THERMODYNAMICS OF THE ABRAHAM GENERAL SOLVATION MODEL: SOLUBILITY AND PARTITION ASPECTS

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Experimental mole fraction solubilities of several carboxylic acids (2-methoxybenzoic acid, 4-methoxybenzoic acid, 4-nitrobenzoic acid, 4-chloro-3-nitrobenzoic acid, 2-chloro-5-nitrobenzoic acid,2-methylbenzoic acid and ibuprofen) and 9-fluorenone, thianthrene and xanthene were measured in a wide range of solvents of varying polarity and hydrogen-bonding characteristics. Results of these measurements were used to calculate gas-to-organic solvent and water-to-organic solvent solubility ratios, which were then substituted into known Abraham process partitioning correlations. The molecular solute descriptors that were obtained as the result of these computations described the measured solubility data to within an average absolute deviation of 0.2 log units. The calculated solute descriptors also enable one to estimate many chemically, biologically and pharmaceutically important properties for the ten solutes studied using published mathematical correlations.

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CHAPTER 1

INTRODUCTION

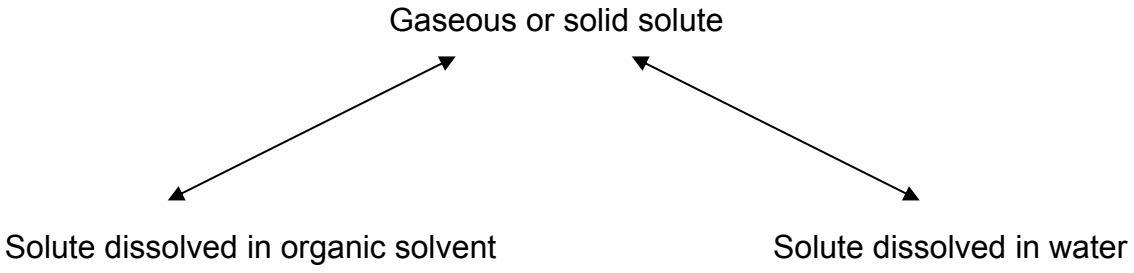
Thesis research involves the measurement of the solubility of select crystalline solutes in different organic solvents of varying polarity and hydrogen-bonding characteristics, and the analysis of the measured experimental data using the Abraham general solvation model. This particular model was selected because of its applicability to processes of both chemical interest (*e.g.*, solubility (1-8) and partition/extraction (9-17) and biological interest (*e.g.*, skin permeation (18), nasal pungency (19) eye irritation (20), brain-blood partition (21) and permeation (22), human (23) and rat (24) intestinal absorption, tissue-blood partition (25), aquatic toxicity (26-31). The same mathematical form is used for all of the different processes. This particular feature allows one to perform easy-to-make measurements, and then use the measured data to predict partitioning behavior of solutes in hard to measure and understand environments, like aspirin crossing the blood brain barrier to relieve a headache. "All chemical and physical properties of molecules and chemical reactions in solutions are related to solvation" (32). The phenomena of a salicylic acid or aspirin molecule traversing numerous biological and chemical barriers to reach its final destination in the brain to bind to a specific receptor and to exert its activity as a pain inhibitor is a complicated series of events.

To completely understand and comprehend a phenomenon like diffusion of a drug through a biological membrane or a simple chemical reaction would require the knowledge of the bulk chemistry and properties of membranes, crystals and solutions. This would, probably, be impossible because what little experimental data one could

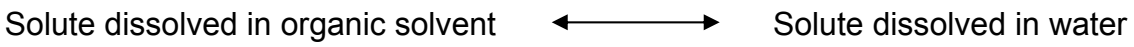
deduce would be coming from a complicated matrix of many different chemicals. It would be impossible to separate different molecular interactions and to assign chemical properties to each physical observation. Even if it were possible to do so, it is doubtful if the value(s) would provide much real insight into the molecular interactions. The large amount of human and mathematical errors involved in such a computation would yield numerical values with extremely large uncertainties. Also, the procedures are usually invasive to the specimen under analysis, and there is no guarantee that the property being studied will not change during the course of the measurement.

To keep the process simple, so as to understand and extract any useful information from such a complicated system, it is necessary to treat the process under consideration as simple partitioning-type models. The given solute molecule, treated as a monomeric species, interacts with different partition barriers. This approach has been successfully accomplished by several research groups and with different analytical separation techniques. For example, high-performance liquid chromatography (HPLC) and gas chromatography (GC) have generated vast amounts of retention data, which is thermodynamically related to partition coefficients. In the case of gas chromatography, the solute partitions between a liquid stationary phase and a gas phase as it travels through the entire length of the chromatographic column. In HPLC the solute partitions between a stationary phase (usually a liquid covalently bonded to or physically adsorbed on an inert, solid silica support material) and a liquid mobile phase. Chromatographic retention values have been successfully described by the Abraham solvation parameter model and yielded numerous correlative/predictive process equations (9, 33-38). There would be a different process equation for each different

stationary phase liquid (GC) or different stationary phase-mobile phase combination (HPLC). Process equations have also been derived from practical partition measurements involving the direct partitioning of a solute between two immiscible liquid phases. Separation by solvent extraction is an example of a direct partitioning process. Process equations have been developed for correlating the solubility of a series of solutes in a given organic solvent. In the case of the solubility correlations, the correlated, measured property is the ratio of the solute's solubility in the organic solvent divided by the solute's solubility in water. The solubility ratio is effectively a hypothetical two-stage partition/transfer process:



with the overall net effect being:



Inherent in the solubility ratio approach is the requirement that the equilibrium solid phase must be the same for the solubility measurements in both the organic solvent and water. The solubilities of solutes that form crystalline hydrates or crystalline solvates cannot be correlated with the Abraham solvation parameter model. From a thermodynamic point of view, this requirement is equivalent to using the same pure solute reference state for describing the chemical potential of the solute in both the organic solvent and aqueous phase.

It should be noted that numerous expressions have appeared in the published chemical and pharmaceutical literature for predicting solute properties that are difficult to measure. Published expressions can be classified into one of the following predictive strategies:

Strategy 1:

Predict the desired hard to measure property from structural information or from quantum mechanical deduced values

Strategy 2:

Predict the desired hard-to-measure property from easy-to-measure properties

Strategy 3:

Use easy-to-measure properties to first calculate solute molecular interaction descriptors, which are then used to predict the desired hard-to-measure properties.

Each predictive strategy does have its advantages and disadvantages. In the case of Strategy 1 predictions can be made solely from structural information, once the predictive expression is determined. As a representative example, Katritzky *et al*. (39) correlated the rat tissue-to-air and human tissue-to-air partition coefficients of a diverse set of volatile organic compounds (VOCs) to structural descriptors employing CODESSA-PRO and ISIDA programs. While statistically significant correlations were obtained for each tissue-to-air partition considered; however, each tissue-to-air correlation unfortunately used a different set of solute descriptors. The use of different solute descriptors makes it difficult (if not impossible) to compare the solubilizing properties and characteristics of the different animal tissues. Should one wish to also

predict the skin permeability of a set of potential drug molecules, a completely different type of solute descriptor would be needed. To my knowledge, there is at the present time no skin permeability correction(s) that utilize structural descriptors based on the CODESSA-Pro or ISIDA programs. One could perhaps use the TOPS-MODE and DRAGON descriptor correlations deduced by Gonzalez *et al*. (40). Even with today's modern computers, the calculations can be quite tedious and time-consuming, particularly if one wishes to predict a large number of properties for a large number of different solutes.

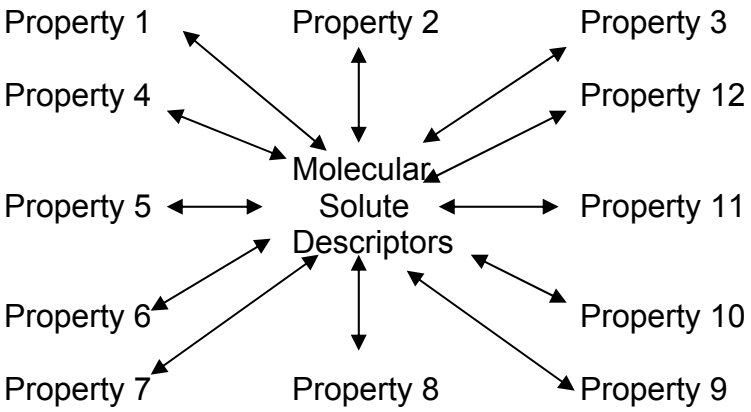
An example of Strategy 2 would be the prediction of human tissue-to-air and rat tissue-to-air partition coefficients using

$$\text{Log } P_{\text{tissue/air}} = \text{constant} + a_1 \log P_{\text{OTOH/Water}} + a_2 \log P_{\text{saline/air}} \qquad (1.1)$$

the solute's measured octanol-to-water, $P_{\text{OTOH/Water}}$, and saline-to-air, $P_{\text{saline/air}}$, partition coefficients (41, 42). The disadvantage with Eqn. 1.1 is that the expression can only be used if the compound's $P_{\text{OTOH/Water}}$ and $P_{\text{saline/air}}$ values are known. If one or both of the values are not readily available, then one must find another method to predict to the desired tissue-to-air partition coefficients. Historically, most Strategy 2 expressions for predicting biological properties used the octanol-to-water partition coefficient as the required easy-to-measure input property. Large compilations of octanol-to-water partition coefficients were both readily available and researchers experienced fairly good success in correlating many of the biological properties with $P_{\text{OTOH/Water}}$ values. Initially, the octanol/water system was considered to mimic biological systems, however, much later studies have shown that this may not be true. Principal component analysis of correlations based on the Abraham model have shown that log $P_{\text{isobutanol/water}}$ partition

system is more representative of biological processes such as skin permeability (43) and aquatic toxicity of narcotic organic chemicals to fish (31).

The Abraham general solvation model is an example of Strategy 3 predictive/-correlative method. The basic model describes the measured solute properties in terms of molecular solute descriptors, and the same mathematical form and solute descriptors are used for every process. Users of the Abraham model do not need to calculate a different set of descriptors for each type of prediction, as would be the case with the Katritzky et al. CODESSA-Pro descriptor correlations (Strategy 1 method). The advantage that the Abraham model has over many of the other existing predictive methods can be seen in the following illustration:



All arrows represent bi-directional calculations in that the solute descriptors can be calculated from any combination of properties, and once the descriptors are known, they can be used to estimate any solute property for which a process equation is available. The solute properties can be either easy to measure or hard to measure. As will be discussed later, the solute descriptors do have physical significance, and their numerical values do contain encoded information pertaining to the different types of

molecular solute-solubilizing media interactions. Such methods are by their nature a drastic simplification as the specific interaction of two or more molecules is considered as resulting in some way from nonspecific properties *i.e.*, determined for the isolated molecule or for a simplified system, with no reference to the real complex system under examination (44). A real biological system would undoubtedly contain more than a single solute molecule. The Abraham model has no provisions for multiple solute effects.

It is hoped that the research presented here will in some small way benefit the pharmaceutical industry, and result in a better understanding of some of the biological processes governing delivery of drugs to the desired target site. In the early days of drug development, around the 1970s, a general idea of what works and what fails was established as a rational drug development knowledge base. "New leads came from natural products; clinical observations of drug side effects; published unexamined patents; presentations and posters at scientific meetings; published reports in scientific journals and collaborations with academic investigators"(45). Based on previous historical records of which analogues in a series of compounds showed good therapeutic activity the bad or problematic compounds were eliminated and the leads for new drugs were considered to be within the realm of acceptable chemical characteristics; the need for screening tools were not very important. So, why do we need models today? The world has changed significantly, and the pharmaceutical industry is much more competitive than it was before. A pharmaceutical company no longer has the time nor financial resources to spend years finding a drug to cure a given disease or ailment. Today new leads come from combinatorial chemistry. With the

luxury of combinatorial chemistry, which allows automated synthesize of a vast number of compounds, one has thousands of possible new leads being analyzed with high throughput screening (HTS) techniques. "In the context of modern combinatorial chemistry and the associated need for high throughput screening assays, animal models are not appropriate for ethical and economical reasons" (46). These initial screening techniques do not consider the important properties that make these possible compounds available in a biological system. "Moreover, current experimental approaches to measure BBB partitioning are not amenable to high-throughput screening (HTS), as is becoming increasingly in demand in preclinical drug discovery" (47). Blood-brain barrier (BBB) partitioning is an important property governing the transport of drugs in the central nervous system.

HTS became popular during the late 1980s and early 1990s and with its advancement it became feasible to analyze thousands of chemicals in various *in vitro* assays. "The screening of very large numbers of compounds necessitated a radical departure from the traditional method of drug solubilization. Compounds were no longer solubilized in aqueous media under thermodynamic equilibrating conditions. Rather, compounds were dissolved in dimethyl sulfoxide (DMSO) as stock solutions typically at about 20-30 mM and then were serially diluted into 96-well plates assays…"(45). In today's ever changing times, when technologies are changing every nanosecond, it can be seen that predictive models are needed that can keep up with screening tools and prevention of toxic chemical production or contamination.

There are various types of models with varying complexity that are successful in predicting partition behavior among different system, types such as *in vivo*, *in vitro*, *in*

silico. Important consideration is given to ADMET (adsorption, distribution, metabolism, excretion, and toxicity) properties when a model intends to predict distribution of a drug or pesticide in a biological environment and it is know the three determining/limiting properties are genotoxic potency, aqueous solubility and human intestinal absorption (HIA). Characteristics that effect drug efficacy or lack thereof are largely dependent upon aqueous solubility; a drug must be available for oral absorption. Bioavailability of a drug that has bad intestinal absorption drastically decreases and it looses its effectiveness and instead becomes a toxicity issue. This type of information should also be considered for human and environmental research with respect to industrial chemicals. The degree of aqueous solubility contributes to uptake, distribution and ultimately bioavailability of a molecule (48).

Models like the Abraham model that can predict and describe complicated biological and chemical interactions, would retire the oldest model, the octanol/water system, and move towards a model that can describe not only physical interactions but more importantly a biological interface. "The octanol-to-water partition coefficient of a molecule is easy to obtain and provides a rough estimate of its hydrophilic/lipophilic properties. The octanol–water phase boundary, however, only represents a physical but not a biological interface"(46). Other experimental partitioning systems have been suggested as possible substitutes for biological systems; however, each suggested system has its own set of problems to consider. For example, some researchers believe that liposome-to-buffer partition coefficients mirror the biological situation more precisely than octanol-to-water partition coefficients. Some authors favor film balance measurements to characterize the incorporation of drugs into a biological membrane

(49, 50). This assay makes use of lipid monolayers spread at the air–water interface and determines lateral film pressure to monitor drug interactions. Although this system comes closer to a biological membrane than octanol–water partition coefficients, one should keep in mind that it represents only half a membrane with the hydrophobic lipid moiety being directed towards the gas phase"(46).

Extension of the Abraham model to additional biological and chemical processes requires measured solute properties for the process(es) that one wishes to describe. In the published literature there is considerable solute property data that has been reported in a fragmentary manner. For example, there might experimental human milk-to-plasma partition coefficients for one or two drug molecules in one publication, two or three additional human milk-to-plasma partition coefficients in a second paper, a few more experimental values in a third paper, *etc*. By carefully searching the chemical and pharmaceutical literature one can likely build sufficiently large databases for developing a few additional process correlations. It takes about 40 to 50 data points to develop a meaningful process correlation. It is doubtful, however, if one would be able to find solute descriptors for every compound for which experimental data was found. Although solute descriptors are known for slightly over 3,000 different organic compounds, there are many important classes of pharmaceutically important and environmentally important compounds that have not been studied with Abraham model. Most notably, solute descriptors are known for relatively few drug molecules and pesticides. Also, solute descriptors are available for relatively few carboxylic acids. To address this concern, the solubilities of several crystalline carboxylic acids (4-Nitrobenzoic acid (51), 4-chloro-3-nitrobenzoic acid, 2-chloro-5-nitrobenzoic acid (52),

2-methoxybenzoic acid, 4-methoxybenzoic acid (53), 2-methylbenzoic acid (54) and ibuprofen (55) were measured as part of the thesis research. Nonsteriodal anti-inflammatory drugs like acetylsalicylic acid (aspirin), ketoprofen, ibuprofen and naproxen contain the –COOH functional group. Solubilities of several noncarboxylic acid solutes (9-fluorenone, xanthene, thianthrene and fluorene) were also studied as part of the thesis work (56, 57).

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CHAPTER 2

REVIEW OF ABRAHAM GENERAL SOLVATION MODEL

Definitions and Types of Molecular Interactions

A solution is a homogenous mixture of two or more substances. The heat of solution (ΔH_{soln}) is the total energy associated with the solution process. The energy related to the attraction between the solvent and the solute has to be comparable to the endothermic process associated with the separation of the pure components. Imagine, dissolving sugar in water, the water molecules are separating to make room for the separating sugar molecules. This is happening simultaneously and both are endothermic processes, driven by the attraction between the solute, sugar and the solvent, water. Ficks law, based on concentration gradient theory, is responsible for passive diffusion of molecules from higher concentration to lower concentration. Spontaneous diffusion will continue as long as a concentration gradient exists.

The right energies and intermolecular attractive forces between adjacent solute and solvent molecules facilitate formation of a solution. The types of the various molecular interactions that can be formed between adjacent molecules depend to a large extent on the functional groups present in the molecule. Intermolecular forces like dipole-dipole and H-bonding are examples of attractions that form liquids, solids and solutions. The permanent and induced dipoles associated with molecules orient themselves on opposite ends, the positive end of the dipole will attract the negative end of a neighboring molecule; this dipole-dipole interaction increases with polarity and results in clustering of the molecule. In non-polar molecules, induced dipole interactions called dispersion forces occur, although they are not strong enough to hold molecules of

the same species together as a pure liquid they do contribute to solute-solvent interactions and this attraction also increases with polarity. When the electron cloud is easily polarized in the presences of an ion or a polar molecule a temporary dipole is created and the molecule is said to have an induced dipole. Hydrogen bonding, H-bonding, is the attraction between a small highly electronegative atom and hydrogen, for example nitrogen, oxygen or fluorine bonded to hydrogen. The hydrogen is at the positive end of a very polar bond. The dipole-dipole interaction that occurs between neighboring molecules is especially strong and produces noticeable physical properties, like high boiling point and low volatilities.

These intermolecular forces are responsible for holding molecules together in the form of liquids and solids. Liquids exhibit short-range order in which small clusters of molecules are constantly forming and breaking apart. The order and disorder of liquids make it impossible to develop a simple model to describe liquids, however, intermolecular forces can be well described in a linear free energy relationship (LFER) based on van der Waals and electron donor/acceptor (H-bonding) interactions. Extensive work has been published that correlates the properties mentioned above to molecular descriptors that can accurately predict solvent-solute interactions or partitioning behavior. For example, a molecule with a greater number of H-bonds and a large molecular weight correlates to less membrane permeation. Describing the mechanism of molecular interactions, like H-bonding, can allow for accurate correlation of molecular chemical characteristics from physical properties (1).

Partition coefficient is the ratio of the concentration of the solute in the organic phase to the concentration in the aqueous phase and is related to membrane

partitioning, which determines the distribution of a molecule between different phases of an environment. In many instances, the partition coefficient can be accurately estimated as the ratio of the solute solubility in the two solvents that form the partitioning system (2-4). Partitioning and solubility information is useful in the many industries, pharmaceutical and medicinal chemists take advantage of this intrinsic information when developing a new drug or determining a dosage. Describing molecules and solvent systems is important in many cases, for example in my research it is beneficial to develop mathematical correlations that are able to predict both the solubility and partition coefficient of compounds like molecular carboxylic acids in alkane solvents, which can not be easily measured. In solubility and partitioning measurements, one measures the total concentration of the solute in various solvents, which includes not only the molar concentration of molecular solute, but all dimeric and ionized forms as well. In the case of water-to-alkane partition coefficients, one can eliminate the dimerization contributions to the partitioning process by working at very low carboxylic acid concentrations where dimerization does not occur to any extent. Adding a small amount of a strong acid to the aqueous phase to prevent ionization can eliminate the ionization contributions. This is not possible in the case of solubility measurements as solute concentration is not adjustable (the concentration corresponds to that of the saturated solution).

Substances will readily dissolve when intermolecular forces in the solutions are similar to those found in the pure substances. Hence the saying, “like dissolves like”, non-polar substances will be miscible with non-polar and the same is true for polar substances, for example, polar water will dissolve ionic and polar molecules like sodium

chloride. It can be seen that intermolecular forces such as hydrogen bonding and polarizability are both very important properties containing intrinsic chemical information about the molecule and play an important role in solution chemistry. Obtaining experimental data for partitioning can be detrimental and expensive. Many models exist that predict molecular interactions with various systems, for example polar surface area (PSA), Δ total cholesterol, acetic acid-extractable cobalt (A-ECo), kidney function using creatinine-based predictive equations, in silico predictive models for aqueous solubility, human intestinal absorption (HIA), and Ames genotoxicity developed principally using artificial neural net (ANN) analysis and topological descriptors. There is a common limiting factor associated with the equations available in the literature, the equations are specifically defined for one processes like human intestinal absorption and the numerical data is only useful in the process being described. Abraham has been able to describe numerous processes with the same process coefficients by including five parameters that have proved to adequately correlate with experimental data.

The unique internal ability of the Abraham general solvation model, a specific mathematical form that can accurately describe solute partitioning between two condensed phases (such as octanol/water and organic solvent/water partition coefficients) or solute transfer from the gas phase to a condensed phase (such as Ostwald and Henrys law constants), suggests that of the existing models, it is the one most likely to be applicable to different processes/systems like predicting a new drug partitioning behavior across the BBB. The Abraham model is developed by using several organic solvents of varying polarity in a linear free energy relationship LFER to relate a series of solutes with a specific partition system, because the model is not

limited by predicting only $P_{octanol/water}$ it can be applied to many different types of partitioning phenomena. As a result of the flexibility, the Abraham model is a continuously refined database for slightly over 3000 molecules in various solvents or processes that nicely correlates physical properties with numerical data in the form of molecular descriptors which describe the chemical properties of the molecule and process coefficients that are specific for individual processes. Most important, the Abraham model can predict the partitioning behavior of a molecule in several systems, for example the partitioning of a pesticide in tissue vs. blood or air vs. blood which might be useful in a toxicological test for pesticide runoff in water systems.

Basic Mathematical Form of the Abraham Model

The Abraham general solvation model is used for predicting free energies of partition in chemical and biological systems**,** calculating molecular descriptors and predicting partition behavior. Free energies of partition provide pertinent information about molecular interactions and are used to calculate partition coefficients that describe the equilibrium of a solute between two immiscible liquid phases. The partition coefficient, $P = C_{org}/C_{Aq}$, is a ratio of the experimental molar solubilities of the solute in the organic phase to the aqueous phase at equilibrium. The Abraham model is made of two linear free energy relationships LFER that describes the partitioning of a solute from a gas phase to a condensed phase, and the second describes partitioning between two condensed phases.

$$SP = c + eE + sS + aA + bB + lL \text{ (gas-condensed phase)} \quad (2.1)$$

$$SP = c + eE + sS + aA + bB + vV \text{ (condensed-condensed phase)} \quad (2.2)$$

The Abraham general solvation model is useful in correlating physical properties and in predicting the partition behavior of a solute among several systems, like the partitioning of a drug in the brain vs. the blood, log (C_{blood}/C_{brain}) or a harmful pesticide or nerve gas in the air vs. the blood, log (C_{blood}/C_{air}). The model is able to predict partition coefficients and calculate molecular descriptors for a large number of processes, like tissue-blood and air-blood for over 3000 compounds. For example, in the pharmaceutical industry predictive equations are important because of the gained insight into the molecules ability to traverse biological membranes without the associated monetary burden involved in the drug discovery process. BBB penetration is one of the most critical pharmacokinetic issues in the design of central nervous system, CNS active drugs and a toxicity concern in the development of other classes of drugs (5). The Abraham general solvation model is designed to insure the molecular descriptors encode (are based on) pertinent information, such as basicity of the solute, allowing the equation to be used for large set of diverse compounds and a variety of different partitioning processes.

The molecular descriptors chosen in predictive equations make them more or less applicable over a wide range of processes. Unlike the Abraham model, most equations are made up of two or three descriptors that are designed to predict one physical property or the other extreme of the spectrum where the equations are computationally derived and can have several and up to 50 molecular descriptors. An example of a limiting equation is an equation that predicts only the octanol-water partition coefficient, $P_{o/w,}$ for a specific solute. The benefit of the Abraham model lies in

the molecular descriptors; it can predict the partitioning for a specific solute in several phases once all four molecular descriptors are known. The diversity and usefulness (they are based on real chemical information) of the descriptors, empower the equation to be more resourceful than other predictive models available. As mentioned earlier, most equations have been optimized to predict one property; also if the equations coefficients are computationally derived the descriptors in such equations may not be based on true chemical information. Instead the descriptors used might simply be those giving the best mathematical fit like predictive QSAR (qualitative structure activity relationships) or quantum mechanical (QM) computer models. In such models the descriptors are based on computational values and give absolutely no consideration to intermolecular forces like H-bonding, therefore lacking important information that facilitates solute-solvent interactions, given the chemical nature of the molecules involved. All models have to be analyzed to see if the information coming out is relative and to know the predictive power of the said equation. A large number of data points need to be included to determine the predictive capability of an equation. The data points will be separated into two data sets the training set which is used to derive the process/equation coefficients (which in the case of the Abraham model would be the c, e, s, a, b, v and l coefficients in Eqns. 2.1 and 2.2) and a test set to assess the predictive power. A large number of data points, at least 30, are necessary for the equation to include a good representation of independent and dependent variables and the data set should include a diverse set of compounds (6). The Abraham model is capable of predicting partition-type behavior among several processes such as, human intestinal absorption, tissue-blood and the uptake of organic compounds on activated

carbon. The fore-mentioned process involve solute transfer between two condensed phases, hence the basic model takes the following mathematical form:

$$SP = c + e\,E + sS + aA + bB + vV \qquad (2.3)$$

The dependent variable SP is a property of a series of solutes in a specific phase or system. Typically, SP is equal to Log P, where P is the partition coefficient. The independent variables *c,e,s,a,b,v(l)* are process (or solvent coefficients) that account for the solvent properties and have been previously calculated for a large number of gas/solvent and water/solvent systems. All of the terms in Eqn. 2.3 have been constructed so as to correspond to particular solute-solubilizing media interactions. The process coefficients will encode the interaction properties of the solvent phase. If transfer between two phases is considered, then the coefficients will indicate the difference in interaction of the two solubilizing medias. The r-coefficient refers to the tendency of the solvent phase to interact through σ- and π-electron pairs, the s-coefficient provides a quantitative measure of the solvent phase's polarizability/dipolarity, the a- and b-coefficients denote the solubilizing phase's hydrogen-bond basicity and acidity, respectively. The v-coefficient will relate to the hydrophobicity of the solublizing media, which itself can be broken down into a cavity tern and a general dispersion interaction term. The aA term on the right-hand side of Eqn. 2.3 quantifies the interactions between the hydrogen-bonding acidic sites on the dissolved solute (the A-parameter measures the solute's hydrogen-bonding acidity as will be discussed in the next section) and the hydrogen-bonding basicity sites of the solvent media. The remaining terms in Eqn. 2.3 represent other types of solute-solvent interactions.

