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# Determination of descriptors by liquid-liquid partition and chromatographic methods

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**DETERMINATION OF DESCRIPTORS BY LIQUID-LIQUID PARTITION AND  
CHROMATOGRAPHIC METHODS**

by

**THUSHARA KARUNASEKARA**

**DISSERTATION**

Submitted to the Graduate School

of Wayne State University,

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Approved by:

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Advisor

Date

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## CHAPTER 1

### INTRODUCTION

Every year more than a thousand new chemical compounds are innovated and released in to the environment as products, byproducts or waste. The environmental and biological fate of these chemicals depends on various environmental and biological processes. To understand the behavior, bioavailability and the effect of these compounds in different environmental and biological compartments, it is important to determine their physicochemical and biochemical properties. Since the experimental determination of some of these properties is expensive and time consuming, and in some cases non-trivial, data are not available for all chemicals in use. Also experimental measurements of these properties show considerable variation due to the extreme difficulty of direct measurements. In this situation correlation models represent an attractive and practical approach for their estimation. However, suitable models depend on the availability of accurate experimental values to construct a correlation model that connects the available experimental data with a set of descriptors encoding structural or easily determined experimental properties for the compounds. These mathematical models provide the connection between two types of properties, the properties that are easy to measure and the properties that are difficult to measure.

Many of the chemical, biological and environmental processes can be related to free energy terms such as equilibrium constants, rate constants, retention factors, and so on. Therefore the free-energy related multi-parameter correlation models have been most successful at bridging the data divide and adequately represent all possible interactions between the compounds and complex environmental and biological systems. Whether or not these studies involve the estimation of retention in separation systems, environmental fate monitoring, the distribution of compounds across biological membranes, and understanding the effect of

chemicals on human health and safety, etc., the ultimate goal is to establish suitable correlation models to facilitate the prediction of a wide range of physicochemical, environmental and biological properties for compounds lacking experimental values [1-7].

As a fundamental phenomenon of chemistry, a compound's structure contains generic information encoded within it, which explains the compound's entire chemical, physical and biological properties. The correlation between these properties and structural properties results in the structure-property or structure-activity relationships (QSPR or QSAR). This starts with generating a reasonable and manageable number of solute descriptors that describe the properties of compounds and/or the behavior of compounds in the selected system. These descriptors are then used to build linear or nonlinear QSPR or QSAR models.

The application of these kinds of relationships was first recorded more than a century ago by Crum-Brown and Fraser in their attempt to correlate physiological properties of a substance in a certain biological system as a function of its chemical constitution [8]. To give a more quantitative picture of individual contributions to the free energy processes, in 1937 Louis Hammett established the well-known "Hammett equation" in which he described linear free energy relationships for the substituent constant and reaction constant to describe reaction rates and equilibrium constants [8,9]. In the 1950s, Taft introduced the first steric parameters for separating polar, steric and resonance effects in linear solvation energy relationships (LSERs) [10]. The contributions of Hammett and Taft laid the foundation for modern relationships between solute-solvent interactions and physicochemical properties. In 1962 Hansch *et al.* combined the new hydrophobic constants, which represent the relative hydrophobicity of a substituent, with Hammett constants to build the Hansch equation and its various extended versions. [11]. These models triggered the rapid explosion in QSAR/QSPR analysis and related applications.

At present, many of the QSPRs/QSARs are multiparameter correlation models and commonly use a wide range of solute descriptors of different types to capture the full range of molecular properties of a compound. A large number of theoretical descriptors with different perspectives can be calculated using structure based computational and theoretical methods, including for example, COSMO-RS, CODESSA, DRAGON, OASIS, MolConnZ [12, 13]. The great advantage of these computational and theoretical methods is that they can be used to calculate descriptors for compounds which are not available or not yet synthesized. Since the molecular structure is the only requirement for their calculation, these descriptors are reproducible. The main drawback of these theoretical approaches is that the descriptors may be difficult to explain and may lack obvious chemical significance. Also, many of these descriptors are target oriented and have specific applications. Therefore, the best set of solute descriptors for any given property cannot be considered as the best set of descriptors for any other (often similar) property. Even though the systems are closely related the term-by-term comparison of systems is not possible under these circumstances [14].

On the other hand, for compounds that are currently available, experimental methods provide a more sensible approach for determining descriptor values. Experimentally derived descriptors get around the above problems and can be used to develop less flexible models with a small number of descriptors (usually 5 to 10). Several methods and different statistical techniques are employed to generate these solute descriptors [8,11,15,]. Among these, multiple linear regression analysis (MLRA) is the most widely use mathematical technique in QSPRs/QSARs. Regression models are simple, manageable and easy to understand, and for this reason, most descriptors are derived using MLRA.

### 1.1. Solvation parameter model

M.H. Abraham and co workers developed a reliable linear solvation energy relationship using MLRA to describe the solvation processes and to introduce a new set of solute descriptors for organic compounds [16-20]. This is generally known as the solvation parameter model and is widely used to model the equilibrium and rate properties of a system. The solvation parameter model assumes a cavity model of solvation and uses a series of descriptors to define solute properties and a complementary series of system constants to represent solvent properties. The transfer of one mole of solute from one phase to another (gas to liquid or liquid to liquid) occurs in three steps: a cavity of the same size as the solute is created in the solvent; the solvent molecules reorganize themselves around the cavity to establish favorable interactions with the solute; and finally, the solute enters the cavity and establishes the appropriate intermolecular interactions with the solvent. Cavity formation requires disruption of solvent-solvent interactions and varies with the cohesive energy of the solvent. Reorganization of the solvent molecules around the cavity to new positions more favorable for solute interactions occurs with little change in the free energy of the system. It can generally be ignored in estimating the change in free energy of the system accompanying solvation. The set up of solute-solvent interactions when the solute is placed in the cavity are delineated as dispersion, interactions of a dipole-type, and hydrogen-bonding. For the case where solute-solvent interactions in the condensed phase with respect to the gas phase exceed solvent-solvent interactions of the condensed phase transfer of the solute to the condensed phase occurs with a distribution constant that reflects the difference in free energy for the two contributing processes. For quantitative calculations it is necessary to parameterize the model, resulting in Eq. (1.1) for transfer from the gas phase to a solvent and Eq. (1.2) for transfer between two condensed phases [14, 21].

$$\log SP = c + eE + sS + aA + bB + lL \quad (1.1)$$

$$\log SP = c + eE + sS + aA + bB + vV \quad (1.2)$$

In these equations the solute-solvent interactions are correlated with a solute property (SP), such as an equilibrium constants or some other property that can be described using free energy terms.

### 1.1.1. Solute descriptors and system constants

The capital letters in Eq. (1.1) and (1.2) are the solute descriptors that define the capability of a solute for electron lone pair interactions, E, dipole-type interactions, S, hydrogen-bonding interactions with the solute acting as a hydrogen bond acid, A, or base, B, the gas-liquid partition coefficient on n-hexadecane at 298.2 K, L, and McGowan's characteristic volume, V. The lower case letters are the system constants that describe the complementary system properties to the solute descriptors with  $e$  determined by interactions with electron lone pairs,  $s$  dipole-type and induced dipole-type interactions,  $a$  hydrogen-bond basicity (because a hydrogen-bond acid solute will interact preferentially with a hydrogen-bond base solvent),  $b$  hydrogen-bond acidity, and  $l$  and  $v$  are determined by the difference in the work require to form a cavity in the receiving and donating phases and contributions from dispersion interactions that are not self-cancelling in the two phases.

### 1.1.2. Determination of solute descriptors

Of the six descriptors used in the solvation parameter model, the value for V descriptor and the value for E descriptor for liquids can be easily obtained by calculation. Their remaining four descriptors are always determined by experiment. Any experimental free-energy property that is convenient to measure and can be accurately determined could be used to estimate descriptor values for compounds that can be processed by the same technique. The V (McGowan's Characteristic volume) descriptor can be calculated from structure according to the Eq.1.3. So can the E descriptor for liquids according to the Eq.1.4 with measured refractive index

values. For solids refractive index values can be easily obtained using computational methods.[14,22-24]

$$V = [\Sigma(\text{all atom contributions}) - 6.56(N-1 + R_g)] / 100 \quad (1.3)$$

Where N is the total number of atoms and  $R_g$  the total number of ring structures. V has the units of  $(\text{cm}^3 \cdot \text{mol}^{-1} / 100)$ .

$$E = 10V [(\eta^2 - 1) / (\eta^2 + 2)] - 2.832V + 0.526 \quad (1.4)$$

Where  $\eta$  is the refractive index of the compound at 20°C for the sodium D-line and V is the McGowan's characteristic volume obtained by Eq. (1.3). E is given in units of  $(\text{cm}^3 \cdot \text{mol}^{-1} / 10)$ .

The S, A, B and L descriptors are always determined by experiment, although advances continue to be made in fragmentation methods, and others, for the estimation of descriptors from structure [14]. The S, A, B, and L descriptors are usually determined as a group, since there are few experimental methods suitable for the determination of individual descriptors. They are also generally determined from multiple experimental measurements to take advantages of averaging effects to handle extreme values from individual measurements and by using different experimental techniques to take advantage of different model characteristic properties. Systems with large system constants are preferred for descriptor measurements since the uncertainty in an individual descriptor measurement is usually estimated as the ratio of the standard deviation of the residuals for the model used to describe the process divided by the model system constant for the associated descriptor.

The L descriptor is the gas-liquid partition coefficient for the solute in n-hexadecane at 298 K. For volatile compounds it can be determined directly using gas chromatography with n-hexadecane as the stationary phase [28]. Alternatively, the L descriptor can be determined together with the other descriptors on a series of stationary phases of different polarity.



To determine the S, A, B and L descriptors it is necessary to set up a series of equations similar to Eq. (1.1) and (1.2) with known system constants that allow the convenient measurement of the partition or retention property for the solute. The descriptors are calculated by finding the unique values for each descriptor that simultaneously minimizes the difference between the experimental solute properties and the model predicted properties across all equations [14, 20, 21]. Chromatographic and liquid-liquid partition methods are the most useful methods for the experimental measurement of solute descriptors. Their higher intrinsic accuracy, higher compound throughput, and the possibility of defining standard systems and reference substances using a defined protocol allow high quality descriptors to be easily and rapidly calculated.

## 1.2. Gas chromatography

Gas chromatography is the unique method to obtain the L descriptor and this method is also suitable for the S and A descriptors. Partition coefficients are combined with retention factors obtained by gas chromatography to calculate the L descriptor and to assist in the calculation of the S and A descriptors. Stationary phases commonly used for gas chromatography have no hydrogen-bond acidity ( $b = 0$ ), therefore, gas chromatography is considered unsuitable for determining the B descriptor [34]. B descriptor can be determined by an alternative technique, and in this case the totally organic biphasic systems are particularly useful.

More than 50 open-tubular columns are available for lower temperature conditions 60-140 °C and these columns are suitable to determine the descriptors for low molecular weight compounds [33]. This system constant database has been extended by introducing 14 columns for intermediate temperature conditions, 160-240 °C [35]. Some stationary phases of different selectivity and their system constants at 100°C are summarized in Table 1.1.

**Table 1.1** System constants for columns selected from different selectivity groups at 100°C ( $b = 0$  for all column types)

Column type	% polar monomer	System constants			
		$e$	$s$	$a$	$l$
Poly(methyloctylsiloxane)		0.175	0.067	0	0.647
Poly(dimethyldiphenylsiloxane)	5	-0.02	0.332	0.247	0.572
Poly(dimethyldiphenylsiloxane)	50	0.054	0.851	0.377	0.566
Poly(methyltrifluoropropylsiloxane)	50	-0.46	1.377	0.195	0.455
Poly(biscyanopropylsiloxane)	100	0.027	2.044	1.947	0.427
Poly(ethylene glycol)	100	0.205	1.407	2.117	0.511

Poly(methyloctylsiloxane) can be considered as the best column for determining the L descriptor, since only L and E make significant contribution to retention. Poly(dimethyldiphenylsiloxane) columns are less suitable for determining the L descriptor directly due to significant dipole type ( $s$ ) and hydrogen bond base ( $a$ ) system constant values. Poly (methyltrifluoropropylsiloxane) and Poly(ethylene glycol) stationary phases are useful for determining the S and A descriptors, respectively. The Poly(biscyanopropylsiloxane) stationary phase is strongly dipolar/polarizable (large  $s$  system constant) as well as strongly hydrogen bond basic (large  $a$  system constant) and can be used to determine S, A and L descriptors simultaneously.

### 1.2.1. Current requirements

To study the complex compounds with high molecular weight it will be necessary to develop a method to calibrate columns at higher temperatures than those achieved previously and to identify the columns suitable for determining the B descriptor. Many of the GC columns can be operated above 300°C. To optimize the operating condition and to determine the descriptors for thermally stable compounds it is necessary to calculate the columns for high temperature conditions. Any group of calibration compounds are suitable for use over a modest temperature range governed by their volatility and the retention window for each column. The calibration

compounds established for the temperature range 60-140°C are unsuitable for higher temperatures. It is necessary to increase both the number of compounds and range of descriptor values to obtain robust models as well as increasing the number of characterized columns to include all those required for descriptor measurements. Although the system constants are temperature dependent polar interactions persist to the highest temperatures studied so far (the numerical values of the system constants are large enough to minimize the error in the descriptor values). The object is to remove the obstacle presented by the temperature range of calibrated columns for descriptor measurements and allow GC to be used as one tool in the calculation of descriptors for compounds with low volatility.

### **1.3. Liquid-liquid partition**

Aqueous liquid-liquid partition can be considered as a standard method for estimating the S, A and B descriptors since a number of these biphasic systems have large values for the associated system constants [20]. Aqueous biphasic systems with octanol, chloroform, cyclohexane, and toluene as the counter solvents were shown to be suitable for the calculation of the S, A, and B descriptors for compounds with reasonable water solubility [45]. A difficulty arises for compounds of low water solubility and for compounds that are unstable in water. Compounds of low water solubility result in partition coefficients that are too large to measure accurately or conveniently. General examples include compounds of low-polarity and all large compounds that lack hydrogen-bonding functional groups. Some specific examples include organosiloxanes, terpenes and related fragrance compounds, plasticizers (phthalate and alkyl esters), and polycyclic aromatic hydrocarbons, steroids, and triglycerides. For these compounds totally organic biphasic systems have the advantage that the compounds are reasonably soluble in organic solvents and yield partition coefficients in a convenient measurement range. Based on the separation properties following totally organic biphasic systems are the most useful for

descriptor measurements: n-heptane-formamide for the S, A and B descriptors; n-heptane-ethylene glycol for the A and B descriptors; n-heptane-propylene carbonate for the A and S descriptors; n-heptane-2,2,2-trifluoroethanol for the B descriptor; diisopentyl ether-ethylene glycol for the B descriptor; and n-heptane-dimethyl sulfoxide for the A descriptor.

However, the selectivity space covered by totally organic biphasic systems is not large and further systems are needed to minimize the uncertainty in descriptors. Several methods are available to determine the partition coefficient of a solute that includes shake flask method, generator column method, liquid-liquid chromatography, and countercurrent chromatography [40,41]. When it is supplemented with chromatographic measurements the shake flask method is flexible, economical and simple to standardize for routine measurements.

### 1.3.1. Current requirements

Aqueous biphasic systems are dominated by the large  $\nu$  system constant resulting in low solubility except for compounds with considerable polar interactions. For the majority of these systems the variation of properties is not so large and demonstrates the overriding controlling influence of water on selectivity. This is not the case for totally organic biphasic systems which stand for the high level of individuality and a wide range of selectivity. None of the organic solvents are as cohesive or as hydrogen-bond acidic as water as indicated by the small  $\nu$  and  $b$  system constants, which are generally less than 2 (for water often close to 4). For molecules of larger size (large value of  $V$ ) the organic biphasic systems facilitate separations based on differences in polar interactions that for aqueous biphasic systems become largely minimized by the high cohesive energy of water driving these solutes into the counter solvent.

Even though totally organic biphasic systems have attractive properties for the separation purposes, those characterized to date lack sufficiently large system constants to stand out for the descriptor measurements. The question becomes how to identify suitable polar solvents. Gas

chromatography suggests that formamide would be a suitable solvent to determine the S and A descriptors [42]. Ethylene glycol (or glycerol) is a reasonable choice for determining the A and B descriptors. Propylene carbonate and dimethyl sulfoxide (DMSO) are other useful organic solvents that can be considered for descriptor measurements.

#### 1.4. REFERENCES

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## CHAPTER 2

### TOTALLY ORGANIC LIQUID-LIQUID PARTITION SYSTEMS

#### 2.1. Introduction

A resurgence of interest in liquid-liquid partitioning as a sample preparation method stems from a series of developments in different formats that facilitated its use on a small scale (liquid-phase microextraction) thus minimize many of the disadvantages responsible for its replacement by (largely) solid-phase extraction methods over the previous decade [1-3]. Solvent-based methods are generally more tolerant of matrix burden and afford a wider selectivity range than is possible with commonly available sorbents. Solvent properties are more reproducible than those of sorbents and liquid-phase microextraction methods compare favorably in terms of cost and equipment needs compared with sorbent-based methods. The new liquid-phase microextraction methods are viewed as competitive or viable replacements for solid-phase extraction methods, both of which are expected to continue to figure prominently in laboratory practice during the next decade [4-6]. Useful liquid-liquid partition systems require the formation of biphasic systems of low mutual solubility. This tends to dictate that the majority of systems described so far have water as one phase and a low to moderately polar organic solvent as the other [4,7,8]. For many applications this is not a problem, but for compounds and sample matrices of low water solubility, or for compounds that are water unstable, predominantly aqueous biphasic systems are of limited use. Totally organic biphasic systems are an attractive alternative for compounds of this type but limited in choice by the high mutual solubility among organic solvents. Suitable systems include n-heptane-ethylene glycol [9], n-hexane-acetonitrile [10], n-heptane-*N,N*-dimethylformamide [11], n-heptane-2,2,2-trifluoroethanol [12], n-heptane-1,1,1,3,3,3-hexafluoroisopropanol [12], toluene-perfluoromethylcyclohexane [13], and n-alkane-dimethyl sulfoxide [11,14], n-heptane-methanol [11], systems. These systems are limited by the

low solubility of some analytes in n-alkane solvents and by the complete miscibility of the counter solvents listed above with more polar solvents than n-alkanes. They afford systems with complementary properties to aqueous-based partition systems but with limited flexibility. It is desirable to have available alternative totally organic biphasic solvent systems that allow a wider range of solubility and selectivity properties to be exploited.

A common application of water-based biphasic systems is the determination of molecular descriptors for use in the solvation parameter model and other models employed for estimating biopartitioning and environmental distribution properties [8,15]. An attractive feature of predominantly aqueous biphasic systems for descriptor measurements is the availability of complementary systems with large values for the  $s$ ,  $a$ , and  $b$  system constants which facilitate the calculation of solute descriptors with low uncertainty [17]. Once a full set of descriptors are defined for a compound they can be used to predict the properties of that compound in a wide range of chromatographic [8,15-20], environmental [21-23], and biological [21,24] processes, in addition to liquid-liquid partitioning systems [8]. For the reasons stated in the previous paragraph aqueous biphasic systems are unsuitable for the accurate determination of descriptor values for compounds virtually insoluble or unstable in water. To overcome this problem totally organic biphasic systems with large system constants or distribution properties strongly determined by a limited number of system constants are attractive. The biphasic system n-heptane-ethylene glycol was shown to be suitable for estimating hydrogen-bonding descriptors for peptides [9]. The biphasic systems n-hexane-acetonitrile, n-heptane-*N,N*-dimethylformamide and n-heptane-2,2,2-trifluoroethanol were used together with chromatographic retention factors to determine a complete set of descriptors for organosilicon compounds [25,26] and for a variety of other compounds difficult to study using water-based partition systems [15,16]. These systems provided a working alternative for those compounds that could not be studied using aqueous

biphasic systems but do not afford the desired balance between the relative range of system constant values best suited for estimating descriptor values, especially the hydrogen-bond basicity B descriptor. The second purpose of this work is to identify additional totally organic biphasic systems suitable for estimating descriptor values for compounds of low water solubility and stability.

The search for an organic solvent with the desired qualities to create flexible biphasic systems for extraction and descriptor measurements led us to reflect on the properties of water that have resulted in its widespread use for these applications. These are its high cohesive energy (which allows it to form so many biphasic systems with different solvents) and its overall capacity for polar interactions (which enable it to selectively extract polar compounds). Our goals could be met by a solvent described as water-like but “water light”. This solvent should be sufficiently cohesive to form a reasonable number of biphasic systems with a range of solvents of different selectivity but not so cohesive that compounds of low polarity reside almost totally in the counter solvent. The solvent should also have a sufficient capacity for dipole-type and hydrogen-bonding interactions to provide a reasonable range of selectivity that we would hope to moderate by choice of different counter solvents to enhance selectivity. These considerations led us to evaluate formamide, ethylene glycol, propylene carbonate and dimethyl sulfoxide for use as suitable base solvents and n-heptane, 1,2-dichloroethane, n-octanol and isopentyl ether as counter solvents forming biphasic systems.

## **2.2. Experimental**

### **2.2.1. Materials**

Formamide, ethylene glycol, propylene carbonate and dimethyl sulfoxide (base solvents) were obtained from Acros Organics (Morris Plains, NJ, USA) and dried over molecular sieves before use. Heptane, 1, 2-Dichloroethane, 1-octanol and isopentyl ether (counter solvents) were

obtained from Sigma-Aldrich (Milwaukee, WI, USA). Common chemicals were of the highest purity available and obtained from several sources. The 30 m x 0.32 mm id HP-5 open-tubular column, 0.25  $\mu\text{m}$  film thickness, was obtained from Agilent Technologies (Folsom, CA, USA).

### 2.2.2. Instrumentation

Gas chromatographic measurements were made with an Agilent Technologies (Palo Alto, CA, USA) HP 6890 gas chromatograph fitted with a split/splitless injector and flame ionization detector using ChemStation software (rev.B.04.01) for data acquisition. Nitrogen was used as carrier gas at a constant flow rate of 2.5 mL/min (velocity 47 cm/s). The split ratio was set to 30:1, septum purge 1 mL/min, inlet temperature 275°C, and detector temperature 300°C. Separations were performed using a temperature program with an initial temperature of 150°C for one minute and then raised to 280°C at 10°C/min. Occasionally, a slightly modified program was required to handle co-elution of solutes with the internal standard or solvent peaks.

### 2.2.3. Determination of partition coefficients

The solvation parameter model was set up as shown below in a form suitable for modeling partition coefficients ( $\log K_p$ ) for neutral compounds in biphasic systems.

$$\log K_p = c + eE + sS + aA + bB + vV \quad (2.1)$$

The method used to determine partition coefficients is described in detail elsewhere [10-12, 39]. The 2.0 mL screw-capped sample vials with PTFE-lined caps (Supelco, Bellefonte, PA, USA) were charged by syringe with 0.75 mL of base solvent, 0.75 mL of counter solvent, 1-10  $\mu\text{L}$  of liquid sample, and 1  $\mu\text{L}$  internal standard. Solid samples were dissolved in either the counter solvent or base solvent (depending on solubility) at a concentration of about 0.5-1.5 mg/mL and added to the vial as described for the pure solvent. Smaller sample sizes were used in some cases to avoid saturation in one of the phases. The vials were shaken for 30s and allowed to stand for 1

h or overnight at room temperature ( $22 \pm 2^\circ\text{C}$ ). Sample volumes of 1  $\mu\text{L}$  from each phase were taken for calculation of the partition coefficients using the relationship

$$K_p = (S_{cs}/S_{bs}) (I_b/I_{cs})K_p^{IS} \quad (2.2)$$

where  $K_p$  is the partition coefficient for compound S,  $S_{sc}$  and  $S_{bs}$  the peak area for compound S in the counter solvent and base solvent, respectively,  $I_{sc}$  and  $I_b$  the peak area of the internal standard in the counter solvent and base solvent, respectively, and  $K_p^{IS}$  the partition coefficient for the internal standard. The internal standards used for totally organic liquid-liquid partition systems and their partition coefficients are listed in Table 2.1.

**Table 2.1.** Internal standards and their partition coefficients.

Biphasic system	Internal standard	Partition coefficient
Heptane-formamide	4-nitrotoluene	$0.968 \pm 0.002$ (n =10)
1, 2-dichloroethane-formamide	4-chloro-3-methylphenol	$1.340 \pm 0.004$ (n =10)
1-octanol-formamide	5-chloro-2-nitroanisole	$1.309 \pm 0.007$ (n =10)
Isopentyl ether-formamide	5-chloro-2-nitroanisole	$1.014 \pm 0.006$ (n =10)
Heptane-propylene carbonate	Biphenyl	$0.857 \pm 0.010$ (n =10)
Isopentyl ether -propylene carbonate	Biphenyl	$1.132 \pm 0.004$ (n =10)
1-octanol -propylene carbonate	Acenaphthene	$1.306 \pm 0.007$ (n =10)
Heptane-ethylene glycol	5-chloro-2-nitroanisole	$0.766 \pm 0.001$ (n =30)
Isopentyl ether-ethylene glycol.	1,3-dinitrobenzene	$0.950 \pm 0.003$ (n =10)
1,2-dichloroethane-ethylene glycol.	4-phenylphenol	$0.933 \pm 0.003$ (n =10)
Heptane-dimethyl sulfoxide (for $K_p$ )	Acenaphthene	$1.022 \pm 0.020$ (n =10)
Heptane-dimethyl sulfoxide (for $K_{ds\ 1\%}$ )	Acenaphthene	$0.978 \pm 0.010$ (n = 7)
Heptane-dimethyl sulfoxide (for $K_{Dry}$ )	Acenaphthene	$1.104 \pm 0.012$ (n =10)
Isopentyl ether-dimethyl sulfoxide	Acenaphthene	$1.104 \pm 0.012$ (n =10)

#### 2.2.4. Calculations

Multiple linear regression analysis and statistical calculations were performed on a Dell Dimension 9200 computer (Austin, TX, USA) using the program PASW v18.0 (PASW, Chicago, IL, USA). The solute descriptors were taken from an in-house database [15,39,40] and are summarized in Tables 2.3-2.6, 2.10-2.12, 2.15-2.17, 2.19 and 2.20 together with the

experimental partition coefficients. The Kennard-Stone algorithm programmed in visual basic for use in Excel 2007 (Microsoft Corporation, Redmond, WA) was used to split the data set into a training set and a test set [41] for validation purposes.

### 2.3. Results and discussion

The solvation parameter model provides a suitable mechanism for studying liquid-liquid partition systems capable of revealing the contribution of intermolecular interactions responsible for differences in individual partition coefficients and for simulating the separation properties (partition coefficients) for compounds with known descriptor values that lack experimental values [8,15,42]. This requires the calculation of the system constants of the solvation parameter models for the partition systems involving the measurement of partition coefficients for a number of varied compounds with known descriptor values. Several methods have been proposed to define a minimum number of compounds to solve Eq. (2.1) by multiple linear regression analysis [43-45]. Models based on small data sets, even if they meet the minimum number requirement, are often of limited utility for predicting further partition coefficients [46,47]. A contributing factor is that the error in the partition coefficients is not random and tends to be correlated with the size of the partition coefficient. Both large and small partition coefficients have larger errors because of the higher uncertainty in the determination of the low concentration of the compound that exists in one of the phases. In practice, the number of solutes should be sufficient to obtain a stable model and to facilitate splitting of the data set into a training set and test set for validation purposes [43,46-49]. The solutes selected to build the model define the descriptor space, which for practical applications should be as wide as possible. The descriptor values for the selected solutes should be somewhat evenly distributed over the descriptor space and each series of descriptors should have a low correlation with each other. The experimental partition coefficients should span a reasonable range of values to facilitate

modeling. Histogram-type plots for each descriptor were scrutinized to visualize how well the descriptor values cover the descriptor space and additional solutes selected were needed [20,42]. Principal component analysis with the descriptor values as variables offers an alternative approach to assess how well the descriptors cover the descriptor space [50]. Unintentional correlation between individual or pairwise descriptor series ( $r > 0.8$ ) result in a loss of capability of the multiple linear regression algorithm to distinguish between the complementary system effects [18,46,47]. The cross-correlation matrix for each model was checked to ensure this was not a problem. The solutes used to define each model were optimized for each system to ensure that a useful range of partition coefficients was maintained. As a consequence, the compounds identified in Tables 2.3-2.6.2, 2.10-2.12, 2.15-2.17, 2.19, and 2.20 are not the same for each system but cover a similar range of descriptor values.

### **2.3.1. Models for formamide-organic solvent partition system**

Relevant solvation properties for water and formamide are summarized in Table 2.2 [28-30]. Formamide has a high cohesive energy compared with typical organic solvents, roughly two-thirds the value for water. It has an extensive three-dimensional hydrogen-bonded structure similar to water at room temperature [31]. Relatively rare for an organic solvent it has a dielectric permittivity higher than that of water. Spectroscopic measurements of chemical probes indicate that it is almost as dipolar/polarizable as water, a significant hydrogen-bond acid but not as hydrogen-bond acidic as water, and about as hydrogen-bond basic as water. Surfactants are known to form micelles in formamide, a property generally associated with aqueous solvents [30,32,33]. In analytical chemistry formamide has been widely used as a non-aqueous solvent for titration, electrochemistry, and electrophoresis [28,29,34], as a denaturing agent for DNA [35], as an additive in supercritical fluid chromatography to modify the polarity of carbon dioxide [36], and as a stationary phase in high performance liquid-liquid chromatography [37]. Abraham

et al. [38] have studied gas-solvent and hypothetical water-solvent partition systems for a number of amides including formamide. They demonstrated that as a solvent it was moderately cohesive, strongly hydrogen-bond basic, and quite dipolar and hydrogen-bond acidic. This combination of solvation properties set it apart from a database of eighteen common organic solvents.

**Table 2.2.** Characteristic solvent properties of water and formamide.

Property	Water	Formamide
Cohesive energy (J/cm <sup>3</sup> )	2302	1575
Dipole moment (D)	1.83	3.37
Dielectric permittivity	78.4	111
Refractive index (20°C)	1.3325	1.4468
Kamlet-Taft parameters		
$\pi^*$	1.09	0.97
$\alpha$	1.17	0.71
$\beta$	0.47	0.48
Reichardt's $E_T^N$	1.00	0.775
Gutmann's donor number (kJ/mol)	138	151
Gutmann's acceptor number (kJ/mol)	54.8	39.8

This work can be considered as an extension of these works applying the solvation parameter model to a wider range of biphasic systems containing formamide to establish the molecular basis of the partition mechanism in these systems. The compounds used in formamide systems, their descriptor values and calculated partition coefficients are listed below.

**Table 2.3.** Descriptor values and partition coefficients for compounds used to characterize the n-heptane-formamide partition system.

Compounds	Solute descriptors					Partition coefficients		
	E	S	A	B	V	$K_p$	SD	$\log K_p$
Acenaphthene	1.604	1.05	0	0.22	1.2586	29.52	0.309	1.47
Acenaphthylene	1.557	1.119	0	0.2	1.2156	7.839	0.219	0.894
Acetophenone	0.806	1.026	0	0.503	1.0139	0.556	0.001	-0.255
Aniline	0.955	1.003	0.249	0.425	0.8162	0.093	0.001	-1.029
Benzaldehyde	0.813	1.025	0	0.394	0.873	0.531	0.017	-0.275
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	1.441	0.003	0.159
Benzonitrile	0.742	1.135	0	0.331	0.8711	0.42	0.004	-0.376



Benzophenone	1.224	1.33	0	0.576	1.4808	2.473	0.037	0.393
Benzyl alcohol	0.803	0.878	0.412	0.557	0.916	0.017	0.001	-1.767
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	6.966	0.021	0.843
Biphenyl	1.312	0.874	0	0.298	1.3242	20.35	0.064	1.309
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604	23.45	0.291	1.37
1-Bromooctane	0.339	0.4	0	0.12	1.4108	368.2	0.014	2.566
3-Bromophenol	1.081	0.792	0.948	0.201	0.9501	0.005	0.001	-2.368
Caffeine	1.518	1.726	0.039	1.232	1.3632	0.013	0.001	-1.876
Carbazole	2.025	1.585	0.367	0.231	1.3154	0.192	0.001	-0.716
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	0.341	0.004	-0.467
4-Chloroaniline	1.056	1.138	0.325	0.331	0.9386	0.104	0.004	-0.983
Chlorobenzene	0.718	0.656	0	0.056	0.8388	12.49	0.007	1.097
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.0384	0.012	0.001	-1.916
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	23.8	0.027	1.377
Cinnamyl alcohol	1.067	0.959	0.49	0.6	1.1548	0.031	0.001	-1.508
Coumarin	1.269	1.61	0	0.524	1.0619	0.049	0.002	-1.314
o-Cresol	0.774	0.745	0.621	0.357	0.916	0.022	0.001	-1.662
Decan-1-ol	0.191	0.44	0.344	0.52	1.5763	8.471	0.036	0.928
Dibenzofuran	1.562	1.094	0	0.106	1.2087	16.08	0.014	1.206
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	6.291	0.055	0.799
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	0.098	0.001	-1.009
1,4-Dichlorobenzene	0.825	0.75	0	0.02	0.9612	17.45	0.499	1.242
2,4-Dichlorophenol	0.96	0.99	0.58	0.14	1.02	0.073	0.001	-1.135
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	0.976	0.016	-0.01
<i>N,N</i> -Dimethylaniline	0.957	0.84	0	0.41	1.096	5.843	0.333	0.766
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	0.181	0.001	-0.743
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.037	0.001	-1.427
Diphenylamine	1.599	1.077	0.341	0.549	1.424	1.544	0.022	0.188
Ethyl benzoate	0.694	0.886	0	0.444	1.2135	4.037	0.009	0.606
Fluoranthene	2.292	1.486	0	0.255	1.5846	26.55	0.584	1.424
Fluorene	1.664	1.12	0	0.252	1.3565	24.41	0.088	1.388
Hexanophenone	0.79	1.026	0	0.503	1.5775	15.47	0.03	1.189
Indole	1.018	1.184	0.39	0.24	0.9464	0.044	0.001	-1.354
Iodobenzene	1.182	0.784	0	0.135	0.9747	8.854	0.305	0.947
Isoamyl ether	0	0.25	0	0.45	1.576	320.9	0.212	2.506
Isocyanopropyltri - ethoxysilane	-0.049	0.634	0	0.832	2.0119	218.8	0.105	2.34
Methacryloxypropyl - trimethoxysilane	0.046	0.869	0	1.024	1.9708	19.32	0.321	1.286
Methyl benzoate	0.738	0.923	0	0.439	1.0726	1.987	0.002	0.298
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	6.251	0.262	0.796
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	25.47	0.106	1.406
2-Methylnaphthalene	1.304	0.881	0	0.244	1.2263	32.66	0.151	1.366

Naphthalene	1.24	0.906	0	0.193	1.0854	15.8	0.03	1.199
1-Naphthol	1.48	1.157	0.796	0.318	1.1441	0.011	0.001	-1.967
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	0.006	0.001	-2.257
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904	0.016	0.001	-1.793
3-Nitroaniline	1.248	1.602	0.466	0.415	0.9904	0.003	0.001	-2.513
Nitrobenzene	0.846	1.138	0	0.269	0.8906	0.5	0.01	-0.301
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	1.242	0.012	0.094
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	0.319	0.006	-0.496
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	1.25	0.004	0.097
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	1.828	0.013	0.262
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	0.968	0.001	-0.014
Nonan-1-ol	0.199	0.44	0.344	0.52	1.4354	5.423	0.113	0.734
Nonan-2-one	0.113	0.662	0	0.496	1.3924	8.843	0.032	0.947
Octanal	0.148	0.633	0	0.421	1.2515	10.72	0.117	1.03
Octan-1-ol	0.199	0.44	0.344	0.52	1.2945	1.843	0.017	0.266
2-Octanone	0.109	0.662	0	0.496	1.2515	5.873	0.052	0.769
Octanophenone	0.779	1.026	0	0.503	1.8593	36.47	0.283	1.562
n-Octyl triethoxysilane	-0.255	0.003	0	0.92	2.503	4.E+04	2.063	4.628
Phalimide	1.276	1.577	0.353	0.522	1.0208	4.E+03	0.001	-2.387
Phthalonitrile	0.804	1.934	0	0.365	1.0256	0.011	0.001	-1.973
Phenanthrene	1.997	1.316	0	0.279	1.4544	17.85	0.066	1.252
Phenyl acetate	0.648	1.055	0	0.521	1.0726	0.611	0.044	-0.214
Phenol	0.769	0.759	0.716	0.319	0.7751	0.005	0.001	-2.304
Phenyl benzoate	1.33	1.42	0	0.47	1.54	4.31	0.088	0.635
1-Phenylethanol	0.787	0.797	0.39	0.636	1.0569	0.065	0.001	-1.19
Phenyl ether	1.216	0.912	0	0.267	1.3829	23.72	0.073	1.375
4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	0.008	0.001	-2.103
Quinoline	1.268	1.09	0	0.562	1.0443	0.583	0.011	-0.235
Resorcinol	1.175	0.935	1.252	0.578	0.8338	8.E-05	0.001	-4.12
o-Toluidine	0.966	1.045	0.193	0.491	0.9571	0.25	0.001	-0.603
m-Toluidine	0.946	1.128	0.112	0.516	0.9571	0.185	0.001	-0.733
p-Toluidine	0.923	1.192	0.147	0.396	0.9571	0.189	0.001	-0.722
p-Tolualdehyde	0.862	1	0	0.42	1.0139	0.818	0.006	-0.087
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	27.26	0.22	1.436
Tri-n-butyrin	0.035	1.193	0	1.578	2.4453	4.284	0.104	0.632
Valerophenone	0.795	1.026	0	0.503	1.4366	7.289	0.032	0.863

**Table 2.4.** Descriptor values and partition coefficients for compounds used to characterize the 1,2-dichloroethane -formamide partition system.

Compounds	Solute descriptors					Partition coefficients		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthene	1.604	1.05	0	0.22	1.2586	0.012	0.001	-1.906
Acenaphthylene	1.557	1.119	0	0.2	1.2156	0.02	0.003	-1.706
Acetanilide	0.96	1.144	0.538	0.708	1.1137	1.939	0.034	0.288
Acetophenone	0.806	1.026	0	0.503	1.0138	0.119	0.016	-0.924
3-Aminopropyltriethoxy-silane	-0.021	0.487	0.124	1.313	1.898	0.035	0.001	-1.457
Aniline	0.955	1.003	0.249	0.425	0.8162	0.474	0.005	-0.324
Benzamide	1.258	1.343	0.648	0.664	0.9728	6.557	0.002	0.817
Benzaldehyde	0.813	1.025	0	0.394	0.873	0.145	0.006	-0.839
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	0.069	0.006	-1.163
Benzonitrile	0.742	1.135	0	0.331	0.8711	0.119	<0.001	-0.924
Benzophenone	1.224	1.33	0	0.576	1.4808	0.037	<0.001	-1.436
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	0.011	0.005	-1.97
Biphenyl	1.312	0.874	0	0.298	1.3242	0.021	0.005	-1.683
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604	0.014	<0.001	-1.853
1-Bromooctane	0.339	0.4	0	0.12	1.4108	0.004	<0.001	-2.407
Caffeine	1.518	1.726	0.039	1.232	1.3632	0.75	0.003	-0.125
Carbazole	2.025	1.585	0.367	0.231	1.3154	0.122	0.004	-0.915
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	0.269	0.002	-0.57
4-Chloroaniline	1.056	1.138	0.325	0.331	0.9386	0.366	0.008	-0.437
Chlorobenzene	0.718	0.656	0	0.056	0.8388	0.044	0.006	-1.361
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.0384	1.34	0.004	0.127
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	0.021	0.015	-1.678
Cinnamyl alcohol	1.067	0.959	0.49	0.6	1.1548	0.753	0.093	-0.123
Coumarin	1.269	1.61	0	0.524	1.0619	0.202	0.042	-0.694
o-Cresol	0.774	0.745	0.621	0.357	0.916	1.439	0.125	0.158
Decan-1-ol	0.191	0.44	0.344	0.52	1.5763	0.028	0.013	-1.556
Dibenzofuran	1.562	1.094	0	0.106	1.2087	0.016	0.001	-1.799
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	0.036	0.006	-1.443
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	0.312	0.039	-0.506
1,4-Dichlorobenzene	0.825	0.75	0	0.02	0.9612	0.025	<0.001	-1.599
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	0.03	0.003	-1.517
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	0.037	0.002	-1.436
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	0.101	<0.001	-0.996
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.13	0.045	-0.887
Diphenylamine	1.676	1.204	0.214	0.555	1.424	0.054	0.004	-1.267
Ethyl benzoate	0.694	0.886	0	0.444	1.2135	0.065	0.03	-1.187
Ethyl 4-Hydroxybenzoate	0.86	1.35	0.69	0.45	1.272	1.46	0.03	0.164

Fluoranthene	2.292	1.486	0	0.255	1.5846	0.005	0.004	-2.284
Fluorene	1.664	1.12	0	0.252	1.3565	0.019	0.003	-1.727
Hexanophenone	0.79	1.026	0	0.503	1.5775	0.014	0.001	-1.842
4-Hydroxybenzaldehyde	1.11	1.241	0.927	0.463	0.9317	10.24	0.092	1.01
Indole	1.018	1.184	0.39	0.24	0.9464	0.438	0.001	-0.359
Iodobenzene	1.182	0.784	0	0.135	0.9747	0.028	0.003	-1.557
Isocyanopropyltriethoxy- silane	-0.049	0.642	0	0.823	2.0119	0.005	0.004	-2.306
Isopentyl ether	0	0.25	0	0.45	1.576	0.006	0.004	-2.255
Methacryloxypropyl- trimethoxysilane	0.046	0.869	0	1.024	1.9708	0.014	0.001	-1.853
Methyl benzoate	0.738	0.923	0	0.439	1.0726	0.054	0.038	-1.271
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	0.02	0.001	-1.695
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	0.014	0.01	-1.855
2-Methylnaphthalene	1.304	0.881	0	0.244	1.2263	0.02	0.014	-1.698
Naphthalene	1.24	0.906	0	0.193	1.0854	0.024	0.002	-1.624
1-Naphthol	1.48	1.157	0.796	0.318	1.0854	0.863	0.001	-0.064
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	1.176	0.005	0.07
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904	0.484	0.023	-0.315
4-Nitroaniline	1.236	1.827	0.597	0.343	0.9904	2.058	0.006	0.313
Nitrobenzene	0.846	1.138	0	0.269	0.8906	0.116	0.014	-0.934
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	0.03	0.021	-1.522
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	0.247	0.003	-0.608
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	0.048	0.034	-1.322
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	0.064	0.006	-1.195
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	0.049	0.008	-1.307
Nonan-1-ol	0.199	0.44	0.344	0.52	1.4354	0.881	0.004	-0.945
Nonan-2-one	0.113	0.662	0	0.496	1.3924	0.023	0.016	-1.636
Octanal	0.148	0.633	0	0.421	1.2515	0.016	0.003	-1.805
Octan-1-ol	0.199	0.44	0.344	0.52	1.2945	0.156	0.014	-0.807
2-Octanone	0.109	0.662	0	0.496	1.2515	0.023	0.011	-1.631
Octanophenone	0.779	1.026	0	0.503	1.8593	0.007	0.001	-2.135
n-Octyltriethoxysilane	-0.255	-0.078	0	0.985	2.503	0.001	<0.001	-2.985
Phthalimide	1.219	1.729	0.214	0.622	1.0208	0.836	0.003	-0.078
Phthalonitrile	0.755	1.942	0	0.36	1.0256	0.164	0.074	-0.784
Phenanthrene	1.997	1.316	0	0.279	1.4544	0.012	0.002	-1.911
Phenyl acetate	0.648	1.055	0	0.521	1.0726	0.068	0.002	-1.165
2-Phenylacetamide	0.95	1.6	0.52	0.79	1.114	4.017	0.077	0.604
Phenol	0.769	0.759	0.716	0.319	0.7751	3.411	0.001	0.533
Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.014	<0.001	-1.866
1-Phenylethanol	0.823	0.819	0.351	0.648	1.0569	1.025	0.041	0.011
2-Phenylethanol	0.787	0.797	0.39	0.636	1.0569	1.076	0.007	0.032
Phenyl ether	1.216	0.912	0	0.267	1.3829	0.011	0.001	-1.942

4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	0.578	0.005	-0.238
Quinoline	1.268	1.09	0	0.562	1.0443	0.167	0.035	-0.778
o-Toluidine	0.966	1.045	0.193	0.491	0.9571	0.272	0.004	-0.565
m-Toluidine	0.946	1.128	0.112	0.516	0.9571	0.193	0.002	-0.714
p-Toluidine	0.923	1.192	0.147	0.396	0.9571	0.309	0.006	-0.509
p-Tolualdehyde	0.862	1	0	0.42	1.0139	0.077	0.054	-1.114
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	0.018	0.013	-1.736
Tri-n-butyryn	0.091	1.23	0	1.507	2.4453	0.008	0.003	-2.096
Valerophenone	0.795	1.026	0	0.503	1.4366	0.025	0.002	-1.599

**Table 2.5.** Descriptor values and partition coefficients for compounds used to characterize the 1-octanol-formamide partition system.

Compounds	Solute descriptors					Partition coefficients		
	E	S	A	B	V	$K_p$	SD	$\log K_p$
Acenaphthene	1.604	1.05	0	0.22	1.2586	11.57	0.007	1.063
Acenaphthylene	1.557	1.119	0	0.2	1.2156	6.63	0.03	0.821
Acetophenone	0.806	1.026	0	0.503	1.0138	1.98	0.003	0.297
3-Aminopropyltriethoxy-silane	-0.02	0.487	0.124	1.313	1.898	13.15	0.026	1.119
Aniline	0.955	1.003	0.249	0.425	0.8162	0.905	0.005	-0.04
Benzamide	1.258	1.343	0.648	0.664	0.9728	0.419	0.091	-0.38
Benzaldehyde	0.813	1.025	0	0.394	0.873	1.441	0.007	0.159
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	1.89	0.004	0.277
Benzonitrile	0.742	1.135	0	0.331	0.8711	1.647	0.019	0.217
Benzophenone	1.224	1.33	0	0.576	1.4808	4.87	0.003	0.688
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	6.73	0.088	0.828
Biphenyl	1.312	0.874	0	0.298	1.3242	12.61	0.032	1.101
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604	11.89	0.007	1.075
3-Bromophenol	1.081	0.792	0.948	0.201	0.9501	2.785	0.014	0.445
4-Bromophenol	1.08	1.17	0.67	0.2	0.9501	1.267	0.068	0.103
Carbazole	2.025	1.585	0.367	0.231	1.3154	4.847	0.005	0.686
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	2.585	0.005	0.412
4-Chloroaniline	1.056	1.138	0.325	0.331	0.9386	1.41	0.006	0.149
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.0384	2.643	0.008	0.422
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	15.36	0.001	1.186
Cinnamyl alcohol	1.067	0.959	0.49	0.6	1.1548	2.321	0.002	0.366
Coumarin	1.269	1.61	0	0.524	1.0619	0.924	0.005	-0.03
Dibenzofuran	1.562	1.094	0	0.106	1.2087	8.75	0.007	0.942
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	6.72	0.003	0.827
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	2.169	0.03	0.336
1,4-Dichlorobenzene	0.825	0.75	0	0.02	0.9612	8.45	0.003	0.927
2,4-Dichlorophenol	0.96	0.99	0.58	0.14	1.02	2.66	0.007	0.425
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	1.129	0.049	0.053

N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	7.752	0.002	0.889
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	2.694	0.001	0.43
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.0569	3.583	0.01	0.554
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.463	0.063	-0.33
Diphenylamine	1.676	1.204	0.214	0.555	1.424	7.097	0.07	0.851
Ethyl benzoate	0.694	0.886	0	0.444	1.2135	4.017	0.002	0.604
Ethyl 4-Hydroxybenzoate	0.86	1.35	0.69	0.45	1.272	1.264	0.036	0.102
Fluoranthene	2.292	1.486	0	0.255	1.5846	12.15	0.005	1.085
Fluorene	1.664	1.12	0	0.252	1.3565	16.89	0.007	1.228
Glycidoxypropyltrimethoxy-silane	0.133	1.09	0	0.97	1.8073	4.206	0.084	0.624
Heptan-2-one	0.108	0.67	0	0.51	1.1106	4.06	<0.001	0.609
Hexanophenone	0.79	1.026	0	0.503	1.5775	11.89	0.005	1.075
4-Hydroxybenzaldehyde	1.11	1.241	0.927	0.463	0.9317	0.475	<0.001	-0.32
Indole	1.018	1.184	0.39	0.24	0.9464	1.43	0.013	0.155
Isocyanopropyltriethoxy-silane	-0.05	0.642	0	0.823	2.0119	28.75	<0.001	1.459
Isopentyl ether	0	0.25	0	0.45	1.576	38.16	0.004	1.582
Methacryloxypropyl-trimethoxysilane	0.046	0.869	0	1.024	1.9708	9.69	0.006	0.985
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	10.02	<0.001	1.001
Methyl benzoate	0.738	0.923	0	0.439	1.0726	3.56	0.007	0.552
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	18.48	0.002	1.267
2-Methylnaphthalene	1.304	0.881	0	0.244	1.2263	18.99	0.005	1.279
Naphthalene	1.24	0.906	0	0.193	1.0854	7.511	0.004	0.876
1-Naphthol	1.48	1.157	0.796	0.318	1.0854	2.855	<0.001	0.456
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	2.604	0.019	0.416
4-Nitroaniline	1.236	1.827	0.597	0.343	0.9904	0.393	0.003	-0.41
Nitrobenzene	0.846	1.138	0	0.269	0.8906	1.645	0.02	0.216
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	3.726	0.057	0.571
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	1.315	0.051	0.119
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	2.669	0.024	0.426
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	2.75	0.001	0.439
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	2.191	0.017	0.341
Nonan-1-ol	0.199	0.44	0.344	0.52	1.4354	21.64	0.003	1.335
Octanal	0.148	0.633	0	0.421	1.2515	12.18	<0.001	1.086
2-Octanone	0.109	0.662	0	0.496	1.2515	7.64	0.002	0.883
Octanophenone	0.779	1.026	0	0.503	1.8593	25.05	0.028	1.399
n-Octyltriethoxysilane	-0.26	-0.08	0	0.985	2.503	448	0.058	2.651
Pentachlorophenol	1.217	0.86	0.61	0.09	1.387	11.86	0.008	1.074
Phthalimide	1.219	1.729	0.214	0.622	1.0208	0.354	0.01	-0.45
Phthalonitrile	0.755	1.942	0	0.36	1.0256	0.456	0.088	-0.34
Phenanthrene	1.997	1.316	0	0.279	1.4544	13.33	0.007	1.125
Phenol	0.769	0.759	0.716	0.319	0.7751	1.602	0.016	0.205
Phenyl acetate	0.648	1.055	0	0.521	1.0726	2.671	0.055	0.427
2-Phenylacetamide	0.95	1.6	0.52	0.79	1.114	0.173	0.013	-0.76
Phenyl benzoate	1.33	1.42	0	0.47	1.54	4.061	0.065	0.609

2-Phenylethanol	0.787	0.797	0.39	0.636	1.0569	2.237	<0.001	0.35
Phenyl ether	1.216	0.912	0	0.267	1.3829	14.86	0.037	1.172
4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	0.173	0.013	-0.76
Quinoline	1.268	1.09	0	0.562	1.0443	0.456	0.088	-0.34
Resorcinol	1.038	0.995	1.312	0.511	0.8338	0.705	0.002	-0.15
Thiophene	0.687	0.56	0	0.15	0.6411	2.793	<0.001	0.446
p-Tolualdehyde	0.862	1	0	0.42	1.0139	2.778	0.001	0.444
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	14.25	0.006	1.154
Tri-n-butyryn	0.091	1.23	0	1.507	2.4453	4.516	0.032	0.655
Valerophenone	0.795	1.026	0	0.503	1.4366	6.599	0.007	0.82

**Table 2.6.** Descriptor values and partition coefficients for compounds used to characterize the isopentyl ether-formamide partition system.

