best described as a random distribution of molecules throughout the entire solution. Nonspecific interactions are present in both complexing and noncomplexing solutions; however, from a practical standpoint one often considers only the dominant specific interactions. Nonspecific interactions in complexing systems, particularly in solutions involving hydrogen-bond formation, are often ignored. Ignoring entropy contributions for the moment, in order for the dissolution process to be spontaneous, the process must be exothermic in nature. This is the only way for the Gibbs energy of the process to be negative in the absence of entropic considerations. The breaking of nonpolar solute – nonpolar solute interactions should require a relatively small amount of energy (endothermic, small positive value). The breaking of water – water interactions, because water is a polar molecule and does undergo hydrogen-bond formation with adjacent water molecules, will require a large amount of energy (endothermic, large positive value). The larger the solute molecule, the greater the number of hydrogen bonds that will have to be broken in order to solubilize the molecule. So far we have a large positive endothermic value. A large amount of energy has been added to finish parts i and ii. Having broken the solute –solute interactions, and created the solvent cavity, the solute molecule is now inserted and allowed to interact with the neighboring solvent molecules. Because the solute molecule is nonpolar, the solute – water molecular interactions will be weak and

6

dispersion in nature. A relatively small amount of energy is released as the result of the nonpolar solute – water interactions. The entire process up to this point is still endothermic in nature, and nonspontaneous. Dissolution generally leads to a positive entropic contribution, and some of the solute does dissolve. Based on the above considerations, it is not too difficult to understand why polar molecules are more apt to dissolve in a polar solvent like water than nonpolar molecules. Strong polar solute – water (or polar solute – polar solvent) interactions are needed to provide the energy needed to break the strong water – water (or polar solvent – polar solvent) interactions. The same types of interactions pertain to organic solvents; however, far fewer solubility measurements have been performed in organic solvents than in aqueous solutions.

From a thermodynamic point-of-view equilibrium constants determine the extent of completion of chemical reactions. Although one tends to write chemical reactions as reactants and products, very few chemical reactions actually consume 100 % of the reactant. Unreacted material still remains in the solution. There are many areas where the partition coefficient controls the equilibrium process. Ignoring activities and activity coefficients, the partition coefficient is a ratio of the equilibrium concentrations of a given substance in the organic layer compared to the concentration of that same substance in the aqueous layer, after the two phases have mixed, and are allowed reach equilibrium. This equilibrium can be described as

$$A_{aq} \leftrightarrow A_{org}$$

The equilibrium constant, or partition coefficient, P, is[1]

$$P = \frac{A_{org}}{A_{aq}}$$

Studies have shown that partition coefficients can be used as approximations of solutes solubility in two phases.   For example, the logarithm of the experimental molar solubility of 2-naphthol in water is log $C_{in\ water}$ = - 2.28[2], and the values for chlorobenzene, chloroform and hexane are log $C_{chlorobenzene}$= -0.65[3], log $C_{chloroform}$ = - 0.55[3] and log C_{hexane} = - 1.90[3], respectively. These values are then combined to give the following calculated logarithm solubility ratios: log Soly ratio = 1.63 (chlorobenzene); log Soly ratio = 1.73 (chloroform); and log Soly ratio = 0.38 (hexane), which are in excellent agreement with the logarithm of the experimental partition coefficients of log P = 1.67[4] (chlorobenzene), log P = 1.74[4] (chloroform) and log P = 0.30[4] (hexane) determined at 293.2 K. For informational purposes the experimental solubilities were measured at a slightly higher temperature of 298.2 K. Additional examples showing good agreement between the calculated experimental solubility ratio and experimental partition coefficient are given elsewhere.[5]   Partition coefficients describing the equilibrium distribution of a solute between two liquid phases are used in design calculations involving extractions to select a suitable organic solvent for separating a desired chemical product from reaction mixture impurities, calculate the volume of organic solvent and number of extractions needed to achieve the desired chemical separation, and the amount of desired product that one can expect to recover as the result of an extraction procedure.

Partitioning processes are also encountered in many pharmaceutical calculations involved with drug design. Effective drug delivery requires that the drug molecule reach the target site at the concentration necessary to achieve the desired therapeutic effect. In most pharmacokinetic computations the drug reaches the target site through the

blood stream, and is then absorbed by the organ. A partition coefficient describes the desired absorption processes. As the drug molecule travels through the body, the blood is also in contact with many other body organs, where absorption may also occur. To determine the dosage of the drug that a patient needs to take, the pharmaceutical chemist must also take into account that a significant fraction of the drug that is actually injected, swallowed or introduced as a nasal spray is lost through degradation (many drugs undergo decomposition in the blood stream) and absorption by other body organs. All absorption processes are described by partition coefficients. In order to calculate how much of the drug is lost one must know the rate constant(s) of all degradation processes, the partition coefficient(s) describing the uptake of the drug by all body organs, and the volumes of the various body organs.

Experimental determination of the partition coefficient data for a single drug molecule is a very difficult and tedious process in that one would have to develop an analytical method that would be capable of identifying and quantifying the concentration of the drug molecule in each body organ from all the other chemicals that might be present. To address this concern, the computation procedure has been simplified significantly, and only a few body organs are actually considered. Pharmacokinetic modeling generally considers the following partitions: liver/blood, muscle/blood, fat/blood and brain/blood. The more sophisticated treatments add lung/blood, heart/blood, spleen/blood, plasma/blood and kidney/blood partitions. Radioactive labeling of the drug molecule is used in developing an analytical method that will be specific for the drug molecule. Radioactive labeling does simplify the analytical procedure; however, one does have to develop analytical methods for discriminating

between the parent drug molecule and any radioactive-labeled metabolites that might have been produced as the result of a degradation process.

Chromatographic headspace sampling methods can be used to determine tissue/air partition coefficients of volatile organic compounds, with very little interference from all of the other chemicals present in the biological sample. A known quantity of blood or homogenized animal tissue is placed in a vial of known volume. The vial is then sealed with an air-tight rubber septum. A known mass of organic solute is syringed into the vial, and the system is allowed to reach equilibrium. After equilibrium is established a sample of the vapor phase is removed for chromatographic analysis. The concentration of the vapor phase is obtained from the analysis, and the concentration of the condensed phase is then calculated from a stoichiometric mass balance and knowledge of the volumes of both the condensed and gas phases. Chromatographic headspace sampling methods are limited in application to volatile organic compounds. Tissue/air and tissue/blood partition coefficients of volatile organic compounds are determined with radioactive-labeled compounds. Radioactive-labeled methods are used to measure *in vivo* partition coefficients, whereas the headspace method is used for *in vitro* measurements.

Most *in vivo* analytical methods require that the animal be sacrificed and the tissues harvested and analyzed at specific times after administering the drug molecule. The experimental values that are obtained as the result of animal studies are subject sometimes to fairly large experimental uncertainties, as even with one animal species, the concentration of the drug molecule present in a given body organ at a given time depends to a large extent on the animal's metabolism and sometimes on the animal's

10

age[6]. Depending upon the animal, a body organ may not be fully developed until the animal is several years old. Tissue samples need to be free of any residual blood. Khor *et al.*[7] have shown that appreciable errors can occur determining the tissue concentration of drug molecules whenever the volume fraction of residual blood is large and the drug is not absorbed substantially by the tissue. Tissue samples from cadavers are used for most of the *in vitro* partition coefficient measurements. The tissue is generally collected immediately after death and stored frozen. The tissue must be used within 24 hours after the person's/animal's death. For skin permeation studies, samples are obtained from cadavers or from individuals having undergone abdominoplasties or "tummy-tucks". The majority of the published *in vivo* tissue/air and tissue/blood partition coefficient data in the pharmaceutical literature is from studies involving rat and mice.

In order to decrease the costs associated with drug design, pharmaceutical chemists have developed mathematical correlations between hard-to-measure experimentally determined tissue/blood partition coefficients (and tissue/air partition coefficients) and easy-to-measure organic solvent/water partition coefficients. Olive oil and 1-octanol were two of the first organic solvents to be used in this regard and in the published literature one can find the following mathematical correlations:[8,9,10,11,12]

$\log P_{\text{human blood/air}} = 0.03 + 0.0072 \log P_{\text{olive oil/air}} + 0.898 \log P_{\text{saline/air}}$

$\log P_{\text{human fat/air}} = 6.59 + 0.447 \log P_{\text{olive oil/air}} + 0.075 \log P_{\text{saline/air}}$

$\log P_{\text{human muscle/air}} = 0.94 + 0.014 \log P_{\text{olive oil/air}} + 0.384 \log P_{\text{saline/air}}$

$\log P_{\text{rat blood/air}} = 1.16 + 0.0054 \log P_{\text{olive oil/air}} + 0.931 \log P_{\text{saline/air}}$

$\log P_{\text{rat fat/air}} = 9.40 + 0.594 \log P_{\text{olive oil/air}} + 0.085 \log P_{\text{saline/air}}$

$\log P_{\text{rat brain/air}} = 1.37 + 0.026 \log P_{\text{olive oil/air}} + 0.879 \log P_{\text{saline/air}}$

$\log P_{\text{rat brain/blood}} = 1.359 + 0.338 \log P_{\text{cyclohexane//water}} - 0.00618 \text{ Molar Volume}$

$\log P_{\text{rat brain/blood}} = -1.22 + 0.266 \log P_{\text{1-octanol/water}}$

$\log P_{\text{rat brain/blood}} = 0.47 + 0.250 \log P_{\text{cyclohexane/water}}$

$\log P_{\text{rat brain/blood}} = 0.679 \log P_{\text{chloroform/water}} - 3.12$

For the partition coefficients involving the gas phase "air", the concentration of the solute in the vapor phase was calculated from the ideal gas law (Molarity = n/v = P/RT) and the solute's measured vapor pressure at body temperature, 37 °C. Most of the published correlations have used either olive oil or 1-octanol as the organic solvent simply because of the enormous amount of published data that is available in the chemical and pharmaceutical literature. Correlations do exist for other solvents like cyclohexane (see above), hexadecane[13,14] and benzene.[13,14] As more experimental data becomes available researchers will undoubtedly use partition coefficient data for other solvents in hopes of deriving better predictive equations. The predictive equation for the rat blood/brain partition coefficient based upon $\log P_{\text{cyclohexane/water}}$ had a much lower standard deviation than the $\log P_{\text{1-octanol/water}}$ correlation. The required input partition coefficients can be measured experimentally from equilibrium partitioning studies, or can be calculated as the ratio of the experimental molar solubility of the solute in the organic solvent and in water. Experimental solubility data is of great importance in the pharmaceutical industry as the numerical values can be used as input parameters to predict many hard-to-measure biological properties like tissue/blood and tissue/air partition coefficients.

Researchers have also developed mathematical equations for correlating tissue/air and tissue/blood partition coefficients using only structural information (bond angles, atomic sizes, quantum mechanically calculated quantities like the energy of the highest occupied molecular orbital, energy of the lowest unoccupied molecular orbital, *etc.*) or using solute descriptors that have been derived from easy-to-measure experimental quantities. It is impossible to discuss the many mathematical correlations that have been derived, and for purposes of this thesis, attention will be focused on the few correlation equations that calculate solute descriptors from measured solubilities and/or partition coefficients, the latter of which can be calculated as the ratio of the solubility of the solute in two phases.

Abraham and coworkers[11,15,16,17,18,19,20] developed the general solvation model

$$\log L = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + \lambda \log L^{(16)} \qquad (1.2)$$

where:

L = Ostwald solubility coefficient (blood-gas and tissue-gas partition

    coefficients at body temperature)

R_2 = solute excess molar refraction

π_2^H = solute dipolarity/ polarizability

α_2^H and β_2^H = hydrogen-bond acidity and hydrogen-bond basicity,

    respectively

$L^{(16)}$ = Ostwald solubility coefficient of hexadecane at 298 K, which can be

    experimentally determined by measuring the gas-liquid chromatographic

    retention time of the solute on a hexadecane stationary phase

r = tendency of phase to interact with solute π and n – electrons

s = phase polarizability/dipolarity

a = phase hydrogen-bond basicity (because basic phases interact with

      acidic solute sites)

b = phase hydrogen-bond acidity (because acidic phases interact with the

      basic solute sites)

λ = measure of phase lipophilicity

In equation 1.2, the independent variable is the logarithm of the tissue/air partition coefficient of the solute molecule under consideration. In the more general model, log L would be replaced by SP (solute property), which could be the ratio of the solubility of the solute in a liquid solvent divided by the gas phase concentration of the solute based on the ideal gas law and experimental vapor pressure of the solute at the system temperature or partition coefficient describing the distribution of a solute between two condensed phases. For processes involving two condensed phases (*i.e.*, octanol/water partition coefficients), the equation/process coefficients refer to differences in the polarizability, hydrogen-bond acidity, hydrogen-bond basicity and lipophilicity of the two condensed phases.

Equation 1.2 has been used to analyze the experimental solubility data of several inert gases and vapors of several volatile organic compounds in water, blood, plasma, brain, muscle, liver, lung, kidney and heart tissues, fat and oil. The analysis involved determining the numerical values of the process coefficients (c, r, s, a, b and λ) through least-squares regression methods. In the analysis numerical values of $R_2, \pi_2^H, \alpha_2^H, \beta_2^H$ and $L^{(16)}$ were known for all of the organic solutes for which experimental tissue/air partition coefficient was measured. For each tissue, six equations of the mathematical

form of eqn. 1.2 can be set up with the numerical values of log L, R_2, π_2^H, α_2^H, β_2^H and

$L^{(16)}$ of the solute under consideration being inserted into each respective equation.

Once this is done, one has a set of six multi-linear equations with six unknowns (r, s, a,

b, λ and c) to solve. The solution of the set of equations will then give the numerical

values of the equation coefficient for a given tissue. The process is repeated for each

tissue. Least-squares regression analysis essentially does the same thing, except that

one has considerably more equations than unknowns, and that the computation

procedure generates the numerical values of the six unknowns that will minimize the

deviations in the back-calculated tissue/air partition coefficients. In calculating equation

coefficients it is best to have more equations to solve than unknowns, as the calculated

values are not as sensitive to experimental uncertainties, and to one or two incorrect

experimental values.

For informational purposes, it should be noted that Kamlet et al.[21] had previously

derived correlation equations

$$SP = SP_\circ + m\overline{V}/100 + s\pi^* + b\beta_m + a\alpha_m \qquad (1.3)$$

where:

SP = solubility properties

$\overline{V}$ = pure solute molar volume

π^* = measure the ability of the solute to stabilize a neighboring charge or

dipole by nonspecific dielectric interactions.

α = hydrogen-bond donor acidity

β = hydrogen-bond donor basicity

$_m$ = non-self-associated "monomer" solute

based on a slightly different set of molecular descriptors. Process coefficients are denoted as SP_o, $_m$, s, b, and a. While the more recent general solvation model of Abraham *et al.* has for the most part replaced the model of Kamlet *et al.*, one will occasionally find in reading the recent literature researchers still reporting correlation equations in terms of the earlier set of descriptors.

Brain/blood partitioning is discussed further as a representative example illustrating the application of equation 1.2 to specific biological tissues. Brain uptake, or the ability of a drug to penetrate the blood-brain barrier (BBB), is of fundamental importance in drug design and drug product formulation, particularly when developing drugs targeted to central nervous system (CNS) disorders, such as brain tumors, Alzheimer disease, Parkinson's disease and psychiatric disorders (*i.e.*, affective disorder, anxiety disorder, attention deficit disorder, *etc.*). For drugs aimed at peripheral tissues an unwanted penetration into the central nervous system can lead to undesired side effects. *In vivo* intracerebral microdialysis methods, involving the placement of probe(s) in the brain, are currently being used to study the uptake of drug molecules into specific areas of the brain.[22,23] Equilibrium microdialysis methods generally measure the concentration of the unbound form of the drug molecule, which may be different from the total stoichiometric concentration, which includes not only the unbound form of the drug molecule, but all bound forms as well. Drug molecules can bind to blood and tissue proteins. Most of the human brain/blood partition coefficient data in the published literature was obtained by microdialysis methods. To date, there has not been a definitive study regarding the trauma that the implanted probes inflict on the tissue, and how the induced trauma affects the measured outcomes[24].

Determination of *in vivo* human tissue/blood partition coefficients from postmortem autopsies is of marginal use because drug redistribution can occur after death. Tissue samples need to be collected and stored frozen immediately in order to prevent redistribution and degradation[25].

Most drug molecules penetrate the BBB by passive diffusion, and physiological properties such as charge and molecular volume, together with organic solvent/water partition coefficients (see equations 1.2 and 1.3 above) have been used as a predictor of brain penetration. For several classes of central nervous system (CNS) active compounds it has been found that penetration through the BBB is optimal for compounds having octanol/water partition coefficients between log $P_{octanol/water}$ = 1.5 and log $P_{octanol/water}$ = 2.1. Platts and coworkers[15] correlated the concentration ratios of 148 different compounds in rat brain and rat blood

$$logBB = logP_{brain/blood} = 0.044 + 0.511\,R_2 - 0.886\,\pi_2^H - 0.724\Sigma\alpha_2^H - 0.666\Sigma\beta_2^H + 0.861V_x$$
$$(1.4)$$

with the Abraham general solvation model. A new solute descriptor, V_x, is needed to describe processes involving solute transfer between two liquid phases. It would not be appropriate to use the Ostwald solute descriptor, $P_{hexadecane/air}$, which involves the transfer of the solute between hexadecane and the gas phase. The new descriptor is called the McGowan volume, and it's numerical value is calculated from the individual atomic sizes and number of bonds in the molecule.[26,27]

Large discrepancies between the experimental and back-calculated log BB values were noted for several molecules containing a carboxylic acid functional group, such as salicylic acid and indomethacin. The authors improved the correlation by

$$\log BB = \log P_{brain/blood} = 0.021 + 0.0463\, R_2 - 0.864\, \pi_2^H - 0.564\, \Sigma\alpha_2^H - 0.731\, \Sigma\beta_2^H$$
$$+\, 0.933\, V_X - 0.567\, I_2$$

<div align="right">(1.5)</div>

inclusion of an indicator variable, I_2, which is set equal to unity for a compound

containing a –COOH fragment and set equal to zero otherwise. Equation 1.5 was found

to mathematically describe the experimental log BB data to within an average standard

deviation of approximately 0.30 log units. At first glance the standard deviation might

seem rather large; however, in evaluating mathematical correlations involving animal

data one must take into account both the correlation's intended application and the

experimental uncertainty associated with the measured data used to derive the

correlation. Independently determined log BB data did exist for several of the drug

molecules considered by Platts *et al.*,[15] and values reported by the different research

groups did differ by as much as 0.50 log units for some of the drug molecules. An

overall standard deviation of 0.30 log units seems reasonable given the uncertainty in

some of the experimental data. The correlation is intended to be used in drug screening

to provide pharmaceutical chemists with some indication of a potential drug's ability to

penetrate the BBB. Based on the estimated log BB and other log $P_{tissue/blood}$ values, and

based on degradation and toxicity considerations, the pharmaceutical chemist can

decide whether or not to pursue the potential drug molecule further. If the decision is to

proceed with the molecule, actual experimental log BB and log $P_{tissue/blood}$

measurements would be performed. The derived correlations were never intended to

take the place of experimental data. The key to using correlations based on the

Abraham general solvation model for drug screening is that one must know the

numerical values of the solute descriptors of the potential drug molecule.

Published studies have further shown high correlations between percutaneous penetration and the physicochemical properties of the penetrant and its vehicle. Potts and Guy[28] proposed

$$\log k_{P(cm/hour)} = 0.791 \log P_{octanol/water} - 0.0061MW - 2.72 \qquad (1.6)$$

a two-parameter equation to describe the permeability coefficients of organic compounds, k_P, through excised human skin *in vitro*. The authors did not provide much in the way of statistical information, except to state that the correlation coefficient was r = 0.819 and that there still remained a significant variance (approximately 33 %) in the data. Not too much emphasis is placed on the numerical values of the three coefficients as several of the experimental data points used in many of the very early skin permeability studies were later found to be either in error,[29,30,31] not of experimental origin,[29,32] and/or not corrected to a common set of experimental conditions[29] (*i.e.*, not corrected to a common temperature). The correlation does establish that a mathematical relationship exists between skin permeability coefficients and octanol-water coefficients, and once the equation is determined, one can use available $P_{octanol/water}$ data or solubility ratios to generate calculated k_P values.

More recently, Abraham and Martins[29] used the general solvation model to correlate skin permeabilities of 119 compounds. The derived correlation

$$\log k_{P(cm/sec)} = -5.426 - 0.106R_2 - 0.473\pi_2^H - 0.473\Sigma\alpha_2^H - 3.000\Sigma\beta_2^H + 2.296V_x \qquad (1.7)$$

was found to back-calculate the observed k_P values to within 0.46 log units. Unlike many of the earlier studies, the authors did correct all of the published k_P values to a

common temperature of 37 °C by assuming an activation energy of 63.76 kJ/mole for the diffusion process. The activation energy was based on measured skin permeability coefficients of select compounds determined over a temperature range of 25 °C to 37 °C. In the case of carboxylic acid penetrants the published data was corrected for ionization, assuming that only the neutral uncharged molecule penetrated the skin. Skin penetration of the negatively charged carboxylate anion was negligible. The correction procedure was more complicated in the case of proton bases (*i.e.*, compounds with – NH_2 functional group) as both the ionic and neutral species contributed to the overall measured skin permeability coefficient. Equation 1.7 can be used to predict skin permeability coefficients of any organic compound, provided that the values of the molecular solute descriptors are known.

Molecular solute descriptors can be conveniently calculated from measured solubility and partition coefficient data. There are approximately 40 organic solvents for which "dry" equation coefficients have been determined.[33,34,35,36,37,38] The solvent coefficients are periodically updated as new experimental data becomes available. In additional there are a few solvents for which "wet" equation coefficients have been determined.[18,34,35,36] The dry solvents strictly pertain to solubility measurements, whereas the wet solvents pertain to practical partition coefficient measurements where the solute is distributed between an organic solvent and water. In partitioning experiments the organic phase is the organic solvent saturated water, and the aqueous phase is water saturated with the organic solvent. For many solvents, the experimental organic solvent/water partition coefficient can be approximated as the ratio of the solubility of the solute in the organic solvent divided by the solubility of the solute water;

however, there are a few organic solvents like dibutyl ether for which the two values are

significantly different.[36]   In the case of dibutyl ether the large differences are caused by

"water dragging" phenomena.[39,40,41] When polar solutes partition into dibutyl ether from

water they drag water molecules into the organic dibutyl ether phase. The observed

differences in the solvation behavior of "wet" versus "dry" dibutyl ether (larger a-, λ- and

v-coefficients for wet dibutyl ether and the more negative s-coefficient for wet dibutyl

ether) were rationalized on the basis of the dissolved water molecules acting as a base

and forming hydrogen-bonded complexes with acidic solutes. The wet solutes would

then interact differently with surrounding solvent molecules than would dry solute

molecules.[36]

The Abraham general solvation model takes the following mathematical form

when expressed in terms of molar solubilities

$$\log(C_{\text{in solvent}} / C_{\text{in water}}) = c + r \cdot R_2 + s \cdot \pi_2^H + a \, \Sigma \alpha_2^H + b \, \Sigma \beta_2^H + v \cdot V_x \qquad (1.8)$$

$$\log(C_{\text{in solvent}} / C_{\text{in gas}}) = c + r \cdot R_2 + s \cdot \pi_2^H + a \, \Sigma \alpha_2^H + b \, \Sigma \beta_2^H + \ell \log L^{(16)} \qquad (1.9)$$

and in terms of partition coefficients

$$\log P_{\text{solvent/water}} = c + r \cdot R_2 + s \cdot \pi_2^H + a \, \Sigma \alpha_2^H + b \, \Sigma \beta_2^H + v \cdot V_x \qquad (1.10)$$

$$\log P_{\text{solvent/air}} = c + r \cdot R_2 + s \cdot \pi_2^H + a \, \Sigma \alpha_2^H + b \, \Sigma \beta_2^H + \ell \log L^{(16)} \qquad (1.11)$$

Application of Eqns. 1.8 - 1.11 is relatively straightforward. One experimentally

determines the solubility and/or organic solvent/water partition coefficient of the solute

under consideration in at least six different organic solvents for which the equation

coefficients are known. The measured solubilities and partition coefficients, along with

the equation coefficients are then inserted into the respective equations. This will give a

set of equations having six unknowns to solve. Published examples can be found in the

literature illustrating the calculation of the solute descriptors for monuron[42], diuron[42],

acetylsalicylic acid[43], *trans*-stilbene[44], naproxen[45], ketoprofen[46], 4-chlorobenzoic acid[47],

3-nitrobenzoic acid[48], benzil[49], 2-methylbenzoic acid[50], 2-methoxybenzoic acid,[51] 4-

methoxybenzoic acid[51] and 3-methylbenzoic acid.[47]

Carboxylic acids are one of the more acidic classes of organic molecules, and

the numerical values of their hydrogen-bond acidity molecular descriptor ($\Sigma\alpha_2^H$-value)

typically falls in the 0.55 to 0.75 range. In determining equation/process coefficients it is

imperative that the solutes used in the regression analysis span as wide a range of

solute descriptors as possible. Carboxylic acids do undergo dimerization in alkane and

aromatic solvents. Experimental solubility data for carboxylic acids dissolved in alkane

and aromatic solvents can not be used because the hydrogen-bonding characteristics of

a self-associated carboxylic acid dimer (cyclic dimer) are significantly different than

those of the monomeric species. In the dimer, the acidic hydrogen of the –COOH group

is hydrogen-bonded to a lone electron pair of the "C=O" oxygen atom, and is no longer

available to hydrogen bond with surrounding solvent molecules. Monuron and diuron

do possess large $\Sigma\alpha_2^H$ acidity descriptor values, and unlike carboxylic acids, both

pesticides exist in monomeric form in alkane and aromatic solvents. Solubility data

measured as part of this thesis study was used in the calculation of the solute

descriptors for the pesticides monuron and diuron.[42]

One of the advantages that the Abraham general solvation parameter model has

over many of the other published predictive methods is that the same solute descriptors

can be used to predict many properties having chemical, biological, environmental and

pharmaceutical importance. The examples that have been cited thus far as primarily

dealt with properties and processes having pharmaceutical interest. Predictive

equations also exist for estimating the nonspecific aquatic toxicity of organic compounds

to the fathead minnow (*Pimephales promelas*)[52]

$$-\log LC_{50} = 0.99 + 0.24\,R_2 + 0.40\,\Sigma\alpha_2^H - 3.65\,\Sigma\beta_2^H + 3.39V_x \qquad [1]$$

to the golden orfe (*Leuciscus idus melanotus*)[52]

$$-\log LC_{50} = 0.15 + 1.40\,R_2 + 1.02\,\Sigma\alpha_2^H - 2.17\,\Sigma\beta_2^H + 2.80V_x \qquad [2]$$

and to the guppy (*Poecilia reticulata*)[52]

$$-\log LC_{50} = 0.71 + 0.60\,R_2 + 0.36\,\Sigma\alpha_2^H - 3.15\,\Sigma\beta_2^H + 3.33V_x \qquad [3]$$

Now dependent variable, -log LC_{50}, is the negative logarithm of the lethal molar

concentration for killing one-half of that aquatic species after a 96-hour exposure to a

given organic chemical. Water is naturally the solvent in all three toxicity studies.