Solute Descriptors and Their Encoded Chemical Information

The molecular descriptors, E, S, A, B, V (and L), describe the solute properties between two condensed phases, specifically the first four terms deal with the ability of the solute to participate in the solute-solvent interaction. In life, molecules have to possess the correct characteristics in order to traverse various biological membranes. Invaluable, molecular descriptors are used in linear free energy relationships to relate physical properties of a molecule to chemical properties that potentially, has uses to identify molecules as toxic or biologically useful. The molecular descriptors in the Abraham solvation model hold chemical information that describe the molecular size and van der Waals, the intermolecular attractive forces, involved with the endothermic process of creating the solvent cavity and the exothermic solute-solvent interaction.

The excess molar refractivity, E, is a measure of the ability of the molecule's bonded electrons to be involved in the solute-solvent dispersive interactions. E is calculated as

$$MR_x = 10[(\eta^2-1)/(\eta^2+2)]V \quad (2.4)$$

$$E = MR_x - 2.83195V + 0.52553 \quad (2.5)$$

the difference between the molar refraction of the molecule and the molar refraction of the alkane with the same McGowan volume V. In the case, where the molecule is complicated or large, calculating the McGowan volume can be tiresome; Abraham *et al*. (7) offers a program called VR to calculate the E and V descriptors. The VR program needs the molecular formula and the number of rings in the compound, R_g to perform the calculation.

Weckwerth and Carr (8) employed principal component analysis to study the

importance of including a solute polarizability correction term in linear solvation energy relationship (LSER). In the Abraham model the correction is the r R term. The authors correlated gas chromatographic retention data for 52 solutes on 7 different stationary phases

$$\text{Log } k' = c + d\,\delta_2 + s\,\pi_2^c + a\,\alpha_2^c + b\beta_2^c + l\,L \qquad (2.6)$$

$$\text{Log } k' = c + r\,R + s\,S + a\,A + b\,B + l\,L \qquad (2.7)$$

where k' is the solute's capacity factor (which is calculable from the measured retention time), and π_2^c, α_2^c and β_2^c refer to the dipolarity/polarizability, hydrogen-bond acidity and hydrogen-bond basicity solute descriptors of the Carr *et al*. LSER (9) The primary and only fundamental difference between Eqns. 2.6 and 2.7 lies in the polarity correction term, d δ_2 (Eqn. 2.6) versus r R (Eqn. 2.7). Through principal component analysis the authors found that there was fairly strong evidence for five factors in the data set (e.g., for using five solute descriptors in the LSER), and that between R versus δ_2, the Abraham R solute descriptor was clearly superior.

V (as well as L) relates to the size of the molecule and will correspond to the size of the solvent cavity that must be created in order to accommodate the solute. The V descriptor is calculated

$$V = \Sigma\, n_{\text{atom of type i}}\, V_{\text{atom of type i}} - 6.58\,B \qquad (2.8)$$

by counting the total number of bonds (B_n) between bonding atoms as one and by the addition of atomic volume fragments, $V_{\text{atom of type i}}$ (10). Single, double and triple bonds are treated equally, regardless of their hybridization. For example, in ethene the total bond count would be five. The total number of bonds can obtained from the molecular formula:

$$B_n = Na - 1 + R_g \quad (2.9)$$

where N_a and R_g denote the number of atoms and number of rings in the molecule, respectively. The vV term in Eqn. 2.3 is included in the linear free energy relationship to account for the cavity effect created by solvent-solvent molecules being broken to make room for the dissolved solute molecules.

A and B are the acidity and basicity descriptors that describe the hydrogen bonding sites present on the solute in question and they lead to a great deal of information, these descriptors alone are being used to predict equilibrium constant K. Abraham successfully predicted the equilibrium constant for the 1:1 reaction in tetrachloromethane at 298 K

$$A\text{-}H + B \leftrightarrow A\text{-}H\text{---}B$$

by the hydrogen bond (HB) acidity α_2^H factor of the AH molecule and by the hydrogen bond basicity β_2^H factor of the B molecule, through the relation (11).

$$\text{Log } K_{AB} = -1.094 + 7.354\ \alpha_2^H\ \beta_2^H \quad (2.10)$$

Over time, both descriptors were redefined and their method of determination changed slightly to reflect increased knowledge and understanding of solute-solvent interactions at the molecular level. The α_2^H and β_2^H values worked well at first when values were readily available from studies of molecular association complexes, and when only non self-associated solvents were considered. Conceptually though, there is a difference in a molecule's hydrogen-bonding characteristics when it is surrounded by a large excess of solvent molecules capable of hydrogen-bond formation, than the basicity (or acidity) of a solute towards a single hydrogen-bond acid (or base). The effective solute hydrogen-bond acidity and basicity descriptors, the modern A and B descriptors, were subsequently introduced to address this concern.

There is an alternative Abraham hydrogen-bond basicity descriptor, B^o, used for select solutes in practical organic solvent-to-water partitions when the "wet" organic solvent contains appreciable quantities of dissolved water. In practical partition and extraction experiments the equilibrium organic phase is saturated with water, and likewise, the aqueous phase is saturated with organic solvent. For most solutes B and B^o are numerically equivalent. Notable exceptions include alkylanilines, alkylpyridines and sulfoxides. Most purely computational models or quantum mechanical (QM) calculations completely ignore hydrogen-bonding interactions that facilitate the solute-solvent attraction. Based on the common fact that oral bioavailability is strongly related to hydrogen bonding properties, it is important to incorporate the fundamental concepts of hydrogen-bonding into the computation in order to arrive at an acceptable predictive model. One additional note about the Abraham acidity and basicity descriptors. Oliferenko *et al*. (12) recently analyzed several existing hydrogen-bond donor and acceptor scales, including the authors' own hydrogen bonding scale. Based on their analysis of published partition coefficient (water-to-chloroform, water-to-hexadecane, water-to-1-octanol, gas-to-water, gas-to-1-octanol, gas-to-hexadecane and gas-to-chloroform), the authors concluded that in the case of aliphatic compounds that the Abraham A and B descriptors were better than the Oliferenko et al. descriptors, which in turn were better than both the COSMOS and purely theoretical linear solvation energy scale descriptors.

The L descriptor is defined as the logarithm of the solute's Ostwald solubility coefficient in hexadecane at 25 ^oC. The numerical of L can be obtained experimentally by direct measurement of the solute's retention volume by gas-liquid chromatography

using a hexadecane stationary phase thermostatted at 25 ^{o}C. Such measurements are not possible for large, nonvolatile solute molecules that do not readily elute from the hexadecane liquid stationary phase. For large, nonvolatile compounds Weckwerth *et al*. (13) have suggested Apolane-87 as a suitable replacement stationary phase solvent. Apolane-87 is a stable, nonvolatile, highly branched nonpolar hydrocarbon liquid that can be used over the temperature range of 30 – 280 °C. A linear relationship exists for calculating the Abraham L descriptor from

$$L = 0.175 + 1.1004 \text{ Log } L_{\text{apolane-87, 40 C}} \qquad (2.11)$$

the solute's measured gas-liquid partition coefficient on apolane-87 at 40 °C, $L_{\text{apolane-87, 40 C}}$. Similar linear relationships could be developed for chromatographic measurements performed at even higher temperatures.

The solute's polarizability/dipolarity descriptor, S, is a quantitative measure of the propensity of a solute to engage in dipole-dipole and induced dipole-dipole interactions. A logical choice for the former would be the solute's dipole moment; however, Abraham and coworkers (14) showed that it was not always possible to separate the contributions of dipole-dipole interactions from those of induced dipole-dipole type interactions. A combined polarizability/dipolarity descriptors was thus introduced (15), with the numerical values of many solutes being determined through gas-liquid chromatographic measurements on polar stationary phases.

Originally, the acidity, basicity and polarizability descriptors were strictly of theoretical origin. That is, the numerical values were deduced by fitting the measured solute properties in accordance to Eqns. 2.1 and 2.2. As with any linear free energy model having theoretical experimentally based solute descriptors, one does have to start somewhere. In the case of the Abraham model, the starting point involved inert

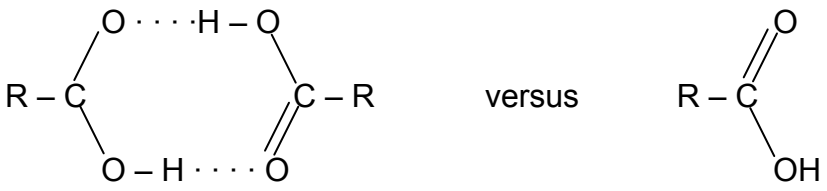
gases and alkane solutes dissolved in organic solvents, and inert gases and organic solutes dissolved in simple alkane solvents. For alkane solutes all of the solute descriptors would be set equal to zero, except for the V-descriptor, which is calculable from the solute's molecular structure. The partitioning behavior of alkane solutes allowed one to get a fairly good estimate of v- and l-process coefficients since all of the other terms in Eqns. 2.1 and 2.2 would be equal to zero. One could then add alkene molecules to the database, and fit by regression analysis the experimental partition and Ostwald coefficients of alkane and alkene solutes, this time determining the r-process coefficient, and if necessary, adjusting the v-process coefficients. By gradually introducing more classes of organic compounds and additional solvent systems, one would be able to calculate preliminary values of S, A and B for a fairly large set of organic compounds. The preliminary values could then be refined as more experimental values and compounds are added to the database. As time passes, the descriptors of certain solutes and equation coefficients of certain processes become more or less fixed, simply because of the vast amount of experimental data that was used in their determination. The current process coefficients for the water-to-hexadecane partition coefficient are based on experimental data for 370 different compounds (16). A few more experimental $P_{hexadecane/water}$ values will not statistically change the existing c, r, s, a, b and v values for this process.

This type of computation is reiterative because the newly calculated solute descriptors (and process coefficients) are then subsequently used to revise the existing process coefficients (and solute descriptors) to give a better overall mathematical description of available experimental data. Reiteration enables one to go from an initial

starting point of having zero solute descriptors and zero known processes coefficients to where the model is today. At the present time, solute descriptors are available for slightly more than 3,000 compounds. Process coefficients are currently available for about 50 different organic solvent-to-water and organic solvent-to-air partitioning processes. Solute descriptors have also been calculated from experimental HPLC and GC retention time measurements.

The descriptors are of experimental origin, and several methods have been developed for calculating the numerical values from various types of experimental data. Methodologies have been developed based on measurements of partition coefficients, chromatographic retention times and indices, Ostwald coefficients and solubility data. A nuclear magnetic resonance (NMR) (17) method based on the difference in the ^{1}H NMR chemical shift of a protic hydrogen in dimethylsulfoxide and $CDCl_3$ can be used to determine the overall, or summation, hydrogen bond acidity descriptor of the solute. The NMR method can measure the overall hydrogen bond acidity of individual functional groups. Which are then summed to give the value for the entire molecule. The estimated error in the solute descriptor A determined by the NMR method is around ± 0.05 units. Solutes that dimerize in $CDCl_3$ cannot be studied with the NMR method.

There are some solutes for which one (or more) experimental method may not be applicable. Most notably, solubility measurements in nonpolar solvents cannot be used in the case of carboxylic acid solutes. In nonpolar solvents, carboxylic acids are known to self-associate and form dimeric species. The properties of the dimeric solute species differ significantly from those of the monomeric carboxylic acid. This fact is quite evident in the following pictorial representation:



Notice that the ability of the carboxylic acid to function as an H-bond donor is completely lost in the cyclic dimeric structure. How does this affect the determination of solute descriptors for carboxylic acid solutes? Well, for one thing it is not possible to experimentally determine the L descriptor from chromatographic retention time measurements on a hexadecane stationary phase. The carboxylic acid solute would not exist in monomeric form under these experimental conditions. Moreover, one must exercise caution in deciding what pieces of available experimental data to use. In aqueous solutions carboxylic acids ionize, and the ionization effects must be removed before one is able to use experimental organic solvent-to-water partition coefficient data, even if the carboxylic acid does not dimerize in the organic solvent under consideration. Fortunately, the ionization effects can be easily eliminated by simply adding a trace amount of strong acid to the aqueous phase prior to equilibration.

It is possible to devise a series of experimental measurements for determining the solute descriptors for a given organic compound. There are sufficient known process coefficients for HPLC, GC, practical organic solvent-to-water partition, and hypothetical organic solvent-to-water partition systems. The latter systems apply to

solubility measurements where the so-called “partition coefficient” is expressed as the solubility ratio of $P = C_{organic}/C_{aqueous}$. If one has a large number of solute molecules to characterize, or if one does not have the compound available (as might be the case in the early stages of drug development), it becomes unfeasible to perform the necessary experimental measurements. There have been several suggested methods for estimating the Abraham solute descriptors from molecular structure considerations. Remember that E and V values are already calculated from molecular structures. Most notably, fragmentation and group contribution methods (18, 19, 20, 21) have proved quite successful in estimating solute descriptors for molecules of moderate size. Arey *et al.* (22) provided a theoretical justification for the Abraham polarizability/dipolarity descriptor, S, and showed that the numerical values could be reasonably estimated from molecular orbital computations. Cacelli *et al.* (11) predicted values of the A and B descriptors based on a reaction field type model. While the published predictions do appear quite promising for fairly simple molecules, there has not been enough comparisons of predicted versus experimentally-based descriptor values to accurately assess the limitations and applications of each estimation scheme. It is too premature for the estimation schemes to be of any real value in the drug screening process. Drug molecules often have many functional groups, and the estimation schemes may not take into consideration all of the synergistic effects and functional group inter-dependencies.

Applications to Pharmaceutically Important Properties – Human Intestinal Absorption

The Abraham model is also useful to the pharmaceutical industry due to its ability to deal with the A, absorption, of ADMET properties. A useful predictive model must deal with the parameters that determine bioavailability/toxicity of a molecule; along with ability to traverse the blood brain barrier and aqueous solubility it is equally important that the molecule get absorbed to ensure genotoxic or xenotoxic effects are minimized. As mentioned, poor solubility account for many failures of drug molecules and the determination of problematic compounds is a useful tool that can save important assets during pharmacokinetic drug development. At present the Lipniski "rule of 5" is a close example of such a device; stating that if two of any five observations are true than the said molecule will exhibit poor absorption properties (23).

1. molecular size exceeds 500
2. number of H-Bond donors (O-H and N-H groups) exceeds 5
3. number of H-Bond acceptors (O or N including contribution from the donor group) exceeds 10
4. C log P exceeds 5.0 or M log P exceeds 4.15

The name "rule of 5" comes about not because there are five rules, but because each of the four parameters were close to 5 or to a multiple of 5. Compound classes that are substrates for biological transporters are exceptions to the rule. However some molecules passing the Lipniski test still turn out to have poor intestinal absorption.

Martin (24) proposed a slightly different method for assessing permeability and bioavailability that also included consideration of the polar surface area and the number of rotatable bonds in the drug molecule. Martin noted that approximately 80 % of the

compounds that failed the “rule-of-five” test were not permeable to caco-2 cells, whereas 48 % of those that passed were not permeable. Forty-three of the 116 compounds that failed the “rule-of-five” test were found to have acceptable rat bioavailability, and 191 compounds out of 436 that passed the “rule-of-five” test had unacceptable rat bioavailability values. Compounds that were negatively charged at pH = 6 to pH =7 comprised a very large percentage of the “rule-of-five” failures. Based on an analysis of caco-2- cell permeability and rat bioavailability for several hundred drug molecules, Martin concluded that the physical properties that govern bioavailability and permeability are completely different for negatively charged species than for either cationic compounds or neutral molecules. For anionic compounds the polar surface area was found to be the most important of the properties Martin considered. A model with ability to accurately determine ADMET properties, specifically absorption early in the drug development process is necessary for the Research and Development pharmaceutical laboratories. Zhao *et al.* (25) modeled human intestinal absorption of a 169 drugs using the Abraham general solvation equation with successful generation of a rapid screening method for prediction.

Bioavailability is related/influenced by chemical properties. Published studies have shown that the number of hydrogen bonds, polarity and size of the molecule largely influence properties like bioavailability. Information derived from chemical properties that influence human intestinal absorption (HIA) of drugs molecules would be useful for the pharmaceutical industry during the selection and design process drug candidates. Previous experimental methods have been used to determine intestinal absorption data that are costly and labor intensive, like data obtained from cultured

colon cells called Caco-2cells (26) and canine kidney cells called madin-darby canine kidney cells (MDCK) (27). Permeability across Caco-2 cell cultures has widely been accepted to represent carrier-mediated transport systems in the small intestine and its permeability is commonly used to estimate human oral absorption of new chemical. This permeation data can also be determined and/or predicted in silico, for example, quantitative structure-permeability relationship (QSPerR) model developed by Ponce et al. (28) which has the ability to successfully predict intestinal-epithelial transport. The model can predict the permeability coefficient in Caco-2 cell culture of 33 drug molecules with diverse functional groups by using quadratic indices of the molecular pseudograph's atom adjacency matrix as their molecular descriptors. Such models would be utilized as an asset for the study of oral absorption for possible new drug leads. It is known that carrier mediated transport absorption of compounds is lower than molecules traversing through intercellular spaces known as the paracellular route of the small intestine and presents a route for the hydrophilic compounds that are unable to permeate the carcinoma colon cells. "Finally, the long culture period with the consequent high-research cost and the difficulty to extrapolate these in vitro results with the in vivo situation are considered as main practical limitations" (28).

Other research groups have proposed in silico methods to estimate HIA. For example, Votano *et al*. (29) developed a predictive model using artificial neural net (ANN) analysis and topological descriptors. Percent oral absorption, %OA, for 417 therapeutic compounds were utilized in the development of the ANN-QSPR (quantitative structure-activity/property relationship) model and after validation with 195 new drugs that gave a prediction of 92% compounds with in 25% of their reported %OA.

For the development of this model 108 descriptors were produced from a data set of about 10,000 diverse compounds. As in the Abraham model, these descriptors are unique to the process in question, HIA, and generated data/molecular descriptors that can be compared to correlate observed properties to molecular structures; it can be noted that 3 or 4 molecular descriptors would be easier to compare than several hundred descriptors.

Rats are the most common animals used in lab test for experimental data of oral absorption; therefore Abraham and coworkers (30) developed a predictive absorption equation using 158 data points and compared its predictive ability to an equation for human absorption with 98 drug compounds from the same data set that had human absorption data available. This type of comparison is useful for determining if the rat model is a good predictive tool for human absorption. The authors determined that in general the rat model is a good approximation for prediction of human absorption of various drug molecules. For well-absorbed drug molecules the model predictions were good, however for 25 poorly absorbed drugs the predicted values were about 8% higher than the human absorption model. After removal of several outliers a reasonably good regression coefficient of $r^2 = 0.77$ was obtained. Any equation predicting human intestinal absorption is subjected to the methodologies in which the original absorption data is obtained, along with inherent errors that pertain to these experimental methods. Bioavailability, urine and feces excretion of oral administrated drugs, and a ratio of cumulative urinary excretion of drug-related material following oral versus intravenous administrated drugs are the most common method used to evaluate human intestinal absorption of therapeutic compounds.

Relating biological activity of a compound to its physicochemical properties is not a straightforward task. Along with methodology errors one must also carefully evaluate the difficulties involved in obtaining accurate data; for example if a drug gets metabolized, solubility issues, dose dependent absorption and formulation/salt dependent absorption. To ensure that the Abraham model would produce the most accurate predictive equation possible the absorption data obtained from different literature sources was strategically divided into categories based on the method in which the data was obtained. The analysis of data resulted in eight different methods that were the basis of the data that was chosen to create the Abraham HIA model. The dependent variable SP in this example of the Abraham model is % absorption; this is quite contrary to linear free energy relationships, however it is conceivable that %absorption could be converted into the logarithm of a rate constant. The result obtained using the Abraham model are in agreement with previously published work; suggesting that polar molecular descriptors such as the hydrogen-bond donors and hydrogen-bond acceptors are the dominant molecular descriptors in which human intestinal absorption should be modeled. The majority of the results indicated that as the hydrophobic area increases and the polarity decreases the absorption is positively influenced. A definite point of interest is the lacking need to correct for ionization, noticeable throughout similar works. The Abraham descriptors always refer to the neutral form. To ascertain whether or not ionization important the authors also included the *I* indicator descriptor in the correlation equation. The *I* indicator descriptor is set equal to unity for a strong acid and base and zero for all other compounds. From this analysis Zhao *et al.* (29) determined that ionization has an insignificant influence on HIA

of a compound. The most important and dominant descriptors are the summation of A and B, solute hydrogen-bond acidity and basicity; the volume descriptor may also be relevant to absorption. The Abraham model correlation developed by Zhao *et al.* is able to successfully predict % human intestinal absorption around +- 15%; but more important are potential future applications involving modification of existing drug structures to encourage better absorption.

Applications to Pharmaceutically Important Properties – Blood-Brain Barrier Penetration

In the pharmaceutical industry poor solubility and poor permeability account for many failures of drug molecules. Enormous amounts of money and time are spent on the development of a possible new drug candidate only to have the candidate be rejected towards the end of the development process due to properties that could be perhaps predicted. Approximately 30 % to 50% of possible new drugs end up being problematic molecules and fail at the pharmacokinetic drug development stage, which is late in the development process. The cost associated with bringing a molecule to development stage that cannot reach its target area to exert its therapeutic activity is expensive, and if at all possible the industry would like to avoid unnecessary waste of these assets. Remember the cost associated with developing new drug molecules is ultimately passed on to the consumer in the form of higher purchase prices. Accurate determination of ADMET (absorption, distribution, metabolism, excretion & toxicity) properties, specifically distribution for CNS drugs that traverse the Blood-Brain barrier would be an invaluable asset to the pharmaceutical industry. Accurate screening

models are needed for the R&D pharmaceutical labs early in the drug development process because such models can facilitate the prediction of prospective drugs with desired ADME properties and potentially avoid research and development on inappropriate molecules.

Lipophilicity is an important parameter for blood-brain barrier (BBB) penetration. “In mammals, the BBB is constituted by brain capillary endothelial cells (BCEC), which form the vascular wall in brain microvessels and are interconnected by highly specialized cell–cell contacts (tight junctions) to form a continuous cell monolayer” (23). It is this biological barrier that inhibits various hydrophilic drugs from exerting their activity in the brain and leading one to understand that permeation only takes place through intercellular spaces between adjacent cells. Treating CNS disease is hindered because the BCEC monolayer therefore the drugs are unable to reach their target area in the brain. “Specialized transport proteins of the multi-drug resistance family in the brain endothelium are known to actively efflux many of these hydrophobic compounds, reducing their CNS access” (23). Polar molecules are considered to have poor BB permeation unless accomplished through active transport across the central nervous system.

The majority of published experimental blood-to-brain partition coefficient pertains to rats. Both *in vitro* and *in vivo* experimental methods have been used. The vial equilibration method proposed by Gargas *et al*. (31) is generally used for the in vitro methods. The animal tissue/organ being studied is harvested by sacrificing the animal, and a small weighed portion of tissue/organ is placed in a sealed pre-weighed glass vial of known volume. A weighed quantity of organic solute is then introduced by syringe

into the vial, and the resulting organic solute + animal organ/tissue sample is then allowed to equilibrate. Once equilibration has been obtained, a sample of the equilibrium headspace gas phase is withdrawn by syringe for quantification by gas chromatographic analysis. The tissue-to-gas partition coefficient, $P_{tissue/gas}$, is then calculated from the measured solute molar concentration in the gas phase, the total volume of the vial, the mass of the animal organ/tissue used and the mass of the organic solute placed into the glass vial. The blood-to-gas partition coefficient, $P_{blood/gas}$, is determined in similar fashion. The blood-to-brain partition coefficient, $P_{brain/blood}$, is then calculated as

$$P_{brain/blood} = P_{brain/gas} / P_{blood/gas} \quad (2.12)$$

the ratio of the brain-to-gas partition coefficient divided by the blood-to-gas value.

The published *in vivo* values are generally determined using radioactive drug molecules. The labeled drug is administered intravenously to the sedated animal. At a predetermined time interval, the animal is sacrificed and the organ/tissue and blood samples immediately harvested. The drug concentration in both the organ/tissue and blood samples is determined by radioactive counting techniques. Limitations of the *in vivo* measurement procedure is that one must synthesize the radio-labeled drug molecule (which is not always an easy task), and the radioactive counting method determines the total amount of radioactive isotope present in both the organ/tissue and blood samples. The measured concentrations thus include both the drug itself plus any degradation products containing the radioactive isotope.

Animal studies can be quite expensive, particularly with the growing number of regulations imposed by different governmental agencies in controlling animal testing.

Financially it is not feasible to conduct animal studies in the very early stages of drug development when one may have more than a thousand potential drug candidates (new leads) to consider. Predictive screening methods enable one to eliminate from possible consideration those potential drug candidates that do not have the desired ADMET properties.

