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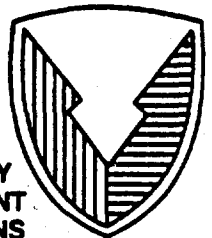
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USING THEORETICAL DESCRIPTORS  
IN STRUCTURAL ACTIVITY RELATIONSHIPS  
I. MOLECULAR VOLUME

by George R. Farni  
RESEARCH DIRECTORATE

January 1988

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Quantitative Structure Activity Relationships (QSAR) have been used successfully in the past to develop predictive equations for a variety of physical and biological properties. A subset of QSAR, Linear Solvation Energy Relationships (LSER), have been used by Kamlet and Taft to predict and correlate over 100 solute/solvent related properties. A major difficulty with LSER is the use of empirically derived descriptors. The use of theoretically determined molecular volumes in place of empirically determined molar volume in LSER equations is discussed. Keywords: reaction kinetics; physical properties; mathematical models; predictions; chemical properties			
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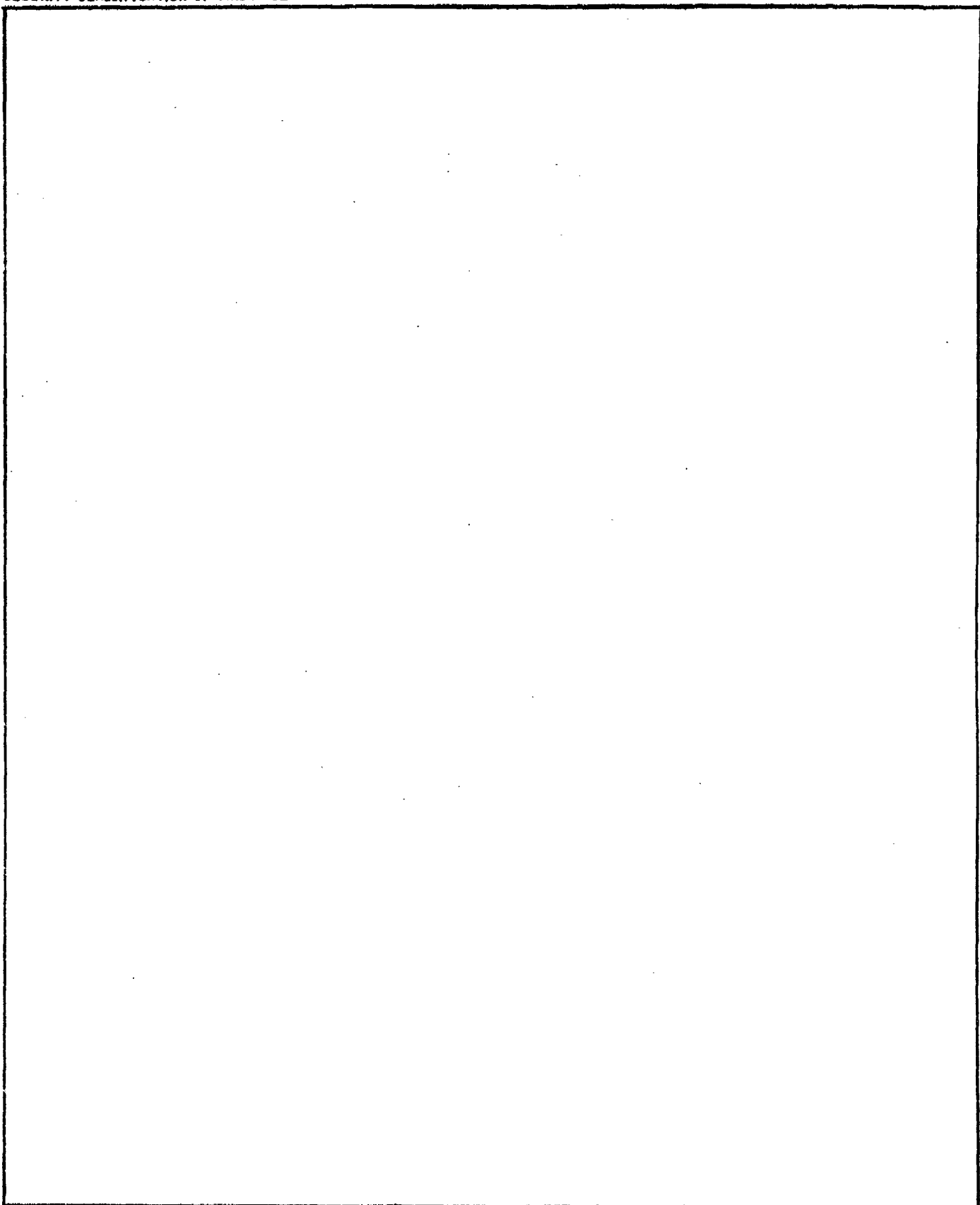
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PREFACE

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USING THEORETICAL DESCRIPTORS  
IN STRUCTURAL ACTIVITY RELATIONSHIPS  
I. MOLECULAR VOLUME

1. INTRODUCTION

In many areas of basic and applied research it is necessary to know the physical properties of various classes of chemical compounds. Often, the physical properties of a particular compound are not known, and synthesis of the compound and measurement of its physical properties are not possible due to time and/or monetary constraints. Therefore, methods need to be developed that will allow for the prediction of physical properties of interest. Two compilations by Reid and Prausnitz<sup>1</sup> and Lyman<sup>2</sup> have been published detailing estimation models for a variety of properties.<sup>1,2</sup>

At the Chemical Research, Development and Engineering Center (CRDEC), many of the existing estimation models for physical properties described in references 1 and 2 do not apply. This is primarily due to the nature of the classes of compounds of interest to the CRDEC. For this reason, either new models must be generated specific to those classes of compounds or existing models must be modified to include them.

In the past several years, numerous parameters have been used in Quantitative Structure Activity Relationships (QSAR) to explain a variety of structure/property interactions.<sup>3-5</sup> Many, indeed most, of these parameters are empirically derived. This implies that the series of compounds to which the equations apply must have had those parameters measured, or that an acceptable method of predicting those parameters must have been generated. Examples of this type of parameter can be seen in the octanol/water partition coefficient,<sup>6</sup> the molar volume,<sup>7</sup> or any of the Taft-Kamlet solvatochromic parameters.<sup>8</sup> It is often difficult to find a compound that has the property (also called activity) and all of the necessary parameters measured. Therefore, it would be beneficial to be able to derive Structure-Activity Relationships (SAR) from theoretically or computationally derived parameters. Several cases of quantum chemically derived parameters being used in SAR equations have been reported.<sup>9,10</sup>

In Linear Solvation Energy Relationships (LSER), a subset of QSAR, Taft, Kamlet, and co-workers have been successful in correlating a variety of properties with a series of parameters defined by them as solvatochromic parameters.<sup>11,12</sup> From these relationships, they have developed a generalized linear solvation energy relationship equation;

$$\begin{aligned} \text{Property} &= \text{cavity term} + \text{polarizability term} & (1) \\ &+ \text{hydrogen bonding terms} + \text{intercept} \end{aligned}$$

Depending upon whether one is dealing with the examination of properties of solvents or solutes, the cavity term is either the Hildebrand Solubility Parameter (for solvents) or molar volume (for solutes). The

polarizability term is a measured quantity from UV-Vis spectroscopy, as are the two hydrogen bonding terms, one for acidity and one for basicity.