Compounds	Solute descriptors					Partition coefficients		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthene	1.604	1.05	0	0.22	1.2586	30.86	0.002	1.489
Acenaphthylene	1.557	1.119	0	0.2	1.2156	20.49	0.003	1.311
Acetophenone	0.806	1.026	0	0.503	1.0138	1.109	0.004	0.045
3-Aminopropyltriethoxy-silane	-0.021	0.487	0.124	1.313	1.898	12.14	0.03	1.084
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	2.786	0.009	0.445
Benzamide	1.258	1.343	0.648	0.664	0.9728	0.037	0.003	-1.427
Benzonitrile	0.742	1.135	0	0.331	0.8711	0.513	0.042	-0.29
Benzophenone	1.224	1.33	0	0.576	1.4808	5.436	0.007	0.735
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	13.33	0.009	1.125
Biphenyl	1.312	0.874	0	0.298	1.3242	33.54	0.001	1.526
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604	35.54	0.003	1.551
1-Bromoheptane	0.343	0.4	0	0.12	1.27	94.29	0.099	1.974
1-Bromohexane	0.349	0.4	0	0.12	1.13	36.75	0.001	1.565
1-Bromooctane	0.339	0.4	0	0.12	1.411	241.5	0.005	2.383
3-Bromophenol	1.081	0.792	0.948	0.201	0.9501	0.747	0.006	-0.127
4-Bromophenol	1.08	1.17	0.67	0.2	0.9501	0.195	0.016	-0.711
Carbazole	2.025	1.585	0.367	0.231	1.3154	3.303	0.086	0.519
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	1.193	0.013	0.077
4-Chloroaniline	1.056	1.138	0.325	0.331	0.9386	0.581	0.001	-0.236
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.0384	0.939	0.002	-0.028
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	41.03	0.003	1.613
4-Chlorophenol	1.016	0.794	0.886	0.205	0.898	0.524	0.002	-0.28
Coumarin	1.269	1.61	0	0.524	1.0619	0.191	0.008	-0.72
Decan-1-ol	0.191	0.44	0.344	0.52	1.5763	39.63	0.094	1.598
Dibenzofuran	1.562	1.094	0	0.106	1.2087	25.47	0.002	1.406
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	12.07	0.006	1.082

3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	1.138	<0.001	0.056
1,4-Dichlorobenzene	0.825	0.75	0	0.02	0.9612	17.82	0.007	1.251
2,4-Dichlorophenol	0.96	0.99	0.58	0.14	1.02	1.043	0.013	0.018
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	2.433	0.088	0.386
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	12.05	0.002	1.081
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.0569	1.372	0.072	0.137
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	0.456	0.005	-0.341
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.21	0.054	-0.678
Diphenylamine	1.676	1.204	0.214	0.555	1.424	5.547	0.01	0.744
Dodecane	0	0	0	0	1.799	4566	0.056	3.66
Ethyl benzoate	0.694	0.886	0	0.444	1.2135	9.204	0.002	0.964
Fluoranthene	2.292	1.486	0	0.255	1.5846	39.38	0.001	1.595
Fluorene	1.664	1.12	0	0.252	1.3565	35.74	0.008	1.553
Heptan-2-one	0.108	0.67	0	0.51	1.1106	3.262	0.006	0.513
Hexachlorobenzene	1.49	0.99	0	0	1.451	115.8	0.007	2.064
Hexanophenone	0.79	1.026	0	0.503	1.5775	25.43	0.009	1.405
4-Hydroxybenzaldehyde	1.11	1.241	0.927	0.463	0.9318	0.041	0.005	-1.39
Indole	1.018	1.184	0.39	0.24	0.9464	0.874	0.019	-0.059
Iodobenzene	1.182	0.784	0	0.135	0.9747	14.21	0.012	1.153
Isocyanopropyltriethoxy-silane	-0.049	0.642	0	0.823	2.0119	68.74	0.001	1.837
Methacryloxypropyl-trimethoxysilane	0.046	0.869	0	1.024	1.9708	11.14	<0.001	1.047
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	15	0.012	1.176
Methyl benzoate	0.738	0.923	0	0.439	1.0726	3.264	0.007	0.514
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	39.7	0.002	1.599
2-Methylnaphthalene	1.304	0.881	0	0.244	1.2263	41.55	0.007	1.619
2-Methylphenol	0.774	0.745	0.621	0.357	0.9158	0.787	0.094	-0.104
Naphthalene	1.24	0.906	0	0.193	1.0854	22.06	0.006	1.344
1-Naphthol	1.48	1.157	0.796	0.318	1.0854	0.973	0.001	-0.012
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	0.579	0.068	-0.237
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904	0.194	0.002	-0.713
4-Nitroaniline	1.236	1.827	0.597	0.343	0.9904	0.028	0.01	-1.546
Nitrobenzene	0.846	1.138	0	0.269	0.8906	1.121	0.001	0.05
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	3.722	0.001	0.571
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	1.355	0.004	0.132
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	2.671	0.003	0.427
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	2.73	0.06	0.436
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	2.204	0.002	0.343
Nonan-1-ol	0.199	0.44	0.344	0.52	1.4354	17.2	0.012	1.236
Nonan-2-one	0.113	0.662	0	0.496	1.3924	15.53	0.014	1.191
Octanal	0.148	0.633	0	0.421	1.2515	14.28	0.009	1.155
Octan-1-ol	0.199	0.44	0.344	0.52	1.295	5.873	0.056	0.769



Octanophenone	0.779	1.026	0	0.503	1.8593	52.67	0.003	1.722
n-Octyltriethoxysilane	-0.255	-0.078	0	0.985	2.503	4111	0.005	3.614
Pentachlorophenol	1.217	0.86	0.61	0.09	1.387	9.089	0.011	0.959
Phenanthrene	1.997	1.316	0	0.279	1.4544	20.12	0.057	1.304
Phenyl acetate	0.648	1.055	0	0.521	1.0726	1.42	0.007	0.152
2-Phenylacetamide	0.95	1.6	0.52	0.79	1.114	0.02	0.003	-1.698
Phenyl benzoate	1.33	1.42	0	0.47	1.54	7.056	0.002	0.849
1-Phenylethanol	0.823	0.819	0.351	0.648	1.0569	0.569	0.035	-0.245
Phenyl ether	1.216	0.912	0	0.267	1.3829	35.23	0.042	1.547
4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	1.059	0.002	0.025
Phthalimide	1.219	1.729	0.214	0.622	1.0208	0.044	0.047	-1.354
Phthalonitrile	0.755	1.942	0	0.36	1.0256	0.038	0.001	-1.418
Quinoline	1.268	1.09	0	0.562	1.0443	1.365	0.001	0.135
Resorcinol	1.038	0.995	1.312	0.511	0.8338	0.012	0.103	-1.910
o-Toluidine	0.966	1.045	0.193	0.491	0.9571	0.921	0.005	-0.036
m-Toluidine	0.946	1.128	0.112	0.516	0.9571	0.956	0.007	-0.02
p-Toluidine	0.923	1.192	0.147	0.396	0.9571	0.746	0.006	-0.127
p-Tolualdehyde	0.862	1	0	0.42	1.0139	1.343	0.018	0.128
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	41.42	0.021	1.617
Tri-n-butyrin	0.091	1.23	0	1.507	2.4453	11.75	0.008	0.655
Valerophenone	0.795	1.026	0	0.503	1.4366	12.36	0.003	1.092

### 2.3.1.1 Heptane-formamide partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.3 to the solvation parameter model gave

$$\log K_p = 0.083 (\pm 0.095) + 0.559 (\pm 0.048)E - 2.244 (\pm 0.069)S - 3.250 (\pm 0.062)A - 1.614 (\pm 0.093)B + 2.384 (\pm 0.067)V \quad (2.3)$$

$$r = 0.996 \quad r_{adj}^2 = 0.991 \quad SE = 0.139 \quad F = 1791 \quad n = 84$$

where  $r$  is the multiple correlation coefficient,  $r_{adj}^2$  the coefficient of determination adjusted for the number of degrees of freedom, SE the standard error of the estimate, F the Fisher statistic, and  $n$  the number of compounds with partition coefficients included in the model. The descriptor space for the model is defined by the highest and lowest values of the descriptors ( $E = -0.26$  to

2.29,  $S = 0$  to 1.93,  $A = 0$  to 1.25,  $B = 0.02$  to 1.58, and  $V = 0.78$  to 2.50). Cross-correlation of the descriptors is minimal with the highest correlation  $r = 0.611$  for  $B$  vs.  $V$ .

The driving force for transfer of solutes to the n-heptane layer is indicated by the system constants with positive coefficients, the  $\nu$  and  $e$  system constants. Since n-heptane is a low polarity solvent it is not surprising that the difference in cohesion between the n-heptane layer and the formamide layer is the dominant factor for solute transfer to n-heptane. The positive  $e$  system constant indicates that formamide is electron lone pair repulsive since by definition n-heptane has an  $E$  value of zero. Polar interactions characterized by the  $s$ ,  $a$ , and  $b$  system constants favor transfer to the formamide layer. These values support the assertion that formamide is strongly hydrogen-bond basic, reasonably dipolar/polarizable, and moderately hydrogen-bond acidic. The n-heptane-formamide biphasic system is well suited for determining the  $A$  system constant and useful for estimating the  $S$  and  $B$  system constants in combination with other totally organic partitioning systems.

To evaluate the predictive ability of the model the data set was split into a training set of 58 compounds and a test set of 26 compounds using the Kennard-Stone algorithm [28]. This approach ensures that the training set and the test set are selected to occupy a similar descriptor space. The model for the training set, Eq (2.4), is virtually identical to Eq. (2.3).

$$\log K_p = 0.070 (\pm 0.115) + 0.552 (\pm 0.057)E - 2.241 (\pm 0.077)S - 3.228 (\pm 0.077)A - 1.623 (\pm 0.103)B + 2.403 (\pm 0.077)V \quad (2.4)$$

$$r = 0.996 \quad r_{adj}^2 = 0.992 \quad SE = 0.145 \quad F = 1367 \quad n = 58$$

Equation (2.4) was then used to predict the partition coefficients ( $\log K_p$ ) for the compounds in the test set and the average error, average absolute error, and root mean square error of the difference between the experimental and model predicted values used to assess the ability of Eq. (2.4) to estimate further values of  $\log K_p$  within the same descriptor space. The average error is

an indication of bias and at 0.007 indicates that this is not a concern for Eq. (2.4). The absolute average error (0.104) and root mean square error (0.126) are an indication of the likely error in predicting further partition coefficients based on Eq. (2.4). Since Eq. (2.4) is similar to Eq. (2.3), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (2.3) should be able to predict partition coefficients to about  $\pm 0.13$  log units for further compounds with known descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.1.2. 1, 2-dichloroethane -formamide partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.4 to the solvation parameter model gave Eq. 2.5.

$$\log K_p = -0.207 (\pm 0.081) - 0.082 (\pm 0.046)E + 0.399 (\pm 0.056)S + 1.957 (\pm 0.060)A \\ + 1.298 (\pm 0.079)B - 1.705 (\pm 0.058)V \quad (2.5)$$

$$r = 0.989 \quad r_{adj}^2 = 0.977 \quad SE = 0.122 \quad F = 738 \quad n = 87$$

The driving force for transfer of solutes to the 1,2-dichloroethane layer is indicated by the system constants with negative coefficients, since the 1,2-dichloroethane-rich layer has a higher density than the formamide-rich layer. This is governed nearly completely by solute size (the  $\nu$  system constant) since the  $e$  system constant is small and only just significant at the 95% confidence level (Student t-test). Polar interactions characterized by the  $s$ ,  $a$ , and  $b$  system constants favor transfer to the formamide-rich layer.

To evaluate the predictive ability of the model the data set was split into a training set of 60 compounds and a test set of 27 compounds. The model for the training set, Eq (2.6), is virtually identical to Eq. (2.5). Equation (2.6) was then used to predict the partition coefficients

$$\log K_p = -0.200 (\pm 0.099) - 0.104 (\pm 0.045)E + 0.428 (\pm 0.058)S + 1.912 (\pm 0.065)A \\ + 1.317 (\pm 0.081)B - 1.716 (\pm 0.067)V \quad (2.6)$$

$$r = 0.992 \quad r_{\text{adj}}^2 = 0.982 \quad \text{SE} = 0.120 \quad F = 649 \quad n = 60$$

(log  $K_p$ ) for the compounds in the test set. The average error is an indication of bias and at 0.059 indicates that this is not significant for Eq. (2.6). The absolute average error (0.112) and root mean square error (0.135) are an indication of the likely error in predicting further partition coefficients based on Eq. (2.6). Since Eq. (2.6) is similar to Eq. (2.5), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (2.5) should be able to predict partition coefficients to about  $\pm 0.13$  log units for further compounds with known descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.1.3. 1-Octanol-formamide partition system

Fitting the partition coefficients (log  $K_p$ ) in Table 2.5 to the solvation parameter model gave Eq.2.6.

$$\begin{aligned} \log K_p = & 0.285 (\pm 0.063) + 0.267 (\pm 0.034)E - 1.053 (\pm 0.043)S - 0.333 (\pm 0.038)A \\ & - 0.929 (\pm 0.066)B + 1.314 (\pm 0.046)V \end{aligned} \quad (2.7)$$

$$r = 0.986 \quad r_{\text{adj}}^2 = 0.970 \quad \text{SE} = 0.095 \quad F = 525 \quad n = 82$$

Positive system constant ( $v$  and  $e$ ) favor transfer to the 1-octanol-rich layer while polar interactions have a negative sign ( $s$ ,  $a$  and  $b$ ) and favor solubility in the formamide-rich layer. 1-Octanol is more competitive than 1,2-dichloroethane as a reservoir for hydrogen-bonding interactions reducing the value of the  $a$  and  $b$  system constants. It is also significantly less competitive for interactions of a dipole-type ( $s$  system constant) but more cohesive (smaller  $v$  system constant) than 1,2-dichloroethane. As before, the Kennard-Stone algorithm was used to split the data set into a training set of 59 compounds and a test set of 23 compounds. The model for the training set is given below.

$$\begin{aligned} \log K_p = & 0.270 (\pm 0.073) + 0.263 (\pm 0.036)E - 1.030 (\pm 0.044)S - 0.325 (\pm 0.043)A \\ & - 0.930 (\pm 0.069)B + 1.305 (\pm 0.050)V \end{aligned} \quad (2.8)$$

$$r = 0.989 \quad r_{adj}^2 = 0.976 \quad SE = 0.094 \quad F = 467 \quad n = 59$$

This is quite similar to Eq. (2.7). For the test set the average error was 0.086, the average absolute error 0.114 and the root mean square error 0.101. Thus, Eq. (2.7) should be able to predict further values of the partition coefficients to about  $\pm 0.11$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.1.4 Isopentyl ether-formamide partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.6 to the solvation parameter model gave

$$\log K_p = 0.130 (\pm 0.082) + 0.564 (\pm 0.041)E - 1.715 (\pm 0.055)S - 1.314 (\pm 0.047)A \\ - 1.407 (\pm 0.074)B + 2.005 (\pm 0.056)V \quad (2.9)$$

$$r = 0.994 \quad r_{adj}^2 = 0.987 \quad SE = 0.119 \quad F = 1347 \quad n = 88$$

Positive system constant ( $v$  and  $e$ ) favor transfer to the isopentyl ether-rich layer while polar interactions have a negative sign ( $s$ ,  $a$  and  $b$ ) and favor solubility in the formamide-rich layer. The relatively low cohesion of isopentyl ether compared with formamide results in a relatively large  $v$  system constant and the polar characteristics of isopentyl ether are reflected in the intermediate values for the  $s$  and  $a$  system constants for the isopentyl ether-formamide partition system. The selectivity of the isopentyl ether-formamide system is closest to the n-heptane-formamide system but with smaller  $s$  and  $a$  system constants reflecting the contribution of the ether oxygen to the partition mechanism. The Kennard-Stone algorithm was used to split the data set into a training set of 62 compounds and a test set of 26 compounds. The model for the training set is given below and is quite similar to Eq. (2.9).

$$\log K_p = 0.076 (\pm 0.101) + 0.568 (\pm 0.048)E - 1.713 (\pm 0.062)S - 1.308 (\pm 0.058)A \\ - 1.403 (\pm 0.082)B + 2.027 (\pm 0.066)V \quad (2.10)$$

$$r = 0.995 \quad r_{adj}^2 = 0.988 \quad SE = 0.127 \quad F = 1033 \quad n = 62$$

For the test set the average error was 0.067, the average absolute error 0.087 and the root mean square error 0.108. Thus, Eq. (2.9) should be able to predict further values of the partition coefficients to about  $\pm 0.12$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.1.5. Comparison of water and formamide for transfer of neutral solutes to organic solvents

Table 2.7 summarizes the system constants for the transfer of neutral organic compounds from water to n-heptane [51,52], 1,2-dichloroethane [15,53], di-n-butyl ether [15,54,55], and 1-octanol [15,52] and from formamide to n-heptane, 1,2-dichloroethane, isopentyl ether, and 1-octanol. System constants are not available for the isopentyl ether-water system and the di-n-butyl ether-water system is used as a surrogate for comparison purposes.

**Table 2.7.** System constants for transfer of neutral organic compounds from water or formamide to organic solvents.

Organic Solvent	System constant				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
<i>(i) From water</i>					
n-Heptane	0.67	-2.061	-3.317	-4.733	4.543
1,2-Dichloroethane	0.159	0.135	-2.247	-4.776	4.177
Di-n-butyl ether	1.183	-1.63	-1.177	-4.524	5.509
1-Octanol	0.684	-1.209	-0.185	-3.355	3.846
<i>(ii) From formamide</i>					
n-Heptane	0.559	-2.244	-3.25	-1.614	2.384
1,2-Dichloroethane	0.082	-0.399	-1.957	-1.298	1.705
Isopentyl ether	0.564	-1.715	-1.314	-1.407	2.005
1-Octanol	0.267	-1.023	-0.333	-0.929	1.314

The selectivity of the water-organic solvent and formamide-organic solvent systems are clearly different but certain general trends can be deduced. Formamide is about one-third to one-half as cohesive as water and only about one-quarter to one-third as hydrogen-bond acidic. The relatively high cohesion and hydrogen-bond acidity are the two characteristic properties that tend

to set water apart from other common solvents. Formamide and water have similar hydrogen-bond basicity and dipolarity/polarizability being the dominant properties that account for the particular characteristics of formamide. With respect to the above comments it should be kept in mind that the systems being compared refer to the equilibrium solvent compositions in which each phase is saturated with its counter solvent and differences in solvent saturation are not specifically taken into account in these comparisons. Formamide can be seen to possess some of the general characteristic solvation properties of water, but only to an extent, and it should be considered complementary in solvation properties to water rather than a substitute.

### 2.3.1.6. General extraction properties of formamide-organic solvent systems

Commonly used liquid-liquid partition systems are summarized in Table 2.8 [15,26,39,56,57]. Principal component analysis with varimax rotation and system constants as

**Table 2.8.** System constants for liquid-liquid partition systems.

Partition system	System constants				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
Formamide-1,2-dichloroethane	0.082	-0.399	-1.957	-1.298	1.705
n-Heptane-formamide	0.561	-2.248	-3.25	-1.603	2.384
n-Heptane- <i>N,N</i> -dimethylformamide	0.038	-1.391	-2.16	-0.593	0.486
n-Heptane-2,2,2-trifluoroethanol	0.882	-1.557	-1.312	-2.928	1.301
n-Heptane-methanol	0.186	-0.686	-1.098	-0.951	0.618
n-Heptane-ethylene glycol	0.374	-1.889	-4.072	-1.942	0.618
n-Hexane-acetonitrile	0.349	-1.439	-1.611	-0.874	0.669
Isopentyl ether-formamide	0.564	-1.715	-1.314	-1.407	2.005
1-Octanol-formamide	0.267	-1.053	-0.333	-0.929	1.314
Cyclohexane-water	0.784	-1.678	-3.74	-4.929	4.577
Di- <i>n</i> -butyl ether-water	0.677	-1.506	-0.807	-5.249	4.815
n-Heptane-water	0.67	-2.061	-3.317	-4.733	4.543
1-Octanol-water	0.684	-1.209	-0.185	-3.355	3.846
Toluene-water	0.527	-0.72	-3.01	-4.824	4.545
Water-Chloroform	0.183	-0.38	-2.469	-3.426	3.973
Water-1,2-dichloroethane	0.159	0.135	-2.247	-4.776	4.177
Water-methanol-chloroform (3:4:8)	0	-0.333	-1.407	-1.501	1.345

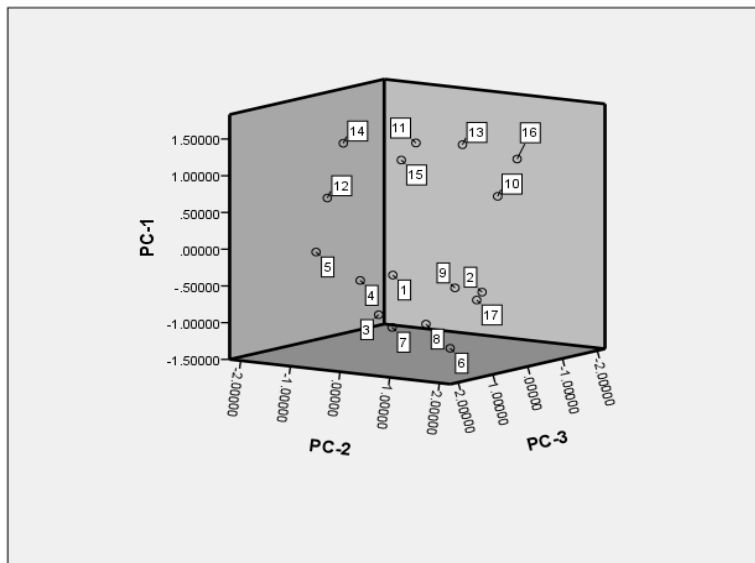
**Table 2.9.** Results from principal component analysis with varimax rotation and Kaiser normalization for the biphasic partition systems indicated in Table 2.8.

<u>(i) Loading on variables on the principal components</u>			
System constant	PC-1	PC-2	PC-3
<i>e</i>	0.499	-0.832	0.094
<i>s</i>	0.135	0.942	0.233
<i>a</i>	-0.156	0.113	0.977
<i>b</i>	-0.977	0.091	0.117
<i>v</i>	0.966	-0.05	-0.12
<u>(ii) Extraction of principal components</u>			
Principal component	Percent variance	Cumulative percent variance	
PC-1	50.5		
PC-2	27.61	78.11	
PC-3	18.46	96.57	

variables can be used to compare the extraction properties of the totally organic biphasic systems and the water-based biphasic systems typically used for descriptor measurements. The first two principal components describe 78% of the variance but the two dimensional score plots provide poor a classification of the partition systems, Table 2.9. The first three principal components explain about 97% of the variance and the three-dimensional plot of these principal components, Figure 2.1, is suitable for classification purposes. Principal component 1 (PC-1) mainly expresses information about the *b* and *v* system constants, principal component 2 (PC-2) the *e* and *s* system constants, and principal component 3 (PC-3) the *a* system constant.

The water-based biphasic systems are grouped at the top of the figure separated in the vertical plane from the totally organic biphasic systems. This highlights the dominant properties of water, its high cohesion and strong hydrogen-bond acidity, which sets the water-based partition systems apart from the other partition systems. The n-heptane-water and cyclohexane-water systems are indicated as having similar selectivity while the other water-based biphasic





**Fig. 2.1.** Score plot of the first three principle components with the system constants as variables for 17 biphasic liquid–liquid partition systems in Table 2.8. Identification: 1, n-heptane–formamide; 2, formamide–1,2-dichloroethane; 3, 1-octanol formamide; 4, isopentyl ether–formamide; 5, n-heptane–2,2,2 trifluoroethanol; 6, n-heptane–N,N-dimethylformamide; 7, n-hexane–acetonitrile; 8, n-heptane–methanol; 9, n-heptane–ethylene glycol; 10, water–chloroform; 11, cyclohexane–water; 12, 1-octanol–water; 13, toluene–water; 14, di-n-butylether–water; 15, n-heptane–water; 16, water–1,2-dichloroethane; 17, Folch partition (chloroform–methanol–water).

systems have complementary properties. The 1-octanol-water and water-chloroform systems are closer to the totally organic partition systems since the water saturated organic counter solvents compete to a greater extent than the other organic solvents as a reservoir of hydrogen-bonding interactions and also reduce the difference in cohesion between the two phases. Just below the water-based biphasic systems are the totally organic biphasic systems with intermediate hydrogen-bond acidity and cohesion. These systems are represented by n-heptane-2,2,2-trifluoroethanol, n-heptane-formamide, n-heptane-ethylene glycol, isopentyl ether-formamide, and formamide-1,2-dichloroethane. For compounds virtually insoluble or unstable in water these totally organic biphasic systems would be the most useful for estimating the B descriptor. The ternary solvent system (water-methanol-chloroform, Folch partition system) and formamide-1,2-

dichloroethane are almost selectivity equivalent and for many sample preparation applications one system could be substituted for the other. For determination of the S descriptor the n-heptane-formamide and n-heptane-water biphasic systems have the most favorable weighting on PC-2 with 1-octanol-formamide and isopentyl ether-formamide indicated as useful systems because the absolute value of the s system constant is intermediate in value and the relative contribution of dipole-type interactions to the partition coefficient is significantly larger than for the other biphasic systems. Of the totally organic biphasic systems n-heptane-formamide, n-heptane-*N,N*-dimethylformamide, and n-heptane-ethylene glycol have a favorable loading on PC-3 for determination of the A descriptor. The E and V descriptor can be obtained by calculation and experimental methods are not generally required for their determination [8,15,16].

### 2.3.2. Models for propylene carbonate-organic solvent partition system

Propylene carbonate has found many applications as a polar solvent in laboratory and chemical engineering applications [58,59]. It is essentially odorless, non-corrosive, non-toxic, biodegradable, nearly insoluble in water, of low viscosity (2.5 cP at 25°C), moderate density (1.2 g/mL at 25°C), high dielectric constant (58.62), and of low volatility (atmospheric boiling point 242°C). In laboratory applications it is widely used as a polar, non-hydrogen-bond donor solvent in synthesis, spectroscopy, and electrochemistry [60,61]. Spectroscopic analysis of solvatochromic indicator compounds suggests that propylene carbonate is of intermediate polarity (Reichardt's dye  $E_T^N = 0.472$ ) with significant dipolarity/polarizability and hydrogen-bond basicity but no hydrogen-bond acidity (Kamlet-Taft solvatochromic parameters  $\pi^* = 0.87$ ,  $\beta = 0.40$ , and  $\alpha = 0$ ) [59,61,62]. Hsu et al used NMR and theoretical calculations to demonstrate the formation of hydrogen-bonds between the phosphorous hexafluoride anion and propylene

carbonate [63] and Wang and Balbuena [64] provided evidence from theoretical calculations for the formation of propylene carbonate dimers in the gas phase stabilized by C-H $\cdots$ O interactions. These interactions are expected to be weak but call into question whether propylene carbonate should be classified as non-hydrogen bond donor solvent. Propylene carbonate was shown to be an effective solvent for the extraction of cationic dyes from water [65] and for the selective extraction of aromatic compounds from naphtha reformat [66]. The compounds used to characterize the propylene carbonate systems, their descriptor values and experimental partition coefficients are summarized in Tables 2.10 to 2.12.

**Table 2.10** Descriptor values and partition coefficients for varied compounds in n-heptane-propylene carbonate.

Compound	Solute descriptors					Partition coefficients		
	E	S	A	B	V	Kp	SD	log Kp
Acenaphthylene	1.557	1.119	0	0.2	1.216	0.59	0.021	-0.229
Acenaphthene	1.604	1.05	0	0.22	1.259	1.368	0.021	0.136
Acetophenone	0.806	1.026	0	0.503	1.014	0.222	0.071	-0.654
Benzamide	1.258	1.343	0.648	0.664	0.973	0.001	0.001	-3.075
Benzensulfonamide	1.169	1.864	0.681	0.679	1.097	9.6E-5	4.0E-5	-4.017
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	0.199	7.4E-7	-0.702
Benzophenone	1.224	1.33	0	0.576	1.481	0.182	0.004	-0.739
Benzyl benzoate	1.264	1.28	0	0.597	1.68	0.25	0.003	-0.602
Bis(trimethyl siloxy)me- thylsilane	-0.45	-0.15	0.032	0.375	1.949	120.78	1.107	2.082
1-Bromohexane	0.349	0.4	0	0.12	1.13	5.082	0.383	0.706
1-Bromonaphthalene	1.598	1.005	0	0.157	1.26	1.227	0.029	0.089
1-Bromooctane	0.339	0.4	0	0.12	1.411	11.376	1.474	1.056
3-Bromophenol	1.081	0.792	0.948	0.201	0.95	0.004	0	-2.369
4-Bromophenol	1.08	1.17	0.67	0.2	0.95	0.002	0.001	-2.669
n-Butyl benzoate	0.668	0.851	0	0.393	1.495	1.245	0.02	0.095
Caffeine	1.518	1.726	0.039	1.232	1.363	0.011	0.003	-1.973
Carbazole	2.025	1.585	0.367	0.231	1.315	0.009	0.001	-2.033
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.038	0.008	6.1E-5	-2.071
2-Chloroaniline	1.026	0.965	0.253	0.321	0.939	0.066	0.001	-1.183
Chlorobenzene	0.718	0.656	0	0.056	0.839	1.291	0.015	0.111
1-Chloronaphthalene	1.419	0.951	0	0.135	1.208	1.469	0.092	0.167

4-Chlorophenol	1.016	0.794	0.886	0.205	0.898	0.006	0.001	-2.233
Cinnamyl alcohol	1.067	0.959	0.49	0.6	1.155	0.015	0.001	-1.825
Coumarin	1.269	1.61	0	0.524	1.062	0.023	0.008	-1.637
Dibenzofuran	1.562	1.094	0	0.106	1.209	0.746	0.016	-0.127
Dibenzylamine	1.34	0.985	0.115	1.063	1.706	0.536	0.022	-0.271
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	0.016	0.005	-1.792
Diethyl phthalate	0.729	1.465	0	0.869	1.711	0.088	0.001	-1.056
Dimethyl phthalate	0.78	1.41	0	0.88	1.429	0.033	0.001	-1.48
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	0.745	0.001	-0.128
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.057	0.073	0.006	-1.138
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.013	0	-1.887
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.065	0.01	0.001	-1.987
Diphenylamine	1.599	1.077	0.341	0.549	1.424	0.06	0.003	-1.225
Ethyl benzoate	0.694	0.886	0	0.444	1.214	0.621	0.004	-0.207
Fluoranthene	2.292	1.486	0	0.255	1.585	0.479	0.015	-0.32
Fluorene	1.664	1.12	0	0.252	1.357	0.873	0.01	-0.059
3-(Glycidoxypropyl) - trimethoxysilane	0.133	1.09	0	0.97	1.807	0.153	0.006	-0.816
Heptane-2-one	0.123	0.662	0	0.496	1.111	0.767	0.017	-0.115
Hexanophenone	0.79	1.026	0	0.503	1.578	0.887	0.028	-0.052
Indole	1.018	1.184	0.39	0.24	0.946	0.01	0.001	-2.013
Isocyanopropyltri- ethoxysilane	-0.05	0.634	0	0.832	2.012	2.046	0.105	0.311
(Methacryloxypropyl) - trimethoxysilane	0.046	0.869	0	1.024	1.971	0.904	0.312	-0.044
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	0.369	0.009	-0.433
Methyl benzoate	0.738	0.923	0	0.439	1.073	0.378	0.045	-0.423
Methyl deconoate	0.057	0.564	0	0.456	1.733	4.571	0.001	0.66
2-Methylnaphthalene	1.304	0.88	0	0.154	1.226	1.205	0.01	0.081
1-Methylnaphthalene	1.337	0.915	0	0.205	1.226	1.164	0.107	0.066
Naphthalene	1.24	0.906	0	0.193	1.085	0.818	0.007	-0.087
1-Naphthol	1.48	1.157	0.796	0.318	1.144	0.004	0.01	-2.426
2-Naphthol	1.457	1.181	0.807	0.345	1.144	0.002	0.001	-2.685
2-Nitroaniline	1.182	1.441	0.386	0.348	0.99	0.006	0.001	-2.242
4-Nitroaniline	1.236	1.827	0.597	0.343	0.99	1.5E-4	3.5E-6	-3.821
Nitrobenzene	0.846	1.138	0	0.269	0.891	0.144	0.008	-0.841
1-Nitronaphthalene	1.367	1.505	0	0.272	1.257	0.104	0.003	-0.983
2-Nitrophenol	0.962	1.086	0.05	0.371	0.949	0.116	0.009	-0.935
2-Nitrotoluene	0.866	1.11	0	0.27	1.032	0.168	0.008	-0.774
3-Nitrotoluene	0.874	1.1	0	0.25	1.032	0.17	0.006	-0.77
4-Nitrotoluene	0.918	1.194	0	0.264	1.032	0.147	0.004	-0.832

Nonan-1-ol	0.199	0.44	0.344	0.52	1.435	0.826	0.011	-0.083
Octanophenone	0.779	1.026	0	0.503	1.859	1.007	2.9E-4	0.003
n-Octyltriethoxysilane	-0.26	0.003	0	0.92	2.503	109.65	1.131	2.04
Pentachlorophenol	1.217	0.86	0.61	0.09	1.387	0.041	0.011	-1.392
Phenanthrene	1.997	1.316	0	0.279	1.454	0.537	0.006	-0.27
Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.206	0.001	-0.687
2-Phenylacetamide	0.95	1.6	0.52	0.79	1.114	0.001	0.001	-3.013
1-Phenylethanol	0.787	0.797	0.39	0.636	1.057	0.067	5.8E-5	-1.171
2-Phenylethanol	0.787	0.797	0.39	0.639	1.057	0.033	0.001	-1.488
4-Phenylphenol	1.51	1.178	0.853	0.437	1.383	0.002	0.001	-2.702
Phthalonitrile	0.804	1.934	0	0.365	1.026	0.003	0.001	-2.568
Pyrene	2.271	1.486	0	0.278	1.585	0.574	0.006	-0.241
Quinoline	1.268	1.09	0	0.562	1.044	0.228	0.003	-0.643
Resorcinol	1.175	0.935	1.252	0.578	0.834	0	0.001	-3.719
Tetrakis(trimethylsiloxy)-silane	-0.99	-0.16	0	0.664	3.263	349.14	2.485	2.543
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	-0.1	0.215	0	0.67	2.736	55.59	0.931	1.745
p-Tolualdehyde	0.862	1	0	0.42	1.014	0.198	0.001	-0.704
Toluene	0.606	0.499	0	0.139	0.857	1.718	0.079	0.235
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.073	0.003	-1.138
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.084	2.564	0.238	0.409
Tri-n-butyrin	0.035	1.193	0	1.578	2.445	0.279	0.007	-0.555
Undecane	0	0	0	0	1.659	72.444	0.931	1.86
Valerophenone	0.795	1.026	0	0.503	1.437	0.603	0.075	-0.22

**Table 2.11** Descriptor values and partition coefficients for varied compounds in Isopentyl ether - propylene carbonate.

Compounds	Descriptors					Partition coefficients		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthene	1.604	1.05	0	0.22	1.2586	1.194	0.011	0.077
Acenaphthylene	1.557	1.119	0	0.2	1.2156	0.615	0.02	-0.21
Benzensulfonamide	1.169	1.864	0.681	0.679	1.097	0.008	0.023	-2.09
1,4-Benzodioxane	0.884	1.054	0	0.354	1.007	0.32	0.008	-0.5
Benzophenone	1.224	1.33	0	0.576	1.4808	0.35	0.041	-0.46
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	0.474	0.028	-0.32
Biphenyl	1.312	0.874	0	0.298	1.3242	1.132	0.001	0.054
bis(trimethylsiloxy)methylsilane	-0.45	-0.15	0.066	0.365	1.9494	53.46	0.003	1.728

1-Bromohexane	0.349	0.4	0	0.12	1.1299	4.111	0.006	0.614
1-Bromonaphthalene	1.598	1.005	0	0.157	1.2604	1.365	0.058	0.135
1-Bromooctane	0.339	0.4	0	0.12	1.4108	8.831	0.013	0.946
3-Bromophenol	1.081	0.792	0.948	0.201	0.9501	0.296	0.003	-0.53
4-Bromophenol	1.08	1.17	0.67	0.2	0.9501	0.149	0.017	-0.83
n-Butyl benzoate	0.668	0.851	0	0.393	1.4953	1.71	0.011	0.233
Caffeine	1.518	1.726	0.039	1.232	1.3632	0.068	0.048	-1.17
Carbazole	2.025	1.585	0.367	0.231	1.3154	0.146	0.028	-0.84
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	0.244	0.002	-0.61
4-Chloroaniline	1.007	1.171	0.33	0.31	0.9386	0.107	0.002	-0.97
Chlorobenzene	0.718	0.656	0	0.056	0.8388	1.563	0.051	0.194
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	1.449	0.079	0.161
4-Chlorophenol	1.016	0.794	0.886	0.205	0.8975	0.244	0.013	-0.61
Cinnamyl alcohol	1.119	0.971	0.451	0.606	1.1548	0.201	0.018	-0.7
Coumarin	1.269	1.61	0	0.524	1.0619	0.067	0.005	-1.18
o-Cresol	0.774	0.745	0.621	0.357	0.916	0.308	0.044	-0.51
Dibenzofuran	1.562	1.094	0	0.106	1.2087	1.03	0.006	0.013
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	0.861	0.035	-0.07
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	0.119	0.005	-0.93
2,4-Dichlorophenol	0.96	0.99	0.58	0.14	1.02	0.36	0.011	-0.44
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	0.201	0.003	-0.7
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	0.091	0.001	-1.04
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	1.047	0.091	0.02
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.0569	0.48	0.048	-0.32
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.0569	0.356	0.01	-0.45
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.032	0.033	-1.5
Diphenylamine	1.635	1.187	0.232	0.544	1.424	0.289	0.002	-0.54
Ethyl benzoate	0.694	0.886	0	0.444	1.2135	0.787	0.028	-0.1
Fluorene	1.664	1.12	0	0.252	1.3565	1.102	0.007	0.042
Glycidoxypopyltrimethoxy- silane	0.133	1.086	0	0.968	1.8073	0.318	0.012	-0.5
Heptan-2-one	0.108	0.67	0	0.51	1.1106	1.191	0.036	0.076
Hexanophenone	0.79	1.026	0	0.503	1.5775	1.315	0.012	0.119
Indole	1.018	1.184	0.39	0.24	0.9464	0.12	0.001	-0.92
Iodobenzene	1.182	0.784	0	0.135	0.9747	1.426	0.088	0.154
Iodobutane	0.628	0.4	0	0.15	0.9304	2.208	0.053	0.344
Isocyanatopropyltri- ethoxysilane	-0.05	0.642	0	0.823	2.0119	2.624	0.101	0.419
(Methacryloxypropyl)tri- methoxysilane	0.046	0.869	0	1.024	1.9708	1.023	0.03	0.01
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	0.598	0.004	-0.22

Methyl benzoate	0.738	0.923	0	0.439	1.0726	0.561	0.032	-0.25
Methyl octanoate	0.069	0.564	0	0.456	1.4511	1.321	0.106	0.121
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	1.452	0.337	0.162
2-Methylnaphthalene	1.304	0.88	0	0.154	1.2263	1.489	0.028	0.173
m-Toluidine	0.946	1.128	0.112	0.516	0.9571	0.157	0.001	-0.8
Naphthalene	1.24	0.906	0	0.193	1.0854	1.074	0.045	0.031
1-Naphthol	1.48	1.157	0.796	0.318	1.1441	0.202	0.033	-0.69
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	0.134	0.009	-0.87
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904	0.057	0.078	-1.25
3-Nitroaniline	1.248	1.602	0.466	0.415	0.9904	0.028	0.007	-1.56
Nitrobenzene	0.846	1.138	0	0.269	0.8906	0.259	0.07	-0.59
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	0.258	0.007	-0.59
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	0.259	0.009	-0.59
2-Nitropropane	0.215	0.884	0.024	0.329	0.7055	0.308	0.596	-0.51
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	0.378	0.001	-0.42
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	0.396	0.001	-0.4
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	0.318	0.042	-0.5
Nonan-2-one	0.113	0.662	0	0.496	1.3924	1.884	0.022	0.275
Octadecane	0	0	0	0	2.6448	133	0.055	2.124
Octan-1-ol	0.199	0.44	0.344	0.52	1.2945	1.374	0.073	0.138
Octanophenone	0.779	1.026	0	0.503	1.8593	2.275	0.06	0.357
n-Octyltriethoxysilane	-0.26	-0.08	0	0.985	2.503	41.88	0.125	1.622
o-Toluidine	0.966	1.045	0.193	0.491	0.9571	0.215	0.001	-0.67
Phenanthrene	1.997	1.316	0	0.279	1.4544	0.785	0.012	-0.11
Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.378	0.101	-0.42
Phenyl ether	1.216	0.912	0	0.267	1.3829	1.279	0.013	0.107
1-Phenylethanol	0.823	0.825	0.35	0.653	1.0569	0.349	0.027	-0.46
2-Phenylethanol	0.787	0.797	0.39	0.636	1.0569	0.224	0.011	-0.65
4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	0.15	0	-0.83
Phthalimide	1.219	1.729	0.214	0.622	1.0208	0.032	0.003	-1.5
Phthalonitrile	0.755	1.942	0	0.36	1.0256	0.017	0.034	-1.78
p-Tolualdehyde	0.862	1	0	0.42	1.0139	0.418	0.009	-0.38
pyrene	2.165	1.518	0	0.261	1.5846	0.897	0.062	-0.05
Quinoline	1.268	1.09	0	0.562	1.0443	0.385	0.001	-0.42
tetrakis(trimethylsiloxy)silane	-0.99	-0.14	0	0.665	3.2627	100.7	0.064	2.003
2,4,6,8-tetramethyl-2,4,6,8-tetraynycyclotetrasiloxane	-0.1	0.215	0	0.67	2.7364	38.19	0.062	1.582
Toluene	0.606	0.499	0	0.139	0.8573	1.667	0.038	0.222
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	2.897	0.03	0.462
Tri-n-butyrin	0.091	1.23	0	1.507	2.4453	0.556	0.011	-0.26
Valerophenone	0.795	1.026	0	0.503	1.4366	0.92	0.013	-0.04

**Table 2.12** Descriptor values and partition coefficients for varied compounds in 1-octanol - propylene carbonate.

Compound	Descriptors					Partition coefficients		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthene	1.604	1.05	0	0.22	1.2586	1.306	0.007	0.116
Acenaphthylene	1.557	1.119	0	0.2	1.2156	0.774	0.007	-0.111
Acetanilide	0.96	1.144	0.538	0.708	1.114	0.656	0.064	-0.183
Benzamide	1.258	1.343	0.648	0.664	0.9728	0.736	0.002	-0.133
Benzenesulfonamide	1.169	1.864	0.681	0.679	1.097	0.121	0.003	-0.917
1,4-Benzodioxan	0.884	1.054	0	0.354	1.007	0.551	0.01	-0.259
Benzophenone	1.224	1.33	0	0.576	1.4808	0.534	0.043	-0.273
Benzyl benzoate	1.264	1.28	0	0.597	1.6804	0.553	0.01	-0.257
Biphenyl	1.317	0.933	0	0.284	1.3242	0.874	0.002	-0.058
Bis(trimethylsiloxy)methylsilane	-0.45	-0.15	0.032	0.375	1.9494	8.558	0.054	0.932
1-Bromohexane	0.349	0.4	0	0.12	1.13	2.581	0.03	0.412
1-Bromooctane	0.339	0.4	0	0.12	1.4108	3.993	0.032	0.601
3-Bromophenol	1.081	0.792	0.948	0.201	0.95	2.074	0.011	0.317
n-Butyl benzoate	0.668	0.851	0	0.393	1.4953	1.304	0.022	0.115
Caffeine	1.518	1.726	0.039	1.232	1.3632	0.317	0.018	-0.499
Carbazole	2.025	1.585	0.367	0.231	1.3154	0.542	0.007	-0.266
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.0384	0.846	0.015	-0.072
2-Chloroaniline	1.026	0.965	0.253	0.321	0.9386	0.518	0.014	-0.286
4-Chloroaniline	1.007	1.171	0.33	0.31	0.9386	0.361	0.006	-0.443
Chlorobenzene	0.718	0.656	0	0.056	0.8388	1.349	0.117	0.13
1-Chloronaphthalene	1.419	0.951	0	0.135	1.2078	1.327	0.015	0.123
4-Chlorophenol	1.016	0.794	0.886	0.205	0.8975	1.717	0.048	0.235
Cinnamyl alcohol	1.067	0.959	0.49	0.6	1.1548	1.196	0.028	0.078
Coumarin	1.269	1.61	0	0.524	1.0619	0.28	0.005	-0.553
Dibenzofuran	1.562	1.094	0	0.106	1.2087	1.026	0.002	0.011
Dibenzylamine	1.34	0.985	0.115	1.063	1.7058	1.404	0.011	0.147
3,4-Dichloroaniline	1.158	1.24	0.35	0.24	1.061	0.404	0.004	-0.394
Diethyl phthalate	0.729	1.465	0	0.869	1.7106	0.373	0.007	-0.429
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	0.898	0.015	-0.047
Dimethyl phthalate	0.78	1.41	0	0.88	1.4288	0.194	0.001	-0.711
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.0569	1.575	0.064	0.197
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.0569	1.519	0.082	0.181
1,3-Dinitrobenzene	1.027	1.756	0	0.399	1.0648	0.11	0.001	-0.957
Dodecane	0	0	0	0	1.7994	9.208	0.037	0.964
Fluoranthene	2.292	1.486	0	0.255	1.585	0.823	0.026	-0.085



Fluorene	1.664	1.12	0	0.252	1.3565	0.953	0.007	-0.021
3-(Glycidoxypropyl)tri- methoxysilane	0.133	1.09	0	0.97	1.8073	0.413	0.016	-0.384
Heptane-2-one	0.123	0.662	0	0.496	1.1106	1.547	0.061	0.19
Hexanophenone	0.79	1.026	0	0.503	1.5775	1.298	0.006	0.113
Indole	1.018	1.184	0.39	0.24	0.9464	0.41	0.002	-0.387
Iodobenzene	0.628	0.4	0	0.15	0.9304	2.428	0.236	0.385
Isocyanopropyltriethoxy- silane	-0.05	0.634	0	0.832	2.0119	2.264	0.414	0.355
Methacryloxypropyltri- methoxysilane	0.046	0.869	0	1.024	1.9708	0.907	0.015	-0.043
2-Methoxynaphthalene	1.449	1.14	0	0.359	1.285	0.584	0.002	-0.234
Methyl benzoate	0.738	0.923	0	0.439	1.0726	0.689	0.06	-0.162
Methyl decanoate	0.057	0.564	0	0.456	1.7329	3.754	0.078	0.574
Methyl octanoate	0.069	0.564	0	0.456	1.4511	2.344	0.017	0.37
1-Methylnaphthalene	1.337	0.915	0	0.205	1.2263	1.195	0.008	0.077
2-Methylnaphthalene	1.304	0.88	0	0.154	1.2263	1.198	0.012	0.079
Naphthalene	1.24	0.906	0	0.193	1.0854	0.909	0.013	-0.041
1-Naphthol	1.48	1.157	0.796	0.318	1.1441	1.063	0.005	0.027
2-Naphthol	1.457	1.181	0.807	0.345	1.1441	1.106	0.009	0.044
2-Nitroaniline	1.182	1.441	0.386	0.348	0.9904	0.27	0.001	-0.569
4-Nitroaniline	1.236	1.827	0.597	0.343	0.9904	0.204	0.004	-0.691
Nitrobenzene	0.846	1.138	0	0.269	0.8906	0.333	0.007	-0.477
1-Nitronaphthalene	1.367	1.505	0	0.272	1.2569	0.281	0.003	-0.551
2-Nitrophenol	0.962	1.086	0.05	0.371	0.9493	0.382	0.001	-0.418
2-Nitropropane	0.215	0.884	0.024	0.329	0.7055	0.32	0.01	-0.495
2-Nitrotoluene	0.866	1.11	0	0.27	1.0315	0.589	0.008	-0.23
3-Nitrotoluene	0.874	1.1	0	0.25	1.0315	0.444	0.008	-0.352
4-Nitrotoluene	0.918	1.194	0	0.264	1.0315	0.421	0.001	-0.376
Octadecane	0	0	0	0	2.6448	20.7	0.687	1.316
Octanophenone	0.779	1.026	0	0.503	1.8593	2.01	0.018	0.303
n-Octyltriethoxysilane	-0.26	0.003	0	0.92	2.503	15.74	0.058	1.197
Phenanthrene	1.997	1.316	0	0.279	1.4544	0.814	0.001	-0.089
Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.44	0.008	-0.357
Phenyl ether	1.216	0.912	0	0.267	1.3829	0.868	0.007	-0.061
2-Phenylethanol	0.787	0.797	0.39	0.639	1.0569	1.199	0.011	0.079
4-Phenylphenol	1.51	1.178	0.853	0.437	1.3829	1.194	0.013	0.077
Phthalimide	1.219	1.729	0.214	0.622	1.0208	0.114	0.015	-0.942
Phthalonitrile	0.755	1.942	0	0.36	1.0256	0.061	0.007	-1.215
Pyrene	2.271	1.486	0	0.278	1.5846	0.813	0.012	-0.09
Resorcinol	1.086	0.97	1.294	0.532	0.8338	1.199	0.042	0.079

Tetrahydrofuran	0.295	0.54	0	0.469	0.6223	1.413	0.068	0.15
Tetrakis(trimethylsiloxy)-silane	-0.99	-0.16	0	0.664	3.2627	34.47	1.49	1.537
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	-0.1	0.215	0	0.67	2.7364	6.238	0.063	0.795
p-Tolualdehyde	0.862	1	0	0.42	1.0139	0.758	0.001	-0.12
o-Toluidine	0.966	1.045	0.193	0.491	0.9571	0.538	0.003	-0.269
m-Toluidine	0.946	1.128	0.112	0.516	0.9571	0.621	0.004	-0.207
p-Toluidine	0.923	1.192	0.147	0.396	0.9571	0.564	0.003	-0.249
Toluene	0.606	0.499	0	0.139	0.8573	1.339	0.093	0.127
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.0836	2.045	0.039	0.311
Tri-n-butyrin	0.091	1.23	0	1.507	2.4453	0.598	0.014	-0.223
Undecane	0	0	0	0	1.6585	5.288	0.41	0.723
Valerophenone	0.795	1.026	0	0.503	1.4366	0.962	0.001	-0.017

### 2.3.2.1. Heptane-propylene carbonate partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.10 to the solvation parameter model gave Eq. 2.11.

$$\log K_p = 0.502 (\pm 0.074) + 0.455 (\pm 0.036)E - 2.087 (\pm 0.052)S - 2.646 (\pm 0.046)A - 0.433 (\pm 0.065)B + 0.807 (\pm 0.043)V \quad (2.11)$$

$$r = 0.996 \quad r_{adj}^2 = 0.992 \quad SE = 0.115 \quad F = 2125 \quad n = 83$$

The driving force for transfer of solutes to the n-heptane layer is indicated by the system constants with positive coefficients, the  $v$  and  $e$  system constants. Since n-heptane is a solvent of low cohesion the small  $v$  coefficient suggests that propylene carbonate possesses no more than weak to intermediate cohesion. The positive  $e$  system constant indicates that propylene carbonate is electron lone-pair repulsive, since by definition n-heptane has an E-value of zero. Polar interactions characterized by the  $s$ ,  $a$ , and  $b$  system constants favor transfer to the propylene carbonate layer. These values support the assertion that propylene carbonate is reasonably dipolar/polarizable and strongly hydrogen-bond basic but weakly hydrogen-bond acidic.

Propylene carbonate is generally assumed to be a non-hydrogen-bond acidic solvent although NMR studies and theoretical calculations suggest some weak hydrogen-bond acidity [63,64]. The  $b$  system constant for propylene carbonate saturated with n-heptane, while small, is statistically significant at the 99% confidence level. Artificially setting the  $b$  system constant to zero results in the model

$$\log K_p = 0.628 (\pm 0.069) + 0.571 (\pm 0.039)E - 2.292 (\pm 0.052)S - 2.708 (\pm 0.056)A + 0.651 (\pm 0.044)V \quad (2.12)$$

$$r = 0.994 \quad r_{adj}^2 = 0.988 \quad SE = 0.143 \quad F = 1708 \quad n = 83$$

which is almost as good as Eq.(2.11). It is necessary, therefore, to be cautious in addressing the question of the hydrogen-bond acidity of propylene carbonate. There is uncertainty in the experimental partition coefficients which might feed into the model resulting in a small but phantom value for the  $b$  system constant. Dividing the data set up into sub sets of different compounds (an example is shown below) favors models that include the  $b$  system constant in fitting the data and we believe that it is reasonable to conclude that propylene carbonate is a weakly hydrogen-bond acidic solvent in support of other recent indications [63,64].