Platts *et al.* (32) studied the largest data set of BB data with the intention to derive a general method for the "high-throughput" prediction of equilibrium BB distribution

$$\text{Log BB} = 0.044 + 0.511E - 0.886\,S - 0.724\,A - 0.666\,B + 0.861\,V \qquad (2.13)$$

$N = 148$, $R^2 = 0.710$, sd = 0.367 and F = 71

from structure. Here and elsewhere, N is the number of compounds studied (e.g., number of experimental data points correlated), R^2 is the squared correlation coefficient, sd is the standard deviation and F is the Fisher-F statistic. Although Eqn. 2.13 provided a reasonable model of log BB, several large discrepancies were observed between the back-calculated and experimental log BB values for carboxylic acid containing molecules such as indomethacin and acetylsalicylic acid (aspirin). The correlation was improved slightly

$$\log \text{BB} = 0.021 + 0.463\,E - 0.864\,S - 0.564\,A - 0.731\,B + 0.933\,V - 0.567\,I \qquad (2.14)$$

$n = 148$, $R^2 = 0.745$, sd = 0.343 and F = 69

by introducing an indicator variable, I, that was set equal to unity for compounds containing a –COOH molecular fragment, and set equal to zero for all other compounds. It is clear from the above correlations that the molecular properties that determine the extent of distribution between the blood and brain are molecular size and dispersion

effects which will increase brain uptake, while polarity/polarizability and hydrogen-bond acidity and basicity tend to decrease it. A similar trend is seen in the water-solvent partition (log P) equations pushing the molecules out of the aqueous phase and into the organic phase. The aqueous phase is able to solubilize the polar molecules exhibiting hydrogen-bonding and the organic phase prefers the bulky solutes. The “polar descriptors” on the other hand show negative S, A, and B coefficients indicative of the bloods ability solubilized more polar molecules with hydrogen-bond donor and acid acceptor ability due to its environment containing these very features; once again “like dissolves like”. This interpretation leads to the conclusion/observation that the blood is more acid, basic and polar/polarizable than the brain. The brain is better at housing bulky solutes; the barrier and solute interact through dispersion forces. The *I* indicator is not clearly understood at this time however it indicates a hindering effect interpreted in the large negative value when a solute containing a $–CO_2H$ group traverses the BBB. The effect is separate from the usual forces that hinder brain penetration such as the intrinsic hydrogen-bonding and polarity properties of neutral acids.

Equations 2.13 and 2.14 represent the most accurate model derived to date. The equations are based on experimental data for 148 compounds. The authors assessed the predictive ability of the derived log BB expressions by splitting the set into a randomly selected test and a training set as described earlier in the introduction. Based on the test and training set analysis, it was concluded that Eqns. 2.13 and 2.14 should be able to predict log BB values of compounds not included in the original regression analyses with an accuracy of 0.35 log units (or better). This method is considered a rapid and reproducible log BB predictive model, log BB can be calculated

from structure at a rate of 700 molecules per minute on a silicon graphics O(2) (32).

Applications to Pharmaceutically Important Properties – Skin Permeation

The skin provides a barrier to the external environment, that helps contain body fluids within the human/animal system, and hopefully excludes all harmful and/or hazardous chemicals from ever entering the body. Through microscopic studies it is known that the skin is composed of three layers: epidermis, dermis and subcutaneous tissues. The outermost layer of epidermis (called the stratum corneum) is the primary barrier against permeation of topically applied or adsorbed chemicals. It is believed that the majority of compounds that permeate the skin cross the bulk of the epidermis (stratum corneum) by either transcellular or intercellular routes. Once across the stratum corneum, the organic molecule diffuses across the viable epidermis and dermis, and is thus transported away by the cutaneous microvasculature (33).

The steady-state transport of molecules through biological membranes can be modeled as a partition-diffusion type process. The permeability coefficient, k_p, relating the solute flux to the concentration gradient across the biological membrane is given by

$$k_p = P_{membrane/water} (D_{membrane} / \square) \qquad (2.15)$$

where $P_{membrane/water}$ denotes the solute's membrane-to-water partition coefficient, $D_{membrane}$ is the solute permanent diffusivity within the membrane, and $\square$ is the diffusion path length. Published studies (34, 35, 36) have shown an exponential functional dependence of $D_{membrane}$ on the solute's molar volume, V_{solute}; in other words $D_{membrane} = D^o \exp(- \beta V_{solute})$. Substitution of the exponential functional dependence of $D_{membrane}$

into Eqn. 2.15 yields the following bilinear mathematical form:

$$\log k_p = f \log P_{octanol/water} + \log (D^o/\square) - \beta V_{solute} \quad (2.16)$$

after suitable algebraic manipulation. Performing a bilinear regression analysis of experimental k_p data versus the octanol-to-water partition coefficient and molar volume for a large number of organic solutes, Potts and Guy (37) showed that a nearly constant value was obtained for log ($D^o/\square$). The membrane-to-water partition coefficient was not available, so the authors used the octanol-to-water partition value as an approximation, *ie*., $\log P_{membrane/water} = f \log P_{octanol/water}$. The authors' observation of a nearly constant value of log ($D^o/\square$) is important in that it suggests that the same fundamental principles that govern partition processes apply to skin permeability as well. The same methods/models that are used to predict organic solvent-to-water partition coefficients could perhaps be used to estimate skin permeabilities.

The experimental determination of skin permeability is expensive, and any predictive method for k_p would be an useful screening tool in the initial stages of drug design when there are a large number of possible drug candidates to consider. Notable examples of drugs being administered topically to the skin include nicotine and birth control patches, as well as rubbing ointments like BenGay, try to list a few others by name. Dermal absorption and penetration is also important in those workplace environments where individuals are exposed to different organic chemicals on a daily basis. Here, unlike the pharmaceutical applications, one does not want the organic chemical to penetrate the worker's skin.

Skin permeability coefficients are generally measured in vitro using a two-compartment Franz-style diffusion cell. The skin membrane is mounted onto the top of

the receptor chamber, with the stratum corneum layer exposed to the donor compartment cell. Human, rat and hairless mouse skin are typically used in permeability studies. Human skin is available from cadavers or from plastic surgery (abdomen reduction surgery). A study by Williams and coworkers (38) found no relationship between measured skin permeability coefficients and specimen age, gender or storage time. An aqueous solution containing the drug molecule being studied is placed into the donor compartment. The receptor compartment is then filled with an equal volume of saline solution. Samples of the receptor fluid are then collected at known equilibration times and the molar drug concentration quantified via standard analytical methods, usually gas chromatography or high-performance liquid chromatography. The volume of receptor fluid in the receiving chamber is maintained constant by replacement of a volume of fresh receptor saline solution equal to the sample volume removed for analysis. The cumulative amount of drug penetrating the skin membrane, as appearing in the receptor fluid at each sampling time-point, adjusted for the receptor fluid volume and the amount of drug removed with each serial aliquot, is calculated and then divided by the surface area of the skin membrane. The resulting values are graphed at their respective equilibration times. The linear portion of the curve corresponds to steady-state penetration. The permeability coefficient is computed by dividing the slope of the linear steady-state penetration by the drug concentration in the donor chamber.

Abraham and Martins (6) compiled literature values of the permeability coefficients for 119 solutes for permeation of human skin from water. The authors adjusted the values for ionization in water and for changes in temperature. Several of

the experimental values had been measured at a temperature other than 37 °C. Earlier studies by Peck *et al.* (39) had shown that skin permeability was indeed temperature dependent. The temperature variation for permeation of solutes from water and from ethanol could be mathematically described by assuming energy of activation to be approximately 15 kcal mol^{-1}. For the ionization contribution, Abraham and Martins assumed a simple additive relationship

$$k_p(\text{total}) = k_p(\text{ionized})\,[\text{ionized}] + k_p(\text{neutral})\,[\text{neutral}] \qquad (2.17)$$

where [ionized] and [neutral] denote the fraction of the ionic and neutral species at the pH of the permeability measurements. Past studies had shown that for proton acids, the value of k_p for the neutral form was very much larger than k_p of the ionic form (40, 41) and as a result, no correction was necessary. This was not the case for proton bases, however, as both the neutral and ionic species were able to permeate human skin. Based on a careful analysis of published permeability coefficients for fentamyl (from pH 7.4 to 9.4), for sufentamil (from pH 7.4 to 9.4), and for ephedrine and scopolamine at several pHs, Abraham and Martins noted that the four sets of published experimental data could be described with an average $k_p(\text{neutral})/k_p(\text{ionic})$ ratio of 17.5. The authors corrected the published permeability coefficients of the amine solutes, and only the values for the neutral species were included in the regression analysis.

Analysis of the corrected skin permeability coefficient data gave the following correlation

$$\text{Log } k_p \text{ (cm } s^{-1}) = -5.426 - 0.106\,E - 0.473\,S - 0.473\,A - 3.000\,B + 2.296\,V \qquad (2.18)$$

N = 119, R = 0.832, sd = 0.461 and F = 112

No experimental values were excluded from the data analysis. The authors further

assessed the predictive of the derived correlation by dividing the entire data set into training and test sets. The full equation, Eqn. 2.18, was found to be almost identical to the average of three training equations based on the three training sets randomly selected from the entire database. Based on their equations, Abraham and Martins concluded that Eqn. 2.18 should be capable of predicting log k_p values of additional compounds to within approximately ±0.5 log units or so, which should be sufficient for many pharmaceutical-type applications. The authors further concluded from the magnitude of the correlation coefficients of Eqn. 2.18 that the main factors that influence skin permeability are the solute's hydrogen bond basicity which lowers log k_p and the solute's volume/size, which increases log k_p. Solute dipolarity/polarizability and hydrogen bond acidity make minor contributions, and both decrease skin permeability.

Applications to Environmentally Important Properties – Aquatic Toxicity

Manufacturing companies have neither the time nor financial resources to determine the toxicities of the thousands of new compounds that are marketed every year. Such studies would require that one measure the toxicity towards each living organism that a given compound would come in contact with through both direct and indirect exposures. Governmental regulatory agencies have established strict experimental protocols for how the toxicity measurements are to be performed as several factors like temperature, pH, dissolved oxygen concentration, photoperiod duration, feeding cycle, animal size and age can affect the numerical results. Established experimental methods reduce the inter-laboratory variations in measured

toxicity values. An initial assessment of toxicity is extremely important in the pharmaceutical industry where researchers must quickly decide which of many possible drug candidates (or drug leads) they wish to actively pursue. Predictive screening method would help researchers eliminate from consideration those possible drug candidates that were likely to be too hazardous for human and other living organism exposure. It would be financially detrimental to the company to spend considerable time in developing synthetic and purification methods to obtain the potential drug molecule in pure form for clinical studies, only to later discover that the molecule was too toxic to ever be approved for human (or other animal) use. The same considerations apply to manufacturing sectors involved in pesticide and fungicide production. For these industries, screening methods would help researchers identify those molecules that exhibited the desired pesticide or fungicide effect towards the directed target organism(s), but which exhibited negligible toxic effects to other organisms. Screening methods would facilitate more useful chemicals that are “more environmentally friendly.”

There are different assays in place to determine the toxicity effect a chemical would have it were to be released into the environment, one of which is a batch of text of asses for aquatic toxicity. Aquatic toxicity is designed to assess the damage that would result after a bad chemical was introduced into our waterways. The fate of an anthropogenic organic compound released into the environment is primarily controlled by a combination of three factors: 1) prevailing environmental conditions at the point(s) of discharge, transport and subsequent residence, 2) the physicochemical properties of the compound, and 3) patterns of use (that is, locus and timing of introduction; *1*).

Factors pertaining to prevailing environmental conditions at the point of discharge and to pattern use of use are not amenable to predictive screening methods. Moreover, manufacturing companies do not really have control on how a consumer will apply; let's say a particular pesticide on vegetation. The company could provide detailed instructions for how the product is to be used; however, there is no guarantee that the consumer will follow the written directions.

Physico-chemical properties, on the other hand, are more controllable and subject to less outside influences. For example, the freezing point of water is 0 ºC (273.15 K), irrespective of the geographical location that the value is measured. Physico-chemical properties are more amenable to screening methods, and the knowledge gained by understanding the underlying molecular principles responsible for the molecule's given physico-chemical properties can be used to predict biological properties as well. Two of the most important physico-chemical properties relating to the environmental behavior of hydrophobic organic compounds are the aqueous solubility and the octanol-to-water partition coefficient (42). Expressions have been published correlating experimental aquatic toxicity data to both properties. It is only naturally to assume that the calculation methods used to predict octanol-to-water partition coefficients and aqueous solubilities might also work for aquatic toxicities.

Expressions have been directed for estimating the toxicity of organic chemicals to various aquatic organisms based on theoretical indices/descriptors calculated solely from molecular structure considerations (43, 44, 45, 46, 47), from descriptors/indices of experimental origin (the Abraham model is one such method) (48, 49, 50, 51), or from group contribution concepts (52, 53). Published correlations have shown varying

degrees of success in terms of their predictive ability. For the most part, predictive methods have experienced better success at estimating the aquatic toxicities of organic compounds that act through noncovalent or nonspecific interactions. Nonpolar narcosis and polar narcosis are two such modes of nonspecific action. Simply stated, nonpolar and polar narcosis results from the disruption of the cells function because of the presence of the toxicant. No chemical reactions are involved. The mere presence of the toxicant is sufficient for the cell disruption. The presence of an organic compound within a cell or organism involves partition process(es), and the same fundamental principles that govern solute partition/transport from one phase to another should be applicable to nonpolar and polar narcotic mechanisms. Most common industrial molecules have either a nonpolar or polar narcotic mode of action. Published studies have shown that predictive methods are less successful in predicting the toxicity of compounds whose model of toxic action involves one of electrophilic or nucleophilic covalent reactivity. Here the cell disruption results from a chemical reaction between the toxicant and a cell site. Chemical reactions do not involve a partition process.

There are several published instances of the Abraham model being applied to toxicity data. Blum and Speece (54) derived a correlation:

$$\log IG_{50}(\mu M) = 6.82 - 4.47\,(V_I/100) - 1.21\,\pi^* - 1.02\,\alpha_m + 3.10\,\beta_m \qquad (2.19)$$

$$n = 50 \qquad s = 0.29 \qquad r^2 = 0.95$$

for describing the mini\um concentration of an organic compound that would result in a 50 % inhibition of growth, IG, for the environmental bacterium *Nitrosomonas*. Equation 2.19 is an earlier form of the Abraham model, before the R descriptor was introduced. The equation is presented in terms of the symbolic notation used at that particular time.

Back then, the solute dipolarity descriptor was denoted as π*, and the hydrogen-bonding acidity and basicity descriptors as α_m and β_m, respectively. The descriptor $V_I/100$ is the intrinsic volume developed by Leahy (55) in units of $cm^3\ mol^{-1}$. In today's modern version of the Abraham model the McGowan volume has replaced the use of the intrinsic volume.

Blum and Speece performed the required external validation by randomly removing 20 % of the experimental log IG_{50} values from the data set, and then recalculating the regression equation using the reduced data set. The resulting new equation was checked to ensure that it was compatible with the original equation at the 95 % confidence level. The omitted data points were also checked to confirm that each point fell within the 95 % confidence interval of its respective predicted value. The statistics of Eqn. 2.19 are quite good given the fact that biological data has a greater experimental uncertainty associated with the numerical values than does chemical data. Equally good correlations were derived for the 50 % inhibition of growth of organic chemicals to aerobic heterotrophic and methanogenic bacteria studied by the authors.

Kamlet *et al.* (56) found that the toxicities of 32 organic nonelectrolytes to the golden orfe fish were well correlated by

$$- \log LC_{50}\ (mM) = -3.19 + 3.29\ (V/100) + 1.14\ \pi^* + 1.52\alpha_m - 4.60\beta_m \qquad (2.20)$$

$$n = 32 \qquad s = 0.19 \qquad R^2 = 0.966$$

an earlier version of the Abraham general solvation model. In Eqn. 2.20 the measured toxicity endpoint is the millimolar solute concentration that would result in a 50 % death of the population of golden orfe in a 48-hour exposure. Several aldehydes and alkylacetates appeared to be outliers in the derived correlation. Both classes of

compounds exhibited toxicities in excess of predicted values based on Eqn. 2.20. The authors rationalized the enhanced toxicity of aldehydes in terms of a Schiff-base chemical reaction

$$\text{enzyme-NH}_2 + \text{O=CH-toxicant} \longrightarrow \text{enzyme-N=CH-toxicant} + \text{water}$$

between the amine group of the fish enzyme and the aldehyde group of the organic toxicant. The enhanced toxicities of esters were consistent with a mechanism involving an *in vivo* hydrolysis chemical reaction. Chemical reactions are not governed by the partition-type interactions upon which the Abraham model is based.

Other published examples involving the application of the Abraham to toxicity data involve tadpole narcosis (57), several species of fish (50, 58), the *Daphnia magna* water flea (50), the *Pseudomonas putida* bacterium (51) and the protozoan *Tetrahymena pyriformis* (51). In each instance, good predictive correlations were obtained. Given the ability of the Abraham model to correlate and predict a wide range of diverse chemical and biological properties, as was discussed in the preceding four sections of Chapter 2, one can understand the importance of continually determining solute descriptor values for even more organic compounds.

Applications to Environmentally Important Properties – Uptake of Chemicals by Plants

Plants accumulate pollutants, herbicides and pesticides by uptake from soil and water through their root systems, or from the atmosphere above their ground parts after wet or dry leaf depositions. For airborne compounds the main route of uptake will likely by via the leaf surface because the total leaf surface area is generally much larger than

the ground area on which the plant is growing. Moreover, the mobility of most organic compounds in the solid and in the transport system of plants is fairly low due to the low solubility of the organic compound in water, and the very strong sorption of the organic compound to lipophilic compartments.

It is widely believed that the uptake of organic compounds through the leaf cuticle is a diffusion process (59, 60). The penetration model developed by Watanabe (61) relates the total amount of penetration (i.e., the maximum uptake of the chemical), U, to the unit partition coefficient, $P_{unit\ partition}$,

$$U = V\ C\ A\ P_{unit\ partition} \qquad (2.21)$$

where V is the volume of the volume of the droplet applied to the leaf surface, C is the molar concentration of the organic compound, and A is the contact (spread) area of the droplet. The unit partition coefficient, $P_{unit\ partition}$, is the ratio of the amount of organic compound partitioned from the droplet into the cuticular membrane relative to the amount applied per unit contact area. Equation 2.21 provides a theoretical bases relating organic compound uptake in plants to a physical property that is amenable to predictive modeling.

Plant uptake of pesticides and other environmental chemicals by leaves and fruits have received considerable attention in recent years, and several predictive methods have been proposed for predicting the water-to-plant cuticle partition coefficient. For example, Sabljic and coworkers (62) suggested the following mathematical expression for estimating water-to-plant cuticle partition coefficients, K_{cw}

$$\text{Log } K_{cw} = 0.26 + 1.32\ {}^{3}\chi^{v} + 1.43\ (\text{no } OH_{aliph}) \qquad (2.22)$$

N = 50, R = 0.985, sd = 0.345 and F = 754

where $^{3}\chi^{v}$ is the third-order valence molecular connectivity index (which is calculable from the nonhydrogen part of the molecular structure) and no OH_{aliph} denotes the number of aliphatic OH groups on the molecule. Partition data for 4 plant types (citrus, Ficus, Lycopersicon and Capsicum) were combined into a single data set for use in deriving Eqn. 2.22. The statistics were improved slightly

$$\text{Log } K_{cw} = 0.37 + 1.31\ {}^{3}\chi^{v} + 1.49\ (\text{no } OH_{aliph}) \qquad (2.23)$$

N = 47, R = 0.992, sd = 0.250 and F = 1418

by removing 1-naphthaleneacetic acid from the data set. 1-Naphthaleneacetic acid was a serious outlier, with residuals between the back-calculated and observed log K_{cw} values ranging from –0.86 to –1.01 log units. Removal of the one compound from the data set decreased the number of experimental data points by 3 (from N = 50 to N = 47) because partition coefficients existed for three of the four types of plants. 1-Naphthaleneacetic acid was an outlier for all three plant types. Equation 2.22 and 2.23, while perhaps useful as strictly predictive expressions, do not provide any meaningful information in regards to the kinds of molecular interactions that are responsible for the organic molecule's uptake into the plant cuticle from an aqueous solution. The coefficients and descriptors used in Eqns. 2.22 and 2.23 encode no useful chemical or structural information.

Platts and Abraham (63) later applied Eqns. 2.1 and 2.2 to available air-to-plant cuticle, L_{ca}

$$\text{Log } L_{ca} = -0.641 + 1.310\ S + 3.116\ A + 0.793\ B + 0.877\ L \qquad (2.24)$$

N = 62, R^2 = 0.994, sd = 0.230 and F = 2361

and water-to-plant cuticle partition coefficient data, K_{cw},

$$\text{Log } K_{ca} = -0.415 + 0.596\ E - 0.413\ S - 0.508\ A + 4.096\ B + 3.908\ V \qquad (2.25)$$

$N = 62$, $R^2 = 0.981$, sd = 0.236 and F = 566

The coefficient e of E in Eqn. 2.24 was found to be insignificant at the 95 % confidence level, and was omitted from the final derived correlation. Equations 2.24 and 2.25 provide valuable insight into the solvation behavior of the plant cuticle matrix. Careful examination of eqn. 2.24 reveals that the equation coefficients are completely different from those corresponding to the air-to-water partition process

$$\text{Log } L_{wa} = -1.27 + 0.82\ E + 2.74\ S + 3.90\ A + 4.81\ B - 0.213\ L \qquad (2.26)$$

indicating that the plant cuticular matrix cannot be highly aqueous in nature. The plant cuticle does resemble a number of organic solvents that are quite strong hydrogen bond bases (reflected by the large A-coefficient). Acidic solutes interact with a basic phase. The nonzero coefficient on the B-solute descriptor shows that the cuticle matrix does have some hydrogen bond acidity character, though not nearly as much as water (0.783 versus 4.81). The major component of the plant cuticle matrix is cutin, which is a high molecular weight polymer of C_{16} and C_{18} hydroxyalkanoic acids. In large hydroxyalkanoic acid polymers of this type one would expect to find reduced hydrogen bond acidity as many of the –OH functional groups should by internally hydrogen-bonded to the –CO- groups of the acid moiety. Strictly predictive expressions, like Eqns. 2.22 and 2.23 above, are not able to provide such insight into the properties of the solubilizing media. Additional applications of the Abraham model to environmentally important properties include the partitioning of organic compounds between water and naturally occurring soil/sediment organic matter (64), sorption of organic vapors to snow (65), adsorption of organic compounds on carbonaceous adsorbents (66), nasal

pungency thresholds (67) and the concentration of a sensory irritant necessary to decrease respiratory frequency in mice by 50 % (68).

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CHAPTER 3

EXPERIMENTAL METHODOLOGY

Theory of Instrumentation

Spectrometers designed to work off of electromagnetic radiation in the wavelength regions of 200-800 nm that promote molecular absorption are called ultraviolet-visible (uv-vis) spectrometers. Absorption of radiation or electronic excitation of a bonding or valence electron to a higher energy level is governed by selection rules. In atomic spectroscopy, there are two spin rules, the first deals with the spin of the electrons and the second with the orbital involved in the transition. There must be only one electron involved and there must be no net change in spin; $\Delta S = 0$ (however, spin-orbit coupling may relax this rule). Orbital selection rules, like the Laporte rule, can also be relaxed in different ways. The orbital angular momentum must change by one unit; $\Delta L = 1$, therefore transitions p-p or d-d are forbidden. Laporte transitions must proceed from a symmetrical orbital (g) to a non-symmetrical orbital (u). Absorption of radiation from a high-pressure hydrogen or deuterium lamp is used for the ultra violet UV region around 200-400 nm and for the visible region around 400-800 nm a filament tungsten lamp can be used. A radiation source is passed through a monochromator, a grating that reflects just one of the wavelengths, to select the appropriate wavelength λ for the analyte in question. Wavelength is the length between two equivalent points on the same wave and is inversely related to frequency *v*:

$$\nu = \frac{c}{\lambda} \tag{3.1}$$

Frequency is the number of oscillations of the field per second and proportional to

energy E needed to excite the electrons involved in the phenomena of absorbance through,

$$E=h\nu \tag{3.2}$$

If one considers electromagnetic radiation in a vacuum or air, it has a constant velocity of propagation v_i better known as the speed of light c, where c = 2.99792 x 10^8m/s, however, when not in air or vacuum the composition of the medium effects the velocity of the radiation and the speed of light is $\frac{c}{n}$, where n is the refractive index of that medium. The frequency is constant for any field because it is determined by the radiation source, therefore the wavelength must decrease when traversing the air/medium barrier (1). Once the radiation is separated into a narrow wavelength band by the monochromator, the beam is split with a chopper; one beam enters the reference cell and the other enters the sample cell. Transmittance *T,* defined as the ratio of the initial power of the radiation source verses the power of the emerging light, is measured by the photomultiplier tube and converted into a signal by a computer.

$$T = \frac{P_o}{P} \tag{3.3}$$

A photomultiplier tube (PMT) and diode array detector (DAD), are examples of transducers, a device used to measure the intensity of radiation by rapidly collecting photons. The measured absorbance**,** A, is related to concentration of the analyte through Beer-Lambert Law or simply Beer's Law (2). For monochromatic light the absorbance is directly proportional to the concentration c of the analyte through path length b in centimeters. This leads to a very useful mathematical equation, in which one can easily relate the concentration and absorbance of an analyte,

$$A = \varepsilon bc \quad (3.4)$$

The molar absorptivity ε, in moles per liter, expresses how much light an analyte can absorbed at a particular wavelength; the greater the molar absorptivity, the greater the absorbance. "High Ordinate accuracy is obtainable because of the stability of source and detector, and concentrations can be inferred directly from the intensity of absorption if the Beer-Lambert Law is obeyed" (3).