All of these parameters are empirical in nature; they must be measured for a particular compound or, at the least, a series of compounds. If a computationally derivable term could replace one or more of these parameters, then the utility of these equations would be greatly enhanced. You would be able to incorporate a larger number of compounds than currently have measured solvatochromic parameters.

In effect, the LSER equation consists of two types of descriptors, a size term (molar volume) and electronic terms (polarizability and hydrogen bond acidities and basicities). The size term has been the easiest term to model, so it is sensible to focus on defining a theoretically derived size term to replace the molar volume.

The Chemometric/Biometric Modeling Branch of CRDEC has a Molecular Modeling, Analysis and Display System (MMADS) in operation, which, among other items, will calculate the minimum energy conformation of molecules, the volumes and areas, and the running of a variety of quantum chemical programs.<sup>13</sup> Described here is the use of the MMADS in deriving molecular volumes and the use of these molecular volumes in LSER equations in place of the molar volumes. The correlation of the molecular volume with the molar volume will also be discussed.

## 2. EXPERIMENTAL METHOD

### 2.1 Experimental Data.

The molar volumes of the compounds used in this study were taken from a series of papers by Kamlet and Taft, as were the octanol/water partition coefficients and the charcoal absorptivity values.<sup>14,15</sup> The fish toxicity data was taken from a paper by H. Konemann.<sup>16</sup> The comparison of molar volume and molecular volume used only compounds from the octanol/water partition coefficient data.

### 2.2 Calculated Molecular Volumes.

The molecular volume was calculated using the MMADS, which is located in the Chemometric/Biometric Modeling Branch, CRDEC. The MMADS runs on a VAX 11/730 under the VMS Operating System. The chemical structures were input into the computer in a variety of methods,\* and the structures were optimized via molecular mechanics.<sup>17</sup> The molecular volumes were then calculated using an algorithm developed by Hopfinger.<sup>18</sup>

All multiple linear regressions were run on a Hewlett-Packard 9845B microcomputer running the HP StatPack.

\*Kwikdraw, the primary method of entering compounds into MMADS, was written by J.M. Leonard, CRDEC.

### 3. RESULTS

Throughout the equations listed below, the molecular volume, molar volume, solvatochromic terms, and the correlated properties will use the following abbreviations:

$P$  = log octanol/water partition coefficient

McVol = molecular volume (calculated)

MolVol = molar volume

$\pi$  = solvatochromic polarizability term

$\beta$  = solvatochromic hydrogen bonding basicity term

$\alpha$  = solvatochromic hydrogen bonding acidity term

#### 3.1 Molecular Volume Vs. Molar Volume.

The primary step in determining if molecular volume could be used in place of molar volume was to determine how well the two size terms correlated with each other. In principle, since both are measures of the bulk of a molecule, they should be highly correlated. Using selected aliphatic compounds used by Taft et al. (Table 1),<sup>14</sup> a linear relationship was determined. The equation for molar volume is shown in equation 2:

$$\text{MolVol}/100 = .943(\text{McVol}/100) + .152 \quad (2)$$

$$R = .979 \quad \text{sd} = .0512 \quad n = 37$$

Figure 1 shows a plot of the molar volume/100 versus the molecular volume/100, along with the best fit curve.

When the alcohols and aromatics listed in Tables 2 and 3, respectively, are added to the compounds in Table 1, the molar volume/molecular relationship is:

$$\text{MolarVol}/100 = .891 (\text{Molecular Volume}/100) + .161 \quad (3)$$

$$R = .969 \quad \text{sd} = .073 \quad n = 80$$

Two general relationships can be noted: one, the calculated molar volume of the aromatics is consistently 9.5 mol/mL too low and, two, the alcohols are consistently off by about 7 mol/mL. If both of these corrections are taken into account, that is, the molecular volume is altered for alcohols and aromatics,\* then the results become:

\*For a complete explanation of underlying physical organic principles, see Taft et al.<sup>14</sup>

$$\text{MolarVol}/100 = .909(\text{Molecular Volume}/100) + .176 \quad (4)$$

$$R = .973 \quad \text{sd} = .071$$

As can be seen from equations 1 and 2, the relationship between molar volume and molecular volume is somewhat class dependent. However, by using the aliphatics as a "base line," both alcohols and aromatics fall off the curve by a consistent amount (for each of the two classes). From this, then, a correction can be applied to either the molar volume or molecular volume to give the aromatics and alcohols a better fit.

Kamlet and Taft<sup>19</sup> noted that when they used molar volume of aromatics in their relationships, they had to make a correction of 10 mol/mL in order to achieve the best results. The average deviation for the aromatics from the aliphatic "base line" is 9.5 mL/mol. In addition, MMADS has no method for checking for volume shrinkage due to hydrogen bonding in alcohols. The reason is that MMADS views a single molecule, isolated in the free state (i.e., gaseous in a vacuum). Therefore, intermolecular forces such as hydrogen bonding and imperfect packing must be added in.

### 3.2 Replacement of Molar Volume with Molecular Volume in LSER Equations.

Since it has been shown that the correlation between molar volume and molecular volume is indeed very high, it seems reasonable that the LSER equations should maintain the same high predictive capability when molar volume is replaced by molecular volume. This section gives several pertinent examples where this has been done.

#### 3.2.1 Octanol/Water Partition Coefficient.

The octanol/water partition coefficient has been used extensively in QSAR equations and in explaining transport properties of chemical compounds through the body. The major reason is that the partitioning of compounds between octanol and water models very well the partitioning of chemicals between lipophilic and hydrophilic regions (e.g., the blood-brain barrier). As such, the octanol/water partition coefficient has generated a lot of interest, and methods have been developed to predict the values for compounds that have not been measured. In modeling of biological activities, Log P has often been the sole, or the major, independent variable. It would therefore make sense that in determining the usefulness of LSER equations and in using theoretically derived descriptors, you would attempt to model this very useful property/parameter.