Similar equations have been developed for immobilization of the water flea (*Daphnia

magna*)[52] and for the inhibition of bioluminescence in prokaryote (*Vibrio fischeri*; the

acute Microtox test).[52] In each case a fairly large database was used in the regression

analysis. A close examination of the experimental values in the databases revealed

that there no alkylamine or carboxylic acid solutes. Most of the experimental data

pertained to neutral organic molecules, and caution should be exercised in applying the

toxicity equations to alkylamines and carboxylic acids.   For molecules that can

dissociate in water, it is very likely that the neutral and ionic forms of the molecule will

exhibit different toxicities. There is no reason that the Abraham general solvation model

cannot be used to correlate toxicities of organic chemicals to other aquatic organisms,

alga and bacterium. There is quite a bit of experimental data in the literature concerning the toxicity of organic compounds to tilapia (*tilapia zilli*),[53] carp, [53,54] tadpoles (*Rana Japonica*),[55] alga *Chlorella vulgaris* [56], bacterium *Sinorhizobium meliloti* [57], *etc*. Researchers have also derived linear correlations between aquatic toxicities and log $K_{octanol/water}$. For the most part, the linear correlations had fairly large standard deviations, and the correlations were not as good as predictive equations based on the Abraham general solvation model. Additional properties that can be predicted with the Abraham general solvation model include: uptake of organic compounds into plant cuticular matrix,[58] RD50 values (exposure concentration in units of parts per million of a chemical necessary to decrease respiratory frequency in mice by 50 %),[59] nasal pungency thresholds in man,[60] eye irritation thresholds (Draize scores),[61,62] human intestinal absorption,[63] brain perfusion (differs from log BB in that time scale in the perfusion technique is much, much shorter – only a few minutes, concentration units are cm^3/(sec • gram),[17,64] rat intestinal absorption,[65] adsorption of compounds onto carbonaceous adsorbents[66] and bioconcentration factors in fish.[67]

The bioconcentration factor, BCF, is an important environmental property. This quantity gives a measure of partitioning of compounds between organisms and their surrounding environment. Experimental determination of BCF values is expensive and time-consuming in that equilibrium may take several days to be achieved, and the analytical method must be specific for the chemical under consideration. The animal must be sacrificed in order to measure BCF values. The experimental values can be measured under both "flow" (river) and "static" (aquarium, lake) conditions. Experimental BCF values are not available for all chemicals in use. Researchers tend

to use estimation methods to supply missing data. For example, Devillers et $al.$[68]

compared the predictive accuracy of seven linear and nonlinear BCF models based on

log P to 436 experimental BCF values recorded for 226 different chemicals. Two of the

specific equations considered were:

$$\log BCF = 0.80 P_{ocatanol/water} - 0.52 \qquad (1.12)$$

and

$$\log BCF = 0.91 \log P_{ocatanol/water} - 1.975 \log(6.8 \times 10^{-7} P_{ocatanol/water} + 1) - 0.786 \qquad (1.13)$$

The authors found that eqn. 1.12 yielded satisfactory predictions for chemicals with log

$P_{octanol/water}$ < 6; whereas eqn. 1.13 was need for highly hydrophobic compounds (log P >

6). All BCF values used in the study pertained to fish. Dimitrov et $al.$[69] also noted

significant scatter in the log BCF versus log $P_{octanol/water}$ for narcotics with log $P_{octanol/water}$

> 5.5. Linear correlations have also been published relating the logarithm of

bioconcentration factors for guppies and rainbow trout and the logarithm of measured

triolein/water partition coefficients.[70]   Triolein (rather than 1-octanol) was used as the

organic solvent in the latter study because of the high lipid content of fish. Triolein and

tricaprylin have been suggested as suitable solvents for mimicking a biological lipid

phase.[71]

The preceding representative examples illustrate the estimation of properties of

biological, pharmaceutical and/or environmental importance from measured partition

coefficients and solubility ratios, and from solute descriptors, which are determined from

measured solubility and partition coefficient data. Chemists use solubility information to

select reaction solvents, and to select solvents for extraction and crystallization

purification processes. Solvent selection is important also in many manufacturing

processes, such as in the design of drug formulations, hand lotions and skin creams, and in the preparation of oil-based paints, varnishes and enamels. Several manufacturing processes use solvents for cleaning and degreasing purposes. Solvent selection also involves health and safety considerations. Several of the organic compounds that were once routinely used as solvents (*i.e.*, benzene and chloroform) are no longer used because the compound was later found to be a possible (or real) carcinogen, mutagen and/or tetragen. Organism biocompatibility is a consideration in solvent selection for synthetic processes involving biological organisms. Here the organic solvent is used as an extraction solvent for removing the biologically-synthesized product. The extraction solvent must be biocompatible so that the organism does not die during the extraction process. Dodecane has been found to be a suitable organic solvent for extracting β-carotene from living *Dunalielle salina* cells in two phase bioreactors.[72,73] Solubility data is of vital importance to the scientific and engineering communities. It is for this reason that I studied the solubility behavior of monuron, diuron, ferrocene, hexachlorobenzene, biphenyl, acenaphthene, and phenanthrene in numerous organic solvents of varying polarity and hydrogen-bonding characteristics. The measured solubility data provides valuable insight into the various solute-solvent interactions, and can be used to predict not only the biological, pharmaceutical and environmental properties listed above, but can also be used to test the applications and limitations of thermodynamic solution models, such as Mobile order theory (discussed in the next chapter). Thermodynamic solution models can provide estimated solubility ratios, which in the absence of measured solubility data, can be

used in the above correlation equations to predict tissue/air, brain/blood, skin permeabilities and aquatic toxicities.

Thesis research has led to the publication of 8 papers[42,74,75-80,76,77,78,79,80] in refereed international journals. Solubility data for monuron, diuron, hexachlorobenzene, biphenyl, acenaphthene, phenanthrene and ferrocene has been made available to the scientific community, and can be now used by other researchers in this field to test the predictive abilities of not only existing correlation equations, but many future equations that will be proposed in later years. To date Riverol *et al.*[81] have used to monuron and diuron solubility in comparisons illustrating solubility predictions based on the UNIFAC and Modified UNIFAC (Dortmund) models, and Abildskov and O'Connell[82] compared measured monuron and diuron solubility data to predicted values calculated from an UNIFAC-based solvent reference model. Thesis solubility data has also been combined with previously published solubility and activity coefficient data for 50+ additional solutes dissolved in tetrahydrofuran, 1,4-dioxane, and dibutyl ether, and used by others[34,36] in deriving log P and log L Abraham solvation model equations for the fore-mentioned ether solvents.

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CHAPTER 2

REVIEW OF BASIC THERMODYNAMIC PRINCIPLES AND RELEVANT SOLUTION

MODELS

Ideal and Non-Ideal Solutions

Several methodologies have been developed to predict the solubility of solutes in

a mathematical fashion. Early models began with an "ideal solution", something that

does not exist, but can make predicting thermodynamic properties of solutions easier.

Non-electrolytic solutions are the most "ideal" solutions and are therefore used to more

accurately predict these properties.

To begin with, the concentrations of the various components in the mixture must

be specified in order for the mixture to be uniquely defined. Molarity (abbreviated as M)

is defined as the number of moles of the chemical of interest per unit of volume.

Molarity is a common unit of concentration in analytical chemistry. Mixtures can also be

described by the mole ratio, which is the number of moles of component A divided by

the number of moles of species B, n_A/n_B.   In the case of a mixture containing multiple

components, it is sometimes more convenient to express the concentration of each

substance in terms of mole fraction, χ. The mole fraction of A is given by

$$\chi_A = {n_A}\big/{(n_A + n_B + n_C + ...)} \qquad (2.1)$$

where n_A, n_B and n_C are the number of mole of components A, B, C in the mixture. For

mixtures containing chemicals of very dissimilar sizes or polymeric species of unknown

molecular weight, it is sometimes more convenient to express the concentrations of all

of the components using volume fraction, φ; defining φ in terms of molar volumes of the

pure liquid components. The molar volume of component i, V_i, is calculated by dividing the molecular weight by the density[1].

$$\varphi_A = {n_A V_A}\big/{(n_A V_A + n_B V_B + n_C V_C + ...)} \qquad (2.2)$$

The denominator in equation 2.2 corresponds to the ideal molar volume approximation, which assumes that the volumes of the mixture components are additive.

Dalton's Law of Partial Pressure states that the total pressure exerted by a mixture of ideal gases is the sum of the partial pressure of the individual gases.

$$P_{total} = P_A + P_B + P_C + ... \qquad (2.3)$$

Raoult's law and the concept of activity coefficients made the thermodynamic treatment of non-ideal solutions possible. Raoult's law states that the partial pressure of component A in a mixture, P_A, is[2]

$$P_A = \chi_A P_A^{\circ} \qquad (2.4)$$

where P_A° = pressure of the vapor above the pure component

χ_A = the mole fraction of A in the mixture

Simply stated, the vapor pressure of A above an ideal solution is directly proportional to the mole fraction of A in solution. Substituting eqn. 2.4 into eqn. 2.3 yields a total vapor pressure equation for an ideal gas mixture above a binary liquid mixture:

$$P_{toal} = \chi_A P_A^{\circ} + \chi_B P_B^{\circ} = \chi_A P_A^{\circ} + (1 - \chi_A)P_B^{\circ} = \chi_A(P_A^{\circ} - P_B^{\circ}) + P_B^{\circ} \qquad (2.5)$$

Since P_A° and P_B° are constants at any given temperature, equation 2.5 can be used to predict the vapor pressures of nearly ideal solutions, that is solutions consisting of similar components. In an ideal solution each component behaves as if it were

essentially pure. The total pressure dependence on the liquid phase mole fraction composition would be linear.

For solutions containing molecules of very dissimilar polarities and hydrogen bonding characteristics, one experimentally observes substantial deviations from the linear relationship given by eqn. 2.5. When the observed vapor pressure is greater than that predicted by Raoult's Law the system exhibits a positive deviation that is due to the differences in polarity between components, such as in binary mixtures containing methanol and hexane. Molecularly, the two substances have not mixed randomly enough and methanol self-associates in localized regions. In the regions of self-association methanol acts as though its mole fraction is greater than that of the "bulk" solution composition. Self-association leads to a greater than predicted vapor pressure. In the case of the binary methanol + hexane system, the self-association of methanol leads to phase separation. The phase diagram of the binary methanol + hexane system at 298.15 K shows two liquid phases over a considerable portion of the binary mole fraction composition range[3,4,5,6,7,8,9]. Negative deviations (lower than expected values) are usually due to complexation between two different solution components, such as the hydrogen bonding between chloroform and dibutyl ether molecules. The two molecules are so strongly attracted to one another that fewer molecules are able to escape into the vapor phase thereby decreasing the observed vapor pressure.

To correct for deviations from solution ideality, the activity coefficient, γ, was introduced into Raoult's Law.

$$P_A = \gamma_A X_A P_A^{\circ} \qquad\qquad (2.6)$$

For an ideal mixture $\gamma = 1$ and this equation becomes Raoult's Law. Activity coefficients make it possible to predict thermodynamic properties of non-ideal mixtures since they are a function of temperature, pressure and composition. Vapor-liquid equilibrium data is used to determine activity coefficients for non-electrolyte solutions and to test empirical predictive methods.

Thermodynamic mixing parameters, when compared to values for an ideal solution are convenient measures of non-ideality. The most important thermodynamic quantities being:

$$G^E = \Delta G^{mix} - RT \sum x_i \ln x_i \tag{2.7}$$

$$S^E = \Delta S^{mix} - R \sum x_i \ln x_i \tag{2.8}$$

$$H^E = \Delta H^{mix} \tag{2.9}$$

the molar excess Gibbs energy, ΔG^E, the excess molar enthalpy ΔH^E and the excess entropy, ΔS^E of mixing. The three excess functions are related to each other by the standard thermodynamic relationship:

$$G^E = H^E - TS^E \tag{2.10}$$

For mixtures with similar components, each of the excess quantities will be close to zero, and the mixture will show very small deviations from Raoult's Law. For simple mixtures, Rowlinson[10,11] has showed endothermic enthalpies of mixing caused by differences in non-specific interactions to be the cause of deviations from ideality. Mixtures similar in dispersion forces that vary greatly in size exhibit negative deviations from ideality caused by a large positive entropy of mixing, *i.e.*, $+\Delta S^{mix}$. When molecules are of similar size, the enthalpy of mixing (ΔH^{mix}) is the dominant factor. The increase in

the enthalpy of mixing is compensated for by an increase in excess entropy, (S^E).

Molecular interactions also cause deviations. Strong attractions like those between chloroform and ether have a negative enthalpy of mixing. Non-specific interactions dominate weak attractions between unlike molecules resulting in positive enthalpies of mixing.

Raoult's law provides a very convenient definition of solution ideality for mixtures containing molecules of comparable molecular size. The measured thermodynamic properties generally do not differ significantly from those of an ideal solution, and the calculated activity coefficients typically fall in the $\gamma = 0.5$ to $\gamma = 5.0$ range. Even for the more non-ideal solutions where phase separation does occur, the calculated activity coefficients are much larger than $\gamma = 5.0$; however, the numerical values are consistent with the molecular interactions believed to be present in the solution. This is not the case in mixtures containing molecules with vastly different molecular sizes. Deviations from ideality become much larger, to the point where the calculated activity coefficients are no longer reasonable given the polarity and hydrogen-bonding characteristics of the dissolved molecules. A new definition of solution ideality is needed for such mixtures.

In their studies of polymeric solutions, Flory[12,13] and Huggins[14,15,16] independently derived a mathematical expression for the entropy of mixing of a polymer dissolved in an alkane solvent. The authors assumed that the dissolved polymer molecule behaves like a flexible CH_2-chain with a large number of equal-sized segments which are identical in size to the alkane solvent. Each segment occupied a single site in the lattice model with adjacent polymer segments occupying adjacent lattice sites. The change in the Gibbs energy

$$\Delta G_{12}^{mix} = RT[n_{solv} \ln \varphi + n_{polymer} \ln \varphi_{polymer}] \qquad (2.11)$$

and entropy of mixing

$$\Delta S_{12}^{mix} = -R[n_{solv} \ln \varphi_{solv} + n_{polymer} \ln \varphi_{polymer}] \qquad (2.12)$$

is given by equations 2.11 and 2.12, respectively, where φ_{solv} and $\varphi_{polymer}$ denote the

volume fractions of the alkane solvent and dissolved polymer molecule. The Flory-

Huggins solution model predicts negative deviations from Raoult's law for an athermal

mixture of components whose molecules differ in size. Careful examination of

equations 2.7, 2.8, 2.11 and 2.12 reveals that the Flory-Huggins model is

mathematically equivalent to Raoult's law when the molecules are identical in size.

Huyskens and Haulait-Pirson[17] suggested as a definition of solution ideality

$$\Delta S^{mix} = -0.5\,R\,\Sigma\chi_i \ln\chi_i - 0.5\,R\,\Sigma\chi_i \ln\varphi_i \qquad (2.13)$$

$$\Delta G^{mix} = 0.5\,R\,T\Sigma\chi_i \ln\chi_i + 0.5\,R\,T\Sigma\chi_i \ln\varphi_i \qquad (2.14)$$

a simple arithmetic average of the entropy of mixing based upon Raoult's law and the

Flory-Huggins model. The authors justified equations 2.13 and 2.14 by stating that the

entropy of mixing of liquids should be a hybrid between that of a crystal (the Flory-

Huggins model was derived assuming that the polymer segments occupied sites on a

rigid crystalline lattice) and that of gas (Raoult's law and Dalton's law of partial

pressures). Nominal exchanges of molecules are described by the $\Sigma\chi_i \ln\chi_i$ term in

equations 2.13 and 2.14, and the enlargements of the motional domains by the $\Sigma\chi_i \ln\varphi_i$

term.

Partition Coefficients

The tendency of a solute to distribute between any two immiscible phases is measured by the equilibrium constant of the chemical in the two phases, which in many analytical and biological processes involves both an aqueous phase and an organic/tissue phase. When a single molecular species is partitioned between two immiscible (or partially miscible) phases, the condition of equilibrium requires that the chemical potentials, μ, of that molecular species in the two phases must be equal. That is

$$\mu_{solute,\,org} = \mu_{solute,\,aq} \tag{2.15}$$

$$\mu^{\circ}_{solute,\,org} + RT \ln(X_{solute,\,org}\, \gamma_{solute,\,org}) = \mu^{\circ}_{solute,\,aq} + RT \ln(X_{solute,\,aq}\, \gamma_{solute,\,aq}) \tag{2.16}$$

where the subscripts "org" and "aq" refer to the organic and aqueous phases, respectively, $\mu^{\circ}_{solute,\,org}$ is the standard-state chemical potential of the solute in the organic phase, $X_{solute,\,org}$ is the mole fraction of the solute in the organic phase, and $\gamma_{solute,\,org}$ is the activity coefficient of the solute at $X_{solute,\,org}$ defined according to some chosen standard-state conditions. In the aqueous phase, $\mu^{\circ}_{solute,\,aq}$, $X_{solute,\,aq}$ and $\gamma_{solute,\,aq}$ have similar meanings.

It is convenient in the present case to define the standard state of the liquid solute as the pure substance at the given temperature and pressure of the partitioning study. For crystalline solutes, the standard state is normally taken to the hypothetical supercooled liquid solute at the given temperature and pressure of the partitioning measurements. The standard state of crystalline solutes will be discussed in greater detail in the sections involving solubilities of crystalline solutes. For now, it will be

sufficient to state that in partitioning studies the same standard state is used to describe the solute in both the organic and aqueous phases, *i.e.*, $\mu_{solute, org} = \mu_{solute, aq}$. Equating the standard-standard chemical potentials, the condition of thermodynamic equilibrium becomes

$$X_{solute, org}\, \gamma_{solute, org} = X_{solute, aq}\, \gamma_{solute, aq} \tag{2.17}$$

Partitioning studies are normally performed at very low solute concentration. In the limit of infinite dilution, all of the different concentration units become co-linear. The mole fraction concentration of the solute in dilute solutions may be expressed as the product of the molar concentration, C_{solute}, and the molar volume of the solvent phase, V_{org} and γ_{aq}. Substitution into equation 2.17 gives the following mathematical relationship

$$C_{solute, org}\, V_{org}\, \gamma_{solute, org} = C_{solute, aq}\, V_{aq}\, \gamma_{solute, aq} \tag{2.18}$$

where $C_{solute,org}$ and $C_{solute,aq}$ denote the molar concentrations (mol/liter) of the solute, and V_{org} and V_{aq} are the molar volumes (liters/mol) of the organic and aqueous phases.

The partition coefficient of a solute, P, is defined as

$$P = K = C_{solute, org}\, /\, C_{solute, aq} = (V_{aq}\, /\, V_{org})(\gamma_{solute, aq}\, /\, \gamma_{solute, org}) \tag{2.19}$$

the ratio of the solute concentrations in the organic and aqueous phases. Careful examination of equations 2.17 and 2.19 reveals that in dilute solutions the partition coefficient based on molarities (or grams/liter) differs from the partition coefficient based on mole fractions by a factor equal to the ratio of the organic phase and aqueous phase molar volumes. The molar volume of the aqueous phase is usually much less than that of the organic phase, and as result, K is smaller than the equilibrium constant expressed in terms of mole fractions. The advantage of using the molar concentration

rather than the mole fraction concentration becomes more apparent in studies involving biological tissues and fluids. Molecular weights of biological tissues and fluids are not known, and it is not possible to express the concentration of a drug molecule dissolved in a tissue or in blood using mole fractions. The volume of a biological tissue or fluid can be experimentally determined, however. The density of many biological tissues and fluids is close to unity[18], and as a first approximation, the molar concentration of a dissolved drug molecular in a biological tissue (and/or fluid) is calculated as the number of moles of the drug molecule per kilogram of tissue (and/or fluid).

Equation 2.19 clearly shows that the partition coefficient is a function of solute activity coefficients in the two immiscible (or partly miscible) phases. For a given organic solvent-water system and temperature, the partition coefficient is constant for a solute only at low solute concentrations where γ_{solute} and V_{phase} approach constant numerical values. The variation of γ_{solute} with concentration can be mathematically described using solution models, such as the van Laar equation[19]

$$\log \gamma_{solute} = B/[1+(B\, X_{solute})/A\, X_{solvent})]^2 \qquad (2.20)$$

$$\log \gamma_{solvent} = A/[1+(A\, X_{solvent})/B\, X_{solute})]^2 \qquad (2.21)$$

the Wilson equation[20,21]

$$\ln \gamma_{solute} = -\ln(X_{solute} + \Lambda_{21}\, X_{solvent}) - X_{solvent}) - X_{solvent}[\Lambda_{12}/(X_{solvent} + \Lambda_{12}\, X_{solute}) - \Lambda_{21}/(\Lambda_{21}\, X_{solvent} + X_{solute})]$$

$$(2.21)$$

$$\ln \gamma_{solvent} = -\ln(X_{solute} + \Lambda_{21} X_{solvent}) - X_{solvent}) - X_{solute}[\Lambda_{12}/(X_{solvent} + \Lambda_{12} X_{solute})$$
$$- \Lambda_{21}/(\Lambda_{21} X_{solvent} + X_{solute})]$$

$$(2.22)$$

the two-suffix Margules equation[22]

$$\ln \gamma_{solute} = X_{solvent}^2 A \qquad (2.23)$$

$$\ln \gamma_{solvent} = X_{solute}^2 A \qquad (2.24)$$

and regular solution theory[21]

$$\ln \gamma_{solute} = \varphi_{solvent}^2 V_{solute} A \qquad (2.25)$$

$$\ln \gamma_{solvent} = \varphi_{solute}^2 V_{solvent} A \qquad (2.26)$$

where all of the non-mole fraction and non-volume fraction quantities represent actual

numerical values deduced by curve-fitting the experimental total vapor pressure data of

the respective solute-water and solute-organic solvent binary systems to

$P_{total} = X_A \gamma_A P_A^\circ + X_B \gamma_B P_B^\circ$. The total pressure is based upon Raoult's law definition of

solution ideality, with the activity coefficients added to account for solution nonideality.

All solution models used to describe the variation of the solute activity coefficient with

mixture composition must give as its limiting conditions $\gamma_i = 1$ as $x_j \to 0$; otherwise the

model fails to obey Raoult's law.

It is conceivable from the above analysis that the partition coefficients of different

solutes may vary to different extents when solutes approach high mole fractions.

Experimental measurements have shown that the activity coefficient of a dissolved

solute generally decreases with an increase in concentration for practically all solutes, except when the solute exhibits negative nonideality. As a mathematical consequence of the variation of solute activity coefficient with solute concentration, compounds that are highly soluble in the organic phase but are sparingly soluble in water might tend to have an increased concentration ratio at high concentrations as the majority of the solute in the system will be distributed to the organic phase. In other words, $\gamma_{solute,org}$ would decrease more rapidly than $\gamma_{solute,aq}$ at high concentration. At high concentrations, the partition coefficient ratio may also vary due to changes in the organic phase molar volume. When solutes have relative low partition coefficients, the concentration effect should normally be less significant because the activity coefficient ratio of $\gamma_{solute,aq} / \gamma_{solute,org}$ may partially cancel the effect. In addition to concentration and molar volume effects, the concentration ratios of acidic and basic solutes are also related to the extent of their dissociation in water and to the extent of their association in the organic solvent phase.

The partition coefficient can be related to the solubility of the solute as follows. For a liquid organic solute of limited solubility in equilibrium with water, the thermodynamic criteria of equilibrium requires that the chemical potential of the organic solute in water be

$$X^*_{solute,\, org}\, Y^*_{solute,\, org} = X^*_{solute,\, aq}\, Y^*_{solute,\, aq} \qquad (2.27)$$

equal to the chemical potential the organic solute in the "organic phase" (see equation 2.17). In this particular case, the organic phase essentially the "pure" organic solute because there is no organic solvent present. A superscript "*" has been added to denote organic phase is different from the more traditional partitioning systems. If water

is not very soluble in the liquid organic solute, the entire left-hand side of equation 2.27 will equal unity, *i.e.*, $X^*_{solute, org} \gamma^*_{solute, org} = 1$. The "organic phase" will for all practical purposes be the neat organic liquid solute. Raoult's law requires that the activity coefficient of a pure liquid be unity. Converting the solute mole fraction concentration to molarity, the molar solubility of the solute in water is

$$C^*_{solute, water} = 1/(\gamma^*_{solute, water} V^*_{water})$$ (2.28)

the reciprocal of the product of the molar volume of the equilibrium aqueous phase (which is essentially pure water) and the solute's activity coefficient in water.

For extraction solvents that are nearly immiscible with water, it can be shown that the combination of equations 2.19 and 2.28 yields the following relationship between the solute's partition coefficient and the solute's solubility in water[23]

$$\log K = -\log C^*_{solute, water} - \log V_{org} - \log \gamma_{solute, org} + \log(\gamma_{solute, water} / \gamma^*_{solute, water})$$ (2.29)

One can similarly assume that the liquid organic solute is nearly insoluble in the organic extraction solvent. This latter assumption allows one to express the logarithm of the solute's partition coefficient in terms of

$$\log K = \log(C^*_{solute, organic} / C^*_{solute, water}) + \log(\gamma_{solute, water} / \gamma^*_{solute, water})$$
$$+ \log(\gamma^*_{solute, organic} / \gamma_{solute, organic})$$ (2.30)

the logarithm of the solute's solubility ratio in the extraction solvent and in water, plus two additional logarithm terms involving the solute's activity coefficient in water, in the neat extraction solvent, in water saturated with the extraction solvent, and in the extraction solvent saturated with water. Equation 2.30 provides a theoretical justification for approximating the partition coefficient by the ratio of the solute's

solubility in two phases, as discussed previously in Chapter 1. Experimental studies

have shown good agreement between the calculated experimental solubility ratio and

partition coefficient for several crystalline solutes[24].

Solubility and Standard State for Crystalline Nonelectrolytes

Most published solution models were developed originally for the mixing of two or

more liquid substances. Here, the change in entropy can be conveniently discussed in

terms of the total number of ways of arranging the various molecules (or segments of

molecules in the case of polymeric materials) on a fixed lattice cell. Molecules in the

pure liquids and/or the lattice would have approximately the same mobility. This would

not be true for crystalline materials, however, because the molecules are rigidly fixed in

space. To apply conventional solution models to systems involving dissolved solids,

one must adopt as the standard state the hypothetical pure subcooled liquid solute

(abbreviated as "pscl").

The activity of the solid solute, a_{solute}^{solid}, is defined as

$$a_{solute}^{solid} = f_{solute(solid)} / f_{solute(pscl)} \qquad (2.31)$$

the ratio of the fugacity of the solid, $f_{solute(solid)}$, to the fugacity of the hypothetical pure

supercooled liquid, $f_{solute(pscl)}$. Fortunately, a systematic extrapolation for the fugacity of

the supercooled liquid can be easily obtained from basic thermodynamic principles and

the following three-step Hess's Law thermodynamic cycle:

Step 1:

Solute (solid, T) - - - - - - > Solute (solid, T_{TP})
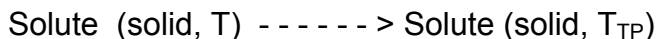
Step 2:

Solute (solid, T_{TP}) - - - - - -> Solute (liquid, T_{TP})

Step 3:

Solute (liquid, T_{TP}) - - - - - - -> Solute (pscl, T)

Overall Process:

Solute (solid, T) - - - - - - - -> Solute (pscl, T)

The change in the Gibbs energy for the overall process, ΔG_{total}, is

$$\Delta G_{total} = RT \ln a_A^{solid} = \Delta G_{step\,I} + \Delta G_{step\,II} + \Delta G_{step\,III} \qquad (2.32)$$

related to the activity of the solid solute, which for convenience is now denoted as

component A. Assuming that the difference in heat capacities between the solid and

supercooled liquid remains constant over the temperature range from T to T_{TP}, the

following expression is obtained

$$\ln(a_A^{solid}) = -\Delta H_{TP}^{fus}(T_{TP} - T)(RTT_{TP})^{-1} + \Delta C_P(T_{TP} - T)(RT)^{-1}$$
$$- (\Delta C_P / R)\ln(T_{TP} / T) \qquad (2.33)$$

where:

ΔH_{TP}^{fus} = heat of fusion at the triple point temperature T_{TP}

T = temperature of the system

ΔC_P = heat capacity of the solute at constant pressure

T_{TP} = triple point temperature of the solute

for the solubility of a crystalline nonelectrolyte in an ideal solution. The expression for

a_A^{solid} must include additional term(s) if the solute undergoes a solid-solid phase

46

transition between its triple point temperature and the temperature at which the solubility measurements are performed. One of the solutes, phenanthrene, does undergo a first-order transition at T_{trans} = 339.2 K. The numerical of a_A^{solid} for phenanthrene was calculated using

$$\ln a_A^{solid} = -\Delta H^{fus}(T_{TP} - T)(RTT_{TP})^{-1} + \Delta C_p(T_{TP} - T)(RT_{TP})^{-1}$$
$$- (\Delta C_p / R)\ln(T_{TP} / T) - \Delta S^{trans} / RT)(T_{trans} - T)$$

(2.34)

The last term in equation 2.34 accounts for the additional solid phase transition[25,26].