Beer's Law has limitations that result in deviation from linearity; for example, Beer's Law does not accurately correlate concentration and absorbance if the concentration is too high due to change in chemical properties such as concentration-dependent chemical equilibrium and molar absorptivity, $c \leq 0.01$ M works for most analytes. Also, linearity breaks down at high concentrations because stray radiation is more likely to be absorbed, therefore the absorbance reading is a function of stray, transmitted power and radiant power; at extremely high concentrations the analyte becomes the solvent and the previous solvent would become the solute. Also, in Beer's Law ε is dependent upon refractive index of the medium so if increase in concentrations changes the refractive index deviation from linearity will be observed. Through ritual mathematical derivation it can be said that linearity is only observed if purely monochromatic light is used, even though the use of purely monochromatic light is virtually impossible. The relationship prevails even if the light isn't pure, typically a small range of wavelengths emerge. However, it has been shown experimentally that the deviation from linearity is not appreciable when the wavelength λ scanned is at the maximum absorbance of the analyte, at which there are small changes in absorbance as a function of wavelength, also it is necessary that the bandwidth be 1/10 the half

width of the absorption peak (4).

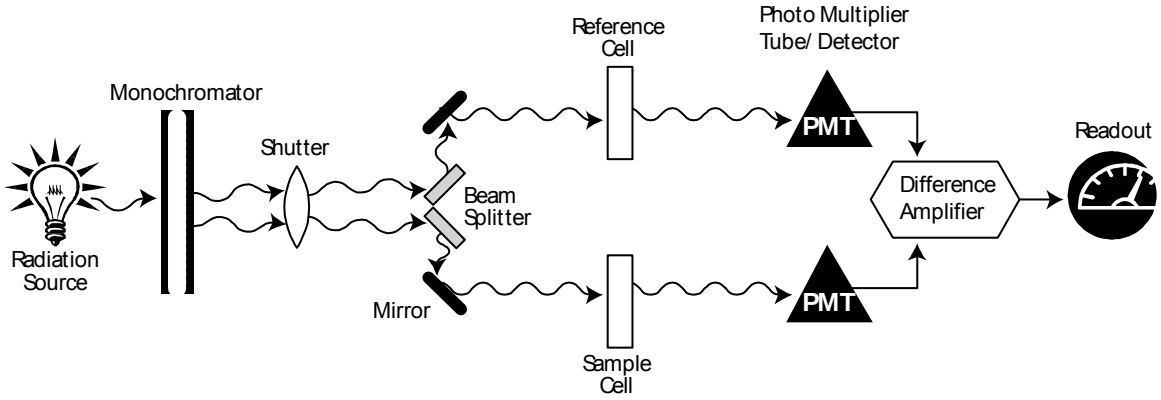

Fig. 3.1 Schematic of a spectrophotometric instrument with a double-beam configuration.

Materials – Solutes and Solvents

Solutes: Xanthene (Aldrich, 98 %), 9-fluorenone (Aldrich, 98 %) and thianthrene (Aldrich, 99+ %) were recrystallized several times from methanol. Melting points of the recrystallized samples were in excellent agreement with published literature values. 2-Methoxybenzoic acid (Aldrich, 99 %), 4-methoxybenzoic acid (Aldrich, 99 %), 4-nitrobenzoic acid (Acros, 99+ %), 2-methylbenzoic acid (Aldrich 99 %), 4-chloro-3-nitrobenzoic acid (Acros, 99.5 %), 2-chloro-5-nitrobenzoic acid (Acros, 99+ %) and ibuprofen (Sigma-Aldrich, 98 %) were purchased from commercial sources and were dried in an oven shortly before use. The purity of the seven carboxylic acid solutes was determined by nonaqueous titration with a freshly standardized sodium methoxide solution to the thymol blue endpoint according to the published method of Fritz and Lisicki (5), except that toluene was substituted for benzene as the titration solvent for

health concerns. The purities of the carboxylic acids as determined by titration were as follows: 99.8 % (± 0.3 %) for 4-methoxybenzoic acid, 99.8 % (± 0.3 %) for 2-methoxybenzoic acid, 99.8 % (± 0.3 %) for 4-nitrobenzoic acid, 99.8 % (± 0.3 %) for 2-methylbenzoic acid, 99.8 % (± 0.3 %) for 4-chloro-3-nitrobenzoic acid, 99.8 % (± 0.3 %) for 2-chloro-5-nitrobenzoic acid and 99.7 % (± 0.3 %) for ibuprofen

Solvents: Hexane (Aldrich, 99 %), heptane (Aldrich, HPLC), octane (Aldrich, 99+ %, anhydrous), nonane (TCI, 99+ %), decane (TCI, 99+ %), undecane (Acros, 99 %), hexadecane (Aldrich, 99 %), cyclohexane (Aldrich, HPLC), methylcyclohexane (Aldrich, 99+ %, anhydrous), *tert*-butylcyclohexane (Aldrich, 99+ %), cyclooctane (Lancaster Synthesis, 99+ %), 2,2,4-trimethylpentane (Aldrich, HPLC), benzene (Aldrich, HPLC, 99.9+ %), toluene (Aldrich, 99.8 %), dichloromethane (Aldrich, 99.8 %, anhydrous), 1,2-dichloroethane (Aldrich, 99.8 %, anhydrous), carbon tetrachloride (Aldrich, 99.5+ %, anhydrous), methanol (Aldrich, 99.8%, anhydrous), ethanol (Aaper Alcohol and Chemical Company, absolute), 1-propanol (Aldrich, 99+%, anhydrous), 1-butanol (Aldrich, HPLC, 99.8+%), 1-pentanol (Aldrich, 99+%), 1-hexanol (Alfa Aesar, 99+%), 1-heptanol (Alfa Aesar, 99+%), 1-octanol (Aldrich, 99+%, anhydrous), 1-decanol (Alfa Aesar, 99+%), 2-propanol (Aldrich, 99+%, anhydrous), 2-butanol (Aldrich, 99+%, anhydrous), 2-methyl-1-propanol (Aldrich, 99+%, anhydrous), 3-methyl-1-butanol (Aldrich, 99%, anhydrous), 2-pentanol (Acros, 99+%), 2-methyl-2-propanol (Arco Chemical Company, 99+%), 4-methyl-2-pentanol (Acros, 99+%), 2-methyl-1-pentanol (Aldrich, 99%), 2-methyl-1-butanol (Aldrich, 99%), 2-ethyl-1-hexanol (Aldrich, 99 %), cyclopentanol (Aldrich, 99+ %), ethylene glycol (Aldrich, 99.8 %, anhydrous), methyl acetate (Aldrich, 99.5%, anhydrous), ethyl acetate (Aldrich, HPLC, 99.9%), propyl

acetate (Aldrich, 99.5 %), butyl acetate (Aldrich, HPLC, 99.7%), pentyl acetate (Aldrich, 99%, anhydrous), methyl butyrate (Aldrich, 99 %), diethyl ether (Aldrich, 99+%, anhydrous), diisopropyl ether (Aldrich, 99%, anhydrous), dibutyl ether (Aldrich, 99.3%, anhydrous), methyl *tert*-butyl ether (Arco, 99.9+ %), tetrahydrofuran (Aldrich, 99.9%, anhydrous), 1,4-dioxane (Aldrich, 99.8%, anhydrous), acetonitrile (Aldrich, 99.8 %, anhydrous), propionitrile (Aldrich, 99 %), butyronitrile (Aldrich, 99 %) and propylene carbonate (Aldrich, 99.7 %, anhydrous) were stored over molecular sieves and distilled shortly before use. GC analysis showed solvent purities to be 99.7 mol % or better.

Sample Equilibration and Chemical Analysis

Sample equilibration: Excess solute and solvent were placed in amber glass bottles and allowed to equilibrate in a constant temperature water bath at 25.0 $\pm$ 0.1 ^{o}C for at least 24 hours (often longer) with periodic agitation. After equilibration, the samples stood unagitated for several hours in the constant temperature bath to allow any finely dispersed solid particles to settle. Attainment of equilibrium was verified both by repetitive measurements the following day (or sometimes after two days) and by approaching equilibrium from supersaturation by pre-equilibrating the solutions at a slightly higher temperature. Samples were carefully examined for the presence of solid just prior to analysis. Additional solid was added to any sample that did not have crystals present, and the equilibrium procedure was repeated by pre-equilibrating the sample at a slightly higher temperature, followed by at least 24 hours of equilibration in a constant temperature water bath at 25.0 $\pm$ 0.1 ^{o}C.

Sample analysis: Aliquots of saturated solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample and diluted quantitatively with methanol (or with 2-propanol for decane, undecane, *tert*-butylcyclohexane and hexadecane solutions) for spectrophotometric analysis on a Bausch and Lomb Spectronic 2000. Both alcohols are optically transparent at the analysis wavelengths used in the concentration determinations. 2-Propanol had to be used as the diluent for the larger alkanes because methanol is not completely miscible with these particular solvents. Binary mixtures of methanol and large alkanes are turbid, which will result in scatter of the incoming excitation radiation. The analysis wavelengths for the ten solutes studied are as follows: 393 nm for 9-fluorenone, 280 nm for xanthene, 255 nm for thianthrene, 272 nm for 4-nitrobenzoic acid, 279 nm for 2-methylbenzoic acid, 295 nm for 2-methoxybenzoic acid, 273 nm for 4-methoxybenzoic acid, 292 nm for 4-chloro-3-nitrobenzoic acid, 280 nm for 2-chloro-5-nitrobenzoic acid and 264 nm for ibuprofen. A Hewlet Packard HP 8450 double beam photodiode array was used in the thesis research to measure the total absorption spectrum of a solute in methanol to obtain the maximum wavelength λ_{max} of absorption for that specific solute. Once the λ_{max} is known, solubility analysis in an array of solvents was performed using a double beam Spectronic 2000.

Molar concentrations of the dilute solutions were determined from a Beer-Lambert law absorbance versus concentration working curve for nine standard solutions. Listed below are the molar absorptivities and concentration ranges of the standard solutions:

9-Fluorenone:

Calculated molar absorptivity varied slightly with concentration, ranging from a value of $\varepsilon_{solute} \approx 241.5$ L mol^{-1} cm^{-1} at 1.62×10^{-3} Molar to $\varepsilon_{solute} \approx 239$ L mol^{-1} cm^{-1} at 5.40×10^{-3} Molar.

Xanthene:

Calculated molar absorptivity varied slightly with concentration, ranging from a value of $\varepsilon_{solute} \approx 2240$ L mol^{-1} cm^{-1} at 1.44×10^{-4} Molar to $\varepsilon_{solute} \approx 2190$ L mol^{-1} cm^{-1} at 4.82×10^{-4} Molar.

Thianthrene:

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 33{,}300$ L mol^{-1} cm^{-1} at 1.73×10^{-5} Molar to $\varepsilon_{solute} \approx 31{,}000$ L mol^{-1} cm^{-1} at 5.77×10^{-5} Molar.

4-Nitrobenzoic acid:

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 10{,}000$ L mol^{-1} cm^{-1} at 4.52×10^{-5} Molar to $\varepsilon_{solute} \approx 9{,}250$ L mol^{-1} cm^{-1} at 1.51×10^{-4} Molar.

2-Methylbenzoic acid:

Calculated molar absorptivity of $\varepsilon_{solute} \approx 1{,}100$ L mol^{-1} cm^{-1} was constant over the concentration range of 2.95×10^{-4} Molar to 1.48×10^{-3} Molar.

2-Methoxybenzoic acid:

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 2{,}400$ L mol^{-1} cm^{-1} at 1.11×10^{-4} Molar to $\varepsilon_{solute} \approx 2{,}790$ L mol^{-1} cm^{-1} at 5.55×10^{-4} Molar.

4-Methoxybenzoic acid:

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 4{,}470$ L mol^{-1} cm^{-1} at 8.04×10^{-5} Molar to $\varepsilon_{solute} \approx 4{,}300$ L mol^{-1} cm^{-1} at 4.02×10^{-4} Molar.

4-Chloro-3-nitrobenzoic acid

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 1{,}100$ L mol^{-1} cm^{-1} at 4.90×10^{-4} Molar to $\varepsilon_{solute} \approx 1{,}020$ L mol^{-1} cm^{-1} at 2.46×10^{-3} Molar.

2-Chloro-5-nitrobenzoic acid:

Calculated molar absorptivity varied systematically with concentration, ranging from a value of $\varepsilon_{solute} \approx 8{,}900$ L mol^{-1} cm^{-1} at 3.26×10^{-5} Molar to $\varepsilon_{solute} \approx 8{,}600$ L mol^{-1} cm^{-1} at 1.63×10^{-4} Molar.

Ibuprofen**:**

Calculated molar absorptivity varied systematically with concentration, ranging

from a value of $\varepsilon_{solute} \approx 280$ L mol^{-1} cm^{-1} at 1.50 x 10^{-3} Molar to $\varepsilon_{solute} \approx 210$ L mol^{-1} cm^{-1} at 7.50 x 10^{-3} Molar.

The effect of organic solvent on the calculated molar absorptivity was investigated by preparing solute solutions of known concentrations containing up to 5 % of the different organic solvents studied. To within experimental uncertainty, identical molar absorptivities were obtained in the absence and presence of the dissolved organic solvent. The small amount of organic solvent that is transferred to the tared volumetric flask as part of the saturated solution does not affect the analysis.

The calculation of the mass percent saturation solubility of the solute, mass % soly, from the measured absorbance is straightforward

$$mass\,\%\,soly = \frac{A_{solute}\,x MM_{solute}\,x\,vol\ flask\ size\,x\,(1/\,dilution\ factor)\ x100\%}{bx\varepsilon_{Solute}\,x\,mass\,of\ sample\,syringed} \qquad (3.5)$$

where MM_{Solute} is the molar mass of the solute and b is the path length of the sample cell, ε_{solute} is the molar absorptivity coefficient of the solute determined from the measured absorbances A_{solute} of the standard solutions of known solute concentration. Solubility data is generally reported in the chemical literature as either mole fraction or molar solubilities. The mass percent saturation solubilities were converted to mole fraction, X_S and molar solubilities, C_S,

$$X_S = \frac{(mass\,\%\,soly\,/\,MM_{solute})}{(mass\,\%\,soly\,/\,MM_{solute}) + [(100 - mass\,\%\,soly)\,/\,MM_{solvent}]} \qquad (3.6)$$

$$C_S = \frac{X_S}{X_S\ xV_{Solute} + (1 - X_S)xV_{Solvent}} \tag{3.7}$$

using Eqns. 3.6 and 3.7, respectively. In Eqn. 3.7 V_{Solute} and $V_{Solvent}$ denote the ideal molar volumes of the solute and solvent. The calculation of molar solubilities will be discussed in greater detail in the next chapter when the various solutes are characterized in terms of the Abraham solvation parameter model. The experimental mole fraction solubilities of 9-fluorenone, xanthene, thianthrene, 4-nitrobenzoic acid, 2-methylbenzoic acid, 2-methoxybenzoic acid, 4-methoxybenzoic acid, 4-chloro-3-nitrobenzoic acid, 2-chloro-5-nitrobenzoic and ibuprofen are listed in Tables 3.1 – 3.10. The tabulated numerical values represent the average of between four and eight independent determinations. Reproducibility ranged from ±1.5 % for the solvents having the lower mole fraction solubilities to ±2.0 % for solvents having the larger mole fraction saturation solubilities. The measured solubility data has resulted in several published papers (6,7,8,9,10,11, 12,13,14).

TABLE 3.1. Experimental 9-Fluorenone Mole Fraction Solubilities, XS, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alkanes	
Hexane	0.01285
Heptane	0.01565
Octane	0.01819
Nonane	0.02073
Decane	0.02316
Undecane	0.02440
Hexadecane	0.03445
Cyclohexane	0.01643
Methylcyclohexane	0.01778
tert-Butylcyclohexane	0.02011
Cyclooctane	0.02420
2,2,4-Trimethylpentane	0.01136
Aromatic Hydrocarbons	
Benzene	0.2725
Toluene	0.2514
Ethers	
Diethyl ether	0.09272
Diisopropyl ether	0.05024
Dibutyl ether	0.06159
Methyl *tert*-butyl ether	0.09097
Alkanenitriles	
Acetonitrile	0.1007
Propionitrile	0.1663
Butyronitrile	0.1907

Solubility data was previously published in reference: Stovall, D. M.; Acree, W.E. Jr.; Abraham, M.H. Fluid Phase Equilib., 232, 113-121 (2005).

TABLE 3.1. (Continued)

Organic Solvent	X_S
Chloroalkanes	
Dichloromethane	0.3964
Carbon tetrachloride	0.1844
Alcohols	
Methanol	0.01623
Ethanol	0.2471
1-Propanol	0.02954
1-Butanol	0.03516
1-Pentanol	0.04495
1-Hexanol	0.05114
1-Heptanol	0.06094
1-Octanol	0.06761
1-Decanol	0.07858
2-Propanol	0.02241
2-Butanol	0.03138
2-Pentanol	0.03813
2-Methyl-1-propanol	0.02385
2-Methyl-2-propanol	0.02913
3-Methyl-1-butanol	0.03391
2-Methyl-2-butanol	0.04422
2-Methyl-1-pentanol	0.04497
4-Methyl-2-pentanol	0.03635
2-Ethyl-1-hexanol	0.05484
Cyclopentanol	0.07347

TABLE 3.2. Experimental Xanthene Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alkanes	
Hexane	0.02949
Heptane	0.03543
Octane	0.03976
Nonane	0.04306
Decane	0.04610
Undecane	0.04704
Hexadecane	0.06835
Cyclohexane	0.04203
Methylcyclohexane	0.04275
Cyclooctane	0.05414
2,2,4-Trimethylpentane	0.02451
Ethers	
Diethyl ether	0.08353
Diisopropyl ether	0.05531
Dibutyl ether	0.08310
Methyl *tert*-butyl ether	0.07846
Chloroalkanes	
1,2-Dichloroethane	0.1549
Carbon tetrachloride	0.1237
Alkanenitriles	
Acetonitrile	0.01970

Solubility data was previously published in reference: Stovall, D. M.; Acree, W.E. Jr.; Abraham, M.H. Fluid Phase Equilib., 232, 113-121 (2005).

TABLE 3.2. (Continued)

Organic Solvent	X_S
Alcohols	
Methanol	0.004455
Ethanol	0.006231
1-Propanol	0.01166
1-Butanol	0.01756
1-Pentanol	0.02212
1-Hexanol	0.02831
1-Heptanol	0.03340
1-Octanol	0.03800
1-Decanol	0.04528
2-Propanol	0.008643
2-Butanol	0.01254
2-Pentanol	0.01766
2-Methyl-1-propanol	0.01077
2-Methyl-2-propanol	0.01112
3-Methyl-1-butanol	0.01633
2-Methyl-2-butanol	0.01946
2-Methyl-1-pentanol	0.01969
4-Methyl-2-pentanol	0.01762
Cyclopentanol	0.02886

TABLE 3.3. Experimental Thianthrene Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Nonane	0.004465
Decane	0.004980
Undecane	0.005636
Hexadecane	0.008166
Diethyl ether	0.008363
Diisopropyl ether	0.006376
1,4-Dixoane	0.02431
1-Decanol	0.007012
Ethylene glycol	0.001278
Acetonitrile	0.001364

Solubility data was previously published in reference: Stovall, D. M.; Acree, W.E. Jr.; Abraham, M.H. Fluid Phase Equilib., 232, 113-121 (2005).

TABLE 3.4. Experimental 4-Nitrobenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Methanol	0.007881
Ethanol	0.008544
1-Propanol	0.007990
1-Butanol	0.007973
1-Pentanol	0.009317
1-Hexanol	0.01051
1-Heptanol	0.01071
1-Octanol	0.009758
1-Decanol	0.01022
2-Propanol	0.008550
2-Butanol	0.008898
2-Pentanol	0.008967
2-Methyl-1-propanol	0.006093
2-Methyl-2-propanol	0.01430
3-Methyl-1-butanol	0.007285
2-Methyl-1-butanol	0.005897
2-Methyl-2-butanol	0.01814
2-Methyl-1-pentanol	0.006460
4-Methyl-2-pentanol	0.008513
Ethers	
Diethyl ether	0.009861
Diisopropyl ether	0.003621
Dibutyl ether	0.002806

Solubility data was previously published in reference: Hoover, K. R.; Coaxum, R.; Pustejovsky, E.; Stovall, D. M.; Acree, W. E. Jr.; Abraham, M. H. Phys. Chem. Liq., 42(4), 339-347 (2004).

TABLE 3.4. (Continued)

Organic Solvent	X_S
Tetrahydrofuran	0.06393
1,4-Dioxane	0.04203
Alkyl acetates	
Methyl acetate	0.01168
Ethyl acetate	0.01237
Butyl acetate	0.01007
Pentyl acetate	0.007469
Miscellaneous	
Propylene carbonate	0.004850

TABLE 3.5. Experimental 2-Methylbenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Ethanol	0.1401
1-Propanol	0.1450
1-Butanol	0.1551
1-Pentanol	0.1646
1-Hexanol	0.1707
1-Heptanol	0.1755
1-Octanol	0.1758
1-Decanol	0.1853
2-Propanol	0.1612
2-Butanol	0.1700
2-Pentanol	0.1856
2-Methyl-1-propanol	0.1229
2-Methyl-2-propanol	0.2138
3-Methyl-1-butanol	0.1473
2-Methyl-1-butanol	0.1381
4-Methyl-2-pentanol	0.1735
Ethers	
Diethyl ether	0.1718
Diisopropyl ether	0.1148
Dibutyl ether	0.0939
Tetrahydrofuran	0.2629
1,4-Dioxane	0.2534

Solubility data was previously published in reference: Coaxum, R.; Hoover, K. R.; Pustejovsky, E.; Stovall, D. M.; Acree, W. E. Jr.; Abraham, M. H. Phys. Chem. Liq., 42, 313-322 (2004).

TABLE 3.5. (Continued)

Organic Solvent	X_S
Alkyl acetates	
Methyl acetate	0.1306
Ethyl acetate	0.1509
Butyl acetate	0.1514
Pentyl acetate	0.1494
Miscellaneous	
Propylene carbonate	0.04081

TABLE 3.6. Experimental 2-Methoxybenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Methanol	0.0911
Ethanol	0.0765
1-Propanol	0.0596
1-Butanol	0.0534
1-Pentanol	0.0519
1-Hexanol	0.0467
1-Heptanol	0.0478
1-Octanol	0.0477
1-Decanol	0.0416
2-Propanol	0.0463
2-Butanol	0.0474
2-Pentanol	0.0427
2-Methyl-1-propanol	0.0383
2-Methyl-2-propanol	0.0498
3-Methyl-1-butanol	0.0400
2-Methyl-1-butanol	0.0427
2-Methyl-1-pentanol	0.0438
4-Methyl-2-pentanol	0.0409
2-Ethyl-1-hexanol	0.04006
Ethers	
Diethyl ether	0.0243
Diisopropyl ether	0.00838
Dibutyl ether	0.00603

Solubility data was previously published in reference: Hoover, K. R.; Stovall, D. M.; Pustejovsky, E.; Coaxum, R.; Pop, K.; Acree, W. E. Jr.; Abraham, M. H. Can. J. Chem., 82, 1353-1360 (2004).

TABLE 3.6. (Continued)

Organic Solvent	X_S
Tetrahydrofuran	0.1774
1,4-Dioxane	0.1441
Alkyl acetates	
Methyl acetate	0.0733
Ethyl acetate	0.655
Butyl acetate	0.0445
Pentyl acetate	0.0379
Miscellaneous	
Propylene carbonate	0.0895

TABLE 3.7. Experimental 4-Methoxybenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Ethanol	0.01185
1-Propanol	0.01008
1-Butanol	0.01088
1-Pentanol	0.01130
1-Hexanol	0.01190
1-Heptanol	0.01234
1-Octanol	0.01275
1-Decanol	0.01278
2-Propanol	0.01060
2-Butanol	0.01175
2-Methyl-1-propanol	0.00740
2-Methyl-2-propanol	0.01561
3-Methyl-1-butanol	0.00916
2-Ethyl-1-hexanol	0.01124
Ethers	
Diethyl ether	0.00952
Diisopropyl ether	0.00377
Dibutyl ether	0.00275
Tetrahydrofuran	0.05811
1,4-Dioxane	0.03476
Alkyl acetates	
Ethyl acetate	0.01308
Butyl acetate	0.01087
Pentyl acetate	0.00949

Solubility data was previously published in reference: Hoover, K. R.; Stovall, D. M.; Pustejovsky, E.; Coaxum, R.; Pop, K.; Acree, W. E. Jr.; Abraham, M. H. Can. J. Chem., 82, 1353-1360 (2004).

TABLE 3.8. Experimental 4-Chloro-3-Nitrobenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Ethanol	0.03348
1-Propanol	0.02812
1-Butanol	0.02874
1-Pentanol	0.03001
1-Hexanol	0.03320
1-Heptanol	0.03481
1-Octanol	0.03589
1-Decanol	0.03507
2-Propanol	0.03036
2-Butanol	0.02962
2-Pentanol	0.03290
2-Methyl-1-propanol	0.01747
2-Methyl-2-propanol	0.03509
3-Methyl-1-butanol	0.02606
2-Methyl-1-pentanol	0.02356
4-Methyl-2-pentanol	0.02890
2-Ethyl-1-hexanol	0.02399
Ethers	
Diethyl ether	0.02459
Diisopropyl ether	0.01289
Dibutyl ether	0.008711
Tetrahydrofuran	0.1710
1,4-Dioxane	0.1339

Solubility data was previously published in reference: Stovall, D. M.; Givens, C.; Keown, S.; Hoover, K. R.; Barnes, R.; Harris, C.; Lozano, J.; Nguyen, M.; Rodriguez, E.; Acree, W. E. Jr.; Abraham, M. H. Phys. Chem. Liq., 43, 351-360 (2005).