The theoretically calculated molecular volume was used in place of the molar volume in three separate correlations. Equation 5 shows the correlation of Log P with the molecular volume for 37 aliphatic compounds (Tables 4 and 5) was:

$$\text{Log P} = 2.662(\text{McVol}) - 1.101(\text{pi}) - 3.607(\text{beta}) + 0.672 \quad (5)$$

$$R = .993 \quad \text{sd} = .157 \quad n = 37$$

Figure 2 shows a plot of the predicted value of Log P versus the observed value.

This compares to a regression of 47 aliphatics from Taft and Kamlet using the molar volume:

$$\text{Log P} = 2.66(\text{MolVol}) - .96(\text{pi}) - 3.38(\text{beta}) + .24 \quad (6)$$

$$R = .991 \quad \text{sd} = .18 \quad n = 47$$

Fourteen aliphatic alcohols were added to the data set (Tables 6 and 7), and the resultant multiple linear regression yielded:

$$\text{Log P} = 2.835(\text{MolVol}) - 1.001(\text{pi}) - 3.769(\text{beta}) + .500 \quad (7)$$

$$R = .991 \quad \text{sd} = .161 \quad n = 52$$

Figure 3 shows graphically the difference between the observed and the predicted values.

Adding the aromatics listed in Table 5 and using the correction factor of 7.5 mol/mL for the alcohols, the following relationship is derived:

$$\text{Log P} = 2.835(\text{McVol}) - 1.001(\text{pi}) - 3.769(\text{beta}) + .500 \quad (8)$$

$$R = .990 \quad \text{sd} = .158 \quad n = 74$$

Taft et al. reported the following relationship for 63 compounds,<sup>14</sup> consisting of aliphatics, aromatics, and alcohols:

$$\text{Log P} = 2.89(\text{MolVol}) - 0.88(\text{pi}) - 3.62(\text{beta}) + 0.12 \quad (9)$$

$$R = .989 \quad \text{sd} = 0.18 \quad n = 63$$

### 3.2.2 Charcoal Adsorptivity.

Kamlet and Taft et al.<sup>19</sup> showed that the distribution of organic solutes between solution (in water) and adsorption on charcoal is a solubility property that can be modeled using the solvatochromic parameters. The property considered is:

$$a = \lim_{C \rightarrow 0} X/C$$

$$C \quad 0$$

where

X = concentration of adsorbate on charcoal

C = equilibrium concentration in solution.

a, therefore, represents the partition coefficient between charcoal and the aqueous phase.

Using the data in Table 8, the following regression was determined using the Taft-Kamlet parameters and molecular volume (Table 9).

$$\text{Log (a)} = .661(\pi) - 2.76(\beta) - 2.77(\text{McVol}) - 1.71 \quad (10)$$

$$R = .966 \quad \text{sd} = .204 \quad n = 35$$

The corresponding relationship derived by Taft and Kamlet<sup>15</sup> using molar volume is:

$$\text{Log (a)} = .65(\pi) - 3.10(\beta) - 3.05(\text{MolVol}) - 2.00 \quad (11)$$

$$R = .975 \quad \text{sd} = .189 \quad n = 37$$

### 3.2.3 Fish Toxicity.

The examples listed so far have shown the validity of the LSER equations and molecular volume to physical/chemical properties. An example of the predictive capability for general toxicological properties can be seen in Konemann's fish toxicity.<sup>16</sup>

Using Konemann's data on the toxicity (LC50) of 50 industrial pollutants on 2- to 3-month-old guppies (*Poecilia reticulata*)<sup>16</sup> and determining the beta and pi from Kamlet and Taft,<sup>19</sup> a relationship for LC50 was determined utilizing both solids and liquids.

$$\text{LC50} = 5.94 + 3.66(\beta) - 3.93(\text{MolVol}) + .03(\pi) \quad (12)$$

$$R = .971 \quad \text{sd} = .420 \quad n = 33$$

The parameters (pi, beta, McVol, and observed and predicted Log LC50) are found in Table 10. The Taft-Kamlet parameters are not capable of handling solids, as liquid density is required in the molar volume.

## 4. DISCUSSION

### 4.1 Molar Volume Vs. Molecular Volume.

It can be seen from the correlations that, indeed, there is an excellent correlation between molecular volume and molar volume. The only real difference in the two measures is that while the molecular volume measures only the theoretical volume of a free-standing molecule with no external or intermolecular forces acting upon it, the molar volume is an "effective volume," measured only in the liquid phase with hydrogen bonding, packing forces, etc. being taken into account. Since the molar volume is defined as the molecular weight/liquid density, additional volumes due to imperfect packing may be included here.

The molar volume has an additional disadvantage in that it is measured from liquid density. This precludes solids and gases from being utilized in LSER equations that incorporate molar volume. The molecular

volume, on the other hand, requires no such caveat and, in principle, may allow incorporation of solids and gases into LSER equations. Please note that volumes calculated in this way do not take into account any intermolecular forces, so solids in some instances may not generate the true molecular volume. In some preliminary work, Leahy found this not to be true.<sup>20</sup>

#### 4.2 Incorporation of Molecular Volume into LSER Equations.

LSER equations using the molecular volume are as good a fit, or nearly so, as those equations using the molar volume. In examining the Konemann toxicity data on fish, it should be noted that 12 of the 23 compounds used were solids; therefore, it would be impossible or meaningless to use the complete set of solvatochromic parameters.

Another important result is that the Kamlet-Taft solvatochromic parameters yield equations that make chemical sense. That is, their parameters have chemical meaning, so that one can grasp the physical significance of the equations as well as the predictive capability. This can be seen clearly in all of the properties given in this paper. It can be illustrated by using the octanol/water partition coefficient as an example. The three significant terms in Equation 8 are molar volume, hydrogen bond basicity, and polarizability. As molar volume increases, the value of Log P also increases, indicating that more of the solute resides in the lipophilic octanol layer. This is consistent with experiment in that large molecules do have lower solubilities in polar solvents (like water). Inversely, an increase in the polarizability and hydrogen bond basicity decrease the Log P value, indicating a favoring of the hydrophilic (water) region. Since both polarizability and hydrogen bonding ability are indicative of charge buildup, this result is also not surprising. In addition, since each of the parameters are roughly scaled to within the same limits, observing the absolute values of the coefficients indicates the relative importance of each variable. In the case of the octanol/water partition coefficient, the hydrogen basicity and size are the most important descriptors.

With the substitution of molecular volume into the equations, the same information is maintained; the signs and relative weighting of the coefficients remain the same.