To simplify equation 2.33, one can substitute the heat of fusion at the melting point for the heat of fusion at the triple point, and the melting point temperature for the triple point temperature. For most substances the triple point and melting point temperatures differ by less than 1°C. The change in heat capacity generally is not known when going from the triple point to the temperature of the system due to the difficulty in determining this value since most substances only subcool a few degrees below their melting points. In most theoretical studies the lack of heat capacity data necessitates that the last two terms in equation 2.33 be dropped from the calculation. The activity of the solid solute is thus calculated from

$$\ln(a_A^{solid}) = -\Delta H^{fus}(T_{MP} - T)(RTT_{MP})^{-1}$$

(2.35)

experimental enthalpy of fusion data and the melting point temperature[27]. The activity of the solid solute is equal to the mole fraction solubility of the solute in an ideal solution. If a given solute were to form an ideal solution with two different solvents, then the solute will have identical mole fraction solubilities in both solvents. Two very important observations can be made regarding the solubility of crystalline solutes in ideal solutions. First, equation 2.35 clearly shows that for a given solute-solvent system, the

47

solubility increases with increasing temperature. The rate of increase is approximately proportional to the enthalpy of fusion and, to a first approximation, the increase does not depend upon the melting point temperature of the solute. Second, for a given solvent and at a fixed temperature, if two crystalline solutes have similar entropies of fusion (*i.e.*, if $\Delta S^{fus} = \Delta H^{fus}/T_{MP}$ is the same for both solutes), then the solid with the lower melting point temperature has the higher mole fraction solubility. Similarly, if two solids have approximately the same melting point temperature, then the solid with the lower enthalpy of fusion will have the higher solubility.

Enthalpy of fusion is available in the chemical literature for several thousand organic compounds[28,29].   If experimental ΔH^{fus} is not readily available, one can still obtain an approximate value for $a_A{}^{solid}$ by using the estimation methods of Walden[30], Tsonopoulos and Prausnitz[31], Yalkowsky[32], and Yalkowsky *et al.* [33], which estimate the entropy of fusion for many simple aromatic compounds at about $\Delta S^{fus} = 56.5 \pm 12.6$ J mol^{-1} K^{-1}. The group contribution method of Chickos *et al.* [27,28] can be used for the more complex organic molecules. Group values are currently available for more than 160 common functional groups. The computational protocol is discussed in detail elsewhere[27]. The latter method has been shown to predict the total entropies of melting of more than 2,000 organic and organometallic compounds to within an overall standard deviation of $\pm$ 13 J mol^{-1} K^{-1}.

Real liquid mixtures rarely exhibit "true" solution ideality, not even mixtures in which the components differ only by isotopic substitution. Benzene + hexadeuterobenzene mixtures[34], benzene + dideuterobenzene mixtures[35], argon-36 + argon-40 mixtures, methane + partially deuterated or fully deuterated methane

mixtures[36,37] and HCl + DCl mixtures[38] all exhibit small positive deviations from Raoult's law. Binary mixtures of H_2S and D_2S show slight negative deviations from Raoult's law[40]. Liquid-phase nonideality is taken into account by

$$\ln a_A^{solid} = \ln(\gamma_A X_A^{sat}) = -\Delta H^{fus}(T_{MP} - T)(RTT_{MP})^{-1} \\ + \Delta C_p(T_{MP} - T)(RT_{MP})^{-1} - (\Delta C_p/R)\ln(T_{MP}/T) \tag{2.36}$$

$$\ln a_A^{solid} = \ln(\gamma_A X_A^{sat}) = -\Delta H^{fus}(T_{MP} - T)(RTT_{MP})^{-1} \tag{2.37}$$

introducing activity coefficients. The activity of the solid solute is equal to the product of the solute's saturation mole fraction solubility, X_A^{sat}, and the activity coefficient, *i.e.*,

$a_A^{solid} = \gamma_A X_A^{sat}$.

Mobile Order Theory

The basic idea behind Mobile Order theory is that molecules are always in motion and that neighbors of a given kind of external atoms in these molecules are always changing. All molecules of a given kind are able to occupy freely the same amount of volume equal to the total volume of the liquid (V), divided by the total number of molecules of the same kind, N_A.

$$DomA = V\!\big/\!N_A \tag{2.38}$$

The highest mobile disorder is achieved when all groups visit all parts of their domain without preference. When there are preferences deviations from the "random" visiting

arise. This can be seen in the case of hydrogen bonding. Specific interactions lead to a specific orientation where the hydroxylic hydrogen (H$^+$) follows the proton acceptor group (R-OH$^-$) of a neighboring molecule most of the time thereby causing a type of "mobile order"[39]. Each R-OH group has three sites for hydrogen bonding: the hydroxyl proton and two lone pairs on the oxygen atom, creating molecules of the following configuration:

$$O{-}H\cdots O{-}H\cdots O{-}H\cdots O{-}H\cdots O{-}H\cdots O{-}H\cdots O{-}H$$
$$\;\;\mid\qquad\;\mid\qquad\;\mid\qquad\;\mid\qquad\;\mid\qquad\;\mid\qquad\;\mid$$
$$\;\;R\qquad R\qquad R\qquad R\qquad R\qquad R\qquad R$$
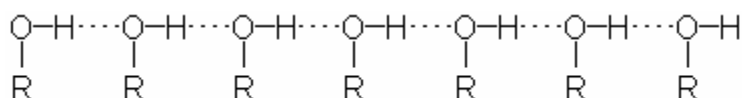
For simplicity, two assumptions are made; only one electron donor site on the oxygen hydrogen bonds and there is no branching in the chain. Experimentally this has been proven. The second hydrogen bond is much weaker after the formation of the first bond if formed in the same manner[40].

Traditionally, an ensemble fraction was used to describe self-associating hydrogen bonds in alcohols. The thermodynamic probability of an atoms being associated with another molecule was calculated using the surface fraction. It was also assumed that self-associating hydrogen bonds cleaved at the ends of the molecule only[41].

$$(\text{R-OH})_n \leftrightarrow (\text{R-OH})_{n-1} + \text{ROH}$$

Guldberg and Waage derived an association constant, K_A, expression for the various monomers, dimers, trimers ...etc[42].

$$K_A = (R-OH)_n /[(R-OH)_{n-1}(R-OH)] \qquad\qquad (2.39)$$

Relating K_A to concentration, C_A, equation 2.39 becomes

$$\alpha_n/[(\alpha_{n-1})(\alpha_1)] = (n/n-1)K_A C_A \qquad (2.40)$$

where α equals the fraction of molecules involved in chain.

To properly describe self-associating solvents, K_A is treated as an insertion constant and is calculated using time fractions instead of ensemble fractions.

$$(Y-1)/Y = K_A C_A \qquad (2.41)$$

or

$$Y = [1+K_A C_A]^{-1} \qquad (2.41)$$

For single chains with no branching, K_A equals the molar concentrations of the associating component and the probability, in time, that R-OH is free from hydrogen bonding, Y[43]. If R-OH is of high dilution or in a non-associating solvent, then $Y = 1$ and time fraction approximately equals ensemble fraction[44]. This explains the accuracy seen in the traditional predictive method using ensemble fractions for dilute systems. Cleavage of the ROH group(s) is actually a random process and can occur at any point in the chain.

$$\text{(R-OH)}_q \leftrightarrow \text{(R-OH)}_m + \text{(ROH)}_n$$

Here, q = m + n. Equation 2.41 describes this type of cleavage process.

Two types of disorder occur when mixing two liquids or a solid and a liquid, static and mobile disorder. Static disorder is calculated as the average number of molecules A that will be replaced by molecule B. Mobile disorder takes into account the fact that molecules are allowed to travel freely through their domain. To increase the domain available to molecule B, molecule A needs to be introduced into the system. Both types

of disorder depend on molecule A, in the first case it is a mole fraction dependence and in the second it is a volume fraction dependence. To take into account the two types of mixing, the classical entropy of mixing equation is[43]

$$\Delta S^{mix} = -R[n_A \ln(X_A^{(1-\alpha)}\varphi_A^{\alpha}) + n_B \ln(X_B^{(1-\alpha)}\varphi_B^{\alpha})] \tag{2.42}$$

Equation 2.42 is the generalized form of the Huyskens and Haulait-Pirson definition of an ideal solution (see equations 2.13 and 2.14). By setting α equal to 0.5, equation 2.16 becomes the arithmetic average of Raoult's law and the Flory-Huggins model. For solutions containing molecules of equal size, equation 2.42 is mathematically equivalent to the entropy of mixing of an ideal solution defined by Raoult's Law.

Mobile Order Theory: Solubility in Pure Solvents

Published studies documenting the application of Mobile Order theory to describe the thermodynamic properties of nonelectrolyte solutions have involved for the most part either solubility predictions for crystalline nonelectrolyte solutes (denoted as component A) dissolved in solvents of varying polarity and hydrogen-bonding characteristics, or the prediction of equilibrium concentration ratios based on the partitioning of organic solutes between two immiscible liquid phases. The thermodynamic treatment of solubility will be considered first as this is the basis of the thesis study. The predictive expression for the saturation volume fraction solubility, φ_A^{sat}, in neat organic solvents based on Mobile Order theory

$$\ln \varphi_A^{sat} = A + B + D + F + O + OH \tag{2.43}$$

takes into account the various contributions to the change in Gibbs energy accompanying the solution process. Depending upon the functional groups present on

the dissolved solute and solvent molecules, the predictive expression may contain up to six terms, as shown in equation 2.43.

The first term in equation 2.43, called the fluidization constant by Ruelle and coworkers[45,46,47] represents the breaking of solute-solute interactions in the crystalline lattice that must occur in order for the solute to dissolve. From a thermodynamic standpoint, the fluidization term corresponds to the formation of the hypothetical pure supercooled liquid standard state. In the supercooled liquid all of the solute-solute interactions in the crystalline lattice have been broken, and the solute is completely surrounded by molecules of its own kind. The numerical value of A is calculated from equations 2.33 - 2.35, depending on the availability of heat capacity data and on whether the solute has a solid-solid phase transition between its normal melting point temperature and the temperature of the solubility measurements.

The second term in equation 2.43, the B term, is a correction factor that takes into account the entropy of mixing arising from molecular size disparity. In Mobile Order theory the entropy of mixing is assumed to be a simple arithmetic average of the entropies of mixing given by Raoult's law and the Flory-Huggins model. The B correction is

$$B = 0.5\varphi_{solv}(V_A / V_{solv} - 1) + 0.5\ln[\varphi_A + \varphi_{solv}(V_A / V_{solv})] \tag{2.44}$$

obtained by differentiating equation 2.42 (with $\alpha = 0.5$) with respect to the number of moles of solute. Molar volumes, V_A and V_{solv}, used in the volume fraction computations refer to the pure liquid components, which in the case of the solute refers to the hypothetical supercooled liquid solute. The best estimate of the solute molar volume is found by adding up the incremental group volumes for each of the functional groups in

the molecule. For example, phenanthrene would have 10 aromatic CH groups and 4 aromatic carbon atoms. The B term can either has either a positive or negative value, depending on whether the V_A/V_{solv} volume ratio is greater than or less than unity.

The D term accounts for the effect on the solubility is related to the difference in the solute-solute, solute-solvent and solvent-solvent nonspecific cohesion interactions in the liquid phase. As a first approximation, the correction factor, D, is calculated from

$$D = -\varphi_{solv}^2 V_A (\delta_A' - \delta_{solv}')^2 (RT)^{-1} \qquad (2.45)$$

an equation of the Scatchard-Hildebrand type[48,49,50,51] with "modified" solubility parameters, δ_A' and δ_{solv}'. Equation 2.45 is based on the assumption that the solute-solvent cohesive force is equal to the geometric mean of the cohesion energy densities of the two equivalent like pairs, solvent-solvent and solute-solute. Careful examination of equation 2.45 reveals that the numerical value of D must always be negative, and that its importance decreases as the modified solubility parameter of the dissolved solute approaches the modified solubility parameter of the solvent. Large differences between the modified solubility parameters of the solute and solvent result in large negative D values, which translates to a decrease in solute solubility when the value of D is inserted into equation 2.43 for the solubility prediction. The D correction represents an "enthalpic" effect, and in the case of equation 2.45 would correspond to a positive enthalpy of mixing, or positive deviations from Raoult's law. Approximating the nonspecific cohesive forces with a solution model that gives positive deviations from Raoult's law seems reasonable based on the prior observation that mixtures of isotopic compounds generally exhibit positive deviations from Raoult's law.

The F term describes the so-called hydrophobic effect,

$$F = -r_{solv} \varphi_{solv} (V_A / V_{solv})$$ (2.46)

which accounts for the reduction in solute solubility that results from the formation of hydrogen-bonded chains between amphiphilic solvent molecules. The F term is needed whenever self-associated solvents are considered, and arises from an increase in the temporary loss of freedom of mobility of the solvent molecules whenever the total volume of the solution is increased by the addition of the solute. In most published applications involving self-associating solvents, $r_s \approx 1$ for molecules with one proton donor site, $r_s \approx 2$ for molecules with two proton donor sites, such as water and alkanediols, and $r_s = 0$ for non-associated solvents such as saturated and aromatic hydrocarbons, ethers, ketones and halogenated derivatives. More precise r_s values for alcohols and for water can be calculated using the following equations[12]:

Alcohols: $$r_S = (K_S \varphi_S / V_S)/(1 + K_S \varphi_S / V_S)$$ (2.47)

Water: $$r_s = [K_{water1} \varphi_{water} / V_{water} + 2K_{water1}K_{water2}(\varphi_{water} / V_{water})^2 /$$
$$[1 + K_{water1} \varphi_{water} / V_{water} + K_{water1}K_{water2}(\varphi_{water} / V_{water})^2]$$

(2.48)

A numerical value of $K_s = 5000$ cm^3 mol^{-1} is usually assumed for all monofunctional alcohols. In the case of water, the first association constant, K_{water1}, is assumed to be of the same magnitude as the association constant of alcohols; however, the second stability constant, $K_{water2} \approx 300$ cm^3 mol^{-1} is markedly smaller[52].

The next to last term in equation 2.43, the O term, corresponds to

$$O = \Sigma v_{Oi} \ln\{1 + K_{Oi}[(\varphi_{solv} / V_{solv}) - v_{Oi}(\varphi_A / V_A)]\}$$ (2.49)

where ν_{Oi} =   the number of identical and independent active type I proton-acceptor

sites on the solute molecule, the increase in the solute's volume fraction solubility that

results from the hydrogen bonds formed between the proton-acceptor sites on the

solute and the proton-donor solvents. The summation extends to each type of proton

acceptor – solvent interaction present in solution. Each particular hydrogen-bond

interaction contributes to an increase in the solute's solubility, and is characterized by

the stability constant, K_{Oi}. The reason for the appearance of φ_A in equation 2.49 is that

when an ether or a carbonyl site of the solute is fixed by an OH proton on the solvent,

then this OH group is no longer available for a second solute molecule.

Finally, the last OH term describes the chemical contributions resulting from both

solute self-association and solute-solvent complexation. The solute molecule has both

proton-donor and proton-acceptor sites. Solute-solvent complexation may involve either

a proton-donor or proton-acceptor solvent. The OH chemical contribution

$$OH = \Sigma \nu_{OHi} \{ \ln[1 + K_{OHi}(\varphi_{solv} / V_{solv}) + K_{AA}(\varphi_A / V_A)] - \ln(1 + K_{AA} / V_A) \} \qquad (2.50)$$

where ν_{OHi} = is the number of identical and independent proton-donor sites of

        type i on the solute molecule

    K_{AA} = is the stability constant that governs the solute self-association in

        solution

Equations 2.44 – 2.50 are valid for solutes having a limited volume fraction solubility.

As noted earlier, the number of terms of the Mobile Order predictive equation

expression is determined by the number and types of functional groups on the solute

and solvent molecules. For example, in the case of an aromatic hydrocarbon solute

56

such as phenanthrene or acenaphthene dissolved in a self-associating alcohol solvent, the predictive expression would take the form of

$$\ln\varphi_A^{sat} = \ln a_A^{solid} - 0.5\varphi_{solv}(V_A/V_{solv} - 1) + 0.5\ln[\varphi_A + \varphi_{solv}(V_A/V_{solv})]$$
$$- \varphi_S^2 V_A(\delta_A' - \delta_S')^2(RT)^{-1} - r_{solv}\varphi_{solv}V_A/V_{solv} \qquad (2.51)$$

Only the A, B, D and F terms would appear in the predictive equation. One could then easily modify the predictive expression to a solvent incapable of self-association by

$$\ln\varphi_A^{sat} = \ln a_A^{solid} - 0.5\varphi_{solv}(V_A/V_{solv} - 1) + 0.5\ln[\varphi_A + \varphi_{solv}(V_A/V_{solv})]$$
$$- \varphi_S^2 V_A(\delta_A' - \delta_S')^2(RT)^{-1} \qquad (2.52)$$

by dropping the last term. Similar expressions can be obtained for systems containing solute-solvent complexation, or for systems involving solute complexation with a self-associating solvent.

To make solubility predictions by means of Mobile Order theory one must know the numerical values of all stability constants, K_O and K_{OH}, characterizing the hydrogen-bonds formed between the proton-acceptor and/or proton-donor sites on the dissolved solvent and the hydrogen-bond acidity/basicity sites on the solvent molecules. The actual numerical values do not necessarily correspond to values obtained from spectroscopic determinations, which are generally performed under a different set of experimental conditions. Spectroscopic measurements are normally made at high dilution in the presence of an inert hydrocarbon diluent. At high dilution the self-association of alcohol molecules is greatly suppressed, and the hydrogen-bonding characteristics of the OH group on the monomeric alcohol would be different than the

hydrogen-bonding characteristics of the "free" OH group at the terminal end of the hydrogen-bonded alcohol chain. Although the values of K_O and K_{OH} theoretically depend on the solute – solvent pair under consideration, Ruelle and coworkers[53] have shown that within a given class of solutes the values of K_O and K_{OH} deduced from experimental solubilities by means of the solubility equation do not vary appreciably within a given family of solvents. The authors found that average values of K_O = 170 cm^3 mol^{-1} and K_O = 110 cm^3 mol^{-1} satisfactorily described the ketone – alcohol and ester – alcohol hydrogen-bond equilibrium in liquid mixtures. Numerical values of K = 80 cm mol^{-1} have been reported for the weak hydrogen bonds between the π-electrons of aromatic rings and the proton-donor OH groups of water[54] K_O = 150 cm^3 mol^{-1} for hydrogen bonds between aliphatic nitriles and the proton-donor OH groups of alcohols[55], and of K_O = 3,500 cm^3 mol^{-1} for both aliphatic ether and aliphatic ester hydrogen-bond interactions with the proton-donor OH groups of water[55]. A few additional values are available in a compilation from studies devoted to partition coefficients[56, 57]. In the papers the authors stated that most stability constants were deduced from experimental solubility data for monofunctional solutes and monofunctional solvents. There is the possibility that one may have to make a few minor adjustments in the numerical values when applying the stability constants to mixtures containing multi-functional solute and solvent molecules. The authors claim that K_O and K_{OH} do not vary appreciably within a given class of solvents will be tested using the experimental monuron and diuron data in alcohol solvents that were measured as part of this thesis research.

Mobile Order Theory: Partition Coefficients

Mobile Order theory can also predict the partition coefficient describing the equilibrium distribution of a solute between two immiscible or partially miscible liquid phases. At equilibrium chemical potential, μ, of the solute species in the two phases must be equal. That is

$$\mu_{\text{solute, org}} = \mu_{\text{solute, aq}} \tag{2.53}$$

$$\mu^{\circ}_{\text{solute, org}} + RT\ln(X_{\text{solute, org}}\, Y_{\text{solute, org}}) = \mu^{\circ}_{\text{solute, aq}} + RT\ln(X_{\text{solute, aq}}\, Y_{\text{solute, aq}}) \tag{2.54}$$

For convenience one of the liquid phases is taken to be an aqueous solution saturated with an organic solvent (subscripted "aq"), and the second liquid phase is an organic solvent saturated with water (subscripted "org"). In equation 2.54 $\mu^{o}_{\text{solute,org}}$ is the standard-state chemical potential of the solute in the organic phase, $X_{\text{solute,org}}$ is the mole fraction of the solute in the organic phase, and $Y_{\text{solute,org}}$ is the activity coefficient of the solute at $X_{\text{solute,org}}$ defined according to some chosen standard-state conditions. The quantities $\mu^{o}_{\text{solute,aq}}$, $X_{\text{solute,aq}}$ and $Y_{\text{solute,aq}}$ have similar meanings in the aqueous phase. The same standard state is used to describe the solute in both the organic and aqueous phases, *i.e.*, $\mu^{o}_{\text{solute,org}} = \mu^{o}_{\text{solute,aq}}$. Equating the standard-standard chemical potentials, the condition of thermodynamic equilibrium becomes

$$X_{\text{solute, org}}\, Y_{\text{solute, org}} = X_{\text{solute, aq}}\, Y_{\text{solute, aq}} \tag{2.55}$$

Partitioning studies are normally performed at very low solute concentration. In the limit of infinite dilution, all of the different concentration units become co-linear. The mole fraction concentration of the solute in dilute solutions may be expressed as the product of the molar concentration, C_{solute}, and the molar volume of the solvent phase,

V_{org} and V_{aq}. Substitution into equation 2.55 gives the following mathematical relationship

$$C_{solute,org} V_{org} \gamma_{solute,org} = C_{solute,aq} V_{aq} \gamma_{solute,aq} \qquad (2.56)$$

where $C_{solute,org}$ and $C_{solute,aq}$ denote the molar concentrations (mol/liter) of the solute, and V_{org} and V_{aq} are the molar volumes (liters/mol) of the organic and aqueous phases. The partition coefficient of a solute is defined as

$$P = K = C_{solute,org} / C_{solute,aq} = (V_{aq} / V_{org})(\gamma_{solute,aq} / \gamma_{solute,org}) \qquad (2.57)$$

the ratio of the solute concentrations in the organic and aqueous phases. Multiplying the numerator and denominator of the molar concentration ratio by the molar volume of the supercooled liquid solute, the partition coefficient of the solute can also be expressed as

$$P = K = \varphi_{solute,org} / \varphi_{solute,aq} \qquad (2.58)$$

the ratio of the solute volume fraction concentrations in the organic and aqueous phases. For dilute solutions, the partition coefficient has the same value when it is expressed in terms of molar concentrations or in terms of volume fractions.

Mobile Order theory expresses the volume fraction solubility of a solute dissolved in water or in a neat organic solvent (see equation 2.43) in terms of a fluidity constant (A term), a configurational entropy of mixing contribution (B term), and up to four terms describing nonspecific cohesive interactions, solvent structuration, and hydrogen-bonding between the various proton-acceptor and proton-donor sites on the respective solute and solvent molecules. For liquid solutes, the fluidity term is set equal to zero. Using equation 2.43 to describe the volume fraction concentration of the solute in both the aqueous and organic phases, the following ln P predictive expression is obtained[58]:

60

$$\ln P = \Delta B + \Delta D + \Delta F + \Delta O + \Delta OH \tag{2.59}$$

where:

$$\Delta B = 0.5 V_{solute}[(1/V_{org}) - (1/V_{aq}) + 0.5\ln(V_{aq}/V_{org}) \tag{2.60}$$

$$\Delta D = -V_{solute}[(\delta_{solute} - \delta_{org})^2 - (\delta_{solute} - \delta_{aq})^2](RT)^{-1} \tag{2.61}$$

$$\Delta F = -V[(r_{org}/V_{org}) - (r_{aq}/V_{aq})] \tag{2.62}$$

$$\Delta O = \Sigma v_{Oi}\ln\{[1 + (K_{Oi,org}/V_{org})]/[1 + (K_{Oi,aq}/V_{aq})]\} \tag{2.63}$$

$$\Delta OH = \Sigma v_{OHi}\ln\{[1 + (K_{OHi,org}/V_{org})]/[1 + (K_{OHi,aq}/V_{aq})]\} \tag{2.64}$$

The fluidity term for crystalline solutes is mathematically eliminated from the log P

expression since the standard state of the solute is the same for both the organic and

aqueous phases.

Except for the solute molar volume, V_{solute}, and solute-solvent hydrogen-bond

stability constants, the quantities in equations 2.60 – 2.64 are solute independent. The

properties pertain to the "aqueous" and "organic" phases. When no solute-solvent

specific interaction takes place in either the organic or aqueous (*i.e.*, for chemical

substances incapable of self-association and forming solute – solvent complexes), the

predictive log P equation reduces to a very simple linear expression

$$\log P = intercept + slope\ V_{solute} \tag{2.65}$$

relating the logarithm of the organic solvent – water partition coefficient of a solute to its

molar volume. In the case of the octanol-water partition coefficient,

$$\log P_{ocatanol/water} = 0.41822 + 0.03328 V_{solute} \tag{2.66}$$

the numerical values of the intercept and slope are obtained by replacing the

structuration factor and the molar volume of each solvent phase by their numerical

values; that is, respectively, r_{aq} = 2.0 and V_{aq} = 18.1 cm^3 mol^{-1} for water and r_{org} = 1.275

and V_{org} =124.2 cm^3 mol^{-1} for the water-saturated 1-octanol solvent. Water has an

appreciable molar solubility in 1-octanol, which increases the structuration factor of the

organic phase from 1.0 (value for monofunctional alcohols) to 1.275 and decreases the

molar volume from 158.3 cm^3 mol^{-1} for pure 1-octanol to 124.2 cm^3 mol^{-1} for the water-

saturated 1-octanol phase. The simple relationship is consistent published

experimental observations that have shown a linear correlation between log $P_{octanol/water}$

and V_{solute} or any related property (surface area, parachor, molar refraction, connectivity

indices, *etc*.)[58,59,60,61,62,63,64].   To date Mobile Order theory has been used successfully to

describe the 1-octanol/water,[65,56] perfluoro-methylcyclohexane/toluene[66]

perfluorohexane/benzene[66], chloroform/water[57] diethyl ether/water[57], carbon

tetrachloride/water[57], hexane/water [57,65] and benzene/water[57] partitioning behavior of a

large number of organic solutes of varying polarity and hydrogen-bonding capability.

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CHAPTER 3

EXPERIMENTAL METHODOLOGY

The solutes chosen for study can be divided into three categories, polycyclic aromatic hydrocarbons (PAHs), pesticides and organometallics. The solutes were either recrystallized from methanol before use or used as received from the manufacturer. Solvents were stored over molecular sieves and ranged from simple alkanes to more complex, substituted substances. Solutions were prepared with solute and excess amounts of solvents and placed in amber bottles in a 25°±0.1°C water bath and allowed to equilibrate for a minimum of three days. Verification of equilibrium was ascertained from various measurements after several days and from supersaturation by pre-equilibrating solutions at higher temperatures.

A series of eight standard solutions were prepared containing known volumes of the solute and diluted with either methanol or 2-propanol. The absorbance was measured and the Beer-Lambert Law

$$A = \varepsilon \cdot b \cdot C \tag{3.1}$$

was used to calculate the molar absorptivity (ε) for all eight solutions thus creating a working curve. The variable b, the path length of the light as it goes through the solution, is 1.0 cm. Concentration and molar absorptivity are directly proportional. Theoretically, ε should be constant, but in practice it varies due to deviations that will be discussed later. Concentrations of the standard solutions and their respective ε values are given in tables 3.1 – 3.9 at the end of this chapter. Tables 3.1 – 3.9 also give the analysis wavelengths. For monuron and diuron two sets of analysis wavelengths were

used. Monuron and diuron solubilities in the alkane solvents were measured at the

lower analysis wavelengths. Solubilities in all other solvents were determined at the

larger analysis wavelengths. Careful examination of the numerical entries in tables 3.1

– 3.9 reveals that, as the concentration increased the molar absorptivity decreased

slightly in the case of the biphenyl, phenanthrene, hexachlorobenzene, diuron and

monuron (at an analysis wavelength of 250 nm) standard solutions. The slight

decrease in ε was not visually noticeable on the absorbance vs. concentration plots. A

squared correlation coefficient of not less than $r^2 = 0.9995$ was obtained in all cases.

Aliquots of saturated solute-solvent mixtures were transferred to tared volumetric

flasks, usually 50 ml, using a syringe to determine the mass of sample analyzed, and

then diluted to the mark with methanol or 2-propanol. Both alcohol diluents are optically

transparent at the analysis wavelengths used. 2-Propanol was used as the diluent for

the larger alkane solvents studied because larger alkanes are not completely miscible

with methanol. Absorbance measurements were recorded. At times, further dilutions

were necessary to ensure measured values fell within the working curve defined by the

standard solutions. Concentrations were determined using the Beer-Lambert Law

absorbance vs. concentration working curve for the standard solutions.