TABLE 3.8. (Continued)

Organic Solvent	X_S
Alkylacetates	
Methyl acetate	0.03520
Ethyl acetate	0.03534
Propyl acetate	0.02966
Butyl acetate	0.03029
Pentyl acetate	0.02420
Methyl butyrate	0.02410
Miscellaneous	
Propylene carbonate	0.01343

TABLE 3.9. Experimental 2-Chloro-5-Nitrobenzoic Acid Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Alcohols	
Ethanol	0.09140
1-Propanol	0.07550
1-Butanol	0.07350
1-Pentanol	0.08109
1-Hexanol	0.07980
1-Heptanol	0.07584
1-Octanol	0.07409
1-Decanol	0.07261
2-Propanol	0.09075
2-Butanol	0.08685
2-Pentanol	0.08349
2-Methyl-1-propanol	0.05947
2-Methyl-2-propanol	0.1158
3-Methyl-1-butanol	0.07483
Ethers	
Diethyl ether	0.05852
Diisopropyl ether	0.02621
Dibutyl ether	0.01630
Tetrahydrofuran	0.2744
Alkylacetates	
Methyl acetate	0.07096
Ethyl acetate	0.07561
Butyl acetate	0.05988
Pentyl acetate	0.06260

Solubility data was previously published in reference: Stovall, D. M.; Givens, C.; Keown, S.; Hoover, K. R.; Barnes, R.; Harris, C.; Lozano, J.; Nguyen, M.; Rodriguez, E.; Acree, W. E. Jr.; Abraham, M. H. Phys. Chem. Liq., 43, 351-360 (2005).

TABLE 3.10. Experimental Ibuprofen Mole Fraction Solubilities, X_S, in Select Organic Solvents at 25 °C

Organic Solvent	X_S
Methanol	0.06054
Ethanol	0.08392
1-Propanol	0.1417
1-Pentanol	0.1833
1-Octanol	0.1993
1-Decanol	0.2166
2-Propanol	0.2334
2-Butanol	0.2040
2-Methyl-1-propanol	0.2011

Solubility data was previously published in reference: Stovall, D. M.; Givens, C.; Keown, S.; Hoover, K. R.; Rodriguez, E.; Acree, W. E. Jr.; Abraham, M. H. Phys. Chem. Liq., 43, 261-268 (2005).

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CHAPTER 4

RESULTS AND DISCUSSION

Methods to Determine Molecular Descriptors

Several calculation methods are possible to obtain molecular descriptors, such as, Visual Basics ® software (http://msdn.microsoft.com/library/toolbar/3.0/trademarks/en-us.mspx) Triple X, Descfit, Microsoft ® Solver software (Microsoft company www.microsoft.com), Regressions and modified regressions. Triple X and Descfit are more advanced programs due to their abilities to handle several solvent systems at one time while dealing with a 'data set' of compounds, where Solver works exceptionally well for determinations involving a single compound. In the 2002 publication by Zissimos et al. the different calculation models were compared for accuracy based on four solvation equations or four log SP systems (octanol/water, chloroform/water, toluene/water and cyclohexane/water partitions) and the combinations that arise from the four corresponding equations to calculate the S, A and B variables; the standard deviations were tabulated and show good comparison (1).

Regression analysis can be used to calculate S, A and B with regression equations derived from compound data base training set consisting of at least 47 compounds with satisfactory range of descriptors and experimentally measured solvation equations or log P values.

$$\text{Descriptor} = w\log P_{oct} + k\log P_{chl} + q\log P_{cycl} + x\log P_{tol} + eE + Vv \qquad (4.1)$$

By using multilinear regression three equations are obtained for the descriptors S, A and B:

$$S = 0.049 - 0.0921\log P_{oct} + 0.229\log P_{chl} - 0.713\log P_{cyc} + 0.625\log P_{tol} + 0.355E - 0.188V \quad (4.2)$$

$(n = 47, r^2 = 0.916, SE = 0.152, F = 73.054)$

$$A = 0.108 + 0.261\log P_{oct} - 0.155\log P_{chl} - 0.248\log P_{cyc} + 0.171 P_{tol} - 0.049 - 0.097V \quad (4.3)$$

$(n = 47, r^2 = 0.964, SE = 0.058, F = 177.194)$

$$B = -0.089 - 0.033\log P_{oct} + 0.338\log P_{chl} + 0.178\log P_{cyc} - 0.587\log P_{tol} + 0.137E + 0.595V \quad (4.4)$$

$(n = 47, r^2 = 0.881, SE = 0.137, F = 49.187)$

Here, and elsewhere, n is the number of data points, r is the correlation coefficient, SE is the standard error in the dependent variable and F is the Fisher F-static (1). In this type of calculation, it is necessary that the descriptor space is considered to cover a range that is realistic to include compounds the solvation property intends to predict for, hence the diversity of the training set used in the prediction of the descriptors is dictated by the nature of the compounds of interest and should be included in the training set. This calculation method is unique in the manner that it estimates one descriptor independently from the rest; this may be an advantage in some cases (1).

Triple X will take up to seven equations and solve for the unknown variables with matrices and a Gauss-Jordan routine for the solution of simultaneous equations developed in Microsoft Visual Basic for Applications. For example, if one has three equations the program will construct three equations and simultaneous solve them for the unknown variables S, A and B. The program statistically obtains the most accurate result for S, A and B by considering all combinations in sets of three of the water-solvent systems available. As a result of the analysis method the five-parameter Abraham

equation becomes a three parameter equations by rearrangement and looks like (1):

$$\text{Log SP} - \text{Ee} - \text{Vv} = \text{Ss} + \text{Aa} + \text{Bb} \qquad (4.5)$$

Descfit and the Solver function both have a similar calculation method, that is, they perform a minimization process on a certain function. Descfit simultaneously uses three or more experimentally measured solvation properties (log SP) with the Abraham solvation equations for several water-solvent systems to calculate descriptors S, A and B for a specific solute by utilizing a procedure named the SIMPLEX method. Assuming that E and V are known parameters the SIMPLEX method treats the unknown descriptors as adjustable parameters and minimizes the root-mean-square-difference (RMSD) between experimental log SP and calculated log SP defined below:

$$RMSD = \sqrt{\frac{\Sigma_{i=1} (\log SP_{calc}(i) - \log SP_{calc}(i))^2}{N_{eqs}}} \qquad (4.6)$$

where the number of Abrahams's solvation equations n_{equ} must be greater than or equal to the number of adjustable parameters; for improved predictive ability a larger number of log SP_{exp} than the number of adjustable parameters are used (1). Also, Descfit allows the user to set one or two of the three adjustable parameters constant; this feature is useful if the descriptor is readily available or can independently be obtained (1,2). A benefit of the Descfit that may make it appealing to industry or a high throughput situation is the ability to run batches of compounds at one time verses the solver function which can take one compound at a time. Unlike the Triple X program, both Descfit and solver require the user to change the combination of solvent systems to obtain the best combinations of descriptors.

Solver uses the General Reduced Gradient (GRG@) nonlinear optimization code developed by Leon Lasdon, University of Texas at Austin, and Allan Waren, Cleveland State University to minimize the sum of squares on the required equations to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (1,2). An aspect one should be aware of when using solver is its inherent ability to get stuck in the local minima if the starting value is far from the optimum value. In our work, we are analyzing only one compound at a time and using realistic starting values with over 50+ log P data points to ensure that our values are within an optimum range. Solver is our choice for calculating S, A and B due to our need to analyze only one compound at a time and because the program is more readily available.

Zissimos et al. show it is possible to get reasonable prediction of descriptors from only for measured solvation properties or log SP. As an independent test of the different computation methods, the authors used the respective calculated descriptors for propranolol, tetracaine, papaverine, tryptamine, diclofenac, chlorpromazine, ibuprofen, lidocaine, depranyl, desipramine, fluoxetine, procaine and miconazole to predict the water-to-1-octanol, water-to-benzene, water-to-dibutyl ether, water-to-diethyl ether, water-to-heptane, water-to-tetrachloromethane and water-to-ethyl acetate partition coefficients. The predicted values were then compared to available experimental data. As an informational note, the 1-octanol/water system was used in the descriptor calculations; however, the authors used the recommended octanol/water partition coefficient from the medicinal chemistry database (3), rather than the values that they measured. The results of the authors' comparison were as follows: the predicted log P values obtained from the data base set of descriptors show a standard

deviation of 0.41. Solver leads to an SD value of 0.46, and Descfit and Triple X to values of 0.49 and 0.76 respectively. Regression is the least accurate method with a standard deviation of 1.13 (1-2) as demonstrated in the analysis of the various computational methods using high-performance liquid chromatographic (HPLC) retention time data. For an independent test of the computation methods, the authors used the calculated descriptors to predict the 1-octanol/water partition coefficient, which was then compared to available experimental data. Of the five methods studied, the modified regression had the smallest standard deviation of 0.33 log units. Regression, Solver and Descfit were slightly less accurate. Triple X was the least accurate method with a standard deviation of 0.48 log units.

Condensed Phase and Gas Phase Transfer Processes Used in Determining Molecular Descriptors

Over the last 30 years, the Abraham process equations have been developed for around 40 dry organic solvents and more than one hundred HPLC and GLC systems. Solute descriptors are now known for more than 3000 different organic and organometalic solutes. In my research, solute descriptors of several carboxylic acid solutes and other crystalline organic compounds will be calculated from the measured solubility of the crystalline solutes in a wide range of organic solvents of varying polarity and hydrogen-bonding characteristics. Each of the solutes absorb in the ultraviolet spectral region. The concentration of the solute in the different saturated solutions can be conveniently determined from measured ultraviolet absorption data. This enables one to calculate molecular descriptors through several fairly simple mathematical

calculations. Absorbance of the solute standard taken at known concentrations is used to establish the calibration curve, from which the molar absorptivity ε can be calculated as the slope of linear calibration curve. Weight percent of the solute can be determined with molecular weight and the absorbance by:

$$\text{Wt\%} = \frac{(C \times MWsolute \times Volume\ flask \times 100\%)}{(SampleWeight\ syringed \times dilution\ factor)} \tag{4.7}$$

where C is the concentration of the solute determined from the ultra violet absorbance, MWs_{olute} is the molecular weight of the solute, any dilution factor necessary to get the sample with in the linear calibration range and the weight of the sample originally syringed from the supersaturated solution. Now, the mole fraction (X_s) can be determined using the weight percent of the solute and the molar mass MM_{solute}. The mole fraction is converted into molar solubility for an organic solvent C_s, by:

$$C_s = \frac{(Xs)}{(Xs\ Vsolute + (1 - Xs)\ Vsolvent)} \tag{4.8}$$

The molar solubility in a specified solvent along with the molar solubility of the solute in water C_w, obtained from literature, is used to calculate the partition coefficient log P by:

$$SP = \log P = \log C_s - \log C_w \tag{4.9}$$

Finally, the calculated partition coefficient log P is utilized in the Abraham equations, therefore the S, A and B variables can be calculated using Microsoft Solver program with the known process coefficients.

In correlation with the Abraham general solvation equations, the equation set for partitioning of a solute in a set of the described solvent systems, along with the

measured solubility data; one can mathematically describe the solubility of a solute of interest in 40 or so dry organic solvents for which the process coefficients and experimental C_w is known (4). The systems include two types of partitioning based on the solvent; the process may pertain to either "wet" practical partition of solute between water saturated with organic solvent and organic solvent saturated with water or the hypothetical "dry" partition. One needs to exercise caution so as not to confuse the two types of partition processes. For solvents that are partially miscible with water, such as 2-methyl-1-propanol (5):

wet: $\log SP = 0.227 + 0.514\,E - 0.693\,S + 0.020\,A - 2.258\,B + 2.776\,Vx$ (4.10)

dry: $\log SP = 0.177 + 0.335\,E - 1.099\,S + 0.069\,A - 3.570\,B + 3.990\,Vx$ (4.11)

ethyl acetate (6):

wet: $\log SP = 0.252 + 1.157\,E - 1.397\,S - 0.054\,A - 3.755\,B + 3.726\,Vx$ (4.12)

dry: $\log SP = 0.358 + 0.362\,E - 0.449\,S - 0.668\,A - 5.016\,B + 4.155\,Vx$ (4.13)

and dibutyl ether (7):

wet: $\log SP = 0.252 + 0.677\,E - 1.506\,S - 0.807\,A - 5.249\,B + 4.815\,Vx$ (4.14)

dry: $\log SP = 0.203 + 0.369\,E - 0.954\,S - 1.488\,A - 5.426\,B + 4.508\,Vx$ (4.15)

the measured partition coefficients are not the same as the calculated solubility ratio. For such organic solvents, there are separate Abraham process equations for the "wet" versus the "dry" solvent as indicated by Equations 4.10 versus 4.11 for 2-methyl-1-propanol, by Equations 4.12 versus 4.13 for ethyl acetate, and by Equations 4.14 versus 4.15 for dibutyl ether. In the case of solvents that are full miscible with water, such as ethanol or 1-propanol, no confusion is possible. Only one set of equation

coefficients have been reported, and the calculated log P value must refer to the hypothetical partition between the two pure solvents. And for solvents that are “almost” completely immiscible with water, such as normal alkanes, cycloalkanes, dichloromethane, trichloromethane, tetrachloromethane and many aromatic solvents (such as benzene and toluene) there should be no confusion because the practical “wet” partition coefficient is nearly identical to the “dry” partition coefficient calculated as the ratio of the solute’s saturation solubilities in the respective “dry” solvent and in water.

Equation coefficients are tabulated in Table 4.1 for the various condensed phase-to-condensed phase transfers for Eqn. 4.16:

$$\log SP = c + e E + s S + a A + b B + v V \qquad (4.16)$$

that will be considered in this study. The correlations are periodically updated as new experimental data becomes available. One of the more notable updates that has occurred is the very recent revision of the water-to-cyclohexane log P partition equation (8)

$$\text{Log P} = 0.127 + 0.816\,E - 1.731\,S - 3.778\,A - 4.905\,B + 4.646\,V \qquad (4.17)$$

N = 370 R = 0.9982 sd = 0.124 F = 20236

The updated equation is based on experimental partition data for 370 different solutes. The 9-fluorenone and xanthene solubility data that was measured as part of this thesis study was included in the regression analysis used in deriving Eqn. 4.17. It would not be fair to use the updated water-to-cyclohexane log P equation in the descriptor calculations for 9-fluorenone, xanthene and thianthrene since the published values (9) of the descriptors of all three compounds were based on the earlier water-to-cyclohexane log P equation that is listed in Table 4.1.

TABLE 4.1. Equation Coefficients for the Abraham Model for Condensed Phase-to-Condensed Phase Solute Transfer

Process/Solvent	c	e	s	a	b	v
Practical Partitions (Wet) and Hypothetical Partitions (Dry):[a]						
1-Octanol (wet)	0.088	0.562	-1.054	0.034	-3.460	3.814
Diethyl ether (wet)	0.248	0.561	-1.016	-0.226	-4.553	4.075
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	0.619	-1.713	-3.532	-4.921	4.482
Decane	0.160	0.585	-1.734	-3.435	-5.078	4.582
Undecane	0.058	0.603	-1.661	-3.421	-5.120	4.619
Dodecane	0.114	0.668	-1.644	-3.545	-5.006	4.459
Hexadecane	0.087	0.667	-1.617	-3.587	-4.869	4.433
Cyclohexane	0.159	0.784	-1.678	-3.740	-4.929	4.577
Methylcyclohexane	0.246	0.782	-1.982	-3.517	-4.293	4.528
2,2,4-Trimethylpentane	0.288	0.382	-1.668	-3.639	-5.000	4.461
Benzene	0.142	0.464	-0.588	-3.099	-4.625	4.491
Toluene	0.143	0.527	-0.720	-3.010	-4.824	4.545
Carbon tetrachloride	0.260	0.573	-1.254	-3.558	-4.558	4.589
1,2-Dichloroethane	0.227	0.278	-0.167	-2.816	-4.324	4.205
Diethyl ether (dry)	0.308	0.377	-0.813	-0.468	-5.012	4.379
Dibutyl ether (dry)	0.203	0.369	-0.954	-1.488	-5.426	4.508
Methyl *tert*-butyl ether (dry)	0.376	0.264	-0.788	-1.078	-5.030	4.410
1,4-Dioxane (dry)	0.098	0.350	-0.083	-0.556	-4.826	4.172
Tetrahydrofuran (dry)	0.207	0.372	-0.392	-0.236	-4.934	4.447
Methanol (dry)	0.329	0.299	-0.671	0.080	-3.389	3.512
Ethanol (dry)	0.208	0.409	-0.959	0.186	-3.645	3.928
1-Propanol (dry)	0.148	0.436	-1.098	0.389	-3.893	4.036

TABLE 4.1 (Continued)

Process/Solvent	c	e	s	a	b	v
2-Propanol (dry)	0.063	0.320	-1.024	0.445	-3.824	4.067
1-Butanol (dry)	0.152	0.437	-1.175	0.098	-3.914	4.119
1-Pentanol (dry)	0.080	0.521	-1.294	0.208	-3.908	4.208
1-Hexanol (dry)	0.044	0.470	-1.153	0.083	-4.057	4.249
1-Heptanol (dry)	-0.026	0.491	-1.258	0.035	-4.155	4.415
1-Octanol (dry)	-0.034	0.490	-1.048	-0.028	-4.229	4.219
1-Decanol (dry)	-0.062	0.754	-1.461	0.063	-4.053	4.293
2-Butanol (dry)	0.106	0.272	-0.988	0.196	-3.805	4.110
2-Methyl-1-propanol (dry)	0.177	0.335	-1.099	0.069	-3.570	3.990
2-Methyl-2-propanol (dry)	0.197	0.136	-0.916	0.318	-4.031	4.112
Ethylene glycol (dry)	-0.243	0.695	-0.670	0.726	-2.399	2.670
Ethyl acetate (dry)	0.358	0.362	-0.449	-0.668	-5.016	4.155
Acetonitrile (dry)	0.413	0.077	0.326	-1.566	-4.391	3.364
SDS[b]	1.201	0.542	-0.400	-0.133	-1.580	2.793
Gas-to-water	-0.994	0.577	2.549	3.813	4.841	-0.869
HPLC Processes:						
HPLC-MKMA-N (k)	-1.216	0.495	-0.438	0.025	-2.757	2.671
HPLC-MKMB-N (k)	-1.082	0.574	-0.500	-0.009	-2.591	2.240
HPLC-ANNA-(k)	-0.010	0.709	-0.934	-0.119	-3.401	3.784
HPLC-HAF-60 (k)	-0.789	0.095	-0.487	-0.337	-1.994	2.181
HPLC-HAF-75 (k)	-0.993	0.041	-0.397	-0.364	-1.629	1.757
HPLC-HAF-90 (k)	-1.176	0.079	-0.417	-0.306	-1.140	1.296
HPLC-TOM-50 (k)	-0.669	0.181	-0.687	-0.252	-1.872	2.491
HPLC-TOM-75 (k)	-0.919	0.096	-0.479	-0.336	-1.266	1.617
HPLC-BK-20/10 (t_r'/10)	1.184	0.027	-0.148	-0.556	-0.839	1.098
HPLC-BK-40/10 (t_r'/10)	1.284	0.023	-0.381	-1.030	-1.734	2.417
ALTDB-2 (k')	-0.560	0.000	-0.480	-0.669	-2.782	3.854
IN-1/IN-2 (k')	-0.101	0.324	-0.807	0.000	-2.989	2.923

TABLE 4.1 (Continued)

Process/Solvent	c	e	s	a	b	v
HPLC-1	2.140	0.375	-1.028	-1.172	-2.932	3.305
HPLC-2	2.281	0.114	-0.573	-0.333	-2.223	2.593
HPLC-3	2.551	0.300	-0.911	-0.945	-1.096	2.042
HPLC-4	2.271	-0.118	-0.282	-1.003	-0.891	1.478
HPLC-5	2.666	0.681	-0.785	-1.635	-2.588	2.340
HPLC-6	-0.167	0.281	-0.486	0.173	-2.175	2.665
HPLC-7	0.113	0.328	-0.532	-0.062	-2.253	2.499
HPLC-C18/TFE (gt_r)	1.430	0.430	-0.620	-0.750	-1.110	1.560
HPLC-Xter/TFE (gt_r)	1.260	0.470	-0.650	-0.810	-1.170	1.660
HPLC-C18/MeOH (gt_r)	1.630	0.070	-0.260	-0.240	-1.260	1.450
HPLC-Xter/MeOH (gt_r)	1.470	0.110	-0.280	-0.280	-1.230	1.460
HPLC-C18/ACN (gt_r)	1.700	0.080	-0.280	-0.420	-1.150	1.190
HPLC-Xter/ACN (gt_r)	1.490	0.180	-0.290	-0.440	-1.180	1.220
Thin layer (RM_w)	0.259	0.239	-0.662	-0.667	-3.006	3.603

[a] The solvents denoted as “dry” are those for which partitions refer transfer to the pure dry solvent. The other partitions are from water (more correctly water-saturated with solvent) to the solvent saturated with water. [b] SDS is aqueous micellar sodium dodecylsulfate.

In applying the Abraham model one does have to make sure that the solute exists in the same form in all of the different solvents and for all of the different processes. Carboxylic acids pose a problem in that dimerization and Ionization are two interactions that the Abraham equations are not well set up for. Carboxylic acids are known to dimerize in saturated hydrocarbon and aromatic hydrocarbon solvents. Solubility measures the total carboxylic acid and to date there is not an experimental means to correct the measured value for dimerization effects. To eliminate any adverse

dimerization effects, alkane and aromatic hydrocarbon solvents were excluded from the carboxylic acid solute solubility studies. Ionization correction is considered unimportant if the organic solvents dielectrtic constant is lower than that of water. It is also fairly small, unless the carboxylic acid is highly soluble in the solvent or has a large acid dissociation constant (4).

For gas phase-to-condensed phase transfer

$$SP = c + eE + sS + aA + bB + lL \text{ (gas-condensed phase)} \quad (4.18)$$

Eqn. 4.18 is used along with process coefficients for the gas phase systems. Equation coefficients for the gas phase-to-condensed phase transfers are given in Table 4.2 for several organic solvents. Predicted SP values can also be converted to saturation molar solubilities, provided that the solid saturated vapor pressure at 298.15 K (VP^o), is available. VP can be transformed into the gas-phase concentration (C_G), and the gas–water and gas-solvent partitions (L_W and L_S) can be obtained through Eqns. 4.19 and 4.20, respectively.

$$SP = \log L_w = \log C_W - \log C_G \quad (4.19)$$

$$SP = \log L_S = \log C_S - \log C_G \quad (4.20)$$

If one is unable to find an experimental vapor pressure for the given solute molecule, and estimated value can be used in the preliminary computations. The Abraham solvation parameter model can provide this estimation. One can first determine a preliminary set of molecular descriptors for the solute molecule under consideration using only the log P correlations. The preliminary set of molecular descriptors can then be inserted into the gas phase-to-water log L equation

$$\text{Log } L_w = -1.271 + 0.822\ E + 2.743\ S + 3.904\ A + 4.814\ B - 0.213\ L \quad (4.21)$$

TABLE 4.2 Equation Coefficients for the Abraham Model for Gas Phase-to-Condensed Phase Solute Transfer

Process/Solvent	c	e	s	a	b	l
Practical Partitions (Wet) and Hypothetical Partitions (Dry):[a]						
1-Octanol (wet)	-0.198	0.002	0.709	3.519	1.429	0.858
Diethyl ether (wet)	0.206	-0.169	0.873	3.402	0.000	0.882
Hexane	0.292	-0.169	0.000	0.000	0.000	0.979
Heptane	0.275	-0.162	0.000	0.000	0.000	0.983
Octane	0.215	-0.049	0.000	0.000	0.000	0.967
Nonane	0.200	-0.145	0.000	0.000	0.000	0.980
Decane	0.156	-0.143	0.000	0.000	0.000	0.989
Undecane	0.113	0.000	0.000	0.000	0.000	0.971
Dodecane	0.053	0.000	0.000	0.000	0.000	0.986
Hexadecane	0.000	0.000	0.000	0.000	0.000	1.000
Cyclohexane	0.163	-0.110	0.000	0.000	0.000	1.013
Methylcyclohexane	0.318	-0.215	0.000	0.000	0.000	1.012
2,2,4-Trimethylpentane	0.275	-0.244	0.000	0.000	0.000	0.972
Benzene	0.107	-0.313	1.053	0.457	0.169	1.020
Toluene	0.121	-0.222	0.938	0.467	0.099	1.012
Carbon tetrachloride	0.282	-0.303	0.460	0.000	0.000	1.047
1,2-Dichloroethane	0.011	-0.150	1.436	0.649	0.736	0.936
Diethyl ether (dry)	0.288	-0.347	0.775	2.985	0.000	0.973
Dibutyl ether (dry)	0.165	-0.421	0.760	2.102	-0.664	1.002
Methyl *tert*-butyl ether (dry)	0.278	-0.489	0.801	2.495	0.000	0.993
1,4-Dioxane (dry)	-0.034	-0.354	1.674	3.021	0.000	0.919
Tetrahydrofuran (dry)	0.189	-0.347	1.238	3.289	0.000	0.982
Methanol (dry)	-0.004	-0.215	1.173	3.701	1.432	0.769
Ethanol (dry)	0.012	-0.206	0.789	3.635	1.311	0.853
1-Propanol (dry)	-0.028	-0.185	0.648	4.022	1.043	0.869
2-Propanol (dry)	-0.060	-0.335	0.702	4.017	1.040	0.893

TABLE 4.2 (Continued)

Process/Solvent	c	e	s	a	b	l
1-Butanol (dry)	-0.039	-0.276	0.539	3.781	0.995	0.934
1-Pentanol (dry)	-0.042	-0.277	0.526	3.779	0.983	0.932
1-Hexanol (dry)	-0.035	-0.298	0.626	3.726	0.729	0.936
1-Heptanol (dry)	-0.062	-0.168	0.429	3.541	1.181	0.927
1-Octanol (dry)	-0.119	-0.203	0.560	3.576	0.702	0.940
1-Decanol (dry)	-0.136	-0.038	0.325	3.674	0.767	0.947
2-Butanol (dry)	-0.013	-0.456	0.780	3.753	1.064	0.906
2-Methyl-1-propanol (dry)	0.012	-0.407	0.670	3.645	1.283	0.895
2-Methyl-2-propanol (dry)	0.071	-0.538	0.818	3.951	0.823	0.905
Ethylene glycol (dry)	-0.876	0.278	1.431	4.584	2.525	0.558
Ethyl acetate (dry)	0.203	-0.335	1.251	2.949	0.000	0.917
Acetonitrile (dry)	-0.007	-0.595	2.461	2.085	0.418	0.738
Gas-to-water	-1.271	0.822	2.743	3.904	4.814	-0.213
GLC Processes:						
LVW2[b] (I/100)	0.139	0.111	0.062	0.000	0.000	0.328
LVW2[b] (I/50)	0.278	0.222	0.124	0.000	0.000	0.656
BBBA[c] (I/50)	-0.046	0.104	0.022	0.152	0.000	0.752
BBBB[d] (I/51)	0.070	0.212	0.044	0.376	0.000	0.706
BBBC[e] (I/52)	-0.024	0.104	0.046	0.164	0.000	0.748
BBBD[f] (I/50)	-0.030	0.042	0.300	0.906	0.000	0.726
RPA[g] (Kovats indices, I/500)	-0.050	0.078	0.267	0.187	0.000	0.416
RPB[g] (Kovats indices, I/50)	0.219	0.054	0.563	0.250	0.000	0.638

[a] The solvents denoted as “dry” are those for which partitions refer transfer to the pure dry solvent. The other partitions are from water (more correctly water-saturated with solvent) to the solvent saturated with water. [b] LVW2: GLC retention indices: stationary phase is SE-52, temperature programmed, I-values are relative to polyaromatic hydrocarbon standards. [c] BBBA: GLC retention indices: stationary phase is OV-1701. [d] BBBB: GLC retention indices: stationary phase is SE-54. [e] BBBC: GLC retention indices: stationary phase is SE-52. [f] BBBD: GLC retention indices: stationary phase is

OV-101. [9] RPA and RPB: GLC retention indices: stationary phase is DB-5 fused silica capillary column.

to predict log L_w, which is then combined with the experimental aqueous solubility to calculate log C_G through equation 4.19above. The value can be adjusted then, if necessary, to reduce the log *L* deviations and to make the log *P* and log L predictions internally consistent (4).