To evaluate the predictive ability of the model the data set was split into a training set of 58 compounds and a test set of 25 compounds. The model for the training set, Eq (2.13), is very similar to Eq. (2.11). Equation (2.13) was then used to predict the partition coefficients ( $\log K_p$ )

$$\log K_p = 0.601 (\pm 0.093) + 0.412 (\pm 0.043)E - 2.076 (\pm 0.058)S - 2.687 (\pm 0.057)A - 0.424 (\pm 0.072)B + 0.753 (\pm 0.051)V \quad (2.13)$$

$$r = 0.997 \quad r_{adj}^2 = 0.993 \quad SE = 0.119 \quad F = 1740 \quad n = 58$$

for the compounds in the test set. The average error is an indication of bias and at 0.014 indicates that this is not a concern for Eq. (2.13). The absolute average error (0.100) and root mean square error (0.121) are an indication of the likely error in predicting further partition coefficients based

on Eq. (2.13). Since Eq. (2.13) is similar to Eq. (2.11), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (2.11) should be able to predict partition coefficients to about  $\pm 0.12$  log units for further compounds with known descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.2.2. Isopentyl ether-propylene carbonate partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.11 to the solvation parameter model gave

$$\log K_p = 0.264 (\pm 0.065) + 0.298 (\pm 0.035)E - 1.432 (\pm 0.049)S - 0.718 (\pm 0.048)A \\ - 0.472 (\pm 0.062)B + 0.729 (\pm 0.037)V \quad (2.14)$$

$$r = 0.990 \quad r_{adj}^2 = 0.979 \quad SE = 0.109 \quad F = 786 \quad n = 86$$

Positive system constant ( $v$  and  $e$ ) favor transfer to the isopentyl ether-rich layer while polar interactions have a negative sign ( $s$ ,  $a$  and  $b$ ) and favor solubility in the propylene carbonate-rich layer. The similar cohesion of isopentyl ether compared with propylene carbonate results in a small value for the  $v$  system constant and the polar characteristics of isopentyl ether are reflected in the intermediate values for the  $s$  and  $a$  system constants. Isopentyl ether has no hydrogen bond acidity and small negative  $b$  system constant for the isopentyl ether-propylene carbonate system supports the assignment of weak hydrogen-bond acidity to propylene carbonate, as discussed for the n-heptane-propylene carbonate partition system (section 2.3.2.1). The Kennard-Stone algorithm was used to split the data set into a training set of 60 compounds and a test set of 26 compounds. The model for the training set is given below and is quite similar to Eq. (2.14).

$$\log K_p = 0.277 (\pm 0.080) + 0.313 (\pm 0.042)E - 1.440 (\pm 0.058)S - 0.722 (\pm 0.064)A \\ - 0.485 (\pm 0.070)B + 0.725 (\pm 0.043)V \quad (2.15)$$

$$r = 0.991 \quad r_{adj}^2 = 0.981 \quad SE = 0.118 \quad F = 607 \quad n = 60$$

For the test set the average error was 0.063, the average absolute error 0.100 and the root mean square error 0.088. Thus, Eq. (2.14) should be able to predict further values of the partition coefficients to about  $\pm 0.11$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.2.3. 1-Octanol-propylene carbonate partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.12 to the solvation parameter model gave

$$\log K_p = 0.282 (\pm 0.064) + 0.256 (\pm 0.033)E - 1.068 (\pm 0.041)S + 0.222 (\pm 0.047)A \\ + 0.365 (\pm 0.032)V \quad (2.16)$$

$$r = 0.971 \quad r_{adj}^2 = 0.941 \quad SE = 0.117 \quad F = 334 \quad n = 85$$

Positive system constant ( $v$ ,  $e$  and  $a$ ) favor transfer to the 1-octanol-rich layer while dipole-type interactions have a negative sign ( $s$ ) favor transfer to the propylene carbonate-rich layer. The  $b$  system constant is statistically indistinguishable from zero. Since 1-octanol is a hydrogen-bond acid this observation is in keeping with earlier conclusions that propylene carbonate is weakly hydrogen-bond acidic. The modest mutual solubility of the solvent pair also needs to be taken into account in assigning interactions to the individual solvents. A notable feature of this system is the relatively large  $s$  system constant compared with the other system constants, highlighting the importance of dipole-type interactions in controlling selectivity. As before, the Kennard-Stone algorithm was used to split the data set into a training set of 59 compounds and a test set of 26 compounds. The model for the training set is given below and is quite similar to Eq. (2.16).

$$\log K_p = 0.377 (\pm 0.078) + 0.266 (\pm 0.040)E - 1.107 (0.047)S - 0.190 (\pm 0.056)A \\ + 0.331 (\pm 0.037)V \quad (2.17)$$

$$r = 0.977 \quad r_{adj}^2 = 0.951 \quad SE = 0.121 \quad F = 285 \quad n = 59$$

For the test set the average error was 0.012, the average absolute error 0.083 and the root mean square error 0.112. Thus, Eq. (2.16) should be able to predict further values of the partition coefficients to about  $\pm 0.12$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

#### 2.3.2.4 General extraction properties of propylene carbonate-organic solvent systems

Principal component analysis with the system constants as variables using oblimin rotation and Kaiser normalization can be used to compare the extraction properties of the totally organic biphasic systems described for descriptor measurements, Table 2.13 [15,26,39,56,57].

**Table 2.13.** System constants for totally organic biphasic partition systems

Partition system	System constants				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
n-Heptane-formamide	0.561	-2.248	-3.25	-1.6	2.384
Formamide-1,2-dichloroethane	0.082	-0.399	-1.957	-1.3	1.705
1-Octanol-formamide	0.267	-1.053	-0.333	-0.93	1.314
Isopentyl ether-formamide	0.564	-1.715	-1.314	-1.41	2.005
n-Heptane-2,2,2-trifluoroethanol	0.882	-1.557	-1.312	-2.93	1.301
n-Heptane-Hexafluoroisopropanol	1.03	-1.712	-0.669	-1.75	1.121
n-Heptane- <i>N,N</i> -dimethylformamide	0.038	-1.391	-2.16	-0.59	0.486
n-Hexane-acetonitrile	0.349	-1.439	-1.611	-0.87	0.669
n-Heptane-methanol	0.186	-0.686	-1.098	-0.95	0.618
n-Heptane-ethylene glycol	0.374	-1.889	-4.072	-1.94	0.618
n-Heptane-propylene carbonate	0.455	-2.087	-2.646	-0.43	0.807
Isopentyl ether-propylene carbonate	0.298	-1.432	-0.718	-0.47	0.729
1-Octanol-propylene carbonate	0.256	-1.068	0.222	0	0.365

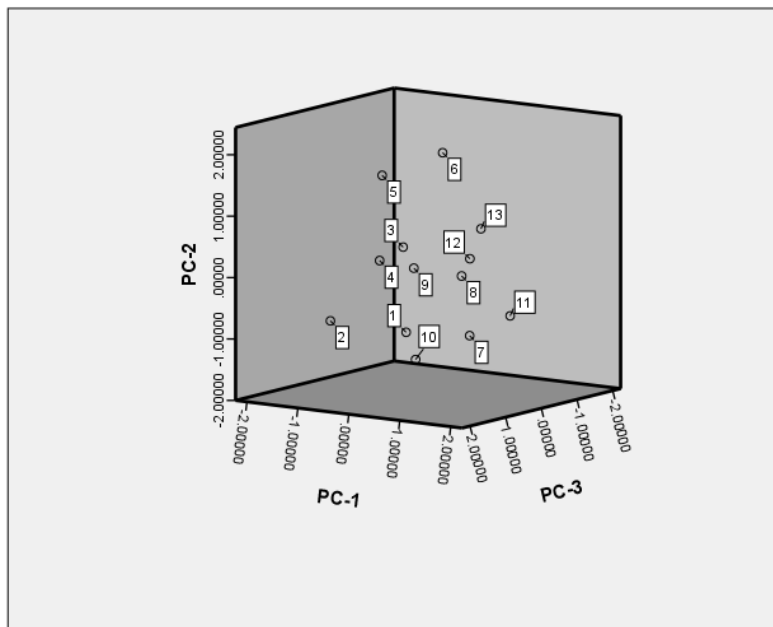
The first two principal components describe 73% of the variance and the two dimensional score plots afford only a poor a classification of the partition systems, Table 2.14. The first three principal components explain 91% of the variance and provide a more useful classification, Figure 2.2. Principal component 1 (PC-1) mainly expresses information about the *b* and *v* system constants, principal component 2 (PC-2) the *a* system constant, and principal component 3 (PC-

3) the  $s$  system constant, Table 2.14. The  $e$  system constant is loaded almost evenly on all three components.

**Table 2.14.** Results from principal component analysis with oblimin rotation and Kaiser normalization for the biphasic partition systems indicated in Table 2.13.

(i) Extraction of principal components			
Principal component	Percent variance	Cumulative percent variance	
PC-1	51.12		
PC-2	22.34	73.46	
PC-3	17.5	90.96	
(ii) Loading variables on the principal components			
System constant	PC-1	PC-2	PC-3
$e$	-0.58	0.489	-0.769
$s$	0.293	0.283	0.947
$a$	0.379	0.885	0.407
$b$	0.918	-0.102	0.417
$v$	-0.859	-0.298	-0.239

Figure 2.2 demonstrates that the 13 totally organic biphasic systems have different selectivity with little clustering. Of the propylene carbonate systems, isopentyl ether-propylene carbonate is close to n-hexane-acetonitrile (but these are not selectivity equivalent) while the other propylene carbonate systems have no near neighbors in the selectivity space. A useful feature of the totally organic biphasic systems is that within the selectivity space defined by the system constants, Table 2.13, they afford reasonable coverage and allow some flexibility in the identification of suitable systems for separations.



**Fig. 2.2.** Score plot of the first three principle components with the system constants as variables for 13 biphasic totally organic partition systems. Identification: 1: n-heptane-formamide; 2: formamide-1,2-dichloroethane; 3: 1-octanol-formamide; 4: isopentyl ether-formamide; 5: n-heptane-2,2,2-trifluoroethanol; 6: n-heptane-hexafluoroisopropanol; 7: n-heptane-N,N-Dimethylformamide; 8: n-hexane-acetonitrile; 9: n-heptane-methanol; 10: n-heptane-ethylene glycol; 11: n-heptane-propylene carbonate; 12: isopentyl ether-propylene carbonate; and 13 = 1-octanol-propylene carbonate.

### 2.3.3. Models for ethylene glycol-organic solvent partition system

Ethylene glycol and its mixtures with water have found many applications in industry as polar solvents and as a reactive intermediate in the production of polymers [67]. Ethylene glycol is essentially odorless, non-corrosive, non-toxic, biodegradable, miscible with water in all proportions and with many organic solvents, of modest viscosity (20.9 cP at 20°C), moderate density (1.11 g/mL at 20°C), and of low volatility. Paterson et al [68] determined partition coefficients for 11 peptides and 20 aromatic compounds in the system n-heptane-ethylene glycol. The partition coefficients were used to build a correlation model for the permeability coefficient across cell membranes. The above partition coefficients together with some further experimental and estimated values were used by Abraham et al [9] to assign system constants (solvation



parameter model) for partitioning in the n-heptane-ethylene glycol system. The model obtained for the partition coefficients,  $\log K_p$ , is

$$\log K_p = 0.343 (\pm 0.066) - 1.247 (\pm 0.112)S - 3.807 (\pm 0.172)A - 2.194 (\pm 0.162)B + 2.065 (\pm 0.089)V \quad (2.18)$$

$$n = 75 \quad r = 0.983 \quad SE = 0.28 \quad F = 488$$

Since n-heptane is a non-polar solvent of low cohesion, and ethylene glycol is virtually insoluble in n-heptane (0.01% m/m at 20°C [68]), the system constants indicate that ethylene glycol is a reasonably cohesive solvent capable of significant polar interactions (dipole-type and hydrogen-bonding interactions). Electron lone pair interactions are not important for partitioning in this system. Abraham and Acree [69] have proposed models for the transfer of neutral molecules and ions from the gas phase to ethylene glycol and for the hypothetical partition system ethylene glycol-water that support the above general assessment of the solvation properties of ethylene glycol. Kazoka and Shatz [70] used mixtures of ethylene glycol and organic solvents to generate dynamic partition systems for separations by liquid-liquid chromatography but reported no partition coefficient data. Silber et al [71] studied the partitioning behavior of two dye molecules in nonaqueous reverse micellar solutions prepared from n-heptane/surfactant/ethylene glycol with a view to demonstrating the possibility of micelle formation in ethylene glycol as a solvent. The compounds used in ethylene glycol systems, their descriptor values and experimental partition coefficients are summarized in Tables 2.15 to 2.17.

**Table 2.15** Descriptor values and partition coefficients for varied compounds in n-heptane-ethylene glycol.

Compound	Solute descriptors					Partition coefficient			
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>	
Acenaphthylene	1.557	1.119	0.000	0.200	1.216	15.136	0.005	1.180	
Acetanilide	0.960	1.144	0.538	0.708	1.114	0.008	3.6E-05	-2.108	

Acetophenone	0.806	1.026	0.000	0.503	1.014	2.455	2.4E-02	0.390
Anisole	0.712	0.768	0.000	0.311	0.916	8.590	0.001	0.934
Benzaldehyde	0.813	1.025	0.000	0.394	0.873	1.330	0.047	0.124
Benzamide	1.258	1.343	0.648	0.664	0.973	0.001	1.1E-04	-2.972
Benzensulfonamide	1.169	1.864	0.681	0.679	1.097	2.2E-4	1.7E-05	-3.661
1,4-Benzodioxane	0.884	1.054	0.000	0.354	1.007	2.891	0.002	0.461
Benzonitrile	0.742	1.135	0.000	0.331	0.871	1.016	1.2E-04	0.007
Benzophenone	1.224	1.330	0.000	0.576	1.481	8.110	0.068	0.909
Benzyl alcohol	0.803	0.882	0.400	0.557	0.916	0.025	2.1E-05	-1.600
Benzyl benzoate	1.264	1.280	0.000	0.597	1.680	20.606	0.022	1.314
Biphenyl	1.312	0.874	0.000	0.298	1.324	29.376	0.100	1.468
3-Bromophenol	1.081	0.792	0.948	0.201	0.950	0.003	2.3E-05	-2.595
4-Bromophenol	1.080	1.170	0.670	0.200	0.950	0.006	5.7E-05	-2.191
n-Butyl benzoate	0.668	0.851	0.000	0.393	1.495	58.749	0.087	1.769
Caffeine	1.518	1.726	0.039	1.232	1.363	0.045	8.5E-03	-1.345
4-Chloro-3-methylphenol	0.920	1.020	0.650	0.230	1.038	0.009	2.4E-04	-2.023
2-Chloroaniline	1.026	0.965	0.253	0.321	0.939	0.345	0.059	-0.462
4-Chloroaniline	1.056	1.138	0.325	0.331	0.939	0.052	0.006	-1.281
1-Chloronaphthalene	1.419	0.951	0.000	0.135	1.208	22.439	0.586	1.351
4-Chlorophenol	1.016	0.794	0.886	0.205	0.898	0.003	3.8E-04	-2.469
Cinnamyl alcohol	1.119	0.971	0.451	0.606	1.155	0.052	0.001	-1.285
Coumarin	1.269	1.610	0.000	0.524	1.062	0.142	0.002	-0.848
m-Cresole	0.810	0.779	0.672	0.351	0.916	0.008	0.003	-2.075
o-Cresole	0.774	0.745	0.621	0.357	0.916	0.032	0.001	-1.499
p-Cresole	0.793	0.769	0.664	0.353	0.916	0.014	0.005	-1.862
Cyclohexanone	0.403	0.895	0.000	0.530	0.861	1.242	0.069	0.094
Dibenzylamine	1.340	0.985	0.115	1.063	1.706	4.710	0.001	0.673
3,4-Dichloroaniline	1.332	1.268	0.443	0.174	1.061	0.059	4.5E-04	-1.226
o-Dichlorobnzene	0.872	0.771	0.000	0.054	0.961	23.121	0.004	1.364
Diethyl phthalate	0.729	1.465	0.000	0.869	1.711	3.133	0.010	0.496
Dimethyl phthalate	0.780	1.410	0.000	0.880	1.429	0.557	4.2E-04	-0.254
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.057	0.207	2.3E-03	-0.684
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.034	0.007	-1.463
1,3-Dinitrobenzene	1.027	1.756	0.000	0.399	1.065	0.262	1.8E-04	-0.582
Diphenylamine	1.675	1.206	0.214	0.555	1.424	1.618	3.7E-02	0.209
Ethyl benzoate	0.694	0.886	0.000	0.444	1.214	6.501	4.2E-02	0.813
Fluoranthene	2.292	1.486	0.000	0.255	1.585	13.836	0.003	1.141
Fluorene	1.664	1.120	0.000	0.252	1.357	18.239	0.003	1.261
Heptan-2-one	0.108	0.670	0.000	0.510	1.111	7.745	0.035	0.889
Hexanophenone	0.790	1.026	0.000	0.503	1.578	24.099	4.0E-03	1.382
Indole	1.018	1.184	0.390	0.240	0.946	0.056	0.004	-1.254

Iodobenzene	1.182	0.784	0.000	0.135	0.975	10.666	0.006	1.028
Iodobutane	0.628	0.400	0.000	0.150	0.930	31.477	4.1E-02	1.498
Isocyanatopropyl-triethoxysilane	-0.049	0.642	0.000	0.823	2.012	144.88	0.059	2.161
Methacryloxypropyl-trimethoxysilane	0.046	0.869	0.000	1.024	1.971	32.659	0.010	1.514
2-Methoxynaphthalene	1.449	1.140	0.000	0.359	1.285	8.810	5.3E-02	0.945
Methyl benzoate	0.738	0.923	0.000	0.439	1.073	3.855	0.045	0.586
Methyl deconoate	0.057	0.564	0.000	0.456	1.733	232.27	0.060	2.366
Methyl octanoate	0.069	0.564	0.000	0.456	1.451	82.604	0.379	1.917
1-Methylnaphthalene	1.337	0.915	0.000	0.205	1.226	22.542	0.097	1.353
2-Methylnaphthalene	1.304	0.880	0.000	0.154	1.226	21.727	0.087	1.337
N,N-Dimethylaniline	0.957	0.840	0.000	0.410	1.096	9.616	0.055	0.983
Naphthalene	1.240	0.906	0.000	0.193	1.085	10.990	0.038	1.041
1-Naphthol	1.480	1.157	0.796	0.318	1.144	0.006	2.5E-04	-2.193
2-Naphthol	1.457	1.181	0.807	0.345	1.144	0.003	1.8E-04	-2.464
2-Nitroaniline	1.182	1.441	0.386	0.348	0.990	0.039	2.3E-04	-1.413
4-Nitroaniline	1.236	1.827	0.597	0.343	0.990	0.001	3.7E-05	-3.050
Nitrobenzene	0.846	1.138	0.000	0.269	0.891	1.327	0.009	0.123
1-Nitronaphthalene	1.367	1.505	0.000	0.272	1.257	2.805	1.2E-03	0.448
2-Nitrophenol	0.962	1.086	0.050	0.371	0.949	1.076	0.006	0.032
2-Nitropropane	0.215	0.884	0.024	0.329	0.706	0.966	0.007	-0.015
2-Nitrotoluene	0.866	1.110	0.000	0.270	1.032	2.831	0.083	0.452
3-Nitrotoluene	0.874	1.100	0.000	0.250	1.032	2.958	0.033	0.471
4-Nitrotoluene	0.918	1.194	0.000	0.264	1.032	2.891	0.021	0.461
Nonan-2-one	0.113	0.662	0.000	0.496	1.392	45.394	0.025	1.657
Octan-1-ol	0.199	0.440	0.344	0.520	1.295	3.451	0.020	0.538
Octanophenone	0.779	1.026	0.000	0.503	1.859	82.224	0.046	1.915
Pentachloro phenole	1.577	1.051	0.625	0.021	1.387	0.247	0.000	-0.607
Phenanthrene	1.997	1.316	0.000	0.279	1.454	13.213	0.064	1.121
Phenyl acetate	0.648	1.055	0.000	0.521	1.073	1.641	0.012	0.215
Phenyl benzoate	1.330	1.420	0.000	0.470	1.540	10.209	0.017	1.009
1-Phenyl ethanol	0.823	0.825	0.350	0.653	1.057	0.064	4.5E-04	-1.191
2-Phenyl ethanol	0.787	0.797	0.390	0.636	1.057	0.077	0.002	-1.114
Phenyl ether	1.216	0.912	0.000	0.267	1.383	20.091	0.044	1.303
2-Phenylacetamide	0.950	1.600	0.520	0.790	1.114	0.002	1.2E-04	-2.656
4-Phenylphenol	1.510	1.178	0.853	0.437	1.383	0.007	0.003	-2.172
Phthalonitrile	0.755	1.942	0.000	0.360	1.026	0.144	1.8E-04	-0.842
pyrene	2.165	1.518	0.000	0.261	1.585	17.906	0.057	1.253
p-Tolualdehyde	0.862	1.000	0.000	0.420	1.014	2.046	0.024	0.311
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.192	0.018	-0.717

o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.243	0.002	-0.614
p-Toluidine	0.923	1.192	0.147	0.396	0.957	0.167	0.001	-0.776
1,2,4-Trichlorobenzene	1.022	0.748	0.000	0.018	1.084	29.444	6.1E-03	1.469
Tri-n-butyryn	0.091	1.230	0.000	1.507	2.445	31.915	0.003	1.504
Valerophenone	0.795	1.026	0.000	0.503	1.437	12.417	0.028	1.094
m-Xylene	0.625	0.507	0.000	0.178	0.998	56.234	0.002	1.750

**Table 2.16** Descriptor values and partition coefficients for varied compounds in Isopentyl ether - ethylene glycol.

Compound	Solute descriptors					Partition coefficient		
	E	S	A	B	V	Kp	SD	log Kp
Acenaphthene	1.604	1.05	0	0.22	1.259	24.774	0.01	1.394
Acenaphthylene	1.557	1.119	0	0.2	1.216	11.35	1.20E-03	1.055
Acetanilide	0.96	1.144	0.538	0.708	1.114	0.104	0.004	-0.982
Acetophenone	0.806	1.026	0	0.503	1.014	2.234	1.50E-03	0.349
Anisole	0.712	0.768	0	0.311	0.916	10.471	3.20E-02	1.02
Benzaldehyde	0.813	1.025	0	0.394	0.873	2.188	0.001	0.34
Benzamide	1.258	1.343	0.648	0.664	0.973	0.02	0.003	-1.696
1,4-Benzodioxane	0.884	1.054	0	0.354	1.007	4.753	1.20E-03	0.677
Benzophenone	1.224	1.33	0	0.576	1.481	7.295	5.50E-02	0.863
Benzyl alcohol	0.803	0.882	0.4	0.557	0.916	0.521	2.20E-02	-0.283
Benzyl benzoate	1.264	1.28	0	0.597	1.68	23.067	0.026	1.363
Biphenyl	1.312	0.874	0	0.298	1.324	24.322	0.022	1.386
1-Bromohexane	0.349	0.4	0	0.12	1.13	129.12	0.023	2.111
1-Bromonaphthalene	1.598	1.005	0	0.157	1.26	23.067	0.047	1.363
1-Bromooctan	0.339	0.4	0	0.12	1.411	345.14	1.30E-02	2.538
3-Bromophenol	1.081	0.792	0.948	0.201	0.95	0.541	6.10E-03	-0.267
4-Bromophenol	1.08	1.17	0.67	0.2	0.95	0.457	0.002	-0.34
n-Butyl benzoate	0.668	0.851	0	0.339	1.495	42.17	3.60E-02	1.625
Caffeine	1.518	1.726	0.039	1.232	1.363	0.037	3.10E-04	-1.434
Carbazole	2.025	1.585	0.367	0.231	1.315	1.422	3.60E-02	0.153
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.038	0.794	0.007	-0.1
2-Chloroaniline	1.026	0.965	0.253	0.321	0.939	1.117	0.011	0.048
4-Chloroaniline	1.056	1.138	0.325	0.331	0.939	0.421	0.003	-0.376
1-Chloronaphthalene	1.419	0.951	0	0.135	1.208	24.322	7.40E-02	1.386
4-Chlorophenol	1.016	0.794	0.886	0.205	0.898	0.429	0.006	-0.368
Cinnamyl alcohol	1.119	0.971	0.451	0.606	1.155	0.445	0.011	-0.352
m-Cresole	0.81	0.779	0.672	0.351	0.916	0.762	0.01	-0.118

o-Cresole	0.774	0.745	0.621	0.357	0.916	0.56	0.013	-0.252
p-Cresole	0.793	0.769	0.664	0.353	0.916	0.442	0.017	-0.355
Cyclohexanone	0.403	0.895	0	0.53	0.861	1.271	0.009	0.104
Dibenzofuran	1.562	1.094	0	0.106	1.209	19.187	0.065	1.283
Dibenzylamine	1.34	0.985	0.115	1.063	1.706	4.457	0.044	0.649
3,4-Dichloroaniline	1.332	1.268	0.443	0.174	1.061	0.61	0.003	-0.215
p-Dichlorobnzene	0.825	0.75	0	0.02	0.961	22.029	0.066	1.343
Diethyl phthalate	0.729	1.465	0	0.869	1.711	5.781	2.20E-03	0.762
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.057	1.517	4.40E-03	0.181
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.906	2.40E-03	-0.043
Ethyl benzoate	0.694	0.886	0	0.444	1.214	8.072	2.20E-03	0.907
Ethylbenzene	0.613	0.499	0	0.139	0.998	45.604	0.073	1.659
Fluoranthene	2.292	1.486	0	0.255	1.585	20.797	1.70E-02	1.318
Fluorene	1.664	1.12	0	0.252	1.357	25.003	5.80E-03	1.398
Glycidoxypopyltri- methoxysilane	0.133	1.086	0	0.968	1.807	8.147	0.009	0.911
Indole	1.018	1.184	0.39	0.24	0.946	0.662	0.005	-0.179
Iodobenzene	1.182	0.784	0	0.135	0.975	13.213	0.008	1.121
Isocyanatopropyltri- ethoxysilane	-0.05	0.642	0	0.823	2.012	186.21	5.90E-02	2.27
Methacryloxypropyltri- methoxsilane	0.046	0.869	0	1.024	1.971	59.704	0.06	1.776
Methyl benzoate	0.738	0.923	0	0.439	1.073	6.026	0.064	0.78
Methyl deconoate	0.057	0.564	0	0.456	1.733	223.87	0.049	2.35
Methyl octanoate	0.069	0.564	0	0.456	1.451	80.168	1.40E-02	1.904
1-Methylnaphthalene	1.337	0.915	0	0.205	1.226	25.003	1.90E-03	1.398
2-Methylnaphthalene	1.304	0.88	0	0.154	1.226	28.576	0.051	1.456
N,N-Dimethylaniline	0.957	0.84	0	0.41	1.096	11.94	0.058	1.077
Naphthalene	1.24	0.906	0	0.193	1.085	15.885	0.007	1.201
1-Naphthol	1.48	1.157	0.796	0.318	1.144	0.579	0.006	-0.237
2-Naphthol	1.457	1.181	0.807	0.345	1.144	0.371	0.004	-0.431
2-Nitroaniline	1.182	1.441	0.386	0.348	0.99	0.333	0.001	-0.478
3-Nitroaniline	1.248	1.602	0.466	0.415	0.99	0.111	0.018	-0.953
4-Nitroaniline	1.236	1.827	0.597	0.343	0.99	0.076	0.004	-1.121
Nitrobenzene	0.846	1.138	0	0.269	0.891	3.177	0.089	0.502
1-Nitronaphthalene	1.367	1.505	0	0.272	1.257	4.977	0.044	0.697
2-Nitrophenol	0.962	1.086	0.05	0.371	0.949	2.265	4.80E-02	0.355
2-Nitropropane	0.215	0.884	0.024	0.329	0.706	2.153	0.007	0.333
2-Nitrotoluene	0.866	1.11	0	0.27	1.032	5.321	8.30E-02	0.726
3-Nitrotoluene	0.874	1.1	0	0.25	1.032	6.095	5.40E-02	0.785
4-Nitrotoluene	0.918	1.194	0	0.264	1.032	5.37	9.30E-02	0.73

Nonan-2-one	0.113	0.662	0	0.496	1.392	29.512	5.20E-03	1.47
2-Octanone	0.109	0.662	0	0.496	1.252	12.274	0.011	1.089
Octanophenone	0.779	1.026	0	0.503	1.859	138.68	0.042	2.142
Pentachlorophenol	1.577	1.051	0.625	0.021	1.387	7.112	0.008	0.852
Phenanthrene	1.997	1.316	0	0.279	1.454	17.742	0.031	1.249
Phenyl acetate	0.648	1.055	0	0.521	1.073	3.155	0.057	0.499
Phenyl benzoate	1.33	1.42	0	0.47	1.54	11.117	0.047	1.046
1-Phenyl ethanol	0.823	0.825	0.35	0.653	1.057	0.596	0.061	-0.225
2-Phenyl ethanol	0.787	0.797	0.39	0.636	1.057	0.46	0.005	-0.337
Phenyl ether	1.216	0.912	0	0.267	1.383	29.854	0.024	1.475
2-Phenylacetamide	0.95	1.6	0.52	0.79	1.114	0.022	2.30E-04	-1.662
4-Phenylphenol	1.51	1.178	0.853	0.437	1.383	0.589	0.01	-0.23
Phthalonitrile	0.755	1.942	0	0.36	1.026	0.255	0.005	-0.593
Pyrene	2.165	1.518	0	0.261	1.585	15.241	0.005	1.183
Resorcinol	1.086	0.97	1.294	0.532	0.834	0.006	0.002	-2.229
Toluene	0.606	0.499	0	0.139	0.857	15.382	0.08	1.187
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.519	3.80E-03	-0.285
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.621	0.026	-0.207
1,2,4-Trichlorobenzene	1.022	0.748	0	0.018	1.084	38.371	6.30E-02	1.584
Tri-n-butyryn	0.04	1.143	0	1.432	2.445	40.738	0.063	1.61
Valerophenone	0.795	1.026	0	0.503	1.437	19.364	5.50E-02	1.287
m-Xylene	0.625	0.507	0	0.178	0.998	48.641	0.024	1.687
o-Xylene	0.663	0.549	0	0.178	0.998	44.157	0.054	1.645
P-Xylene	0.615	0.494	0	0.16	0.998	50.816	0.057	1.706

**Table 2.17** Descriptor values and partition coefficients for varied compounds in 1,2-dichloroethane -ethylene glycol.

Compound	Solute descriptors					Partition coefficient		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthene	1.604	1.050	0.000	0.220	1.259	0.012	0.007	-1.913
Acenaphthylene	1.557	1.119	0.000	0.200	1.216	0.013	4.1E-04	-1.879
Acetanilide	0.960	1.144	0.538	0.708	1.114	0.906	0.002	-0.043
Acetophenone	0.806	1.026	0.000	0.503	1.014	0.049	0.002	-1.305
Aniline	0.955	1.003	0.249	0.425	0.816	0.278	0.003	-0.556
Anisole	0.712	0.768	0.000	0.311	0.916	0.042	0.004	-1.375
Anthracene	1.923	1.309	0.000	0.253	1.454	0.011	0.000	-1.954
Benzaldehyde	0.813	1.025	0.000	0.394	0.873	0.064	0.004	-1.195
Benzamide	1.258	1.343	0.648	0.664	0.973	4.960	0.002	0.695
1,4-Benzodioxane	0.884	1.054	0.000	0.354	1.007	0.026	0.001	-1.590

Benzonitrile	0.742	1.135	0.000	0.331	0.871	0.053	0.002	-1.278
Benzophenone	1.224	1.330	0.000	0.576	1.481	0.014	0.000	-1.854
Benzyl alcohol	0.803	0.882	0.400	0.557	0.916	0.762	0.002	-0.118
Benzyl benzoate	1.264	1.280	0.000	0.597	1.680	0.013	0.001	-1.897
Biphenyl	1.312	0.874	0.000	0.298	1.324	0.012	4.9E-04	-1.906
1-Bromohexane	0.349	0.400	0.000	0.120	1.130	0.012	4.3E-04	-1.912
1-Bromonaphthalene	1.598	1.005	0.000	0.157	1.260	0.012	5.3E-05	-1.911
1-Bromooctane	0.339	0.400	0.000	0.120	1.411	0.008	2.6E-04	-2.110
3-Bromophenol	1.081	0.785	0.942	0.203	0.950	4.910	0.009	0.691
n-butyl benzoate	0.668	0.851	0.000	0.339	1.495	0.005	0.001	-2.326
Caffeine	1.518	1.726	0.039	1.232	1.363	0.099	0.001	-1.004
Carbazole	2.025	1.585	0.367	0.231	1.315	0.088	0.001	-1.054
4-Chloro-3-methylphenol	0.920	1.020	0.650	0.230	1.038	1.644	0.002	0.216
2-Chloroaniline	1.026	0.965	0.253	0.321	0.939	0.130	0.006	-0.888
4-Chloroaniline	1.056	1.138	0.325	0.331	0.939	0.244	0.005	-0.613
Chlorobenzene	0.718	0.656	0.000	0.056	0.839	0.026	0.002	-1.582
1-Chloronaphthalene	1.419	0.951	0.000	0.135	1.208	0.011	0.001	-1.943
4-Chlorophenol	1.016	0.794	0.886	0.205	0.898	3.165	0.001	0.500
Cinnamyl alcohol	1.119	0.971	0.451	0.606	1.155	0.442	0.012	-0.355
Coumarin	1.269	1.610	0.000	0.524	1.062	0.048	0.001	-1.318
m-Cresole	0.810	0.779	0.672	0.351	0.916	1.868	0.001	0.271
o-Cresole	0.774	0.745	0.621	0.357	0.916	1.286	0.005	0.109
p-Cresole	0.793	0.769	0.664	0.353	0.916	1.606	0.060	0.206
Cyclohexanone	0.403	0.895	0.000	0.530	0.861	0.058	0.002	-1.234
Dibenzofuran	1.562	1.094	0.000	0.106	1.209	0.012	3.1E-04	-1.921
3,4-Dichloroaniline	1.158	1.240	0.350	0.240	1.061	0.237	0.009	-0.625
p-Dichlorobenzene	0.852	0.692	0.000	0.008	0.961	0.020	1.5E-04	-1.701
Diethyl phthalate	0.729	1.465	0.000	0.869	1.711	0.010	1.3E-04	-2.000
Dimethyl phthalate	0.780	1.410	0.000	0.880	1.429	0.020	0.001	-1.702
N,N-Dimethylaniline	0.957	0.840	0.000	0.410	1.096	0.016	0.001	-1.801
2,6-Dimethylphenol	0.773	0.791	0.408	0.402	1.057	0.236	0.009	-0.627
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.978	2.8E-04	-0.010
1,3-Dinitrobenzene	1.027	1.756	0.000	0.399	1.065	0.027	0.001	-1.573
Diphenylamine	1.570	1.260	0.209	0.501	1.424	0.027	1.6E-04	-1.569
Ethyl benzoate	0.694	0.886	0.000	0.444	1.214	0.017	0.003	-1.759
Ethylbenzene	0.613	0.499	0.000	0.139	0.998	0.024	0.001	-1.627
Fluoranthene	2.292	1.486	0.000	0.255	1.585	0.006	0.008	-2.203
Fluorene	1.664	1.120	0.000	0.252	1.357	0.009	3.6E-04	-2.067
Glycidoxypropyltri- methoxysilane	0.133	1.086	0.000	0.968	1.807	0.015	0.001	-1.827
Heptan-2-one	0.108	0.670	0.000	0.510	1.111	0.028	0.001	-1.556

Hexanophenone	0.790	1.026	0.000	0.503	1.578	0.009	0.002	-2.037
Indole	1.018	1.184	0.390	0.240	0.946	0.225	0.006	-0.648
Iodobenzene	1.182	0.784	0.000	0.135	0.975	0.023	0.001	-1.638
Isocyanatopropyltri- ethoxysilane	-0.049	0.642	0.000	0.823	2.012	0.003	0.000	-2.524
Methacryloxypropyltri- methoxysilane	0.046	0.869	0.000	1.024	1.971	0.005	0.005	-2.297
2-Methoxynaphthalene	1.449	1.140	0.000	0.359	1.285	0.010	0.001	-1.986
Methyl benzoate	0.738	0.923	0.000	0.439	1.073	0.024	3.6E-04	-1.626
Methyl deconoate	0.057	0.564	0.000	0.456	1.733	0.003	0.004	-2.507
Methyl octanoate	0.069	0.564	0.000	0.456	1.451	0.007	0.003	-2.128
2-Methylnaphthalene	1.304	0.880	0.000	0.154	1.226	0.009	0.001	-2.042
Naphthalene	1.240	0.906	0.000	0.193	1.085	0.016	8.5E-05	-1.787
1-Naphthol	1.480	1.157	0.796	0.318	1.144	1.457	0.022	0.163
2-Naphthol	1.457	1.181	0.807	0.345	1.144	1.666	0.005	0.222
2-Nitroaniline	1.182	1.441	0.386	0.348	0.990	0.223	0.009	-0.651
3-Nitroaniline	1.248	1.602	0.466	0.415	0.990	0.313	0.002	-0.504
4-Nitroaniline	1.236	1.827	0.597	0.343	0.990	0.851	0.001	-0.070
Nitrobenzene	0.846	1.138	0.000	0.269	0.891	0.026	0.002	-1.578
4-Nitrobenzyl alcohol	1.003	1.333	0.499	0.591	1.090	1.088	0.002	0.037
1-Nitronaphthalene	1.367	1.505	0.000	0.272	1.257	0.017	0.001	-1.782
2-Nitrophenol	0.962	1.086	0.050	0.371	0.949	0.049	0.002	-1.312
2-Nitrotoluene	0.866	1.110	0.000	0.270	1.032	0.019	0.002	-1.720
3-Nitrotoluene	0.874	1.100	0.000	0.250	1.032	0.015	0.007	-1.816
4-Nitrotoluene	0.918	1.194	0.000	0.264	1.032	0.016	0.001	-1.796
Nonan-2-one	0.113	0.662	0.000	0.496	1.392	0.010	0.027	-1.998
Octanophenone	0.779	1.026	0.000	0.503	1.859	0.003	0.012	-2.543
Pentachlorophenol	1.577	1.051	0.625	0.021	1.387	0.267	0.005	-0.574
Phenanthrene	1.997	1.316	0.000	0.279	1.454	0.009	0.006	-2.069
Phenol	0.769	0.759	0.716	0.319	0.775	3.597	0.016	0.556
Phenyl acetate	0.648	1.055	0.000	0.521	1.073	0.023	0.002	-1.647
Phenyl benzoate	1.330	1.420	0.000	0.470	1.540	0.007	0.000	-2.177
1-Phenyl ethanol	0.823	0.825	0.350	0.653	1.057	0.560	0.011	-0.251
2-Phenyl ethanol	0.787	0.797	0.390	0.636	1.057	0.530	0.019	-0.276
Phenyl ether	1.216	0.912	0.000	0.267	1.383	0.007	0.031	-2.179
Phthalonitrile	0.755	1.942	0.000	0.360	1.026	0.037	0.001	-1.437
pyrene	2.165	1.518	0.000	0.261	1.585	0.007	2.0E-04	-2.132
Resorcinol	1.086	0.970	1.294	0.532	0.834	125.4	0.014	2.098
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.143	0.002	-0.843
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.154	0.017	-0.812
p-Toluidine	0.923	1.19	0.15	0.4	0.957	0.168	0.010	-0.775



1,2,4-Trichlorobenzene	1.022	0.75	0	0.02	1.084	0.012	0.002	-1.915
Tri-n-butyrin	0.128	1.22	0	1.49	2.445	0.006	0.003	-2.237
Valerophenone	0.795	1.03	0	0.5	1.437	0.008	0.001	-2.071
m-Xylene	0.625	0.51	0	0.18	0.998	0.014	2.4E-04	-1.848

### 2.3.3.1. n-Heptane-ethylene glycol biphasic system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.15 to the solvation parameter model for the n-heptane-ethylene glycol system gave

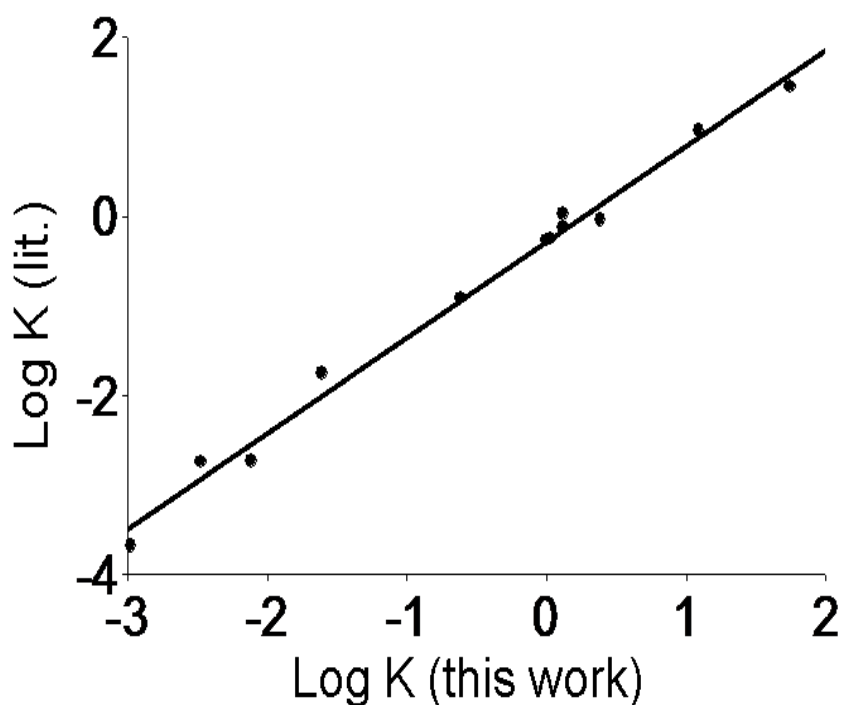
$$\log K_p = 0.302 (\pm 0.081) + 0.093 (\pm 0.046)E - 1.527 (\pm 0.062)S - 3.758 (\pm 0.056)A - 1.539 (\pm 0.087)B + 2.151 (\pm 0.063)V \quad (2.19)$$

$$r = 0.996 \quad r_{adj}^2 = 0.991 \quad SE = 0.136 \quad F = 1961 \quad n = 88$$

The driving force for transfer of solutes to the n-heptane layer is indicated by the system constants with positive coefficients, the  $v$  and  $e$  system constants. Since n-heptane is a solvent of low cohesion the large  $v$  coefficient suggests that ethylene glycol is a reasonably cohesive solvent. The positive  $e$  system constant is small and barely significant indicating that electron lone-pair interactions are weak for ethylene glycol. Polar interactions characterized by the  $s$ ,  $a$ , and  $b$  system constants favor transfer to the ethylene glycol layer. These values support the assertion that ethylene glycol is a reasonably dipolar/polarizable, strongly hydrogen-bond basic, and moderately hydrogen-bond acidic solvent.

There is good qualitative agreement with the model proposed by Abraham [9] for the n-heptane-ethylene glycol biphasic system as can be seen by comparing Eq. (2.18) and Eq. (2.19). Since different descriptors are used for the two models combining the two data sets and using the same family of descriptors should provide an optimum model. There are twelve experimental partition coefficients in common in the two data sets which can be used to determine whether the two sets of measured partition coefficients are chemically homogeneous. For the twelve

compounds with paired values the regression model is illustrated in Figure 2.3 and led to the following relationship.



**Fig. 2.3.** Plot of partition coefficients taken from [9] against those measured in this work showing a high level of correlation.

$$\log K_p(\text{this work}) = 0.265 (\pm 0.050) + 0.926 (\pm 0.029) \log K_p(\text{Abraham}) \quad (2.20)$$

$$r = 0.995 \quad r_{\text{adj}}^2 = 0.989 \quad \text{SE} = 0.152 \quad F = 1011 \quad n = 12$$

The two sets of experimental partition coefficients are highly correlated but not identical. The 95% confidence interval for the intercept, 0.152-0.377, does not include zero and a small constant difference between the two data sets exists. The 95% confidence interval for the slope, 0.861-0.991, just fails to include 1, suggesting a small chemical bias in the two datasets, but compared with the intercept the contribution to the difference in the two data sets is less important. A bias could arise from the difference in the experimental techniques used for either set of measurements. For the results in Table 2.15 (this work) an obvious source would be the value taken for the internal standard in Eq. (2.19). To test this hypothesis the partition coefficient

for 5-chloro-2-nitroanisole, the internal standard for the n-heptane-ethylene glycol system, was determined by two additional methods. Calibration was used to determine the concentration of 5-chloro-2-nitroanisole in each layer independently by gas chromatography. In a second set of experiments the equilibrium concentration of 5-chloro-2-nitroanisole in each layer was determined by uv absorption spectroscopy. In each of the three experimental determinations the concentration of 5-chloro-2-nitroanisole was varied to ensure measurements were made in a concentration range where the partition coefficient was independent of concentration. The originally determined value for the partition coefficient for 5-chloro-2-nitroanisole,  $K_p = 0.766 \pm 0.001$  ( $n = 10$ ), compares favorably with the value obtained by gas chromatography using independent calibration of the equilibrated phases,  $K_p = 0.769 \pm 0.006$  ( $n = 10$ ), and the value obtained by uv absorption spectroscopy,  $K_p = 0.763 \pm 0.0002$  ( $n = 10$ ).

To accommodate the bias between the two data sets and too establish whether both data sets could be explained by a single model and indicator variable, I, was introduced into the solvation parameter model having a value of 0 for the data in Table 2.15 and 1 for the data taken from [9] for which optimized descriptor values were available. This provided the model

$$\log K_p = 0.358 (\pm 0.073) + 0.093 (\pm 0.043)E - 1.553 (\pm 0.058)S - 3.781 (\pm 0.049)A - 1.548 (\pm 0.078)B + 2.133 (\pm 0.054)V - 0.177 (\pm 0.037)I \quad (2.21)$$

$$r = 0.996 \quad r_{adj}^2 = 0.992 \quad SE = 0.130 \quad F = 2236 \quad n = 109$$

which statistically is just as good as Eq. (2.19) and has similar system constants. Also either Eq. (2.19) or Eq. (2.21) can explain both sets of partition coefficients if different intercept terms,  $c$  constants, are used. To fit Eq. (2.21) to the combined data set three values were removed from the Abraham data set. These are pyridine (experimental = -1.070 compared with the value predicted by Eq. (2.21) = -0.452), acetanilide (experimental = -2.74 and predicted by Eq. (2.21)

= -2.26), and benzamide (experimental = -3.69 and predicted by Eq. (2.21) = -3.19). Only pyridine is a true outlier to the model with acetanilide and benzamide as extreme values which can be retained or removed with only a minor effect on the model. Benzamide and acetanilide, however, are two of the compounds used in the regression model, Eq. (2.20) and Figure 2.3, explaining the small difference in chemical interactions (slope  $\neq 1$  at the 95% confidence level) between the two data sets. No further method of data analysis can uncover the reason for the small bias in the two sets of partition coefficients but the chemical reasons for the distribution of varied compounds between the n-heptane and ethylene glycol phases is adequately described by the system constants of Eq. (2.19) and Eq. (2.21).

To evaluate the predictive ability of the model the data set in Table 2.15 was split into a training set of 61 compounds and a test set of 27 compounds using the Kennard-Stone algorithm.

The model for the training set, Eq (2.22), is similar to Eq. (2.19). Equation (2.22) was then used

$$\log K_p = 0.367 (\pm 0.096) + 0.114 (\pm 0.052)E - 1.554 (\pm 0.067)S - 3.743 (\pm 0.068)A - 1.448 (\pm 0.092)B + 2.077 (\pm 0.071)V \quad (2.22)$$

$$r = 0.996 \quad r_{adj}^2 = 0.992 \quad SE = 0.135 \quad F = 1476 \quad n = 61$$

to predict the partition coefficients ( $\log K_p$ ) for the compounds in the test set. The average error is an indication of bias and at 0.055 is not a concern for Eq. (2.22). The absolute average error (0.095) and root mean square error (0.134) are an indication of the likely error in predicting further partition coefficients based on Eq. (2.22). Since Eq. (2.22) is similar to Eq. (2.19), which is preferred because it is based on a larger number of compounds, it is reasonable to conclude that Eq. (2.19) should be able to predict partition coefficients to about  $\pm 0.13$  log units for further compounds with known descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.3.2. Isopentyl ether-ethylene glycol biphasic system

Fitting the partition coefficients ( $\log K_p$ ) for the isopentyl ether-ethylene glycol system in Table 2.16 to the solvation parameter model gave

$$\log K_p = 0.419 (\pm 0.076) - 0.090 (\pm 0.045)E - 1.159 (\pm 0.065)S - 1.530 (\pm 0.053)A - 1.901 (\pm 0.084)B + 2.089 (\pm 0.061)V \quad (2.23)$$

$$r = 0.991 \quad r_{adj}^2 = 0.982 \quad SE = 0.133 \quad F = 960 \quad n = 89$$

The high cohesion of the ethylene glycol layer favors the transfer of solutes to the isopentyl ether layer (positive  $\nu$  system constant) while polar interactions have a negative sign ( $s$ ,  $a$  and  $b$ ) and favor solubility in the ethylene glycol layer. Electron lone-pair interactions favor transfer to the ethylene glycol layer but the  $e$  system constant is small and relatively unimportant. Isopentyl ether is more dipolar/polarizable and hydrogen-bond basic than n-heptane and this is reflected in the smaller values for the  $s$  and  $a$  system constants compared with the n-heptane-ethylene glycol system. Isopentyl ether and n-heptane are weakly cohesive solvents and this is reflected in the similar  $\nu$  system constants for the two partition systems. The Kennard-Stone algorithm was used to split the data set into a training set of 62 compounds and a test set of 27 compounds. The model for the training set is given below and is quite similar to Eq. (2.23). For the test set the

$$\log K_p = 0.302 (\pm 0.095) - 0.080 (\pm 0.051)E - 1.114 (\pm 0.074)S - 1.550 (\pm 0.064)A - 1.914 (\pm 0.092)B + 2.138 (\pm 0.070)V \quad (2.24)$$

$$r = 0.992 \quad r_{adj}^2 = 0.984 \quad SE = 0.136 \quad F = 732 \quad n = 62$$

average error was 0.018, the average absolute error 0.110 and the root mean square error 0.138. Thus, Eq. (2.23) should be able to predict further values of the partition coefficients to about  $\pm 0.14$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.3.3 Ethylene glycol-1,2-dichloroethane biphasic system

Fitting the partition coefficients in Table 2.17 to the solvation parameter model gave

$$\log K_p = -0.639 (\pm 0.065) + 0.096 (\pm 0.029)E + 2.468 (\pm 0.048)A + 0.991 (\pm 0.065)B - 1.307 (\pm 0.053)V \quad (2.25)$$

$$r = 0.992 \quad r_{adj}^2 = 0.983 \quad SE = 0.120 \quad F = 1343 \quad n = 93$$

On account of the higher density of 1,2-dichloroethane the ethylene glycol layer is the upper phase in this system. The driving force for transfer to the 1,2-dichloroethane layer is the relatively high cohesion of the ethylene glycol layer (negative  $v$  system constant). Hydrogen-bonding interactions favor transfer to the ethylene glycol layer. Interactions of a dipole-type are equal in both phases ( $s = 0$ ) and do not contribute to the distribution mechanism. This is a useful property since selectivity for solutes of similar size is governed almost entirely by their capacity for hydrogen-bonding interactions. Electron lone-pair interactions are small and of little importance in the partitioning mechanism. As before, the Kennard-Stone algorithm was used to split the data set into a training set of 65 compounds and a test set of 28 compounds. The model for the training set is given below

$$\log K_p = -0.649 (\pm 0.084) + 0.078 (\pm 0.036)E + 2.507 (\pm 0.062)A + 0.935 (\pm 0.075)B - 1.271 (\pm 0.066)V \quad (2.26)$$

$$r = 0.991 \quad r_{adj}^2 = 0.982 \quad SE = 0.129 \quad F = 861 \quad n = 65$$

and is quite similar to Eq. (2.25). For the test set the average error was 0.010, the average absolute error 0.097 and the root mean square error 0.098. Thus, Eq. (2.25) should be able to predict further values of the partition coefficients to about  $\pm 0.10$  log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

### 2.3.3.4 General extraction properties of organic solvent-ethylene glycol systems

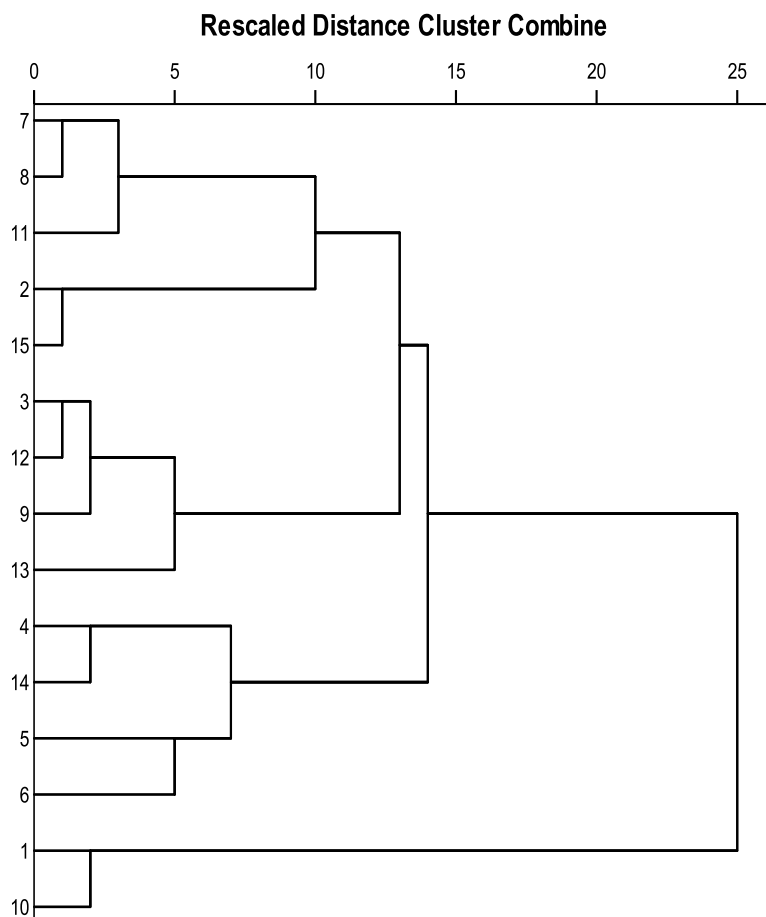
Hierarchical cluster analysis using the average linkage between groups agglomeration algorithm and the system constants as variables was used to compare the extraction properties of the totally organic biphasic systems, Table 2.18 [15,26,39,56,57].