#### 5. CONCLUSIONS

It has been shown that the Generalized Linear Solvation Energy Relationship of Taft and Kamlet can be useful in predicting a wide variety of the properties of the solute/solvent interaction as well as rationalizing chemical behavior. With the substitution of the molar volume by molecular volume, the predictive capability remains the same, as does the content of information. Since crystal packing forces are not being taken into account, you would think that the theoretical molecular volumes alone would be insufficient to describe the size and shape of solids. However, from this study and Leahy's work,<sup>20</sup> this does not appear to be the case. The molecular volume, at least to a first approximation, seems to allow for the incorporation of solids into the correlation equations with no apparent degradation of fit, although the addition of a packing force term may further increase the correlation.

Table 1. Molecular Volume vs. Molar Volume

Compound	McVol/100 A <sup>3</sup>	MolVol/100 experimental A <sup>3</sup>	MolVol/100 predicted A <sup>3</sup>	Residual
Hexane	1.184	1.305	1.268	0.037
Cyclohexane	1.063	1.180	1.154	0.026
Neopentane	1.004	1.176	1.099	0.077
Pentane	1.007	1.152	1.102	0.051
Cyclopentane	0.891	1.034	0.992	0.042
Butane	0.830	0.980	0.935	0.045
Cl <sub>2</sub> C=CCl <sub>2</sub>	0.981	1.016	1.077	-0.061
CCl <sub>4</sub>	0.907	0.968	1.007	-0.039
Tripropyl amine	1.832	1.895	1.879	0.016
Butyl chloride	0.983	1.044	1.079	-0.035
CH <sub>3</sub> CCl <sub>3</sub>	0.932	0.989	1.031	-0.042
Propane	0.653	0.810	0.768	0.043
nCH <sub>3</sub> CHCl <sub>2</sub>	0.679	0.897	0.792	0.105
Propyl chloride	0.806	0.880	0.912	-0.032
ClH <sub>2</sub> CCl <sub>2</sub> Cl	0.783	0.787	0.890	-0.103
Triethyl amine	1.303	1.401	1.381	0.020
2-Hexanone	1.160	1.235	1.246	-0.011
N-Methyl pyridine	1.185	1.316	1.269	0.047
Ethyl propionate	1.051	1.146	1.143	0.003
2-Pentanone	0.983	1.065	1.079	-0.014
Diethyl ether	0.905	1.046	1.005	0.041
Butyraldehyde	0.804	0.883	0.910	-0.270
Cyclohexanone	1.039	1.136	1.132	0.004
Ethyl acetate	0.873	0.978	0.975	0.003
Ethyl dimethyl amine	0.952	1.110	1.049	0.050
Propionaldehyde	0.627	0.720	0.743	-0.023
Tetrahydrofuran	0.785	0.911	0.892	0.019
Diethyl acetamide	1.287	1.265	1.365	-0.100
Butanone	0.807	0.895	0.913	-0.018
Methyl acetate	0.696	0.798	0.808	-0.010
Trimethyl amine	0.776	0.950	0.884	0.066
Propionitrile	0.585	0.704	0.704	0.000
Dimethyl ether	0.546	0.706	0.669	0.039
Propanone	0.629	0.734	0.745	-0.011
Acetonitrile	0.403	0.521	0.532	-0.012
Dimethyl acetamide	0.933	0.924	1.032	-0.108
Dimethyl formamide	0.753	0.774	0.862	-0.088



Table 2. Molecular and Molar Volumes for Alcohols

Compound	MolVol/100 A <sup>3</sup>	MolVol/100 experimental A <sup>3</sup>	MolVol/100 predicted A <sup>3</sup>	Residual
Methanol	0.361	0.490	0.405	0.090
Ethanol	0.540	0.661	0.584	0.077
n-Propanol	0.717	0.828	0.780	0.048
2-Propanol	0.716	0.827	0.765	0.062
n-Butanol	0.894	0.995	0.915	0.080
2-Methyl-1-propanol	0.893	0.994	0.920	0.074
2-Butanol	0.893	0.994	0.917	0.077
t-Butanol	0.892	0.993	0.939	0.054
Pentanol	1.077	1.168	1.082	0.086
3-Pentanol	1.070	1.161	1.073	0.088
2,2-Dimethyl-1- propanol	1.068	1.159	1.085	0.074
t-Pentanol	1.068	1.159	1.094	0.065
3-Methyl-2-butanol	1.043	1.133	1.093	0.40
n-Hexanol	1.248	1.329	1.256	0.073
3,3-Dimethyl-2- butanol	1.243	1.172	1.258	0.066

Note: The predicted values and differences are based upon equation 2

Table 3. Molecular and Molar Volumes for Aromatics

Compound	McVol/100 A <sup>3</sup>	MolVol/100 experimental A <sup>3</sup>	MolVol/100 predicted A <sup>3</sup>	Residual
PhCH <sub>2</sub> CH <sub>2</sub> CN	1.215	1.210	1.298	-0.088
PhCH <sub>2</sub> CH <sub>2</sub> COOH	1.681	1.656	1.737	-0.081
PhCH <sub>2</sub> COCH <sub>3</sub>	1.260	1.221	1.340	-0.120
PhCH <sub>2</sub> COOCH <sub>3</sub>	1.326	1.312	1.402	-0.090
CH <sub>3</sub> COOCH <sub>2</sub> Ph	1.326	1.324	1.402	-0.078
CH <sub>3</sub> COOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Ph	1.680	1.556	1.736	-0.180
PhCH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	1.406	1.377	1.478	-0.101
PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	1.530	1.502	1.595	-0.093
CH <sub>3</sub> COOCH <sub>2</sub> CH <sub>2</sub> Ph	1.502	1.409	1.568	-0.159
PhCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> C(O)CH <sub>3</sub>	1.614	1.542	1.674	-0.132
PhCH(COOCH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	2.080	2.228	2.113	0.115
PhOCH <sub>2</sub> COOCH <sub>2</sub> CH <sub>3</sub>	1.502	1.346	1.568	-0.222
PhOCH <sub>2</sub> C(O)N(CH <sub>3</sub> ) <sub>2</sub>	1.630	1.577	1.689	-0.112
PhCH <sub>2</sub> OH	0.993	0.969	1.088	-0.119
p-CH <sub>3</sub> -Ph-CH <sub>2</sub> OH	1.173	1.120	1.258	-0.138
PhCH <sub>2</sub> CH <sub>2</sub> OH	1.153	1.098	1.239	-0.146
PhCH <sub>2</sub> CH <sub>2</sub> OH	1.242	1.251	1.323	-0.072
Benzene	0.749	0.789	0.858	-0.069
PhCOOCH <sub>2</sub> CH <sub>3</sub>	1.317	1.330	1.394	-0.064
PhC(O)CH <sub>3</sub>	1.071	1.069	1.162	-0.093
PhN(CH <sub>3</sub> ) <sub>2</sub>	1.233	1.167	1.315	-0.148
PhCHO	0.893	0.919	0.994	-0.075
PhCH <sub>3</sub>	0.928	0.963	1.027	-0.064
PhOCH <sub>3</sub>	0.996	0.986	1.091	-0.105
PhOCH <sub>2</sub> H <sub>3</sub>	1.096	1.164	1.186	-0.022
PhOCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	1.273	1.324	1.352	-0.028