Molecular Solute Descriptors for 9-Fluorenone, Thianthrene and Xanthene

Molecular descriptors for 9-fluorenone, thianthrene and xanthene were determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system equations, a set of equations with known processes coefficients (*c,e,s,a,b,v* and *l*), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (9).

For 9-fluorenone, the molar solute solubility C_S is determined by dividing the mole fraction X_S of 9-fluorenone, found in Table 3.1 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 146.0 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility for 9-fluorenone in water, log C_W = –3.98 is used to calculate log P with Eqn. 4.9. The molar solubility of 9-fluorenone in water was measured as part of the thesis research. There is no published literature data to compare the above molar aqueous solubility value against. Zdanowicz and

Strauss (10) reported a value of 8.02 x 10^{-5} Molar (which corresponds to log C_w = -4.096) for the solubility of 9-fluorenone in an aqueous 0.1 Molar LiCl solution. Dissolved salts generally decrease the aqueous solubility of organic compounds. The phenomenum is commonly referred to as the so-called "salting-out effect." My slightly larger measured volue of log C_W = -3.98 is in accord with what one would expect based on the salting-out effect. Estimation of the hypothetical liquid molar volumes (V_{Solute}) or the ideal molar volume approximation for 9-fluorenone, thianthrene, and xanthene could have errors that should be considered, although errors associated with the estimation should be negligible because they are not overly soluble in many of the solvent studied therefore, X_sV_{solute} term will contribute very little to the molar volume of the saturated solution.

Available practical partition coefficient for 1-octanol (wet) (11-12) and chromatographic retention data for LVW2 (I/50) obtained from GLC with temperature-programmed condition using SE-52 as the stationary phase and the retention indices *I*-values determined relative to polyaromatic hydrocarbon standards (13), and RPA and RPB data obtained from GLC retention indices using a DB-5 fused silica capillary column as the stationary phase (14) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 69 equations with known partition data and equation coefficients. The McGowan volume of 9-fluorenone was calculated with the method described in Chapter 2 in the section titled: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.3722 and the excess molar refraction estimated as E = 1.600. As described earlier, Microsoft Solver was employed to yield

the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 4.20 (9-fluorenone) which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.3 and 4.4). The numerical values of the solute descriptors for 9-fluorenone acid are E = 1.600, S = 1.490, A = 0.000, B = 0.350 with V = 1.3722 and L = 7.4737. The molecular descriptors reproduce the experimental log *P* and log *L* values for 9-fluorenone to within an overall standard deviation of 0.145 log unit. According to my experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 9-fluorenone to within 0.20 log units.

The published determination of the solute descriptors for 9-fluorenone was based on the 69 experimental data points listed in Tables 4.3 and 4.4. After the descriptor values were published, log P and log L correlations were developed for both “dry” 3-methyl-1-butanol (15):

$$\text{Log P} = 0.123 + 0.370\ \text{E} - 1.243\ \text{S} + 0.074\ \text{A} - 3.781\ \text{B} + 4.208\ \text{V} \qquad (4.22)$$

$$\text{Log L} = -0.014 - 0.341\ \text{E} + 0.525\ \text{S} + 3.666\ \text{A} + 1.096\ \text{B} + 0.925\ \text{L} \qquad (4.23)$$

TABLE 4.3. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 9-Fluorenone

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol		3.580	3.439	
Hexane	-1.011	2.969	3.014	-0.966
Heptane	-0.974	3.006	2.903	-1.077
Octane	-0.953	3.027	3.233	-0.747
Nonane	-0.937	3.043	3.106	-0.874
Decane	-0.925	3.055	3.022	-0.958
Undecane	-0.935	3.045	3.095	-0.885
Hexadecane	-0.924	3.056	3.124	-0.856
Cyclohexane	-0.824	3.156	3.469	-0.511
Methylcyclohexane	-0.859	3.121	3.255	-0.725
2,2,4-Trimethylpentane	-1.164	2.816	2.922	-1.058
Benzene	0.414	4.394	4.552	0.572
Toluene	0.333	4.313	4.462	0.482
Carbon tetrachloride	0.240	4.220	4.000	0.002
Dibutyl ether (dry)	-0.438	3.542	3.659	-0.438
Methyl *tert*-butyl ether (dry)	-0.125	3.855	3.915	-0.065
Methanol (dry)	-0.417	3.563	3.441	-0.539
Ethanol (dry)	-0.387	3.593	3.548	-0.432
1-Propanol (dry)	-0.417	3.563	3.385	-0.595
2-Propanol (dry)	-0.544	3.436	3.292	-0.688
1-Butanol (dry)	-0.427	3.553	3.384	-0.596
1-Pentanol (dry)	-0.390	3.590	3.392	-0.588
1-Hexanol (dry)	-0.392	3.588	3.489	-0.491
1-Heptanol (dry)	-0.368	3.612	3.489	-0.491
1-Octanol (dry)	-0.367	3.613	3.498	-0.482

TABLE 4.3 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Decanol (dry)	-0.379	3.601	3.440	-0.540
2-Butanol (dry)	-0.477	3.503	3.377	-0.603
2-Methyl-1-propanol (dry)	-0.596	3.384	3.301	-0.679
2-Methyl-2-propanol (dry)	-0.517	3.463	3.281	-0.699
Ethylene glycol (dry)	-1.226	2.754	2.695	-1.285
Acetonitrile (dry)	0.209	4.189	4.101	0.121
Gas-to-water		4.200	4.229	

TABLE 4.4. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 9-Fluorenone

Solvent/Process	log C_S^{exp}	Equation 4.18		
		log L^{exp}	log L^{calc}	log C_S^{exp}
1-Octanol		7.780	7.774	
Hexane	-1.011	7.169	7.338	-0.842
Heptane	-0.974	7.206	7.362	-0.818
Octane	-0.953	7.227	7.364	-0.816
Nonane	-0.937	7.243	7.292	-0.888
Decane	-0.925	7.255	7.319	-0.861
Undecane	-0.935	7.245	7.370	-0.810
Hexadecane	-0.924	7.256	7.474	-0.706
Cyclohexane	-0.824	7.356	7.558	-0.622
Methylcyclohexane	-0.859	7.321	7.537	-0.643
2,2,4-Trimethylpentane	-1.164	7.016	7.149	-1.031
Benzene	0.414	8.594	8.857	0.677
Toluene	0.333	8.513	8.761	0.581
Carbon tetrachloride	0.240	8.420	8.308	0.128
Dibutyl ether (dry)	-0.438	7.742	7.880	-0.300
Methyl *tert*-butyl ether (dry)	-0.125	8.055	8.110	-0.070
Methanol (dry)	-0.417	7.763	7.648	-0.532
Ethanol (dry)	-0.387	7.793	7.692	-0.488
1-Propanol (dry)	-0.417	7.763	7.501	-0.679
2-Propanol (dry)	-0.544	7.636	7.488	-0.692
1-Butanol (dry)	-0.427	7.753	7.655	-0.525
1-Pentanol (dry)	-0.390	7.790	7.608	-0.572
1-Hexanol (dry)	-0.392	7.788	7.671	-0.509
1-Heptanol (dry)	-0.368	7.812	7.650	-0.530
1-Octanol (dry)	-0.367	7.813	7.653	-0.527

TABLE 4.4. (Continued)

			Equation 4.18	
Solvent/Process	log C_S^{exp}	log L^{exp}	log L^{calc}	log C_S^{exp}
1-Decanol (dry)	-0.379	7.801	7.633	-0.547
2-Butanol (dry)	-0.477	7.703	7.563	-0.617
2-Methyl-1-propanol (dry)	-0.596	7.584	7.497	-0.683
2-Methyl-2-propanol (dry)	-0.517	7.663	7.481	-0.699
Ethylene glycol (dry)	-1.226	6.954	6.755	-1.425
Acetonitrile (dry)	0.209	8.389	8.370	0.190
LVW2 (I/50)		5.896	5.721	
RPA (Kovats, K/500)		3.505	3.578	
RPB (Lee, I/50)		5.878	5.910	
Gas-to-water		4.200	4.224	

Numerical values of the descriptors used in these calculations are: E= 1.600, S = 1.490, A= 0.000, B= 0.350, V= 1.3722 and L = 7.4737. P is defined as the solubility ratio in the case of the “dry”, i.e., $P = C_S/C_W$, or the practical partition coefficient, or the chromatographic retention data. L is defined as the solubility in the organic solvent divided by the gas phase concentration, i.e., $L = C_S/C_G$, except as noted. In the case of the chromatographic stationary phases log L is defined to be the retention index divided by either 500 or 50 to give the proper scaling for the regression.

and “dry” 2-pentanol (15):

$$\text{Log P} = 0.115 + 0.455\ \text{E} - 1.331\ \text{S} + 0.206\ \text{A} - 3.745\ \text{B} + 4.201\ \text{V} \quad (4.24)$$

$$\text{Log L} = -0.031 - 0.325\ \text{E} + 0.496\ \text{S} + 3.792\ \text{A} + 1.024\ \text{B} + 0.934\ \text{L} \quad (4.25)$$

It would not be feasible to re-evaluate (and/or update) the values of the solute descriptors of every compound every time that a new process correlation was

developed. Instead, Eqns. 4.22 – 4.25 will be used as an independent test of the predictive ability (rather than descriptive ability) of the Abraham model. Substituting the values of E = 1.600, S = 1.490, A = 0.000, B = 0.350, V = 1.3772 and L = 7.4737 into Eqns. 4.22 – 4.25, values of log P^{calc} = 3.447 and log L^{calc} = 7.470, and of Log P^{calc} = 3.454 and log L^{calc} = 7.481, are calculated for 3-methyl-1-butanol and 2-pentanol, respectively. Calculated values compare quite favorably to the experimental values of log P^{exp} = 3.465 and log L^{exp} = 7.665 for 9-fluorenone dissolved in 3-methyl-1-butanol, and of log P^{exp} = 3.516 and log L^{exp} = 7.716 for 9-fluorenone dissolved in 2-pentanol. The average absolute deviation of the four predicted values from the observed values is 0.128 log units, which is within the overall average deviation of 0.145 log units based on the solute descriptor calculations.

For thianthrene, the molar solute solubility C_S is determined by dividing the mole fraction X_S of thianthrene, found in Table 3.3 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 156.0 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility for thianthrene in water, log C_W = – 5.95 is used to calculate log P with Eqn. 4.9. Available practical partition coefficient for 1-octanol (wet) (11-14) and chromatographic retention data for LVW2 (I/50) obtained from GLC with temperature-programmed condition using SE-52 as the stationary phase and the retention indices *I*-values determined relative to polyaromatic hydrocarbon standards (13), the BBBA (I/50) data obtained form GLC retention indices using OV-1701 as the stationary phase, BBBB (I/51) used SE-54 as the stationary phase, BBBC (I/52) used SE-52 as the stationary phase and BBBD (I/50) used OV-101 as the stationary phase (16) were retrieved from the chemical literature and added to our experimental log P

and log L values measured in this thesis to give a total of 62 equations with known partition data and equation coefficients. The McGowan volume of thianthrene was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.5426 and the excess molar refraction estimated as E = 2.240. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 4.00 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.5 and 4.6).

The numerical values of the solute descriptors for thianthrene are E = 2.240, S = 1.390, A = 0.000, B = 0.360 with V = 1.5426 and L = 8.5414. The molecular descriptors reproduce the experimental log *P* and log *L* values for thianthrene to within an overall standard deviation of 0.121 log unit. As a predictive application, the calculated solute descriptors for thianthrene were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for thianthrene dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 4.355 and log L^{calc} = 8.245 for 3-methyl-1-butanol, and log P^{calc} = 4.416 and log L^{calc} = 8.275 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 4.294 and log L^{calc} = 8.294, and log P^{calc} = 4.227 and log L^{calc} = 8.227, based on the measured experimental solubility of thianthrene in

TABLE 4.5. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of Thianthrene

Solvent/Process	log C_S^{exp}	Equation 4.16		
		log P^{exp}	log P^{calc}	log C_S^{exp}
1-Octanol (wet)		4.570	4.520	
Hexane	-1.610	4.340	4.249	-1.701
Heptane	-1.630	4.320	4.265	-1.685
Octane	-1.620	4.330	4.529	-1.421
Nonane	-1.605	4.345	4.388	-1.562
Decane	-1.594	4.356	4.300	-1.650
Undecane	-1.574	4.376	4.382	-1.568
Hexadecane	-1.555	4.395	4.419	-1.531
Cyclohexane	-1.270	4.680	4.869	-1.081
Methylcyclohexane	-1.310	4.640	4.682	-1.268
2,2,4-Trimethylpentane	-1.790	4.160	4.061	-1.889
Diethyl ether (dry)	-1.100	4.850	4.973	-0.977
Dibutyl ether (dry)	-1.240	4.710	4.704	-1.246
Methyl *tert*-butyl ether (dry)	-1.100	4.850	4.864	-1.086
1,4-Dioxane (dry)	-0.556	5.394	5.465	-0.485
Methanol (dry)	-1.940	4.010	4.264	-1.686
1-Propanol (dry)	-1.670	4.280	4.423	-1.527
2-Propanol (dry)	-1.880	4.070	4.254	-1.696
1-Butanol (dry)	-1.610	4.340	4.445	-1.505
1-Pentanol (dry)	-1.550	4.400	4.533	-1.417
1-Hexanol (dry)	-1.510	4.440	4.588	-1.362
1-Heptanol (dry)	-1.450	4.500	4.640	-1.310
1-Octanol (dry)	-1.460	4.490	4.593	-1.357
1-Decanol (dry)	-1.469	4.481	4.759	-1.191
2-Butanol (dry)	-1.750	4.200	4.312	-1.638

TABLE 4.5 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
2-Methyl-1-propanol (dry)	-1.800	4.150	4.270	-1.680
Acetonitrile (dry)	-1.590	4.360	4.647	-1.303
Gas-to-water		4.000	4.244	

TABLE 4.6. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of Thianthrene

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		8.570	8.635	
Hexane	-1.610	8.340	8.275	-1.675
Heptane	-1.630	8.320	8.308	-1.642
Octane	-1.620	8.330	8.365	-1.585
Nonane	-1.605	8.245	8.246	-1.704
Decane	-1.594	8.256	8.283	-1.667
Undecane	-1.574	8.376	8.407	-1.543
Hexadecane	-1.555	8.395	8.541	-1.409
Cyclohexane	-1.270	8.680	8.569	-1.381
Methylcyclohexane	-1.310	8.640	8.480	-1.470
2,2,4-Trimethylpentane	-1.790	8.160	8.031	-1.919
Diethyl ether (dry)	-1.100	8.850	8.899	-1.051
Dibutyl ether (dry)	-1.240	8.710	8.598	-1.352
Methyl *tert*-butyl ether (dry)	-1.100	8.850	8.778	-1.172
1,4-Dioxane (dry)	-0.556	9.340	9.349	-0.601
Methanol (dry)	-1.940	8.010	8.229	-1.721
1-Propanol (dry)	-1.670	8.280	8.256	-1.694
2-Propanol (dry)	-1.880	8.070	8.167	-1.783
1-Butanol (dry)	-1.610	8.340	8.432	-1.518
1-Pentanol (dry)	-1.550	8.400	8.383	-1.567
1-Hexanol (dry)	-1.510	8.440	8.425	-1.525
1-Heptanol (dry)	-1.450	8.500	8.501	-1.449
1-Octanol (dry)	-1.460	8.490	8.477	-1.473
1-Decanol (dry)	-1.469	8.481	8.595	-1.335
2-Butanol (dry)	-1.750	8.200	8.171	-1.779

TABLE 4.6 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
2-Methyl-1-propanol (dry)	-1.800	8.150	8.138	-1.812
Acetonitrile (dry)	-1.590	8.360	8.535	-1.415
LVW2 (I/50)		6.603	6.551	
BBBA (I/50)		6.572	6.641	
BBBB (I/51)		6.603	6.636	
BBBC (I/52)		6.598	6.662	
BBBD (I/50)		6.572	6.682	
Gas-to-water		4.000	4.297	

Numerical values of the descriptors used in these calculations are: *E*= 2.240, *S* = 1.390, *A*= 0.000, *B*= 0.360, *V*= 1.5426 and *L* = 8.5414. *P* is defined as the solubility ratio in the case of the "dry", i.e., *P* =*C*S/*C*W or the practical partition coefficient or the chromatographic retention data. *L* is defined as the solubility in the organic solvent divided by the gas phase concentration, i.e., *L* =*C*S/*C*G, except as noted. In the case of the chromatographic stationary phases log *L* is defined to be the retention index divided by either 50, 51 or 52 as noted in the first column.

3-methyl-1-butanol and 2-pentanol (17), respectively. According to my experience with the Abraham solvation parameter model, the preceding molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of thianthrene to within 0.20 log units.

For xanthene, the molar solute solubility C_S is determined by dividing the mole fraction X_S of xanthene, found in Table 3.2 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 150.0 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility for xanthene in water, log C_W = – 5.210 is used to

calculate log P with Eqn. 4.9. Available practical partition coefficient for 1-octanol (wet) and chromatographic retention data for LVW2, RPA (Kovats, I/500), RPB (Lee, I/50) (11-14) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 69 equations with known partition data and equation coefficients. The McGowan volume of xanthene was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.4152 and the excess molar refraction estimated as E = 1.502. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 2.50 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.7 and 4.8).

The numerical values of the solute descriptors for xanthene are E = 1.502, S = 1.070, A = 0.000, B = 0.230 with V = 1.4152 and L = 7.1533. The molecular descriptors reproduce the experimental log *P* and log *L* values for xanthene to within an overall standard deviation of 0.086 log unit. As a predictive application, the calculated solute descriptors for xanthene were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for xanthene dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 4.434 and log L^{calc} = 6.902 for 3-methyl-1-butanol, and log P^{calc} = 4.458 and log

TABLE 4.7. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of Xanthene

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (wet)		4.560	4.406	
Hexane	-0.651	4.559	4.439	-0.771
Heptane	-0.620	4.590	4.467	-0.743
Octane	-0.613	4.597	4.665	-0.545
Nonane	-0.618	4.592	4.548	-0.662
Decane	-0.624	4.586	4.500	-0.710
Undecane	-0.648	4.562	4.547	-0.663
Hexadecane	-0.619	4.591	4.512	-0.698
Cyclohexane	-0.366	4.844	4.885	-0.325
Methylcyclohexane	-0.481	4.729	4.720	-0.490
2,2,4-Trimethylpentane	-0.830	4.380	4.382	-0.828
Benzene	0.200	5.410	5.502	0.292
Diethyl ether (dry)	-0.034	5.176	5.049	-0.161
Dibutyl ether (dry)	-0.307	4.903	4.868	-0.342
Methyl *tert*-butyl ether (dry)	-0.191	5.019	5.014	-0.192
Carbon tetrachloride	0.077	5.287	5.218	0.006
1,2-Dichloroethane	0.236	5.446	5.422	0.212
Methanol (dry)	-0.966	4.244	4.251	-0.959
Ethanol (dry)	-0.970	4.240	4.517	-0.693
1-Propanol (dry)	-0.814	4.396	4.444	-0.766
2-Propanol (dry)	-0.953	4.257	4.324	-0.886
1-Butanol (dry)	-0.724	4.486	4.483	-0.727
1-Pentanol (dry)	-0.695	4.515	4.534	-0.676
1-Hexanol (dry)	-0.648	4.562	4.596	-0.614
1-Heptanol (dry)	-0.629	4.581	4.658	-0.552

TABLE 4.7 (Continued)

Solvent/Process	log C_S^{exp}	log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (dry)	-0.619	4.591	4.579	-0.631
1-Decanol (dry)	-0.622	4.588	4.651	-0.559
2-Butanol (dry)	-0.871	4.339	4.399	-0.811
Methyl-1-propanol (dry)	-0.938	4.272	4.330	-0.880
2-Methyl-2-propanol (dry)	-0.931	4.279	4.313	-0.897
Acetonitrile (dry)	-0.445	4.765	4.628	-0.582
Gas-to-water		2.500	2.484	

TABLE 4.8. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of Xanthene

Solvent/Process	log C_S^{exp}	Equation 4.18		
		log L^{exp}	log L^{calc}	log C_S^{exp}
1-Octanol (wet)		7.060	7.030	
Hexane	-0.651	7.059	7.041	-0.669
Heptane	-0.620	7.090	7.063	-0.647
Octane	-0.613	7.097	7.059	-0.651
Nonane	-0.618	7.092	6.992	-0.718
Decane	-0.624	7.086	7.016	-0.694
Undecane	-0.648	7.062	7.059	-0.651
Hexadecane	-0.619	7.091	7.153	-0.557
Cyclohexane	-0.366	7.344	7.244	-0.466
Methylcyclohexane	-0.481	7.229	7.234	-0.476
2,2,4-Trimethylpentane	-0.830	6.880	6.861	-0.849
Benzene	0.200	7.910	8.009	0.389
Diethyl ether (dry)	-0.034	7.676	7.566	-0.144
Dibutyl ether (dry)	-0.307	7.403	7.361	-0.349
Methyl *tert*-butyl ether (dry)	-0.191	7.591	7.504	-0.206
Carbon tetrachloride	0.077	7.787	7.809	0.099
1,2-Dichloroethane	0.236	7.946	8.187	0.477
Methanol (dry)	-0.966	6.744	6.758	-0.952
Ethanol (dry)	-0.970	6.740	6.950	-0.760
1-Propanol (dry)	-0.814	6.896	6.844	-0.866
2-Propanol (dry)	-0.953	6.757	6.815	-0.895
1-Butanol (dry)	-0.724	6.986	7.036	-0.674
1-Pentanol (dry)	-0.695	7.015	6.998	-0.712
1-Hexanol (dry)	-0.648	7.062	7.050	-0.660
1-Heptanol (dry)	-0.629	7.081	7.047	-0.663

TABLE 4.8 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (dry)	-0.619	7.091	7.053	-0.657
1-Decanol (dry)	-0.622	7.088	7.105	-0.605
2-Butanol (dry)	-0.871	6.839	6.862	-0.848
Methyl-1-propanol (dry)	-0.938	6.772	6.815	-0.895
2-Methyl-2-propanol (dry)	-0.931	6.779	6.801	-0.909
Acetonitrile (dry)	-0.445	7.265	7.108	-0.602
LVW2		2.805	2.718	
RPA (Kovats, I/500)		3.323	3.329	
RPB (Lee, I/50)		5.621	5.466	
Gas-to-water		2.500	2.482	

Numerical values of the descriptors used in these calculations are: *E*= 1.502, *S* = 1.070, *A*= 0.000, *B*= 0.230, *V*= 1.4152 and *L* = 7.1533. *P* is defined as the solubility ratio in the case of the "dry", i.e., *P* =*C*S/*C*W, or the practical partition coefficient or the chromatographic retention data. *L* is defined as the solubility in the organic solvent divided by the gas phase concentration, i.e., *L* =*C*S/*C*G, except as noted. In the case of the chromatographic stationary phases log L is defined to be the retention index divided by 100, 500 or 50.

L^{calc} = 6.927 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 4.380 and log L^{calc} = 6.880, and log P^{calc} = 4.415 and log L^{calc} = 6.915, based on the measured experimental solubility of xanthene in 3-methyl-1-butanol and 2-pentanol (see Table 3.2 for solubility data), respectively. According to my experience with the Abraham solvation parameter model, the preceding molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of xanthene to within 0.20 log units.

Molecular Solute Descriptors for 2-Methoxybenzoic Acid and 4-Methoxybenzoic Acid

Molecular descriptors for 2-methoxybenzoic acid and 4-methoxybenzoic acid are determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system equations, a set of equations with known processes coefficients (*c,e,s,a,b,v* and *l*), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (4).

The molar solute solubility C_S is determined by dividing the mole fraction X_S of 2-methoxybenzoic acid, found in Table 3.6 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 124.1 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility corrected for ionization for 2-methoxybenzoic acid in water, log C_W = –1.554 is used to calculate log P with Eqn. 4.9. Estimation of the hypothetical liquid molar volumes (V_{Solute}) or the ideal molar volume approximations for 2-methoxybenzoic acid and 4-methoxybenzoic acid could have errors that should be considered, although errors associated with the estimation should be negligible because they are not overly soluble in many of the solvent studied therefore, X_sV_{solute} term will contribute very little to the molar volume of the saturated solution.