**Table 2.18.** System constants for totally organic biphasic partition systems.

Partition system	System constants				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
n-Heptane-formamide	0.561	-2.248	-3.25	-1.603	2.384
Formamide-1,2-dichloroethane	0.082	-0.399	-1.957	-1.298	1.705
1-Octanol-formamide	0.267	-1.053	-0.333	-0.929	1.314
Isopentyl ether-formamide	0.564	-1.715	-1.314	-1.407	2.005
n-Heptane-2,2,2-trifluoroethanol	0.882	-1.557	-1.312	-2.928	1.301
n-Heptane-Hexafluoroisopropanol	1.03	-1.712	-0.669	-1.746	1.121
n-Heptane- <i>N,N</i> -dimethylformamide	0.038	-1.391	-2.16	-0.593	0.486
n-Hexane-acetonitrile	0.349	-1.439	-1.611	-0.874	0.669
n-Heptane-methanol	0.186	-0.686	-1.098	-0.951	0.618
n-Heptane-propylene carbonate	0.455	-2.087	-2.646	-0.433	0.807
Isopentyl ether-propylene carbonate	0.298	-1.432	-0.718	-0.472	0.729
1-Octanol-propylene carbonate	0.256	-1.068	0.222	0	0.365
n-Heptane-ethylene glycol	0.098	-1.553	-3.781	-1.548	2.133
Ethylene glycol-1,2-dichloroethane	-0.096	0	-2.46	-0.991	1.307
Isopentyl ether-ethylene glycol	-0.09	-1.159	-1.53	-1.901	2.089

The dendrogram, Figure 2.4, demonstrates that the 15 totally organic biphasic systems encompass a wide range of selectivity with little clustering. The nearest neighbors for the three ethylene glycol systems are the formamide systems with the same counter solvent. The individual system pairs are not identical but close in properties such that the difference in selectivity between the ethylene glycol and formamide systems is less than the difference in selectivity with the other solvent systems. Thus, formamide would be a suitable replacement for ethylene glycol with n-heptane, 1,2-dichloroethane, and isopentyl ether as counter solvents, and *vice versa*, for some applications. The dendrogram indicates five selectivity groups whose

membership is significantly different to their nearest neighbours. Group 1 contains n-heptane-formamide and n-heptane-ethylene glycol; Group 2 contains n-heptane-trifluoroethanol, n-heptane-hexafluoroisopropanol, isopentyl ether-ethylene glycol, and isopentyl ether-formamide.



**Fig.2.4.** Dendrogram from hierarchical cluster analysis using the average linkage between groups agglomeration algorithm for the totally organic biphasic systems. Identification: 1: n-heptane-formamide, 2: formamide-1,2-dichloroethane, 3: n-octanol-formamide, 4: isopentyl ether-formamide, 5: n-heptane-2,2,2-trifluoroethanol, 6: n-heptane-1,1,1,3,3,3-hexafluoroisopropanol, 7: n-heptane-N,Ndimethylformamide, 8: n-hexane-acetonitrile, 9: n-heptane-methanol, 10: n-heptane-ethylene glycol, 11: n-heptane-propylene carbonate, 12: isopentyl ether-propylene carbonate, 13: n-octanol-propylenecarbonate, 14: isopentyl ether-ethylene glycol, and 15: ethyleneglycol-1,2-dichloroethane.

Group 3 contains n-octanol-propylene carbonate, n-heptane-methanol, isopentyl ether-propylene carbonate, and octanol-formamide; Group 4 contains formamide-1,2-dichloroethane and ethylene



glycol-1,2-dichloroethane; and Group 5 contains n-heptane-propylene carbonate, n-hexane-acetonitrile, and n-heptane-*N,N*-dimethylformamide. Group 1 biphasic systems have the largest opposing contributions from cohesion (positive  $\nu$  system constant) and polar interaction (negative  $s$ ,  $a$ , and  $b$  system constants). Group 2 systems have intermediate values for the  $s$  and  $a$  system constants combined with the largest values for the  $b$  system constant with either high and opposing values for the  $\nu$  system constant (formamide and ethylene glycol systems) or moderate values (2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoroisopropanol systems). Group 3 systems are characterized by intermediate values for polar interactions (negative  $s$ ,  $a$ , and  $b$  system constants) with weak to intermediate values for the opposing contribution from cohesion (positive  $\nu$  system constant). The n-octanol-propylene carbonate system is only loosely connected with this group and could be considered as behaving independently. Group 4 systems are characterized by a high  $a/s$  system constants ratio, and intermediate  $b$  and  $\nu$  system constant values. They provide unique selectivity for the separation of hydrogen-bond acid compounds from dipolar/polarizable compounds. Group 5 systems are characterized by a high ratio of the  $a/b$  system constants, intermediate to large  $s$  system constants and weak cohesion (small value for the  $\nu$  system constant) as a driving force opposing the polar interactions. A useful feature of the totally organic biphasic systems is that within the selectivity space defined by the system constants, Table 2.18, they afford reasonable coverage and allow some flexibility in the identification of suitable systems for separations.

#### **2.3.4. Models for dimethyl sulfoxide-organic solvent partition system**

Dimethyl sulfoxide has found many applications in synthesis, spectroscopy, and chemical engineering applications as a polar, non-hydrogen-bond acid solvent [72]. Over time it has become the *de facto* solvent of choice for solubilizing compounds for high throughput screening in the pharmaceutical industry on account of its ability to dissolve a wide range of chemical

types, low volatility, relatively low toxicity, miscibility with water, and limited deleterious effects at low concentrations in bioassays [73,74]. Spectroscopic analysis of solvatochromic indicator compounds suggests that dimethyl sulfoxide is of intermediate polarity (Reichardt's dye  $E_T^N = 0.444$ ) with significant dipolarity/polarizability and hydrogen-bond basicity but no hydrogen-bond acidity (Kamlet-Taft solvatochromic parameters  $\pi^* = 1.00$ ,  $\beta = 0.76$ , and  $\alpha = 0$ ) [72,75]. The biphasic system n-pentane-dimethyl sulfoxide has been widely used for the isolation of polycyclic aromatic compounds from complex matrices prior to chromatographic analysis [76-78]. Berthod et al. used dimethyl sulfoxide as a stationary phase for the separation of aromatic compounds by nonaqueous countercurrent chromatography with n-heptane as a mobile phase [79]. These authors also determined the mutual solubility of n-heptane in dimethyl sulfoxide (1.6 mol % or 11 g/L) and dimethyl sulfoxide in n-heptane (0.2 mol % or 2.2 g/L) as well as several partition coefficients for alkylbenzenes and polycyclic aromatic hydrocarbons. Geiser et al. employed dimethyl sulfoxide alone and solvent mixtures containing dimethyl sulfoxide for separations using nonaqueous capillary electrophoresis [80].

Although generally considered to be a non-hydrogen-bond acidic solvent Leggett used an indirect method to calculate the Kamlet-Taft  $\alpha$  value for dimethyl sulfoxide suggesting a value of 0.25, typical of a weak hydrogen-bond acid [81]. Using molecular dynamics Vaisman demonstrated the presence of weak C-H $\cdots$ O hydrogen bonds in water-dimethyl sulfoxide mixtures [82]. These observations were supported by more detailed computational studies of the water-dimethyl sulfoxide and methanol-dimethyl sulfoxide systems and confirmed by NMR and IR spectroscopic measurements [83,84]. Although most authors have attempted to explain the solvent properties of dimethyl sulfoxide with models that assume it to be a non-hydrogen-bond acid the above reports are of particularly interest since it was found necessary to conclude that

dimethyl sulfoxide is a weak hydrogen-bond acid solvent to explain the observed partitioning of hydrogen-bond bases for the two totally organic biphasic systems described here.

As in earlier studies, the general method used to characterize the contribution of intermolecular interactions to the partitioning of solutes in biphasic organic solvent systems is based on the solvation parameter model in which the partition coefficient for neutral compounds,  $\log K_p$ , is described by a series of product terms made up of descriptors (solute properties) and system constants (complementary solvent properties). The compounds used to characterize the dimethyl sulfoxide systems, their descriptor values and experimental partition coefficients are summarized in Tables 2.19 and 2.20.

**Table 2.19.** Compounds and their Partition coefficients and descriptor values used to characterize the n-heptane-dimethyl sulfoxide partition system.

Compound	Solute descriptors					Partition coefficient		
	E	S	A	B	V	$K_p$	SD	$\log K_p$
Acenaphthylene	1.54	1.122	0	0.21	1.216	0.392	0.006	-0.407
Acetanilide	0.96	1.135	0.543	0.71	1.114	8.0E-4	8.0E-5	-3.076
Acetophenone	0.806	1.026	0	0.503	1.014	0.149	0.009	-0.827
Aniline	0.955	1.003	0.249	0.425	0.816	0.023	0.009	-1.646
Anisole	0.712	0.768	0	0.311	0.916	0.481	0.036	-0.318
Anthracene	1.942	1.301	0	0.26	1.454	0.347	0.024	-0.46
Benzaldehyde	0.813	1.025	0	0.394	0.873	0.127	1.2E-4	-0.898
Benzamide	1.26	1.325	0.684	0.663	0.973	1.2E-4	2.6E-5	-3.918
Benzensulfonamide	1.176	1.845	0.675	0.684	1.097	8.0E-5	2.0E-5	-4.119
1,4-Benzodioxan	0.884	1.06	0	0.296	1.007	0.148	0.001	-0.829
Benzonitrile	0.742	1.135	0	0.331	0.871	0.106	0.003	-0.974
Benzophenone	1.224	1.33	0	0.576	1.481	0.167	0.005	-0.778
Benzyl alcohol	0.803	0.882	0.4	0.557	0.916	0.007	6.9E-4	-2.186
Benzyl benzoate	1.248	1.304	0	0.584	1.68	0.216	0.007	-0.665
Biphenyl	1.319	0.952	0	0.279	1.324	0.669	0.008	-0.175
1-Bromohexane	0.349	0.4	0	0.12	1.13	6.135	0.501	0.788
1-Bromooctane	0.339	0.4	0	0.12	1.411	15.007	0.33	1.176
3-Bromophenol	1.081	0.777	0.931	0.208	0.95	2.1E-3	8.5E-5	-2.671
4-Bromophenol	1.08	1.17	0.67	0.2	0.95	1.1E-3	1.9E-4	-2.954
n-Butyl benzoate	0.668	0.845	0	0.401	1.495	1.704	0.075	0.232

Caffeine	1.606	1.705	0.055	1.245	1.363	2.8E-3	2.8E-4	-2.55
Carbazole	2.05	1.555	0.394	0.221	1.315	2.2E-3	1.5E-4	-2.66
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.038	3.6E-3	1.2E-4	-2.444
1-Chloronaphthalene	1.41	0.939	0	0.138	1.208	0.816	0.022	-0.088
4-Chlorophenol	1.015	0.793	0.871	0.208	0.898	2.4E-3	1.5E-4	-2.619
Cinnamyl alcohol	1.081	0.987	0.481	0.594	1.155	5.7E-3	1.5E-4	-2.243
Coumarin	1.292	1.623	0	0.522	1.062	0.012	0.001	-1.935
m-Cresol	0.81	0.779	0.672	0.351	0.916	3.0E-3	1.2E-4	-2.525
o-Cresol	0.774	0.745	0.621	0.357	0.916	5.6E-3	2.0E-4	-2.256
Dibenzofuran	1.594	1.096	0	0.114	1.209	0.445	0.008	-0.352
Dibenzylamine	1.34	1.015	0.095	0.987	1.706	0.267	0.01	-0.574
3,4-Dichloroaniline	1.368	1.275	0.415	0.24	1.061	0.006	4.0E-5	-2.251
Diethyl phthalate	0.729	1.418	0	0.883	1.711	0.091	0.003	-1.043
Dimethyl phthalate	0.78	1.41	0	0.88	1.429	0.028	0.001	-1.557
2,6-Dimethylphenol	0.784	0.795	0.404	0.404	1.057	0.018	0.003	-1.756
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	4.8E-3	2.3E-4	-2.317
1,3-Dinitrobenzene	1.088	1.76	0	0.413	1.065	6.0E-3	1.1E-4	-2.225
Dodecane	0	0	0	0	1.799	508.75	0.152	2.707
Ethyl benzoate	0.694	0.89	0	0.45	1.214	0.672	0.031	-0.173
Fluoranthene	2.305	1.482	0	0.277	1.585	0.208	0.008	-0.683
Fluorene	1.67	1.104	0	0.257	1.357	0.57	0.012	-0.244
3-Glycidoxypropyl trimethoxysilane	0.067	1.105	0	0.987	1.807	0.217	0.093	-0.665
Hexanophenone	0.79	1.026	0	0.503	1.578	1.006	0.022	0.002
Iodobenzene	1.182	0.784	0	0.135	0.975	0.745	0.003	-0.128
Isocyanatopropyl- triethoxysilane	-0.05	0.652	0	0.833	2.012	2.339	0.121	0.369
Methacryloxypropyl- trimethoxysilane	0.046	0.871	0	1.014	1.971	0.784	0.026	-0.106
2-Methoxynaphthalene	1.45	1.147	0	0.356	1.285	0.258	0.001	-0.588
Methyl benzoate	0.738	0.923	0	0.439	1.073	0.4	0.013	-0.398
Methyl deconoate	0.057	0.564	0	0.456	1.733	11.519	0.469	1.061
Methyl octanoate	0.069	0.564	0	0.456	1.451	4.501	0.89	0.653
1-Methylnaphthalene	1.337	0.909	0	0.201	1.226	1.003	0.034	0.001
2-Methylnaphthalene	1.304	0.895	0	0.189	1.226	1.049	0.024	0.021
N,N-Dimethylaniline	0.956	0.824	0	0.368	1.098	0.863	0.029	-0.064
Naphthalene	1.236	0.902	0	0.193	1.085	0.658	0.02	-0.182
1-Naphthol	1.442	1.127	0.757	0.329	1.144	6.0E-4	3.2E-5	-3.204
2-Naphthol	1.461	1.188	0.785	0.345	1.144	1.1E-3	9.8E-5	-2.977
2-Nitroaniline	1.214	1.458	0.352	0.354	0.99	1.5E-3	3.3E-5	-2.817
3-Nitroaniline	1.286	1.66	0.412	0.415	0.99	1.2E-3	9.1E-5	-2.922

4-Nitroaniline	1.223	1.826	0.603	0.341	0.99	2.0E-4	7.2E-5	-3.8
Nitrobenzene	0.846	1.138	0	0.269	0.891	0.096	0.001	-1.017
4-Nitrobenzyl alcohol	0.996	1.289	0.491	0.602	1.09	2.4E-3	1.8E-4	-2.629
1-Nitronaphthalene	1.387	1.476	0	0.29	1.26	0.063	0.003	-1.204
1-Nitrohexane	0.209	0.927	0.047	0.269	1.128	0.546	0.04	-0.263
2-Nitropropane	0.215	0.892	0.016	0.328	0.706	0.178	0.012	-0.751
2-Nitrotoluene	0.866	1.11	0	0.27	1.032	0.159	2.4E-4	-0.799
3-Nitrotoluene	0.874	1.1	0	0.25	1.032	0.179	0.005	-0.746
4-Nitrotoluene	0.898	1.181	0	0.265	1.032	0.163	0.007	-0.787
Nonan-2-one	0.113	0.662	0	0.496	1.392	2.126	0.081	0.328
Octadecane	0	0	0	0	2.645	1905	2.04	3.28
Octan-1-ol	0.199	0.44	0.344	0.52	1.295	0.114	0.051	-0.943
Octan-2-ol	0.176	0.436	0.255	0.496	1.295	0.309	0.104	-0.511
Octanophenone	0.779	0.992	0	0.5	1.859	2.443	0.072	0.388
n-Octyltriethoxysilane	-0.26	-0.05	0	0.975	2.503	136.15	0.86	2.134
Pentachlorophenol	1.689	1.026	0.633	0.065	1.387	9.2E-3	3.9E-4	-2.035
Phenanthrene	1.996	1.312	0	0.28	1.454	0.311	0.013	-0.508
Phenyl acetate	0.648	1.051	0	0.522	1.073	0.11	0.007	-0.959
Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.159	0.004	-0.798
1-Phenyl ethanol	0.823	0.77	0.408	0.671	1.057	0.01	5.8E-4	-1.997
2-Phenyl ethanol	0.787	0.814	0.411	0.63	1.057	0.01	0.002	-1.99
Phenyl ether	1.216	0.912	0	0.267	1.383	0.662	0.006	-0.179
4-Phenylphenol	1.524	1.22	0.794	0.44	1.383	6.0E-4	7.3E-6	-3.191
Phthalimide	1.179	1.681	0.263	0.585	1.021	9.0E-4	1.3E-5	-3.059
Phthalonitrile	0.729	1.942	0	0.387	1.026	2.3E-3	6.6E-4	-2.641
Pyrene	2.3	1.475	0	0.286	1.585	0.269	0.013	-0.57
Quinoline	1.268	1.09	0	0.562	1.044	0.171	0.002	-0.768
1,2,4,5-Tetrachlorobenzene	0.975	0.714	0	0	1.206	2.566	0.004	0.409
Tetradecane	0	0	0	0	2.081	1045.9	1.375	3.02
Tetrakis(trimethylsiloxy)-silane	-0.99	-0.16	0	0.664	3.263	2092.7	1.402	3.321
2,4,6,8-Tetramethyl-2,4,6,8-tetraynecyclotetrasiloxane	-0.1	0.215	0	0.67	2.736	183.36	0.0655	2.263
p-Tolualdehyde	0.862	1	0	0.42	1.014	0.142	0.063	-0.849
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.013	2.3E-4	-1.886
p-Toluidine	0.923	1.192	0.147	0.396	0.957	0.014	0.007	-1.848
1,2,4-Trichlorobenzene	1.022	0.738	0	0.029	1.084	1.774	0.076	0.249
Tri-n-butyrin	0.064	1.189	0	1.456	2.445	0.362	0.018	-0.442
Undecane	0	0	0	0	1.659	146.18	0.9641	2.165
Valerophenone	0.795	0.984	0	0.513	1.437	0.6874	0.002	-0.163

**Table 2.20.** Compounds and their Partition coefficients and descriptor values used to characterize the isopentyl ether-dimethyl sulfoxide partition system.

Compound	Solute descriptors					Partition coefficient		
	E	S	A	B	V	K <sub>p</sub>	SD	log K <sub>p</sub>
Acenaphthylene	1.54	1.122	0	0.21	1.216	0.494	0.002	-0.306
Acetanilide	0.96	1.135	0.543	0.71	1.114	0.012	0.002	-1.912
Acetophenone	0.806	1.026	0	0.503	1.014	0.258	0.02	-0.589
Anisole	0.712	0.768	0	0.311	0.916	0.758	0.018	-0.121
Anthracene	1.942	1.301	0	0.26	1.454	0.433	0.02	-0.364
Benzensulfonamide	1.176	1.845	0.675	0.684	1.097	5.1E-4	2.8E-5	-3.294
1,4-Benzodioxan	0.884	1.06	0	0.296	1.007	0.268	0.005	-0.572
Benzonitrile	0.742	1.135	0	0.331	0.871	0.074	0.007	-1.132
Benzophenone	1.224	1.33	0	0.576	1.481	0.289	0.005	-0.539
Benzyl alcohol	0.803	0.882	0.4	0.557	0.916	0.028	0.001	-1.56
Benzyl benzoate	1.248	1.304	0	0.584	1.68	0.347	0.01	-0.459
Biphenyl	1.319	0.952	0	0.279	1.324	0.795	0.006	-0.1
1-Bromohexane	0.349	0.4	0	0.12	1.13	5.49	0.566	0.74
1-Bromooctane	0.339	0.4	0	0.12	1.411	12.439	0.146	1.095
4-Bromophenol	1.08	1.17	0.67	0.2	0.95	0.011	3.7E-4	-1.957
n-Butyl benzoate	0.668	0.845	0	0.401	1.495	1.836	0.026	0.264
Caffeine	1.606	1.705	0.055	1.245	1.363	0.012	0.004	-1.903
Carbazole	2.05	1.555	0.394	0.221	1.315	0.021	0.001	-1.675
4-Chloro-3-methylphenol	0.92	1.02	0.65	0.23	1.038	0.025	0.002	-1.604
2-Chloroaniline	1.026	0.997	0.237	0.317	0.939	0.063	0.002	-1.198
4-Chloroaniline	1.006	1.169	0.345	0.308	0.939	0.014	2.7E-4	-1.86
1-Chloronaphthalene	1.41	0.939	0	0.138	1.208	0.921	0.019	-0.036
4-Chlorophenol	1.015	0.793	0.871	0.208	0.898	8.6E-3	1.8E-3	-2.066
Cinnamyl alcohol	1.081	0.987	0.481	0.594	1.155	0.016	4.4E-4	-1.785
Coumarin	1.292	1.623	0	0.522	1.062	0.031	8.4E-4	-1.506
m-Cresol	0.81	0.779	0.672	0.351	0.916	0.017	4.6E-4	-1.762
o-Cresol	0.774	0.745	0.621	0.357	0.916	0.027	0.009	-1.571
p-Cresol	0.793	0.769	0.664	0.353	0.916	0.019	0.062	-1.723
Dibenzofuran	1.594	1.096	0	0.114	1.209	0.639	0.04	-0.194
Dibenzylamine	1.34	1.015	0.095	0.987	1.706	0.425	0.001	-0.372
3,4-Dichloroaniline	1.368	1.275	0.415	0.24	1.061	0.013	0.001	-1.872
Diethyl phthalate	0.729	1.418	0	0.883	1.711	0.188	0.004	-0.727
Dimethyl phthalate	0.78	1.41	0	0.88	1.429	0.068	0.002	-1.167
2,6-Dimethylphenol	0.784	0.795	0.404	0.404	1.057	0.059	0.003	-1.232
3,5-Dimethylphenol	0.768	0.764	0.669	0.347	1.057	0.036	0.002	-1.441
1,3-Dinitrobenzene	1.088	1.76	0	0.413	1.065	0.019	0.001	-1.715

Diphenylamine	1.583	1.277	0.17	0.495	1.424	0.104	0.002	-0.982
Dodecane	0	0	0	0	1.799	200.49	55.966	2.302
Ethyl benzoate	0.694	0.89	0	0.45	1.214	0.664	0.059	-0.178
Fluoranthene	2.305	1.482	0	0.277	1.585	0.309	0.019	-0.51
Fluorene	1.67	1.104	0	0.257	1.357	0.646	0.009	-0.19
3-Glycidoxypropyl- trimethoxysilane	0.067	1.105	0	0.987	1.807	0.269	0.012	-0.571
Hexanophenone	0.79	1.026	0	0.503	1.578	1.264	0.017	0.102
Indole	1.028	1.202	0.394	0.236	0.946	0.017	0.001	-1.775
Iodobenzene	1.182	0.784	0	0.135	0.975	0.84	0.052	-0.076
Isocyanatopropyltriethoxy- silane	-0.05	0.652	0	0.833	2.012	3.131	0.274	0.496
Methacryloxypropyl- trimethoxysilane	0.046	0.871	0	1.014	1.971	1.056	0.036	0.024
2-Methoxynaphthalene	1.45	1.147	0	0.356	1.285	0.356	0.003	-0.448
Methyl benzoate	0.738	0.923	0	0.439	1.073	0.388	0.165	-0.411
Methyl deconoate	0.057	0.564	0	0.456	1.733	10.311	0.709	1.013
Methyl octanoate	0.069	0.564	0	0.456	1.451	4.591	0.224	0.662
1-Methylnaphthalene	1.337	0.909	0	0.201	1.226	1.036	0.032	0.015
2-Methylnaphthalene	1.304	0.895	0	0.189	1.226	1.104	0.023	0.043
N,N-Dimethylaniline	0.956	0.824	0	0.368	1.098	0.882	0.039	-0.054
Naphthalene	1.236	0.902	0	0.193	1.085	0.655	0.028	-0.184
1-Naphthol	1.442	1.127	0.757	0.329	1.144	0.012	8.0E-4	-1.93
2-Naphthol	1.461	1.188	0.785	0.345	1.144	6.3E-3	4.3E-4	-2.204
2-Nitroaniline	1.214	1.458	0.352	0.354	0.99	8.7E-3	0.013	-2.062
3-Nitroaniline	1.286	1.66	0.412	0.415	0.99	3.5E-3	2.5E-5	-2.454
4-Nitroaniline	1.223	1.826	0.603	0.341	0.99	7.4E-4	0	-3.129
Nitrobenzene	0.846	1.138	0	0.269	0.891	0.202	0.006	-0.694
4-Nitrobenzyl alcohol	0.98	1.362	0.547	0.571	1.09	3.1E-3	5.0E-4	-2.515
1-Nitronaphthalene	1.387	1.476	0	0.29	1.26	0.139	0.002	-0.857
2-Nitropropane	0.215	0.892	0.016	0.328	0.706	0.287	0.008	-0.542
2-Nitrotoluene	0.866	1.11	0	0.27	1.032	0.289	0.018	-0.539
3-Nitrotoluene	0.874	1.1	0	0.25	1.032	0.294	0.017	-0.531
4-Nitrotoluene	0.898	1.181	0	0.265	1.032	0.305	0.002	-0.516
Nonan-2-one	0.113	0.662	0	0.496	1.392	2.767	0.171	0.442
Octan-1-ol	0.199	0.44	0.344	0.52	1.295	0.547	0.047	-0.262
Octanophenone	0.779	0.992	0	0.5	1.859	2.753	0.153	0.44
n-Octyltriethoxysilane	-0.26	-0.05	0	0.975	2.503	92.3	0.813	1.965
Pentachlorophenol	1.689	1.026	0.633	0.065	1.387	0.074	0.008	-1.129
Phenanthrene	1.996	1.312	0	0.28	1.454	0.371	0.011	-0.431
Phenyl acetate	0.648	1.051	0	0.522	1.073	0.171	0.099	-0.767

Phenyl benzoate	1.33	1.42	0	0.47	1.54	0.254	4.8E-4	-0.595
1-Phenyl ethanol	0.823	0.77	0.408	0.671	1.057	0.045	0.012	-1.348
2-Phenyl ethanol	0.787	0.814	0.411	0.63	1.057	0.036	0.008	-1.439
Phenyl ether	1.216	0.912	0	0.267	1.383	0.798	0.006	-0.098
2-Phenylacetamide	0.95	1.587	0.517	0.771	1.114	1.4E-3	9.7E-4	-2.845
4-Phenylphenol	1.524	1.22	0.794	0.44	1.383	6.9E-3	4.0E-5	-2.16
Phthalimide	1.227	1.688	0.284	0.581	1.021	2.5E-3	8.2E-5	-2.606
Phthalonitrile	0.729	1.942	0	0.387	1.026	0.016	0.004	-1.786
Pyrene	2.3	1.475	0	0.286	1.585	0.356	0.029	-0.448
1,2,4,5-Tetrachlorobenzene	0.975	0.714	0	0	1.206	2.458	0.042	0.391
Tetradecane	0	0	0	0	2.081	331.82	0.114	2.521
Tetrakis(trimethylsiloxy)-silane	-0.99	-0.13	0	0.682	3.263	1159.3	1.564	3.064
2,4,6,8-Tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane	-0.1	0.215	0	0.67	2.736	166	0.508	2.22
Thiophene	0.687	0.56	0	0.15	0.641	0.667	0.023	-0.176
p-Tolualdehyde	0.862	1	0	0.42	1.014	0.257	0.088	-0.591
Toluene	0.606	0.499	0	0.139	0.857	2.446	0.186	0.388
m-Toluidine	0.946	1.128	0.112	0.516	0.957	0.065	0.034	-1.187
o-Toluidine	0.966	1.045	0.193	0.491	0.957	0.039	0.001	-1.414
p-Toluidine	0.923	1.192	0.147	0.396	0.957	0.031	0.0051	-1.502
1,2,4-Trichlorobenzene	1.022	0.738	0	0.029	1.084	1.693	0.045	0.229
Tri-n-butyrin	0.064	1.189	0	1.456	2.445	0.576	0.037	-0.24
Undecane	0	0	0	0	1.659	89.475	0.662	1.952
Valerophenone	0.795	0.984	0	0.513	1.437	0.906	0.009	-0.043

### 2.2.4.1 n-Heptane-dimethyl sulfoxide partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.19 to the solvation parameter model gave

$$\log K_p = 0.269 (\pm 0.100) + 0.055 (\pm 0.050)E - 1.775 (\pm 0.075)S - 3.096 (\pm 0.070)A - 1.126 (\pm 0.090)B + 1.185 (\pm 0.054)V \quad (2.27)$$

$$r = 0.994 \quad r_{adj}^2 = 0.988 \quad SE = 0.172 \quad F = 1562 \quad n = 97.$$

The e system constant is not statistically significant and difference in electron lone pair interactions in the two phases makes no contribution to the partition process. Setting the e system



constant to zero (or using the stepwise entry criteria) results in the preferred model

$$\log K_p = 0.272 (\pm 0.100) - 1.715 (\pm 0.052)S - 3.085 (\pm 0.070)A - 1.177 (\pm 0.077)B + 1.191 (\pm 0.054)V \quad (2.28)$$

$$r = 0.994 \quad r_{\text{adj}}^2 = 0.988 \quad SE = 0.172 \quad F = 1948 \quad n = 97$$

The driving force for transfer of solutes to the n-heptane layer is indicated by the system constants with positive coefficients, in this case the  $v$  system constant only. Since n-heptane is a weak cohesive solvent the small  $v$  coefficient indicates that dimethyl sulfoxide is no more than a moderately cohesive solvent. Polar interactions characterized by the  $s$ ,  $a$ , and  $b$  system constants favor transfer to the dimethyl sulfoxide layer from which we can infer that dimethyl sulfoxide is reasonably dipolar/polarizable, strongly hydrogen-bond basic and weakly hydrogen-bond acidic. Dimethyl sulfoxide is generally regarded to be a non-hydrogen-bond acid solvent, although recent spectroscopic studies and theoretical calculations suggest some weak hydrogen-bond acidity [81-84].

To evaluate the predictive ability of the model the data set was split into a training set of 67 compounds and a test set of 30 compounds using the Kennard-Stone algorithm. The model for the training set, Eq (2.29), is similar to Eq. (2.28). Equation (2.29) was then used to predict the

$$\log K_p = 0.440 (\pm 0.145) - 1.794 (\pm 0.070)S - 3.256 (\pm 0.102)A - 1.100 (\pm 0.102)B + 1.104 (\pm 0.074)V \quad (2.29)$$

$$r = 0.993 \quad r_{\text{adj}}^2 = 0.986 \quad SE = 0.207 \quad F = 1172 \quad n = 67$$

partition coefficients ( $\log K_p$ ) for the compounds in the test set. The average error is an indication of bias and at 0.036 indicates that this is not a concern for Eq. (2.29). The absolute average error (0.171) and root mean square error (0.189) are an indication of the likely error in predicting further partition coefficients based on Eq. (2.29). Since Eq. (2.29) is similar to Eq. (2.28), which is preferred because it is based on a larger number of compounds, it is reasonable

to conclude that Eq. (2.28) should be able to predict partition coefficients to about  $\pm 0.18$  log units for further compounds with known descriptors that lie within or close to the descriptor space used to define the model.

#### 2.2.4.2 Effect of water on the n-heptane-dimethyl sulfoxide partition system

Table 2.21 summarizes the system constants for other totally organic biphasic solvent systems and n-heptane-water [15,26,39,56,57] facilitating a comparison of the hydrogen-bond acidity of dimethyl sulfoxide with other organic solvents and water with low solubility in n-heptane.

**Table 2.21.** System constants for totally organic biphasic partition systems.

System	System constants					
	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
Ethylene glycol-1,2-dichloroethane	-0.639	0.096	0	2.468	0.991	-1.307
Formamide-1,2-dichloroethane	-0.207	-0.082	0.399	1.957	1.298	-1.705
n-Heptane-ethylene glycol	0.358	0.093	-1.553	-3.781	-1.548	2.133
n-Heptane-N,N-dimethylformamide	0.255	0.038	-1.391	-2.16	-0.593	0.486
n-Heptane-dimethyl sulfoxide	0.289	0	-1.781	-3.088	-1.167	1.18
n-Heptane-formamide	0.083	0.559	-2.244	-3.25	-1.614	2.387
n-Heptane-hexafluoroisopropanol	-0.49	1.03	-1.712	-0.669	-1.746	1.121
n-Heptane-methanol	-0.158	0.186	-0.686	-1.098	-0.951	0.618
n-Heptane-propylene carbonate	0.502	0.455	-2.087	-2.646	-0.433	0.807
n-Heptane-trifluoroethanol	0.013	0.882	-1.557	-1.312	-2.928	1.301
n-Hexane-acetonitrile	0.152	0.349	-1.439	-1.611	-0.874	0.669
Isopentyl ether-dimethyl sulfoxide	0.154	0	-1.452	-2.153	-0.972	1.116
Isopentyl ether-ethylene glycol	0.419	-0.09	-1.159	-1.53	-1.901	2.089
Isopentyl ether-formamide	0.13	0.564	-1.715	-1.314	-1.407	2.005
Isopentyl ether-propylene carbonate	0.264	0.298	-1.432	-0.718	-0.472	0.729
Octan-1-ol-formamide	0.285	0.267	-1.053	-0.333	-0.929	1.314
Octan-1-ol-propylene carbonate	0.282	0.256	-1.068	-0.222	0	0.365

The *b* system constant for dimethyl sulfoxide is larger than the values for *N,N*-dimethylformamide, propylene carbonate, and acetonitrile (n-hexane as counter solvent). It is significantly larger than the value for methanol, although in this case the mutual solubility of

methanol in n-heptane, and *vice versa*, is quite high compared with the above solvent systems. Ethylene glycol, 3,3,3-trifluoroethanol, formamide and water are stronger hydrogen-bond acids than dimethyl sulfoxide, as would be expected. In the case of water, which is the strongest hydrogen-bond acid in Table 2.21, it is about one-quarter as strong. Compared with the other organic solvents dimethyl sulfoxide saturated with n-heptane is positioned near the middle range for these solvent systems in terms of their hydrogen-bond acidity.

Analysis of the dimethyl sulfoxide by gas chromatography with flame ionization detection failed to detect any organic impurities at a concentration greater than 0.1% (w/w), which might be considered sufficient to affect its solvation properties. The dimethyl sulfoxide used in this study is indicated to be 99.7% pure with the main contaminant water at < 0.2% (w/w). Since water is a strong hydrogen-bond acid the effect of water on the n-heptane-dimethyl sulfoxide partition system was investigated. At the end of the experiments the water level of the dimethyl sulfoxide was determined to be 0.25% (w/w) by Karl-Fisher titration, and had not been contaminated during laboratory operations due to its hygroscopicity. To ascertain what effect this concentration of water might have on the calculated hydrogen-bond acidity of the dimethyl sulfoxide the solvent was intentionally contaminated with a further 1% (v/v) water (corresponding to a total water concentration of about 1.17% w/w). This solvent was then used to determine the partition coefficients for a representative group of compounds covering the same descriptor space as the original data set (determined using the Kennard-Stone method). The compounds and their partition coefficients calculated using original DMSO solvent ( $K_p$ ), dried DMSO solvent ( $K_{Dry}$ ), and intentionally contaminated DMSO solvent ( $K_{ds+1\%}$ ) are indicated in Table 2.22.

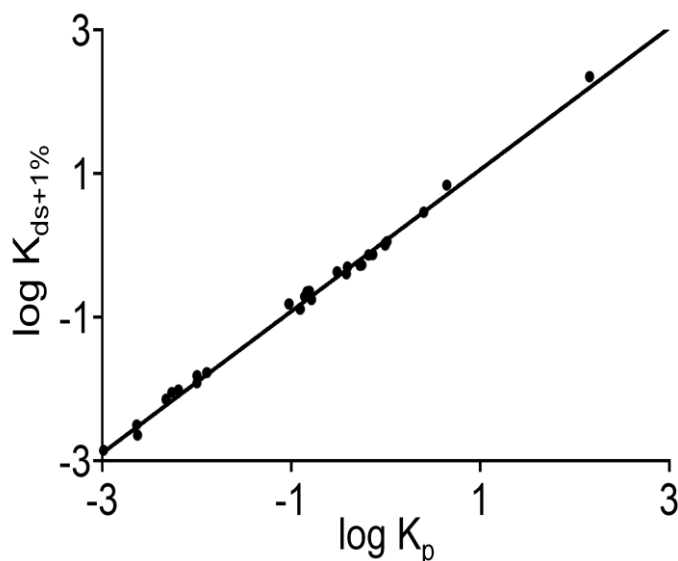
**Table 2.22.** Partition coefficients (n-heptane-DMSO system) for a sub set of compounds determined using three different DMSO solvents

Compound	K <sub>P</sub>	K <sub>ds+1%</sub>	K <sub>Dry</sub>
Acenaphthylene	-0.407	-0.434	-0.409
Acetophenone	-0.827	-0.855	-0.658
Benzaldehyde	-0.898	-0.92	-0.904
1,4-Benzodioxan	-0.829	-0.807	-0.67
Benzophenone	-0.778	-0.821	-0.77
Benzyl alcohol	-2.186	-2.123	-2.029
Biphenyl	-0.175	-0.176	-0.149
4-Chlorophenol	-2.619	-2.646	-2.658
o-Cresol	-2.256	-2.269	-2.064
3,5-Dimethyl phenol	-2.317	-2.28	-2.159
Fluorene	-0.244	-0.266	-0.29
Hexanophenone	0.002	-0.028	-0.012
Iodobenzene	-0.128	-0.133	-0.142
Methyl benzoate	-0.398	-0.437	-0.317
1-Methylnaphthalene	0.001	-0.01	0.013
2-Methylnaphthalene	0.021	0.023	0.039
Methyl octanoate	0.653	0.73	0.823
2-Naphthol	-2.977	-2.883	-2.869
Nitrobenzene	-1.017	-1.01	-0.829
4-Nitrobenzyl alcohol	-2.629	-2.577	-2.513
1-Nitrohexane	-0.263	-0.284	-0.295
2-Nitrotoluene	-0.799	-0.802	-0.654
4-Nitrotoluene	-0.787	-0.814	-0.74
Phenanthrene	-0.508	-0.574	-0.383
2-Phenyl ethanol	-1.99	-2.1	-1.829
1,2,4,5-Tetrachlorobenzene	0.409	0.376	0.447
p-Tolualdehyde	-0.849	-0.708	-0.728
m-Toluidine	-2.085	-2.084	-1.929
o-Toluidine	-1.886	-1.854	-1.785
Undecane	2.165	2.161	2.333

The partition coefficients for the two data sets, with and without the intentional addition of water, are plotted in Figure 2.5. The regression model for the plot is

$$\log K_{ds+1\%} = 0.987 (\pm 0.013) \log K_p + 0.067 (\pm 0.018) \quad (2.30)$$

$$r^2 = 0.9954 \quad SE = 0.078 \quad F = 6038 \quad n = 30$$



**Fig.2.5** Plot of the partition coefficients for a representative group of compounds in the n-heptane -dimethyl sulfoxide biphasic system containing intentionally added water (1%, v/v),  $\log K_{ds+1\%}$ , against the system without water addition,  $\log K_p$ .

where  $\log K_{ds+1\%}$  is the partition coefficient for the n-heptane-dimethyl sulfoxide biphasic system to which 1% (v/v) water was added to the dimethyl sulfoxide. The 95% confidence interval for the slope of Eq. (2.30) includes 1 (0.960 – 1.013) so there is no obvious chemical difference for the two data sets. The 95% confidence interval for the intercept (0.104 – 0.030) does not include zero suggesting that the addition of water results in a small bias, which can probably be accounted for by the small difference in the cohesive energy of the two solvent systems resulting from the addition of water to the dimethyl sulfoxide. The distribution of the residuals for Eq. (2.30) is normal. For both data sets the solvation parameter model was used to assess whether the added water had a noticeable effect on the system constants. The models for the two n-heptane-dimethyl sulfoxide systems are

$$\log K_p = -0.142 (\pm 0.229) - 1.537 (\pm 0.135)S - 2.848 (\pm 0.125)A - 1.378 (\pm 0.214)B + 1.444 (\pm 0.144)V \quad (2.31)$$

$$r = 0.991 \quad r_{adj}^2 = 0.979 \quad SE = 0.165 \quad F = 338 \quad n = 30$$

and

$$\log K_{ds+1\%} = -0.526 (\pm 0.268) - 1.430 (\pm 0.158)S - 2.582 (\pm 0.145)A - 1.414 (\pm 0.253)B + 1.737 (\pm 0.169)V \quad (2.32)$$

$$r = 0.987 \quad r_{adj}^2 = 0.970 \quad SE = 0.195 \quad F = 235 \quad n = 30$$

Both models are similar but not identical to either Eq. (2.28) or (2.29), which are based on a larger number of compounds. Since the partition coefficients used for Eq. (2.31) are a subset of those used in Eq. (2.28), Eq. (2.31) is likely a local model. Eq. (2.28) can explain both data sets with a root mean square error of prediction of about 0.17 log units supporting this hypothesis. At the 95% confidence level the differences in the  $c$  term and the  $v$  and  $a$  system constants for Eq. (2.31) and Eq. (2.32) are significant while the  $s$  and  $b$  system constants are not. The differences in the system constants can probably be accounted for by the small difference in cohesion of the dimethyl sulfoxide as a result of the addition of water.

Dimethyl sulfoxide-water mixtures are known to form micro heterogeneous environments, albeit at water concentrations considerably higher than those in which water is present as a contaminant ( $< 0.01$  mole fraction) [85-89]. Compared with solvents such as methanol and acetonitrile the formation of solvent clusters containing water in dimethyl sulfoxide-water mixtures is only observed at relatively high water concentrations (mole fraction  $> 0.8$ ). For low mole fractions of water, solutes are preferentially solvated by dimethyl sulfoxide in dimethyl sulfoxide-water mixtures and from what is known of the structure of dimethyl sulfoxide-water mixtures there is little to suggest that trace amounts of water would have a significant effect on partition coefficients. Solvent effects employing binary mixtures are inherently non-linear, however, and so to confirm the hypothesis that trace amounts of water are unable to account for a significant fraction of the hydrogen-bond acidity assigned to dimethyl sulfoxide in this study the partition coefficients for the same thirty representative compounds

identified above where determined using a thoroughly dried sample of dimethyl sulfoxide certified to contain less than 0.005% (w/w) water. The partition coefficients are summarized in Table 2.22 and the regression model for the plot of the data set for dimethyl sulfoxide containing 0.25% (w/w) water and dry dimethyl sulfoxide ( $\log K_{\text{Dry}}$ ) is:

$$\log K_p = 1.004 (\pm 0.008) \log K_{\text{Dry}} + 0.007 (\pm 0.011) \quad (2.33)$$

$$r^2 = 0.9983 \quad SE = 0.048 \quad F = 16695 \quad n = 30$$

The 95% confidence interval for the slope of Eq. (2.33) includes 1 (0.988 – 1.020) and the intercept includes zero (-0.016 – 0.030). Thus, there is no significant chemical difference between the two data sets. The average error for the two data sets (assuming the hypothesis that they should be identical) is 0.003 and the average absolute error 0.048. The average error is an indication of the lack of bias (takes the sign of the residuals into account) and the average absolute error is an indication of the typical difference between values in the two data sets independent of the sign of the residuals. Both values support the conclusion that the differences between the two data sets are no larger than could be explained by typical experimental error.

The solvation parameter model for the dry dimethyl sulfoxide data set (Table 2.22) is

$$\log K_{\text{dry}} = -0.394 (\pm 0.266) - 1.495 (\pm 0.145)S - 2.721 (\pm 0.135)A - 1.366 (\pm 0.231)B + 1.604 (\pm 0.169)V \quad (2.34)$$

$$r = 0.989 \quad r_{\text{adj}}^2 = 0.975 \quad SE = 0.178 \quad F = 289 \quad n = 30$$

The difference in the system constants for the n-heptane-dimethyl sulfoxide containing 0.25% (w/w) water model, Eq. (2.31), and the n-heptane-dry dimethyl sulfoxide model, Eq. (2.34) are not significant at the 95% confidence level. m-Toluidine is an extreme value in Eq. (2.34) but was retained so that the comparison could be made for the two models using exactly the same compounds.

In terms of why the above experiments were performed, there is no indication that low concentrations of water in dimethyl sulfoxide are solely or largely responsible for its observed hydrogen-bond acidity.

#### **2.2.4.3 Mechanism for the isolation of polycyclic aromatic compounds by n-heptane-dimethyl sulfoxide partition**

The success of dimethyl sulfoxide as a general solvent for different compound types is accounted for by the modest penalty paid to form a cavity in the solvent (moderate cohesive energy) combined with a significant capacity for dipole-type and hydrogen-bonding interactions. Its selectivity for the isolation of polycyclic aromatic compounds from aliphatic hydrocarbons and similar low-polarity compounds is due to the presence of a sufficient barrier to diminish the solubility of low-polarity compounds in the dimethyl sulfoxide layer aided by specific polar interactions with polycyclic aromatic compounds that provide for their transfer to the dimethyl sulfoxide layer. Some representative examples of the contribution of the different intermolecular interactions to the partition coefficient in the n-heptane-dimethyl sulfoxide biphasic system are summarized in Table 2.23.

For the polycyclic aromatic hydrocarbons the driving force for transfer to the dimethyl sulfoxide layer is their dipolarity/polarizability ( $sS$  term) supplemented by their hydrogen-bond basicity ( $bB$ ). These interactions exceed the opposing contribution from cavity formation (as well as differences in dispersion interactions in the two phases that are not cancelled when the solute is transferred) indicated as the  $\nu V$  contribution. Although polycyclic aromatic hydrocarbons have relatively large  $E$  descriptor values, electron lone pair interactions do not contribute to the selective extraction of these compounds because electron lone pair interactions are about the same in both phases ( $e = 0$ ). For compounds which are less dipolar/polarizable than the polycyclic aromatic hydrocarbons but of a similar size, for example, bicyclohexane and



phenylcyclohexane, the contribution of dipole-type interactions are unable to compensate for the difficulty of cavity formation in dimethyl sulfoxide and the partition coefficients for these compounds favor the n-heptane layer.

**Table 2.23.** The contribution of different intermolecular interactions to the transfer of polycyclic aromatic compounds to the dimethyl sulfoxide layer in the n-heptane-dimethyl sulfoxide partition system.

Compound	Contribution to the partition coefficient (log $K_p$ )						Estimated partition coefficient ( $K_p$ )
	<i>eE</i>	<i>sS</i>	<i>aA</i>	<i>bB</i>	<i>vV</i>	<i>c</i>	
Anthracene	0	2.317	0	0.303	-1.716	-0.289	4.12
Biphenyl	0	1.696	0	0.326	-1.562	-0.289	1.48
Fluorene	0	1.966	0	0.3	-1.601	-0.289	2.38
Fluoranthene	0	2.639	0	0.323	-1.87	-0.289	6.35
Pyrene	0	2.627	0	0.334	-1.87	-0.289	6.33
Naphthalene	0	1.606	0	0.225	-1.28	-0.289	1.83
1-Acetonaphthone	0	2.486	0	0.644	-1.632	-0.289	16.2
1-Nitronaphthalene	0	2.629	0	0.338	-1.489	-0.289	15.5
1-Naphthol	0	2.007	2.338	0.384	-1.35	-0.289	1230
Bicyclohexane	0	0.534	0	0	-1.867	-0.289	0.024
Phenylcyclohexane	0	1.058	0	0.082	-1.715	-0.289	0.14

The reason then that the n-heptane-dimethyl sulfoxide system is effective for the isolation of polycyclic aromatic hydrocarbons is that the barrier to transfer to dimethyl sulfoxide represented by the cavity term (*vV*) is sufficiently high to minimize transfer of low-polarity hydrocarbons but not so high that it can not be overcome by polar interactions possible for polycyclic aromatic hydrocarbons (*sS* and *bB*). For polycyclic aromatic compounds with polar functional groups transfer to dimethyl sulfoxide is favored by these additional polar interactions, especially for compounds which are strong hydrogen-bond acids, such as 1-naphthol, since dimethyl sulfoxide is a strong hydrogen-bond base. The n-heptane-dimethyl sulfoxide system cannot be expected to provide selectivity for the separation of polycyclic aromatic hydrocarbons and polycyclic aromatic compounds with polar functional groups since both types of compounds

favor residence in the dimethyl sulfoxide layer and are only differentiated by the magnitude of their partition coefficients.

#### 2.2.4.5 Isopentyl ether-dimethyl sulfoxide partition system

Fitting the partition coefficients ( $\log K_p$ ) in Table 2.20 to the solvation parameter model gave

$$\log K_p = 0.154 (\pm 0.070) - 1.452 (\pm 0.037)S - 2.153 (\pm 0.053)A - 0.972 (\pm 0.059)B + 1.116 (\pm 0.041)V \quad (2.35)$$

$$r = 0.995 \quad r_{adj}^2 = 0.989 \quad SE = 0.125 \quad F = 2214 \quad n = 98$$

The higher cohesive energy of the dimethyl sulfoxide layer favors transfer of all compounds to the isopentyl ether layer (positive  $v$  system constant) while polar interactions favor transfer to the dimethyl sulfoxide layer ( $s$ ,  $a$  and  $b$ ). Since isopentyl ether is more dipolar/polarizable and hydrogen-bond basic than n-heptane it should compete more effectively with dimethyl sulfoxide for these interactions, which is reflected in the smaller values for the  $s$  and  $a$  system constants in Eq. (2.35) compared with Eq. (2.28). Isopentyl ether is a non-hydrogen-bond acid, and apart from differences in mutual solubility, the isopentyl ether-dimethyl sulfoxide biphasic system is expected to have a similar  $b$  system constant to the n-heptane-dimethyl sulfoxide biphasic system, which is indeed the case. Although the barrier represented by the difference in the cohesive energy for the two phases is similar the contribution of polar interactions to the transfer of polycyclic aromatic compounds to dimethyl sulfoxide is smaller and isopentyl ether-dimethyl sulfoxide is not expected to be as effective as the n-heptane-dimethyl sulfoxide system for the separation of polycyclic aromatic hydrocarbons from low-polarity hydrocarbons.

The Kennard-Stone algorithm was used to split the data set into a training set of 68 compounds and a test set of 30 compounds. The model for the training set is

$$\log K_p = 0.197 (\pm 0.085) - 1.458 (\pm 0.043)S - 2.173 (\pm 0.065)A - 0.948 (\pm 0.070) + 1.081 (\pm 0.048)V \quad (2.36)$$

$$r = 0.995 \quad r_{adj}^2 = 0.990 \quad SE = 0.131 \quad F = 1705 \quad n = 68$$

and is quite similar to Eq. (2.35). For the test set the average error was 0.087, the average absolute error 0.128 and the root mean square error 0.113. Thus, Eq. (2.35) should be able to predict further values of the partition coefficients to about 0.13 log units for compounds with descriptor values that lie within or close to the descriptor space used to define the model.