Note: The predicted values and the resulting differences are based upon equation 2

Table 4. Octanol/Water Partition Coefficient

Compound	McVol/100 A <sup>3</sup>	MolVol/100 A <sup>3</sup>	beta	pi	Log P (experimental)
Hexane	1.184	1.305	0.00	-0.08	3.90
Cylcohexane	1.063	1.180	0.00	0.0	3.44
Neopentane	1.004	1.176	0.00	0.0	3.11
Pentane	1.007	1.152	0.00	-0.08	3.39
Cyclopentane	0.891	1.034	0.00	0.0	3.00
Butane	0.830	0.980	0.00	-0.08	2.89
C12C=CC12	0.981	1.016	0.10	0.08	2.88
CC14	0.907	0.968	0.10	0.08	2.83
Tripropyl amine	1.832	1.895	0.69	0.14	2.79
Butyl chloride	0.983	1.044	0.10	0.39	2.64
CH3CC13	0.932	0.989	0.10	0.29	2.49
Propane	0.653	0.810	0.00	-0.08	2.30
n-CH3CHC12	0.679	0.897	0.10	0.23	2.29
Propyl chloride	0.806	0.880	0.10	0.39	2.04
C1H2CCH2C1	0.783	0.787	0.10	0.81	1.48
Triethyl amine	1.303	1.401	0.71	0.14	1.45
2-Hexanone	1.160	1.235	0.65	0.50	1.38
N-Methyl pyridine	1.185	1.316	0.70	0.15	1.30
Ethyl propionate	1.051	1.146	0.46	0.47	1.20
2-Pentanone	0.983	1.065	0.50	0.67	0.91
Diethyl ether	0.905	1.046	0.47	0.27	0.89
Butyraldehyde	0.804	0.883	0.38	0.50	0.88
Cyclohexanone	1.039	1.136	0.53	0.76	0.81
Ethyl acetate	0.873	0.978	0.45	0.55	0.73
Ethyl dimethyl amine	0.952	1.110	0.70	0.14	0.70
Propionaldehyde	0.627	0.720	0.38	0.50	0.60
Tetrahydrofuran	0.785	0.911	0.55	0.58	0.46
Diethyl acetamide	1.287	1.265	0.78	0.86	0.34
Butanone	0.807	0.895	0.48	0.67	0.29
Methyl acetate	0.696	0.798	0.42	0.60	0.18
Trimethyl amine	0.776	0.950	0.65	0.14	0.16
Prpionitrile	0.585	0.704	0.35	0.71	0.10
Dimethyl ether	0.546	0.706	0.47	0.27	0.10
Propanone	0.629	0.734	0.48	0.71	-0.24
Acetonitrile	0.403	0.521	0.35	0.75	-0.34
Dimethyl acetamide	0.933	0.924	0.76	0.88	-0.77
Dimethyl formamide	0.753	0.774	0.69	0.88	-1.01

Table 5. Predicted Values for Equations 7 and 8

Compound	Eq 7 predicted	Experimental - predicted	Eq 8 predicted	Residual
Hexane	3.94	-0.04	3.96	-0.06
Cyclohexane	3.51	-0.07	3.52	-0.08
Neopentane	3.35	-0.24	3.51	-0.40
Pentane	3.44	-0.05	3.49	-0.10
Cyclopentane	3.03	-0.03	3.08	-0.08
Butane	2.93	-0.04	2.97	-0.08
C12C=CC12	2.82	-0.06	2.60	-0.28
CC14	2.61	0.22	2.45	0.38
Tripropyl amine	2.95	-0.16	3.00	-0.21
Butyl chloride	2.52	0.12	2.48	0.16
CH3CC13	2.48	0.01	2.38	0.11
Propane	2.43	-0.13	2.45	-0.15
n-CH3CHC12	1.82	0.47	2.14	0.15
Propyl chloride	2.02	0.02	1.98	0.06
C1H2CCH2C1	1.53	-0.05	1.42	0.01
Triethyl amine	1.38	0.07	1.43	0.02
2-Hexanone	1.25	0.13	1.38	0.00
N-Methyl pyridine	1.07	0.23	1.20	0.10
Ethyl propionate	1.28	-0.07	1.38	-0.17
2-Pentanone	0.73	0.18	0.85	0.06
Diethyl ether	1.02	-0.13	1.17	-0.28
Butyraldehyde	0.85	0.03	0.86	0.17
Cyclohexanone	0.69	0.12	0.89	-0.08
Ethyl acetate	0.73	0.00	0.85	-0.12
Ethyl dimethyl amine	0.42	0.28	0.55	0.15
Propionaldehyde	0.34	0.25	0.37	0.22
Tetrahydrofuran	0.07	0.39	0.26	0.20
Diethyl acetamide	0.35	0.00	0.28	0.06
Butanone	0.31	-0.02	0.41	-0.12
Methyl acetate	0.29	-0.11	0.39	-0.21
Trimethyl amine	0.11	0.05	0.29	-0.13
Prpiononitrile	0.13	-0.03	0.29	-0.19
Dimethyl ether	0.10	0.09	0.14	-0.04
Propanone	-0.24	0.00	-0.10	-0.14
Acetonitrile	-0.43	0.09	-0.29	-0.05
Dimethyl acetamide	-0.60	-0.17	-0.69	-0.08
Dimethyl formamide	-0.08	-0.16	-0.88	-0.12

Table 6. Octanol/Water Partition Coefficients and Solvatochromic Parameters for Alcohols

Compound	McVol/100 A <sup>3</sup>	MolVol/100 A <sup>3</sup>	beta	pi	Log P (Experimental)
Methanol	0.361	0.490	0.40	0.40	-0.65
Ethanol	0.540	0.661	0.45	0.40	-0.30
n-Propanol	0.717	0.828	0.45	0.40	0.28
2-Propanol	0.716	0.827	0.51	0.40	0.05
n-Butanol	0.894	0.995	0.45	0.40	0.99
2-Methyl-1-propanol	0.893	0.994	0.45	0.40	0.76
2-Butanol	0.893	0.994	0.51	0.40	0.61
t-Butanol	0.892	0.993	0.57	0.40	0.36
Pentanol	1.077	1.168	0.45	0.40	1.48
3-Pentanol	1.070	1.161	0.51	0.40	1.21
2,2-Dimethyl-1-propanol	1.068	1.159	0.45	0.40	1.34
t-Pentanol	1.068	1.159	0.57	0.40	0.89
3-Methyl-2-butanol	1.043	1.133	0.51	0.40	1.28
n-Hexanol	1.248	1.329	0.45	0.40	2.03
3,3-Dimethyl-2-butanol	1.243	1.172	0.51	0.40	1.48

Note: A value of .071 is added as a hydrogen bonding correction factor to McVol/100 values.