Dibutyl ether was excluded from the correlations of all carboxylic acids because it was felt that dimerization was inevitable in this larger ether solvent as discussed in Chapter 4 in the section titled: Condensed Phase and Gas Phase Transfer Processes Used in Determining Molecular Descriptors. In adequate description of the solubility behavior of several carboxylic acids (benzoic acid, 2-hydroxybenzoic acid, 4-

hydroxybenzoic acid, and 3-nitrobenzoic acid) in dibutyl ether was noticed when the equation coefficients were calculated for the equations. When dimerization is an issue one would expect the calculated log *P* values to be less than observed log *P* values, as was the case with dibutyl ether.

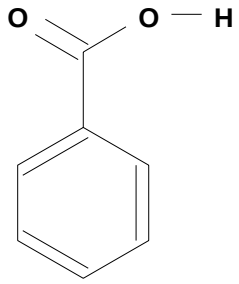
Available practical partition coefficient for 1-octanol (wet), hexane, benzene, toluene and diethyl ether (wet) (11,18,19) and chromatographic retention data for ALTDB-2 (k) (20,21) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 47 equations with known partition data and equation coefficients. The McGowan volume of 2-methoxybenozic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.1313 and the excess molar refraction estimated as E = 0.899. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 6.80 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.9 and 4.10). The numerical values of the solute descriptors for 2-methoxybenzoic acid are E = 0.899, S = 1.410, A = 0.450, B = 0.620 with V = 1.1313 and L = 5.636. The molecular descriptors reproduce the experimental log *P* and log *L* values for 2-methoxybenzoic acid to within an overall standard deviation of 0.146 log unit. As a predictive application, the calculated solute

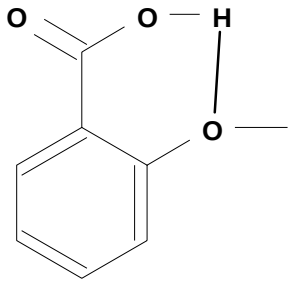
descriptors for 2-methoxybenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 2-methoxybenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 1.153 and log L^{calc} = 7.960 for 3-methyl-1-butanol, and log P^{calc} = 1.171 and log L^{calc} = 7.980 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 1.111 and log L^{calc} = 7.841, and log P^{calc} = 1.141 and log L^{calc} = 7.941, based on the measured experimental solubility of 2-methoxybenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. The average absolute deviation of the four predicted values from the observed values is 0.058 log units, which is within the overall average deviation of 0.146 log units based on the solute descriptor calculations. According to my experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 2-methoxybenzoic acids to within 0.20 log units for organic solvents in which carboxylic acid dimerization does not occur.

As an informational note the hydrogen-bond acidity (A = 0.450) descriptor of 2-methoxybenzoic acid is slightly smaller than the known acidity (A = 0.590) for benzoic acid and can be reasoned by intramolecular hydrogen bonding of the hydrogen on the carboxyl group with one of the lone electron pairs associated with the oxygen in the methoxy group shown in figure 4.1, also the basicity (B = 0.620) of 2-methoxybenzoic acid is slightly larger than basicity (B = 0.400) of benzoic acid for the same reasons. Electron density is increased due to the two lone electron pairs on the oxygen atom of the methoxy-substituent group and they provide additional donor sites. The

intramolecular hydrogen bonding indicated by both solution IR, and proton, ^{13}C, and ^{17}O NMR measurements confirm this line of reason.



benzoic acid



2-methoxybenzoic acid

Fig. 4.1 Molecular structure of benzoic acid and 2-methoxybenzoic acid (4,22-26).

TABLE 4.9. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Methoxybenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (wet)		1.590	1.292	
Hexane		-1.360	-1.207	
Benzene		0.750	0.549	
Toluene		0.450	0.398	
Diethyl ether (wet)		0.780	1.005	
Diethyl ether (dry)	-0.638	0.916	1.118	-0.436
Tetrahydrofuran (dry)	0.299	1.853	1.854	0.300
1,4-Dioxane (dry)	0.197	1.751	1.773	0.219
Methanol (dry)	0.267	1.821	1.560	0.006
Ethanol (dry)	0.074	1.628	1.491	-0.063
1-Propanol (dry)	-0.120	1.434	1.319	-0.235
2-Propanol (dry)	-0.392	1.162	1.337	-0.217
1-Butanol (dry)	-0.247	1.307	1.163	-0.391
1-Pentanol (dry)	-0.327	1.227	1.155	-0.399
1-Hexanol (dry)	-0.430	1.124	1.170	-0.384
1-Heptanol (dry)	-0.471	1.083	1.076	-0.478
1-Octanol (dry)	-0.518	1.036	1.067	-0.487
1-Decanol (dry)	-0.658	0.896	0.928	-0.626
2-Butanol (dry)	-0.299	1.255	1.336	-0.218
2-Methyl-1-propanol (dry)	-0.392	1.162	1.260	-0.294
2-Methyl-2-propanol (dry)	-0.286	1.268	1.323	-0.231
Ethyl acetate (dry)	-0.187	1.367	1.340	-0.214
ALTDB-2 (k)		1.380	1.097	
Gas-to-water		6.800	6.853	

TABLE 4.10. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Methoxybenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		8.390	8.109	
Hexane		5.440	5.658	
Benzene		7.550	7.370	
Toluene		7.250	7.219	
Diethyl ether (wet)		7.580	7.787	
Diethyl ether (dry)	-0.638	7.716	7.896	-0.458
Tetrahydrofuran (dry)	0.299	8.653	8.637	0.283
1,4-Dioxane (dry)	0.197	8.551	8.547	0.193
Methanol (dry)	0.267	8.621	8.344	-0.010
Ethanol (dry)	0.074	8.428	8.196	-0.158
1-Propanol (dry)	-0.120	8.234	8.037	-0.317
2-Propanol (dry)	-0.392	7.962	8.114	-0.240
1-Butanol (dry)	-0.370	8.107	8.058	-0.296
1-Pentanol (dry)	-0.327	8.027	8.014	-0.340
1-Hexanol (dry)	-0.430	7.924	7.984	-0.370
1-Heptanol (dry)	-0.471	7.883	7.942	-0.412
1-Octanol (dry)	-0.518	7.836	7.824	-0.530
1-Decanol (dry)	-0.658	7.696	7.754	-0.600
2-Butanol (dry)	-0.299	8.055	8.132	-0.222
2-Methyl-1-propanol (dry)	-0.392	7.962	8.071	-0.283
2-Methyl-2-propanol (dry)	-0.286	8.068	8.130	-0.224
Ethyl acetate (dry)	-0.187	8.168	8.161	-0.193
Gas-to-water		6.800	6.877	

Numerical values of the descriptors used in these calculations are: E = 0.899, S = 1.410, A = 0.450, B = 0.620, V = 1.1313 and L = 5.636.

The occurance of intramolecular hydrogen-bond formation between adjacent functional groups can have a rather noticeable effect on the numerical values of the molecular solute descriptors as just shown. In case of 2-methoxybenzoic acid there was a noticeable decrease in the molecule's hydrogen-bond acidity descriptor. A similar effect is found in 2-nitrophenol versus 4-nitrophenol. The former has a very strong intramolecular hydrogen bond (A = 0.05), whereas 4-nitrophenol (A = 0.82) has no internal hydrogen bonds. The hydrogen bond acidity descriptor of 2-nitro-4-methylphenol (A = 0.05) and 6-nitro-3-methylphenol (A = 0.05) are also significantly smaller than the hydrogen bond acidity descriptor of 4-nitro-3-methylphenol (A = 0.83). (27), as are the hydrogen bond acidity descriptors of 2,4-dinitrophenol (A = 0.09), 2,5-dinitrophenol (A = 0.11) and 2,6-dinitrophenol (A = 0.17) much less than the hydrogen bond acidity descriptors of either 3,4-dinitrophenol (A = 1.14) or 3,5-dinitrophenol (A = 1.05) (28).

For 4-methoxybenzoic acid, the molar solute solubility C_S is determined by dividing the mole fraction X_S of 4-methoxybenzoic acid, found in Table 3.7 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 124.1cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility corrected for ionization for 4-methoxybenzoic acid in water, log C_W = – 2.800 is used to calculate log P with Eqn. 4.9.

Available practical partition coefficient for 1-octanol (wet), benzene, toluene and diethyl ether (wet) (11,18,19) and chromatographic retention data for SDS, aqueous micellar sodium dodecylsulfate and IN-1/IN-2 (k')) (20,21) were retrieved from the chemical literature and added to our experimental log P and log L values measured in

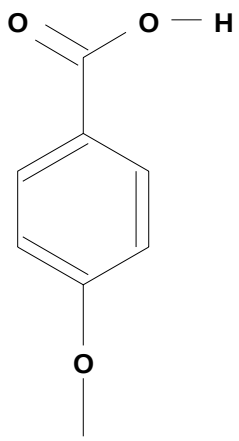
this thesis to give a total of 44 equations with known partition data and equation coefficients. The McGowan volume of 4-methoxybenzoic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.1313 and the excess molar refraction estimated as E = 0.899. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

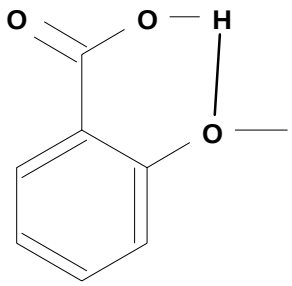
An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 6.70 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.11 and 4.12).

The numerical values of the solute descriptors for 4-methoxybenzoic acid are E = 0.899, S = 1.250, A = 0.620, B = 0.520 with V = 1.1313 and L = 5.741. The molecular descriptors reproduce the experimental log *P* and log *L* values for 4-methoxybenzoic acid to within an overall standard deviation of 0.114 log unit. To demonstrate the predictive application of the Abraham model, the calculated solute descriptors for 4-methoxybenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 4-methoxybenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 1.743 and log L^{calc} = 8.487 for 3-methyl-1-butanol, and log P^{calc} = 1.793 and log L^{calc} = 8.541 for 2-pentanol. Again, the calculated values are in excellent agreement with the experimental values of log P^{calc} = 1.721 and log L^{calc} = 8.421, and log P^{calc} = 1.823 and log L^{calc} = 8.523, based on the measured experimental solubility of 4-

methoxybenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. According to my past experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 4-methoxybenzoic acid to within 0.20 log units for organic solvents in which carboxylic acid dimerization does not occur.

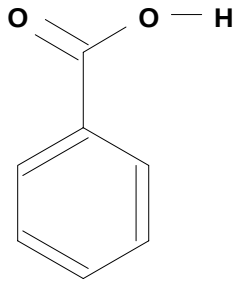
The value for 2-methoxybenzoic acid's hydrogen-bond basicity (B = 0.62) is larger than that of 4-methoxybenzoic acid (B =0.52). Because the descriptors refer to the entire molecule and not the individual functional groups, one cannot conclusively state why 2-methoxybenzoic acid has the larger B-value. Naively, one would have expected a much smaller value based simply on the fact that there is one less lone electron pairs avaialbe on the oxygen atom of the C=O group for hydrogen-bond formation. Structrual considerations imposed by the intramolecular hydrogen bond though may make the other lone electron pairs more accessible. The hydrogen-bond acidity (A = 0.620) descriptor of 4-methoxybenzoic acid is larger than the known acidity (A = 0.590) for benzoic acid and can be reasoned due to the of the lone electron pairs associated with the oxygen in the methoxy group increasing the electron density allowing the molecule to house more negative charge in other words create a more stable conjugate base. See Figures 4.2 and 4.3 for the molecular structures of the benzoic acid and the two methoxybenzoic acid derivatives.

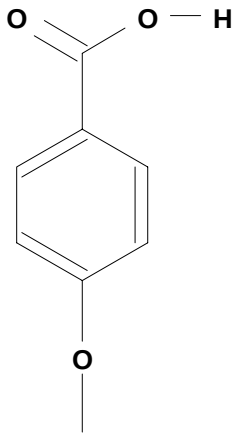




4-methoxybenzoic acid 2-methoxybenzoic acid

Fig. 4.2. Molecular structures of 4-methoxybenzoic acid and 2-methoxybenzoic acid.





benzoic acid 4-methoxybenzoic acid

Fig. 4.3. Moleculars structure of benzoic acid and 4-methoxybenzoic acid.

TABLE 4.11. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Methoxybenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (wet)		1.960	1.812	
Benzene		0.460	0.578	
Toluene		0.540	0.484	
Diethyl ether (wet)		1.490	1.585	
Diethyl ether (dry)	-1.043	1.757	1.688	-1.112
Tetrahydrofuran (dry)	-0.162	2.638	2.370	-0.430
1,4-Dioxane (dry)	-0.401	2.399	2.174	-0.626
Ethanol (dry)	-0.702	2.098	2.041	-0.759
1-Propanol (dry)	-0.875	1.925	1.950	-0.850
2-Propanol (dry)	-0.864	1.936	1.959	-0.841
1-Butanol (dry)	-0.929	1.871	1.759	-1.041
1-Pentanol (dry)	-0.984	1.816	1.788	-1.012
1-Hexanol (dry)	-1.022	1.778	1.774	-1.026
1-Heptanol (dry)	-1.060	1.740	1.699	-1.101
1-Octanol (dry)	-1.093	1.707	1.653	-1.147
1-Decanol (dry)	-1.174	1.626	1.578	-1.222
2-Butanol (dry)	-0.898	1.902	1.908	-0.892
2-Methyl-1-propanol (dry)	-1.100	1.700	1.805	-0.995
Ethyl acetate (dry)	-0.879	1.921	1.800	-1.000
SDS		3.490	3.444	
IN-1/IN-2 (k')		2.330	2.065	
Gas-to-Water		6.700	6.609	

TABLE 4.12. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Methoxybenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		8.560	8.541	
Benzene		7.160	7.369	
Toluene		7.240	7.245	
Diethyl ether (wet)		8.190	8.318	
Diethyl ether (dry)	-1.043	8.457	8.381	-1.119
Tetrahydrofuran (dry)	-0.162	9.338	9.101	-0.399
1,4-Dioxane (dry)	-0.401	9.099	8.889	-0.611
Ethanol (dry)	-0.702	8.798	8.646	-0.854
1-Propanol (dry)	-0.875	8.625	8.641	-0.859
2-Propanol (dry)	-0.864	8.636	8.674	-0.826
1-Butanol (dry)	-0.929	8.571	8.613	-0.887
1-Pentanol (dry)	-0.984	8.516	8.571	-0.929
1-Hexanol (dry)	-1.022	8.478	8.542	-0.958
1-Heptanol (dry)	-1.060	8.440	8.455	-1.045
1-Octanol (dry)	-1.093	8.407	8.370	-1.130
1-Decanol (dry)	-1.174	8.326	8.350	-1.150
2-Butanol (dry)	-0.898	8.602	8.634	-0.866
2-Methyl-1-propanol (dry)	-1.100	8.400	8.549	-0.951
Ethyl acetate (dry)	-0.879	8.621	8.558	-0.942
Gas-to-Water		6.700	6.598	

Numerical values of the descriptors used in these calculations are: E = 0.899, S = 1.250, A = 0.620, B = 0.520, V = 1.1313, and L = 5.741.

Molecular Solute Descriptors for 4-Nitrobenzoic Acid

A search of the published chemical literature found only one found that Rhuaire (29) had previously reported the solubility of 4-nitrobenzoic acid in ethanol. Our experimental value of X_S = 0.008544 is in very good agreement with the published literature value of X_S = 0.008675. Molecular descriptors for 4-nitrobenzoic acid were determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system equations, a set of equations with known processes coefficients (*c,e,s,a,b,v* and *l*), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (30).

The molar solute solubility C_S is determined by dividing the mole fraction X_S of 4-nitrobenzoic acid, found in Table 3.4 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 117.7 cm^3 mol^{-1} being used for the molar volume of the solute.

The molar solute solubility corrected for ionization for 4-nitrobenzoic acid in water, log C_W = –2.98 (corrected for ionization) (29) is used to calculate log P with Eqn. 4.9. Estimation of the hypothetical liquid molar volumes of 4-nitrobenzoic acid (V_{Solute}) or the ideal molar volume approximation could have errors that should be considered, although errors associated with the estimation should be negligible because 4-nitrobenzoic acid is not overly soluble in many of the solvent studied therefore, X_sV_{solute} term will contribute very little to the molar volume of the saturated solution.

Available practical partition coefficient for 1-octanol (wet) (11,18,31) and

chromatographic retention data for process equations denoted as LVW2 (I/50), RPA (Kovats, K/500), RPB (Lee, I/50) (32-35) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 51 equations with known partition data and equation coefficients. The McGowan volume of 4-nitrobenzoic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.1059 and the excess molar refraction estimated as E = 0.990. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 6.90 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.13 and 4.14).

The numerical values of the solute descriptors for 4-nitrobenzoic acid are E = 0.990, S = 1.520, A = 0.680, B = 0.400 with V = 1.1059 and L = 5.7699. The molecular descriptors reproduce the experimental log *P* and log *L* values for 4-nitrobenzoic acid to within an overall standard deviation of 0.076 log unit. As a predictive application, the calculated solute descriptors for 2-nitrobenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 4-nitrobenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations gave values of log P^{calc} = 1.792 and log L^{calc} = 8.713 for 3-methyl-1-butanol, and log P^{calc} = 1.830 and log L^{calc} = 8.777 for 2-pentanol. Again, the calculated values

TABLE 4.13. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16		
		log P^{exp}	log P^{calc}	log C_S^{exp}
1-Octanol (wet)		1.890	1.899	
Chloroform		0.870	0.978	
Toluene		0.505	0.620	
SDS		3.490	3.496	
Diethyl ether (wet)		1.800	1.791	
Diethyl ether (dry)	-0.902	2.078	1.965	-1.015
Tetrahydrofuran (dry)	-0.117	2.863	2.763	-0.217
1,4-Dioxane (dry)	-0.317	2.663	2.624	-0.356
Methanol (dry)	-0.719	2.261	2.188	-0.792
Ethanol (dry)	-0.841	2.139	2.168	-0.812
1-Propanol (dry)	-0.975	2.005	2.081	-0.899
2-Propanol (dry)	-0.956	2.024	2.094	-0.886
1-Butanol (dry)	-1.063	1.917	1.853	-1.127
1-Pentanol (dry)	-1.067	1.913	1.861	-1.119
1-Hexanol (dry)	-1.076	1.904	1.889	-1.091
1-Heptanol (dry)	-1.121	1.859	1.792	-1.188
1-Octanol (dry)	-1.209	1.771	1.813	-1.167
1-Decanol (dry)	-1.271	1.709	1.633	-1.347
2-Butanol (dry)	-1.017	1.963	2.030	-0.950
2-Methyl-1-propanol (dry)	-1.183	1.797	1.870	-1.110
2-Methyl-2-propanol (dry)	-0.821	2.159	2.091	-0.889
Ethyl acetate (dry)	-0.902	2.078	2.168	-0.812
HPLC MKMA-N (k)		0.360	0.476	
HPLC MKMB-N (k)		0.160	0.161	
HPLC ANNA (k)		1.953	2.016	

TABLE 4.13 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
HPLC TOM-50 (k)		0.334	0.301	
HPLC TOM-75 (k)		-0.450	-0.499	
HPLC HAF-60 (k)		0.013	-0.050	
HPLC HAF-75 (k)		-0.462	-0.512	
HPLC HAF-90 (k)		-0.987	-0.969	
Gas-to-Water		6.900	7.020	

TABLE 4.14. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		8.790	8.797	
Chloroform		7.770	7.884	
Toluene		7.405	7.523	
Diethyl ether (wet)		8.700	8.768	
Diethyl ether (dry)	-0.902	8.978	8.766	-1.114
Tetrahydrofuran (dry)	-0.117	9.763	9.630	-0.250
1,4-Dioxane (dry)	-0.317	9.563	9.517	-0.363
Methanol (dry)	-0.719	9.161	9.093	-0.787
Ethanol (dry)	-0.841	9.039	8.925	-0.955
1-Propanol (dry)	-0.975	8.905	8.940	-0.940
2-Propanol (dry)	-0.956	8.924	8.976	-0.904
1-Butanol (dry)	-1.063	8.819	8.868	-1.012
1-Pentanol (dry)	-1.067	8.813	8.824	-1.056
1-Hexanol (dry)	-1.076	8.804	8.847	-1.033
1-Heptanol (dry)	-1.121	8.759	8.653	-1.227
1-Octanol (dry)	-1.209	8.671	8.661	-1.219
1-Decanol (dry)	-1.271	8.609	8.590	-1.290
2-Butanol (dry)	-1.017	8.863	8.926	-0.954
2-Methyl-1-propanol (dry)	-1.183	8.697	8.783	-1.097
2-Methyl-2-propanol (dry)	-0.821	9.059	9.019	-0.861
Ethyl acetate (dry)	-0.902	8.978	9.069	-0.811
Gas-to-Water		6.900	7.063	

Numerical values of the descriptors used in these calculations are: E = 0.990, S = 1.520, A = 0.680, B = 0.400,V = 0.1059, and Log L = 5.7699.

are in very good agreement with the experimental values of log P^{calc} = 1.802 and log L^{calc} = 8.702, and log P^{calc} = 1.892 and log L^{calc} = 8.793, based on the measured experimental solubility of 4-nitrobenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. According to my past experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 4-nitrobenzoic acid to within 0.20 log units.

Molecular Solute Descriptors for 2-Methylbenzoic Acid

Published literature values do exist fo rthe solubility of 2-methylbenozic acid (also called o-toluic acid) in both ethanol and 2-propanol. The experimental mole fraction solubilities measured as part of the thesis research: X_S = 0.1401 versus X_S = 0.1460 (29) and X_S = 0.1432 (36) for ethanol; and X_S = 0.1612 versus X_S = 0.1580 (36-37) for 2-propanol are in excellent agreement with published literature values. Domanska and Hofman reported the solubility 2-methylbenzoic acid at several temperatures, and the values at 298.15 K that are used for comparison were obtained from a ln X_S versus 1/T graph.

Molecular descriptors for 2-methylbenzoic acid (also called *o*-toluic acid) were determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system

equations, a set of equations with known processes coefficients (c,e,s,a,b,v and l), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (9).

The molar solute solubility C_S is determined by dividing the mole fraction X_S of 2-methylbenzoic acid, found in Table 3.5 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 121.8 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility for 2-methylbenzoic acid in water, log C_W = –2.06 (38-39) is used to calculate log P with Eqn. 4.9. Estimation of the hypothetical liquid molar volumes of 2-methylbenzoic acid (V_{Solute}) or the ideal molar volume approximation could have errors that should be considered, although errors associated with the estimation should be negligible because 2-methylbenzoic acid is not overly soluble in many of the solvent studied therefore, X_sV_{solute} term will contribute very little to the molar volume of the saturated solution.

Available practical partition coefficient for 1-octanol (wet) (11,40-41) and chromatographic retention data for LVW2 (l/50), RPA (Kovats, K/500), RPB (Lee, l/50) (42-43) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 47 equations with known partition data and equation coefficients. The McGowan volume of 2-methylbenzoic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.0726 and the excess molar refraction estimated as E = 0.730. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 4.30 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.15 and 4.16).

The numerical values of the solute descriptors for 2-methylbenzoic acid are E = 0.730, S = 0.840, A = 0.420, B = 0.440 with V = 1.0726 and L = 4.6770. The molecular descriptors reproduce the experimental log *P* and log *L* values for 2-methylbenzoic acid to within an overall standard deviation of 0.076 log unit. The acidity solute descriptor is slightly less than the A-descriptor of benzoic acid, likely due to steric reasons. The presence of the ortho-CH_3 group likely reduces the molecule's tendency to form hydrogen bonds due to steric considerations. As a predictive application, the calculated solute descriptors for 2-methylbenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 2-methylbenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 2.230 and log L^{calc} = 6.525 for 3-methyl-1-butanol, and log P^{calc} = 2.274 and log L^{calc} = 6.559 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 2.181 and log L^{calc} = 6.481, and log P^{calc} = 2.280 and log L^{calc} = 6.580, based on the measured experimental solubility of 2-methylbenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. Based on the above predictions and my experience with the Abraham solvation parameter model, the preceding molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 2-methylbenzoic acid to within 0.20 log units.