#### 2.2.4.6 General partition properties of dimethyl sulfoxide-organic solvent systems

With the models reported here, system constants have been calculated for seventeen totally organic biphasic systems, Table 2.24 [15,26,39,56,57]. Hierarchical cluster analysis using

**Table 2.24.** System constants for totally organic biphasic partition systems

System	System constants					
	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>
Ethylene glycol-1,2-dichloroethane	-0.639	0.096	0	2.468	0.991	-1.307
Formamide-1,2-dichloroethane	-0.207	-0.082	0.399	1.957	1.298	-1.705
n-Heptane-ethylene glycol	0.358	0.093	-1.553	-3.781	-1.548	2.133
n-Heptane-N,N-dimethylformamide	0.255	0.038	-1.391	-2.16	-0.593	0.486
n-Heptane-dimethyl sulfoxide	0.289	0	-1.781	-3.088	-1.167	1.18
n-Heptane-formamide	0.083	0.559	-2.244	-3.25	-1.614	2.387
n-Heptane-hexafluoroisopropanol	-0.49	1.03	-1.712	-0.669	-1.746	1.121
n-Heptane-methanol	-0.158	0.186	-0.686	-1.098	-0.951	0.618
n-Heptane-propylene carbonate	0.502	0.455	-2.087	-2.646	-0.433	0.807
n-Heptane-trifluoroethanol	0.013	0.882	-1.557	-1.312	-2.928	1.301
n-Hexane-acetonitrile	0.152	0.349	-1.439	-1.611	-0.874	0.669
Isopentyl ether-dimethyl sulfoxide	0.154	0	-1.452	-2.153	-0.972	1.116
Isopentyl ether-ethylene glycol	0.419	-0.09	-1.159	-1.53	-1.901	2.089
Isopentyl ether-formamide	0.13	0.564	-1.715	-1.314	-1.407	2.005
Isopentyl ether-propylene carbonate	0.264	0.298	-1.432	-0.718	-0.472	0.729
Octan-1-ol-formamide	0.285	0.267	-1.053	-0.333	-0.929	1.314
Octan-1-ol-propylene carbonate	0.282	0.256	-1.068	-0.222	0	0.365

the average linkage between groups algorithm with the system constants as variables was used to

compare extraction properties of these biphasic systems. The dendrogram, Figure 2.6, demonstrates that the solvent systems encompass a wide selectivity range with little clustering. Although groups can be identified in the dendrogram these are generally composed of neighbors best described as the nearest equivalent system rather than selectivity equivalent system. The n-heptane-dimethyl sulfoxide system has n-heptane-propylene carbonate as its nearest neighbor and isopentyl ether-dimethyl sulfoxide the n-hexane-acetonitrile and n-heptane-*N,N*-dimethylformamide systems as nearest neighbors. Within these solvent groups the individual solvent systems are sufficiently dissimilar in their solvation properties that one system could substitute for the other in only the broadest sense but none of the paired systems duplicate each other. A useful feature of the totally organic biphasic systems presented in Figure 2.6 is that they afford reasonable coverage of the available selectivity space allowing some flexibility in the identification of systems for sample preparation.

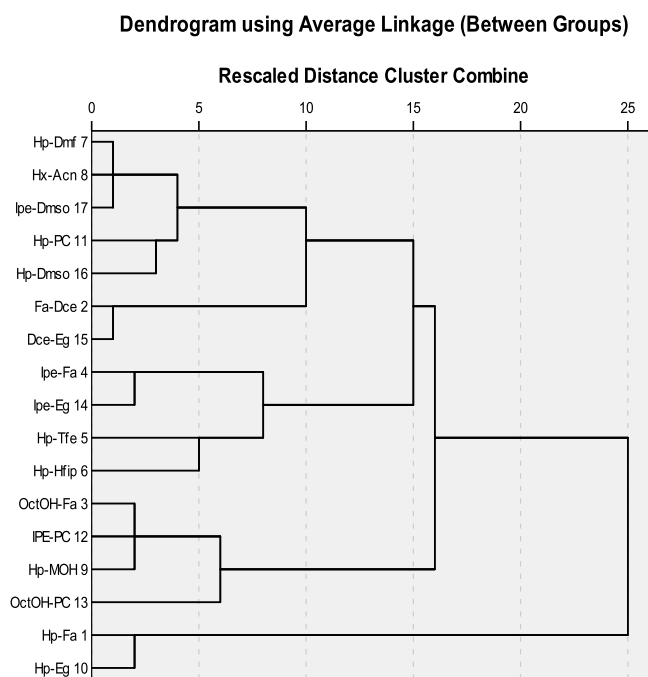


Figure 2.6. Cluster dendrogram for the average linkage between groups agglomeration algorithm for the totally organic biphasic systems with the system constants of the solvation parameter models (Table 2.24) as variables.

### 2.2.5. Determination of descriptor values by liquid-liquid partition in totally organic systems

Biphasic systems with numerically large system constants are preferred for the calculation of solute descriptors because they afford descriptors with a lower uncertainty. The V descriptor is available by calculation and the E descriptor can be measured or estimated reasonably well for most compounds. Experimental methods are required to determine the S, A and B descriptors, and for these descriptors, totally organic biphasic systems are attractive for compounds of low water solubility (or compounds unstable in water). For this purpose n-heptane-formamide (for A, B and S), n-heptane-ethylene glycol (for A and B), n-heptane-propylene carbonate (for A and S), n-heptane-2,2,2-trifluoroethanol (for B) and isopentyl ether-ethylene glycol (for B) are the most suitable systems. The n-heptane-dimethyl sulfoxide system could be included in this list (for A) if an additional biphasic system was desired. The other biphasic systems with a non-alkane counter solvent could be useful for compounds with low n-heptane solubility when water-based biphasic systems are also inappropriate. For robust descriptor values it is recommended to use several experimental techniques, including chromatographic and solubility methods, together with liquid-liquid partition when practical [8,15]. Gas chromatography is virtually indispensable for the determination of the L descriptor and useful for estimating the A and S descriptors, but cannot be used to estimate the B descriptor, since common stationary phases used for gas chromatography lack hydrogen-bond acidity [91]. Reversed-phase liquid chromatography and micellar electrokinetic chromatography are suitable for estimating the B descriptor, but are often less useful for estimating the S and A descriptors owing to the small system constants associated with these descriptor interactions. This is particularly so for strongly hydrophobic compounds that are excessively retained or

require the use of predominantly organic mobile phases for their elution in reversed-phase liquid chromatography. For compounds of reasonable water solubility aqueous liquid-liquid partition is a useful method for estimating the S, A and B descriptors [8,42] but for compounds unstable or virtually insoluble in water an alternative approach is needed [25,26]. For these compounds, such as the organosiloxanes, phthalate esters and essential oils, a combination of gas chromatography with totally organic liquid-liquid partition is the preferred approach. These compounds are either decomposed or virtually totally insoluble in aqueous systems and require non-aqueous systems for descriptor measurements.

**Footnote:**

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(2) T. Karunasekara, C.F. Poole. "Models for Liquid-Liquid Partition in the System Ethylene Glycol-Organic Solvent and their use for Estimating Descriptors for Organic Compounds". *Chromatographia*, 73 (2011) 941-951.

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## CHAPTER 3

### SOLVENT CLASSIFICATION FOR CHROMATOGRAPHY AND EXTRACTION

#### 3.1 Introduction

Solvents are an indispensable tool of the separation scientist, whether as a means to dissolve solids to facilitate their introduction into separation systems, to conveniently vary sample amounts through dilution, or as one phase in two-phase separation systems, such as the mobile phase in liquid chromatography. During studies of chromatography and extraction scientists acquire an enormous amount of empirical knowledge about the way solvents behave and utilize this knowledge in the design of further experiments. Methods aimed at placing this empirical knowledge on more formal quantitative scales of solvent properties have been far less successful.

One of the most common solvent classification schemes are scales of solvent polarity. The concept of solvent polarity is easily understood qualitatively but otherwise of limited value because of the lack of a universal definition. To some it is the capacity of a solvent to enter into all possible intermolecular interactions, while to others, it describes a solvent's ability to participate in interactions of a dipole-type. A large number of easy to measure, single-property scales, such as the dielectric constant, Reichardt's solvatochromic absorption scale, etc, have been used to provide a quantitative scale for solvent polarity [1-4]. The absence of a single reference compound or bulk physical property that is uniquely polar, however, renders all these scales unfit for purpose. Each scale measures some specific characteristic related to the selected probe or physical property chosen, with often little in common with other scales supposedly calibrated to determine the same general property, and with no logical reason to prefer one scale over another.

In the absence of any general single parameter scale, solvent classification is most often based on a combination of solvent properties treated as variables with chemometric techniques employed to reduce the dimensionality and/or cluster the data according to a selected similarity metric [3,5-7]. An early, and still relevant approach, proposed by Chastrette et al [8] employed eight solvent characteristics (molar refraction, molecular dipole moment, Hildebrand's solubility parameter, refractive index, boiling point, Kirkwood function, and HOMO and LUMO energies) and principal component analysis to assign each of 83 solvents into nine selectivity groups. Some solvents were assigned unlikely neighbors but, otherwise, the results obtained were in reasonable agreement with empirical knowledge. Gramatica et al [6] used a set of structural, empirical and topological molecular descriptors with clustering and neural network techniques to classify 152 solvents into five groups with broadly similar properties. The solvent classes were identified as aprotic polar, aromatic apolar or lightly polar, electron pair donors, hydrogen bonding donors, and aliphatic aprotic apolar. Such a broad classification, however, is too general for chromatographic applications since solvents in the same group provide quite different separation possibilities. Durand et al [7] developed an alternative approach for solvent classification based solely on theoretical descriptors that could be calculated from molecular structure. The theoretical descriptors were generated through analysis of the COSMO-RS (conductor-like screening model for real solvents) potential energy surface profiles resulting in the classification of 153 solvents into 10 groups. These were identified as strong electron-pair donor bases, weak electron pair donor bases, aprotic dipolar, aprotic highly dipolar, apolar, asymmetric halogenated hydrocarbons, amphiprotic, polar protic, organic acids, and polar structured solvents. The classification used 61 theoretical descriptors, many of which were highly correlated, but could be reduced to three orthogonal principal components with a loss of about 13% of the information in the original data set. Some of the theoretical descriptors have

uncommon descriptions understood only by the specialist, and the classification approach lacks context for experimental scientists. The results appear quite logical, however, even if the reasoning is obscure. The collapse of the dimensionality of the variable space results in a significant loss of information and the score plots (visualization of the solvent space) could lead to inconsistencies.

Separation scientists have generally adopted semi-empirical approaches for solvent classification with a view to rank solvents according to their strength (solvent strength) and selectivity (solvent selectivity) [9-12]. The solvent strength is a single parameter estimate of the solvent's ability to cause migration in a chromatographic system. Solvent strength is a system property and cannot be considered a fundamental solvent property. For example, water is a weak solvent in reversed-phase liquid chromatography but a strong solvent in normal-phase liquid chromatography. There is no universal scale of solvent strength.

Solvent selectivity is the parameter that describes the capability of solvents to provide a separation based on their ability to form complementary intermolecular interactions in the separation system. Solvents can have similar solvent strength but different selectivity resulting in significant differences in band spacing and possibly migration order. General models of solvent selectivity include the solubility parameter model, solvatochromic parameters, Snyder's solvent selectivity triangle, and the solvation parameter model. The Hildebrand solubility parameter (total solubility parameter) is easily calculated from the physical properties of pure solvents and is defined as the square root of the solvent vaporization energy divided by its molar volume [13]. The original solubility parameter concept was developed as an extension of regular solution theory in which the principal intermolecular interactions were dominated by dispersion forces. This approach was extended to polar solvents by decomposing the total solubility parameter into a series of polar partial solubility parameters treated as additive quantities [14,15]. The larger the

value for the polar partial solubility parameter the greater potential of the solvent to participate in that interaction with maximum solvency achieved for solutes and solvents with matched (similar values for the dispersion, induction and orientation parameters and complementary values for the hydrogen-bonding) partial solubility parameters. The polar partial solubility parameters are only approximate, however, since there is no general agreement as to the best method of calculation and there is considerable disagreement among reported values for the same polar partial solubility parameters. Contemporary applications of the solubility parameter model are limited to the solubility of polymers and the prediction of mobile phases for size-exclusion and precipitation chromatography.

The solvatochromic parameters are derived from uv-visible absorption measurements for probe compounds selected to determine, usually, only a single intermolecular interaction. In addition, the solvatochromic parameters are averages of the results from several probe compounds for each parameter and are (almost) independent of probe identity. The most comprehensive solvatochromic treatment of solvent selectivity are the  $\pi^*$  (solvent dipolarity/polarizability),  $\alpha$  (solvent hydrogen-bond acidity) and  $\beta$  (solvent hydrogen-bond basicity) scales of Kamlet and Taft [5,9,10,16,17]. The main problem with solvent classification schemes based on the solvatochromic parameters is that it considers only the polar interactions of the solvents and not their cohesive energy [10,18]. The transfer of solute from one solvent to another occurs with (approximate) cancellation of dispersion interactions, but the energy required for cavity formation in the two solvents is not necessarily self-cancelling, and when one of these solvents is water, cancellation of the cavity term is unlikely. Solvent classification schemes need to consider the cohesive energy of the solvent as well as the solvent's capability for polar interactions [19-21].

Snyder's solvent selectivity triangle is the most enduring method for solvent classification used by separation scientists [9,22,23]. Snyder classified solvents based on their interactions with three prototypical compounds determined by their gas-liquid partition coefficients corrected for differences in solvent size, polarizability and dispersion interactions. Each value was then corrected empirically to give a value of zero for the polar partition coefficient for saturated hydrocarbon solvents. Snyder chose the compounds nitromethane, ethanol and dioxane as prototypical compounds to assign a solvent's capability for dipole-type, hydrogen-bond base and hydrogen-bond acid, interactions, respectively. The sum of the three polar partition coefficients was used to provide a measure of the solvent strength ( $P'$ ) and the ratio of the individual polar partition coefficients to their sum a measure of selectivity ( $x_n$ ,  $x_e$  and  $x_d$ ). Representing each solvent by the three solvent selectivity coordinates and plotting the results on the surface of a triangle ( $x_n + x_e + x_d = 1$ ) resulted in the classification of solvents into eight selectivity groups with solvents in the same group having similar properties [11,12]. Representative solvents from different groups were recommended for the initial stage of method development. A main strength of the solvent selectivity triangle approach was its simple visual interpretation, although it was obvious that some solvents were incorrectly classified with respect to their neighbors [23].

The most significant limitation of the solvent selectivity triangle approach is the association of an individual intermolecular interaction with a single prototypical compound and the incomplete correction for differences in cohesive energy of the solvents [5,10,22,23]. The solubility of the prototypical compounds is the result of multiple intermolecular interactions and not due to a single dominant interaction. Ethanol, for example, is dipolar and hydrogen-bond acidic and basic, and could have a significant coordinate on the  $x_e$  scale without participating in solvent hydrogen-bond base interactions at all. Since there are no compounds that are strong



hydrogen-bond acids or bases that are not simultaneously dipolar, it is impossible to characterize intermolecular interactions based on the properties of single (prototypical) compounds.

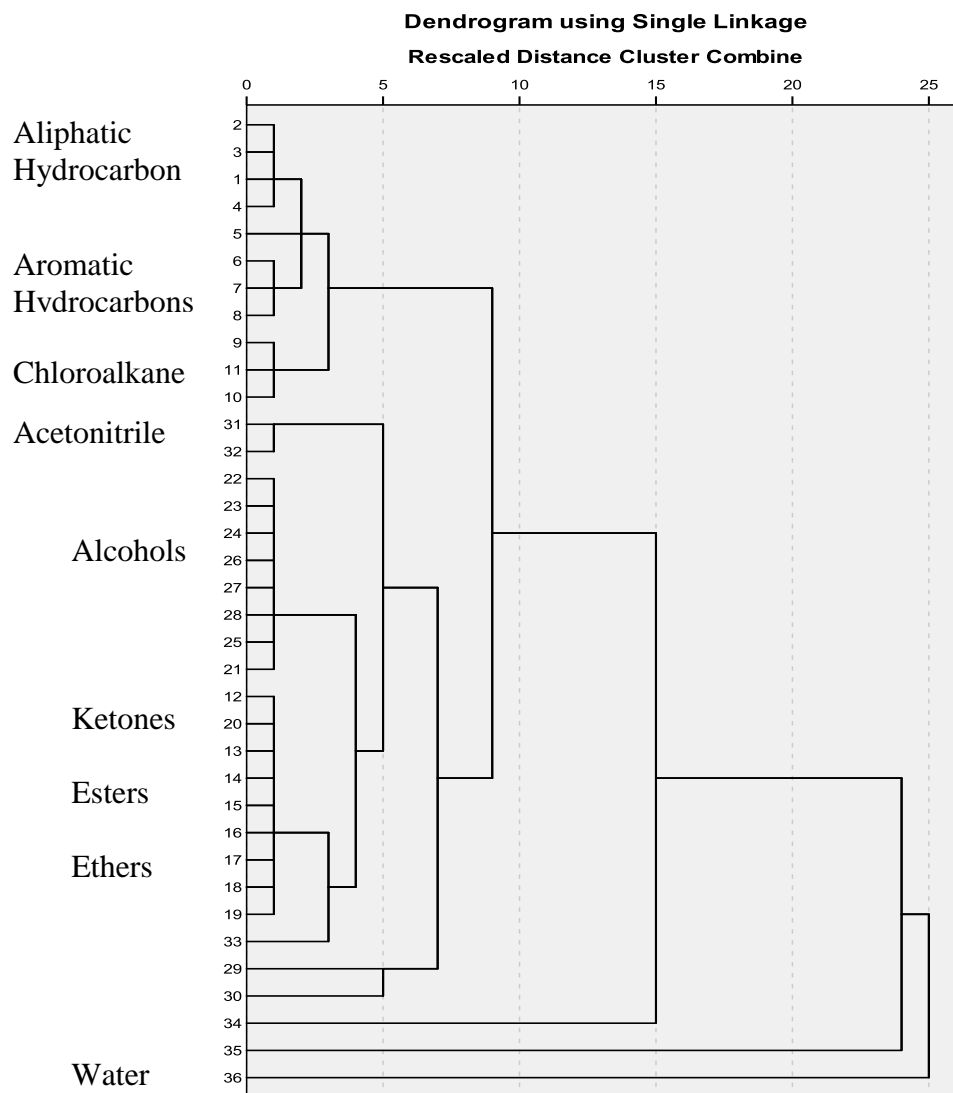
Linear solvation energy relationships, which do not depend on the properties of any single compound, but use a number of varied compounds to assign the contribution of individual intermolecular interactions and cohesive energy to the solvation process, have proven more successful for solvent classification and for modeling retention in separation processes. Of these approaches, the solvation parameter model proposed by M. H. Abraham, has been the most widely used [10,11,24-29].

### 3.2 Solvent Classification

The solvation parameter model described solvent properties in terms of five system constants ( $e$ ,  $s$ ,  $a$ ,  $b$ , and  $l$ ) summarized in Table 3.1 for solvents of general interest for separation processes [28,31-44]. The table has been organized according to the classification which follows, but even as such it is no simple matter to visualize the connections between individual solvents. The data is five co-ordinates and cannot be represented in a three-dimensional space without reducing the dimensionality of the data. Principal component analysis is ineffective in this case as the first two principal components describe only 80% of the variance. Although 99.3% of the variance is extracted by four principal components none of the resulting score plots provide a useful solvent classification. Hierarchical cluster analysis provides an alternative approach for classification in which the Euclidian distance between solvents in five dimensional space with the system constants as co-ordinates is used to compute a similarity matrix. Solvents that are near neighbors in hyperspace are grouped together and solvents further removed from each other, or from a group of solvents, are placed into a different class until all the solvents have been included in the analysis.

**Table 3.1** System constants for gas to solvent transfer for solvents commonly used for separation processes

Solvent	System constants						Ref.
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>	<i>c</i>	
Cyclohexane	-0.11	0	0	0	1.013	0.163	28
n-Hexane	-0.169	0	0	0	0.979	0.292	28
n-Heptane	-0.162	0	0	0	0.983	0.275	28
2,2,4-Trimethylpentane	-0.23	0	0	0	0.975	0.264	28
Carbon tetrachloride	-0.435	0.544	0	0	1.069	0.217	32
Benzene	-0.313	1.053	0.457	0.169	1.02	0.107	28
Toluene	-0.222	0.938	0.467	0.099	1.012	0.121	33
Chlorobenzene	-0.399	1.156	0.313	0.171	1.032	0.064	33
Dichloromethane	-0.572	1.492	0.46	0.847	0.965	0.192	32
Chloroform	-0.56	1.259	0.374	1.333	0.976	0.157	32
1,2-Dichloroethane	-0.337	1.6	0.774	0.637	0.921	0.017	34
Acetone	-0.387	1.733	3.06	0	0.866	0.127	35
Butan-2-one	-0.474	1.671	2.878	0	0.916	0.112	35
Cyclohexanone	-0.441	1.725	2.786	0	0.957	-0.086	35
Ethyl Acetate	-0.352	1.316	2.891	0	0.916	0.182	36
Butyl Acetate	-0.414	1.212	2.623	0	0.954	0.147	36
Diethyl ether	-0.379	0.904	2.937	0	0.963	0.288	37
Methyl <i>t</i> -Butyl Ether	-0.536	0.89	2.632	0	0.999	0.231	37
Tetrahydrofuran	-0.347	1.238	3.289	0	0.982	0.189	38
Dioxane	-0.354	1.674	3.021	0	0.919	-0.034	38
Methanol	-0.338	1.317	3.826	1.396	0.773	-0.039	39
Ethanol	-0.232	0.867	3.894	1.192	0.846	0.017	39
Propan-1-ol	-0.246	0.749	3.888	1.076	0.874	-0.042	39
Propan-2-ol	-0.324	0.713	4.036	1.055	0.884	-0.048	40
Butan-1-ol	-0.285	0.765	3.705	0.879	0.89	-0.004	39
Butan-2-ol	-0.387	0.719	3.736	1.088	0.905	-0.034	40
Hexan-1-ol	-0.205	0.583	3.621	0.891	0.913	-0.014	39
Octan-1-ol	-0.203	0.56	3.576	0.702	0.939	-0.12	41
Acetonitrile	-0.595	2.461	2.085	0.418	0.738	-0.007	28
Propylene carbonate	-0.413	2.587	2.207	0.455	0.719	-0.356	44
Ethylene Glycol	0.132	1.657	4.457	2.355	0.565	-0.887	44
Formamide	0.31	2.292	4.13	1.933	0.442	-0.8	43
N,N-Dimethylformamide	-0.869	2.107	3.774	0	1.011	-0.391	43
Dimethyl sulfoxide	0.131	2.811	5.474	0	0.734	-0.619	28
2,2,2-Trifluoroethanol	-0.547	1.339	2.213	3.807	0.645	-0.092	28
Water	0.822	2.743	3.904	4.814	-0.213	-1.271	42

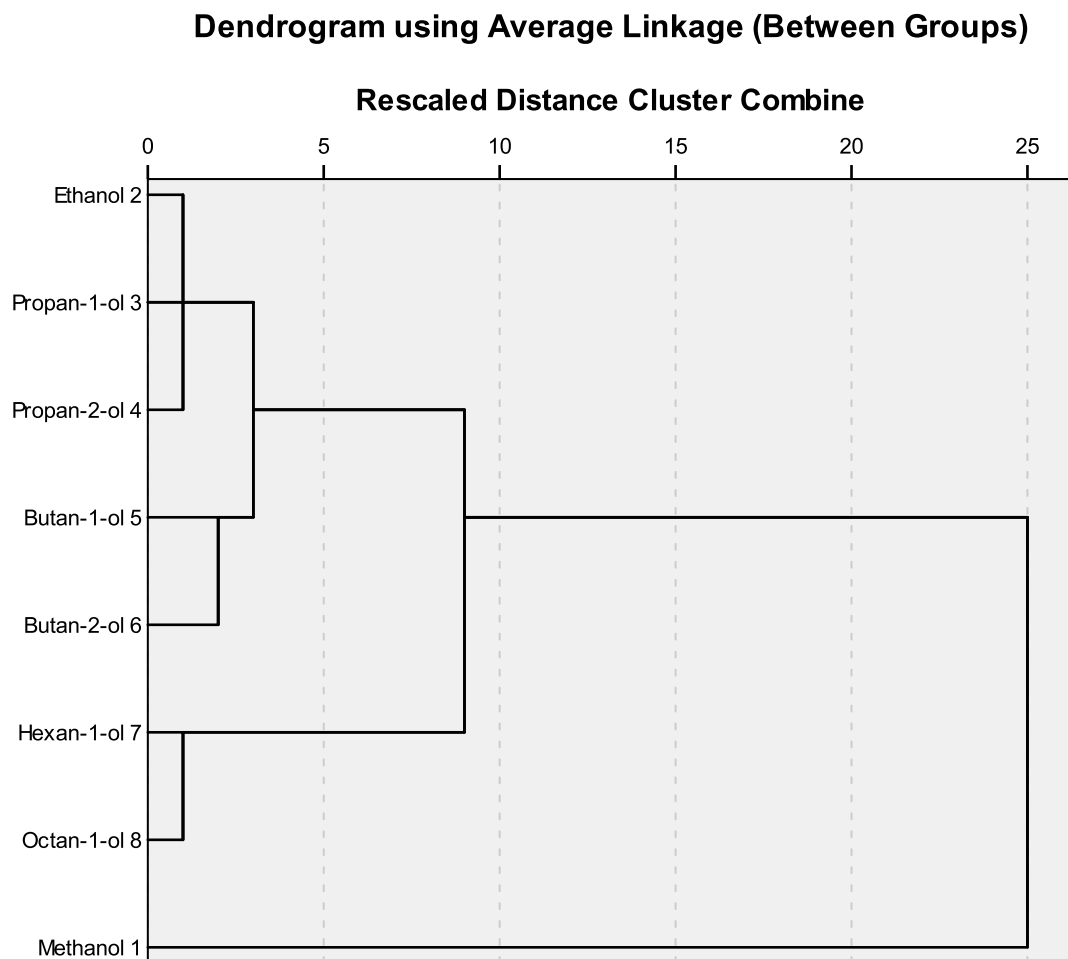


**Fig.3.1.** Nearest neighbor agglomeration cluster dendrogram for the 36 solvents indicated in Table 3.1. Identification: 1 = cyclohexane; 2 = n-Hexane; 3 = n-Heptane; 4 = 2,2,4-Trimethylpentane; 5 = Carbon tetrachloride; 6 = Benzene; 7 = Toluene; 8 = Chlorobenzene; 9 = Dichloromethane; 10 = Chloroform; 11 = 1,2-Dichloroethane; 12 = Acetone; 13 = Butan-2-one; 14 = Cyclohexanone; 15 = Ethyl Acetate; 16 = Butyl Acetate; 17 = Diethyl Ether; 18 = Methyl *t*-Butyl Ether; 19 = Tetrahydrofuran; 20 = Dioxane; 21 = Methanol; 22 = Ethanol; 23 = Propan-1-ol; 24 = Propan-2-ol; 25 = Butan-1-ol; 26 = Butan-2-ol; 27 = Hexan-1-ol; 28 = Octan-1-ol; 29 = Ethylene Glycol; 30 = Formamide; 31 = Acetonitrile; 32 = Propylene Carbonate; 33 = *N,N*-Dimethylformamide; 34 = Dimethyl Sulfoxide; 35 = 2,2,2-Trifluoroethanol; and 36 = Water.

The results are visualized as a dendrogram, such as the example shown in Figure 3.1 for the 36 solvents in Table 3.1. The solvents are classified into seven clusters with four solvents behaving independently. Cluster 1 contains the apolar n-alkane and cycloalkane solvents of low

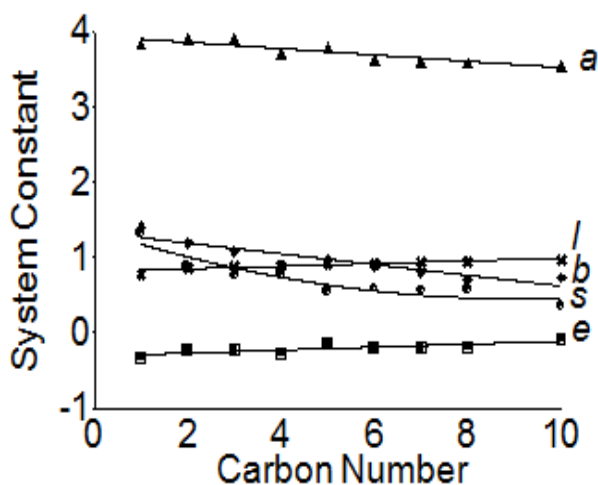
cohesion and very weak or nonexistent polar interactions. These are separated from cluster 2, which contains the aromatic hydrocarbons and chlorobenzene. These solvents have low cohesion and weak polar interactions. Cluster 3 contains the haloalkanes, which have low cohesion, weak polar interactions but are significantly more hydrogen bond acidic than the solvents in cluster 2. Cluster 4 contains acetonitrile and propylene carbonate, which are strongly dipolar, weakly hydrogen-bond acidic and basic, and of moderate cohesion. They are distinguished from the other strongly dipolar solvents by their characteristic  $s/a$  ratio. Cluster 5 contains the alcohols, which are amphiprotic solvents (moderately dipolar, strong hydrogen-bond bases, intermediate hydrogen-bond acids, and moderately cohesive). Cluster 6 contains the ketones, esters and ethers, which are weakly cohesive solvents with moderate dipolarity and strong hydrogen-bond basicity but no hydrogen-bond acidity. Cluster 7 contains the amphiprotic solvents ethylene glycol and formamide, which are significantly more cohesive, dipolar, and hydrogen-bond acidic than the alcohols forming Cluster 5. Of the four solvents behaving independently only water is likely to be truly independent. It is easily the most cohesive solvent in Table 3.1 and the strongest hydrogen-bond acid. 2,2,2-Trifluoroethanol is significantly more hydrogen-bond acidic and less hydrogen-bond basic than a typical alcohol (Cluster 5) but presumably has properties similar to other partially fluorinated alcohols in which the hydroxyl group is influenced by the electronegativity of fluorine. *N,N*-dimethylformamide is more dipolar and hydrogen-bond basic than the other aprotic dipolar solvents in Cluster 6 but presumably other *N*-alkylamides would have similar properties.

The above approach can be used to explore the homogeneity of some of the larger clusters of Figure 3.1. A cluster dendrogram for the eight normal and secondary alcohols of cluster 5 of Figure 3.1 is shown in Figure 3.2. It is obvious that these solvents as well as having a



**Fig.3.2.** Average linkage agglomeration cluster dendrogram for the alcohols of group 5 of Figure 3.1.

certain character in common these have smaller differences in selectivity that would be quite useful in separations. Methanol is reasonable different to the other n-alcohols (more dipolar, hydrogen-bond acidic and cohesive). The alcohols with two to four carbon atoms, in term, are slightly different to n-hexanol and n-octanol. For solvent screening purpose it would be reasonable to take two solvents from this group, of which one would be methanol, and for the other the choice is less critical, and as a compromise propan-2-ol would be a reasonable choice. The effect of the n-alkyl chain length on the system constants for a wider range of n-alcohols is illustrated in Figure 3.3 [39-41].

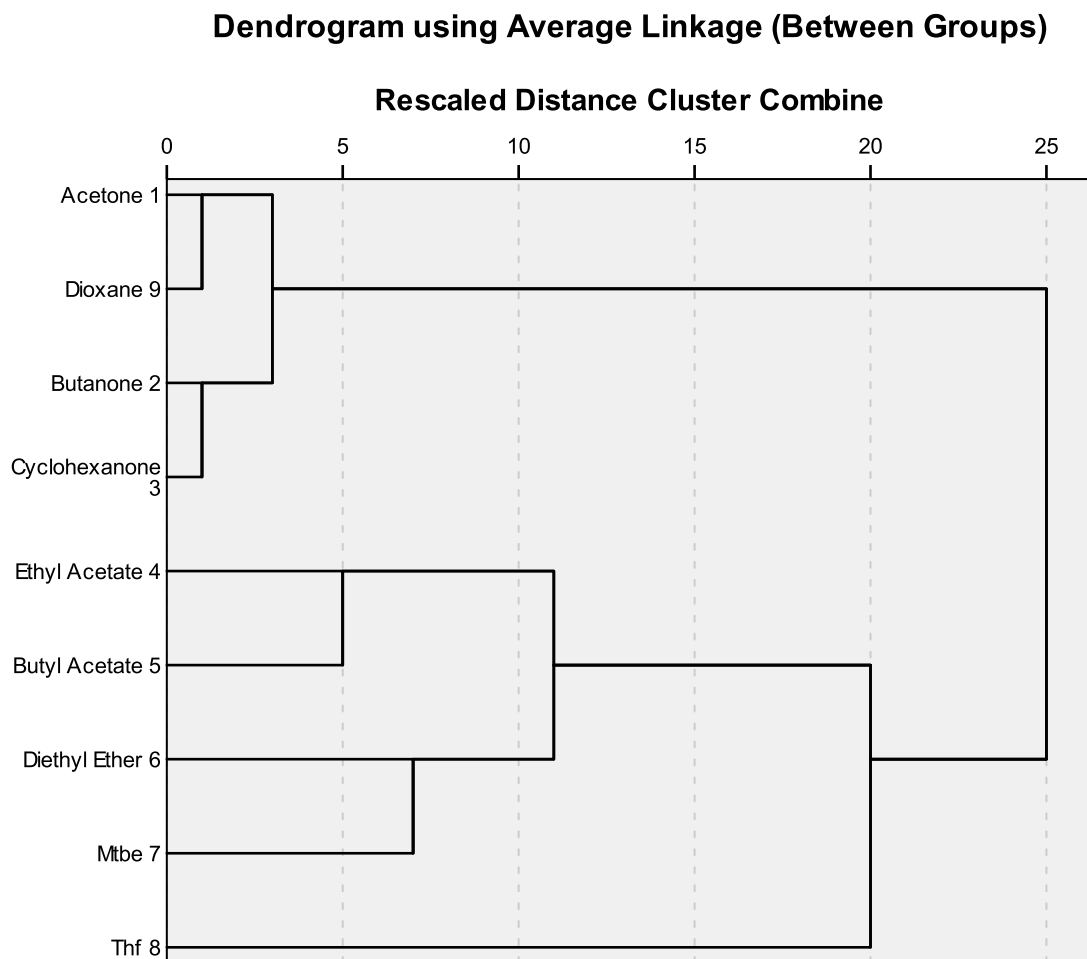


**Figure 3.3.** Variation of the system constants with alkyl chain length (carbon number) for n-alcohols.

The system constant change smoothly in a linear fashion for *e*, *l*, *a* and *b*, while a second order fit is more realistic for *s*. The range for the change in system constants with carbon number are different, so while the hydrogen-bond basicity is not strongly influenced by the alkyl chain length the dipolarity/polarizability and hydrogen-bond acidity are. The different range and rate of change of the system constants with alkyl chain length is the reason why the solvent properties of the n-alcohols cannot be adequately represented by a single member chosen from this group.

Group 6 contains nine ketones, esters and ethers. The dendrogram for this group is shown in Figure 3.4. The ketones form one reasonably homogeneous group including the ether dioxane, which has solvent properties very similar to acetone. The two alkyl esters while separated from the ketones are only slightly less dipolar/polarizable and for screening purposes could be combined with the ketones. This group could be adequately represented by any of the ketones.

Of the three remaining ethers, tetrahydrofuran is more dipolar/polarizable and hydrogen-bond



**Fig. 3.4.** Average linkage agglomeration cluster dendrogram for the ketones, esters and ethers of group 6 of Figure 3.1. Identification: Mtbe = Methyl *t*-Butyl Ether; and Thf = Tetrahydrofuran.

basic than diethyl ether and methyl *t*-butyl ether, but in terms of differentiation within Group 6, methyl *t*-butyl ether or diethyl ether would be a good second choice because of their larger  $a / s$  ratio.

Based on the above considerations it is possible to recommend a series of solvents for the screening stage in method development for separations. Screening requires that solvents be as different as possible while for optimization solvents with similar properties to the solvents identified in the screening step are employed [10-12]. Solvents for the screening step in

separations (at least as far as the database of 36 solvents allows) are summarized in Table 3.1. The classification does not differ radically from that of Snyder except that solvents with unlikely assignments using the Snyder solvent selectivity triangle are now more logically identified as behaving independently or assigned a reasonable group membership.

**Table 3.2** Solvents recommended for the screening stage in method development for liquid chromatography.

Classification	Solvent	Cluster
Apolar	n-Heptane (any n-alkane)	1
Apolar Aromatic	Toluene	2
Haloalkane Chloroform	Dichloromethane	3
Dipolar and weakly aprotic	Acetonitrile	4
Amphiprotic	Methanol Propan-2-ol	5
Polar and non-hydrogen- bond acidic	Acetone Methyl <i>t</i> -butyl ether	6
Polar and cohesive	Formamide	7
Polar (independent)	2,2,2-Trifluoroethanol <i>N,N</i> -Dimethylformamide Dimethyl sulfoxide Water	

### 3.3 Liquid-Liquid Extraction

For liquid-liquid distribution biphasic systems of low mutual solubility and different densities are needed. The requirement of low mutual solubility limits the number of binary solvent pairs available, and typically, the individual solvents will be from different selectivity groups since solvents in the same selectivity group are usually completely miscible. It is



convenient to divide these biphasic systems into two categories: (i) aqueous systems with water as one solvent and the other an organic solvent with low hydrogen-bonding capability, and (ii) totally organic biphasic systems in which one phase is usually a solvent of low polarity and the other a solvent of high polarity and/or high cohesion. The distribution of neutral compounds in these systems can be described by the solvation parameter model in which the system constants now refer to a difference in a property between two condensed phases and the L descriptor is replaced by the characteristic volume V [26-29]. Eq. (3.1) is commonly used to describe liquid-liquid partitioning.

$$\log K = c + eE + sS + aA + bB + vV \quad (3.1)$$

The V descriptor can be calculated from structure (unlike L) and is justified for the above application since transfer of a solute between two condensed phases occurs with nearly complete cancellation of the dispersion interactions in the two phases. The  $v$  system constant is dominated by differences in the cavity term for the two solvents.

### 3.3.1 Aqueous biphasic systems

The system constants for aqueous biphasic liquid-liquid partition systems are summarized in Table 3.3 [28,32-34,36,37,44,47,48] and the mutual solubility of the phases in Table 3.4 [49]. Water is the most cohesive and hydrogen-bond acidic of the solvents in Table 3.3. Typical values for the  $v$  system constant fall into the range 4.0-4.6 except for ethyl acetate, propylene carbonate, and octan-1-ol with values of 3.666, 3.421, and 3.814, respectively. The latter solvents all contain appreciable amounts of water at equilibrium. It is most likely the relatively high solubility of water in these solvents that accounts for their smaller  $v$  system constants compared with the other solvents. The driving force for partition into the organic solvent in the aqueous biphasic systems is the difference in cohesion between the water saturated with organic solvent and the organic solvent saturated with water phases. This is supported by electron lone pair

interactions,  $e$  system constant, but these contributions are generally much less important than the difference in cohesion. The sign of the  $b$  system constant indicates that it favors partition into the aqueous phase. Typical values for the  $b$  system constant fall between 4.5-5.0 except for the haloalkanes (dichloromethane = -4.09, chloroform = -3.514, and 1,2-dichloroethane = -4.29), ethyl and butyl acetate (-4.261 and -4.151, respectively), propylene carbonate (-4.407) and octan-1-ol (-3.46) as a consequence of the solubility of water in the organic solvent and because some of these solvents are weak to moderate hydrogen-bond acids and can compete with water to some extent in interactions with hydrogen-bond bases.

**Table 3.3.** System constants for water to solvent transfer for liquid-liquid partition systems commonly used for separation processes

Solvent	System constants						Ref.
	$e$	$s$	$a$	$b$	$v$	$c$	
Hexane	0.579	-1.723	-3.599	-4.764	4.344	0.361	28
Heptane	0.67	-2.061	-3.317	-4.733	4.543	0.325	28
2,2,4-Trimethylpentane	0.555	-1.737	-3.677	-4.864	4.417	0.318	28
Cyclohexane	0.784	-1.678	-3.74	-4.929	4.577	0.159	28
Carbon tetrachloride	0.532	-1.159	-3.56	-4.594	4.618	0.199	32
Benzene	0.464	-0.588	-3.099	-4.625	4.491	0.142	28
Toluene	0.527	-0.72	-3.01	-4.824	4.545	0.143	33
Chlorobenzene	0.381	-0.521	-3.183	-4.7	4.614	0.065	33
1-Chlorobutane	0.273	-0.569	-2.918	-4.883	4.456	0.222	32
Dichloromethane	0.102	-0.187	-3.058	-4.09	4.324	0.319	32
Chloroform	0.105	-0.403	-3.112	-3.514	4.395	0.191	32
1,2-Dichloroethane	0.294	-0.134	-2.807	-4.291	4.18	0.183	34
Ethyl Acetate	0.591	-0.669	-0.325	-4.261	3.666	0.441	36
Butyl Acetate	0.428	-0.094	-0.241	-4.151	4.046	0.475	36
Diethyl Ether	0.358	-0.82	-0.588	-4.956	4.35	0.35	37
Methyl <i>t</i> -Butyl Ether	0.307	-0.817	-0.618	-5.097	4.425	0.341	37
Propylene Carbonate	0.168	-0.504	-1.283	-4.407	3.421	0.004	44
Octan-1-ol	0.562	-1.054	0.034	-3.46	3.814	0.088	47
Folch partition*	0.014	-0.413	-1.583	-1.344	1.378	-1.336	48

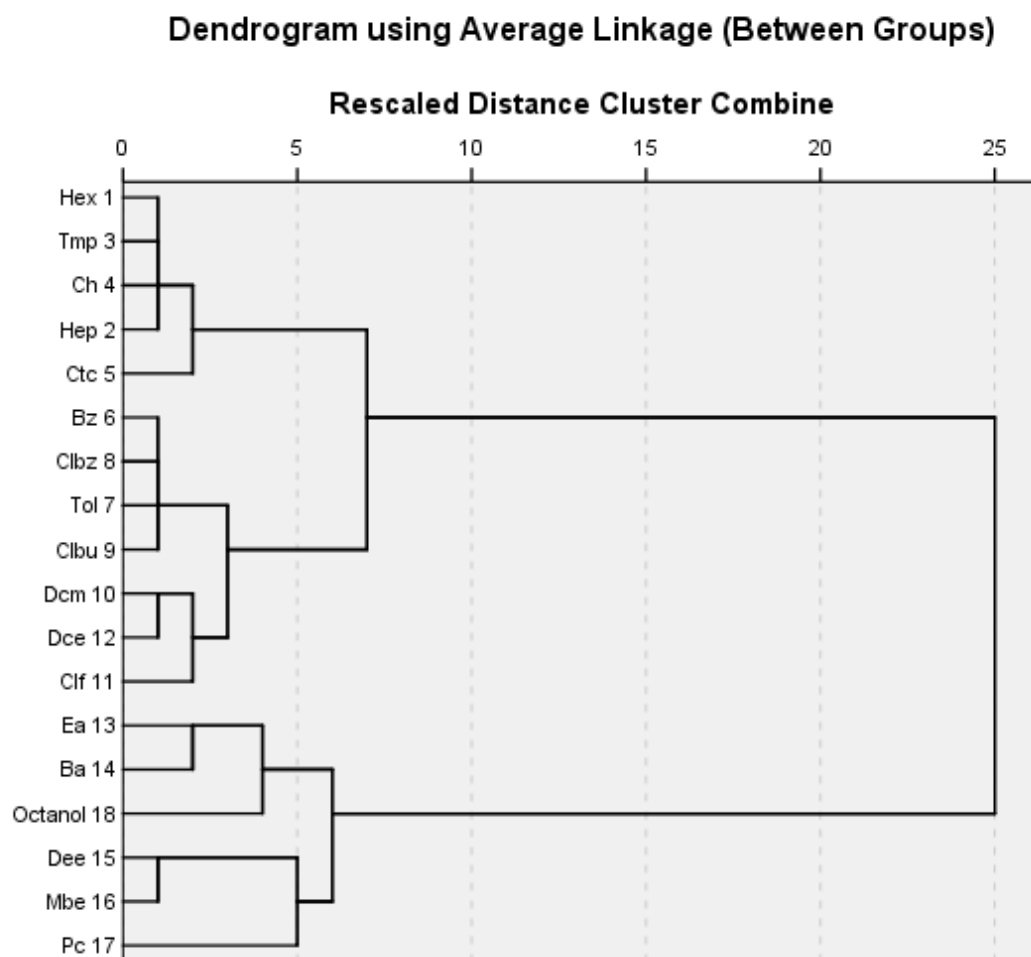
\*Chloroform-methanol-water (8:4:3 v/v)

The main variation among the biphasic systems is observed for dipole-type interactions ( $s = 0 - 2.0$ ) and hydrogen-bond basicity ( $a = 0 - 3.7$ ). These interactions, with the singular exception of n-octanol, are signed negative favoring partition into the aqueous phase. Thus for these interactions there is greater competition between water saturated with organic solvent and the organic solvent saturated with water. Even so, the dominant driving force in the partition mechanism remains the characteristic properties of water.

**Table 3.4.** Mutual solubility of organic solvents and water (% w/w) at 20-25°C

Solvent	Solubility of solvent in Water	Solubility of water in solvent
n-Hexane	0.014	0.01
n-Heptane	0.0003	0.01
2,2,4-Trimethylpentane	0.0002	0.006
Cyclohexane	0.05	0.04
Benzene	0.18	0.073
Toluene	0.052	0.033
Chlorobenzene	0.05	0.04
Dichloromethane	1.6	0.24
Chloroform	0.815	0.056
1,2-Dichloroethane	0.87	0.35
Ethyl Acetate	8.7	3.3
Butyl Acetate	0.68	1.2
Diethyl Ether	6.89	1.26
Methyl t-Butyl Ether	4.6	1.5
Propylene Carbonate	17.5	8.3
n-Octanol	0.058	3.82

Hierarchical cluster analysis with the system constants as variables can be used to classify selectivity differences for the aqueous biphasic partition systems in the manner described for solvent classification. The results are shown in Figure 3.5. For solvents of low mutual solubility classification of the aqueous biphasic systems follows the trends anticipated from the results of the classification of organic solvents discussed previously. The hydrocarbon



**Figure 3.5.** Average linkage agglomeration cluster dendrogram for the aqueous biphasic liquid-liquid partition systems summarized in Table 3.3. Identification of organic countersolvent: Hex = n-Hexane; Hep = n-Heptane; Tmp = 2,2,4-Trimethylpentane; Ch = Cyclohexane; Ctc = Carbon Tetrachloride; Bz = Benzene; Tol = Toluene; ClBz = Chlorobenzene; Dcm = Dichloromethane; Dce = 1,2-Dichloroethane; Chlf = Chloroform, Ea = Ethyl Acetate; Ba = n-Butyl Acetate; and Octanol = 1-Octanol.

countersolvents have similar properties to carbon tetrachloride and form one group with slightly different selectivity to the aromatic hydrocarbons which form a separate group. The haloalkane solvents (except for 1-chlorobutane which is grouped with the aromatic hydrocarbon solvents) are clustered together as the third group. The fourth cluster contains the alkyl ethers and acetates with modest within class differences. Propylene carbonate and octan-1-ol aqueous biphasic systems behave independently. The acetates, ethers, propylene carbonate and octan-1-ol

systems are significantly different to the first three clusters, but since these solvents also possess the highest mutual solubility, this is probably due as much to the solubility of water in the organic countersolvent as the characteristic properties of the countersolvent itself. The dynamic range of system constants for the aqueous biphasic systems is not large and so selectivity differences are reasonably small and tend to be dominated by the high cohesion and strong hydrogen-bond acidity of water. Figure 3.5 serve as a reasonable guide for the initial screening of aqueous biphasic systems for separation purposes.

Ternary and quaternary solvent systems are widely used in separation processes but with the exception of Folch's partition system employed for the isolation of lipids from biological tissues, these have not been studied using the solvation parameter model [48]. The Folch system, Table 3.3, is quite unlike the other aqueous systems in that water is distributed in significant amounts to both phases and so its separation characteristics are closer to those of the totally organic biphasic systems than the other aqueous biphasic system in Table 3.3. It is likely that ternary and quaternary aqueous biphasic systems could be useful as a means of extending the selectivity range of the aqueous biphasic systems studied so far.

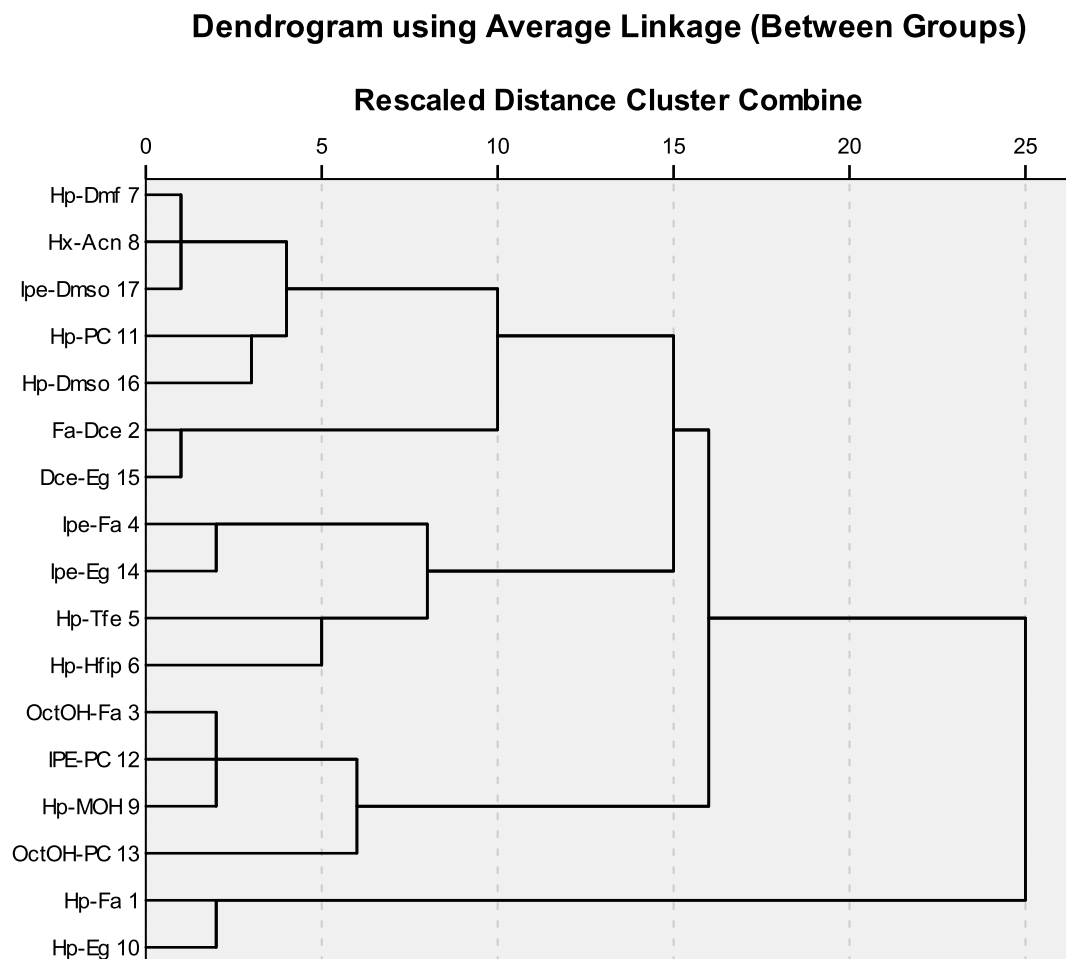
### **3.3.2 Totally organic liquid-liquid biphasic systems**

The system constants for the totally organic biphasic systems included in previous chapters are summarized in Table 3.5 [29,50-54]. One reason for treating these systems separately is that there is no overlap of the selectivity with the aqueous biphasic systems. Cluster analysis of the systems in Table 3.3 and 3.5 (not shown) indicates division into two families corresponding to the solvent systems entered in each table. This is a further example of the exceptional properties of water and its ability to dominate the partitioning process in systems with low mutual solubility.