Table 7. Predicted Values for Equations 7 and 8

Compound	Eq 7 predicted	Experimental - predicted	Eq 8 predicted	Residual
Methanol	-0.39	-0.27	-0.60	-0.05
Ethanol	-0.07	-0.23	-0.24	-0.06
n-Propanol	0.44	-0.16	0.35	-0.07
2-Propanol	-0.21	-0.16	0.08	-0.03
n-Butanol	0.94	0.05	0.76	0.23
2-Methyl-1-propanol	0.94	-0.18	-0.78	-0.02
2-Butanol	0.71	-0.10	0.54	0.07
t-Butanol	0.48	-0.12	0.38	-0.02
Pentanol	1.45	0.02	1.27	0.21
3-Pentanol	1.21	0.00	1.02	0.19
2,2-Dimethyl-1- propanol				
t-Pentanol	1.43	-0.09	1.28	0.06
3-Methyl-2-butanol	1.13	0.15	1.08	0.20
n-Hexanol	1.94	0.09	1.80	0.23
3,3-Dimethyl-2- butanol	1.70	-0.22	0.51	-0.10

Table 8. Charcoal Adsorption Solvatochromic Parameters

Compound (experimental)	$\rho_i$	$\beta$	MolVol/100 $A^3$	McVol/100 $A^3$	Log alpha
Acetone	0.71	0.48	0.734	0.629	-0.88
2-Butanone	0.68	0.48	0.896	0.807	-0.34
2-Pentanol	0.67	0.50	1.063	0.983	-0.19
2-Hexanone	0.67	0.50	1.235	1.160	0.64
4-Methyl-2-pentanone	0.67	0.48	1.225	1.160	0.71
5-Methyl-2-hexanone	0.65	0.48	1.285	1.336	0.72
Methyl acetate	0.60	0.42	0.798	0.696	-0.64
Ethyl acetate	0.55	0.42	0.978	0.873	-0.11
Propyl acetate	0.52	0.45	1.15	1.050	0.52
Butyl acetate	0.46	0.45	1.316	1.227	1.02
Amyl acetate	0.48	0.45	1.487	1.400	0.82
i-Propyl acetate	0.52	0.45	1.17	1.050	0.20
i-Butyl acetate	0.50	0.45	1.33	1.227	0.60
Propionaldehyde	0.65	0.40	0.72	0.63	-0.71
Butyraldehyde	0.60	0.41	0.882	0.804	-0.16
Valeraldehyde	0.60	0.41	1.064	0.981	0.38
Acrolein	0.70	0.45	0.667	0.518	-0.63
Vinyl acetate	0.55	0.40	0.924	0.769	0.11
Diethyl ether	0.27	0.47	1.046	0.905	-0.26
Di-n-propyl ether	0.27	0.46	1.359	1.255	0.84
Di-i-propyl ether	0.27	0.49	1.350	1.253	0.54
1,2-Dichloroethane	0.81	0.10	0.787	0.783	0.57
1,2-Dichloropropane	0.75	0.10	0.976	0.958	1.16
Ethanol	0.40	0.45	0.584	0.54	-1.35
n-Propanol	0.40	0.45	0.748	0.717	-0.83
n-Butanol	0.40	0.45	0.915	0.894	-0.14
n-Pentanol	0.40	0.45	1.082	1.077	0.32
n-Hexanol	0.40	0.45	1.256	1.248	0.96
i-Propanol	0.40	0.51	0.765	0.716	-1.21
2-Methyl-1-propanol	0.40	0.45	0.92	0.893	-0.37
2-Methyl-2-propanol	0.40	0.57	0.839	0.892	-0.65
2-Ethyl-1-butanol	0.40	0.45	1.227	1.247	0.73
2-Ethyl-1-hexanol	0.40	0.45	2.565	2.597	2.03
2-Propen-1-ol	0.40	0.45	0.680	0.618	-0.89
Cyclohexane	0.40	0.53	1.136	1.039	0.17

Note: a value of .071 has been added to the McVol/100 for all alcohols to account for hydrogen bonding.

Table 9. Predicted Values for Equations 10 and 11

Compound	Eq 10 predicted	Experimental - predicted	Eq 11 predicted	Residual
Acetone	-0.82	-0.06	-0.80	-0.08
2-Butanone	-0.34	0.0	-0.35	0.01
2-Pentanol	0.08	0.11	0.07	0.12
2-Hexanone	0.57	0.07	0.58	0.06
4-Methyl-2-pentanone	0.63	0.08	0.61	0.10
5-Methyl-2-hexanone	1.10	-0.38	0.78	-0.06
Methyl acetate	-0.54	-0.10	-0.48	-0.16
Ethyl acetate	-0.08	-0.03	0.02	-0.13
Propyl acetate	0.31	0.21	0.41	0.11
Butyl acetate	0.76	0.26	0.86	0.16
Amyl acetate	1.26	-0.42	1.37	-0.53
i-Propyl acetate	0.31	-0.11	0.47	-0.27
i-Butyl acetate	0.78	-0.18	0.93	-0.33
Propionaldehyde	-0.64	-0.12	-0.61	-0.15
Butyraldehyde	-0.21	0.05	-0.20	0.04
Valeraldehyde	0.28	0.10	0.33	0.05
Acrolein	-1.05	0.42	-0.91	0.28
Vinyl acetate	-0.32	0.43	-0.07	0.18
Diethyl ether	-0.32	0.06	-0.09	-0.17
Di-n-propyl ether	0.68	0.16	0.86	-0.02
Di-i-propyl ether	0.59	-0.06	0.74	-0.20
1,2-Dichloroethane	0.72	-0.15	0.63	-0.06
1,2-Dichloropropane	1.17	-0.01	1.15	0.01
Ethanol	-1.19	-0.16	-1.31	-0.04
n-Propanol	-0.70	-0.13	-0.83	0.00
n-Butanol	-0.21	0.07	-0.34	0.20
n-Pentanol	0.30	0.02	0.15	0.17
n-Hexanol	0.77	0.19	0.66	0.30
i-Propanol	-0.86	-0.35	-0.97	-0.24
2-Methyl-1-propanol	-0.21	-0.16	-0.32	-0.05
2-Methyl-2-propanol	-0.54	-0.11	-0.66	-0.01
2-Ethyl-1-butanol	0.77	-0.04	0.57	0.16
2-Ethyl-1-hexanol	1.74	0.29	1.56	0.47
2-Propen-1-ol	-0.97	0.08	-1.02	0.13
Cyclohexane	0.21	-0.04	0.24	-0.07