Experimental molar concentrations were converted to (mass/mass) solubility

fractions by multiplying the molar mass of the solute, the volume of the volumetric flask,

and the dilution factor, if any. This value was then divided by the mass of the saturated

solution being analyzed. Mole fraction solubilities were then calculated using the

(mass/mass) solubility fraction using the molar masses of the solute and solvent[1].

Instrumentation

The Bausch and Lomb Spectronic 2000 was used to collect the molecular UV/Vis data for each solute. This instrument is a double beam, in-time spectrophotometer whereby a rotating mirror or "chopper" is used to separate the beam. The "chopper" is made up of pie shaped segments, one-half of which are mirrored, half transparent. Half of the time the beam travels from the monochrometer to the reference cell and the other half from the monochrometer to the sample cell. The beams are recombined by another mirror and reflected towards the photomultiplier tube (PMT), where a change in P_o and P between the two beams is detected and that change is displayed on the readout device.
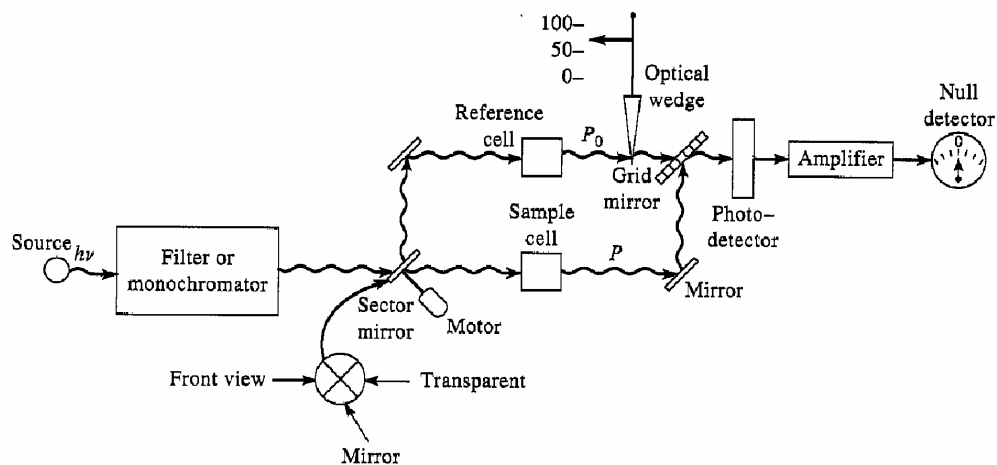
Figure 3.1: Block diagram of a typical double beam UV/Vis spectrophotometer. From Principles of Instrumental Analysis 5th edition by SKOOG. © 1998. Reprinted with permission of Brooks/Cole, a division of Thompson Learning: www.thomsonrights.com. Fax 800-730-2215.

69

There are two types of radiation sources on this instrument, a deuterium lamp used for measurement in the ultraviolet region, and a tungsten filament bulb for measurements in the visible region. The reference and sample cells are made of 1-cm^2 square quartz cuvettes. Quartz is used because it does not absorb light in the visible or ultraviolet regions and therefore will not interfere with our measurements. The radiation beam is filtered by a monochrometer, and detected with a photomultiplier tube. The surface (cathode end) of the PMT emits electrons when exposed to radiation. These electrons in turn strike another surface (called a dynode) more positive than the first, releasing even more electrons. The process continues until approximately 10^6 electrons have been produced. The electrons are then collected at the anode end of the PMT and the current is amplified, measured and the data sent to a readout device.

Double beam instruments have an advantage over single beam instruments in that they can compensate for short-term fluctuations in the radiation output source, drift in the PMT and amplifier, and wide variations of source intensity with wavelength. They also offer continuous recording of transmittance or absorbance[2].

Beer-Lambert Law

Molecular absorption spectroscopy is used to quantitatively determine the concentration of various organic and inorganic species in the saturated solutions. Absorption is normally measured in the ultraviolet/visible spectrum between 160 – 780 nanometers. The Beer-Lambert Law was used to calculate concentrations of dilute solutions. For monochromatic radiation, the Beer-Lambert Law states that the absorbance of a

species is proportional to the pathlength (b) through a medium and the concentration (C) of the species[2].

$$A = a \cdot b \cdot C \qquad (3.2)$$

The constant a, is a proportionality constant whose units depend on b and C. When b is in units of centimeters and concentration in molarity, a is substituted with the molar absorptivity, ε whose units become $L \cdot mol^{-1} \cdot cm^{-1}$. Concentration of the absorbing species is linear with respect to the absorbance, A.

$$A = -\log T = \log(P_o / P) = \varepsilon \cdot b \cdot C \qquad (3.3)$$

A = absorbance

T = transmittance

P_o = power/intensity of transmitted beam

P = power/intensity of incident beam

Absolute values of P_o and P are difficult to measure in the laboratory. Difficulties arise from the fact that the species being analyzed is in a container, usually a transparent cell where reflections at the air/wall and wall/solution interfaces attenuate the beam. Also, scattering of the incoming radiation caused by large molecules found in the beam's path and absorption by the walls of the container distort this value. Such problems are overcome by measuring the absorbance or transmittance of the neat solvent in the cuvette, and then referencing all solution absorbance measurements back to the solvent reference blank.

$$T = P_{solution} / P_{Solvent} = P / P_o \qquad (3.4)$$

71

$$A = \log(P_{solvent} / P_{solution}) = \log(P_o / P) \tag{3.5}$$

Beer-Lambert Law: Derivation[a]

Assume a block of absorbing matter (solid, liquid, gas) where P_o represents the light going into the block perpendicular to the surface, and P is the decrease in the amount of light exiting the block. Along the length of the material b, P_o encounters n number of absorbing species. A cross-section of this block would have an area S and a thickness described by dx. This cross-section contains dn absorbing species. This is where absorption would occur. The quantity dS represents the sum of the area where absorption would occur. The probability that the incoming light would encounter an area with a light absorbing species is dS/S. The fraction of light absorbed by the species in this area is dP_x/P where P_x is the power of the beam entering the section and dP_x is the quantity of light absorbed in the section, represents the average probability of photon capture in the area by the absorbing species[3].

$$-dP_x / P_x = dS / S = a \cdot dn \tag{3.6}$$

where a is the proportionality constant called the capture cross-section. Integration of both sides of equation 3.6 gives

$$-\int_{P_o}^{P} dP_x / P_x = \int_{0}^{x} a \cdot dn / S \tag{3.7}$$

Evaluation of the integrals yields the following:

$$-\ln(P/P_o) = an/S \tag{3.8}$$

Converting to base 10 logarithms and inverting the first half of the equation to change the sign yields:

$$\log(P_o/P) = an/2.303S \tag{3.9}$$

The area of the cross-section, S, can be expressed in volume (V) in cm^3 and length (b) in cm.

$$S = \frac{V}{b}cm^2 \tag{3.10}$$

Substituting Eqn 3.10 into 3.9:

$$\log(P_o/P) = anb/2.303V \tag{3.11}$$

As it stands, in Eqn 3.11 n/V has units of particles/cm^3. To convert this to molarity:

$$\# \text{ of moles} = n\,particles/6.023x10^{23} \tag{3.12}$$

$$C = [n\,moles/6.023x10^{23}] \cdot [(1000\,cm^3)/(V\,cm^3)] = 1000n/6.023x10^{23}\,mol/L \tag{3.13}$$

$$\log(P_o/P) = (6.023x10^{23}\,abC)/(2.303 \times 1000) \tag{3.14}$$

Collecting all the variables and setting them equal to ε:

$$\varepsilon = (6.02x1023 \cdot a)/(2.303x1000) \tag{3.15}$$

Making all the proper substitutions, we arrive at Eqn 3.3, the Beer-Lambert Law:

$$A = \log(P_o/P) = \varepsilon \cdot b \cdot C$$

For mixtures containing more than one light absorbing species, the Beer-Lambert law still applies. Absorbance for this type of system is given by the following:

$$A_{total} = A_1 + A_2 + A_3 + ... = \varepsilon_1 bC_1 + \varepsilon_2 bC_2 + \varepsilon_3 bC_3 + ... \qquad (3.16)$$

Beer-Lambert Law: Limitations[b]

Absorbance is generally linearly related to the path length (b) and concentration, although there are exceptions. These exceptions are due to the real limitations and instrumental limitations to the Beer-Lambert Law. Real limitations are associated with the concentration of the analytes. The Beer-Lambert Law works best with analytes of low concentration, usually lower than 0.1M. Above 0.1M there is a decrease in the average distance between the molecules responsible for absorption. This causes each molecule to affect the charge distribution of its neighboring molecules, affecting their ability to absorb at a given wavelength. The same affect is seen in mixtures with low concentrations of the absorbing species and high concentrations of other species, particularly electrolytes due to the electrostatic interactions resulting from the close proximity of the molecules. The effect can be reduced by diluting the solution.

Deviations from the Beer-Lambert Law also occur because ε is dependant on the refractive index (n) of the medium[4] through which that light passes. Changes in concentration can alter the refractive index of a solution. To remedy this problem ε is

replaced by $\varepsilon \cdot n / (n^2+2)^2$. Normally at concentrations below 0.1 M, this correction is not significant.

Chemical deviations from the Beer-Lambert Law arise from interactions between the solvent and the light absorbing species. There can be dissociation, association or the formation of a product with a different absorption wavelength if the species interact with each other. One must take care when choosing solvents to prevent these types of interactions.

Instrumental deviations are due in part to the polychromatic nature light. Only true monochromatic light adheres to the Beer-Lambert Law. Unfortunately, true monochromatic light is not possible because instruments with a continuum source form a band of wavelengths around a desired one.

Assuming a beam of light contains two wavelengths, λ_1 and λ_2, and the power of the entering beam is P' + P", and exiting beam is P'_o + $P"_o$ then,

$$A_1 = \log(P'_o / P') = \varepsilon_1 bC \tag{3.17}$$

or

$$P'_o / P' = 10^{\varepsilon_1 b C} \tag{3.18}$$

$$P' = P'_o \cdot 10^{-\varepsilon_1 b C} \tag{3.19}$$

The same three equations can be generated for P".

The measured absorbance is:

$$A_{measured} = \log(P'_o + P"_o)/(P' + P") \tag{3.20}$$

Substituting P' for P" and rearranging:

$$A_{measured} = \log(P'_o + P''_o) - \log(P'_o 10^{-\varepsilon_1 bC} + P''_o 10^{-\varepsilon_1 bC}) \qquad (3.21)$$

If $\varepsilon_1 = \varepsilon_2$, then $A_{measured} = \varepsilon_1 bC$ and the Beer-Lambert Law holds. However, if $\varepsilon_1 \neq \varepsilon_2$, then the concentration and absorbance are no longer linear and one cannot use the Beer-Lambert Law to calculate concentration. As long as the chromaphore's absorption does not change over the changing wavelength there is no appreciable deviation. Usually, the greater the difference between the two molar absorptivities the greater the deviation will be.

Stray radiation is another factor in instrumental deviations. The radiation exiting the monochrometer is sometimes contaminated with a small amount of stray radiation. Scattering and reflections from surfaces within the instrument can reach the detector. This radiation may not have passed through the sample and will vary in wavelength from the source wavelength. At high concentrations and longer path lengths, stray radiation will cause deviations from linearity[5]. Generally, instrumental deviations lead to absorbencies that are smaller than theoretical values and to negative absorbance errors[6].

Table 3.1 Representative Absorbance Data for Standard Solutions of Biphenyl
Measured at 250 nm

Molarity	Absorbance	ε (L• mol^{-1}• cm^{-1})
2.073×10^{-5}	0.347	1.674×10^4
3.109×10^{-5}	0.518	1.666×10^4
4.146×10^{-5}	0.686	1.655×10^4
5.183×10^{-5}	0.851	1.642×10^4
6.219×10^{-5}	1.021	1.642×10^4
7.256×10^{-5}	1.189	1.639×10^4
8.292×10^{-5}	1.351	1.629×10^4
9.329×10^{-5}	1.515	1.624×10^4
1.037×10^{-4}	1.680	1.620×10^4

Verification of Beer-Lambert Law for Biphenyl

$y = 16059x + 0.0187$
$R^2 = 1$
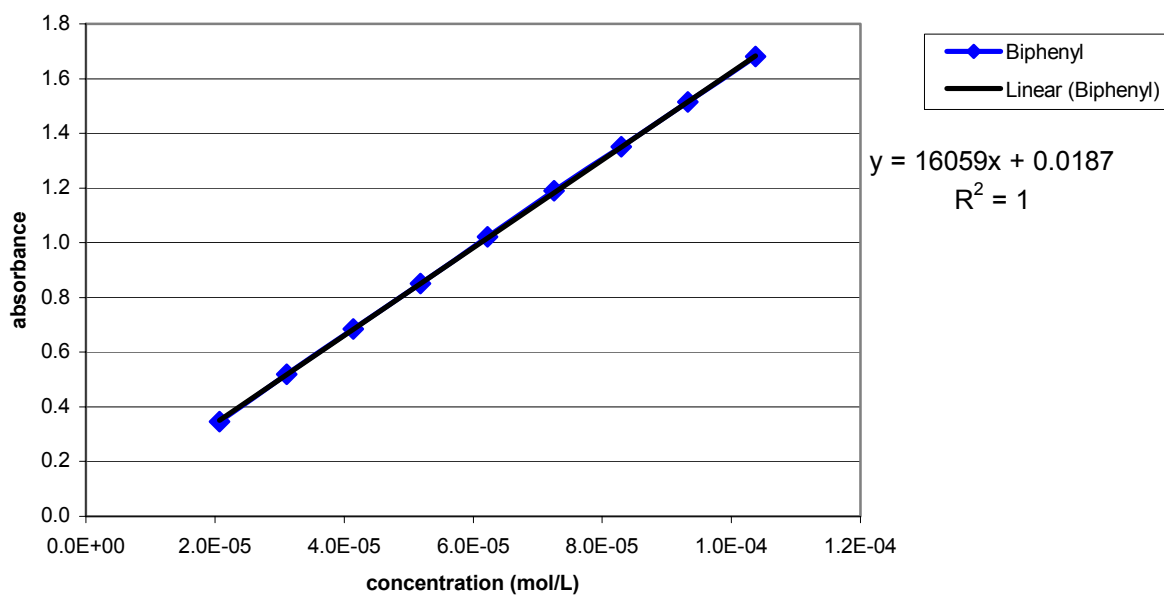
Table 3.2 Representative Absorbance Data for Standard Solutions of Acenaphthene

Measured at 289 nm

Molarity	Absorbance	ε (L$\bullet$ mol$^{-1}\bullet$ cm^{-1})
6.760×10^{-5}	0.432	6.390×10^3
1.014×10^{-4}	0.648	6.390×10^3
1.352×10^{-4}	0.868	6.420×10^3
1.690×10^{-4}	1.083	6.408×10^3
2.028×10^{-4}	1.282	6.321×10^3
2.366×10^{-4}	1.506	6.365×10^3
2.704×10^{-4}	1.699	6.283×10^3

Verification of Beer-Lambert Law for Acenaphthene

$y = 6267x + 0$

$R^2 = 1$
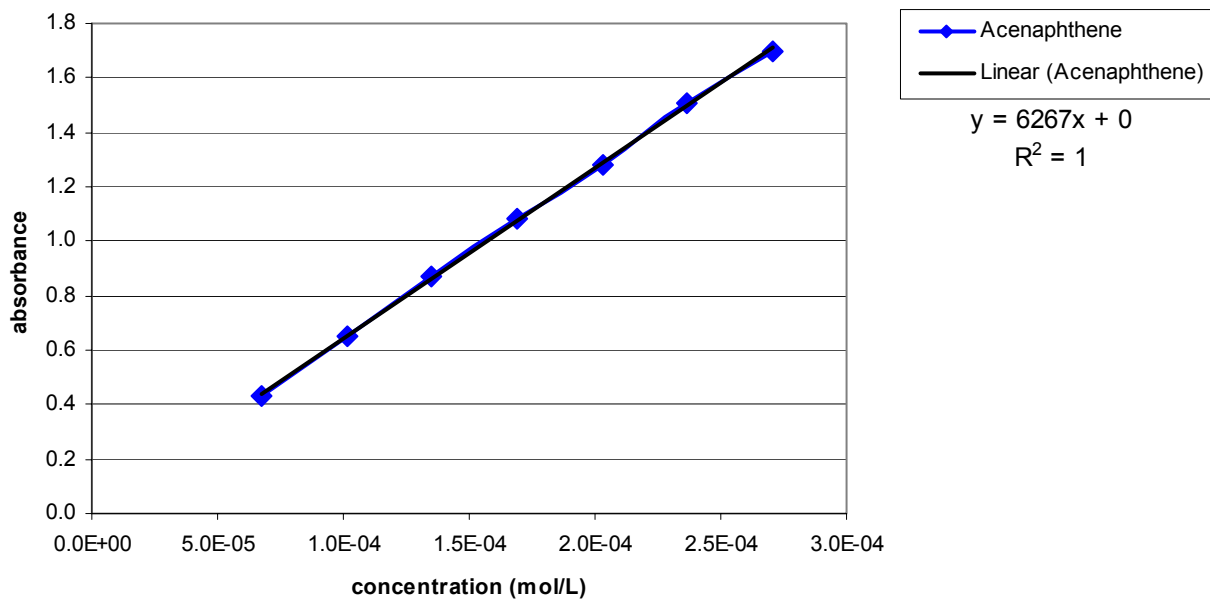
Table 3.3 Representative Absorbance Data for Standard Solutions of Phenanthrene

Measured at 346 nm

Molarity	Absorbance	ε (L• mol^{-1}• cm^{-1})
2.494×10^{-3}	0.536	2.149×10^{2}
3.325×10^{-3}	0.701	2.108×10^{2}
4.156×10^{-3}	0.870	2.093×10^{2}
4.988×10^{-3}	1.017	2.039×10^{2}
5.819×10^{-3}	1.175	2.019×10^{2}
6.650×10^{-3}	1.301	1.957×10^{2}
7.482×10^{-3}	1.433	1.915×10^{2}
8.313×10^{-3}	1.560	1.877×10^{2}

Verification of Beer-Lambert Law for Phenanthrene

$y = 175.84x + 0.12$

$R^2 = 1.00$
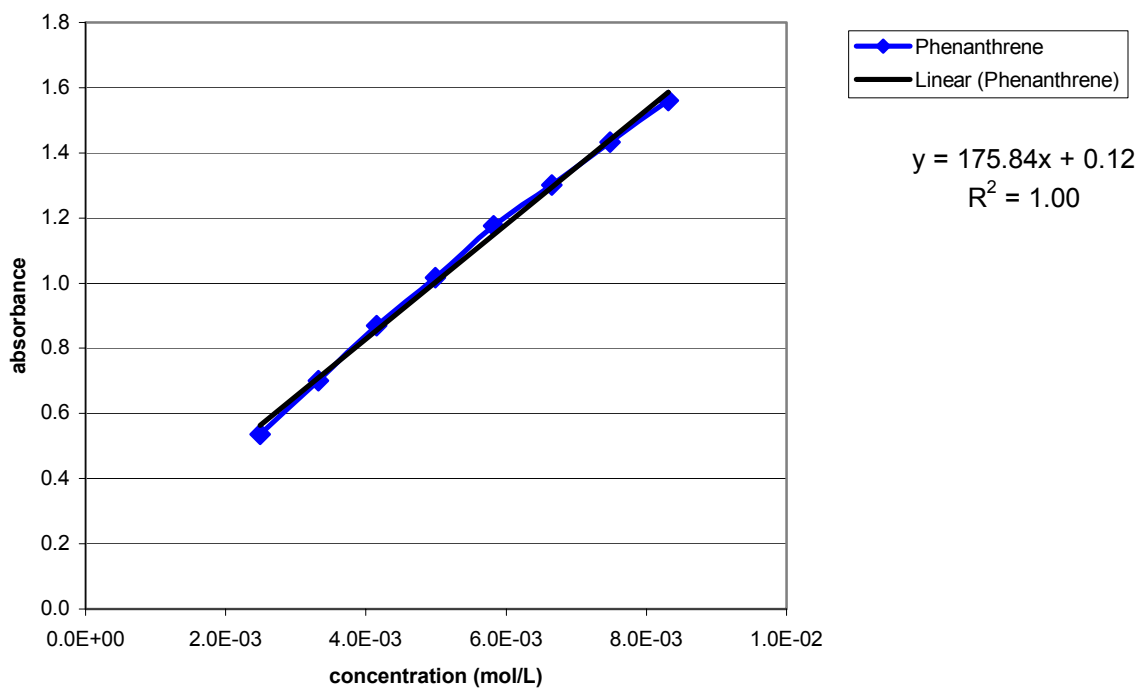
Table 3.4 Representative Absorbance Data for Standard Solutions of Ferrocene

Measured at 440 nm

Molarity	Absorbance	ε (L• mol^{-1}• cm^{-1})
3.294×10^{-3}	0.307	9.320×10^{1}
4.393×10^{-3}	0.408	9.288×10^{1}
5.491×10^{-3}	0.515	9.379×10^{1}
6.589×10^{-3}	0.609	9.243×10^{1}
7.687×10^{-3}	0.713	9.275×10^{1}
8.785×10^{-3}	0.810	9.220×10^{1}
9.883×10^{-3}	0.921	9.319×10^{1}
1.098×10^{-2}	1.016	9.253×10^{1}

Verification of Beer-Lambert Law for Ferrocene

$y = 92.343x + 0.0033$

$R^2 = 0.9998$
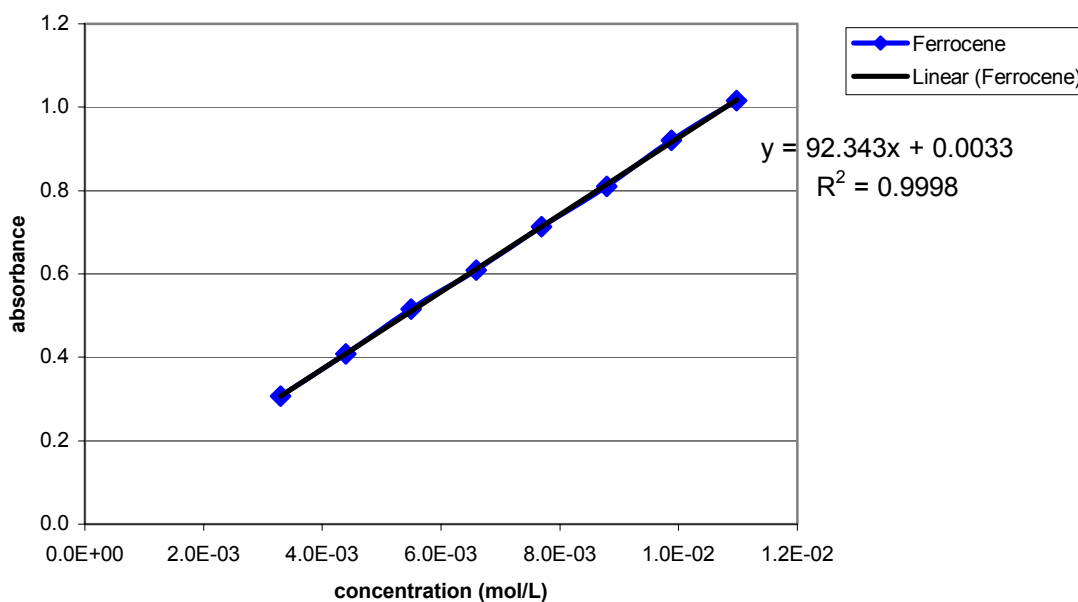
Table 3.5 Representative Absorbance Data for Standard Solutions of

Hexachlorobenzene Measured at 291 nm

Molarity	Absorbance	ε (L$\cdot$ mol$^{-1}\cdot$ cm^{-1})
1.414×10^{-3}	0.325	2.297×10^{2}
1.768×10^{-3}	0.405	2.291×10^{2}
2.122×10^{-3}	0.481	2.267×10^{2}
2.475×10^{-3}	0.558	2.255×10^{2}
2.829×10^{-3}	0.634	2.241×10^{2}
3.182×10^{-3}	0.709	2.228×10^{2}
3.536×10^{-3}	0.785	2.220×10^{2}

Verification of Beer-Lambert Law for Hexachlorobenzene

$y = 216.24x + 0.0215$
$R^2 = 0.9999$
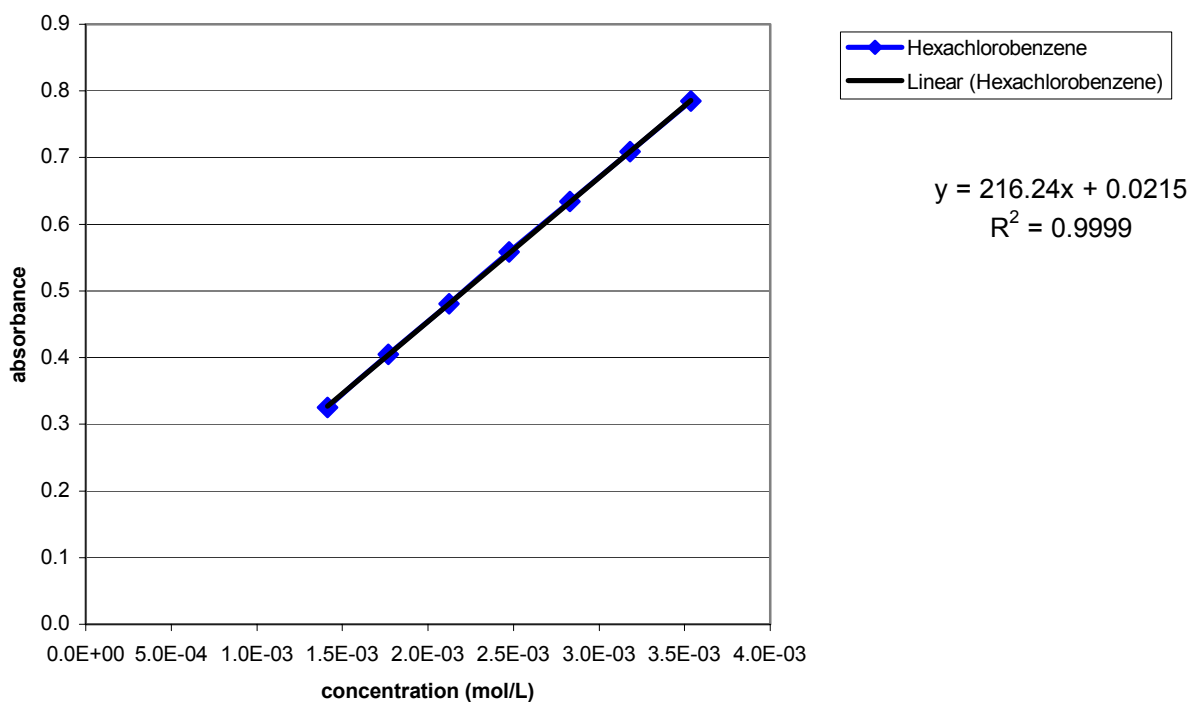
Table 3.6 Representative Absorbance Data for Standard Solutions of Diuron Measured at 254 nm

Molarity	Absorbance	ε (L• mol^{-1}• cm^{-1})
1.833×10^{-5}	0.384	2.095×10^4
2.749×10^{-5}	0.571	2.077×10^4
3.665×10^{-5}	0.760	2.074×10^4
4.582×10^{-5}	0.941	2.054×10^4
5.498×10^{-5}	1.114	2.026×10^4
6.414×10^{-5}	1.293	2.016×10^4
7.331×10^{-5}	1.464	1.997×10^4
8.247×10^{-5}	1.630	1.976×10^4
9.163×10^{-5}	1.794	1.958×10^4