**Table 3.5.** System constants for totally organic biphasic partition systems used for separation processes

Solvent	System constants					
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>	<i>c</i>
n-Heptane-ethylene glycol	0.093	-1.553	-3.781	-1.548	2.133	0.358
n-Heptane-N,N-dimethylformamide	0.038	-1.391	-2.16	-0.593	0.486	0.255
n-Heptane-dimethyl sulfoxide	0	-1.781	-3.088	-1.167	1.18	0.289
n-Heptane-formamide	0.559	-2.244	-3.25	-1.614	2.387	0.083
n-Heptane-hexafluoroisopropanol	1.03	-1.712	-0.669	-1.746	1.121	-0.49
n-Heptane-methanol	0.186	-0.686	-1.098	-0.951	0.618	-0.16
n-Heptane-propylene carbonate	0.455	-2.087	-2.646	-0.433	0.807	0.502
n-Heptane-trifluoroethanol	0.882	-1.557	-1.312	-2.928	1.301	0.013
n-Hexane-acetonitrile	0.349	-1.439	-1.611	-0.874	0.669	0.152
Ethylene glycol-1,2-dichloroethane	0.096	0	2.468	0.991	-1.31	-0.64
Formamide-1,2-dichloroethane	-0.082	0.399	1.957	1.298	-1.71	-0.21
Isopentyl ether-dimethyl sulfoxide	0	-1.452	-2.153	-0.972	1.116	0.154
Isopentyl ether-ethylene glycol	-0.09	-1.159	-1.53	-1.901	2.089	0.419
Isopentyl ether-formamide	0.564	-1.715	-1.314	-1.407	2.005	0.13
Isopentyl ether-propylene carbonate	0.298	-1.432	-0.718	-0.472	0.729	0.264
Octan-1-ol-formamide	0.267	-1.053	-0.333	-0.929	1.314	0.285
Octan-1-ol-propylene carbonate	0.256	-1.068	-0.222	0	0.365	0.282

For the aqueous biphasic systems the  $v$  system constant is generally  $> 4$  while for the totally organic biphasic systems it falls into the range 0.3-2.4. Water is significantly more cohesive than all of the organic solvents in Table 3.1 and size becomes a dominant factor in determining partition coefficients in the aqueous biphasic systems. Similarly, the  $b$  system constant of the aqueous biphasic systems is typically  $> 4$  while for the totally organic biphasic systems it is generally  $< 2$  (the exception is the n-heptane-2,2,2-trifluoroethanol system with  $b = 2.928$ ). The strong hydrogen-bond acidity of water has a significant influence on the distribution of hydrogen-bond bases that is not observed, in general, for the totally organic biphasic solvent systems. There is extensive overlap of the range for the  $e$ ,  $a$  and  $s$  system constants for the aqueous and totally organic biphasic systems. The interactions represented by these system constants have similar importance in both types of biphasic systems.



**Fig 3.6.** Average linkage agglomeration cluster dendrogram for the totally organic liquid-liquid partition systems summarized in Table 3.5. Identification: Acn = Acetonitrile; Dce = 1,2-Dichloroethane; Dmf = *N,N*-Dimethylformamide; DMSO = Dimethyl sulfoxide; Eg = Ethylene Glycol; Fa = Formamide; Hp = *n*-Heptane; Hfip = Hexafluoroisopropanol; Hx = *n*-hexane; Ipe = Isopropyl Ether; MOH = Methanol; OctOH = Octan-1-ol; PC = Propylene Carbonate; Tfe = 2,2,2-Trifluoroethane

The results of cluster analysis for the totally organic biphasic systems are summarized in Figure 3.6. The dendrogram demonstrates that the solvent systems encompass a wide selectivity range with little redundancy. Although four major clusters can be recognized in the dendrogram each cluster is generally composed of neighbors best described as the nearest equivalent system rather than selectivity equivalent systems. An example from each major group could be used for general screening but for optimization further members of a group should be evaluated due to the

considerable difference in selectivity within each group. Redundancy among the aqueous biphasic systems is common because of the extreme properties of water while the lack of redundancy in the totally organic biphasic systems reflects the wider range of solvent properties for the polar solvents and the limited contribution of countersolvents, such as n-heptane, in contributing to polar interactions and cohesion observed for the totally organic biphasic systems.

**Footnote:**

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## CHAPTER 4

### SOLUTE DESCRIPTORS FOR FRAGRANCE COMPOUNDS AND PLASTICIZERS

#### 4.1. Introduction

Essential oils are liquids containing volatile aroma compounds obtained mainly from plant materials by steam distillation, infusion, extraction or cold-pressing [1]. They are widely used in the cosmetics, perfumery, pharmaceuticals, beverage, personal care, and food industries where their attractive odor and/or flavor is exploited to enhance the value of consumer products. Fragrances may also contain synthetic aroma compounds as well as compounds of natural origin. Several natural fragrances are terpene hydrocarbons and their oxygenated derivatives with high structural diversity. Some fragrance compounds are known or suspect allergens and subject to regulatory control [2]. For perspective, when used as cosmetic products in the European Union it is required to inform consumers of the presence of potential allergenic compounds in cosmetic products if present at a concentration that exceeds 0.001% in leave-on products or 0.01% in rinse-off products [2] with similar regulations in force in other countries and trading blocks around the globe. Effective analytical methods employing headspace and/or extraction methods for isolation and gas chromatography for separation with mass spectrometric detection have been developed for cosmetics to support compliance with regulatory requirements [3-6].

The dialkyl esters formed from phthalic, adipic, and succinic acids, etc., and the alkyl monoesters of oleic and stearic acids, etc., are widely used in industry as solvents and plasticizers with an estimated worldwide production of several million tonnes per year [7]. The phthalate esters dominate the market for plasticizers. The stability, fluidity and low volatility of high molecular weight phthalate esters make them highly suitable as additives to plastics like poly(vinyl chloride), where they are used in amounts up to 60% (*w/w*), to increase flexibility and workability brought about by a decrease in the glass transition temperature of the polymer. Low

molecular weight phthalate esters are more typically used in epoxy resins and cellulose ester-based plastics, adhesives, as heat transfer fluids, and as solvents in cosmetics, personal care products, and inks. In virtually all applications phthalate esters are physically combined in the final product and can be extracted or released into the environment to various extents during production and manufacture, the normal use of products, and after their disposal. On account of their large production volume and high potential for bioaccumulation they are regarded as persistent organic contaminants and regulated by several environmental agencies worldwide [8-10]. A considered debate persists concerning their potential for negative health effects with differing opinions expressed as to their potential for carcinogenesis (suspected in animals but not proven in humans), endocrine disrupting ability, damage to liver and kidney and the development of reproductive organs [9,11]. Photodegradation by free radical attack is the dominant degradation pathway in the atmosphere while biodegradation dominates in surface waters, sediments and soil [8,9,12].

The environmental fate of these compounds depends upon a variety of physicochemical and biological processes. The purpose of this work is the experimental determination of descriptor values for fragrance and plasticizers to facilitate the estimation of a range of physicochemical and biological properties available through use of the solvation parameter model. These descriptors also provide chemical insight into how different compounds behave in transfer systems. The low vapor pressure of higher molecular weight phthalate esters and extremely low water solubility of both compound types contribute to the difficulty of measuring properties usually taken to calculate solute descriptor (e.g; water solubility, retention factors, and partition coefficient). We encountered a similar problem in calculating descriptors for organosilicon compounds and developed an alternative procedure that uses a combination of gas chromatography and partitioning in totally organic solvent systems for this purpose [13,14].The

same iteration procedure is used here to determine the solute descriptors for fragrance compounds and phthalate esters.

The solvation parameter model as generally used in studies of transfer properties takes two forms as described in chapter 1. For transfer from a gas phase to a condensed phase (for example, gas-liquid chromatography)

$$\log k = c + eE + sS + aA + bB + lL \quad (4.1)$$

and for transfer between condensed phases (for example, as in liquid-liquid partition)

$$\log K_p = c + eE + sS + aA + bB + vV \quad (4.2)$$

where the dependent variable is an experimental property such as a chromatographic retention factor,  $k$ , or a partition coefficient,  $K_p$ .

## 4.2 Experimental

### 4.2.1 Materials

The solvents ethylene glycol, propylene carbonate, 1,2-dichloroethane, and formamide were obtained from Acros Organics (Morris Plains, NJ, USA) and n-heptane, isopentyl ether, dimethyl sulfoxide, and 2,2,2-trifluoroethanol from Sigma-Aldrich (Milwaukee, WI, USA). The solvents were dried over molecular sieves prior to use. The plasticizers were obtained from Chem Service (West Chester, PA, USA). The fragrance chemicals and their source are identified in Table 4.1. The columns used to determine retention factors by gas chromatography and their system constants over the temperature range 60-280°C are identified in Table 4.2 [20-23]. The HP-5 column, Table 4.2, was used in the measurement of liquid-liquid partition coefficients. The 5 cm x 4.6 mm Synergi Polar-RP column for reversed-phase liquid chromatography was obtained from Phenomenex (Torrence, CA, USA).

**Table 4.1.** Plant-derived and synthetic fragrance compounds with those indicated as known or suspect allergens according to European Union regulations [2]

Common name	Systematic chemical name	Source*
<i>(i) Allegens</i>		
Amyl cinnamal	(Phenylmethylene)heptanal	TCI
Anise alcohol	4-Methoxybenzyl alcohol	CS
Benzyl alcohol		SA
Benzyl benzoate		ACROS
Benzyl cinnamate	Benzyl 3-phenylpropenoate	TCI
Benzyl salicylate	Benzyl 2-hydroxybenzoate	TCI
Cinnamyl alcohol	3-phenyl-2-propen-1-ol	ACROS
Citral (geranial)	3,7-Dimethylocta-2,6-dienal (E-isomer)	CS
Citral (neral)	(Z-isomer)	CS
Coumarin	2H-1-Benzopyran-2-one	SA
Eugenol	2-Methoxy-4-prop-2-enylphenol	ACROS
Farnesol	3,7,11-trimethyldodeca-2,6,10-trien-1-ol	SA
Geraniol	3,7-Dimethylocta-2,6-dien-1-ol	TCI
Hydroxycitronellal	3,7-dimethyl-7-hydroxyoctanal	SA
$\alpha$ -Isomethyl ionone	3-Methyl-4(2,6,6-trimethyl-1-cyclohex-2-enyl)-but-3-en-2-one	SA
Lilial	3-(4- <i>tert</i> -butylphenyl)butanal	TCI
Limonene	1-Methyl-4-(1-methethenyl)cyclohexene	CS
Linalool	3,7-Dimethyl-1,6-dien-3-ol	ACROS
Methyleugenol	1,2-Dimethoxy-4-prop-2-enylbenzene	TCI
<i>(ii) Not known to be allergens</i>		
Borneol	1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-ol	ACROS
Camphor	1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one	CS
Carvone	2-Methyl-5-(1-methylethenyl)-2-cyclohexanone	ACROS
Citronellal	3,7-Dimethylocta-2,6-dienal	CS
2-Methoxycinnamaldehyde		SA
$\alpha$ -Pinene/ $\beta$ -Pinene	4,7,7-Trimethylcyclo[3.1.1]hept-3-ene	CS
Terpinen-4-ol	4-Isopropyl-1-methyl-1-cyclohexen-4-ol	ACROS
Vanillin	4-Hydroxy-3-methoxybenzaldehyde	SA

\*ACROS = ACROS Organics, Morris Plains, NJ, USA; CS = Chem Services Inc., West Chester, PA, USA; SA = Sigma-Aldrich, Milwaukee, WI, USA; and TCI = TCI America, Portland, OR, USA

**Table 4.2.** Wall-coated open-tubular columns used for descriptor calculations by gas chromatography. Columns are calibrated for use over the temperature range 60-280°C

Column	Source*	Dimensions	Film thickness
SPB-Octyl	A	30 m x 0.25 mm	0.25 µm
HP-5	B	30 m x 0.32 mm	0.25 µm
Rtx-440	C	30 m x 0.25 mm	0.50 µm
DB-225	B	15 m x 0.32 mm	0.25 µm
HP-88	B	25 m x 0.25 mm	0.20 µm
Rtx-OPP	C	30 m x 0.32 mm	0.15 µm
Rtx-5Sil MS	C	30 m x 0.25 mm	0.50 µm
HP-Innowax	B	60 m x 0.53 mm	1.00 µm
DB-1701			
Rxi-17			

\*A = Supelco, Bellefonte, PA, USA; B = Agilent Technologies, Folsom, CA, USA; and C = Restek Corporation (Bellefonte, PA, USA).

#### 4.2.2 Instrumentation

Gas chromatographic measurements were made with an Agilent Technologies (Palo Alto, CA, USA) HP6890 gas chromatograph fitted with a split/splitless injector and flame ionization detector using Chemstation software (rev. 8.04.01) for data acquisition. Nitrogen was used as the carrier gas at a constant velocity of 47 cm/s. The split ratio was set to 30:1, septum purge 1 mL/min, injector temperature 275°C, and detector temperature 300°C. Isothermal retention factors were determined at 20°C intervals at several temperatures in the range 160-280°C as dictated by the retention characteristics of each compound and the thermal stability of the column. For the measurement of liquid-liquid partition coefficients a temperature program was used starting at 150°C for 1 min and then raised to 280°C at 25°C/min on the HP-5 column identified in Table 4.2. The temperature program was modified as required to handle co-elution of solutes with the internal standard or solvent peaks and to elute some of the less volatile phthalate esters.



Liquid chromatographic measurements were made with a Hitachi D-7000 liquid chromatograph (Hitachi Instruments, San Jose, CA, USA) fitted with a photodiode array detector and column oven set to 45°C. All measurements were made with a column flow rate of 1.5 mL/min. The column hold-up time was determined by injection of an aqueous solution of sodium nitrate (26 mg/mL). The extracolumn residence time was measured by replacing the column with a zero-volume connector and used to correct all retention factors [24]. Retention factors were measured at increments of 10% (v/v) organic solvent for the composition range 30-70% (v/v) methanol or acetonitrile. System constants for the Synergi Polar-RP stationary phase with acetonitrile-water and methanol-water mobile phases were taken from [25].

#### **4.2.3 Partition coefficients from literature sources (for fragrance compounds)**

Liquid-liquid partition coefficients in n-hexane-acetonitrile for  $\alpha$ -pinene,  $\beta$ -pinene, limonene, linalool, borneol, camphor, neral, geranial, farnesol, and eugenol were taken from [26] and used with the system constants given in [27]. Partition coefficient for vanillin in 1,2-dichloroethane-water [28] and chloroform-water [29] were used with the system constants given in [17]. Partition coefficients for vanillin [28,30], eugenol [31,32], carvone [32], terpinen-4-ol [32],  $\alpha$ -pinene [33,45],  $\beta$ -pinene [34], limonene [33,34], linalool [33,35], geraniol [35], anise alcohol [36], borneol [36], camphor [36], and benzyl salicylate [37] in octanol-water were used for verification of the descriptor values with the system constants given in [17]. Henry's law constants for  $\alpha$ -pinene [34],  $\beta$ -pinene [34,38], limonene [34,38,39], linalool [39,40], and carvone [50] were converted to gas-water partition coefficients and used with the system constants given in [17].

#### **4.2.4 Retention factors and partition coefficients from literature sources (for plasticizers)**

Liquid-liquid partition coefficients in n-octanol-water ( $\log K_{ow}$ ) for dimethyl phthalate

(1.61) [8], diethyl phthalate (2.42) [41], di-n-butyl phthalate (4.5) [41], di-isobutyl phthalate (4.46) [8], di(2-ethylhexyl) phthalate (7.45) [8], butyl benzyl phthalate (4.91) [42], and dicyclohexyl phthalate (5.01) [44] were taken from the sources cited. Reversed-phase liquid chromatographic retention factors for diethyl phthalate and di-n-butyl phthalate with acetonitrile-water and methanol-water mobile phases containing 10-70 % (v/v) organic solvent on Discovery HSF5 [45], HSC18 [45], Ascentis C18 [46], Sunfire C18 [47], HyPurity C18 [48], Fluophase RP [49], Betasil C18 [49], XBridge C8 [50], XBridge Phenyl [50], XTerra Phenyl [50], XBridge RP-18 Shield [51], Synergi Hydro RP [43], and Synergi Fusion [43] were taken from the sources cited.

#### 4.2.5 Calculations

All calculations were performed on a Dell Dimension 9200 computer (Austin, TX, USA) using the Solver add-in module in Excel 2007 (Microsoft Corporation, Redmond, WA). The V descriptor was calculated from the molecular formula by summing atom constants and correcting for the number of bonds in the molecule as described in either cite reference or refer to earlier chapter section. It has units of  $\text{cm}^3\text{mol}^{-1}/100$ . The E descriptor was calculated by

$$E = 10V[(\eta^2-1)/(\eta^2+2)] - 2.832V + 0.526 \quad (4.3)$$

where  $\eta$  is the refractive index at 20°C for the sodium D-line . It has units of  $\text{cm}^3\text{mol}^{-1}/10$ . Refractive index values for diethyl phthalate, di-n-octyl phthalate and diethyl sebacate were taken from [52]. Other values were taken from the manufacturer's literature.

To determine the S, A, B and L descriptors it is necessary to set up a series of equations similar to Eq. (4.1) and (4.2) with known system constants that allow the convenient measurement of the partition or retention property for the solute. The descriptors are calculated by finding the unique values for each descriptor that simultaneously minimizes the difference

between the experimental solute properties and the model predicted properties across all equations [17]. The descriptor values were optimized using the Solver method [15-17]. Solver is an optimization package that adjusts selected changing cells (descriptors) to minimize the value in a target cell (standard deviation of the residuals).

$$\text{Standard deviation} = [\sum(\log k_{\text{exp}} - \log k_{\text{cal}})^2/n - 1]^{1/2} \quad (4.4)$$

where  $\log k_{\text{exp}}$  is the experimental retention factor (or partition coefficient),  $\log k_{\text{cal}}$  the model predicted retention factor (or partition coefficient) used in Eq. (4.1) or (4.2), and  $n$  the number of experimental retention factors and partition coefficients for each solute on all columns and temperatures or mobile phase composition and liquid-liquid partition coefficient for all biphasic partition systems.

## 4.3 Results and discussion

### 4.3.1 Fragrance compounds

Retention factors at temperatures appropriate for the compounds indicated in Table 4.1 on the columns identified in Table 4.2 were measured and combined with liquid-liquid partition coefficients for the calculation of descriptor values using the Solver method [17-19]. The descriptors are summarized in Table 4.3. The V descriptor, for all compounds, and the E descriptor, for compounds that are liquid at 20°C, are obtained by calculation. The other descriptors, and the E descriptor for solids, are experimental values. The standard deviation of the residuals supports the conclusion that the descriptors for each compound in Table 4.3 adequately define the properties of the compounds across the experimental systems used for their determination. In the case of farnesol two isomers were observed by gas chromatography on several stationary phases. Since farnesol has four possible structural isomers and individual standards are not available, we were unable to establish the identity of the two peaks observed by

**Table 4.3.** Descriptors for fragrance compounds

Compound	Descriptor						Statistics	
	E	S	A	B	L	V	SD	n
<i>(i) Allegens</i>								
Amyl cinnamal	1.212	1.05	0	0.736	7.133	1.816	0.051	60
Anise alcohol	0.899	0.967	0.537	0.778	5.328	1.116	0.036	69
Benzyl alcohol	0.803	0.871	0.41	0.558	4.248	0.916	0.038	372
Benzyl benzoate	1.264	1.316	0	0.582	7.499	1.68	0.044	143
Benzyl cinnamate	1.311	1.542	0	0.612	8.963	1.919	0.032	40
Benzyl salicylate	1.413	1.338	0.012	0.433	8	1.739	0.038	47
Cinnamyl alcohol	1.096	0.994	0.489	0.592	5.424	1.155	0.04	300
Citral (geranial)	0.61	0.938	0	0.659	5.463	1.447	0.051	58
Citral (neral)	0.589	0.901	0	0.65	5.391	1.447	0.048	68
Coumarin	1.288	1.62	0	0.522	6.015	1.062	0.048	241
Eugenol	0.946	0.865	0.353	0.54	5.785	1.354	0.042	70
Farnesol (isomer 1)	0.675	0.591	0.375	0.791	7.511	2.152	0.038	57
Farnesol (isomer 2)	0.757	0.576	0.372	0.834	7.628	2.152	0.041	55
Geraniol	0.493	0.625	0.282	0.606	5.434	1.49	0.033	72
Hydroxycitronellal	0.262	1.006	0.379	1.1	6.039	1.592	0.028	37
$\alpha$ -Isomethyl ionone	0.762	1.007	0	0.71	6.402	1.902	0.052	59
Lilial	0.775	0.995	0	0.594	6.654	1.859	0.037	59
Limonene	0.497	0.336	0	0.174	4.693	1.323	0.043	62
Linalool	0.391	0.482	0.244	0.745	4.803	1.49	0.028	124
Methyleugenol	0.939	1.05	0	0.781	5.942	1.465	0.041	61
<i>(ii) Not known to be allegens</i>								
Borneol	0.757	0.714	0.158	0.653	5.091	1.359	0.036	139
Camphor	0.506	0.829	0	0.671	5.043	1.316	0.046	146
Carvone	0.638	0.929	0	0.61	5.402	1.339	0.039	132
Citronellal	0.287	0.68	0	0.758	5.071	1.49	0.044	76
2-Methoxycinnamaldehyde	1.219	1.522	0	0.623	6.313	1.311	0.035	58
$\alpha$ -Pinene	0.441	0.19	0	0.225	4.348	1.257	0.034	55
$\beta$ -Pinene	0.525	0.233	0	0.2	4.584	1.257	0.047	46
Terpinen-4-ol	0.553	0.584	0.147	0.651	5.226	1.425	0.033	160
Vanillin	1.107	1.392	0.382	0.664	5.673	1.131	0.028	59

gas chromatography, or determine whether each peak is a single isomer or mixture of at least two of the possible structural isomers. Descriptors for the two peaks are indicated in Table 4.3 as isomer 1 and isomer 2 in the elution order observed on columns of low polarity. To estimate

physicochemical properties for farnesol, section 4.3.2, an average value for the two isomers was used. For a few compounds ( $n > 100$  in Table 4.3) additional data from an earlier study [17] by gas chromatography for additional stationary phases to those shown in Table 4.2, and retention factors by reversed-phase liquid chromatography and micellar electrokinetic chromatography were included in the descriptor calculations.

### 4.3.2 Estimates of physicochemical properties

Now that the full range of descriptors are available for the fragrance compounds in Table 4.1 they can be used to estimate the behavior of these compounds in a variety of chromatographic, environmental and biological systems. The purpose of this section is to illustrate this possibility for some properties of relevance to the role of fragrance chemicals in odor responsiveness, skin absorption and environmental fate. These are just a few of the properties that can now be estimated using existing models.

The single most widely used physicochemical property for the prediction of the distribution and fate of neutral organic compounds in the environment and biological systems is the octanol-water partition coefficient [36,53,54]. Estimated octanol-water partition coefficients ( $\log K_{OW}$ ) determined using the system constants in [17] are compared with experimental values for seventeen compounds in Table 4.4 [28,30-37]. The relative error for the two sets of data is -0.011 indicating that there is no significant bias in the capability of the model to predict the octanol-water partition coefficients using the descriptors in Table 4.3. The relative absolute error of 0.127 suggests that the descriptors are suitable for the prediction of the partition coefficients with no greater uncertainty than is anticipated in the measurement of experimental partition coefficients. The latter is unknown in absolute terms, of course, but from the general agreement between independently determined experimental partition coefficients is not expected to be less

**Table 4.4.** Comparison of estimated and experimental octanol-water partition coefficients for fragrance compounds.

Compound	Octanol-water partition coefficient (log K <sub>OW</sub> )	
	Estimated <sup>1</sup>	Experimental <sup>2</sup>
Amyl cinnamal	4.16	
Anise alcohol	1.11	1.10
Benzyl alcohol	1.16	1.10
Benzyl benzoate	3.87	3.97
Benzyl cinnamate	4.44	
Benzyl salicylate	4.67	4.31
Cinnamyl alcohol	2.00	1.70
Citral (geranial)	2.72	
Citral (neral)	2.78	
Coumarin	1.34	1.39
Eugenol	3.02	2.99
Farnesol	5.35	
Geraniol	3.31	3.47
Hydroxycitronellal	1.41	
$\alpha$ -Isomethyl ionone	4.32	
Lilial	4.57	
Limonene	4.52	4.48 (av)
Linalool	2.95	2.97
Methyleugenol	2.59	
<i>(ii) Not known to be allegens</i>		
Borneol	2.74	2.72
Camphor	2.24	2.13 (av)
Carvone	2.50	2.71
Citronellal	2.65	
2-Methoxycinnamaldehyde	2.03	
$\alpha$ -Pinene	4.23	4.66
$\beta$ -Pinene	4.30	4.22
Terpinen-4-ol	3.02	2.86 (av)
Vanillin	1.21	1.19 (av)

<sup>1</sup> Estimated using  $\log K_{OW} = 0.083 + 0.684E - 1.209S - 0.185A - 3.355B + 3.846V$  [17]

<sup>2</sup> Where multiple experimental values for log K<sub>OW</sub> were reported an average value (av) is indicated.

than about 0.2-0.3 log units [53]. In Table 4.5 are assembled estimated values for sensor irritation threshold, log (1/SIT) [56], odor detection threshold, log (1/ODT) [55,56], nasal pungency threshold, (log 1/NPT) [55,56,57], skin permeability coefficient from water (log k<sub>p</sub>) [58,59], skin-water partition coefficient (log K<sub>SC</sub>) [58,59], absorption to ambient air particles (log

$K_A$ ) [60,64] or adsorption to diesel soot particles ( $\log K_{DS}$ ) [61,64], air-water partition coefficients ( $\log K_W$ ) [17], and film water adsorption ( $\log K_{AW}$ ) [62,63].

Table 4.5. Estimated properties for biological and environmental processes calculated with the solvation parameter model. Sensory irritation threshold, odor detection threshold and nasal pungency threshold have units of parts per million, skin permeability coefficients from water cm/s, absorption to air particulates  $m^3/g$ , adsorption to diesel soot  $m^{-1}$ , and adsorption to film water  $m^{-1}$ .

	Biological <sup>1</sup>				Environmental <sup>1</sup>				
	$\log$ (1/SIT)	$\log$ (1/ODT)	$\log$ (1/NPT)	$\log k_p$	$\log$ $K_{SC}$	$\log$ $K_A$	$\log$ $K_{DS}$	$\log$ $K_W$	$\log$ $K_{AW}$
Amyl cinnamal	0.17	3.69	0.73	-4.09	2.30	1.20	0.61	4.15	-1.08
Anise alcohol				-6.01	0.80	0.94	0.54	6.51	2E-3
Benzyl alcohol	-1.09	1.38	-1.12	-5.69	0.90	-0.58	-1.45	4.99	-2.04
Benzyl benzoate	0.66	4.27	1.16	-4.07	2.34	1.67	1.04	4.18	-1.23
Benzyl cinnamate				-3.72	2.69	3.22	2.97	4.60	0.04
Benzyl salicylate				-3.52	2.82	2.04	1.30	3.54	-1.58
Cinnamyl alcohol	0.29	2.79	0.33	-5.37	1.35	0.76	0.05	5.62	-1.01
Citral (geranial)	-1.35	1.84	-1.03	-4.59	1.60	-0.35	-0.94	3.65	-2.02
Citral (neral)	-1.48	1.69	-1.16	-4.54	1.62	-0.45	-1.05	3.51	-2.12
Coumarin	-0.03	3.71	0.25	-5.46	1.27	0.57	-0.45	3.27	-1.85
Eugenol	-0.19	2.44	-0.02	-4.61	1.81	0.62	-0.04	5.26	-2.13
Farnesol	1.13	3.51	1.50	-3.45	2.67	2.25	2.41	4.22	0.86
Geraniol	-0.99	1.48	-0.81	-4.30	1.81	0.03	-0.37	4.15	0.79
Hydroxycitronellal	1.11	3.45	1.16	-5.75	0.76	1.57	2.02	6.98	1.84
$\alpha$ -Isomethyl ionone	-0.47	2.81	-0.06	-3.75	2.37	0.57	0.14	7.05	1.60
Lilial	-0.47	2.80	-0.04	-3.49	2.55	0.71	0.23	3.27	-1.60
Limonene	-3.58	-0.70	-3.22	-3.12	2.51	-1.93	-3.09	-0.22	-5.00
Linalool	-1.62	0.85	-1.43	-4.62	1.50	-0.66	-1.07	3.67	-1.53
Methyleugenol	-0.64	2.76	-0.24	-4.93	1.51	0.21	-0.42	4.57	-1.41
Borneol				-4.76	1.54	-0.53	-1.27	3.72	-2.11
Camphor				-4.86	1.32	-0.80	-1.41	3.44	-2.26

Carvon	-1.48	1.72	-1.16	-4.69	1.52	-0.45	-1.12	3.43	-2.29
Citronellal	-1.92	1.04	-1.61	-4.63	1.40	-0.81	-1.19	3.27	-1.84
2-Methoxycinnamaldehyde				-5.13	1.51	0.83	0.01	5.31	-1.57
$\alpha$ -Pinene	-4.01	-1.18	-3.63	-3.35	2.29	-2.33	-3.52	-0.36	-5.12
$\beta$ -Pinene	-3.79	-0.93	-3.40	-3.30	2.36	-2.11	-3.32	-0.37	-5.10
Terpinen-4-ol	-1.60	1.15	-1.32	-4.51	1.62	-0.52	-1.08	3.14	-2.02
Vanillin				-5.78	1.07	1.15	0.52	6.69	-0.52

<sup>1</sup> Models employed for property estimations

$$\log (1/\text{SIT}) = -7.839 + 1.620\text{S} + 3.431\text{A} + 1.413\text{B} + 0.759\text{L} \quad [56]$$

$$\log (1/\text{ODT}) = -5.27 + 0.51\text{E} + 1.96\text{S} + 1.48\text{A} + 1.53\text{B} + 0.723\text{L} \quad [55]$$

$$\log (1/\text{NPT}) = -7.89 + 0.20\text{E} + 1.32\text{S} + 2.71\text{A} + 1.52\text{B} + 0.823\text{L} \quad [55]$$

$$\log k_{\text{P}} = -5.426 - 0.106\text{E} - 0.473\text{S} - 0.473\text{A} - 3.000\text{B} + 2.296\text{V} \quad [58]$$

$$\log K_{\text{SC}} = 0.341 + 0.341\text{E} - 0.206\text{S} - 0.024\text{A} - 2.178\text{B} + 1.850\text{V} \quad [58]$$

$$\log K_{\text{A}} = -6.515 - 0.209\text{E} + 0.958\text{S} + 2.534\text{A} + 0.680\text{B} + 0.906\text{L} \quad [64]$$

$$\log K_{\text{DS}} = -8.61 - 1.02\text{E} + 1.10\text{S} + 3.19\text{A} + 1.49\text{B} + 1.15\text{L} \quad [64]$$

$$\log K_{\text{W}} = -0.929 + 0.474\text{E} + 3.042\text{S} + 3.819\text{A} + 4.531\text{B} - 0.286\text{L} \quad [64]$$

$$\log K_{\text{AW}} = -8.63 - 0.95\text{E} + 1.06\text{S} + 3.49\text{A} + 4.01\text{B} + 0.65\text{L} \quad [62]$$

These measurements are generally made according to a specific protocol that has to be followed to obtain comparable results. The sensory impact of volatile chemicals in humans results predominantly from the stimulation of the olfactory nerve (odor detection) and the trigeminal nerve (eye irritation and pungency detection) [56,57]. The independently derived models for eye irritation and nasal pungency are almost equivalent and can be combined into a more general model for sensory irritation thresholds [56]. Underlying these models is that sensory perception can be predicted from the transfer of volatile chemicals from the gas phase to a receptor phase area. The models do not account for selective interactions that some compounds might have with specific receptors in the receptor phase area but can be helpful in identifying the contribution of specific receptor interactions to the overall sensory stimulation caused by volatile chemicals. The estimated values for the volatile fragrance compounds in Table 4.5 (estimates are not given for solid compounds of low volatility because these may not be compatible with the experimental



protocol) indicate a wide range of sensitivities covering 5 to 6 orders of magnitude. A distinguishing feature of the different measures of odor responsiveness is the  $a/b$  system constant ratio at 2.43 for the sensory irritation threshold, 1.78 for the nasal pungency threshold, and 0.97 for the odor detection threshold. The capability of a compound to participate in hydrogen-bonding interactions (A and B descriptors) is important for odor responsiveness, as well as its capability to produce vapors soluble in low-polarity regions of the receptor (L descriptor). Interactions of a dipole-type also contribute to sensory thresholds but vary less among the three sensory threshold models ( $s$  varies from 1.3 to 1.6). There are a few experimental values for the odor detection threshold ( $\log 1/ODT$ ) for linalool (experimental = 0.02 and estimated = 0.85), geraniol (experimental = 1.05 and estimated = 1.48), limonene (experimental = -0.99 [R-enantiomer] and -0.66 [S-enantiomer] and estimated = -0.70),  $\alpha$ -pinene (experimental = -1.28 and estimated = -1.18), and  $\beta$ -pinene (experimental = -1.07 and estimated = -0.93) [56]. There is good agreement for geraniol, limonene (the solvation parameter model contains no term to distinguish individual enantiomers),  $\alpha$ -pinene, and  $\beta$ -pinene but poor agreement for linalool. There are too few experimental values for the odor detection threshold for the fragrance compounds in Table 4.1 to comment in a general sense on the difference between the experimental and predicted threshold values. The agreement, accept for perhaps linalool, is quite good given the difficulty of the experimental measurements and the understandably wide standard deviations for the experimental values [55,56].

The skin permeability coefficients and partition coefficients provide useful information on the rate (permeability) and uptake (partition) by dermal absorption from exposure to fragrance chemicals in aqueous solution [58,59]. Most fragrance compounds are expected to transfer from water to skin relatively quickly (intermediate to large permeability coefficients) and accumulate in the skin (intermediate to high partition ratios). The permeability coefficient ( $\log k_p$ ) covers the

range from about -6 to -3 and the partition coefficient ( $\log K_{sc}$ ) from 0.8 to 3. The driving force for the rate and extent of solute transfer is size (V descriptor) with the property that favors slower transfer and distribution to the aqueous phase is hydrogen-bond basicity (B descriptor). Thus compounds like benzyl alcohol and anise alcohol are poorly absorbed by skin compared with the terpene derivatives and benzyl esters. For benzyl alcohol the prediction ( $\log k_p = -5.69$ ) is in good agreement with the experimental value -5.30 [58]. This is the only experimental value we are aware of for the compounds in Table 4.1.

Absorption by air particles [60,64] and adsorption by diesel soot particles [61,64] provide insight into particle phase deposition of volatile chemicals in atmospheric aerosols. In both cases the capacity for polar interactions (S, A, and B descriptor) favors particle sorption processes as well as non-polar interactions represented by the L descriptor. For the fragrance compounds  $\log K_A$  covers the range -2.5 to 3.3 and  $\log K_{DS}$  the range -3.5 to 3. These are wide ranges and indicate that there is no general conclusion that can be made for fragrance compounds as a group and it is necessary to consider compounds individually to assess the ability of air particulates to remove fragrance compounds from the atmosphere. The mechanism is less efficient for the small low polarity terpenes (for example, limonene,  $\alpha$ -pinene, etc.) and efficient mechanism for larger and polar terpene derivatives and related compounds (for example, benzyl cinnamate, farnasol, hydroxycitronellal, etc.)

The partition of trace volatile compounds from air to water ( $\log K_W$ ) demonstrates efficient absorption of most fragrance compounds by bulk water (such as rain droplets). The exception is weakly polar terpenes, such as  $\alpha$ -pinene,  $\beta$ -pinene and limonene which are only poorly absorbed compared to the more polar compounds in Table 4.5. The predicted partition coefficients cover a wide range from -0.2 to about 7 with small molecules that are capable of strong hydrogen-bonding interactions having the most favorable partition coefficients. Except for

carvone there is good agreement between experimental and predicted air-water partition coefficients for the seven compounds with experimental values [benzyl alcohol = 4.86 (predict 4.99), camphor = 3.44 (predict 3.44), carvone = 4.24 (predict 3.43), limonene = -0.20 (predict -0.22), linalool = 3.72 (predict = 3.67),  $\alpha$ -pinene = -0.40 (predict -0.36), and  $\beta$ -pinene = -0.44 (predict -0.37)]. Adsorption to film water shows significant characteristic differences to absorption by bulk water accounted for largely by the difference in cavity formation and dispersion interactions for immersion of a compound into bulk water and interactions of a compound with the surface layer of water molecules as well as a significant contribution from electron lone pair repulsion for adsorption on film water. Also, interactions of a dipole-type contribute less to adsorption by film water compared with absorption by bulk water. Compounds such as anise alcohol and vanillin have favorable partition coefficients for absorption by bulk water but are only weakly adsorbed by film water. The predictions in Table 4.5 provide an indication that for a number of fragrance compounds the efficiency of removal from aerosols by bulk water and film-supported water are expected to be quite different.

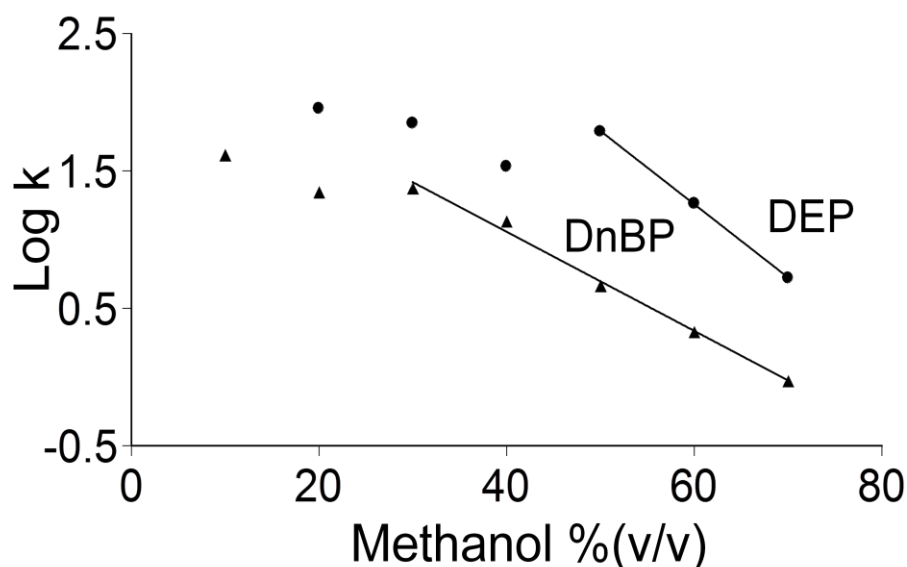
#### 4.3.3. Phthalate esters

The dialkyl phthalate esters have been widely used as stationary phases in packed-column gas chromatography [65] and their solvation characteristics established using the solvation parameter model [66]. The dialkyl phthalates are weakly polar solvents of low volatility. The dominant interaction responsible for retention is dispersion with small contributions from dipole-type and solvent hydrogen-bond base interactions. The dialkyl phthalates are non-hydrogen-bond acids. Based on structure and the experimental data for their properties as solvents it is reasonable to assign a value of zero for the hydrogen-bond acidity descriptor for these compounds ( $A = 0$ ) and for the other compounds in this study. Apart from dicyclohexyl phthalate, all other compounds are liquids and the E descriptor can be calculated using Eq. (4.3).

The E descriptor for dicyclohexyl phthalate was estimated from fragment constants [16,17]. The V descriptor was calculated from the molecular formula by summing atom constants and correcting for the number of bonds in the molecule as described in [17]. That leaves the L, S and B descriptor to be determined by experiment.

Reversed-phase liquid chromatography is a useful technique for the determination of the B descriptor and to a lesser extent the S descriptor [16-19]. For the phthalate esters and similar large and bulky compounds steric resistance is a potential problem [15,17,45-51] and was found to affect the retention factors for many of the compounds of interest to this study. Steric resistance results from the inability of a compound to embed itself completely into a solvated stationary phase because of its size or shape. It can be recognized by a characteristic discontinuity in plots of the retention factor ( $\log k$ ) as a function of the volume fraction of organic solvent for binary mobile phases.

As an example Figure 4.1 presents data for diethyl phthalate and dibutyl phthalate on Synergi Fusion-RP (a polar embedded  $C_{18}$  stationary phase) with a methanol-water mobile phase. For diethyl phthalate reliable retention factors can be determined for methanol compositions higher than 30% (v/v) and for dibutyl phthalate only higher than 50% (v/v) methanol. The results become uncertain for higher homologs limiting the use of this stationary phase, and also most of those trialed for this application. The determination of the B descriptor requires some balance between high water content (larger value of the  $b$  system constant) and acceptable retention (high volume fractions of methanol to avoid excessive retention). A reasonable balance of these properties was obtained for the Synergi Polar-RP column (monomeric ether-linked phenyl phase with a propyl chain as spacer). This column was used to obtain retention factors for as many of the compounds indicated in Table 4.5 as possible, but



**Figure 4.1.** Illustration of the loss of retention at low organic solvent compositions due to steric resistance on a Synergi Fusion-RP stationary phase for diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP). Diethyl phthalate can only completely embed itself into the stationary phase at methanol compositions higher than 30% (v/v) and in the case of di-n-butyl phthalate greater than 50% (v/v) methanol (the experimental points connected by a solid line). In the high organic solvent range where normal retention is observed retention factors can be predicted by the solvation parameter model. The high organic solvent region corresponds to moderate  $b$  system constants and is less effective for estimating the B descriptor than the high water composition region.

many of the higher molecular weight compounds had to be excluded from the descriptor calculations due to steric resistance.

Experimental and literature retention factors together with the liquid-liquid partition coefficients were combined into compound databases and used to determine those descriptors that could not be obtained by direct calculation using the Solver method [14,16,17,23]. The descriptors are summarized in Table 4.6 together with the standard deviation of the residuals (SE) and the total number of experimental retention factors and partition coefficients included in the calculation ( $n$ ). The standard deviation of the residuals supports the conclusion that the descriptors for each compound in Table 4.6 adequately define the properties of the compounds across the experimental systems used for their determination.

**Table 4.6.** Descriptors for Plasticizers (A = 0 for all compounds)

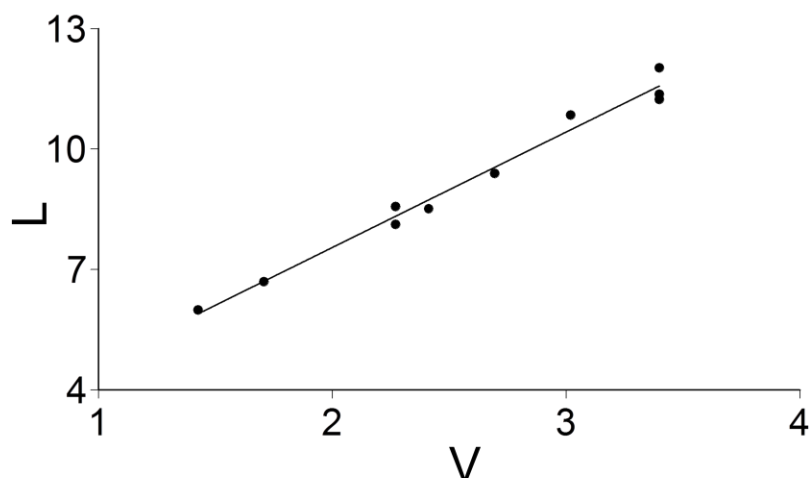
Compound	Descriptors					Statistics	
	E	S	B	L	V	SE	n
Dimethyl phthalate	0.795	1.487	0.81	5.977	1.4288	0.039	65
Diethyl phthalate	0.725	1.394	0.887	6.677	1.7106	0.038	226
Di-n-butyl phthalate	0.694	1.299	0.938	8.553	2.2742	0.035	144
Di-n-octyl phthalate	0.662	1.255	1.157	12.037	3.4014	0.05	37
Dicyclohexyl phthalate	1.405	1.508	1.067	10.799	2.6206	0.042	43
Di-isobutyl phthalate	0.672	1.235	0.948	8.108	2.2742	0.036	73
Di-2-ethylhexyl phthalate	0.693	1.155	1.189	11.324	3.4014	0.048	44
Di-2-octyl phthalate	0.644	1.129	1.096	11.242	3.4014	0.043	40
Butyl benzyl phthalate	1.296	1.728	1.01	9.799	2.4593	0.041	44
Butyl cyclohexyl phthalate	1.083	1.408	0.936	9.636	2.4474	0.047	51
Butyl n-heptyl phthalate	0.806	1.182	1.132	9.373	2.6969	0.048	26
Butyl n-pentyl phthalate	0.753	1.288	1.033	8.495	2.4151	0.038	48
Benzyl 2-ethylhexyl phthalate	1.405	1.301	1.342	10.833	3.0229	0.046	37
Di-(2-methoxyethyl) phthalate	0.788	1.749	1.483	8.337	2.1098	0.054	52
Di-(2-ethoxyethyl) phthalate	0.619	1.558	1.501	9.049	2.3916	0.056	50
Di-(2-butoxyethyl) phthalate	0.641	1.582	1.492	10.689	2.9552	0.046	37
Butyl oleate	0.024	0.634	0.587	10.867	3.2398	0.04	48
Butyl stearate	0.051	0.463	0.675	11.056	3.2828	0.052	46
Methyl arbutate	1.222	1.147	1.071	10.186	2.7301	0.051	46
Diethyl adipate	0.085	1.009	0.868	5.926	1.6664	0.044	44
Dicyclohexyl adipate	0.649	1.28	1.083	10.039	2.5108	0.049	43
Dibutyl succinate	0.091	0.935	0.968	6.884	1.9482	0.037	58
Diethyl sebacate	0.043	1.058	0.98	7.878	2.23	0.029	54
Diethyl diethylmalonate	0.01	0.729	0.858	5.645	1.8073	0.033	54

For the phthalate esters there is a useful correlation between the L (an experimental value) and the V (a calculated value) descriptors as shown in Figure 4.2.

The regression model can be described by the relationship

$$L = 2.85 (\pm 0.15)V + 1.95 (\pm 0.39) \quad (4.5)$$

$$r^2 = 0.971 \quad F = 372 \quad SE = 0.328 \quad n = 13$$



**Figure 4.2.** Plot of the L descriptor against the V descriptor for phthalate esters with alkyl and aromatic side chains (the values for the alkoxyalkyl side chains are not shown to simplify the diagram for comparison with Figure 3. All values are included in the correlation model Eq. (4.5).

where  $r^2$  is the coefficient of determination, F the Fisher statistic, and SE the standard error of the estimate. It is noteworthy that although the straight, branched, aromatic, and 2-alkoxyethyl side chains can be fit to this relationship the phthalate esters with cyclic aliphatic side chains cannot. Since V is easily calculated for any of the phthalate esters Eq. (4.5) should prove useful for estimating the L descriptor for phthalate esters that lack experimental values, at least for the range of chain lengths indicated for the phthalate esters in Table 4.6.

For branched alkyl chains van Noort et al [67] has suggested that the V descriptor over estimates the solvent accessible area for the branched alkyl chains and calculated a correction factor for the V descriptor for branched chains which placed normal chain and branched chain hydrocarbons on a common plot of vapor pressure against the corrected V descriptor, indicated as  $V_{cor}$ , here and elsewhere. Since adjusting the V descriptor effects the calculation of the other descriptors using the Solver method we have recalculated the descriptors for the phthalate esters containing branched chains as described by van Noort et al using the correction factors indicated in [67], Table 4.7.

**Table 4.7** Descriptors for branched chain phthalate esters calculated using corrected McGowan volume according to van Noort et al [49] ( $A = 0$  for all compounds).

Compound	Descriptors					Statistics	
	E	S	B	L	$V_{\text{cor}}$	SD	n
Benzyl 2-ethylhexyl phthalate	1.41	1.29	1.307	10.853	2.9719	0.05	37
Di-isobutyl phthalate	0.66	1.218	0.856	8.145	2.1722	0.035	73
Di-2-ethylhexyl phthalate	0.688	1.131	1.113	11.372	3.2994	0.04	42
Di-2-octyl phthalate	0.638	1.12	1.007	11.262	3.2994	0.05	40

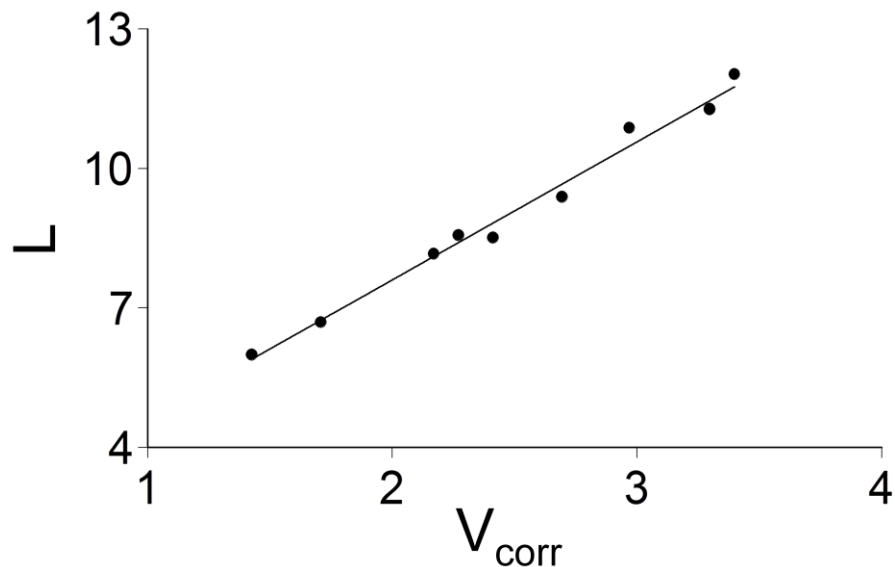
Since these are quite large compounds containing only one or two branched carbon centers the change in  $V$  compared with  $V_{\text{cor}}$  is relatively small, and consequently the change in the other descriptors is also small. The most notable being a reduction in the value for the B descriptor. The statistics for the models with  $V_{\text{cor}}$  are about the same as the models using  $V$ . The plot of L descriptor against  $V_{\text{cor}}$  shows a slight improvement in the fit, Eq. (4.6) and Figure 4.3. The points at the top right corner and those around the middle of Figure 4.2 show a shift in location and a better agreement with the best fit line through the data, as shown in Figure 4.3. This would tend to agree with the findings of van Noort et al [67] but the evidence from this study, although supportive, is in no sense definitive and we have continued to use the models calculated with  $V$  in the rest of this chapter.

For the dialkyl phthalate esters in the absence of steric hindrance or induction effects there is a reasonable expectation that the descriptors for dipolarity/polarizability and hydrogen-bond basicity should be independent of the alkyl chain length, at least beyond a certain minimum chain length. The S and the B descriptors are plotted against the V descriptor (to represent increasing chain length) in Figure 4.4.

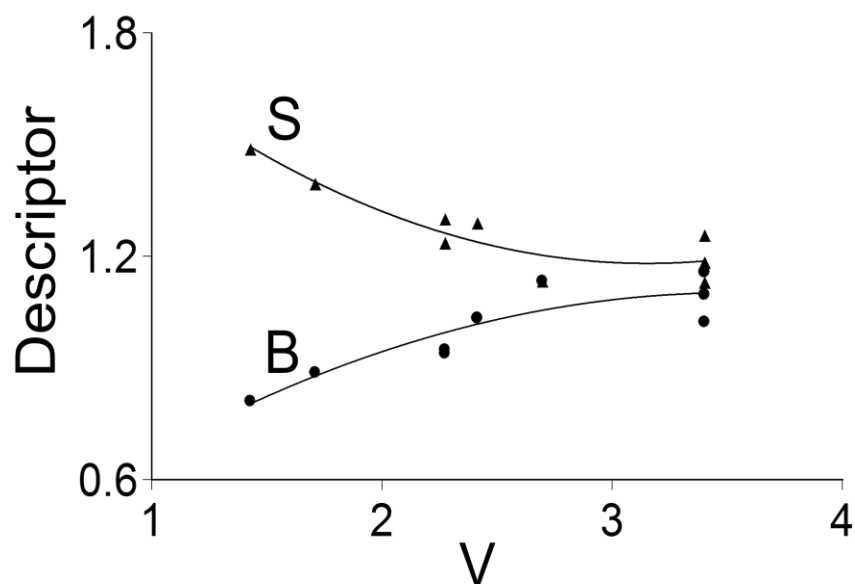
$$L = 2.95 (\pm 0.13)V_{\text{cor}} + 1.78 (\pm 0.33) \quad (4.6)$$

$$r^2 = 0.980 \quad F = 537 \quad SE = 0.273 \quad n = 13$$





**Figure 4.3.** Plot of the L descriptor against the  $V_{corr}$  descriptor for phthalate esters with alkyl and aromatic side chains (the values for the alkoxyalkyl side chains are not shown to simplify the diagram for comparison with Figure 4.2. All values are included in the correlation model Eq(4.6).



**Figure 4.4.** Plot of experimental S and B descriptors against V for the dialkyl phthalates indicating the plateau region for alkyl chains containing more than 4 carbon atoms.

There is a general decrease in the S descriptor and increase in the B descriptor for short chain lengths (up to about butyl) after which a near plateau value for  $S = 1.220 (\pm 0.066, n = 7)$  is

obtained. For the B descriptor a plateau value exists for chain lengths slightly longer than butyl (the dialkyl phthalates with n-butyl and isobutyl side chains have experimental B values just slightly smaller than those for higher homologs) and the B value seems to converge to a constant value of 1.121 ( $\pm 0.060$ ,  $n = 5$ ). Thus, it seems preferable to fix S for the dialkyl phthalates with n-butyl and larger side chains and B for the dialkyl phthalate side chains longer than n-butyl. Since the V and E descriptors are fixed by calculation the Solver method can be used to recalculate the L descriptor and to ascertain how well the new descriptors fit the experimental data, Table 4.8. These values seem quite reasonable with similar or slightly poorer statistics to the models in which only V and E are fixed, Table 4.6. The descriptors in Table 4.8 are the preferred values for the phthalate esters with dialkyl chains at least equal to butyl and longer.