Table 10. Konemann's Fish Toxicity Parameters and Predicted and Observed Results

Compound	pi	beta	MolVol/100 A <sup>3</sup>	Log LC50 (exp)	Log LC50 (pred)	Residual
Benzene	0.19	0.10	0.749	2.91	3.37	-0.46
Toluene	0.14	0.11	0.928	2.87	2.70	0.17
Chlorobenzene	0.31	0.07	0.902	2.23	2.66	-0.43
o-Dichlorobenzene	0.39	0.04	1.052	1.60	1.97	-0.37
Dichloromethane	0.62	0.00	0.653	3.54	3.40	0.14
Carbon tetrachloride	0.08	0.00	0.907	2.93	2.38	0.55
Diethyl ether	0.20	0.47	0.905	4.46	4.12	0.34
Acetone	0.71	0.48	0.629	5.04	5.25	-0.21
Chloroform	0.38	0.10	0.692	2.93	3.60	-0.61
o-Xylene	0.03	0.12	1.108	2.52	2.03	0.49
1,2-Dichloroethane	0.61	0.10	0.783	3.03	3.25	-0.22
1,1,2-Trichloroethane	0.29	0.10	0.935	3.00	2.64	0.36
1,1,2,2-Tetrachloro- ethane	0.75	0.10	1.087	2.85	2.06	0.79
1,2-Dichloroethane	0.40	0.10	0.958	3.01	2.56	0.45
1,2-Dichloropropane	0.39	0.10	0.983	3.02	2.46	0.56
1-Chlorobutane	0.40	0.45	0.469	5.38	5.76	-0.38
Ethanol	0.40	0.51	0.645	5.07	5.29	-0.22
i-Propanol	0.40	0.57	0.821	4.68	4.82	-0.14
t-Butanol	0.40	0.51	0.999	4.05	3.90	0.15
3-Pentanol	0.92	0.52	0.533	5.90	5.78	0.12
1,2,3-Trichloro- benzene	0.40	0.02	1.202	1.11	1.30	-0.19
1,2,4-Trichloro- benzene	0.40	0.02	1.205	1.12	1.29	-0.17
1,3,5-Trichloro- benzene	0.40	0.02	1.207	1.26	1.28	-0.02
1,2,3,4-Tetrachloro- benzene	0.40	0.00	1.351	0.57	0.64	-0.07
1,2,3,5-Tetrachloro- benzene	0.40	0.00	1.354	0.57	0.63	-0.06
1,2,3,4-Tetrachloro- benzene	0.40	0.00	1.355	0.15	0.62	-0.48
Pentachlorobenzene	0.40	0.00	1.501	0.05	0.05	-0.20
m-xylene	0.07	0.12	1.108	2.55	2.03	0.52
1-Dichloro-m- xylene	0.40	0.07	1.415	-0.16	0.64	-0.80
2,4,-Trichloro-m- xylene	0.40	0.02	1.385	0.58	0.58	-0.50
3,4-Dichloro-m-xylene	0.40	0.02	1.382	0.94	0.59	0.35

Note: The predicted values are based upon equation 12.