Verification of Beer-Lambert Law for Diuron @ 254 nm

y = 19239x + 0.0479
R^2 = 0.9995
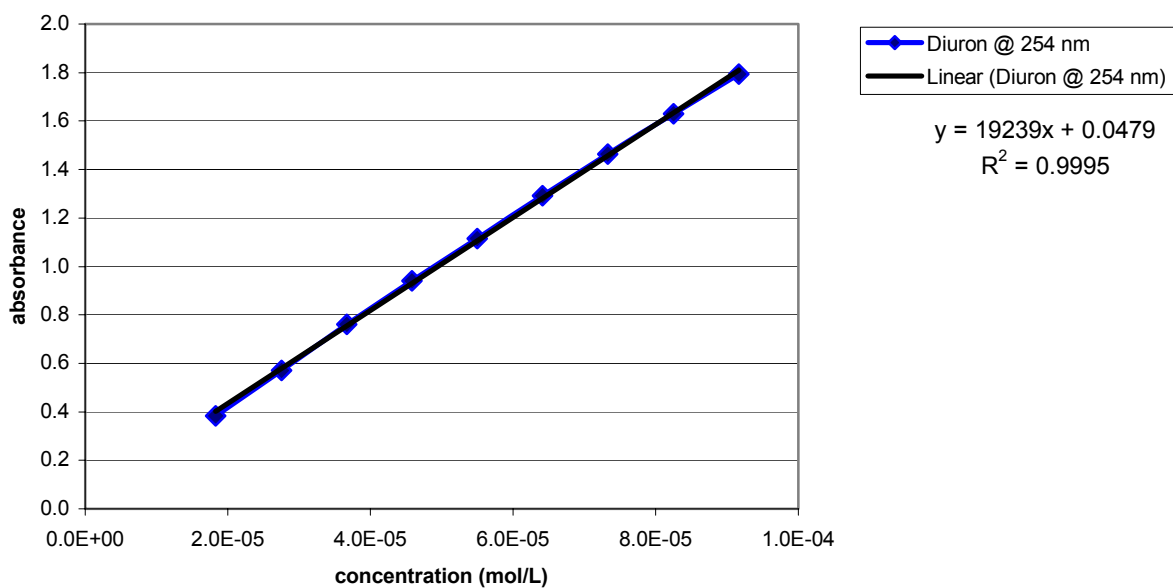
Table 3.7 Representative Absorbance Data for Standard Solutions of Diuron Measured at 286 nm

Molarity	Absorbance	ε (L• mol^{-1}• cm^{-1})
1.833×10^{-4}	0.257	1.402×10^{3}
2.749×10^{-4}	0.390	1.419×10^{3}
3.665×10^{-4}	0.511	1.394×10^{3}
4.582×10^{-4}	0.636	1.388×10^{3}
5.498×10^{-4}	0.765	1.391×10^{3}
6.414×10^{-4}	0.889	1.386×10^{3}
7.331×10^{-4}	1.016	1.386×10^{3}
8.247×10^{-4}	1.141	1.384×10^{3}
9.163×10^{-4}	1.260	1.375×10^{3}
1.008×10^{-3}	1.384	1.373×10^{3}
1.100×10^{-3}	1.507	1.370×10^{3}

Verification of Beer-Lambert Law for Diuron @ 286 nm

$y = 1362.3x + 0.013$
$R^2 = 0.9999$

Table 3.8 Representative Absorbance Data for Standard Solutions of Monuron

Measured at 250 nm

Molarity	Absorbance	ε (L$\cdot$mol$^{-1}\cdot$cm^{-1})
1.936×10^{-5}	0.399	2.061×10^{4}
2.904×10^{-5}	0.593	2.042×10^{4}
3.873×10^{-5}	0.788	2.035×10^{4}
4.841×10^{-5}	0.982	2.029×10^{4}
5.809×10^{-5}	1.177	2.026×10^{4}
6.777×10^{-5}	1.357	2.002×10^{4}
7.745×10^{-5}	1.540	1.988×10^{4}

Verification of Beer-Lambert Law for Monuron @ 250 nm

$y = 19698x + 0.023$
$R^2 = 0.9998$

Table 3.9 Representative Absorbance Data for Standard Solutions of Monuron

Measured at 278 nm

Molarity	Absorbance	ε (L$\cdot$ mol$^{-1}\cdot$ cm^{-1})
2.579×10^{-4}	0.306	1.187×10^{3}
3.869×10^{-4}	0.460	1.189×10^{3}
5.159×10^{-4}	0.612	1.186×10^{3}
6.449×10^{-4}	0.766	1.188×10^{3}
7.738×10^{-4}	0.908	1.173×10^{3}
9.028×10^{-4}	1.070	1.185×10^{3}
1.032×10^{-3}	1.215	1.177×10^{3}
1.161×10^{-3}	1.376	1.185×10^{3}
1.290×10^{-3}	1.524	1.181×10^{3}

Verification of Beer-Lambert Law for Monuron @ 278 nm

$y = 1179.5x + 0.0024$
$R^2 = 0.9999$
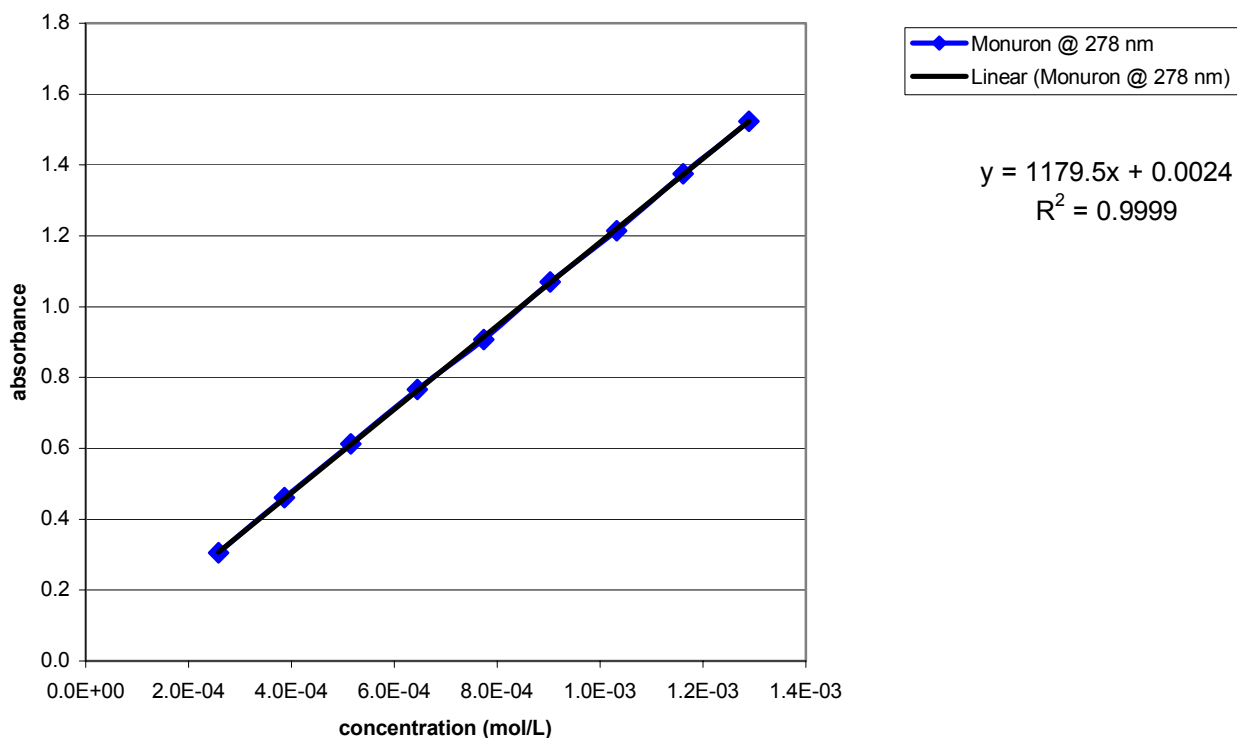
Table 3.10 List of Solvents Used in the Solubility Determinations

Chemical	Manufacturer	Purity
n-hexane	Aldrich	99%
n-heptane	Aldrich	HPLC
n-octane	Aldrich	99+%, anhydrous
n-nonane	TCI	99+%
n-decane	TCI	99+%
n-hexadecane	Aldrich	99%
cyclohexane	Aldrich	HPLC
cyclooctane	Lancaster Synthesis	99+%
cyclooctane	Aldrich	99+%
methylcyclohexane	Aldrich	99+%, anhydrous
2,2,4-trimethylpentane	Aldrich	HPLC
tert-butylcyclohexane	Aldrich	99+%
dibutyl ether	Aldrich	99%
methanol	Aldrich	99.9%
ethanol	Aaper Alcohol and Chemical Co.	absolute
1-propanol	Aldrich	99+%, anhydrous
2-propanol	Aldrich	99+%, anhydrous
1-butanol	Aldrich	HPLC 99.8+%
2-butanol	Aldrich	99%, anhydrous
1-pentanol	Aldrich	99+%
2-pentanol	Acros	99+%

Table 3.10 cont'd

Chemical	Manufacturer	Purity
1-hexanol	Alfa Aesar	99+%
1-heptanol	Alfa Aesar	99+%
1-octanol	Aldrich	99%, anhydrous
1-decanol	Alfa Aesar	99+%
2-methyl-1-propanol	Aldrich	99+%, anhydrous
2-methyl-2-propanol	Arco Chemical Co.	99+%
2-methyl-2-butanol	Acros	99+%
3-methyl-1-butanol	Aldrich	99+%, anhydrous
2-methyl-1-pentanol	Aldrich	99%
4-methyl-2-pentanol	Acros	99+%
2-ethyl-1-hexanol	Aldrich	99+%
cyclopentanol	Aldrich	99%
2,2,2-trifluoroethanol	Aldrich	99+%
ethylene glycol	Aldrich	99.8%, anhydrous
tetrahydrofuran	Aldrich	99.9%, anhydrous
1,4-dioxane	Aldrich	99.8%, anhydrous
methyl *tert*-butyl ether	Arco	99.9+%
1-chlorobutane	Sigma-Aldrich	HPLC, 99.5%
1-chlorohexane	Aldrich	99%
1-chlorooctane	Aldrich	99%
dichloromethane	Aldrich	99.8%, anhydrous

Table 3.10 cont'd

Chemical	Manufacturer	Purity
tetrachloromethane	Aldrich	HPLC, 99.9+%
chloroform	Aldrich	HPLC, 99.9%
1,2-dichloroethane	Aldrich	HPLC, 99.8%
chlorocyclohexane	Aldrich	99%
methyl acetate	Aldrich	99.5%, anhydrous
ethyl acetate	Aldrich	HPLC, 99.9%
butyl acetate	Aldrich	HPLC, 99.7%
benzene	Aldrich	HPLC, 99.9+%
toluene	Aldrich	99.8%, anhydrous
ethylbenzene	Aldrich	99.8%, anhydrous
chlorobenzene	Aldrich	HPLC, 99.9+%
acetonitrile	Aldrich	99.8%, anhydrous
aniline	Aldrich	ACS Reagent, 99.5+%
2-propanone	Aldrich	HPLC, 99.9+%
2-butanone	Aldrich	HPLC, 99.5+%
cyclohexanone	Aldrich	99.80%
o-xylene	Aldrich	HPLC, 99%
m-xylene	Aldrich	99+%, anhydrous
p-xylene	Aldrich	99+%, anhydrous
dimethyl sulfoxide	Aldrich	HPLC, 99.9%

Table 3.11 List of Solutes Used in the Solubility Determinations

Chemical	Manufacturer	Purity
monuron	Aldrich	99% (used as received)
ferrocene	Aldrich	97% (used as received)
phenanthrene	Aldrich	98% (recrystallized from methanol)
acenaphthene	Aldrich	98% (recrystallized from methanol)
biphenyl	Aldrich	99% (recrystallized from methanol)
diuron	Sigma	98% (used as received)
hexachlorobenzene	Aldrich	99% (recrystallized from methanol)

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CHAPTER 4

INTERPRETATION OF DATA

As part of the thesis research solubilities of seven organic compounds were

studied in a wide range of organic solvents of varying polarity and hydrogen bonding

characteristics. Each solute was selected for its individual properties in order to fully

investigate different aspects of mobile order theory. The pesticides monuron, diuron,

and hexachlorobenzene were selected for their functional groups allowing for

differences in polarity and hydrogen bonding ability. Moreover, hexachlorobenzene was

used as a pesticide in the United States until the mid-1960's. Today, it is not

commercially produced, but is still of interest because it is a byproduct in certain

chemical manufacturing areas. Hexachlorobenzene is a polychlorinated, non-polar

molecule that does not exhibit hydrogen-bonding.   At the time this work was

undertaken very little data existed for organometallics, hence the decision to study

ferrocene solubilities. The polycyclic aromatic hydrocarbons (PAH's) acenaphthene,

phenanthrene, and biphenyl were chosen because they are incapable of hydrogen-bond

formation, and because of their environmental importance.

To properly report experimental solubility data, consistency in data is extremely

important. Mole fraction solubilities were measured in 26 – 49 different organic solvents

with an average of 4 - 8 independent determinations for each solvent. Analysis of

replicate samples showed that the reproducibility was to within ± 2%. Attainment of

equilibrium was verified by performing replicate measurements on selected samples

after an additional 2-3 days equilibration time, and by approaching equilibrium from

supersaturation by pre-equilibrating the solutions at a slightly higher temperature. Replicate measurements verified that equilibrium had been attained in all cases.

Pesticide Solutes: Monuron, Diuron and Hexachlorobenzene

For convenience the solubility data will be discussed according to solute classification, beginning first with the three pesticide solutes (monuron, diuron, and hexachlorobenzene), followed by the three polycyclic aromatic hydrocarbon solutes (biphenyl, acenaphthene and phenanthrene) and finally by the single organometallic solute (ferrocene). The experimental mole fraction solubilities of monuron, diuron and hexachlorobenzene are tabulated in tables 4.1 and 4.2. A search of the chemical literature for experimental monuron, diuron and hexachlorobenzene solubility data in neat organic solvents using "Scifinder Scholar" did not turn up any relevant references. To my knowledge there is no published experimental solubility data for these three pesticide solutes dissolved in neat organic solvents.

Mobile Order Theory is one of the few available solution models capable of describing the solubility of solutes in a wide range of solvents. In the case of monuron and diuron, both solutes contain an –NC(O)NH– moiety that can be act as a hydrogen-bond acid or a hydrogen-bond base (due to the lone pair of electrons on the oxygen and nitrogen atoms) depending upon the surrounding solvent molecules. The measured mole fraction solubility data in table 4.1 reveals that both solutes are more soluble in dibutyl ether, χ_A^{sat} = 0.001383 and χ_A^{sat} = 0.0005037 for monuron and diuron, respectively, than in saturated hydrocarbons, χ_A^{sat} (n-octane) = 0.00006571 and χ_A^{sat} (n-nonane) = 0.00007811 for monuron[1], and χ_A^{sat} (n-octane) = 0.00002934 and χ_A^{sat} (n-

nonane) = 0.00003615 for diuron[2]. One would assume based on these observations that the introduction of the ether functional group causes the –NC(O)NH– group to behave as a hydrogen-bond acid, interacting with the lone electron pairs on the oxygen atom of ether forming an association complex. The assumption though is not correct as will be shown shortly. Mobile Order theory predicts the mole fraction solubility of monuron in dibutyl ether to within 28 % without introducing any solute-solvent complexes.

Predictive application of Mobile Order theory is relatively straightforward, and a computation example will be given to illustrate the calculation of the modified solubility parameter of monuron. First the activity of solid monuron is calculated using equation 2.35

$$\ln(a_A^{solid}) = -\Delta H^{fus}(T_{MP} - T)(RTT_{MP})^{-1}$$

$$\ln a_A^{solid} = -29460(447.6 - 298.15)/(8.314 \times 298.15 \times 447.6)$$

$$\ln a_A^{solid} = -3.9682$$

$$a_A^{solid} = 0.01891$$

and published enthalpy of fusion data, ΔH^{fus} = 29.460 kJ/mole, at the normal melting point temperature, T_{MP} = 447.6 K[3]. The two heat capacity terms were set equal to zero because heat capacity data for subcooled liquid monuron could not be found. Values for ΔH^{fus} and T_{MP} for the other six solutes studied are also available in published literature and are listed in table 4.3. Next, the experimental mole fraction solubility of

monuron in n-hexane, χ_A^{sat} = 0.00005489 is converted into the volume fraction solubility (φ_A^{sat})

$$\varphi_A^{sat} = (0.00005489)(152.8)/[(0.00005489)(152.8) + (1 - 0.00005489)(131.51)]$$
$$= 0.000063776$$

and then substituted directly into equation 2.51, along with the molar volume and modified solubility parameter of n-hexane:

$$\ln\varphi_A^{sat} = \ln a_A^{solid} - 0.5\varphi_{solv}(V_A / V_{solv} - 1) + 0.5\ln[\varphi_A + \varphi_{solv}(V_A / V_{solv})]$$
$$- \varphi_S^2 V_A(\delta_A' - \delta_S')^2(RT)^{-1} - r_{solv}\varphi_{solv}V_A / V_{solv}$$

$$\ln 0.000063776 = \ln 0.01891 - 0.5(1.0 - 0.000063776)[(152.8/131.51) - 1.0]$$
$$+ 0.5\ln[0.000063776 + (1.0 - 0.000063776)(158.2/131.51)$$
$$- (1.0 - 0.000063776)^2(152.8)(\delta_A' - 14.56)^2(8.314\times298.15)^{-1}$$

The above equation is solved and yields a value of for the modified solubility parameter of monuron, δ_A' = 24.30 MPa$^{1/2}$, which perfectly describes the solute's mole fraction solubility in n-hexane. The $r_{solv}\varphi_{solv}V_A / V_{solv}$ term is excluded from the calculation because the solute is not dissolved in a self-associating solvent. The modified solubility parameter computations were repeated using the experimental solubility data for monuron dissolved in n-heptane ($\chi_A^{sat\ t}$ = 0.00005565 to give δ_A' = 24.38 MPa$^{1/2}$) and in n-octane (χ_A^{sat} = 0.00006571 to give δ_A' = 24.44 MPa$^{1/2}$). The three calculated

94

values were then averaged to give $\delta_A' = 24.37$ MPa$^{1/2}$, which was used in subsequent

Mobile order theory solubility predictions for monuron. Calculated modified solubility

parameters for diuron, hexachlorobenzene, biphenyl, acenaphthene, phenanthrene and

ferrocene were obtained in similar fashion, and the numerical values that were obtained

are listed in table 4.4. Solvent molar volumes and modified solubility parameters used

in the Mobile Order theory predictions are tabulated in table 4.5. Modified solubility

parameters account for only nonspecific interactions, and in the case of the alcoholic

solvents the hydrogen-bonding contributions have been removed. Numerical values of

δ_{solv}' were obtained from published tabulations,[4,5,6,7] and were either deduced by

regressing actual solubility data of solid n-alkanes in organic solvents in accordance

with the configurational entropic model of Huyskens and Haulait-Pirson[8] or estimated

using known values for similar organic solvents.

Now that the modified solubility parameter and activity of solid monuron are

known, one can predict the solubility of monuron in organic solvent by substituting the

numerical values into the appropriate predictive equation. As noted in chapter 2, the

predictive equation may contain up to six terms, depending upon the functional groups

present in both the solute and solvent molecules. For solute-solvent pairs that interact

only through simple dispersion forces, the predictive equation contains only the A, B

and D terms (see eqn. 2.43). This form of the predictive equation will likely be

applicable for the saturated hydrocarbon and aromatic hydrocarbon solvents that are

incapable of hydrogen-bond formation. For the other solvents studied, the predictive

equation may contain provisions for the formation of solute-solvent hydrogen-bonded

complexes. Preliminary calculations using equation 2.51 (with r_{solv} set equal to zero)

indicated that it was possible to predict the solubility of monuron and diuron in ether, alkyl acetate and chloroalkane solvents to within the same degree of predictive accuracy as in the saturated hydrocarbon solvents. This suggests that one does not need to include provisions for monuron-solvent and diuron-solvent complexation in these solvents. Such was not the case, however, with the alcohol solvents. Significant differences were noted between the experimental solubilities for both monuron and diuron in alcohol solvents and predicted values based on eqn. 2.51 (with r_{solv} set equal to unity). The most plausible explanation for the failure of eqn. 2.51 in the case of the alcohol solvents is that the monuron and diuron forms hydrogen-bonded complexes with the alcohol solvents. Since hydrogen bond formation was not suggested in the case of the ether solvents, it will be assumed that the –NC(O)NH– group behaves as a hydrogen-bond base interacting specifically with hydroxylic proton of alcohol solvent molecules in solution.

   To properly describe the solubility of monuron and diuron equation 2.51 has to be modified to include the term $O = \Sigma v_{Oi} \ln[1 + K_{Oi}(\varphi_{solv}/V_{solv})]$ describe the effect of hydrogen-bond formation on solubility. Each hydrogen-bond interaction, either at the oxygen or nitrogen, increases the solubility of the solute in a given solvent. The predictive equation then becomes[1, 2]:

$$
\begin{aligned}
\ln \varphi_A^{sat} = {} & \ln a_A^{solid} - 0.5 \varphi_{solv}(V_A / V_{solv} - 1) + 0.5 \ln[\varphi_A + \varphi_{solv}(V_A / V_{solv})] \\
& - \varphi_S^2 V_A (\delta_A' - \delta_S')^2 (RT)^{-1} - r_{solv} \varphi_{solv} V_A / V_{solv} \\
& + \Sigma v_{Oi} \ln[1 + K_{Oi}(\varphi_{solv} / V_{solv})]
\end{aligned}
\qquad (4.1)
$$

where v_{Oi} represents the number of active and independent type *i* proton acceptor sites available on the solute. Solute-solute dimerization was not included in the predictive expression because of the very low solubility of both monuron and diuron. At very low pesticide concentrations it is very unlikely that two pesticide molecules would be adjacent to each other. Numerical values of K_O for the *presumed* solute amide-alcohol complexation were not listed in published tabulations,[9,10,11] so it was decided to calculate the K_O values for the different alcohol solvents studied by substituting the measured volume fraction solubility and solvent properties into eqn. 4.1, and then solving the resulting expression for the numerical value of K_O that "perfectly" described the solubility data. Performing this set of calculations the following numerical values were obtained for the monuron-alcohol stability constants: $K_O = 2,200$ cm^3 mol^{-1} for methanol; $K = 4,000$ cm^3 mol^{-1} for ethanol and 2-propanol; $K_O = 6,000$ cm^3 mol^{-1} for 1-propanol; $K_O = 7,000$ cm^3 mol^{-1} for 1-butanol; $K_O = 8,000$ cm^3 mol^{-1} for 2-butanol; $K_O = 9,500$ cm^3 mol^{-1} for 1-pentanol; and $K_O = 14,000$ cm^3 mol^{-1} for 2-methyl-1-propanol, 2-methyl-2-propanol and for 1-hexanol through 1-decanol. The solubility data for diuron dissolved in alcohol solvents were treated in similar fashion, to yield diuron-alcohol stability constants of: $K_O = 2,500$ cm^3 mol^{-1} for methanol; $K = 6,500$ cm^3 mol^{-1} for ethanol; $K_O = 10,000$ cm^3 mol^{-1} for 1-propanol and 2-propanol; $K_O = 12,000$ cm^3 mol^{-1} for 1-butanol; $K_O = 15,000$ cm^3 mol^{-1} for 2-butanol; $K_O = 18,000$ cm^3 mol^{-1} for 1-pentanol; and $K_O = 25,000$ cm^3 mol^{-1} for 2-methyl-1-propanol; $K_O = 30,000$ cm^3 mol^{-1} for 1-hexanol and 1-heptanol; and $K_O = 32,000$ cm^3 mol^{-1} for 1-octanol and 1-decanol. Computations could only be performed for about half of the alcohol solvents studied. Modified solubility parameters could not be found in the chemical literature for many of

the branched alcohols. The stability constant calculations indicate that the numerical values of K_O may not be as constant within a given solute-solvent class as Ruelle and coworkers[12][13][14] suggested earlier. Ruelle and coworkers studied very alcohol solvents (methanol, ethanol, 1-propanol and sometimes 1-butanol). When the study is extended to branched alcohols and to the larger alcohol solvent molecules, differences in the calculated K_O values become more apparent.

Tables 4.1, 4.2, and 4.6 – 4.8 compare the experimental mole fraction solubilities of monuron, diuron and hexachlorobenzene to predicted values based on Mobile Order theory. Numerical entries listed in the columns labeled χ_{calc} represent outright predictions, except for the entries for the alcohol solvents in table 4.1. The latter entries represent "back-calculated" values, rather than predicted values, because the experimental data was used in the K_O computation. Back-calculated values are excluded from consideration in assessing the predictive ability of Mobile Order theory since the values are not really predicted. For illustration purposes the comparison has also been depicted graphically in Figures 4.1 – 4.3 as a plot of ln χ_{calc} versus ln χ_{exp}. A 45° diagonal line corresponds to ln χ_{calc} = ln χ_{exp}, which indicates a "perfect" prediction. The predicted values lie both above and below the diagonal line, suggesting a more or less random predictive error. A systematic overprediction/underprediction occurs when all (or most) of the predictive values fall to one side of this line. A systematic error might occur if one fail to take into account hydrogen-bond formation in a large number of solvents or if one uses the wrong numerical value of δ_A' in the predictive equations. A systematic error could also indicate that the model is inappropriate for the systems being studied.

Careful examination of the numerical entries in table 4.1, 4.2, and 4.6 - 4.8 reveals that Mobile Order theory is capable of predicting the solubility of monuron and diuron in non-alcoholic organic solvents to within an overall average absolute deviation of 48.4% and 60.1%, respectively, without introducing any solute-solvent stability constants. If an ideal solution had been assumed, the average absolute deviation would have been 14,410% for monuron, and 17,590% for diuron. For an ideal solution the mole fraction solubility of monuron would be given by $\chi_A^{sat} = a_A^{solid}$ = 0.01891 and the mole fraction solubility of diuron would be $\chi_A^{sat} = a_A^{solid}$ = 0.01590. In the case of hexachlorobenzene, Mobile Order theory predicts the mole fraction solubility to within an overall average deviation of 210 %, with the alcohol solvents being included in the comparison of the solutes; hexachlorobenzene does have highest melting point temperature. It is conceivable that the numerical value of a_A^{solid} could be in error because the heat capacity terms were dropped from the calculation. The heat capacity terms become more important with increasing melting point temperature. This is an inherent limitation imposed on all thermodynamic models that calculate activities of solid solutes relative to the pure supercooled liquid. Mobile Order Theory is by no means perfect, but does provide reasonable approximations for the solubility behavior of the three pesticide solutes studied.

Solute descriptors were also derived for monuron and diuron using the Abraham Solvation Parameter Model described in Chapter 1.

$$\log L = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + vV_x$$

$$\log L = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + \ell \log L^{(16)}$$

At the present time, solute descriptors can be crudely estimated from the molecular structure of the compound using a group contribution approach. The reliability of group contribution methods requires knowledge of descriptors for a many compounds containing as wide of a range of functional groups as possible. The solute descriptor R_2 can be obtained from measured refractive index or in the case of solids from the hypothetical refractive index or estimated from the different molecular fragments present in the molecule. The McGowan volume, Vx, can be calculated from a table of atomic sizes and the number of bonds in the compound. The remaining solute descriptors, $\pi_2^H, \alpha_2^H, \beta_2^H$ (and $L^{(16)}$ if needed), are then calculated by simultaneously solving a set of 3 -4 equations. One can also choose to solve for all descriptors mathematically using 5 – 6 equations containing 5 – 6 unknowns as discussed in the next paragraph.

Partition coefficients between water and solvent are calculated as[15]

$$P = C_s / C_w \tag{4.2}$$

$$\log P = \log C_s - \log C_w \tag{4.3}$$

the ratio of the solubility of the solid in the solvent divided by the solubility of the solute in water provided that

    a. there is no solvate or hydrate formation

    b. secondary activity coefficient must be unity or close to unity

    c. C_w must refer to the neutral form of the solute if the solute ionizes in solution.