**Table 4.8.** Descriptors with an average value assigned to S and B for dialkyl phthalate esters based on Figure 4.4

Compound	Descriptors					Statistics	
	E	S	B	L	V	SD	n
Di-n-butyl phthalate	0.694	1.22	0.961	8.67	2.274	0.046	144
Di-n-octyl phthalate	0.662	1.22	1.121	12.11	3.401	0.079	37
Di-isobutyl phthalate	0.672	1.22	0.958	8.127	2.274	0.037	73
Di-2-ethylhexyl phthalate	0.693	1.22	1.121	11.2	3.401	0.059	42
Di-2-octyl phthalate	0.644	1.22	1.121	11.08	3.401	0.093	40
Butyl n-pentyl phthalate	0.753	1.22	1.121	8.594	2.415	0.048	48
Butyl n-heptyl phthalate	0.806	1.22	1.121	9.301	2.697	0.053	26

The descriptor values for the phthalate esters determined in this study can be compared with those available in the literature [68,69] and with the L descriptors determined by Stenzel et al [70]. These values are summarized in Table 4.9. Since E is calculated from an experimental refractive index value the small differences in the E descriptor are explained by minor differences in chosen experimental refractive index values. There is good agreement for the L

**Table 4.9.** Descriptor values for dialkyl phthalate esters taken from literature sources (A = 0 for all compounds and V is the same as the values in Table 4.6).

Compound	Descriptors			
	E	S	B	L
Dimethyl phthalate	0.78	1.4	0.84	6.051
Diethyl phthalate	0.729	1.4	0.88	6.75
Di-n-butyl phthalate	0.7	1.4	0.86	8.59
Di-n-octyl phthalate	0.676	1.4	0.87	
Dicyclohexyl phthalate				11
Di-isobutyl phthalate	0.66	1.4	0.88	
Di-2-ethylhexyl phthalate	0.659	1.34	0.88	11.79

descriptors (relative differences < 2%) except for di-2-ethylhexyl phthalate where the difference, while not large, is significant. The L descriptors of Stenzel et al [70] are single column values while those in this study are averaged over eight columns with several retention factor measurements at different temperatures on each column and should be more reliable. The agreement for the S and B descriptor is not as good. The S descriptor is indicated as 1.400 for the di-n-alkyl phthalates (except for di-2-ethylhexyl phthalate assigned a value of 1.34) independent of chain length while in this study the S descriptor was shown to be generally smaller and to vary with chain length at least up to n-butyl. The B descriptor values are systematically lower than those observed in this study. Without knowledge of how the descriptors were calculated these differences cannot be rationalized, but the use of aqueous based partition methods, commonly used to calculate descriptors, can be problematic for the dialkyl phthalates due to the wide variation of partition coefficients found in the literature (see section 4.4.3). The difference for dimethyl phthalate and diethyl phthalate is much smaller for the two sets of descriptors and for these low-molecular-weight phthalate esters more accurate values of water-based partition coefficients are available.

#### 4.3.4 Mono- and diesters

The descriptors for eight mono- and diesters commonly used as plasticizers are presented in Table 4.6. The descriptors are internally consistent and make chemical sense. The descriptors are well determined statistically but we have no reference values to compare them to. We will demonstrate their suitability for predicting environmental properties in section 4.3.5

#### 4.3.5 Comparison of predicted physicochemical properties with experimental values for phthalate esters

Water solubility, octanol-water partition coefficients, and vapor pressure are three important properties used to assess the environmental distribution and fate of organic compounds. Experimental values are available for some of the lower molecular weight phthalate esters but these values are generally quite dispersed and differ by two orders of magnitude or more for some phthalates. This reflects the difficulty of the measurements for compounds of extremely low water solubility and vapor pressure. An attempt has been made to identify likely true values by expert assessment [41,42,71-74] and we have adopted these values for comparison with calculated values obtained using the descriptors obtained in this study. In general, these tend to be recent measurements using the slow-stir or no stir methods with long equilibration times. In Table 4.10 we summarize the experimental value based on expert assessment, the range of experimental values, and our calculated values for the water-based physicochemical properties identified above. The models used for the calculations are given below the table [17,75]. There is a good correlation between the experimental water solubility and octanol-water partition coefficient data and the calculated values except for di-2-ethylhexyl phthalate. The calculated values suggest that di-2-ethylhexyl phthalate is about 1 log unit less soluble in water and about the same amount more soluble in n-octanol in the biphasic octanol-water system. The experimental values for dioctyl phthalate and di-2-ethylhexyl phthalate differ by about the same

Table 4.10. Comparison of experimental and calculated water-based properties for dialkyl phthalate esters

Compound	Solubility (-log [S <sub>w</sub> ])		Octanol –water partition coefficient (log K <sub>ow</sub> )			
	Experi- mental	range	calculated <sup>1</sup>	experi- mental	range	calculated <sup>2</sup>
Dimethyl phthalate	1.64	1.42-1.98	1.40	1.61	1.47-1.90	1.61
Diethyl phthalate	2.38	2.31-2.93	2.25	2.42	2.21-3.27	2.55
Di-n-butyl phthalate	4.40	4.33-5.27	4.23	4.50	3.74-5.15	4.60
Di-n-octyl phthalate	7.88	5.12-8.99	7.64	8.18	5.22-8.54	8.08
Di-isobutyl phthalate	4.14	4.14-4.74	4.22	4.48	4.11-4.48	4.60
Di-2-ethylhexyl phthalate	7.00	5.99-8.81	8.05	7.50	4.20-8.39	8.40
Dicyclohexyl phthalate				5.01		5.72
Butyl benzyl phthalate	5.04	3.89-5.67	4.98	4.73	3.57-5.33	4.95

$${}^1 \log [S_w] = 0.518 - 1.00 E + 0.771 S + 2.168 A + 4.238 B - 3.362 AB - 3.987 V \quad [75]$$

$${}^2 \log K_{ow} = 0.083 + 0.684 E - 1.209 S - 0.185 A - 3.355 B + 3.846 V \quad [17]$$

amount and is unexpected for two isomeric compounds. The plots for the experimental versus calculated water solubility and octanol-water partition are shown in Figures 4.5 and 4.6, with the position of di-2-ethylhexyl phthalate marked on the figures. If di-2-ethylhexyl phthalate is treated as an extreme value and removed from the regressions the following models were obtained for the dialkyl phthalates.

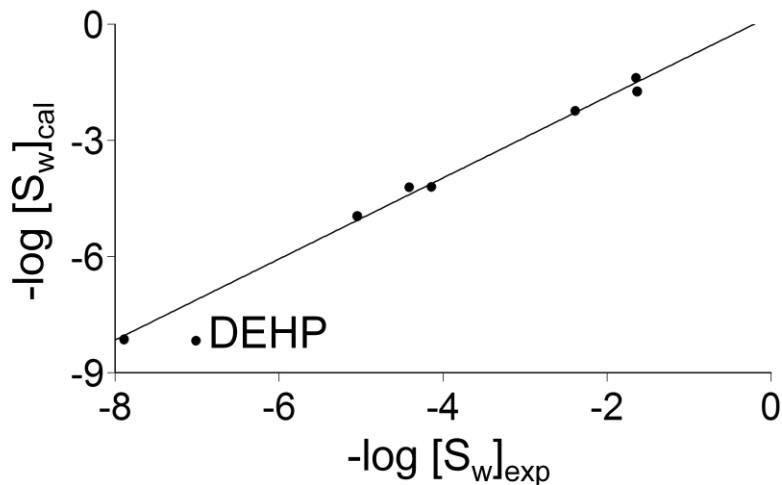
$$\log [S_w]_{\text{exp}} = -0.204 (\pm 0.124) + 0.951 (\pm 0.028) \log [S_w]_{\text{cal}} \quad (4.7)$$

$$r^2 = 0.996 \quad SE = 0.161 \quad F = 1158 \quad n = 7$$

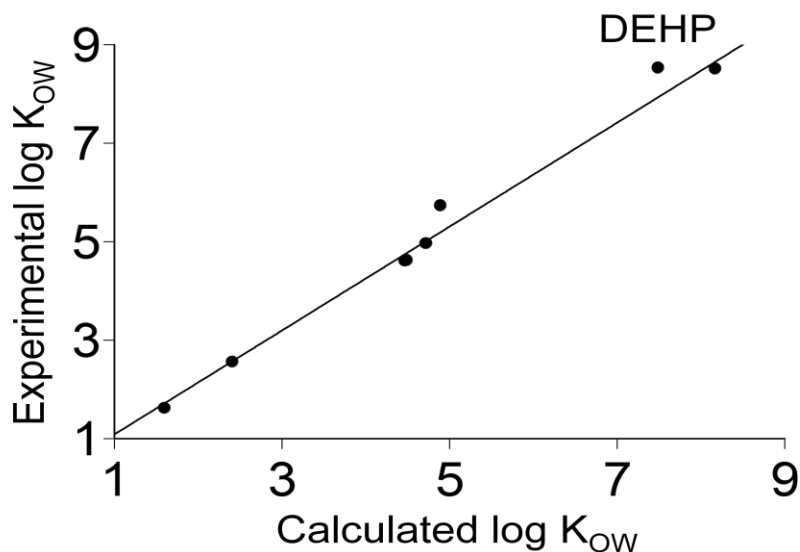
$$\log (K_{ow})_{\text{exp}} = 0.0054 (\pm 0.238) + 0.936 (\pm 0.047) \log (K_{ow})_{\text{cal}} \quad (4.8)$$

$$r^2 = 0.988 \quad SE = 0.255 \quad F = 399 \quad n = 7$$

Figure 4.5 and Eq. (4.7) contain an additional point for the solubility of diethyl adipate reported in [72]. In both equations the slope includes 1 and the intercept 0 at the 95% confidence level. Thus, there is no bias in the calculated solubility and octanol-water partition coefficients compared with the experimental values and both Eq. (4.7) and (4.8) demonstrate that the descriptors for the dialkyl phthalate esters identified in Table 4.10 allow the aqueous solubility



**Figure 4.5.** Plot of the calculated water solubility ( $-\log [S_w]$ ) against the experimental values (Table 4.10) for the dialkyl phthalate esters. Included on this figure is the data point for diethyl adipate (experimental = 1.62 and calculated 1.75). DEHP = di(2-ethylhexyl) phthalate.



**Figure 4.6.** Plot of the calculated octanol-water partition coefficients ( $\log K_{ow}$ ) against the experimental values (Table 4.10) for the dialkyl phthalate esters. DEHP = di(2-ethylhexyl) phthalate.

and octanol-water partition coefficients to be adequately estimated.

Quina et al have proposed a model for the estimation of the vapor pressure of organic compounds using the solvation parameter model that includes a fitting factor to modify the S

descriptor for different compound types [76]. No fitting factor is indicated for dialkyl phthalates but we were able to obtain a suitable correlation model using the fitting factor indicated for aromatic compounds. Before pursuing this model, however, we wanted to see whether a simpler approach based on the L or V descriptor might suffice for those dialkyl phthalate esters with reported experimental vapor pressure measurements, again guided by expert evaluation for selection of the appropriate vapor pressure value [8,9,73,74]. These dialkyl phthalate esters are indicated in Table 4.11 and led to the following correlation model against V, preferred because V can be obtained directly from structure and it gave a slightly better fit with the experimental data.

$$\log V_p = 2.74 (\pm 0.29) - 2.61 (\pm 0.11) V \quad (4.9)$$

$$r^2 = 0.987 \quad SE = 0.212 \quad F = 392 \quad n = 7$$

**Table 4.11.** Experimental data for vapor pressure (Pa) of dialkyl phthalate esters and their calculated values.

Compound	Vapor pressure (- log V <sub>p</sub> )			
	Experimental	Eq. (10)	SPARC	EPI Suite
Dimethyl phthalate	0.575	0.489	1.25	0.27
Diethyl phthalate	0.876	1.151	1.83	0.57
Di-n-butyl phthalate	2.444	2.4	3.47	1.79
Di-n-octyl phthalate	4.886	4.949	7.41	4.67
Di-isobutyl phthalate	2.325	2.4	3.3	0.59
Di-2-ethylhexyl phthalate	4.886	4.949	6.85	3.12
n-Butyl benzyl phthalate	3.174	2.818	5.44	2.69

From the data in Table 4.11 it can be seen that the simple Eq. (4.9) provides a much better estimate of the vapor pressure than either SPARC or EPI Suite internet software widely used for environmental property estimations (details of the SPARC and EPI Suite programs and the calculation of vapor pressure for the dialky phthalates is given in [77]). The inclusion of phthalate esters of more complex structure would likely require a more complex approach such as that

described by Quina et al [76], but the scarcity of experimental values for the vapor pressure of phthalate esters renders the development of such an approach of theoretical interest only as there is insufficient experimental data for validation. Thus, we have not pursued this topic further.

#### **4.3.6. Estimation of physicochemical properties of environmental interest for the remaining compounds in Table 4.6**

Now that the full range of descriptors are available for the plasticizers in Table 4.6 they can be used to estimate the behavior of these compounds in a variety of chromatographic, environmental, and biological systems. The purpose of this section is to illustrate this possibility for some properties of relevance to the distribution and fate of plasticizers in the environment. Table 4.12 includes a few of the properties that can now be estimated using existing models.

The aqueous solubility of the plasticizers covers roughly nine orders of magnitude. None of these compounds have high water solubility but the most soluble are the low-molecular-weight phthalate esters and diesters. Also, the phthalate esters with ether oxygen groups in the side chain are more soluble than the dialkyl phthalate esters of similar chain length. The monoesters of long chain fatty acids are predicted to have very low water solubility as well as the phthalate esters containing straight and branched chain alkyl groups with eight or more carbon atoms. The transport of plasticizers through environmental compartments by water is expected to be slow due to poor solubility except for the lowest molecular-weight compounds. The partitioning of plasticizers into organic matter can be estimated from the octanol-water and soil-water sorption coefficients. Apart from the low-molecular-weight phthalate esters with dialkyl and alkyloxyalkyl side chains with fewer than four carbon atoms and diethyl adipate plasticizers are predicted to be readily absorbed by organic matter from water. This is also apparent for the sorption coefficients for soil. The octanol-water partition coefficients cover about eight orders of magnitude with the higher -molecular-weight plasticizers expected to be virtually quantitatively



**Table 4.12.** Estimation of physicochemical properties of environmental interest for plasticizers (predictive models are listed below the table)

Compound	Property estimated using calculated descriptors				
	$-\log [S_w]$	$\log K_{ow}$	$\log K_{aw}$	$\log K_{oa}$	$\log K_{oc}$
Dimethyl phthalate	1.4	1.61	5.95	6.66	1.88
Diethyl phthalate	2.25	2.55	5.79	7.34	2.27
Di-n-butyl phthalate	4.23	4.61	5	9.16	3.22
Di-n-octyl phthalate	7.64	8.08	5.14	12.53	4.99
Di-cyclohexyl phthalate	5.66	5.72	6.09	11.26	4.46
Di-isobutyl phthalate	4.22	4.6	5.14	8.66	3.22
Di-2-ethylhexyl phthalate	8.05	8.56	5.01	11.61	5.21
Di-2-octyl phthalate	8.17	8.48	4.58	11.6	5.24
Butyl benzyl phthalate	4.98	4.95	6.74	10.39	3.95
Butyl cyclohexyl phthalate	5.27	5.39	5.37	10.07	3.93
Butyl n-heptyl phthalate	5.35	5.77	5.61	9.87	3.53
Butyl n-pentyl phthalate	4.18	4.65	5.78	9.23	3.2
Benzyl 2-ethylhexyl phthalate	6.25	6.59	6.7	11.46	4.45
Di-(2-methoxyethyl) phthalate	1.05	1.65	9.12	9.52	1.77
Di-(2-ethoxyethyl) phthalate	2.08	2.79	8.35	10.12	2.19
Di-(2-butoxyethyl) phthalate	4.37	4.97	7.92	11.62	3.4
Butyl oleate	9.45	9.82	0.57	10.65	5.6
Butyl stearate	9.4	9.92	0.41	10.83	5.51
Methyl arbutate	6.17	6.44	5.1	10.58	4.32
Diethyl adipate	1.75	2.42	4.44	6.52	1.72
Dicyclohexyl adipate	4.57	5	5.33	10.54	3.41
Dibutyl succinate	2.52	3.26	4.39	7.46	2.08
Diethyl sebacate	3.45	4.12	4.52	8.43	2.61
Diethyl diethylmalonate	2.5	3.28	3.58	6.15	1.98

Water solubility in mol/L[75]

$$\log [S_w] = 0.518 - 1.004 E + 0.771 S + 2.168 A + 4.238 B - 3.362 AB - 3.987 V$$

Octanol-water partition coefficient [17]

$$\log K_{ow} = 0.083 + 0.684 E - 1.209 S - 0.185 A - 3.355 B + 3.486 V$$

Air-water partition coefficient [17]

$$\log K_{aw} = -0.929 + 0.474 E + 3.042 S + 3.819 A + 4.551 B - 0.286 L$$

Air-octanol partition coefficient [17]

$$\log K_{oa} = -0.053 - 0.066 E + 0.391 S + 3.564 A + 0.890 B + 0.914 L$$

Soil-water distribution constant (volume of water/mass of organic carbon)[78]

$$\log K_{oc} = 0.21 + 0.74 E - 0.31 A - 2.27 B + 2.09 V$$

extracted by organic matter. The same general trend is seen for the soil-water sorption

coefficients which cover about five orders of magnitude. On account of their low vapor pressure and very low water solubility the plasticizers will transfer inefficiently from air to water but their extremely large air-octanol partition coefficients indicates that the plasticizers will accumulate in particle organic matter and in aerosols. This should be the dominant phase for these compounds in the atmosphere.

Many of the properties predicted for the plasticizers in Table 4.12 would be difficult to determine experimentally (indicated by the lack of experimental data for these compounds). Estimation methods are then useful for predicting the environmental distribution of these compounds and for assessing differences in the distribution of individual compounds. It is of note that the physicochemical properties estimated for these compounds were obtained using non-aqueous systems, which provide easier accesses to reliable experimental data, from which it is possible to predict the largely inaccessible experimental data for water-containing systems.

**Footnote:**

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## CHAPTER 5

### COMPOUNDS FOR EXPANDING THE DESCRIPTOR SPACE FOR CHARACTERIZING SEPARATION SYSTEMS

#### 5.1 Introduction

The solvation parameter model is widely used to characterize the retention and distribution properties of separation systems [1-3]. It provides a quantitative description of the contributions of cavity formation and intermolecular interactions to the retention or distribution property of the separation system such as the partition coefficient, retention factor, etc. The system constants of the solvation parameter model contain the information that describes solvation within the separation system in a form suitable for classification, selection, optimization, and prediction of properties for compounds with established descriptor values. Reasonably large system constant databases are available for open-tubular columns for gas chromatography [4-6], column types and mobile phases for reversed-phase liquid chromatography [3,7], surfactants for micellar electrokinetic chromatography [8-10], column types for supercritical fluid chromatography [11,12], chemically bonded layers for thin-layer chromatography [13], sorbents for solid-phase extraction [14,15], and partition properties for biphasic solvent systems included in previous chapters[1.16-18]. The system constants can be derived by multiple linear regression analysis of measured experimental distribution properties ( $\log SP$ ) of a set of varied compounds with known descriptor values. The solvation parameter models set up to determine the system constants for gas-liquid partition systems and liquid-liquid partition systems are represented by Eq.5.1 and Eq.5.2 respectively.

$$\log SP = c + eE + sS + aA + bB + lL \quad (5.1)$$

$$\log SP = c + eE + sS + aA + bB + vV \quad (5.2)$$



There are a several factors, both statistical and experimental, that must apply for the system constants to be reliable for the estimation of properties for compounds not included in the original data set [1-3]. One important feature is the descriptor space, defined by the range of values for each descriptor. This range should be as large as practical to ensure that the global models with robust properties are obtained. Local models may fit limited data sets quite well but are limited in their ability to predict properties in other areas of the descriptor space. In addition, the compounds used to characterize separation systems should occupy the descriptor space as evenly as possible to avoid weighting the models to regions of the descriptor space containing compound clusters. Earlier a collection of compounds and their descriptor values were proposed for characterizing separation systems [3]. This collection was subsequently extended to facilitate the characterization of open-tubular columns for gas chromatography at intermediate temperatures taking volatility requirements into account [5,6]. To characterize columns at higher temperatures, and to extend the descriptor space for the characterization of biphasic solvent systems, additional compounds with lower volatility (larger size) and with a varied and wide range of intermolecular interactions is required. Identification of a new set of compounds and their application to characterize open-tubular columns at high temperatures are included in this chapter.

## 5.2 Experimental

### 5.2.1 Materials

Heptane, 2,2,2-trifluoroethanol, diisopentyl ether, and *N,N*-dimethylformamide were obtained from Sigma-Aldrich (Milwaukee, WI, USA). Formamide, propylene carbonate, ethylene glycol, and dimethyl sulfoxide (containing < 0.2% v/v water) were obtained from Acros Organics (Morris Plains, NJ, USA). Hexane, acetonitrile and methanol were OmniSolv grade from EMD Chemicals ( Gibbstown, NJ, USA ). Common chemicals were of the highest purity

**Table 5.1.** Open-tubular columns used for descriptor measurements by gas chromatography

Name	Type	Manufac.*	Dimensions		
			L	ID	FT
SPB-Octyl	Poly(methyloctylsiloxane)	Supelco	30	0.25	1
HP-5	Poly(dimethyldiphenylsiloxane) 5% diphenylsiloxane monomer	Agilent	30	0.32	0.3
Rxi-5Sil MS	Silphenylene-dimethylsiloxane copolymer	Restek	30	0.25	0.5
Stx-500	Carborane-siloxane copolymer	Restek	30	0.25	0.2
Rxi-17	Poly(dimethyldiphenylsiloxane) 50% diphenylsiloxane monomer	Restek	30	0.25	0.5
Rtx-50	Poly(methylphenylsiloxane)	Restek	30	0.25	0.5
Rtx-440	Proprietary structure	Restek	30	0.25	0.5
Rtx-OPP	Poly(dimethylmethyltrifluoropropylsiloxane)	Restek	30	0.32	0.2
DB-1701	Poly(cyanopropylphenyldimethylsiloxane) 14% cyanopropylphenyl monomer	Agilent	15	0.32	0.3
DB-225	Poly(cyanopropylphenyldimethylsiloxane) 50% cyanopropylphenyl monomer	Agilent	15	0.32	0.3
HP-88	Bis(cyanopropylsiloxane)- <i>co</i> - methylsilylene	Agilent	25	0.25	0.2

L-Length(m) , ID-Internal diameter(mm), FT-Film thickness ( $\mu\text{m}$ )

\* Supelco (Bellefonte, PA, USA), Restek (Bellefonte, PA, USA) and Agilent Technologies (Folsom, CA, USA)

available and obtained from several sources. The open-tubular columns used for gas chromatography and their sources are summarized in Table 5.1.

### 5.2.2 Instrumentation

Gas chromatographic measurements were made with an Agilent Technologies (Palo Alto, CA, USA) HP6890 gas chromatograph fitted with a split/splitless injector and flame ionization detector using Chemstation software (rev. 8.04.01) for data acquisition. Nitrogen was used as the carrier gas at a constant velocity of 47 cm/s. The split ratio was set to 30:1, septum purge 1 mL/min, injector temperature 275°C, and detector temperature 300°C. Isothermal retention factors were determined at 20°C intervals at several temperatures in the range 160-320°C as

dictated by the retention characteristics of each compound and the thermal stability of the column. For the measurement of liquid-liquid partition coefficients a temperature program was used starting at 150°C for 1 min and then raised to 280°C at 25°C/min on the HP-5 column identified in Table 5.1. The temperature program was modified as required to handle co-elution of solutes with the internal standard or solvent peaks and to elute some of the less volatile compounds.

### 5.2.3 Determination of partition coefficients

The method use to determine the partition coefficients is described in the experimental section of Chapter 2. The biphasic solvent systems and their system constants used for the calculation of descriptor values are summarized in Table 5.2.

**Table 5.2.** System constants for totally organic biphasic solvent systems used for descriptor determinations

Liquid-Liquid Partition system	System constants					
	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>	<i>c</i>
n-Heptane-ethylene glycol	0.095	-1.486	-3.797	-1.536	2.075	0.338
n-Heptane-N,N-dimethyl-formamide	0.036	-1.392	-2.054	-0.579	0.487	0.259
n-Heptane-dimethyl sulfoxide	0	-1.769	-3.277	-1.112	1.146	0.367
n-Heptane-formamide	0.554	-2.169	-3.356	-1.671	2.267	0.151
n-Heptane-methanol	0.209	-0.728	-1.14	-0.917	0.593	-0.133
n-Heptane-propylene carbonate	0.435	-2.087	-2.678	-0.441	0.796	0.538
n-Heptane-trifluoroethanol	0.91	-1.581	-1.271	-2.852	1.307	-0.021
n-Hexane-acetonitrile	0.387	-1.483	-1.675	-0.837	0.669	0.153
Isopentyl ether-ethylene glycol	-0.13	-1.093	-1.537	-1.919	2.093	0.388
Isopentyl ether-dimethyl sulfoxide	0	-1.465	-2.175	-0.958	1.111	0.183
Formamide-1,2-dichloroethane	-0.089	0.423	2.028	1.263	-1.64	-0.297

The system constants in Table 5.2 differ from those in the original models. They have been updated by including additional compounds and re-determining descriptor values for other compounds.

#### 5.2.4 Retention factors and partition coefficients from literature sources

The descriptor database includes partial data for some compounds used for the characterization of open-tubular columns for gas chromatography at intermediate temperatures [3,6,25]. Experimental partition coefficients and gas and liquid chromatographic retention factors for fragrance compounds, plasticizers, and organosilicon compounds [22,23] were used for selected compounds included in this study. Liquid-liquid partition coefficients for octanol-water, chloroform-water, 1,2-dichloroethane-water, and hexadecane-water for compounds not included in the above data bases were used where available [26-29]. In addition, the octanol-water partition coefficient for progesterone [30] and gas-octanol partition coefficients for polycyclic aromatic hydrocarbons [31] were taken from the cited sources. The majority of the experimental data used for descriptor calculations was measured in our laboratory to supplement literature values.

#### 5.2.5 Calculations

Descriptors were calculated using the method described in chapter 4. To determine the system constants for a gas chromatographic stationary phase, a set of isothermal retention factors for about 80 varied compounds is analyzed using multiple linear regression analysis. These initial system constants are simultaneously optimized with the solute descriptors until the system constants and descriptors are stable [3].

### 5.3 Results and Discussion

The compounds and their descriptor values selected for the characterization of open-tubular columns in the temperature range 200 to 300°C are summarized in Table 5.3. The V descriptor was obtained by standard calculation methods and is not subject to experimental optimization [32]. The E descriptor for liquids was determined from the refractive index and was

**Table 5.3.** Compounds and their descriptor values for characterizing open-tubular columns over the temperature range 200-300°C

Compound	Descriptors						Statistics	
	E	S	A	B	L	V	SD	n
1-Acetonaphthone	1.517	1.417	0	0.557	6.67	1.3829	0.033	97
2-Acetonaphthone	1.429	1.457	0	0.601	6.795	1.3829	0.036	96
4-Acetylbiphenyl	1.504	1.517	0	0.626	7.672	1.6217	0.03	74
Androsterone	1.371	1.651	0.43	1.574	10.791	2.4257	0.045	37
Anthracene	1.98	1.278	0	0.27	7.736	1.4544	0.035	92
Benzenesulfonamide	1.189	1.873	0.654	0.682	6.054	1.0971	0.042	228
Benzyl cinnamate	1.285	1.543	0	0.612	8.952	1.9192	0.032	51
Benzyl ether	1.212	1.113	0	0.719	7.164	1.6647	0.042	90
Benzyl salicylate	1.413	1.345	0.008	0.435	7.988	1.7391	0.034	58
1-Bromodecane	0.332	0.418	0	0.27	7.263	1.9744	0.032	64
Butylbenzyl phthalate	1.296	1.734	0	1.002	9.796	2.4593	0.041	61
Butyl oleate	0.024	0.645	0	0.573	10.846	3.2396	0.039	59
Butyl stearate	0.051	0.474	0	0.669	11.043	3.2828	0.046	57
Carbazole	2.051	1.553	0.388	0.229	7.533	1.3154	0.038	78
Cholestane	1.22	0.412	0	0	12.997	3.4785	0.037	38
Cholesterol	1.353	1.087	0.212	0.558	13.389	3.4942	0.044	33
Chrysene	2.647	1.667	0	0.302	10.123	1.8234	0.034	51
Di(n-butoxyethyl) phthalate	0.641	1.575	0	1.515	10.674	2.9552	0.034	47
Di-n-butyl phthalate	0.694	1.315	0	0.934	8.493	2.2742	0.035	156
Di-n-butyl succinate	0.091	0.94	0	0.965	6.867	1.9482	0.035	71
2,6-Dichloro-4-nitroaniline	1.263	1.494	0.369	0.319	7.25	1.2352	0.037	61
Dicyclohexyl phthalate	1.405	1.535	0	1.045	10.72	2.6206	0.037	55
1,3-Diethyl-1,3-diphenylurea	1.692	1.295	0	1.304	7.952	2.244	0.039	61
N,N-Diethyldodecamide	0.331	0.936	0	0.948	8.737	2.2635	0.038	61
Di(2-ethoxyethyl) phthalate	0.619	1.56	0	1.5	9.041	2.3916	0.042	59
Diethyl phthalate	0.725	1.934	0	0.888	6.678	1.7106	0.035	239
Diethyl sebacate	0.043	1.058	0	0.981	7.871	2.23	0.029	66
Dihydrocholesterol	1.333	1.046	0.207	0.633	13.525	3.5372	0.034	35
N,N-Dimethyldodecylamine	0.08	0.199	0	1.467	7.032	2.181	0.031	54
Di-n-octyl phthalate	0.662	1.281	0	1.131	11.959	3.4014	0.047	49
Diphenylamine	1.704	1.278	0.149	0.532	6.799	1.424	0.05	76
N,N-Diphenyl-p-phenylenediamine	2.873	1.917	0.487	1.057	10.241	2.1316	0.044	41
Dodecamethylcyclo-	-0.88	-0.12	0	0.808	6.073	3.5172	0.057	84

hexasiloxane								
1,12-Dodecanediol	0.455	0.805	0.819	1.219	7.532	1.9168	0.036	95
Dotricontane	0	0	0	0	15.122	4.6174	0.06	10
Fluoranthene	2.31	1.47	0	0.286	8.75	1.5846	0.04	73
Glycidyoxypropyl-trimethoxysilane	0.067	1.12	0	0.981	6.202	1.8073	0.043	101
Hexachlorobenzene	1.401	0.882	0	0	7.671	1.4508	0.053	94
Isocyanatopropyltriethoxysilane-	-0.05	0.661	0	0.854	5.942	2.0119	0.034	106
$\alpha$ -Isomethyl ionone	0.762	1.011	0	0.708	6.399	1.9023	0.047	67
2-Methoxycinnamaldehyde	1.16	1.521	0	0.598	6.318	1.3114	0.026	67
Methyl abietate	1.246	1.146	0	1.08	10.203	2.7301	0.048	57
1-Naphthol	1.455	1.123	0.757	0.333	6.163	1.1441	0.036	229
2-Naphthol	1.453	1.174	0.783	0.347	6.148	1.1441	0.042	273
2-(1-Naphthyl)ethanol	1.592	1.233	0.44	0.742	6.989	1.4259	0.029	88
Nicotinamide	1.191	1.798	0.431	0.773	5.355	0.9317	0.034	72
Nicotine	0.861	0.958	0	1.082	5.922	1.371	0.04	75
4-Nitrobenzyl alcohol	1.01	1.365	0.499	0.584	6.344	1.0902	0.038	258
1-Nitronaphthalene	1.393	1.479	0	0.29	6.844	1.2596	0.038	96
Octadecane	0	0	0	0	8.652	2.6448	0.029	65
Octaethylcyclotetrasiloxane	-0.27	-0.15	0	0.944	8.313	3.472	0.04	65
Octanophenone	0.779	0.988	0	0.501	7.386	1.8593	0.036	167
Octyltriethoxysilane	-0.26	-0	0	0.953	6.986	2.503	0.047	47
Pentachlorophenol	1.745	0.956	0.665	0.061	7.502	1.3371	0.027	57
Perylene	2.511	1.87	0	0.349	11.874	1.9536	0.038	34
Phenanthrene	1.935	1.284	0	0.284	7.683	1.4544	0.031	213
Phenylcyclohexane	0.879	0.607	0	0.245	6.061	1.4532	0.037	90
Phenyl ether	1.221	0.979	0	0.267	6.058	1.3829	0.043	89
4-Phenylphenol	1.518	1.188	0.797	0.447	7.059	1.3829	0.038	226
Progesterone	1.585	2.214	0	1.388	11.665	2.6215	0.05	113
Resorcinol	1.02	0.985	1.369	0.503	4.862	0.8338	0.04	128
Tetracosane	0	0	0	0	11.403	3.4902	0.052	16
Trans-stilbene	1.621	1.218	0	0.285	7.299	1.563	0.033	93
Tribenzylamine	1.821	1.27	0	0.631	9.727	2.4545	0.038	56
Tri-n-butyrin <sup>1</sup>	0.118	1.22	0	1.343	8.015	2.4453	0.031	81
Triisopropanolamine	0.629	1.335	0.412	1.499	5.882	1.6526	0.03	72
Trimethoprim <sup>2</sup>	1.76	1.947	0.075	2.081	10.594	2.1813	0.037	37
Triphenylamine	2.441	0.981	0	0.754	8.767	2.0318	0.042	71
Triphenylmethane	1.865	1.152	0	0.549	8.631	2.0729	0.041	69
Vanillin	1.12	1.385	0.385	0.673	5.673	1.1313	0.032	68

<sup>1</sup> Glycerol tri-n-butyrate

<sup>2</sup> 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine

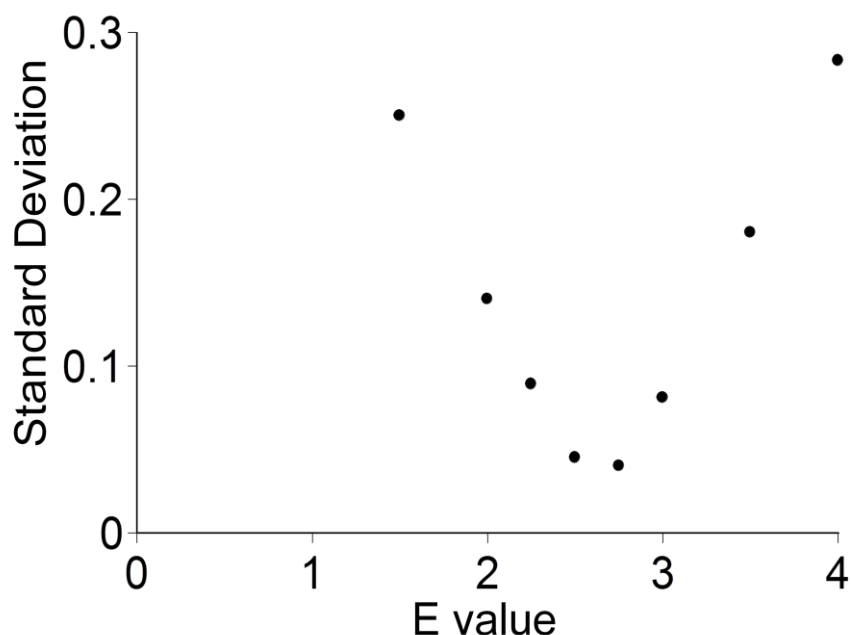
taken as the correct estimate of the descriptor [33]. Since many of the compounds in Table 5.3 are solids, the E descriptor cannot be calculated directly, and must be either estimated using theoretical refractive index values or determined experimentally together with the other descriptors. There are many software programs that provide an estimate of the hypothetical refractive index for solids. Unfortunately these programs often produce different values for the theoretical refractive indices and there is no particular reason to accept the values from one program over another. For example, in Table 5.4 we compare the E descriptor for some steroids and polycyclic aromatic hydrocarbons calculated using ChemSketch (ACD Labs, Toronto, Canada) and published values from AbsSolv [16,41,42] with those determined by experiment in this work.

**Table 5.4** Comparison of experimental and calculated E descriptor values for steroids and polycyclic aromatic hydrocarbons

Compound	E descriptor		
	Experimental	ACD Labs	AbsSolv
Cholestane	1.22	0.766	
Cholesterol	1.353	1.338	1.36
Dihydrocholesterol	1.33	0.982	
Cholesteryl acetate	1.234	1.222	1.22
Progesterone	1.585	1.352	1.45
Anthracene	1.98	2.121	2.29
Acenaphthene	1.35	1.783	1.604
Fluorene	1.669	1.602	1.588
Fluoranthene	2.31	3.129	2.377
Chrysene	2.647	2.946	3.027
Pyrene	2.296	3.129	2.808

The two sets of calculated E descriptors show only poor agreement for some compounds and provide both good and poor agreement with the experimental values. However, it is impossible

to deduce when a calculated value is the true value for the E descriptor. Experimental values are of course subject to measurement uncertainty and for reliable measurement should be based on a reasonable number of models in which the E descriptor has a reasonable sharp descriptor well, as shown in Figure 5.1 for chrysene.



**Figure 5.1.** Descriptor well using the Solver method for the estimation of the E descriptor for chrysene. The standard deviation of the residuals (y-coordinate axis) is calculated by entering the calculated value for V, setting  $A = 0$  (chrysene is not a hydrogen-bond acid), selecting different test values for E (x-coordinate), and allowing the S,A and B descriptors to assume any value that minimizes the standard deviation that makes chemical sense (which was all calculated values in this case).

It is useful to include separation systems in the estimation of the E descriptor in which one component is a fluorine-containing solvent, since these tend to have reasonably large values for the  $e$  system constant. The E descriptors in Table 5.3 are calculated values for liquids and experimental values for solids. For liquids the calculated values and experimental values show good agreement, as required for useful models containing both liquid and solid compounds.



The S, A, B and L descriptors are derived from experimental partition coefficients and retention factors using the Solver method with the values for V fixed and E allowed to vary for solids [1,3,5]. The standard deviation and the number of experimental values included in the calculation are given in Table 5.3. These cannot indicate the accuracy of individual descriptor values but confirm that the descriptors can explain the associated properties (partition coefficients and retention factors in varied systems) adequately to be useful for building models for additional systems, for example, for column characterization.

The method most widely used for the determination of the S, A, and B descriptors is liquid-liquid partition in aqueous biphasic systems [1]. These systems have large values for the  $s$ ,  $a$  and  $b$  system constants, which minimizes the uncertainty in the extracted values for the complementary descriptors. These systems also have large values for the  $v$  system constant resulting in experimental difficulties in the measurement of partition coefficients for compounds of low water solubility or stability [5,6,]. This is the case for many of the compounds in Table 5.3 and influenced the choice of non-aqueous biphasic systems for the measurements described in this report. Where experimental aqueous partition coefficients were available from the literature (section 5.2.4) they were used in the calculation of the descriptors in Table 5.3. As an example of the difficulty of determining descriptors for compounds of low water solubility the partition coefficients for cholesterol used for the calculation of descriptors are summarized in Table 5.5. The partition coefficients ( $\log K_p$ ) for the totally organic biphasic systems fall into the range -0.26 to 2.33 and can be easily measured by standard laboratory procedures. For the aqueous biphasic systems the partition coefficients ( $\log K_p$ ) are estimated to fall into the range 11 to 13 and would be extremely difficult to measure accurately by methods usually employed for partition coefficients. There are no reported experimental values for these partition coefficients to our knowledge. This also provides an example of the use of totally organic biphasic systems to

**Table 5.5** Experimental and calculated values of the partition coefficient ( $\log K_p$ ) for cholesterol\*

Biphasic system	Experimental	Calculated
n-Heptane-propylene carbonate	0.748	0.824
n-Heptane-trifluoroethanol	2.332	2.365
n-Heptane-dimethylformamide	-0.261	-0.263
n-Heptane-dimethyl sulfoxide	1.114	1.132
n-Heptane-methanol	0.73	0.677
n-Hexane-acetonitrile	0.672	0.579
Isopentyl ether-dimethyl sulfoxide	1.514	1.476
Isopentyl ether-propylene carbonate	1.081	1.129
Octan-1-ol-propylene carbonate	0.567	0.61
Octanol-water		11.08
Chloroform-water		12.68
Cyclohexane-water		11.85
Toluene-water		12.62

\* With  $V = 3.492$  and assigned values  $E = 1.353$ ,  $S = 1.087$ ,  $A = 0.212$ , and  $B = 0.558$

expand the descriptor space by including compounds difficult to characterize by conventional methods.

Gas chromatography is the preferred method for the determination of the L descriptor, but since none of the common stationary phases are significant hydrogen-bond acids, it is not generally used to estimate the B descriptor. This must be obtained from liquid-liquid partition, solubility measurements, or from reversed-phase liquid or micellar electrokinetic chromatographic systems with an aqueous mobile phase [1,3,5,36-49]. Gas chromatography can be used to assist in the determination of the E, S and A descriptors, although the complementary system constants tend to be smaller than those of liquid-liquid partition systems. Retention factors in gas chromatography can be measured with higher accuracy than liquid-liquid partition coefficients, reducing the uncertainty of the descriptor measurements. To determine the full set of six descriptors a combination of gas chromatography and liquid-liquid partition is a useful

approach, and can be supplemented by other chromatographic techniques. This is the approach used here to assemble the data in Table 5.3.

### 5.3.1 System constants for open-tubular columns at high temperatures

The compounds in Table 5.3 were used to determine the system constants for open-tubular columns over the temperature range 200-300°C. Since these columns are to be used to determine descriptors for further compounds of low volatility a conservative approach was adopted to define the useful maximum operating temperature. This was 320°C for Rxi-Sil MS, 300°C for HP-5, Rtx-440 and Rtx-OPP, and 260°C for SPB-Octyl. These stationary phases are of low to moderate polarity. Higher polarity stationary phases, however, are generally less thermally stable and cannot be used for extended times at temperatures close to 300°C without significant deterioration. Stationary phases of this type were previously characterized for use in the temperature range 160-240°C [4-6] but result in inconveniently long retention times for compounds of low volatility of current interest. A wider temperature operating range is required to extend the type of compounds that can be characterized using the methods described here. This is particularly so for the L descriptor, which is difficult to determine for compounds of low volatility by other experimental techniques.

**Table 5.6.** System constants for open-tubular columns (high temperature)

SP	T(°C)	System constants					Statistics*				
		<i>e</i>	<i>s</i>	<i>a</i>	<i>l</i>	<i>c</i>	<i>r</i>	$r_a^2$	F	SE	n
HP-5	200	0.056 (0.004)	0.203 (0.005)	0.117 (0.006)	0.324 (0.001)	-2.600 (0.010)	1.000	0.999	18848	0.014	72
	220	0.070 (0.003)	0.184 (0.004)	0.107 (0.005)	0.295 (0.001)	-2.623 (0.008)	1.000	0.999	25419	0.010	66
	240	0.076 (0.003)	0.174 (0.004)	0.097 (0.005)	0.265 (0.001)	-2.601 (0.008)	1.000	0.999	23187	0.009	59
	260	0.089 (0.005)	0.181 (0.008)	0.080 (0.012)	0.245 (0.001)	-2.668 (0.011)	0.999	0.998	13205	0.025	89
	280	0.095	0.160	0.092	0.223	-2.661	0.999	0.999	11470	0.020	73

	(0.004)(0.007)(0.023)(0.001)(0.012)									
300	0.104 0.138 0.105 0.210 -2.648	0.999	0.999	12299	0.018	68				
	(0.004)(0.007)(0.009)(0.001)(0.011)									
Rtx-440										
200	0.079 0.263 0.159 0.347 -2.403	1.000	0.999	28445	0.015	87				
	(0.004)(0.005)(0.006)(0.001)(0.008)									
220	0.093 0.246 0.144 0.319 -2.445	0.999	0.999	17678	0.019	88				
	(0.005)(0.006)(0.007)(0.001)(0.010)									
240	0.109 0.217 0.128 0.285 -2.400	1.000	0.999	24680	0.013	80				
	(0.003)(0.005)(0.005)(0.001)(0.008)									
260	0.119 0.211 0.119 0.266 -2.467	0.999	0.998	11309	0.026	88				
	(0.005)(0.008)(0.012)(0.002)(0.012)									
280	0.127 0.195 0.102 0.244 -2.486	0.999	0.998	8911	0.027	87				
	(0.005)(0.008)(0.013)(0.001)(0.012)									
300	0.135 0.186 0.093 0.226 -2.520	0.999	0.997	6153	0.031	77				
	(0.006)(0.010)(0.015)(0.002)(0.016)									
SPB-Octyl										
200	0.190 0.047 0.000 0.350 -1.968	0.999	0.998	15258	0.022	88				
	(0.006)(0.007) (0.002)(0.012)									
220	0.190 0.047 0.000 0.325 -1.975	0.999	0.998	15264	0.022	88				
	(0.006)(0.007) (0.002)(0.012)									
240	0.198 0.044 0.000 0.289 -1.986	0.999	0.998	14158	0.022	89				
	(0.006)(0.007) (0.002)(0.010)									
260	0.200 0.043 0.000 0.263 -2.010	0.998	0.996	7226	0.036	90				
	(0.008)(0.012) (0.002)(0.015)									
Rxi-5Sil MS										
200	0.057 0.233 0.130 0.360 -2.492	0.999	0.997	6545	0.023	78				
	(0.006)(0.008)(0.008) (0.002)(0.016)									
220	0.069 0.212 0.117 0.328 -2.502	0.999	0.997	6536	0.023	80				
	(0.006)(0.008)(0.008) (0.002)(0.016)									
240	0.091 0.192 0.108 0.298 -2.512	0.999	0.997	6466	0.017	80				
	(0.005)(0.008)(0.007) (0.002)(0.015)									
260	0.098 0.169 0.112 0.254 -2.385	1.000	0.999	18808	0.018	77				
	(0.004)(0.005)(0.010) (0.001)(0.010)									
280	0.107 0.146 0.111 0.228 -2.340	1.000	0.999	21163	0.014	71				
	(0.003)(0.005)(0.009) (0.001)(0.009)									
300	0.113 0.136 0.097 0.207 -2.348	0.999	0.997	7149	0.029	89				
	(0.006)(0.009)(0.014) (0.001)(0.013)									
320	0.113 0.120 0.120 0.184 -2.271	0.997	0.993	3048	0.039	88				
	(0.008)(0.013)(0.019) (0.002)(0.018)									
Rtx-OPP										
200	-0.076 0.561 0.130 0.300 -2.560	0.998	0.997	7129	0.033	94				
	(0.008)(0.010)(0.011) (0.002)(0.015)									

220	-0.052	0.520	0.133	0.273	-2.583	0.998	0.996	5204	0.032	86
	(0.008)	(0.011)	(0.011)	(0.002)	(0.016)					
240	-0.031	0.475	0.119	0.243	-2.543	0.997	0.994	3533	0.033	82
	(0.008)	(0.011)	(0.012)	(0.003)	(0.019)					
260	0.011	0.421	0.109	0.214	-2.518	0.998	0.994	3567	0.035	75
	(0.008)	(0.012)	(0.021)	(0.002)	(0.022)					
280	0.018	0.406	0.129	0.196	-2.558	0.997	0.993	2359	0.039	69
	(0.009)	(0.013)	(0.023)	(0.002)	(0.024)					
300	0.041	0.332	0.117	0.178	-2.498	0.995	0.990	1699	0.046	73
	(0.009)	(0.016)	(0.023)	(0.002)	(0.026)					

\* SP = stationary phase, T=temperature r = overall correlation coefficient;  $r_a^2$  = adjusted coefficient of determination corrected for the number of degrees of freedom; SE = standard error of the estimate (standard deviation for the residuals); F = Fisher statistic; n = number of retention factors included in the model; and the number in parentheses is the standard deviation for the system constant.

The system constants for the high-temperature-stable stationary phases are summarized in Table 5.6. At any temperature the selected compounds have to cover an experimentally acceptable range of retention factors (they need to be retained,  $k > 0$ , and not excessively retained,  $k < 250$ ). This limits the choice of compounds from Table 5.3 at any particular temperature with different compounds being used at each temperature with only moderate overlap for narrow temperature ranges. The outstanding feature of the data in Table 5.6 is the persistence of the contributions of polar interactions to retention at the highest temperatures studied. Interactions of a dipole-type ( $s$  system constant) are weak but statistically significant and characterized by a weak temperature dependence. Since SPB-Octyl is the preferred phase for the experimental determination of the L descriptor, for compounds with a significant value for the S descriptor a systematic error will result unless the S descriptor is included in the calculation (in other words, the experimental measurement of the L descriptor requires knowledge of the S descriptor if accurate values of the L descriptor are to be obtained for polar compounds on SPB-Octyl).

The weakly polar stationary phases approach a shallow plateau region at higher

temperatures for the  $s$  and  $a$  system constants, which are non-zero and remain important over the full temperature range. These systems constants are too small for the accurate determination of the A and S descriptors. The accurate determination of the L descriptor for compounds of low volatility on these phases requires a knowledge of the A and S descriptors.

The contribution of the  $e$  system constant to retention increases in importance with temperature. This might seem strange at first sight since the system constants are generally expected to decline with an increase in temperature. This is a feature of the E descriptor being set to 0 for the n-alkanes. The electron distribution for n-alkanes is less polarizable than highly-fluorinated compounds and organosiloxanes [22,23] which, consequently, have negative values for the E descriptor. Since the common stationary phases are poly(organosiloxanes) the change in the  $e$  system constant with temperature (becoming increasingly positive and resulting in a increase in retention with increasing temperature) arises from the different temperature dependence of the electron polarizability for hydrocarbons and organosiloxanes that reduces to a seemingly relatively higher contribution from electron lone pair interactions as the temperature increases. This assists in estimating the E descriptor for solid compounds of low volatility which lack an experimental refractive index value.

The  $l$  system constant is the most important in relative terms for determining retention on the stationary phases in Table 5.6. Given the accuracy with which retention factors can be determined high temperature gas chromatography is suitable for the determination of the L descriptor for compounds of low volatility as a component of a set of measurements that simultaneously allow estimation of E (for solids) and the S and A descriptors. From a practical point of view at temperatures up to 300°C the weakly polar stationary phases Rtx-440 and Rtx-OPP retain selectivity differences between themselves and the low polarity stationary phases

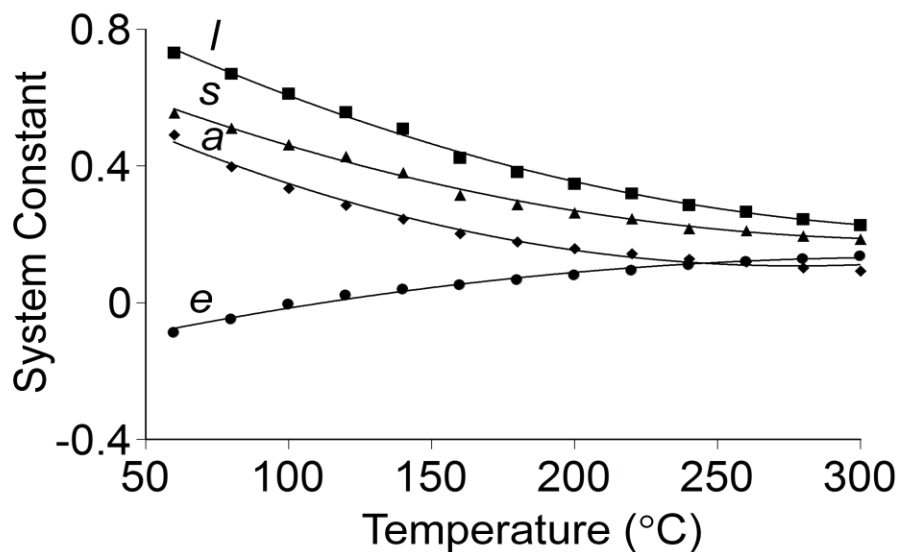
(HP-5 and Rxi-Sil 5 MS). This indicates that at high temperatures the stationary phases in Table 5.6 preserve useful selectivity differences and have not become selectivity equivalent by raising the column temperature.

### 5.3.2 Influence of temperature on the system constants

A grander view of the affect of temperature on intermolecular interactions for gas chromatography is possible by combining the measurements made here with those obtained previously for lower temperature ranges. This possibility is demonstrated for Rtx-440 (this stationary phase has a proprietary structure with retention properties similar to poly[cyanopropylphenyldimethylsiloxane] stationary phases containing 6% polar monomer but is less hydrogen-bond basic) [40]. System constants for Rtx-440 for the temperature range 60-180°C from [6, 40] were recalculated using more recent descriptor values and are summarized in Table 5.7.