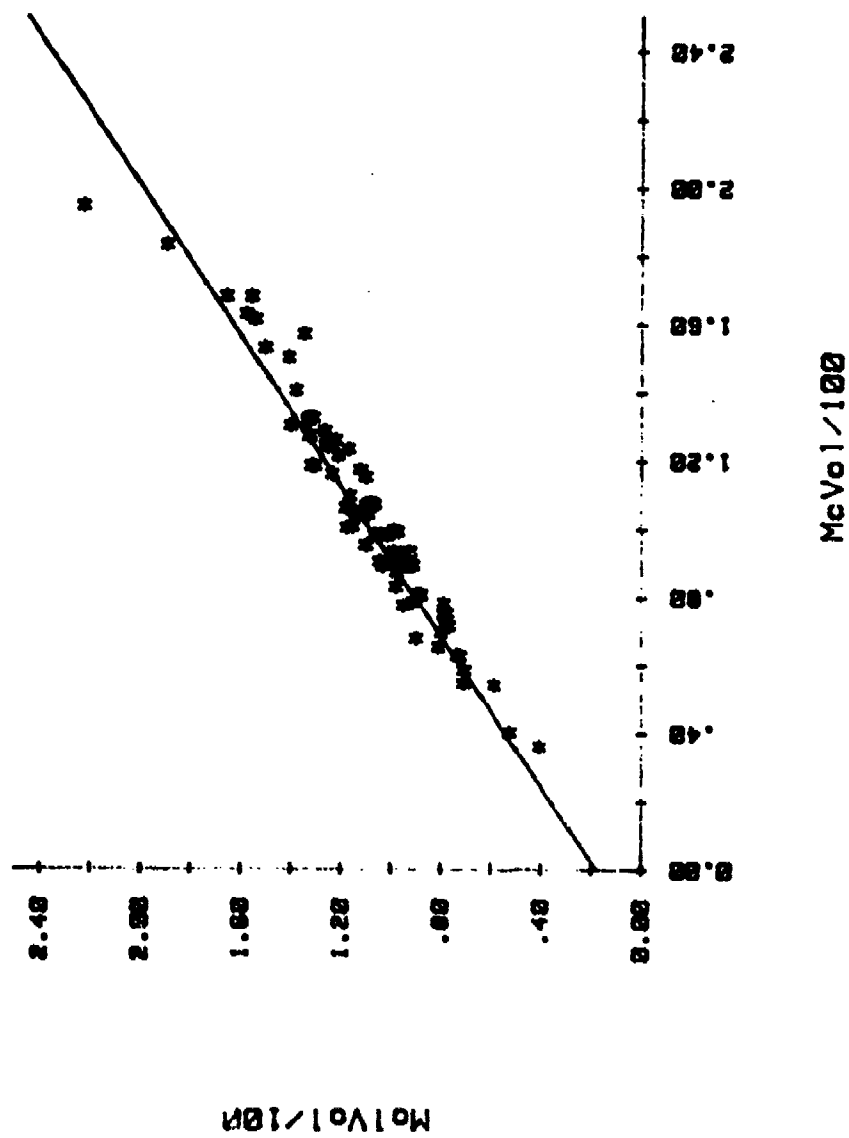
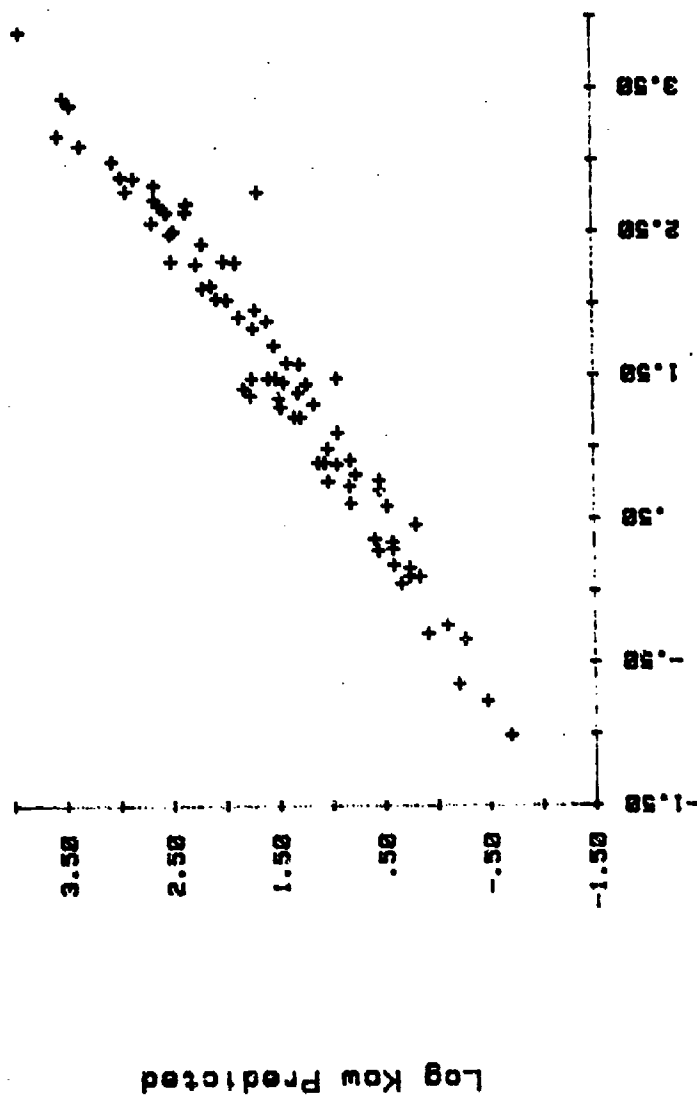


Figure 1. Correlation of Molecular Volume and Molar Volume



Log Kow Experimental

Figure 2. Experimental Vs. Predicted Octanol/Water Partition Coefficient (Aliphatic Only)

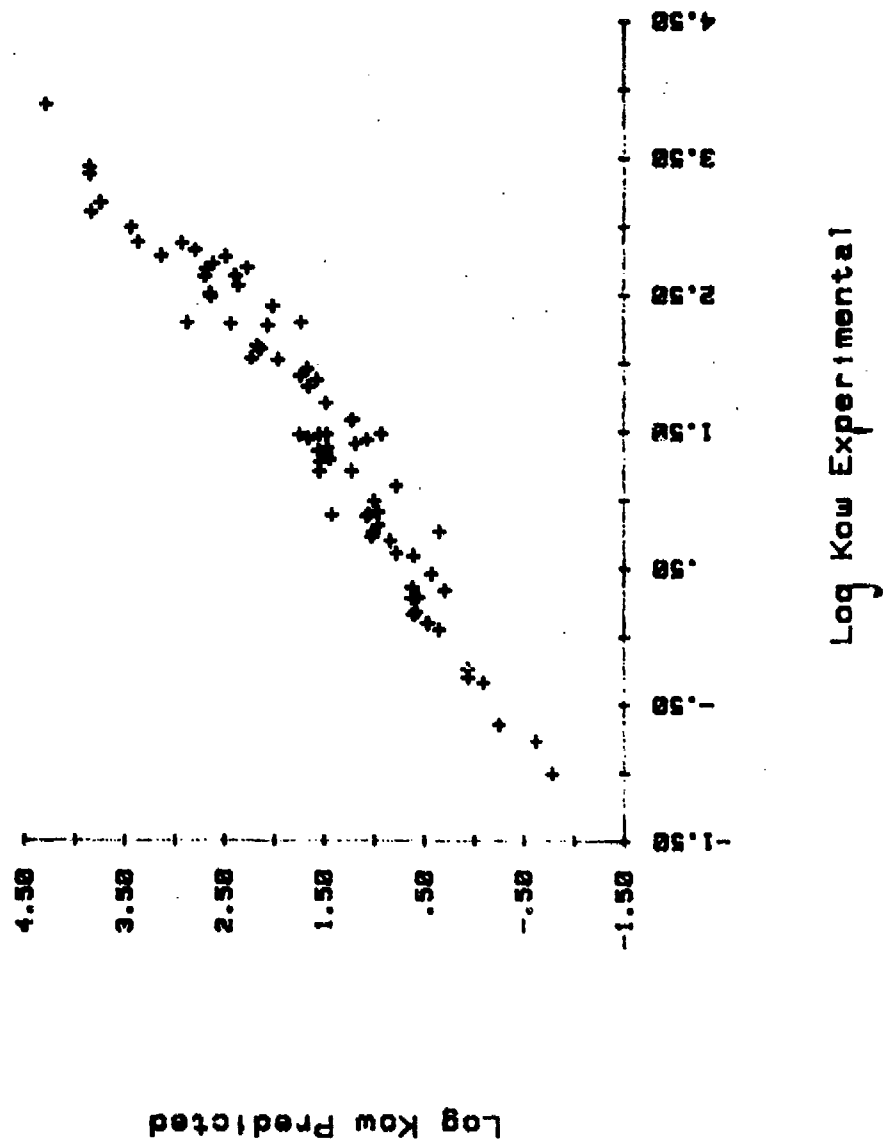


Figure 3. Experimental Vs. Predicted Octanol/Water Partition Coefficients (Aliphatics, Alcohol, and Aromatics)

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