If these three conditions are met, log P values can be calculated for as many solvents as there are C_s values available. The solute descriptors for monuron and diuron can be calculated using the known solubility in water, C_w, and the measured molar solubility,

C_s, in any five solvents for which equation coefficients. To illustrate the computation, the solubility equations for hexane, heptane, octane, nonane and decane have been written:

$$\log(C_{hexane} / C_{water}) = 0.361 + 0.579\,R_2 - 1.723\pi_2^H - 3.599\,\Sigma\alpha_2^H$$
$$- 4.764\,\Sigma\beta_2^H + 4.344 V_x \qquad [1]$$

$$\log(C_{heptane} / C_{water}) = 0.325 + 0.670 R_2 - 2.061\pi_2^H - 3.317\Sigma\alpha_2^H$$
$$- 4.733\Sigma\beta_2^H + 4.543 V_x \qquad [2]$$

$$\log(C_{octane} / C_{water}) = 0.223 + 0.642 R_2 - 1.647\pi_2^H - 3.480\Sigma\alpha_2^H$$
$$- 5.067\Sigma\beta_2^H + 4.526 V_x \qquad [3]$$

$$\log(C_{nonane} / C_{water}) = 0.240 + 0.619 R_2 - 1.713\pi_2^H - 3.532\Sigma\alpha_2^H$$
$$- 4.921\Sigma\beta_2^H + 4.482 V_x \qquad [4]$$

$$\log(C_{decane} / C_{water}) = 0.160 + 0.585 R_2 - 1.734\pi_2^H - 3.435\Sigma\alpha_2^H$$
$$- 5.078\Sigma\beta_2^H + 4.582 V_x \qquad [5]$$

with the actual numerical values of the equation coefficients (c, r, s, a, b and v) inserted into the generalized model equation. Equation coefficients are listed in table 4.9. A more complete listing of solvent coefficients is published elsewhere.[16,17,18,19,20,21]

Numerical values of the solute descriptors are obtained by simultaneous solving the five equations given above. Unfortunately, the actual numerical values will be quite sensitive to experimental errors/uncertainties in the inputted molar solubilities. To circumvent this problem, one generally determines the actual numerical values using more than the bare minimum number of experimental data points. The computational

method involves multi-linear least squares analysis, which minimizes the sum of the squares of the differences between the calculated ln (C_s/C_w) and experimental ln (C_s/C_w) values for each solvent for which equation coefficients and ln (C_s/C_w) exist. Linear least squares analysis is a special case of multi-linear least squares analysis. Here one uses several experimentally measured (x,y) pairs of data points to determine the slope and intercept of the straight line. Multi-linear least squares does exactly the same thing, except that one now has a "slope" (an equation coefficient) for each independent variable.

Table 4.10 compares the calculated values of the Abraham solute descriptors for monuron and diuron to numerical values of similar pesticide molecules. [Statistical treatment of all data for which solute descriptors are reported was graciously done by C.E. Green of the University College London using multi-linear least squares analysis and other in-house mathematical programs.][15] The numerical values of the solute descriptors do have chemical significance, and the quantities do reflect the relative strength of solute-solvent interactions in solution. After careful review of the solute descriptors one comes to the conclusion that the Cl atoms in the monuron, diuron and other 3-phenyl-1,1-dimethylureas[15] play an important role in determining solubility. Comparing the values in table 4.10 one can see that the addition of electron withdrawing Cl atoms causes an increase in the polarizability/dipolarity coefficient (π_2^H) and in the hydrogen-bond acidity (α_2^H). Conversely, adding Cl atoms causes the hydrogen-bond basicity (β_2^H) to decrease. Also, the placement of the Cl atom is vital. In the *para* position the electron withdrawing capabilities of the Cl atom is enhanced compared to the *meta* position and increases α_2^H and decreases β_2^H. For informational

purposes, solute descriptors were not calculated for hexachlorobenzene because numerical values were already known for this solute. Solute descriptors for hexachlorobenzene were previously determined using practical organic solvent/water partition coefficient data. Once the solute descriptors are known they can be used to predict other properties such as plant cuticular matrix,[22] nasal pungency thresholds in man,[23] bioconcentration factors in fish[24] and human intestinal absorption.[25]

Polycyclic Aromatic Hydrocarbon Solutes: Biphenyl, Acenaphthene and Phenanthrene

Polycyclic aromatic hydrocarbons (PAHs) continue to be studied due to their relevance to our environment. They are found in air, water, and soil as pollutants. One important aspect of the solubility of PAH's concerns petroleum spills and how to clean-up PAH samples whether it be in the ocean or land, and how the contaminated solid and water affect living species of the area. Biphenyl[26], acenaphthene[27] and phenanthrene[28] were selected as representative PAH solutes for the thesis research. Each solute contains an aromatic ring system with no polar functional groups attached, and interactions with surrounding solvent molecules should involve fairly weak dipole – induced dipole interactions in the case of the polar solute molecules and non-specific dispersive forces in the case of the saturated hydrocarbon solvents.

The experimental mole fraction solubilities of biphenyl, acenaphthene and phenanthrene are listed in table 4.11 for the organic solvents that were studied as part of the thesis research. Included in table 4.11 are published values for biphenyl dissolved in carbon disulfide and several saturated hydrocarbon, aromatic hydrocarbon,

chloroalkane solvents[29]. The literature values are clearly denoted in the tables. For biphenyl solubility data is available in the pharmaceutical literature for binary aqueous-methanol solvent mixtures. Khossravi and Connors[30] reported a molar solubility of C_A^{sat} = 0.4245 for biphenyl dissolved in neat methanol at 298.15 K. Molar solubilities can be converted into mole fraction solubilities using the molar volumes of methanol, V_{solv} = 40.7 cm^3 mol^{-1}, and biphenyl, V_A = 149.4 cm^3 mol^{-1}. Performing this conversion, a literature mole fraction solubility of x_A^{sat} = 0.01811 was calculated, which differs by less than 2 % from my experimental value of x_A^{sat} = 0.01851 that is given in table 4.11. Slight differences in chemical purities and experimental methodologies can lead to differences of a few percent between experimental values determined by two different research groups.

In the case of phenanthrene, published solubility data was found for 7 of the 41 organic solvents that I studied. Doane and Drickamer[31] measured the solubility of phenanthrene in several saturated alkane solvents as a function of pressure. At a pressure of 1 atm, the authors' measured mole fraction solubilities were x_A^{sat} = 0.0326, x_A^{sat} = 0.0401 and x_A^{sat} = 0.0464 for n-hexane, n-heptane and n-octane, respectively. The experimental values that I determined differ by less than 5 % from the values reported by Doane and Drickamer. Speyers[32] measured the solubility of phenanthrene in neat ethanol at five temperatures, from T = 273.2 K to T = 343.4 K, and did not include 298.15 K. One can obtain an "interpolated" value however, by curve-fitting the five measured data points to

$$\ln x_A^{sat} = 50.276 - 30{,}276/T + 4167980/T^2$$

a ln χ_A^{sat} versus 1/T polynomial. Three terms were needed to accurately describe the Speyer data. Using the above mathematical representation, an interpolated value of χ_A^{sat} = 0.01144 is obtained for the mole fraction solubility of phenanthrene at 298.15 K. The interpolated value is in excellent agreement with my experimental value of χ_A^{sat} = 0.01114.

Three different research groups[33,34,35] measured the solubility of phenanthrene in cyclohexane as a function of temperature. Least-sqaures analysis of the three sets of experimental data gave the following three polynomials:

$$\ln \chi_A^{sat} = 15.405 - 5,611/T$$
$$\ln \chi_A^{sat} = 13.666 - 5071/T$$
$$\ln \chi_A^{sat} = 62.745 - 35,818/T + 4,803,930/T^2$$

from which extrapolated/interpolated mole fraction solubilities of χ_A^{sat} = 0.03289, χ_A^{sat} = 0.03537 and χ_A^{sat} = 0.03517 at 298.15 K are calculated. My experimental value of χ_A^{sat} = 0.03648 is slightly larger the values reported by both Choi *et al.* and Gordon and Scott.

McLaughlin and Zainal[36] also measured the solubility of phenanthrene in carbon tetrachloride at five temperatures. The experimental solubility data is described by the following mathematical expression

$$\ln \chi_A^{sat} = 9.9251 - 3,562.8/T$$

from which an interpolated mole fraction of χ_A^{sat} = 0.1246 at T = 298.15 K is calculated.

My measured value of χ_A^{sat} = 0.1262 is in excellent agreement with the literature value

of McLaughlin and Zainal. Finally, Li *et al.*[37] determined the mole fraction solubility of

six aromatic hydrocarbons in acetonitrile. No experimental details were given in the

paper in regards to the chemical purities and experimental methodology. The published

mole fraction solubility for phenanthrene in acetonitrile, χ_A^{sat} = 0.03267, is slightly

greater than the experimental value of χ_A^{sat} = 0.03267 that is listed in table 4.11. A

search of the chemical literature failed to turn up any experimental solubility data for

acenaphthene in the organic solvents considered here.

Mobile Order theory was used to predict the solubility of biphenyl, acenaphthene

and phenanthrene in the organic solvents studied. For the most part, the computations

were identical to those described in the preceding section, except that the computation

of a_A^{solid} for phenanthrene was more complicated because the solute does undergo a

solid-solid phase transition between 298.15 K and T_{mp}. The pertinent calorimetric data

for phenanthrene is ΔH_{fus} = 16.474 kJ mol^{-1}, $\Delta C_{p,A}$ = 12.586 J mol^{-1} K^{-1}, T_{MP} = 372.4 K,

ΔS_{trans} = 3.853 J mol^{-1} K^{-1} and T_{trans} = 339.2 K.[38] The O term in equation 4.1 is set

equal to zero because there is no hydrogen-bonding (complexation) between the PAH

solutes and the solvent. Average absolute deviations for biphenyl, acenaphthene and

phenanthrene using Mobile Order Theory were calculated to be 13.0%, 37.8% and

62.2%, respectively. Graphical comparisons are given in Figures 4.4 – 4.6. The next to

last entry in table 4.11 shows that Mobile Order theory does grossly overpredicts the

solubility of phenanthrene in acetonitrile. Similar failures were noted previously in the

case of pyrene,[39] fluoranthene[40] and anthracene[41]. It is believed that the overprediction results from either the failure of model to properly describe the nonspecific interactions between acetonitrile and polycyclic aromatic hydrocarbons, or perhaps from an incorrect value for this particular solvent's modified solubility parameter. For whatever reason, Mobile Order theory does not give very good predictions of PAH solubilities in acetonitrile. If acetonitrile is excluded from the phenanthrene comparison, the average absolute deviation between predicted and observed phenanthrene solubilities is reduced considerably, to a value of 41.3 %. If ideal conditions had been assumed, average absolute deviation was calculated at 613% for biphenyl, 1080% for acenaphthene, and 1610% for phenanthrene. Clearly predictions based on Mobile Order theory are much better than assuming an ideal solution. Solute descriptors for biphenyl, acenaphthene and phenanthrene were already known prior to the thesis work from practical partition coefficient measurements, so there is no need to apply the Abraham general solvation model to the three PAHs.

Organometallic Solute: Ferrocene

Ferrocene was included in this study because at the time the experimental research was begun Mobile Order theory had never been applied to an organometallic compound. Ferrocene has an iron core that is sandwiched between two anionic cyclopentadienyl rings, and each ring carbon bonds to the metal center. Ferrocene is a stable compound that rarely undergoes reactions where one cyclopentadienyl ring is substituted for another ligand. It does however undergo reactions on the cyclopentadienyl rings such as electrophillic acyl substitution[42]. Published ferrocene

solubility data[43,44,45,46,47,48] was found for 10 of the 46 organic solvents studied, and my

measured values differed from the literature values by up to ±25% (see tables 4.15 and

4.16) in the worst case.

Mobile Order Theory was used to predict the solubility of behavior in as many

organic solvents as possible. When multiple experimental values existed for a given

solvent, the predicted value was compared to the value that I measured rather than to a

published literature value. In doing comparisons it is probably best to take all

experimental values from a single source, rather than from multiple sources, in order to

reduce fluctuations caused by differences in experimental methodologies. Some of the

literature values were determined using a gravimetric method of analysis, which is more

prone to experimental errors and is not specific for the solute being analyzed. In the

gravimetric method a known volume/weight of saturated solution is evaporated to

dryness and the remaining residue is then weighed. The calculated mole fraction

solubility is based on the weight of residue remaining, and if the residue was not

thoroughly dried, the weight would include solvent molecules. Also, any nonvolatile

chemical impurities in the solvent and solute samples would contribute to the weight of

the residue. Spectroscopic methods are more specific in that trace impurities would

have to absorb at the solute's analysis wavelength in order to affect significantly the

measured solubility. Also three of the literature studies concerned ferrocene solubility

determinations in binary aqueous-organic solvent mixtures, and it was not clear from the

reading the experimental methodology whether the organic solvents were dried prior to

use.

Table 4.15 summarizes the predictive ability of mobile order theory for the 42 different organic solvents for which both ferrocene solubility data and modified solubility parameters could be found. The numerical values of a_A^{solid} = 0.140 and V_A = 135.0 cm^3 mol^{-1} were taken from the chemical literature.[43] Examination of the numerical entries reveals that Mobile Order theory provides a fairly reasonable estimate of the solubility behavior of ferrocene in wide range of organic solvents of varying polarity and hydrogen-bonding characteristics. Average absolute deviation between predicted and observed values was on the order of 108 % (see Figure 4.7 for graphical comparison), which is considerably less than the overall standard deviation of 627 % that one would get by assuming an ideal solution ($\chi_A^{sat} = a_A^{solid}$ = 0.140). It should be noted that in the case of acetonitrile, the predicted value differed significantly from the observed more fraction solubility. It this solvent is excluded from consideration the average deviation drops significantly. Large deviations from several of the other solvents might be due to ferrocene-solvent complexation, which was not taken into account in the solubility predictions. Solute descriptors for ferrocene were determined[49] just prior to the thesis work on this solute was begun so there is no need to apply the Abraham general solvation model to this solute. Solute descriptors were based literature solubility data in table 4.16, and available practical organic solvent/water partition coefficient data.

Conclusions

The comparisons presented in this chapter have shown that Mobile Order theory does provide a very reasonable mathematical description of the solubility behavior of polycyclic aromatic hydrocarbons (solutes that interact mainly through simple

dispersion-type interactions), the pesticide solutes monuron and diuron (solutes capable of interacting with alcohol solvents through hydrogen-bond formation), the pesticide solute hexachlorobenzene (solute that interacts with surrounding solvent molecules mainly through simple dispersion-type interactions), and the organometallic solute ferrocene. The specific solute-solvent systems considered involve not only very simple systems containing only nonspecific interactions, but the more complex hydrogen-bonding systems as well. Solubility studies for monuron and diuron dissolved in alcohol solvents did suggest that solute-solvent K_O stability constants might not be as constant within given families of molecules as Ruelle and coworkers[50,51] suggested from their earlier solubility studies in methanol, ethanol, 1-propanol and 1-butanol. The authors considered only a very limited number of alcohol molecules. At this point in time, it is unclear whether a single K_O value averaged over a given solute-solvent class adequately describes all of the solute and solvents within the class, or whether one should use a different K_O value for each solute-solvent pair. Clearly additional research is needed into the solubility behavior in hydrogen-bonding systems in order to better understand how solvent size and steric hindrance affect hydrogen-bond formation.

Additional research is also needed on self-associating solute molecules. All published solubility studies involving Mobile Order theory have involved solutes incapable of self-association. Many of the drug molecules in common use contain – COOH functional groups, and it is important to determine whether or Mobile Order theory can be applied to carboxylic acid solute molecules. Studies using carboxylic acid solute molecules will allow one to more thoroughly study hydrogen-bond formation.

Table 4.1 Monuron and Diuron: Experimental mole fraction solubilities vs. calculated mole fraction solubilities.

Organic Solvent	X_{exp}		X_{calc}	
	Monuron	Diuron	Monuron	Diuron
n-hexane	0.00005489	0.00001828	0.00005058	0.00002695
n-heptane	0.00005565	0.00002703	0.00005673	0.00002428
n-octane	0.00006571	0.00002934	0.00007112	0.00003100
n-nonane	0.00007811	0.00003615	0.00009228	0.00004110
n-decane	0.00010076	0.00004192	0.0001008	0.00004510
n-hexadecane	0.00008653	0.00006794	0.0001825	0.00008515
cyclohexane	0.00005088	0.00002676	0.00007086	0.00003135
methylcyclohexane	0.00007012	0.00004661	0.00008531	0.00003820
cyclooctane		0.00006082		0.00006239
tert-butylcyclohexane	0.00009920	0.00007557	0.0001491	0.00006969
2,2,4-trimethylpentane	0.00004697	0.00002694	0.00003662	0.00001495
benzene	0.001365	0.0008410	0.003444	0.0022760
toluene	0.001155	0.0008907	0.001761	0.0010760
ethylbenzene	0.0007931	0.0007200	0.001612	0.0009725
chlorobenzene		0.001686		0.003156
dichloromethane	0.009436	0.002922	0.01015	0.007678
chloroform	0.012400	0.005354	0.00318	0.002087
carbon tetrachloride	0.0003361	0.0002389	0.0007384	0.0004137

Table 4.1 cont'd

| Organic Solvent | X_{exp} | | X_{calc} | |
	Monuron	Diuron	Monuron	Diuron
1,2-dichloroethane	0.006743	0.004258	0.01102	0.008415
1-chlorobutane		0.001086		0.0004240
1-chlorooctane		0.001980		0.0009077
chlorocylohexane		0.001427		0.001369
dibutyl ether	0.001383	0.0005037	0.0009972	0.0005495
tetrahydrofuran	0.026430	0.03060	0.004502	0.003008
1,4-dioxane		0.007188		0.007564
methanol	0.013640	0.007681	0.01236	0.007045
ethanol	0.01143	0.009406	0.01133	0.009082
1-propanol	0.01287	0.01068	0.01277	0.01024
2-propanol	0.008095	0.007700	0.01085	0.01461
1-butanol	0.01358	0.01197	0.01427	0.01186
2-butanol	0.009261	0.008521	0.009343	0.008053
2-methyl-1-propanol	0.01060	0.008479	0.01069	0.008273
2-methyl-2-propanol	0.006547	0.006467	0.007075	
1-pentanol	0.01483	0.01402	0.01512	0.01382
2-pentanol	0.01056	0.009004		
3-methyl-1-butanol	0.01249	0.01073		
2-methyl-2-butanol	0.004726	0.005469		

Table 4.1 cont'd

Organic Solvent	χ_{exp} Monuron	χ_{exp} Diuron	χ_{calc} Monuron	χ_{calc} Diuron
1-hexanol	0.01496	0.01442	0.01462	0.01477
2-methyl-1-pentanol	0.01206	0.01122		
4-methyl-2-pentanol	0.008105	0.007564		
1-heptanol	0.01478	0.01506	0.01433	0.01447
1-octanol	0.01457	0.01581	0.01400	0.01520
2-ethyl-1-hexanol	0.01096	0.009674		
1-decanol	0.01320	0.01397	0.01314	0.01418
cyclopentanol	0.01534	0.01437		
ethylene glycol		0.00000009565		
butyl acetate	0.008675	0.009931	0.004923	0.003288
ethyl acetate	0.01007	0.009135	0.009278	0.006795
acetonitrile		0.004296		0.02345

Table 4.2 Hexachlorobenzene: Experimental mole fraction solubilities vs. calculated mole fraction solubilities.

Organic Solvent	X_{exp}	X_{calc}
n-hexane	0.00262	0.00289
n-heptane	0.00314	0.00307
n-octane	0.00371	0.00349
n-nonane	0.00410	0.00404
n-decane	0.00460	0.00425
n-hexadecane	0.00681	0.00601
cyclohexane	0.00295	0.00357
methylcyclohexane	0.03870	0.00390
tert-butylcyclohexane	0.00471	0.00523
2,2,4-trimethylpentane	0.00252	0.00238
1,2-dichloroethane	0.00286	0.0213
1-chlorobutane	0.00383	0.0119
1-chlorohexane	0.00508	0.0149
1-chlorooctane	0.00606	0.0149
chlorocylohexane	0.00610	0.0168
dibutyl ether	0.00440	0.0127
methyl *tert*-butyl ether	0.00320	
tetrahydrofuran	0.00592	0.0220
1,4-dioxane	0.00397	0.0208
methanol	0.0000902	0.000861

Table 4.2 cont'd

Organic Solvent	X_{exp}	X_{calc}
ethanol	0.000236	0.00140
1-propanol	0.000398	0.00179
2-propanol	0.000298	0.00206
1-butanol	0.000667	0.00229
2-butanol	0.000521	0.00183
2-methyl-1-propanol	0.000533	0.00149
2-methyl-2-propanol	0.000517	0.00126
1-pentanol	0.00103	0.00251
2-pentanol	0.000860	
3-methyl-1-butanol	0.000770	
2-methyl-2-butanol	0.00120	
1-hexanol	0.00144	0.00243
2-methyl-1-pentanol	0.00140	
4-methyl-2-pentanol	0.00143	
1-heptanol	0.00190	0.00277
1-octanol	0.00238	0.00308
2-ethyl-1-hexanol	0.00174	
1-decanol	0.00380	0.00364
cyclopentanol	0.000920	
butyl acetate	0.00365	0.0193
ethyl acetate	0.00211	0.0200

Table 4.2 cont'd

Organic Solvent	χ_{exp}	χ_{calc}
methyl acetate	0.00148	

Table 4.3 Solute enthalpies of fusion and melting point temperatures

Solutes	ΔH^{fus}(J mol^{-1})	T_{MP} (Kelvin)
monuron	29,460[3]	447.6
diuron	33,890[51]	429.7
hexachlorobenzene	23,850[3]	505
ferrocene		446
biphenyl	18,410[51]	343
acenaphthene	21,540[52]	366.56
phenanthrene	16,474[38]	372.4

Table 4.4 Solute molar volumes and modified solubility parameters

Solutes	δ' (MPa)$^{1/2}$	V (cm^{3}mol^{-1})
monuron	24.37	152.8
diuron	24.57	164.8
hexachlorobenzene	20.10	155.6
ferrocene	20.43	135.0
biphenyl	19.51	149.4
acenaphthene	19.60	137.77
phenanthrene	20.45	155.8

Table 4.5 Solvent molar volumes and modified solubility parameter

Solvent	Molar Mass	δ' (MPa)$^{1/2}$	V (cm^{3}mol^{-1})
n-hexane	86.18	14.56	131.51
n-heptane	100.20	14.66	147.48
n-octane	114.23	14.85	163.46
n-nonane	128.26	15.07	179.87
n-decane	142.28	15.14	195.88
n-hexadecane	226.44	15.61	294.12
cyclohexane	84.16	14.82	108.76
methylcyclohexane	98.19	15.00	128.32
cis-1,2-dimethylcyclohexane	112.21	15.50	145.4
trans-1,2-dimethylcyclohexane	112.21	15.50	145.4
cis-1,3-dimethylcyclohexane	112.21	15.50	145.4
cis-1,4-dimethylcyclohexane	112.21	15.50	145.4
trans-1,4-dimethylcyclohexane	112.21	15.50	145.4
cyclooctane	112.21	15.40	134.9
2,2,4-trimethylpentane	114.23	14.30	166.09
tert-butylcyclohexane	140.27	15.50	173.9
benzene	78.11	18.95	89.4
toluene	92.14	18.10	106.84
ethylbenzene	106.17	18.02	123.1
chlorobenzene	112.56	19.48	102.1

Table 4.5 cont'd

Solvent	Molar Mass	δ' $(MPa)^{1/2}$	V (cm^3mol^{-1})
m-xylene	106.17	17.20	123.2
p-xylene	106.17	17.30	123.9
dibutyl ether	130.23	17.45	170.3
tetrahydrofuran	72.11	19.30	81.4
1,4-dioxane	88.11	20.89	85.8
methanol	32.04	19.25	40.7
ethanol	46.07	17.81	58.7
1-propanol	60.10	17.29	75.10
2-propanol	60.10	17.60	79.60
1-butanol	74.12	17.16	92.00
2-butanol	74.12	16.60	92.4
2-methyl-1-propanol	74.12	16.14	92.8
2-methyl-2-propanol	74.12	15.78	94.3
1-pentanol	88.15	16.85	108.6
1-hexanol	102.17	16.40	125.2
1-heptanol	116.20	16.39	141.9
1-octanol	130.23	16.38	158.3
1-decanol	158.28	16.35	191.6
ethylene glycol	62.07	19.90	56.0
methyl acetate	74.08	21.71	79.8
ethyl acetate	88.11	20.79	98.5

Table 4.5 cont'd

Solvent	Molar Mass	δ' (MPa)$^{1/2}$	V (cm^{3}mol^{-1})
butyl acetate	116.16	19.66	132.5
dichloromethane	84.93	20.53	64.5
1,1-dichloroethane	98.96	18.51	84.8
1,2-dichloroethane	98.96	20.99	78.8
1-chlorobutane	92.57	17.12	105.0
1-chlorohexane	120.62	18.00	138.1
1-chlorooctane	148.67	18.00	171.1
chlorocyclohexane	118.60	18.45	120.3
chloroform	119.38	18.77	80.7
tetrachloromethane	153.82	17.04	97.8
2-propanone	58.08	21.91	74.0
2-butanone	72.11	20.90	90.2
acetonitrile	41.05	23.62	52.9
pyridine	79.10	20.94	80.9
carbon disulfide	76.14	20.50	60.0

Table 4.6 Monuron: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[a]	% deviation[b]
n-hexane	-9.20	-9.89	-0.69	-7.85
n-heptane	-9.80	-9.78	0.02	1.94
n-octane	-9.63	-9.55	0.08	8.23
n-nonane	-9.46	-9.29	0.17	18.14
n-decane	-9.20	-9.20	0.00	0.04
n-hexadecane	-9.36	-8.61	0.75	110.91
cyclohexane	-9.89	-9.55	0.33	39.27
methylcyclohexane	-9.57	-9.37	0.20	21.66
tert-butylcyclohexane	-9.22	-8.81	0.41	50.30
2,2,4-trimethylpentane	-9.97	-10.21	-0.25	-22.04
benzene	-6.60	-5.67	0.93	152.31
toluene	-6.76	-6.34	0.42	52.47
ethylbenzene	-7.14	-6.43	0.71	103.25
dichloromethane	-4.66	-4.59	0.07	7.57
chloroform	-4.39	-5.75	-1.36	-74.35
carbon tetrachloride	-8.00	-7.21	0.79	119.70
1,2-dichloroethane	-5.00	-4.51	0.49	63.43
tetrahydrofuran	-3.63	-5.40	-1.77	-82.97
methanol	-4.29	-4.39	-0.10	-9.38

Table 4.6 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[a]	% deviation[b]
ethanol	-4.47	-4.48	0.01	-0.87
1-propanol	--4.35	-4.36	0.01	-0.78
2-propanol	-4.82	-4.52	0.29	34.03
1-butanol	-4.30	-4.25	0.05	5.08
2-butanol	-4.68	-4.67	0.01	0.89
2-methyl-1-propanol	-4.55	-4.54	0.01	0.85
2-methyl-2-propanol	-5.03	-4.95	0.08	8.06
1-pentanol	-4.21	-4.19	0.02	1.96
2-pentanol	-4.55			
3-methyl-1-butanol	-4.38			
2-methyl-2-butanol	-5.35			
1-hexanol	-4.20	-4.23	-0.02	-2.27
2-methyl-1-pentanol	-4.42			
4-methyl-2-pentanol	-4.82			
1-heptanol	-4.21	-4.25	-0.03	-3.04
1-octanol	-4.23	-4.27	-0.04	-3.91
2-ethyl-1-hexanol	-4.51			
1-decanol	-4.33	-4.33	0.00	-0.45
cyclopentanol	-4.18			
ethylene glycol				
butyl acetate	-4.75	-5.31	-0.57	-43.25

Table 4.6 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[a]	% deviation[b]
ethyl acetate	-4.60	-4.68	-0.08	-7.86

[a] Δln = ln Xcalc – ln Xexp.