TABLE 4.15. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Methylbenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (wet)		2.270	2.196	
Chloroform		1.760	1.756	
Toluene		1.230	1.411	
Cyclohexane		0.650	0.492	
Diethyl ether (wet)		2.050	2.077	
Diethyl ether (dry)	0.203	2.263	2.195	0.135
Tetrahydrofuran (dry)	0.456	2.516	2.649	0.589
1,4-Dioxane (dry)	0.427	2.487	2.402	0.342
Ethanol (dry)	0.325	2.385	2.389	0.329
1-Propanol (dry)	0.248	2.308	2.323	0.263
2-Propanol (dry)	0.282	2.342	2.303	0.243
1-Butanol (dry)	0.205	2.265	2.220	0.160
1-Pentanol (dry)	0.172	2.232	2.255	0.195
1-Hexanol (dry)	0.137	2.197	2.226	0.166
1-Heptanol (dry)	0.103	2.163	2.198	0.138
1-Octanol (dry)	0.063	2.123	2.096	0.036
1-Decanol (dry)	0.016	2.076	2.109	0..049
2-Butanol (dry)	0.242	2.302	2.291	0.231
2-Methyl-1-propanol (dry)	0.106	2.166	2.236	0.176
2-Methyl-2-propanol (dry)	0.329	2.389	2.297	0.237
Ethyl acetate (dry)	0.170	2.230	2.214	0.154
HPLC BK-20/10 (t_r'/10)		1.658	1.654	
HPLC BK-40/10 (t_r'/10)		2.352	2.378	
Thin layer (RM_w)		1.967	2.139	
Gas-to-water		4.300	4.368	

TABLE 4.16. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Methylbenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		6.570	6.519	
Chloroform		6.060	6.123	
Toluene		5.530	5.720	
Cyclohexane		4.950	4.820	
Diethyl ether (wet)		6.350	6.370	
Diethyl ether (dry)	0.203	6.563	6.490	0.130
Tetrahydrofuran (dry)	0.456	6.816	6.950	0.590
1,4-Dioxane (dry)	0.427	6.787	6.681	0.321
Ethanol (dry)	0.325	6.685	6.617	0.257
1-Propanol (dry)	0.248	6.608	6.594	0.234
2-Propanol (dry)	0.282	6.642	6.606	0.246
1-Butanol (dry)	0.205	6.565	6.609	0.249
1-Pentanol (dry)	0.172	6.532	6.576	0.216
1-Hexanol (dry)	0.137	6.497	6.537	0.177
1-Heptanol (dry)	0.103	6.460	6.518	0.158
1-Octanol (dry)	0.063	6.423	6.405	0.045
1-Decanol (dry)	0.016	6.376	6.419	0.059
2-Butanol (dry)	0.242	6.602	6.591	0.231
2-Methyl-1-propanol (dry)	0.106	6.466	6.559	0.199
2-Methyl-2-propanol (dry)	0.329	6.689	6.620	0.260
Ethyl acetate (dry)	0.170	6.530	6.537	0.177
Gas-to-water		4.300	4.395	

Molecular Solute Descriptors for 4-Chloro-3-nitrobenzoic Acid and 2-Chloro-5-nitrobenzoic Acid

Molecular descriptors for 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid were determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system equations, a set of equations with known processes coefficients (*c,e,s,a,b,v* and *l*), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (44).

The molar solute solubility C_S is determined by dividing the mole fraction X_S of 4-chloro-3-nitrobenzoic acid, found in Table 3.8 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 130.38 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility corrected for ionization for 4-chloro-3-nitrobenzoic acid in water, log C_W = –3.00 (45) is used to calculate log P with Eqn. 4.9. Estimation of the hypothetical liquid molar volumes (V_{Solute}) or the ideal molar volume approximation of 4-chloro-3-nitrobenzoic acid could have errors that should be considered, although errors associated with the estimation should be negligible because the carboxylic acid is not overly soluble in many of the solvents studied therefore, X_sV_{solute} term will contribute very little to the molar volume of the saturated solution.

Available practical partition coefficient for 1-octanol (wet) (11) was retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 37 equations with known partition data and equation

coefficients. The McGowan volume of 4-chloro-3-nitrobenzoic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.2283 and the excess molar refraction estimated as E = 1.250. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 7.21 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.17 and 4.18).

The numerical values of the solute descriptors for 4-chloro-3-nitrobenzoic acid are E = 1.250, S = 1.470, A = 0.700, B = 0.440 with V = 1.2283 and L = 6.6848. The molecular descriptors reproduce the experimental log *P* and log *L* values for 4-chloro-3-nitrobenzoic acid to within an overall standard deviation of 0.067 log unit. As a predictive application, the calculated solute descriptors for 4-chloro-3-nitrobenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 4-chloro-3-nitrobenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 2.316 and log L^{calc} = 9.561 for 3-methyl-1-butanol, and log P^{calc} = 2.383 and log L^{calc} = 9.639 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 2.373 and log L^{calc} = 9.583, and log P^{calc} = 2.475 and log L^{calc} =

TABLE 4.17. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Chloro-3-nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16		
		log P^{exp}	log P^{calc}	log C_S^{exp}
1-Octanol (wet)		2.385	2.427	
Diethyl ether (dry)	-0.632	2.368	2.430	-0.570
Tetrahydrofuran (dry)	0.280	3.280	3.222	0.220
1,4-Dioxane (dry)	0.165	3.165	3.025	0.025
Ethanol (dry)	-0.290	2.710	2.661	-0.339
1-Propanol (dry)	-0.433	2.567	2.596	-0.404
2-Propanol (dry)	-0.413	2.587	2.610	-0.390
1-Butanol (dry)	-0.510	2.490	2.375	-0.625
1-Pentanol (dry)	-0.561	2.439	2.424	-0.576
1-Hexanol (dry)	-0.577	2.423	2.429	-0.571
1-Heptanol (dry)	-0.609	2.391	2.358	-0.642
1-Octanol (dry)	-0.642	2.358	2.340	-0.660
1-Decanol (dry)	-0.733	2.267	2.267	-0.733
2-Butanol (dry)	-0.499	2.501	2.478	-0.522
2-Methyl-1-propanol (dry)	-0.728	2.272	2.359	-0.641
2-Methyl-2-propanol (dry)	-0.435	2.565	2.520	-0.480
Ethyl acetate (dry)	-0.450	2.550	2.579	-0.421
Gas-to-water		7.210	7.206	

TABLE 4.18. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 4-Chloro-3-nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		9.595	9.674	
Diethyl ether (dry)	-0.632	9.578	9.587	-0.623
Tetrahydrofuran (dry)	0.280	10.490	10.442	0.232
1,4-Dioxane (dry)	0.165	10.375	10.242	0.032
Ethanol (dry)	-0.290	9.920	9.738	-0.472
1-Propanol (dry)	-0.433	9.777	9.777	-0.433
2-Propanol (dry)	-0.413	9.797	9.780	-0.430
1-Butanol (dry)	-0.510	9.700	9.740	-0.470
1-Pentanol (dry)	-0.561	9.649	9.693	-0.517
1-Hexanol (dry)	-0.577	9.633	9.699	-0.511
1-Heptanol (dry)	-0.609	9.601	9.554	-0.656
1-Octanol (dry)	-0.642	9.568	9.539	-0.671
1-Decanol (dry)	-0.733	9.477	9.534	-0.676
2-Butanol (dry)	-0.499	9.711	9.701	-0.510
2-Methyl-1-propanol (dry)	-0.728	9.482	9.587	-0.623
2-Methyl-2-propanol (dry)	-0.435	9.775	9.779	-0.431
Ethyl acetate (dry)	-0.450	9.760	9.818	-0.392
Gas-to-water		7.210	7.216	

log L^{calc} = 9.685, based on the measured experimental solubility of 4-chloro-3-nitrobenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. According to my experience and the above calculations, the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical

organic solvent–water partition coefficients of 4-chloro-3-nitrobenzoic acid to within 0.20 log units.

For 2-chloro-5-nitrobenzoic acid, the molar solute solubility C_S is determined by dividing the mole fraction X_S of 2-chloro-5-nitrobenzoic acid, found in Table 3.9 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 130.38cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility corrected for ionization for 2-chloro-5-nitrobenzoic acid in water, log C_W = – 2.588, is used to calculate log P with Eqn. 4.9.

The available practical partition coefficient for 1-octanol (wet) (11) was retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 35 equations with known partition data and equation coefficients. The McGowan volume of 2-chloro-5-nitrobenzoic acid was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.2283 and the excess molar refraction estimated as E = 1.250. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 6.95 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.19 and 4.20).

The numerical values of the solute descriptors for 2-chloro-5-nitrobenzoic acid

are E = 1.250, S = 1.400, A = 0.670, B = 0.460 with V = 1.2283 and L = 6.5131. The molecular descriptors reproduce the experimental log *P* and log *L* values for 2-chloro-5-nitrobenzoic acid to within an overall standard deviation of 0.113 log unit. As a predictive application, the calculated solute descriptors for 2-chloro-5-nitrobenzoic acid were substituted into Eqns. 4.22 – 4.25 to estimate the water-to-organic solvent and gas-to-organic solvent partition coefficients for 2-chloro-5-nitrobenzoic acid dissolved in 3-methyl-1-butanol and 2-pentanol. The caculations yielded values of log P^{calc} = 2.325 and log L^{calc} = 9.278 for 3-methyl-1-butanol, and log P^{calc} = 2.396 and log L^{calc} = 9.351 for 2-pentanol. The calculated values are in excellent agreement with the experimental values of log P^{calc} = 2.415 and log L^{calc} = 9.365, and log P^{calc} = 2.463 and log L^{calc} = 9.413, based on the measured experimental solubility of 2-chloro-5-nitrobenzoic acid in 3-methyl-1-butanol and 2-pentanol, respectively. According to my past experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of 2-chloro-5-nitrobenzoic acid to within 0.20 log units for organic solvents in which carboxylic acid dimerization does not occur.

TABLE 4.19. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Chloro-5-nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.16		
		log P^{exp}	log P^{calc}	log C_S^{exp}
1-Octanol (wet)		2.130	2.431	
Diethyl ether (dry)	-0.171	2.417	2.401	-0.187
Tetrahydrofuran (dry)	0.461	3.049	3.158	0.570
Ethanol (dry)	0.146	2.734	2.649	0.061
1-Propanol (dry)	-0.022	2.566	2.583	-0.005
2-Propanol (dry)	0.045	2.633	2.588	0.000
1-Butanol (dry)	-0.111	2.477	2.376	-0.212
1-Pentanol (dry)	-0.134	2.454	2.430	-0.158
1-Hexanol (dry)	-0.198	2.390	2.426	-0.162
1-Heptanol (dry)	-0.269	2.319	2.362	-0.226
1-Octanol (dry)	-0.324	2.264	2.329	-0.259
1-Decanol (dry)	-0.411	2.177	2.286	-0.302
2-Butanol (dry)	-0.042	2.546	2.469	-0.119
2-Methyl-1-propanol (dry)	-0.204	2.384	2.362	-0.226
2-Methyl-2-propanol (dry)	0.070	2.658	2.494	-0.094
Ethyl acetate (dry)	-0.126	2.462	2.531	-0.057
Gas-to-Water		6.950	7.010	

TABLE 4.20. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of 2-Chloro-5-nitrobenzoic Acid

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		9.080	9.400	
Diethyl ether (dry)	-0.171	9.367	9.276	-0.262
Tetrahydrofuran (dry)	0.461	9.999	10.088	0.550
Ethanol (dry)	0.146	9.680	9.453	-0.085
1-Propanol (dry)	-0.022	9.516	9.482	-0.056
2-Propanol (dry)	0.045	9.583	9.479	-0.059
1-Butanol (dry)	-0.111	9.427	9.448	-0.090
1-Pentanol (dry)	-0.134	9.404	9.402	-0.136
1-Hexanol (dry)	-0.198	9.340	9.397	-0.141
1-Heptanol (dry)	-0.269	9.269	9.282	-0.256
1-Octanol (dry)	-0.324	9.214	9.245	-0.293
1-Decanol (dry)	-0.411	9.127	9.254	-0.284
2-Butanol (dry)	-0.042	9.496	9.404	-0.134
2-Methyl-1-propanol (dry)	-0.204	9.334	9.303	-0.235
2-Methyl-2-propanol (dry)	0.070	9.608	9.464	-0.074
Ethyl acetate (dry)	-0.126	9.412	9.484	-0.054
Gas-to-Water		6.950	7.040	

Molecular Solute Descriptors for Ibuprofen

Molecular descriptors for ibuprofen are determined by converting the molar solubility C_S into calculated log P values. The calculated log P value can be compared with the experimentally determined values. Once log P is calculated, Microsoft solver, a program chosen due to its availability and simplicity, is used to minimize the sum of squares on the set of described system equations, a set of equations with known processes coefficients (*c,e,s,a,b,v* and *l*), to fit the targeted cells S, A and B until the overall sums of squares are at a minimum (46).

The molar solute solubility C_S is determined by dividing the mole fraction X_S of ibuprofen, found in Table 3.10 by the ideal molar volume of the saturated solution, with a value of V_{solute} = 208.0 cm^3 mol^{-1} being used for the molar volume of the solute. The molar solute solubility corrected for ionization for ibuprofen in water, log C_W = –3.76 (38,47) is used to calculate log P with Eqn. 4.9. Estimation of the hypothetical liquid molar volumes (V_{Solute}) or the ideal molar volume approximations for ibuprofen could have errors that should be considered, although errors associated with the estimation should be negligible because ibuprofen is not overly soluble in many of the solvent studied therefore, $X_s V_{solute}$ term will contribute very little to the molar volume of the saturated solution.

Dibutyl ether was excluded from the correlations of all carboxylic acids because it was felt that dimerization was inevitable in this larger ether solvent as discussed in Chapter 4 in the section: Condensed Phase and Gas Phase Transfer Processes Used in Determining Molecular Descriptors. In adequate description of the solubility behavior

of several carboxylic acids (benzoic acid, 2-hydroxybenzoic acid, 4-hydroxybenzoic acid, and 3-nitrobenzoic acid) in dibutyl ether was noticed when the equation coefficients were calculated for the equations. When dimerization is an issue one would expect the calculated log *P* values to be less than observed log *P* values, as was the case with dibutyl ether.

Available practical partition coefficient for 1-octanol (wet), cyclohexane, toluene, chloroform and 1,2-dichloroethane (1,11,48-50) and chromatographic retention data for the processes denoted as HPLC-1 (CHI), HPLC-2 (CHI) , HPLC-3 (CHI),HPLC-4 (CHI), HPLC-5 (CHI), HPLC-6 (CHI), HPLC-7 (CHI), HPLC-C18/TFE (gt_r) and HPLC-Xter/TFE (gt_r) (2,51) were retrieved from the chemical literature and added to our experimental log P and log L values measured in this thesis to give a total of 50 equations with known partition data and equation coefficients. The McGowan volume of ibuprofen was calculated with the method described in Chapter 2 in the section: Solute Descriptors and Their Encoded Chemical Information; the value determined for the McGowan volume was V = 1.7771 and the excess molar refraction estimated as E = 0.730. As described earlier, Microsoft Solver was employed to yield the numerical values of the remaining solute descriptors that best described the experimental log *P* and log *L* values.

An internally consistent set of log P and log L values are obtained by calculating the log C_G values. The vapor concentration corresponds to a gas-to-water partition of log L_W = 5.700 which is in good agreement with the calculated values based upon Eqns. 4.16 and 4.18 (last numerical entries in Tables 4.21 and 4.22).

The numerical values of the solute descriptors for ibuprofen are E = 0.730, S = 0.695, A = 0.565, B = 0.790 with V = 1.7771 and L = 7.184. The molecular descriptors

TABLE 4.21. Comparison Between Observed and Back-Calculated Condensed Phase-to-Condensed Phase Partitions and Molar Solubilities of Ibuprofen

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
1-Octanol (wet)		3.970	3.829	
Chloroform		3.025	3.100	
1,2-Dichloroethane		2.870	2.779	
Cyclohexane		1.877	1.692	
Toluene		2.484	2.592	
Methanol (dry)	0.070	3.830	3.689	-0.071
Ethanol (dry)	0.070	3.830	4.045	0.285
1-Propanol (dry)	0.180	3.940	4.019	0.259
2-Propanol (dry)	0.330	4.090	4.018	0.258
1-Butanol (dry)	0.160	3.920	3.936	0.176
1-Pentanol (dry)	0.160	3.920	4.068	0.308
1-Hexanol (dry)	0.190	3.950	3.978	0.218
1-Heptanol (dry)	0.160	3.920	4.040	0.280
1-Octanol (dry)	0.070	3.830	3.735	-0.025
1-Decanol (dry)	0.045	3.805	3.935	0.175
2-Butanol (dry)	0.245	4.006	3.840	0.080
2-Methyl-1-propanol (dry)	0.239	3.999	3.966	0.206
HPLC-1 (CHI)		4.578	4.594	
HPLC-2 (CHI)		4.543	4.629	
HPLC-3 (CHI)		4.357	4.366	
HPLC-4 (CHI)		3.352	3.345	
HPLC-5 (CHI)		3.675	3.808	
HPLC-6 (CHI)		2.756	2.815	
HPLC-7 (CHI)		2.585	2.608	
HPLC-C18/TFE (gt_r)		2.940	2.785	
HPLC-Xter/TFE (gt_r)		2.850	2.719	

TABLE 4.21 (Continued)

Solvent/Process	log C_S^{exp}	Equation 4.16 log P^{exp}	Equation 4.16 log P^{calc}	Equation 4.16 log C_S^{exp}
HPLC-C18/MeOH (gt_r)		3.020	2.946	
HPLC-Xter/MeOH (gt_r)		2.920	2.820	
HPLC-C18/ACN (gt_r)		2.590	2.533	
HPLC-Xter/ACN (gt_r)		2.480	2.407	
Gas-to-Water		5.700	5.633	

TABLE 4.22. Comparison Between Observed and Back-Calculated Gas Phase-to-Condensed Phase Partitions and Molar Solubilities of Ibuprofen

Solvent/Process	log C_S^{exp}	Equation 4.18 log L^{exp}	Equation 4.18 log L^{calc}	Equation 4.18 log C_S^{exp}
1-Octanol (wet)		9.670	9.576	
Chloroform		8.725	8.961	
1,2-Dichloroethane		8.570	8.571	
Cyclohexane		7.577	7.360	
Toluene		8.184	8.222	
Methanol (dry)	0.070	9.530	9.400	-0.060
Ethanol (dry)	0.070	9.530	9.626	0.166
1-Propanol (dry)	0.180	9.640	9.625	0.165
2-Propanol (dry)	0.330	9.790	9.675	0.215
1-Butanol (dry)	0.160	9.620	9.769	0.309
1-Pentanol (dry)	0.160	9.620	9.727	0.267
1-Hexanol (dry)	0.190	9.650	9.587	0.127
1-Heptanol (dry)	0.160	9.620	9.706	0.246
1-Octanol (dry)	0.070	9.530	9.441	-0.019
1-Decanol (dry)	0.045	9.505	9.546	0.086
2-Butanol (dry)	0.245	9.706	9.565	0.105
2-Methyl-1-propanol (dry)	0.239	9.699	9.682	0.222
Gas-to-Water		5.700	5.714	

reproduce the experimental log *P* and log *L* values for ibuprofen to within an overall standard deviation of 0.112 log unit. According to past experience with the Abraham solvation parameter model, the following molecular descriptors could be used to predict both the solubility and practical organic solvent–water partition coefficients of ibuprofen to within 0.20 log units for organic solvents in which carboxylic acid dimerization does

not occur.

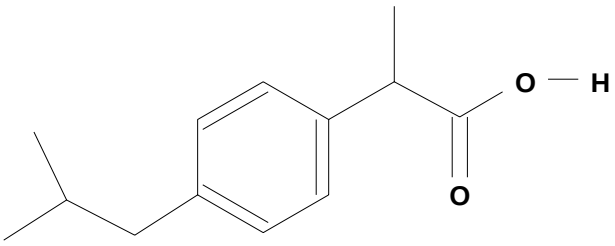
Although, the calculated descriptors for ibuprofen account very well for the experimental solubilities and partition coefficients, one needs to address the question of whether or not the calculated values reflect the chemical properties of the drug molecule. One way to do this is to fragment the molecule into the isobutylbenzene moiety (minus one of the aromatic ring hydrogen atoms, *i.e*., $CH_3CH(CH_3)CH_2C_6H_5$-) and the isobutanoic moiety (isobutanoic acid minus one of the methyl hydrogen atoms, *i.e*., -$CH_2CH(CH_3)COOH$). The known solute descriptors of isobutylbenzene and isobutonoic acid are as follows in Table 4.23

TABLE 4.23 Theoretical Estimation of the Solute Descriptors for Ibuprofen

		Equation 4.16		
Compound	E	S	A	B
isobutylbenzene	0.600	0.500	0.000	0.150
isobutonoic acid	0.200	0.600	0.600	0.450
Sum	0.800	1.100	0.600	0.600
Calculated for Ibuprofen	0.730	0.695	0.565	0.790

one does not expect the values to be identical because the molecules overall polarizability and hydrogen bonding characteristics are not a simple group addibility of the molecule's fragmental values. Past experience has shown that of the four solute descriptors, E, A and B are more group additive than the S descriptor. Recall that one of the ways to estimate the E descriptor is from known fragmental values; the found and summed fragment values are reasonably close, indicating that the found values E =

0.730, S = 0.695, A = 0.565 and B = 0.790 are indeed quite reasonable.



Ibuprofen

Fig. 4.4. Molecular structure of ibuprofen.

Concluding Remarks

The Abraham solvation parameter model does provide a fairly accurate description of the wter-to-organic solvent and gas-to-organic solvent partitioning behavior of many organic systems, as well as the solubility behavior of crystalline polycyclic aromatic hetero-atom compounds and carboxylic acid solutes in a wide range of organic solvents of varying polarity and hydrogen-bonding characteristics. In the case of carboxylic acid solutes the model is at the present time limited to systems where carboxylic acid dimerization does not occur. Furture studies should more carefully exam the solubility of carboxylic acids in benzene, toluene, carbon tetrachloride and saturated alkane solvents to determine whether or not one can calculate realistical values fo the solute descriptors for carboxylic acids in the dimerized form. At this point in time there is insufficient experimental data to make any reasonable assessment.

Process coefficients are presently available for about 50 different organic

solvents. While the number is more than sufficient for solute descriptor determinations based on solubility determinations, it would be nice to have a larger range of organic solvents from which to select. Spectrophotometric measurements afford a convenient means to measure solubility, and more "optically transparent" solvents would be preferred. Currently there is only a single "dry" alkyl ester solvent (e.g., ethyl acetate). Future work should focus on developing process coefficients for additional alkyl esters, such as methyl acetate and butyl acetate. Solubilities of 4-nitrobenzoic acid, 2-methylbenzoic acid, 2-methoxybenzoic, 4-methoxybenzoic acid, 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid for just this reason.

Published studies have shown that equation coefficients for practical "wet" and hypothetical "dry" partition processes can differ, particularly if there is an appreciable amount of water dissolved in the equilibrated organic phase. Most of the "wet" process equations were developed more than 10 years ago, and the equations need to be re-examined in light of recently published experimental data. As noted previously, process equations are periodically updated as additional experimental data becomes available. For several of the process equations there has been no recent update.

Finally, given the continued success of the Abraham solvation parameter model there needs to be a systematic study undertaken directed towards developing good predictive methods for calculating numerical values of the solute descriptors. It is not feasible to experimentally measure partition coefficient and/or solubility data for every known compound. Such measurements defeat the purpose of developing predictive methods for high throughput screening. In drug design one needs to be able to quickly eliminate unfavorable molecules from considerable, preferably before one has spent the

time synthesizing and purifying the compound. It is hoped that the solubility data measured as part of the thesis research will prove useful in both the development of new process equations and the development of a computational method for obtaining solute descriptors based more on structural information (and less on direct experimental measurements).

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GLOSSARY

δ	diffusion path length
π_2^c	dipolarity/polarizability solute descriptor
v	frequency
ΔH_{soln}	change in heat of solution
α_2^c	hydrogen-bond acidity solute descriptor
β_2^c	hydrogen-bond basicity solute descriptor
λ_{max}	maximum wavelength of absorption for that specific solute
ε	molar absorptivity
ε_{solute}	molar absorptivity coefficient of the solute
X_S	mole fraction
d δ_2	polarity correction term
n	refractive index
k’	solute’s chromatographic capacity factor
λ	wavelength
A	contact (spread) area of the droplet
A	measured absorbance
ADMET	adsorption, distribution, metabolism, excretion, and toxicity
A-Eco	acetic acid-extractable cobalt
ANN	artificial neural net
ANN-QSPR	artificial neural net-quantitative structure-activity/property Relationship

Apolane-87	a stable, nonvolatile, highly branched nonpolar hydrocarbon liquid that can be used over the temperature range of 30 – 280 °C
Aspirin	acetylsalicylic acid
BBB	blood-brain barrier
BCEC	brain capillary endothelial cells
B_n	total number of bonds between bonding atoms
B^o	alternative Abraham hydrogen-bond basicity descriptor
c	speed of light
C	molar concentration of the organic compound
C_G	gas-phase concentration
C_S	molar solubility in the organic solvent
C_w	the molar solubility of the solute in water
Caco-2cells	cultured colon cells
$CDCl_3$	deuterated chloroform
CNS	central nervous system
DAD	diode array detector
DMSO	dimethyl sulfoxide
$D_{membrane}$	solute permanent diffusivity within the membrane
E	energy
E	excess molar refractivity
F	Fisher-F statistic
g	gerade is a symmetrical orbital
GC	gas chromatography

GRG@	General Reduced Gradient
HIA	human intestinal absorption
HPLC	high-performance liquid chromatography
HTS	high throughput screening
IG	inhibition of growth
k_p	skin permeability coefficient
ΔL	orbital angular momentum
$L_{apolane\text{-}87,\ 40\ C}$	gas-liquid partition coefficient on apolane-87 at 40 °C
LFER	linear free energy relationship
LSER	linear solvation energy relationship
L_S	gas-solvent partitions
log (C_{blood}/C_{brain})	partitioning of a drug in the brain vs. the blood
log (C_{blood}/C_{air})	harmful pesticide or nerve gas in the air vs. the blood
L_W	gas–water partitions
mass % soly	mass percent saturation solubility of the solute
MDCK	madin-darby canine kidney cells
MM_{Solute}	molar mass of the solute
N_a	number of atoms
N	number of compounds
NMR	nuclear magnetic resonance
OH_{aliph}	denotes the number of aliphatic OH groups on the molecule
$P = C_{org}/C_{Aq}$	partition coefficient
PMT	photomultiplier tube

$P_{o/w}$	octanol-water partition coefficient
PSA	polar surface area
$P_{unit\ partition}$	unit partition coefficient
QM	quantum mechanical
QSAR	qualitative structure activity relationships
QSPerR	quantitative structure-permeabiity relationship
R^2	squared correlation coefficient
r R	Abraham model correction term
R&D	research and development
R_g	number of rings in the compound
RMSD	root-mean-square-difference
S	solute's polarizability/dipolarity descriptor
ΔS	spin orbital selection rules,
sd	standard deviation
stratum corneum	outermost layer of epidermis
T	Transmittance
u	ungerade is a non-symmetrical orbital
uv-vis	ultraviolet-visible spectrometers
V	McGowan volume
$V_{atom\ of\ type\ i}$.	atomic volume fragments
VOCs	volatile organic compounds
VP°	solid saturated vapor pressure at 298.15 K
V_{solute}	solute's molar volume

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