[b] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.7 Diuron: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[c]	% deviation[d]
n-hexane	-10.91	-10.52	0.39	47.43
n-heptane	-10.52	-10.63	-0.11	-10.17
n-octane	-10.44	-10.38	0.06	5.66
n-nonane	-10.23	-10.10	0.13	13.69
n-decane	-10.08	-10.01	0.07	7.59
n-hexadecane	-9.60	-9.37	0.23	25.33
cyclohexane	-10.53	-10.37	0.16	17.15
methylcyclohexane	-9.97	-10.17	-0.20	-18.04
cyclooctane	-9.71	-9.68	0.03	2.58
tert-butylcyclohexane	-9.49	-9.57	-0.08	-7.78
2,2,4-trimethylpentane	-10.52	-11.11	-0.59	-44.51
benzene	-7.08	-6.09	1.00	170.63
toluene	-7.02	-6.83	0.19	20.80
ethylbenzene	-7.24	-6.94	0.30	35.07
chlorobenzene	-6.39	-5.76	0.63	87.19
dichloromethane	-5.84	-4.87	0.97	162.77
chloroform	-5.23	-6.17	-0.94	-61.02
carbon tetrachloride	-8.34	-7.79	0.55	73.17
1,2-dichloroethane	-5.46	-4.78	0.68	97.63

Table 4.7 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[c]	% deviation[d]
1-chlorobutane	-6.83	-7.77	-0.94	-60.96
1-chlorooctane	-6.22	-7.00	-0.78	-54.16
chlorocylohexane	-6.55	-6.59	-0.04	-4.06
dibutyl ether	-7.59	-7.51	0.09	9.09
tetrahydrofuran	-3.49	-5.81	-2.32	-90.17
1,4-dioxane	-4.94	-4.88	0.05	5.23
methanol	-4.87	-4.96	-0.09	-8.28
ethanol	-4.67	-4.70	-0.04	-3.44
1-propanol	-4.54	-4.58	-0.04	-4.12
2-propanol	-4.87	-4.23	0.64	89.74
1-butanol	-4.43	-4.43	-0.01	-0.92
2-butanol	-4.77	-4.82	-0.06	-5.49
2-methyl-1-propanol	-4.77	-4.79	-0.02	-2.43
2-methyl-2-propanol	-5.04			
1-pentanol	-4.27	-4.28	-0.01	-1.43
2-pentanol	-4.71			
3-methyl-1-butanol	-4.53			
2-methyl-2-butanol	-5.21			
1-hexanol	-4.24	-4.22	0.02	2.43
2-methyl-1-pentanol	-4.49			
4-methyl-2-pentanol	-4.88			

Table 4.7 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[c]	% deviation[d]
1-heptanol	-4.20	-4.24	-0.04	-3.92
1-octanol	-4.15	-4.19	-0.04	-3.86
2-ethyl-1-hexanol	-4.64			
1-decanol	-4.27	-4.26	0.01	1.50
cyclopentanol	-4.24			
ethylene glycol	-16.16			
butyl acetate	-4.61	-5.72	-1.11	-66.89
ethyl acetate	-4.70	-4.99	-0.30	-25.62
acetonitrile	-5.45	-3.75	1.70	445.86

[c] Δln = ln Xcalc – ln Xexp.

[d] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.8 Hexachlorobenzene: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[e]	%deviation[f]
n-hexane	-5.94	-5.85	0.10	10.31
n-heptane	-5.76	-5.79	-0.02	-2.23
n-octane	-5.60	-5.66	-0.06	-5.93
n-nonane	-5.50	-5.51	-0.01	-1.46
n-decane	-5.38	-5.46	-0.08	-7.61
n-hexadecane	-4.99	-5.11	-0.12	-11.75
cyclohexane	-5.83	-5.64	0.19	21.02
methylcyclohexane	-5.55	-5.55	0.01	0.78
tert-butylcyclohexane	-5.36	-5.25	0.10	11.04
2,2,4-trimethylpentane	-5.98	-6.04	-0.06	-5.56
1,2-dichloroethane	-5.86	-3.85	2.01	644.76
1-chlorobutane	-5.56	-4.43	1.13	210.70
1-chlorohexane	-5.28	-4.21	1.08	193.31
1-chlorooctane	-5.11	-4.21	0.90	145.87
chlorocylohexane	-5.10	-4.09	1.01	175.41
dibutyl ether	-5.43	-4.37	1.06	188.64
methyl *tert*-butyl ether	-5.74			
tetrahydrofuran	-5.13	-3.82	1.31	271.62
1,4-dioxane	-5.53	-3.87	1.66	423.93

Table 4.8 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[e]	%deviation[f]
methanol	-9.31	-7.06	2.26	854.55
ethanol	-8.35	-6.57	1.78	493.22
1-propanol	-7.83	-6.33	1.50	349.75
2-propanol	-8.12	-6.19	1.93	591.28
1-butanol	-7.31	-6.08	1.23	243.33
2-butanol	-7.56	-6.30	1.26	251.25
2-methyl-1-propanol	-7.54	-6.51	1.03	179.55
2-methyl-2-propanol	-7.57	-6.68	0.89	143.71
1-pentanol	-6.88	-5.99	0.89	143.69
2-pentanol	-7.06			
3-methyl-1-butanol	-7.17			
2-methyl-2-butanol	-6.73			
1-hexanol	-6.54	-6.02	0.52	68.75
2-methyl-1-pentanol	-6.57			
4-methyl-2-pentanol	-6.55			
1-heptanol	-6.27	-5.89	0.38	45.79
1-octanol	-6.04	-5.78	0.26	29.41
2-ethyl-1-hexanol	-6.35			
1-decanol	-5.57	-5.62	-0.04	-4.21
cyclopentanol	-6.99			
butyl acetate	-5.61	-3.95	1.67	428.77

129

Table 4.8 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[e]	%deviation[f]
ethyl acetate	-6.16	-3.91	2.25	847.87
methyl acetate	-6.52			

[e] Δln = ln Xcalc – ln Xexp.

[f] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.9 Solvent coefficients for the Abraham general solvation model[g]

Solvents	c	r	s	a	b	v
hexane	0.361	0.579	-1.723	-3.599	-4.764	4.344
heptane	0.325	0.670	-2.061	-3.317	-4.733	4.543
octane	0.223	0.642	-1.647	-3.480	-5.067	4.526
nonane	0.240	.0619	-1.713	-3.532	-4.921	4.482
decane	0.160	0.585	-1.734	-3.435	-5.078	4.582

Table 4.10 Solute descriptor for 3-phenyl-1,1-dimethylureas[h]

Ureas	R_2	π_2^H	α_2^H	β_2^H	V_x	$\log L^{(16)}$
fenuron	1.05	1.31	0.37	0.96	1.3544	6.58
3-(m-chlorophenyl)-1,1-dimethylurea	1.15	1.54	0.41	0.80	1.4768	7.18
monuron	1.14	1.50	0.47	0.78	1.4768	7.18
chlorotoluron	1.11	1.50	0.47	0.81	1.6177	7.72
diuron	1.28	1.60	0.57	0.70	1.5992	80.6
metoxuron	1.24	1.78	0.32	1.07	1.6764	8.34
fluometuron	0.65	1.19	0.41	0.79	1.5484	6.68

Table 4.11 Polycyclic Aromatic Hydrocarbons: Experimental mole fraction solubilities vs. calculated mole fraction

solubilities based on Mobile Order theory.

	X_{exp}			X_{calc}		
Organic Solvent	**Biphenyl**	**Acenaphthene**	**Phenanthrene**	**Biphenyl**	**Acenaphthene**	**Phenanthrene**
n-hexane	0.124 [i]	0.05192	0.03189	0.1317	0.0567	0.03529
n-heptane	0.138 [i]	0.06075	0.03888	0.1329	0.05899	0.037116
n-octane	0.147 [i]	0.06826	0.04443	0.1441	0.06496	0.04232
n-nonane	0.1551	0.0721	0.04785	0.1593	0.07268	0.0493
n-decane	0.1636	0.07852	0.05531	0.1626	0.07535	0.05154
n-hexadecane	0.2151	0.1065	0.07972	0.2001	0.098	0.07194
cyclohexane	0.190 [i]	0.07043	0.03648	0.1780	0.06935	0.04724
methylcyclohexane	0.183 [i]	0.08093	0.04572	0.1758	0.07278	0.04572
cis-1,2-dimethylcyclohexane	0.195 [i]			0.2122		
trans-1,2-dimethylcyclohexane	0.183 [i]			0.2122		
cis-1,3-dimethylcyclohexane	0.172 [i]			0.2122		

[i] Data referenced from W. Chang, Ph.D. dissertation, North Dakota State University, Fargo, North Dakota (1969).

Table 4.11 cont'd

Organic Solvent	X_{exp}			X_{calc}		
	Biphenyl	Acenaphthene	Phenanthrene	Biphenyl	Acenaphthene	Phenanthrene
cis-1,4-dimethylcyclohexane	0.182 [i]			0.2122		
trans-1,4-dimethylcyclohexane	0.173 [i]			0.2122		
cyclooctane	0.2194	0.09739	0.06002	0.2096	0.08769	0.06638
tert-butylcyclohexane	0.1740	0.07763	0.05124	0.2002	0.0894	0.06684
2,2,4-trimethylpentane	0.1094	0.04668	0.02486	0.0996	0.04718	0.02721
benzene	0.381 [i]			0.3911		
toluene	0.377 [i]			0.3749		
ethylbenzene	0.363 [i]			0.3686		
chlorobenzene	0.397 [i]			0.3892		
dichloromethane	0.412 [i]			0.3935		
chloroform	0.422 [i]			0.3934		
carbon tetrachloride	0.342 [i]		0.1262	0.3503		0.1807
1,1-dichloroethane	0.381 [i]			0.3894		

Table 4.11 cont'd

Organic Solvent	X_{exp}			X_{calc}		
	Biphenyl	Acenaphthene	Phenanthrene	Biphenyl	Acenaphthene	Phenanthrene
1,2-dichloroethane	0.397 [i]			0.3866		
1,2-dibromoethane	0.389 [i]			0.3855		
dibutyl ether	0.2660	0.1116	0.09454	0.3414	0.1645	0.1784
tetrahydrofuran		0.1973	0.2884		0.2061	0.2662
1,4-dioxane		0.1415	0.2165		0.1955	0.2705
methanol	0.01851	0.00544	0.00589	0.02429	0.01333	0.01244
ethanol	0.03456	0.01068	0.01114	0.04443	0.02285	0.01919
1-propanol	0.04620	0.01686	0.01355	0.05864	0.02959	0.02396
2-propanol	0.03533	0.01336	0.00977	0.06572	0.03296	0.02811
1-butanol	0.05788	0.02373	0.01771	0.07459	0.03727	0.0304
2-butanol	0.05005	0.01877	0.01178	0.06239	0.03156	0.02146
2-methyl-1-propanol	0.03906	0.01691	0.0102	0.05210	0.02679	0.01837
2-methyl-2-propanol	0.04118	0.01705				

Table 4.11 cont'd

Organic Solvent	X_{exp}			X_{calc}		
	Biphenyl	Acenaphthene	Phenanthrene	Biphenyl	Acenaphthene	Phenanthrene
1-pentanol	0.07573	0.03176	0.02491	0.08253	0.04126	0.03259
2-pentanol	0.06525	0.02443	0.01764			
3-methyl-1-butanol	0.05664	0.02347	0.01606			
2-methyl-2-butanol	0.07120	0.02867	0.01926			
1-hexanol	0.08592	0.03922	0.03028	0.81770	0.04124	0.03056
2-methyl-1-pentanol	0.07216	0.02904	0.01801			
4-methyl-2-pentanol	0.06115	0.02551	0.01754			
1-heptanol	0.1001	0.04617	0.03937	0.09205	0.04642	0.0347
1-octanol	0.1097	0.05089	0.0518	0.1012	0.0511	0.03844
2-ethyl-1-hexanol	0.09481	0.04402	0.02876			
cyclopentanol			0.0307			
ethylene glycol	0.00269	0.001157	0.001134	0.00268	0.001941	0.001457
2,2,2-trifluoroethanol			0.001826			

Table 4.11 cont'd

Organic Solvent	X$_{exp}$ Biphenyl	Acenaphthene	Phenanthrene	X$_{calc}$ Biphenyl	Acenaphthene	Phenanthrene
2-butanone		0.1307	0.209		0.1936	0.2686
aniline			0.1101			
cyclohexanone			0.2716			
butyl acetate		0.137	0.1812		0.1977	0.2555
ethyl acetate		0.1086	0.1499		0.1927	0.2661
acetonitrile			0.03267			0.2569
carbon disulfide	0.3690 [i]			0.3701		

Table 4.12 Biphenyl: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[j]	% deviation[k]
n-hexane	-2.09	-2.03	0.06	6.21
n-heptane	-1.98	-2.02	-0.04	-3.70
n-octane	-1.92	-1.94	-0.02	-1.97
n-nonane	-1.86	-1.84	0.03	2.71
n-decane	-1.81	-1.82	-0.01	-0.61
n-hexadecane	-1.54	-1.61	-0.07	-6.97
cyclohexane	-1.66	-1.73	-0.07	-6.32
methylcyclohexane	-1.70	-1.74	-0.04	-3.93
cis-1,2-dimethylcyclohexane	-1.63	-1.55	0.08	8.82
trans-1,2-dimethylcyclohexane	-1.70	-1.55	0.15	15.96
cis-1,3-dimethylcyclohexane	-1.76	-1.55	0.21	23.37
cis-1,4-dimethylcyclohexane	-1.70	-1.55	0.15	16.59
trans-1,4-dimethylcyclohexane	-1.75	-1.55	0.20	22.66
cyclooctane	-1.52	-1.56	-0.05	-4.47
tert-butylcyclohexane	-1.75	-1.61	0.14	15.06
2,2,4-trimethylpentane	-2.21	-2.31	-0.09	-8.96
benzene	-0.96	-0.94	0.03	2.65
toluene	-0.98	-0.98	-0.01	-0.56
ethylbenzene	-1.01	-1.00	0.02	1.54

Table 4.12 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[j]	% deviation[k]
chlorobenzene	-0.92	-0.94	-0.02	-1.96
dichloromethane	-0.89	-0.93	-0.05	-4.49
chloroform	-0.86	-0.93	-0.07	-6.78
carbon tetrachloride	-1.07	-1.05	0.02	2.43
1,1-dichloroethane	-0.96	-0.94	0.02	2.20
1,2-dichloroethane	-0.92	-0.95	-0.03	-2.62
1,2-dibromoethane	-0.94	-0.95	-0.01	-0.90
dibutyl ether	-1.32	-1.07	0.25	28.35
methanol	-3.99	-3.72	0.27	31.23
ethanol	-3.37	-3.11	0.25	28.56
1-propanol	-3.07	-2.84	0.24	26.93
2-propanol	-3.34	-2.72	0.62	86.02
1-butanol	-2.85	-2.60	0.25	28.87
2-butanol	-2.99	-2.77	0.22	24.66
2-methyl-1-propanol	-3.24	-2.95	0.29	33.38
2-methyl-2-propanol	-3.19			
1-pentanol	-2.58	-2.49	0.09	8.98
2-pentanol	-2.73			
3-methyl-1-butanol	-2.87			
2-methyl-2-butanol	-2.64			
1-hexanol	-2.45	-2.50	-0.05	-4.83

Table 4.12 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[j]	% deviation[k]
2-methyl-1-pentanol	-2.63			
4-methyl-2-pentanol	-2.79			
1-heptanol	-2.30	-2.39	-0.08	-8.04
1-octanol	-2.21	-2.29	-0.08	-7.75
2-ethyl-1-hexanol	-2.36			
ethylene glycol	-5.92	-5.92	0.00	-0.37
carbon disulfide	-1.00	-0.99	0.00	0.30

[j] Δln = ln Xcalc – ln Xexp.

[k] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.13 Acenaphthene: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln^l	% deviation^m
n-hexane	-2.96	-2.87	0.09	9.21
n-heptane	-2.80	-2.83	-0.03	-2.90
n-octane	-2.68	-2.73	-0.05	-4.83
n-nonane	-2.63	-2.62	0.01	0.80
n-decane	-2.54	-2.59	-0.04	-4.04
n-hexadecane	-2.24	-2.32	-0.08	-7.98
cyclohexane	-2.65	-2.67	-0.02	-1.53
methylcyclohexane	-2.51	-2.62	-0.11	-10.07
cyclooctane	-2.33	-2.43	-0.10	-9.96
tert-butylcyclohexane	-2.56	-2.41	0.14	15.16
2,2,4-trimethylpentane	-3.06	-3.05	0.01	1.07
dibutyl ether	-2.19	-1.80	0.39	47.40
tetrahydrofuran	-1.62	-1.58	0.04	4.46
1,4-dioxane	-1.96	-1.63	0.32	38.16
methanol	-5.21	-4.32	0.90	145.04
ethanol	-4.54	-3.78	0.76	113.95
1-propanol	-4.08	-3.52	0.56	75.50
2-propanol	-4.32	-3.41	0.90	146.71
1-butanol	-3.74	-3.29	0.45	57.06

Table 4.13 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[l]	% deviation[m]
2-butanol	-3.98	-3.46	0.52	68.14
2-methyl-1-propanol	-4.08	-3.62	0.46	58.43
2-methyl-2-propanol	-4.07			
1-pentanol	-3.45	-3.19	0.26	29.91
2-pentanol	-3.71			
3-methyl-1-butanol	-3.75			
2-methyl-2-butanol	-3.55			
1-hexanol	-3.24	-3.19	0.05	5.15
2-methyl-1-pentanol	-3.54			
4-methyl-2-pentanol	-3.67			
1-heptanol	-3.08	-3.07	0.01	0.54
1-octanol	-2.98	-2.97	0.00	0.41
2-ethyl-1-hexanol	-3.12			
ethylene glycol	-6.76	-6.24	0.52	67.76
2-butanone	-2.03	-1.64	0.39	48.13
butyl acetate	-1.99	-1.62	0.37	44.31
ethyl acetate	-2.22	-1.65	0.57	77.44

[l] Δln = ln Xcalc – ln Xexp.

[m] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.14 Phenanthrene: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[n]	% deviation[o]
n-hexane	-3.45	-3.34	0.10	10.66
n-heptane	-3.25	-3.29	-0.05	-4.42
n-octane	-3.11	-3.16	-0.05	-4.75
n-nonane	-3.04	-3.01	0.03	3.03
n-decane	-2.89	-2.97	-0.07	-6.82
n-hexadecane	-2.53	-2.63	-0.10	-9.76
cyclohexane	-3.31	-3.05	0.26	29.50
methylcyclohexane	-3.09	-2.99	0.10	10.37
cyclooctane	-2.81	-2.71	0.10	10.60
tert-butylcyclohexane	-2.97	-2.71	0.27	30.44
2,2,4-trimethylpentane	-3.69	-3.60	0.09	9.45
carbon tetrachloride	-2.07	-1.71	0.36	43.19
dibutyl ether	-2.36	-1.74	0.61	84.90
tetrahydrofuran	-1.24	-1.32	-0.08	-7.70
1,4-dioxane	-1.53	-1.31	0.22	24.94
methanol	-5.13	-4.39	0.75	111.21
ethanol	-4.50	-3.95	0.54	72.26
1-propanol	-4.30	-3.73	0.57	76.83
2-propanol	-4.63	-3.57	1.06	187.72

Table 4.14 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[n]	% deviation[o]
1-butanol	-4.03	-3.49	0.54	71.65
2-butanol	-4.44	-3.75	0.69	99.15
2-methyl-1-propanol	-4.59	-4.00	0.59	80.10
1-pentanol	-3.69	-3.42	0.27	30.83
2-pentanol	-4.04			
3-methyl-1-butanol	-4.13			
2-methyl-2-butanol	-3.95			
1-hexanol	-3.50	-3.49	0.01	0.92
2-methyl-1-pentanol	-4.02			
4-methyl-2-pentanol	-4.04			
1-heptanol	-3.23	-3.36	-0.13	-11.86
1-octanol	-2.92	-3.26	-0.34	-29.05
2-ethyl-1-hexanol	-3.55			
cyclopentanol	-3.48			
ethylene glycol	-6.78	-6.53	0.25	28.48
2,2,2-triflouroethanol	-6.31			
2-butanone	-1.57	-1.31	0.25	28.52
aniline	-2.21			
cyclohexanone	-1.30			
butyl acetate	-1.71	-1.36	0.34	41.00

144

Table 4.14 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[n]	% deviation[o]
ethyl acetate	-1.90	-1.32	0.57	77.52
acetonitrile	-3.42	-1.36	2.06	686.35

[n] Δln = ln Xcalc – ln Xexp.

[o] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Table 4.15 Ferrocene: Experimental mole fraction solubilities vs. calculated mole fraction solubilities based on Mobile Order theory.

Organic Solvent	X_{exp}	X_{calc}
n-hexane	0.02260	0.02346
n-heptane	0.02489	0.02485
n-octane	0.02713	0.02801
n-nonane	0.02901	0.03216
n-decane	0.03097	0.03372
n-hexadecane	0.03963	0.04672
cyclohexane	0.03300	0.02877
methylcyclohexane	0.03372	0.03121
cyclooctane	0.04680	0.03927
tert-butylcyclohexane	0.03612	0.04111
2,2,4-trimethylpentane	0.02179	0.01950
benzene	0.08756	0.13390
toluene	0.08321	0.11380
ethylbenzene	0.07703	0.10980
o-xylene	0.08014	
m-xylene	0.07436	0.08817
p-xylene	0.07785	0.09090
1,2-dichloroethane	0.07735	0.1466
1-chlorobutane	0.05962	0.08863
1-chlorooctane	0.06062	0.1083

Table 4.15 cont'd

Organic Solvent	X_{exp}	X_{calc}
tetrachloromethane	0.0692[49]	0.0882
dibutyl ether	0.05107	0.09365
methyl *tert*-butyl ether	0.04120	
1,4-dioxane	0.0683[49]	0.1447
methanol	0.003298	0.008894
ethanol	0.005976	0.01322
1-propanol	0.008917	0.01629
2-propanol	0.007078	0.01866
1-butanol	0.01181	0.02027
2-butanol	0.01027	0.01634
2-methyl-1-propanol	0.009621	0.01135
2-methyl-2-propanol	0.009215	0.02184
1-pentanol	0.01352	
2-pentanol	0.01263	
3-methyl-1-butanol	0.01225	
2-methyl-2-butanol	0.01554	
1-hexanol	0.01735	0.02101
2-methyl-1-pentanol	0.01426	
4-methyl-2-pentanol	0.01343	
1-heptanol	0.02050	0.02366
1-octanol	0.02215	0.02606

Table 4.15 cont'd

Organic Solvent	χ_{exp}	χ_{calc}
2-ethyl-1-hexanol	0.01667	
1-decanol	0.02767	0.03029
cyclopentanol	0.01774	
2-propanone	0.024[47]	0.140
butyl acetate	0.05580	0.1367
ethyl acetate	0.04300	0.1421
methyl acetate	0.03258	0.1400
acetonitrile	0.007557[45]	0.1257
dimethyl sulfoxide	0.01410	
carbon disulfide	0.0669[49]	0.1585
pyridine	0.07048[45]	0.1461

Table 4.16 Comparison of ferrocene experimental mole fraction solubilities and

literature values

Solvent	Obs. exp. values	Literature values
n-hexane	0.02260	0.02197[47] 0.01968[48]
n-heptane	0.02489	0.0262[43] 0.024[44] 0.02502[47] 0.02238[48]
n-octane	0.02713	0.0232[48]
cyclohexane	0.03300	0.0388[43] 0.0342[44] 0.03680[47] 0.022625[48]
benzene	0.08756	0.071[44] 0.08391[47] 0.1311[48]
toluene	0.08321	0.08269[47] 0.1269[48]
methanol	0.003298	0.003657[45]
ethanol	0.005976	0.004731[47]
1-butanol	0.01181	0.00853[47]
dimethyl sulfoxide	0.01410	0.01474[46]

Table 4.17 Ferrocene: Deviations between experimental versus predicted solubilities based on Mobile Order theory

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[p]	% deviation[q]
n-hexane	3.79	3.75	-0.04	-0.99
n-heptane	3.69	3.69	0.00	0.04
n-octane	3.61	3.58	-0.03	-0.88
n-nonane	3.54	3.44	-0.10	-2.91
n-decane	3.47	3.39	-0.09	-2.45
n-hexadecane	3.23	3.06	-0.16	-5.10
cyclohexane	3.41	3.55	0.14	4.02
methylcyclohexane	3.39	3.47	0.08	2.28
cyclooctane	3.06	3.24	0.18	5.73
tert-butylcyclohexane	3.32	3.19	-0.13	-3.90
2,2,4-trimethylpentane	3.83	3.94	0.11	2.90
benzene	2.44	2.01	-0.42	-17.44
toluene	2.49	2.17	-0.31	-12.59
ethylbenzene	2.56	2.21	-0.35	-13.83
o-xylene	2.52			
m-xylene	2.60	2.43	-0.17	-6.55
p-xylene	2.55	2.40	-0.15	-6.07
1,2-dichloroethane	2.56	1.92	-0.64	-24.98
1-chlorobutane	2.82	2.42	-0.40	-14.06

Table 4.17 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[p]	% deviation[q]
1-chlorooctane	2.80	2.22	-0.58	-20.70
tetrachloromethane	2.67	2.43	-0.24	-9.08
dibutyl ether	2.97	2.37	-0.61	-20.39
methyl *tert*-butyl ether	3.19			
1,4-dioxane	2.68	1.93	-0.75	-27.97
methanol	5.71	4.72	-0.99	-17.36
ethanol	5.12	4.33	-0.79	-15.51
1-propanol	4.72	4.12	-0.60	-12.77
2-propanol	4.95	3.98	-0.97	-19.58
1-butanol	4.44	3.90	-0.54	-12.17
2-butanol	4.58	4.11	-0.46	-10.14
2-methyl-1-propanol	4.64	4.32	-0.33	-7.02
2-methyl-2-propanol	4.69	4.48	-0.21	-4.45
1-pentanol	4.30	3.82	-0.48	-11.14
2-pentanol	4.37			
3-methyl-1-butanol	4.40			
2-methyl-2-butanol	4.16			
1-hexanol	4.05	3.86	-0.19	-4.72
2-methyl-1-pentanol	4.25			
4-methyl-2-pentanol	4.31			

Table 4.17 cont'd

Organic Solvent	ln χ_{exp}	ln χ_{calc}	Δ ln[p]	% deviation[q]
1-heptanol	3.89	3.74	-0.14	-3.69
1-octanol	3.81	3.65	-0.16	-4.27
2-ethyl-1-hexanol	4.09			
1-decanol	3.59	3.50	-0.09	-2.52
cyclopentanol	4.03			
2-propanone	3.73	1.97	-1.76	-47.28
butyl acetate	2.89	1.99	-0.90	-31.05
ethyl acetate	3.15	1.95	-1.20	-37.99
methyl acetate	3.42	1.97	-1.46	-42.58
acetonitrile	4.89	2.07	-2.81	-57.55
dimethyl sulfoxide	4.26			
carbon disulfide	2.70	1.84	-0.86	-31.89
pyridine	2.65	1.92	-0.73	-27.48

[p] Δln = ln Xcalc – ln Xexp.

[q] % deviation = 100 [(Xcalc – Xexp) / Xexp].

Figure 4.1 Monuron: Graphical representation of predicted vs. experimental mole fraction solubilities (χ_A^{sat})

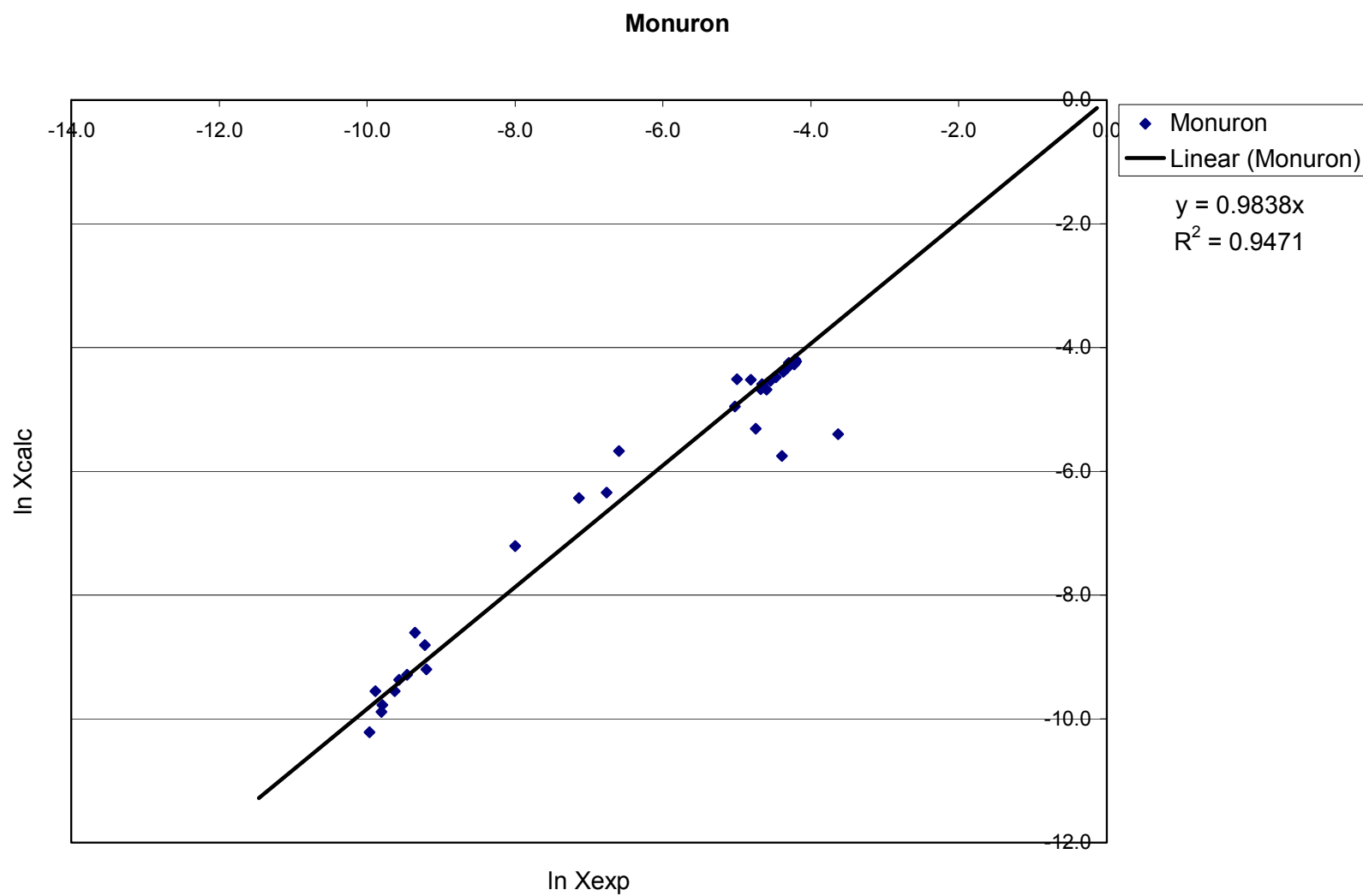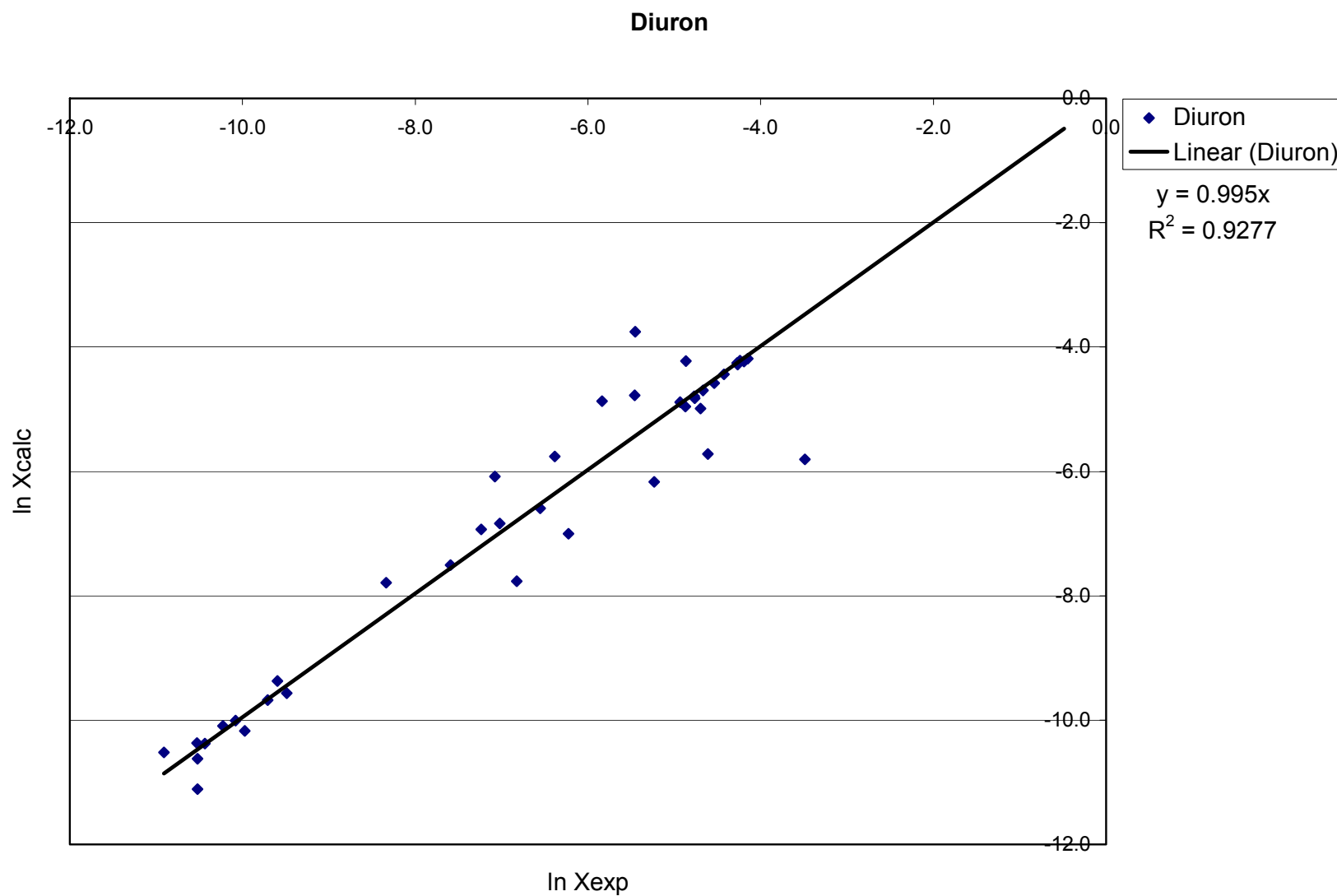Figure 4.2 Diuron: Graphical representation of predicted vs. experimental mole fraction solubilities (χ_A^{sat})

Diuron

y = 0.995x
R^2 = 0.9277

In Xcalc

In Xexp

Figure 4.3 Hexachlorobenzene: Graphical representation of predicted vs. experimental mole fraction solubilities (X_A^{sat})
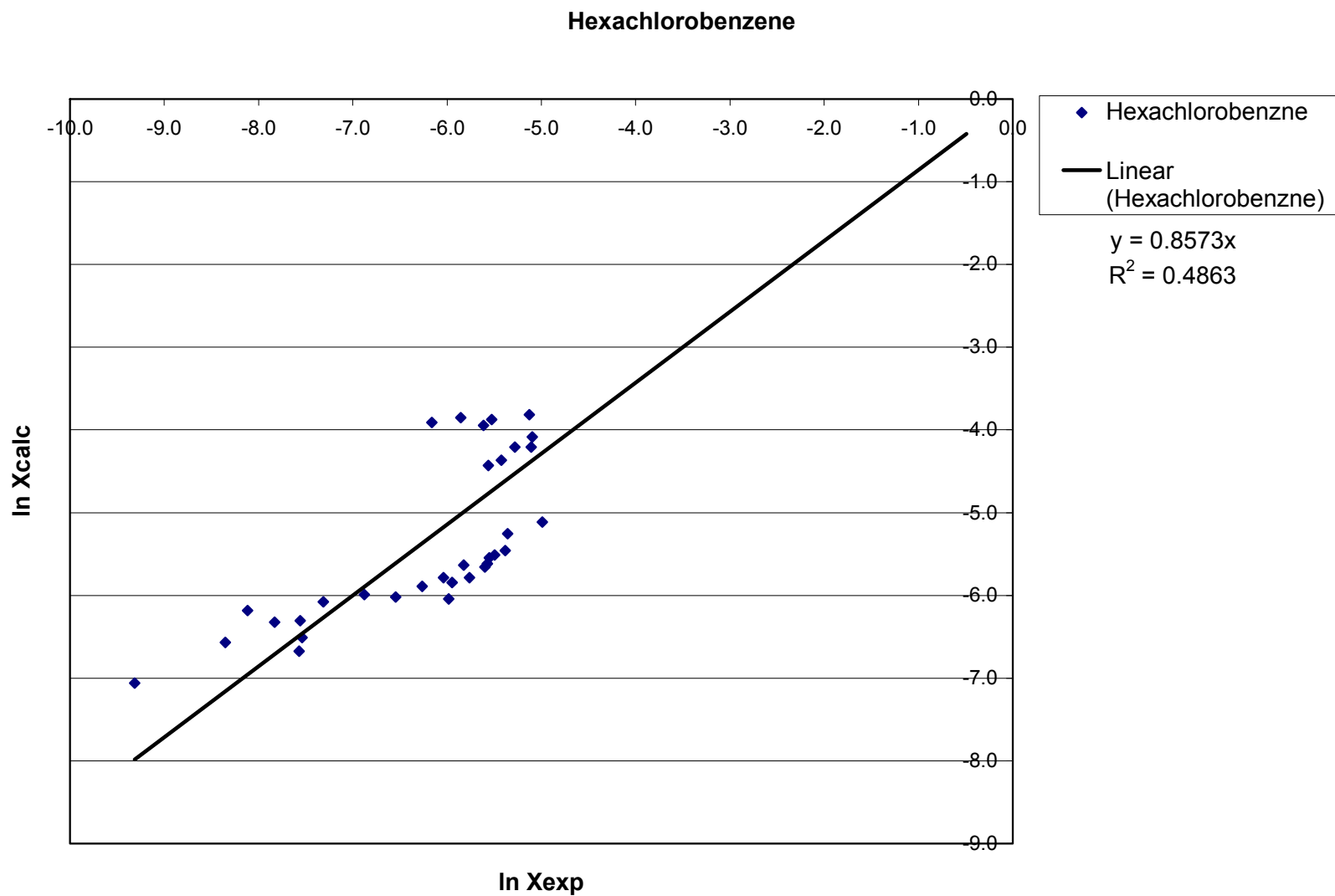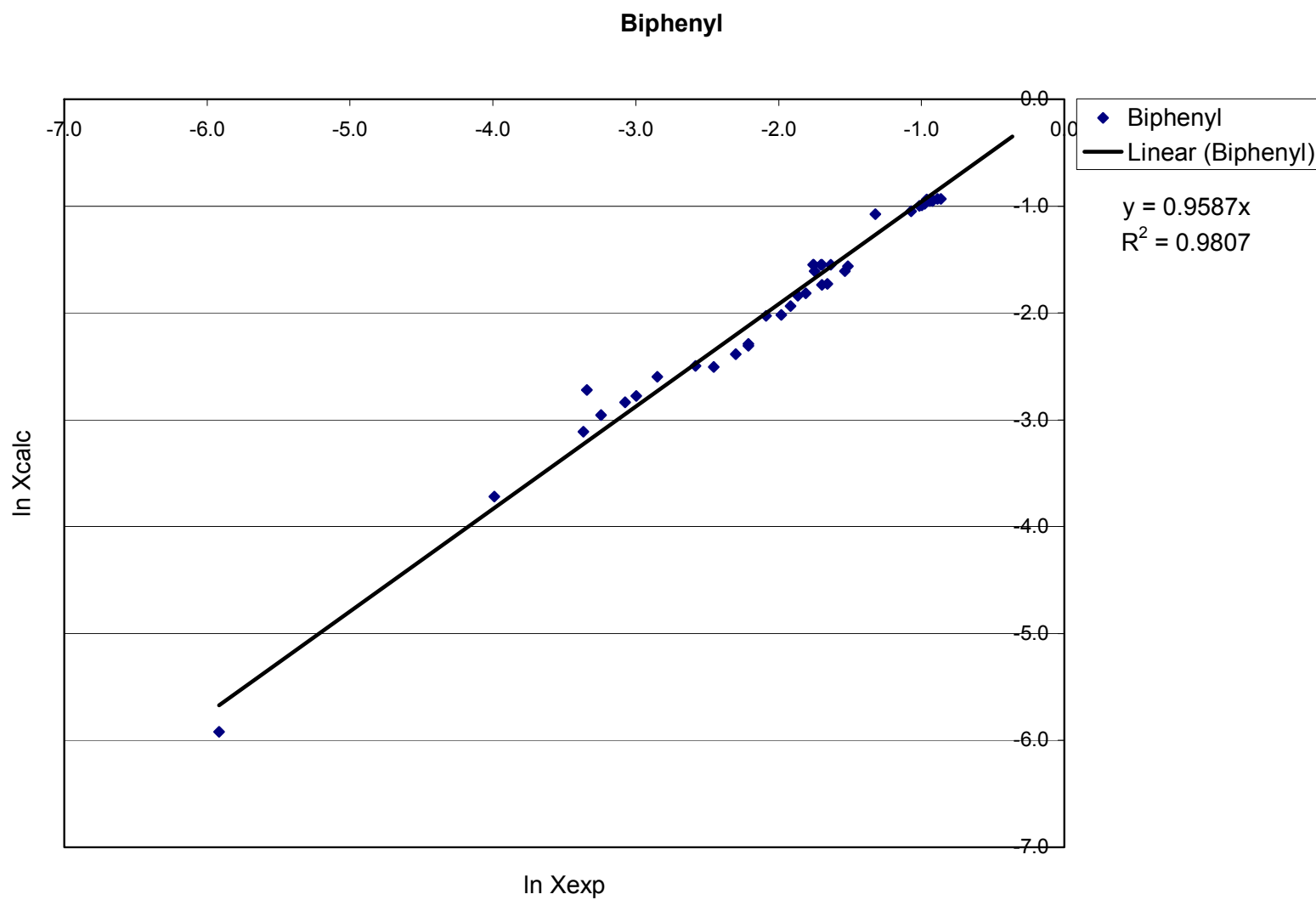

Hexachlorobenzene

y = 0.8573x
R^2 = 0.4863

Figure 4.4 Biphenyl: Graphical representation of predicted vs. experimental mole fraction solubilities (χ_A^{sat})

Biphenyl

y = 0.9587x
R^2 = 0.9807

In Xcalc

In Xexp

Figure 4.5 Acenaphthene: Graphical representation of predicted vs. experimental mole fraction solubilities (χ_A^{sat})

Acenaphthene

Legend:
♦ Acenaphthene
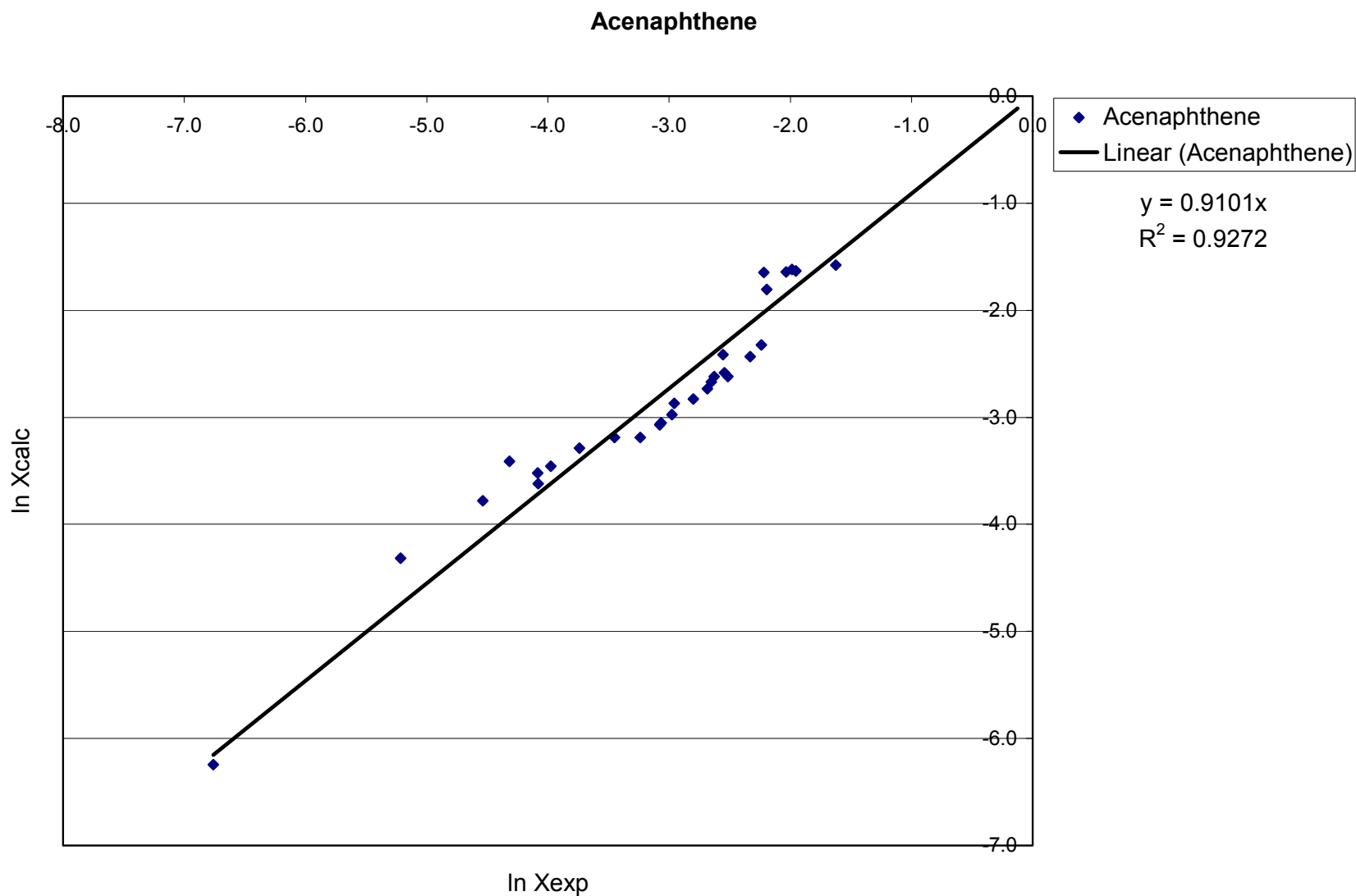— Linear (Acenaphthene)

$y = 0.9101x$

$R^2 = 0.9272$

Y-axis: ln Xcalc

X-axis: ln Xexp

Figure 4.6 Phenanthrene: Graphical representation of predicted vs. experimental mole fraction solubilities (X_A^{sat})

Phenanthrene

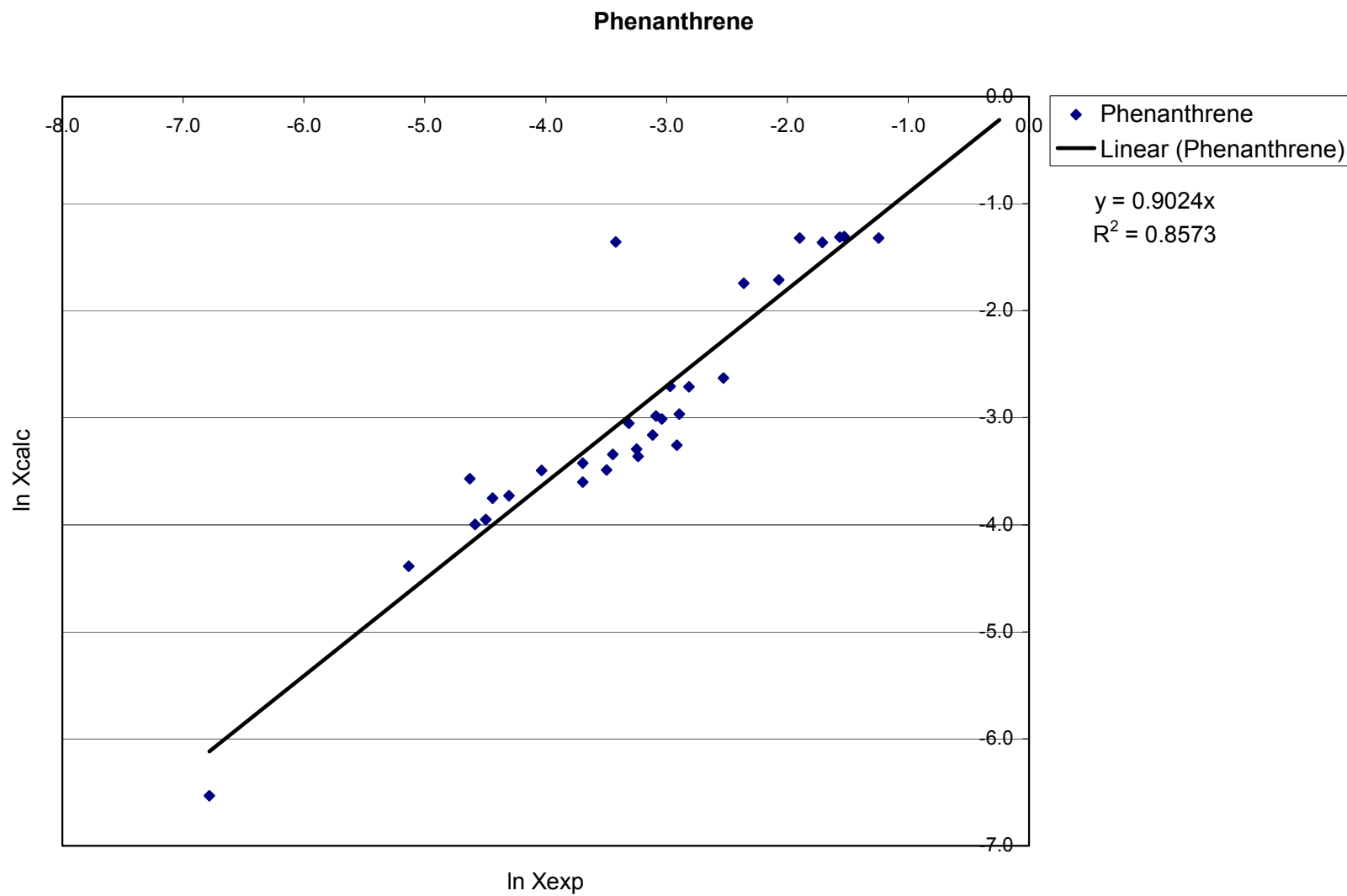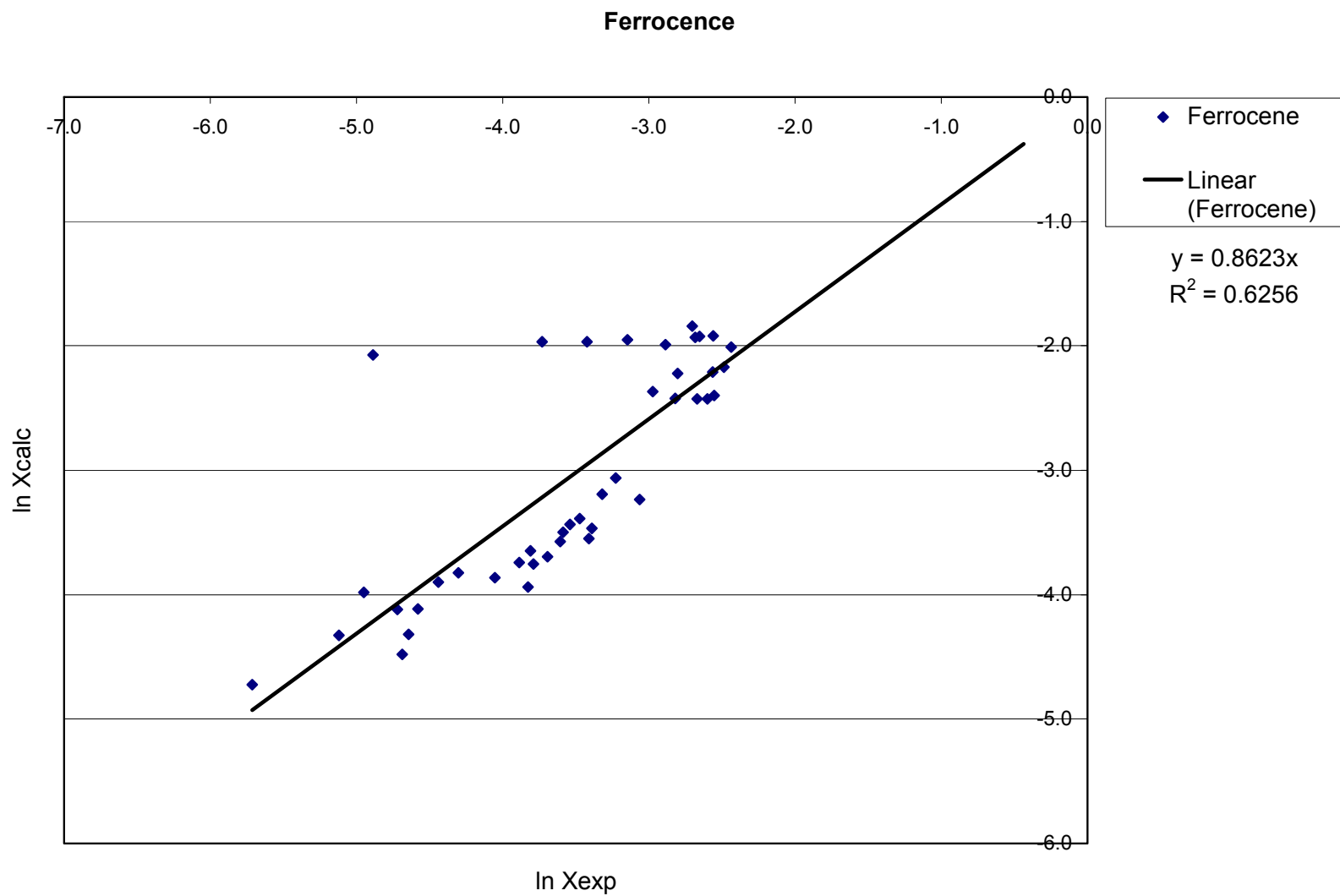
y = 0.9024x
R^2 = 0.8573

In Xcalc

In Xexp

Figure 4.7 Ferrocene: Graphical representation of predicted vs. experimental mole fraction solubilities (X_A^{sat})

Ferrocence

In Xexp

In Xcalc

y = 0.8623x
R^2 = 0.6256

Ferrocene

Linear (Ferrocene)

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APPENDIX

GLOSSARY OF SYMBOLS

a_{solute}^{solid}	activity of the solid solute, defined as the ratio of the fugacity of the solid, to the fugacity of the hypothetical pure supercooled liquid
A	absorbance
a	phase hydrogen-bond basicity (because basic phases interact with acidic solute sites)
b	phase hydrogen-bond acidity (because acidic phases interact with the basic solute sites)
BBB	blood-brain barrier
C	molar concentration
CNS	central nervous system
K_A	association constant for the various monomers, dimers, trimers …etc.
L	Ostwald solubility coefficient (blood-gas and tissue-gas partition coefficients at body temperature)
$L^{(16)}$	Ostwald solubility coefficient of hexadecane at 298 K, which can be experimentally determined by measuring the gas-liquid chromatographic retention time of the solute on a hexadecane stationary phase
log C	logarithm of the experimental molar solubility
log P	logarithm of the experimental partition coefficients of
log Soly ratio	logarithm solubility ratios

P	partition coefficient or equilibrium constant
P_A°	pressure of the vapor above the pure component
P_o	power/intensity of transmitted beam
pscl	pure subcooled liquid solute
r	tendency of phase to interact with solute π and n – electrons
R_2	solute excess molar refraction
	respectively
s	phase polarizability/dipolarity
SP	solubility properties
T	temperature of the system
T_{TP}	triple point temperature of the solute
V	molar volume
$\overline{V}$	pure solute molar volume
V_i	volume of component
ΔC_P	heat capacity of the solute at constant pressure
ΔH_{TP}^{fus}	heat of fusion at the triple point temperature T_{TP}
ΔG^E	molar excess Gibbs energy
ΔH^E	excess molar enthalpy
ΔS^E	excess entropy of mixing

GREEK LETTERS

α_2^H and β_2^H	hydrogen-bond acidity and hydrogen-bond basicity,
α	the fraction of molecules involved in chain
γ	the activity coefficient
ε	molar absorptivity (L cm^{-1} mol^{-1})
λ	measure of phase lipophilicity
μ	chemical potentials
π^*	measure the ability of the solute to stabilize a neighboring charge or dipole by nonspecific dielectric interactions.
π_2^H	solute dipolarity/ polarizability
φ	volume fraction
χ	mole fraction
χ_A	the mole fraction of A in the mixture

SUB-SCRIPTS AND SUPERSCRIPTS

aq	refer to the aqueous phases
m	non-self-associated "monomer" solute
org	refer to the organic phase
sat	indicates a saturated solution

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