**Table 5.7** System constants for the stationary phase Rtx-440 for the temperature range 60-180°C

T(°C)	System constant					Statistics				
	<i>e</i>	<i>s</i>	<i>a</i>	<i>l</i>	<i>c</i>	<i>r</i>	$r_a^2$	F	SE	n
60	-0.089 (0.011)	0.555 (0.012)	0.491 (0.013)	0.731 (0.004)	-2.356 (0.014)	0.999	0.999	14139	0.020	68
80	-0.050 (0.009)	0.511 (0.011)	0.398 (0.010)	0.669 (0.003)	-2.458 (0.012)	1.000	0.998	19737	0.019	83
100	-0.006 (0.009)	0.462 (0.011)	0.335 (0.008)	0.611 (0.003)	-2.532 (0.013)	0.999	0.999	17116	0.019	83
120	0.021 (0.007)	0.428 (0.009)	0.285 (0.007)	0.557 (0.003)	-2.576 (0.013)	0.999	0.999	14420	0.015	76
140	0.049 (0.009)	0.381 (0.012)	0.245 (0.009)	0.508 (0.003)	-2.611 (0.017)	0.999	0.997	6911	0.019	73
160	0.050 (0.006)	0.315 (0.007)	0.202 (0.008)	0.423 (0.002)	-2.389 (0.012)	0.999	0.999	17100	0.020	85
180	0.065 (0.004)	0.287 (0.006)	0.178 (0.007)	0.382 (0.001)	-2.392 (0.009)	1.000	0.999	24225	0.017	88



**Figure 5.2** Plot of the system constants against temperature for the stationary phase Rtx-440.

The change in system constants for Rtx-440 over the temperature range 60-300°C is plotted in Figure 5.2. The rate of change for the system constants with temperature is larger at lower temperatures than higher temperatures. The system constants approach a plateau region at the highest temperatures. Within the plateau region the system constants change only weakly with temperature. The persistence of polar interactions at high temperatures for weakly polar stationary phases, such as Rtx-440, is important for method development for compounds of low volatility. The temperature at which the contributions from polar interactions could be considered negligible in gas chromatography is likely to be considerable higher than 300°C and the myth that “all stationary phases have identical selectivity at high temperatures” could only be true at temperatures probably beyond those typically employed. It would be wrong to extrapolate the results presented here to very-high temperature gas chromatography (temperatures > 400°C). This would require a long extrapolation, but there are few stationary phases suitable for use at these temperatures, and selectivity differences are restricted by the limited variety of stationary phases.



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## CHAPTER 6

### CONCLUSION

#### 6.1 Totally organic liquid-liquid partition systems

The solvation parameter model is a valuable tool to characterize the separation properties of partition systems and to estimate the physicochemical properties for organic compounds of environmental and biological interest. Totally organic liquid-liquid partition systems provide an alternative approach to aqueous biphasic systems for the determination of solute descriptors for compounds of low water solubility. Formamide, propylene carbonate, ethylene glycol and dimethyl sulfoxide are demonstrated to be useful solvents for liquid-liquid partition forming several complementary biphasic systems with organic counter solvents suitable for sample preparation and descriptor measurements. Formamide is significantly more cohesive than typical organic solvents but probably about half as cohesive as water. It is moderately hydrogen-bond acidic compared with water and about as hydrogen-bond basic and dipolar/polarizable. Propylene carbonate is a weak to moderately cohesive solvent, strongly dipolar and hydrogen-bond basic, and weakly hydrogen-bond acidic. Ethylene glycol is a relatively cohesive solvent, moderately dipolar and hydrogen-bond acidic, and strongly hydrogen-bond basic. Dimethyl sulfoxide is a moderately cohesive solvent, reasonably dipolar/polarizable, strongly hydrogen-bond basic and weakly hydrogen-bond acidic. Its moderate cohesion and strong polar interactions make it suitable for the isolation of polar compounds in general, and the separation of polycyclic aromatic compounds from low-polarity hydrocarbons, in particular.

#### 6.2 Solvent Classification for Chromatography and Extraction

A combination of the system constants derived from the solvation parameter model and hierarchical cluster analysis provides a successful classification of solvents commonly employed in separation processes. As the first step of method development solvents selected from each of

the seven selectivity groups (Table 3.1) and the four solvents that behave independently afford a suitable approach for screening solvents with a broad range of selectivity. Expanding group membership allows further refinement of within group solvent selection due to small characteristic differences in selectivity associated with solvents of different molecular weight and functional group type. The same classification approach was also successful for distinguishing between liquid-liquid extraction systems. Aqueous biphasic systems (Table 3.3) are dominated by the characteristic properties of water and have different selectivity to the totally organic biphasic systems (Table 3.5). While the range of selectivity for the aqueous biphasic systems is quite narrow, resulting in a small number of systems with different separation properties, there is little grouping of the totally organic biphasic systems, which represent a broad continuum of separation properties. For compounds with known descriptor values the models for the liquid-liquid partition systems allows simple calculations to be used to identify the optimum separation system for specific applications. For compounds that lack descriptor values the results of cluster analysis provide a framework for screening liquid-liquid extraction systems as a selection tool.

### **6.3 Solute descriptors for fragrance compounds and plasticizers.**

Chromatographic and liquid-liquid partition methods facilitate the calculation of descriptors for fragrance compounds and plasticizers. The use of gas chromatography and totally organic liquid-liquid partition systems are particularly useful for compounds of low water solubility and facilitate the calculation of transfer properties in aqueous systems that are challenging to measure directly. Descriptors for the 28 fragrance compounds and 24 plasticizers determined in this study should allow the prediction of a wide range of chromatographic, physicochemical, biological and environmental properties for these compounds using established predictive models.

#### **6.4 Compounds for expanding the descriptor space for characterizing separation systems**

A collection of compounds was identified for extending the descriptor space and compound variation for characterizing separation systems. The combination of retention factors determined by gas chromatography and liquid-liquid partition coefficients in totally organic systems facilitates the measurement of descriptors for compounds difficult to measure by conventional methods. As an application of the data set a number of weakly polar stationary phases were characterized over the temperature range 200-300°C. An important observation from these studies is the persistence of polar interactions to the highest temperatures studied and the conservation of selectivity differences between stationary phases at the highest temperatures studied. In the case of Rtx-440 it is demonstrated that the solvation parameter model can provide a window on the changes of intermolecular interactions over a very wide temperature range (60-300°C). System maps, such as Figure 5.2, provide an attractive method for determining the initial separation conditions by computer simulations for method development for compounds with known descriptor values.

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**GC retention data****DB 225**

	RT	RT	RT	RT	RT	RT	RT	RT	RT
	240.0	220.0	200.0	180.0	160.0	140.0	120.0	100.0	80.0
Methane	0.21	0.37	0.38	0.39	0.40	0.42	0.43	0.45	0.45
1-Acetonaphthone	0.37	0.84	1.25	2.17	4.22	9.30	24.29	73.66	
2-Acetonaphthone	0.4	0.91	1.39	2.45	4.88	11.02	29.15	88.90	
4-Acetylbiphenyl	0.53	1.35	2.36			27.91	84.17		
trans-Androsterone	3.93	13.90	33.63	90.95					
Anthracene	0.48	1.14	1.85			16.40	44.10		
1-Bromododecane		0.41	0.46	0.53	0.65	0.90	1.49	2.96	7.55
2-Chlorophenol		0.42	0.46	0.51	0.62	0.82	1.26	2.28	5.02
Cholestane	1.12	3.45	7.43	17.96	49.34				
Cholesterol	4.41	16.97	44.74						
Cholesteryl acetate	4.4	17.38	46.20						
Chrysene	2.43	8.06	17.61	43.74					
4-Cyanophenol	0.55	1.41	2.46	4.97	11.38	29.68	89.31		
Dibenzyl ether	0.33	0.71	1.01			7.18	18.68	57.91	
2,6-Dichloro-4-nitroaniline	0.62	1.64	2.90	5.83	13.22	34.04	100.76		
N,N-diethylcarbanilide	0.46	1.13	1.88	3.56	7.98	20.12	60.54		
N,N-diethyldodecanamide	0.38	0.90	1.48	2.85		17.92	58.30		
Dihydrocholesterol	4.34	16.67	43.38						
N,N-dimethyldodecylamine		0.40	0.45	0.52	0.64	0.92	1.63	3.62	10.62
Di-n-butylsuccinate	0.27	0.52	0.68	0.98	1.71	3.56	9.16	27.71	
Diphenyl ether	0.26	0.49	0.59		1.16	2.01	4.19	10.24	29.84
N,N-diphenylphenylenediamine	6.76	27.30	75.94						
1,12-Dodecanediol	0.41	1.00				23.70	79.98		
4-Fluoroaniline		0.42	0.46	0.54	0.67	0.93	1.50	2.93	6.67
Hexachlorobenzene	0.33	0.69				5.50	13.11	36.28	
4-Hydroxybenzyl alcohol	0.38	0.94				15.78	47.33		
Methyl nonanoate	0.21	0.46	0.42	0.48	0.56	0.72	1.07	1.98	4.44
2-(1-Naphthyl)ethanol	0.48	1.17				20.26	59.15		
Nicotinamide	0.49	1.21	1.99	3.78	8.24	20.36	58.53		
Nicotine	0.25	0.49	0.58	0.74	1.07	1.77	3.46	8.12	21.65
4-Nitrobenzyl alcohol	0.52	1.31	2.20	4.30	9.56	24.20	70.54		

Octan-2-ol	0.34	0.40	0.43	0.48	0.56	0.71	1.05	1.97	
Perylene	7.76	29.35	72.56						
Phenylcyclohexane	0.29	0.44			1.08	1.84	3.74	9.29	
Progesterone	10.2	40.29							
trans-Stilbene	0.37	0.82			10.13	27.47	86.59		
Styrene			0.40	0.44	0.48	0.56	0.71	1.01	1.96
1,2,4,5-Tetrachlorobenzene	0.24	0.45	0.51	0.63	0.83	1.26	2.19	4.62	11.66
Tribenzylamine	0.87	2.60	5.32	12.55	33.77				
Triisopropanolamine	0.35	0.76	1.13	1.96	4.01	9.16	27.74	94.10	
Trimethoprin	0.31	0.65	0.89	1.41	2.57	5.50	13.77	40.61	
Triphenylamine	0.54	1.39			11.46	31.45	96.96		
Triphenylmethane	0.53	1.39			11.99	32.75	105.37		
Amyl Cinnamal	0.31	0.66	0.93	1.48	2.84	6.32	16.78	51.54	
Anise alcohol	0.28	0.54	0.69	0.97	1.62	3.13	7.37		39.44
Benzyl cinnamate	0.8	2.32	4.69	10.73	28.44	85.70			
Benzyl salicylate	0.49	1.21	2.08	4.06	9.23	24.00	71.80		
Boroneol	0.24	0.43	0.47	0.54	0.68	0.95	1.55	3.09	7.57
d-Camphor	0.23	0.42	0.47	0.54	0.67	0.92	1.43	2.66	5.86
Carvone	0.24	0.45	0.52	0.63	0.85	1.31	2.38	5.19	13.35
Cinnamal	0.27	0.52	0.65	0.87	1.34	2.41	5.07	12.50	36.07
Citral-1	0.24	0.45	0.51	0.60	0.79	1.21	2.20	4.86	12.56
Citral-2	0.24	0.45	0.55	0.63	0.86	1.36	2.57	5.95	16.16
Citronellol		0.41	0.44	0.48	0.57	0.74	1.11	2.02	4.45
Eugenol	0.26	0.51	0.63	0.86	1.35	2.50	5.55	14.68	44.58
Farnesol-1	0.3	0.63	0.84	1.35	2.62	5.99	17.20	58.00	
Farnesol-2	0.3	0.63	0.88	1.45	2.86	6.65	19.33	65.71	
Geraniol		0.43	0.48	0.57	0.75	1.14	2.15	4.98	14.33
Hydroxy citronellal	0.26	0.49	0.58	0.77	1.17	2.11	4.76	12.76	
Hydroxy citronellal-2		0.68	1.00	1.71	3.58	8.94			
$\alpha$ -Isomethylionone	0.26	0.50	0.62	0.82	1.26	2.25	4.09	12.40	
Lilial	0.28	0.55	0.71	1.04	1.76	3.51	8.49	23.87	
d-Limonene					0.45	0.50	0.59	0.75	1.07
Linalool		0.40	0.42	0.46	0.52	0.65	0.93	1.62	3.51
Methyleugenol	0.26	0.49	0.59	0.79	1.24	2.33	5.40	14.97	
2-Mthoxy cinnamaldehyde	0.36	0.79	1.17	2.00	3.94	8.90	23.73	68.60	
Pinene-1							0.51	0.61	0.70
Pinene-2							0.51	0.63	0.87
Terpine-4-ol		0.41	0.45	0.51	0.61	0.81	1.28	4.57	5.63

Vaniline	0.35	0.76	1.10	1.80	3.40	7.45	19.13	37.63	
Benzyl 2-ethylhexyl Phthalate	1.16	3.97	9.39	25.92	82.65				
Bis(2ethylhexyl) phthalate	1.17	4.00	9.51	26.17	82.77				
Bis (ethoxyethyl) Phthalate	0.86	2.64	5.72	14.04	41.38				
Bis(2-n-butoxyethyl) Phthalate	1.59	5.67	14.10	39.52					
Bis(methoxyethyl) Phthalate	0.8	2.39	4.98	11.89	32.75				
Butyl 2-ethylhexyl Phthalate	1.08	3.97	9.47	25.78	82.10				
Butyl benzyl Phthalate	1.53	5.20							
Butyl cyclohexyl Phthalate	0.93	2.85	6.07	14.61	40.71				
Butyl decyl Phthalate	0.5	1.31	3.93	5.06	12.60				
Butyloctyl phthalate	0.94	2.97		19.23	34.91				
Dibutyl phthalate	0.51	1.31	2.41	5.09	12.76	36.12			
Dicapryl Phthalate	1.1	3.71	8.85	24.10	75.32				
Dicyclohexyl phthalate	1.98	6.89							
Diethyl Phthalate	0.34	0.73	1.09	1.85	3.72	8.75	24.67		
Diisobutyl phthalate	0.42	1.02							
Dimethyl Phthalate	0.31	0.64	0.89	1.40	2.56	5.50	13.90	40.04	
Di-octylphthalate	1.96	7.27	19.09	55.71					
Butyl oleate	0.47	1.26	2.41	5.40	14.70	46.25			
Butyl stearate	0.45	1.20	2.29	5.17	6.81	19.55	68.46		
Ethyl oleate	0.37	0.90	1.52	3.04	7.45	21.35	54.95		
Dibutyl succinate	0.26	0.53	0.68	0.98	1.71	3.59	9.05	27.29	
Dietyl adipate	0.25	0.47	0.56	0.73	1.11	2.02	4.39	11.85	39.47
Diethyl dietyl malonate		0.42	0.47	0.54	0.70	1.03	1.78	3.94	10.92
Diethyl sebacate	0.33	0.71	1.07	1.87	4.01	10.28	31.41		
Methyl abietate	0.85	2.51	5.17	12.07	32.67				

HP 88

	RT	RT	RT	RT	RT	RT	RT	RT	RT	RT
	240°C	220°C	200°C	180°C	160°C	140°C	120°C	100°C	880°C	60°C
Methane	0.67	0.68	0.69	0.70	0.71	0.73	0.74	0.75	0.77	0.79
1-Acetonaphthone			2.57							
2-Acetonaphthone			2.91							
4-Acetylbiphenyl			4.58							
trans-Androsterone		26.66	62.95							
Anthracene			3.57							
1-Bromododecane			0.76							
2-Chlorophenol		0.80	0.89							
Cholestane		1.81	3.09							
Cholesterol		11.05	27.18							
Cholesteryl acetate		8.04	19.67							
Chrysene		16.35	36.89							
2,6-Dichloro-4-nitroaniline		3.86	7.06							
N,N-diethylcarbanilide		1.58	2.42							
N,N-diethyldodecanamide		1.15	1.63							
Dihydrocholesterol		10.65	26.02							
N,N-dimethyldodecylamine		0.77	0.83							
Di-n-butylsuccinate		0.87	1.03							
1,12-Dodecanediol		1.91	3.31							
4-Fluoroaniline		0.84	0.96							
4-Hydroxybenzyl alcohol		3.55	6.70							
Methyl nonanoate		0.71	0.99							
Nicotinamide		4.62	8.64							
Nicotine		0.86	0.98							
4-Nitrobenzyl alcohol		3.95	7.28							
Octan-2-ol		0.73								
Progesterone		70.84								
Styrene		0.78	0.83							
1,2,4,5-Tetrachlorobenzene		0.78	0.86	1.01						
Tribenzylamine		3.04	5.93							
Triisopropanolamine		1.82	2.94							
Trimethoprin		0.86								
Amyl Cinnamal	0.90	1.07	1.40	2.12	3.77	8.05	20.42	61.88		
Anise alcohol	0.97	1.17	1.58	2.47	4.42	9.32	23.38	69.38		

Benzyl cinnamate	2.31		8.08	18.89	50.43					
Benzyl salicylate	1.43	2.09	3.52	6.93	15.64	40.73				
Boroneol	0.73	0.78	0.83	0.95	1.15	1.57	2.52	4.96	12.19	36.15
d-Camphor	0.74	0.78	0.83	0.93	1.10	1.43	2.12	3.75	8.02	19.20
Carvone	0.76	0.82	0.91	1.06	1.37	2.02	3.51	7.38	18.63	57.68
Cinnamal	0.91	1.04	1.31	1.83	2.92	5.49	11.87	30.31		
Citral-1	0.75	0.79	0.88	1.01	1.26	1.84	3.17	6.73	11.49	
Citral-2	0.75	0.79	0.88	1.05	1.35	2.04	3.69	8.19	22.24	
Citronellol	0.70	0.73	0.76	0.82	0.92	1.12	1.53	2.55	5.35	14.38
Eugenol	0.86	0.98	1.23	1.71	2.78	5.45	12.63	35.00		
Farnesol-1	0.82	0.95	1.17	1.71	3.02	6.66	18.12			
Farnesol-2	0.83	0.99	1.21	1.80	3.22	7.23	19.88			
Geraniol	0.73	0.77	0.84	0.97	1.23	1.82	3.31	7.51	21.67	
Hydroxy citronellal	0.81	0.91	1.10	1.47	2.28	4.27	9.67	26.35		
$\alpha$ -Isomethylionone	0.77	0.83	0.94	1.17	1.61	2.61	5.12	12.21	35.52	
Lilial	0.82	0.92	1.11	1.52	2.40	1.41	2.08	3.58	7.49	19.14
d-Limonene						4.58	5.84	11.48		
Linalool	0.73	0.72	0.75	0.80	0.88	1.05	1.43	2.40	5.23	15.01
Methyleugenol	0.78	0.87	1.02	1.34	2.05	3.85	8.93	25.60	90.24	
2-Mthoxy cinnamaldehyde	1.20	1.62	2.47	4.29	8.59	20.26	53.41			
Terpine-4-ol	0.71	0.74	0.80	0.86	1.00	1.26	1.87	3.41	7.78	22.52
Vaniline	0.74	0.78	0.83	0.92	1.10	1.41	2.10	3.67	7.81	19.43
tri-isopropanol amine	1.29	1.82	2.94	5.52	12.17					
Benzyl 2-ethylhexyl Phthalate	5.66	10.36	25.58							
Bis (2- ethylhexyl)phthalate	1.79	3.14	6.61	17.27	52.13					
Bis (ethoxyethyl) Phthalate	2.30	4.19	8.86	22.40						
Bis(2-n-butoxyethyl) Phthalate	3.16	6.39	15.15	42.99						
Bis(methoxyethyl) Phthalate	2.56	4.66	9.87	20.33	53.66					
Butyl 2-ethylhexyl Phthalate	1.80	3.08	6.50	18.06	50.26					
Butyl benzyl Phthalate				47.73						
Butyl cyclohexyl Phthalate	2.09	3.56	7.11	16.78	45.22					
Butyl decyl Phthalate	2.80	15.30								
Butyloctyl phthalate	3.21			15.27						
Dibutyl phthalate	1.28	1.85	3.18	6.49	15.64	44.50				

Dicapryl Phthalate	1.68	2.86	5.98	15.41	46.63		
Dicyclohexyl phthalate				46.11			
Diethyl Phthalate	1.04	1.33	1.93	3.26	6.55	15.54	42.84
Diisobutyl phthalate	1.10	1.48	2.31	4.34	9.65	25.72	
Dimethyl Phthalate	1.03	1.28	1.78	2.90	5.45	12.07	
Di-octylphthalate	2.10	5.80	13.42	30.91	67.71		
Butyl oleate	0.90	1.10	1.58	2.90	6.56	19.02	
Butyl stearate	0.87	1.07	1.47	2.62	5.96	17.21	
Ethyl oleate		0.97	1.26	3.78	5.09	10.53	
Dibutyl succinate	0.79	0.88	1.04	1.39	2.19	4.22	
Diethyl adipate	0.77	0.78	0.95	1.18	1.69	2.93	
Diethyl diethyl malonate	0.71	0.74	0.79	0.87	1.04	1.40	
Diethyl sebacate	0.87	1.04	1.38	2.20	4.26	10.16	
Methyl abietate	1.58	2.46	4.52	8.85	21.97	22.14	

**HP inovax**

	RT 220C	RT 200C	RT 180C	RT 160C	RT 140C	RT 120C	RT 100C
Methane	1.90	1.95	2.00	2.05	2.11	2.18	2.26
1-Acetonaphthone		46.67					
2-Acetonaphthone		54.41					
4-Acetylbiphenyl	23.34	65.48					
2-Chlorophenol		9.88	17.89				
Cholestane	44.78						
2,6-Dichloro-4-nitroaniline	25.67	60.68					
N,N-diethylcarbanilide	5.79	11.77					
N,N-diethyldodecanamide		34.14					
N,N-dimethyldodecylamine		6.21					
Di-n-butylsuccinate		13.87					
1,12-Dodecanediol		28.76					
4-Fluoroaniline		9.77					
Methyl nonanoate		18.43					
Nicotinamide		6.86					
Nicotine		11.38					
Octan-2-ol		5.19					
Styrene		5.00					
1,2,4,5-Tetrachlorobenzene		9.96					
Tribenzylamine		23.20					
tri-isopropanol amine	9.90		24.67	120.65			

Amyl Cinnamal	7.51	4.23	22.62	46.85			
Anise alcohol	7.69	7.27	24.12	51.31			
Benzyl cinnamate	31.24	92.24					
Benzyl salicylate	25.30						
Boroneol	3.09	7.92	5.17	7.81	13.42	26.62	
d-Camphor	2.76	6.69	4.01	5.39	8.01	13.40	25.55
Carvone	3.34	8.82	5.88	9.06	15.72	31.09	
Cinnamal	5.24	15.98	12.60	23.14	47.92		
Citral-1	2.99	7.66	4.96	7.42	12.63	24.71	
Citral-2	3.14	8.21	5.47	8.48	15.01	30.60	
Citronellol	2.46	5.79	3.35	4.38	6.38	10.69	20.89
Eugenol	6.16	20.12	17.20	34.66			
Farnesol-(1)	7.80	28.24	26.97	61.38			
Farnesol-(2)	8.33	30.52	29.44	67.60			
Geraniol	3.36	9.24	6.59	11.23	22.21	51.37	
Hydroxy citronellal	3.94	11.39	8.64	12.31	32.70	79.59	
$\alpha$ -Isomethylionone	3.75	10.42	7.42	12.33	23.16	49.67	
Lilial	5.05	15.47	12.31	22.95	48.46		
d-Limonene	2.17	4.82	2.53	2.88	3.44	4.46	6.47
Linalool	2.46	5.89	3.48	4.71	7.26	13.19	28.56
Methyleugenol	4.50	13.59	10.77	20.29	44.03		
2-Mthoxy cinnamaldehyde	11.36	41.57	39.38				
Pinene-1	2.06		2.28	2.46	2.72	3.14	3.85
Pinene-2	2.12	4.46	2.41	2.67	3.05	3.71	4.91
Terpine-4-ol	2.77	6.83	4.21	5.96	9.53	17.56	37.66
Vaniline	18.25	65.20					
Benzyl 2-ethylhexyl Phthalate	85.26	152.27					
Bis (2-ethylhexyl)phthalate	60.13	129.11					
Bis (ethoxyethyl) Phthalate	52.64						
Bis(2-n-butoxyethyl) Phthalate	92.18						
Bis(methoxyethyl) Phthalate	43.21	95.78					
Butyl 2-ethylhexyl Phthalate	62.36	133.90					
Butyl benzyl Phthalate	121.66						
Butyl decyl Phthalate	20.00	41.67	98.98				
Butyl oleate	16.82	33.82	72.34				
Butyl stearate	11.70	20.80	53.88				
Butyloctyl phthalate	54.78						
Dibutyl phthalate	19.45	38.86	86.09				
Dibutyl succinate	4.54	6.70	12.67	31.56			

Dicapryl Phthalate	61.24			
Dicyclohexyl phthalate	118.09			
Diethyl diethyl malonate	2.71	3.24	5.90	12.66
Diethyl Phthalate	9.39	16.29	37.23	76.90
Diethyl sebacate	7.78	13.41	28.98	67.09
Diethyl adipate	2.27	3.24		
Diisobutyl phthalate	13.43	25.24		
Dimethyl Phthalate	8.24	13.78	28.87	60.12
Di-octylphthalate	99.90			
Ethyl oleate	9.89	20.50	47.91	
Methyl abietate	47.63			

### RTx 440 Data

	RT	RT	RT	RT	RT	RT	RT	RT
	240°C	220°C	200°C	180°C	160°C	140°C	120°C	100°C
Methane	2.42	2.37	2.31	2.25	2.16	2.10	2.02	1.95
1-Acetonaphthone	4.77	6.04	8.39		22.62	44.46	98.90	
2-Acetonaphthone	5.09	6.57				52.24	118.02	
4-Acetylbiophenyl	7.39	10.73						
trans-Androsterone	46.02							
Anthracene	7.41	10.52						
1-Bromododecane	3.23	3.56				12.41	23.68	52.27
2-Chlorophenol	3.21	2.76	2.84	3.00	3.29	3.86	5.03	7.42
Cholestane	82.18							
Chrysene	37.05	68.11						
4-Cyanophenol	3.55	4.03	4.94	6.68	10.39	18.56	38.91	
Dibensyl ether	5.07	6.60				58.94		
2,6-Dichloro-4-nitroaniline	6.21	8.51	12.91	21.74	41.40			
N,N-diethylcarbanilide	7.89	11.69	19.32	35.70	74.39			
N,N-diethyldodecanamide	7.80	11.98	20.83	41.28	92.60			
N,N-dimethyldodecylamine	3.60	4.19	5.31	7.57	12.39	23.54	51.68	
Di-n-butylsuccinate	3.90	4.77	6.35	9.66	16.97	34.63	81.76	
Diphenyl ether	3.62	4.15		6.88	10.44	18.02	35.39	
N,N-diphenylphenylenediamine	36.64							
1,12-Dodecanediol	5.57	7.68			120.57			



4-Fluoroaniline	2.74	2.74	2.84	3.01	3.34	3.98	5.28	8.12
Hexachlorobenzene	6.00	8.02						
4-Hydroxybenzyl alcohol	3.37	3.74				14.47	28.55	
Methyl nonanoate	2.97	3.13	3.32	3.85	4.89	8.58	15.83	35.82
2-(1-Naphthyl)ethanol	5.59	7.40	10.91	17.90	32.96			
Nicotinamide	3.65	4.16	5.15	7.02	10.79	19.03	38.66	
Nicotine	3.46	3.85	4.58	5.91	8.51	13.91	25.95	55.87
4-Nitrobenzyl alcohol	4.36	5.35	7.23	10.89	18.59	36.14	80.23	
Octan-2-ol	2.67	2.67	2.72	2.84	3.09	3.60	4.64	7.03
Perylene								
Phenylcyclohexane	3.38	3.71				12.26	22.07	46.07
Progesterone								
trans-Stilbene	5.79	7.84						
Styrene	2.63	2.62	2.63	2.68	2.82	3.08	3.59	4.68
1,2,4,5-Tetrachlorobenzene	3.44	3.82	4.52	5.79	8.22	13.12	24.00	50.09
Tribenzylamine	20.65	37.10	74.30					
Triisopropanolamine	3.63	4.22	5.29	7.43	11.83	21.89	47.31	
Trimethoprin	3.20	3.46	3.94	4.85	6.64	10.34	18.80	40.16
Triphenylamine	10.91	17.38						
Triphenylmethane	10.32	16.28	28.71					
Amyl Cinnamal	4.82	6.21	8.99	14.56	26.81	56.07		
Anise alcohol	3.21	3.49	4.06	5.07	7.06	11.22	20.62	44.17
Benzyl cinnamate	13.17	22.01	41.40	86.41				
Benzyl salicylate	7.82	11.55	19.07	35.58	73.53			
Boroneol	3.00	3.13	3.41	3.93	4.84	6.73	10.58	19.18
d-Camphor	2.96	3.10	3.34	3.80	4.61	6.28	9.58	16.97
Carvone	3.10	3.35	3.75	4.54	6.00	9.08	15.68	31.51
Cinnamal	3.23	3.52	4.05	5.04	6.93	10.85	19.51	40.43
Citral-1	3.06	3.21	3.57	4.24	5.54	8.28	14.30	28.88
Citral-2	3.06	3.29	3.71	4.50	6.04	9.32	16.69	35.00
Citronellol	2.84	2.94	3.13	3.50	4.24	5.76	8.97	16.47
Eugenol	3.35	3.76	4.47	5.81	8.55	14.38	27.92	62.94
Farnesol-1	4.84	6.37	9.42	15.77	30.42	67.04		
Farnesol-2	5.06	6.78	9.55	17.38	34.03	75.92		
Geraniol	2.99	3.19	3.56	4.23	5.61	8.46	14.91	31.19
Hydroxy citronellal	3.11	3.36	3.83	4.71	10.94	20.55	18.96	41.37
Hydroxy citronellal-2	3.11	3.36	4.91		10.94	20.55		
$\alpha$ -Isomethylionone	3.76	4.41	5.59	7.86	12.54	22.85	47.78	115.49

Lilial	4.08	4.94	6.56	9.73	16.39	31.60	69.75	
d-Limonene	2.73	2.76	2.84	3.02	3.37	4.04	5.38	8.26
Linalool	2.77	2.83	2.96	3.24	3.77	4.82	7.06	12.19
Methyleugenol	3.41	3.86	4.67	6.31	9.61	17.15	35.51	85.95
2-Mthoxy cinnamaldehyde		5.18	6.97	10.57	18.00	35.30	78.88	
Pinene-1	2.65	2.65	2.67	2.73	2.90	3.24	3.86	5.20
Pinene-2	2.65	2.65	2.77	2.88	3.13	3.62	4.53	6.46
Terpine-4-ol	2.97	3.12	3.39	3.90	4.89	6.87	10.94	20.53
Vaniline	3.63	4.19	5.17	7.03	10.80	19.02	38.14	89.40
Benzyl 2-ethylhexyl Phthalate	34.63	71.34						
Bis (2- ethylhexyl)phthalate	34.66	71.58						
Bis (ethoxyethyl) Phthalate	12.07	20.82	40.26	88.37				
Bis(2-n-butoxyethyl) Phthalate	30.94	62.84						
Bis(methoxyethyl) Phthalate	9.37	15.08	27.32	56.01				
Butyl 2-ethylhexyl Phthalate	34.61	70.82						
Butyl benzyl Phthalate	23.31		91.70					
Butyl cyclohexyl Phthalate	16.45	29.08	57.18					
Butyl decyl Phthalate	8.28	12.82	22.51	44.48				
Butyloctyl phthalate	8.27	12.83	22.42	44.53				
Dibutyl phthalate	8.30	12.95	22.67	45.18				
Dicapryl Phthalate	34.65	71.66						
Dicyclohexyl phthalate	35.76							
Diethyl Phthalate	4.34	5.40	7.52	11.82	21.13	43.43		
Diisobutyl phthalate	6.73							
Dimethyl Phthalate	3.72	4.31	5.49	7.76	12.40	22.77	48.33	
Di-octylphthalate	62.37	139.14						
Butyl oleate	20.86	39.83	85.91					
Butyl stearate	22.13	22.83	45.67					
Ethyl oleate	12.55	21.93	35.23					
Dibutyl succinate	3.91	4.74	6.35	9.67	12.40	34.59	81.92	
Dietyl adipate	3.24	3.61	4.28	5.65	8.49	14.87	30.68	75.01
Diethyl dietyl malonate	2.98	3.20	3.56	4.30	5.75	8.83	15.90	33.99

Diethyl sebacate	5.52	7.72	12.21	22.32	46.75
Methyl abietate	22.93	42.14	85.42		

### Rtx OPP Data

#### Part 1

	RT	RT	RT	RT	RT
	260°C	240°C	220°C	200°C	180°C
Methane	0.99	1.01	1.02	1.04	1.06
1-Acetonaphthone				2.50	
2-Acetonaphthone				2.72	
4-Acetylbiphenyl				4.04	
trans-Androsterone				40.77	
Anthracene				3.41	
1-Bromododecane				1.36	
2-Chlorophenol		1.07	1.09	1.14	1.21
Cholestane				31.03	75.66
Cholesterol				80.68	
Cholesteryl acetate				121.7	
Chrysene		5.53	9.78	19.43	42.61
4-Cyanophenol		1.30	1.51	1.85	2.52
N,N-diethylcarbanilide		1.90	2.58	3.99	7.04
N,N-diethyldodecanamide		2.05	2.97	5.00	9.75
Dihydrocholesterol				88.35	
N,N-dimethyldodecylamine			1.26	1.45	1.82
Di-n-butylsuccinate		1.33	1.57	2.05	2.99
Diphenyl ether				1.49	
N,N-diphenylp-phenylenediamine					3.61
1,12-Dodecanediol		1.55	1.98	2.84	4.77
4-Fluoroaniline			1.14	1.16	1.27
Methyl nonanoate		1.14	1.16	1.32	1.51
Nicotinamide					2.92
Nicotine		1.21	1.32	1.53	1.89
Octan-2-ol			1.71	1.77	1.20
Perylene		13.40	26.95	60.09	
Progesterone		24.60	53.53		
Styrene			1.72	2.51	6.82
1,2,4,5-Tetrachlorobenzene		1.16	1.27	1.42	1.70

Tribenzylamine					19.29
Triisopropanolamine					2.81
Trimethoprin	1.15	1.22	1.34		1.56
tri-isopropanol amine	1.20				2.81
Amyl Cinnamal	1.28	1.46	1.77	2.41	3.72
Anise alcohol	1.10	1.15	1.24	1.42	1.73
Benzyl cinnamate	1.89	2.56	3.98	7.00	14.33
Benzyl salicylate	1.53	1.86	2.56	3.95	7.03
Boroneol	1.11	1.11	1.16	1.26	1.42
d-Camphor	1.10	1.14	1.21	1.36	1.58
Carvone	1.10	1.16	1.26	1.43	1.73
Cinnamal	1.16	1.21	1.32	1.54	1.94
Citral-1		1.17	1.27	1.46	1.74
Citral-2		1.17	1.27	1.46	1.81
Citronellol		1.10	1.15	1.25	1.42
Eugenol		1.19	1.30	1.49	1.86
Farnesol-1	1.23	1.39	1.67	2.14	3.20
Farnesol-2	1.23	1.39	1.67	2.24	3.41
Geraniol		1.10	1.17	1.29	1.46
Hydroxy citronellal-:1	1.12	1.20	1.31		1.95
Hydroxy citronellal-2	1.12	1.20	1.41	1.77	2.34
$\alpha$ -Isomethylionone	1.20	1.32	1.52	1.91	2.62
Lilial	1.20	1.35	1.54	1.95	2.75
d-Limonene		1.00	1.44	1.75	1.18
Linalool		1.00	1.09	1.15	1.26
Methyleugenol		1.17	1.28	1.47	1.85
2-Mthoxy cinnamaldehyde	1.29	1.47	1.78	2.39	3.63
Pinene-1					
Pinene-2			1.07	1.24	
Terpine-4-ol-1st			1.14	1.24	1.38
Terpine-4-ol-2nd					
Vaniline	1.20	1.33	1.53	1.90	2.59
Benzyl 2-ethylhexyl Phthalate					66.33
Bis (2-ethylhexyl)phthalate					33.26
Bis (ethoxyethyl) Phthalate					20.18
Bis(2-n-butoxyethyl) Phthalate					69.78
Bis(methoxyethyl) Phthalate					14.71
Butyl 2-ethylhexyl Phthalate					76.67

Butyl benzyl Phthalate				16.75	
Butyl cyclohexyl Phthalate					25.60
Butyl decyl Phthalate					10.81
Butyloctyl phthalate	4.57				
Dibutyl phthalate	2.20	3.26	5.57		11.23
Dicapryl Phthalate					65.65
Dicyclohexyl phthalate					62.60
Diethyl Phthalate					3.91
Diisobutyl phthalate	1.95	2.73	4.40		8.29
Dimethyl Phthalate	1.33	1.56	1.30		2.85
Di-octylphthalate	9.59	20.30	49.09		
Butyl oleate					34.49
Butyl stearate					26.90
Ethyl oleate	2.27	3.46	6.22		
Dibutyl succinate					3.02
Diethyl adipate					2.13
Diethyl diethyl malonate					1.67
Diethyl sebacate					5.97
Methyl abietate	3.38				24.12

## Part 2

	RT	RT	RT	RT	RT	RT
	160°C	140°C	120°C	100°C	80°C	60°C
Methane	1.08	1.12	1.14	1.17	1.21	1.25
Amyl Cinnamal	6.58	13.73	33.43			
Anise alcohol	2.31	3.55	6.40	13.82	35.90	
Benzyl cinnamate	33.12	88.92				
Benzyl salicylate	14.11	33.48				
Boroneol	1.69	2.21	3.28	5.71	11.94	30.72
d-Camphor	1.97	2.72	4.31	8.11	17.94	47.40
Carvone	2.28	3.39	5.88	12.25	30.29	
Cinnamal	2.67	4.25	7.88	17.33	44.79	
Citral-1	2.29	3.46	6.17	13.21	33.84	
Citral-2	2.44	3.81	7.05	15.51	40.99	
Citronellol	1.70	2.30	3.54	6.60	14.90	41.14
Eugenol	2.57	4.12	7.80	17.69	47.76	
Farnesol-1	5.52	11.42	28.16			
Farnesol-2	5.99	12.61	30.15			

Geraniol	1.84	2.54	4.20	8.35	20.46	61.50
Hydroxy citronellal-:1	2.76	4.51	8.98	21.00		
Hydroxy citronellal-2	3.73	7.16	17.32	48.62	112.88	
$\alpha$ -Isomethylionone	4.14	7.55	16.32	41.33		
Lilial	4.43	8.30	17.28	48.61		
d-Limonene	1.28	1.44	1.76	2.38	3.77	7.49
Linalool	1.45	1.73	2.38	4.34	7.51	18.77
Methyleugenol	2.59	4.24	8.43	20.27	59.10	
2-Mthoxy cinnamaldehyde	6.30	12.84	30.20			
Pinene-1		1.32	1.52	1.88	2.63	4.36
Pinene-2	1.65	1.40	1.66	2.15	3.22	5.73
Terpine-4-ol-1st	1.64	2.12	3.11	5.42	11.41	29.01
Terpine-4-ol-2nd		3.39				
Vaniline	4.04	7.36	15.51	38.38		
tri-isopropanol amine	4.60	9.04	21.30			
Benzyl 2-ethylhexyl Phthalate						
Bis (2-ethylhexyl)phthalate	65.31					
Bis (ethoxyethyl) Phthalate	51.48					
Bis(methoxyethyl) Phthalate	35.75					
Butyl cyclohexyl Phthalate	56.98					
Butyl decyl Phthalate	25.90					
Dibutyl phthalate	26.04					
Diethyl Phthalate	7.16	15.53	39.22			
Diisobutyl phthalate	18.15	46.25				
Dimethyl Phthalate	4.66	9.00				
Butyl oleate	75.71					
Butyl stearate	58.99					
Ethyl oleate		39.25				
Dibutyl succinate	5.16	10.59				
Diethyl adipate	3.17	5.68				
Diethyl diethyl malonate	2.21	3.43				
Diethyl sebacate	12.56	31.49				
Methyl abietate						

**Rxi-55il MS****Part 1**

	RT	RT	RT	RT	RT
	280°C	260°C	240°C	220°C	200°C
Methane	2.29	2.24	2.16	2.11	2.04
1-Acetonaphthone					6.26
2-Acetonaphthone					6.82
4-Acetylbiphenyl					11.78
trans-Androsterone					11.53
Anthracene					3.59
1-Bromododecane					
2-Chlorophenol			2.39	2.42	2.47
Chrysene				40.99	
4-Cyanophenol			2.94	3.29	3.92
Di-n-butylsuccinate			3.29	3.92	5.12
Diphenyl ether			3.07	3.46	4.12
N,N-diphenyl-phenylenediamine					44.34
1,12-Dodecanediol			4.42	5.91	8.87
4-Fluoroaniline			2.39	2.41	2.45
4-Hydroxybenzyl alcohol			2.85	3.07	3.54
Methyl nonanoate			2.60	2.72	2.99
Octan-2-ol			2.34	2.35	2.40
Progesterone			54.68	109.83	
Styrene			2.32	2.30	2.31
1,2,4,5-Tetrachlorobenzene			2.93	3.21	3.70
Tribenzylamine					
Triisopropanolamine					
Trimethoprin			2.74	2.91	3.25
Triphenylamine					21.11
Triphenylmethane					19.71
Amyl Cinnamal	3.07	3.37	3.94	4.96	6.88
Anise alcohol	2.58	2.64	2.75	2.95	3.29
Benzyl cinnamate	4.84	6.35	9.21	14.85	26.68
Benzyl salicylate	3.81	4.57	5.92	8.41	13.47
Boroneol	2.53	2.58	2.62	2.72	2.94
d-Camphor	2.52	2.54	2.59	2.68	2.87

Carvone	2.57	2.61	2.69	2.84	3.15
Cinnamal	2.60	2.66	2.76	2.95	3.31
Citral-1	2.55	2.59	2.63	2.82	3.03
Citral-2	2.55	2.59	2.67	2.76	3.13
Citronellol	2.47	2.47	2.50	2.59	2.73
Eugenol	2.66	2.73	2.88	3.15	3.67
Farnesol-1	3.09	3.42	4.02	5.16	7.95
Farnesol-2	3.15	3.52	4.18	5.44	7.41
Geraniol	2.53	2.56	2.61	2.77	3.04
Hydroxy citronellal-1	2.56	2.60	2.69	2.84	3.99
Hydroxy citronellal-2	2.67	2.76	2.95	3.28	3.99
$\alpha$ -Isomethylionone	2.81	2.97	3.23	3.71	4.65
Lilial	2.88	3.07	3.40	4.00	5.19
d-Limonene	2.43	2.42	2.41	2.42	2.51
Linalool	2.45	2.43	2.44	2.47	2.59
Methyleugenol	2.66	2.75	2.92	3.22	3.83
2-Mthoxy cinnamaldehyde	2.89	3.09	3.44	4.07	5.27
Pinene-1	2.41	2.37	2.35	2.35	2.37
Pinene-2	2.41	2.37	2.39	2.40	2.45
Terpine-4-ol	2.52	2.29	2.60	2.71	2.92
Vaniline	2.73	2.85	3.04	3.39	4.03
tri-isopropanol amine	2.73	2.84			
Bis (ethoxyethyl) Phthalate	4.59				
Bis(2-n-butoxyethyl) Phthalate	7.77				
Bis(methoxyethyl) Phthalate					
Butyl 2-ethylhexyl Phthalate	3.12				
Butyloctyl phthalate	6.43	9.37	15.34	28.24	58.80
Dibutyl phthalate	3.92	4.80	6.43	9.66	16.44
Dicyclohexyl phthalate	9.13	14.09	24.25	48.48	
Diethyl Phthalate	2.94				
Diisobutyl phthalate			5.32	7.57	12.13
Dimethyl Phthalate			3.10	3.54	4.33
Di-octylphthalate	22.26		42.49		
Ethyl oleate			9.71	16.54	32.33
Diethyl diethyl malonate	2.57				
Diethyl sebacate					
Methyl abietate			15.90	28.41	56.37



## Part 2

	RT	RT	RT	RT	RT
	180°C	160°C	140°C	120°C	100°C
Methane	1.99	1.93	1.86	1.80	1.73
Amyl Cinnamal	10.84	19.39	39.76	93.22	
Anise alcohol	4.03	5.42	8.31	14.72	30.22
Benzyl cinnamate	54.34	124.22			
Benzyl salicylate	24.07	49.00			
Boroneol	3.34	4.11	5.62	8.72	15.70
d-Camphor	3.23	3.90	5.21	7.85	13.67
Carvone	3.72	4.82	7.06	11.86	23.22
Cinnamal	3.98	5.29	7.96	13.71	27.53
Citral-1	3.55	4.56	6.64	11.08	22.06
Citral-2	3.73	4.91	7.37	12.73	26.29
Citronellol	3.02	3.63	4.84	7.38	13.39
Eugenol	4.63	6.59	10.70	20.04	44.05
Farnesol-1	12.11	22.81	49.58		
Farnesol-2	13.20	25.27	55.57		
Geraniol	3.57	4.64	6.81	11.82	24.12
Hydroxy citronellal-1	3.85	5.17	7.88	14.17	29.92
Hydroxy citronellal-2	5.34	8.36	15.32	34.22	91.38
$\alpha$ -Isomethylionone	6.42	10.01	17.97	37.23	
Lilial	7.45	12.16	22.86	49.56	
d-Limonene	2.66	2.95	3.54	4.68	7.21
Linalool	2.81	3.24	4.14	5.97	10.16
Methyleugenol	4.97	7.40	12.66	25.28	59.38
2-Mthoxy cinnamaldehyde	7.59	12.55	23.61	50.95	
Pinene-1	2.43	2.60	2.91	3.50	4.72
Pinene-2	2.56	2.79	3.22	4.05	5.77
Terpine-4-ol	3.32	4.11	5.65	8.87	16.24
tri-isopropanol amine	5.60	8.49	15.20	32.48	
Vaniline	5.29	7.81	13.20	25.40	62.28
Bis (ethoxyethyl) Phthalate	57.07				
Bis(2-n-butoxyethyl) Phthalate	95.83				
Bis(methoxyethyl) Phthalate	35.82	71.56			
Butyl 2-ethylhexyl Phthalate	138.20				
Butyl benzyl Phthalate	27.94				
Butyl cyclohexyl Phthalate	53.72				

Butyl decyl Phthalate	72.00		
Butyloctyl phthalate			
Dibutyl phthalate	32.05	70.67	
Dicapryl Phthalate			
Dicyclohexyl phthalate			
Diethyl Phthalate	8.86	15.41	30.64
Diisobutyl phthalate	22.35	46.61	
Dimethyl Phthalate	5.96	9.20	16.43
Di-octylphthalate			
Butyl oleate	80.37		
Butyl stearate	46.19		
Ethyl oleate	67.21		
Dibutyl succinate	7.61	13.14	26.11
Diethyl adipate	4.61	6.75	11.50
Diethyl diethyl malonate	3.69	4.89	7.40
Diethyl sebacate	16.70		80.65
Methyl abietate			

**SPB-Octyl**

	RT	RT	RT	RT	RT	RT	RT	RT
	240°C	220°C	200°C	180°C	160°C	140°C	120°C	100°C
Methane	1.01	1.01	1.02	1.04				
1-Acetonaphthone	2.99	4.17		10.67	19.58	40.53	92.08	
2-Acetonaphthone	3.24	4.61				47.01	108.35	
4-Acetylbiphenyl	5.04	7.91			53.60			
trans-Androsterone	35.21	69.02						
Anthracene	5.87	9.24						
1-Bromododecane	1.82	2.29				14.19	29.88	71.86
2-Chlorophenol	1.27	1.37	1.54	1.78	2.19	2.91	4.26	7.05
Chrysene	34.71							
4-Cyanophenol	1.60	1.90	2.39	3.26	5.11	9.01	18.17	46.59
Dibensyl ether	3.35					57.80		
2,6-Dichloro-4-nitroaniline	3.94	5.82	9.38	16.48	32.07			
N,N-diethylcarbanilide	5.30	8.41	14.70	28.26	59.94			
N,N-diethyldodecanamide	5.50	9.22	17.20	36.15	84.81			
N,N-dimethyldodecylamine	2.22	3.01	4.48	7.54	14.24	30.40	74.56	

Di-n-butylsuccinate	2.10	2.81	4.12	6.79	12.57	26.31	62.83	
Diphenyl ether	2.09	2.68		5.65	9.46	17.63	36.84	
N,N-diphenylp-phenylenediamine	46.63							
1,12-Dodecanediol	3.25	4.82				69.08		
4-Fluoroaniline	1.22	1.31	1.43	1.64	1.97	2.52	3.57	5.71
Hexachlorobenzene	5.00	7.70			47.37			
4-Hydroxybenzyl alcohol	1.58	1.85				7.60	14.56	32.19
Methyl nonanoate	1.41	1.61	1.93	2.58	3.70	6.15	11.82	25.02
2-(1-Naphthyl)ethanol	3.54	5.14				56.51		
Nicotinamide	1.71	2.05	2.62	3.61	5.53	9.49	19.06	44.47
Nicotine	1.91	2.37	3.15	4.59	7.34	13.10	26.13	
4-Nitrobenzyl alcohol	2.21	2.86	4.01	6.17	10.52	20.08	42.71	
Octan-2-ol	1.20	1.29	1.41	1.62	1.98	2.61	3.86	6.54
Phenylcyclohexane	1.96	2.45				13.82	27.58	
trans-Stilbene	4.13	6.24						
Styrene	1.19	1.26	1.37	1.53	1.80	2.25	3.07	4.66
Tribenzylamine	17.65	33.68	70.54					
Triisopropanolamine	1.81	2.22	2.97	4.33		13.33	28.86	72.71
Trimethoprin	28.85	67.98	2.25	2.98	4.37	7.15	13.43	
Triphenylamine	8.61	14.83	27.89	57.76				
Triphenylmethane	8.15	13.89						
Amyl Cinnamal	3.09	4.37	6.93	12.21	23.78	51.83		
Anise alcohol	1.60	1.87	2.33	3.15	4.73	7.85	14.69	31.33
Benzyl cinnamate	9.66	16.78	32.61	69.95				
Benzyl salicylate	5.68	9.01	15.97	31.15	67.21			
Boroneol	1.54	1.75	2.11	2.75	3.85	5.98	10.37	20.29
d-Camphor	1.49	1.68	1.99	2.54	3.49	5.28	8.91	17.08
Carvone	1.60	1.86	2.32	3.14	4.66	7.68	14.23	30.10
Cinnamal	1.66	1.95	2.46	3.35	5.02	8.34	15.55	32.61
Citral-1	1.55	1.79	2.24	2.82	4.12	6.73	14.51	26.39
Citral-2	1.55	1.79	2.52	3.03	4.54	7.62	15.51	30.12
Citronellol	1.37	1.53	1.79	2.24	3.07	4.69	8.11	16.04
Eugenol	1.79	2.17	2.86	4.11	6.60	11.91	24.09	55.54
Farnesol-1	3.08	4.76	7.10	12.98	26.36	60.07		
Farnesol-2	3.26	5.22	7.82	14.31	29.42	67.78		
Geraniol	1.50	1.71	2.10	2.80	4.10	6.78	12.72	27.42
Hydroxy citronellal	1.54	1.78	2.21	2.98	4.44	7.43	14.11	30.63
Hydroxy citronellal-2	1.54	1.78	2.21	3.96	6.58	12.52		72.79

$\alpha$ -Isomethylionone	2.25	2.91	4.17	6.57	11.57	22.70	45.21	126.54
Lilial	2.46	3.28	4.84	7.89	14.26	29.12	66.22	
d-Limonene	1.33	1.44	1.65	1.98	2.57	3.66	5.84	10.56
Linalool	1.32	1.44	1.65	2.01	2.63	3.85	6.35	11.98
Methyleugenol	1.84	2.27	3.08	4.60	7.72	14.61	31.37	77.83
2-Mthoxy cinnamaldehyde		3.14	4.57	7.35	13.13	26.25	59.17	
Pinene-1	1.25	1.33	1.46	1.67	2.03	2.66	3.83	6.23
Pinene-2	1.25	1.40	1.58	1.85	2.32	3.16	4.75	8.07
Terpine-4-ol	1.53	1.75	2.14	2.81	4.03	6.43	11.51	23.53
Vaniline	1.88	2.30	3.06	4.41	7.10	12.72	25.59	58.25
Benzyl 2-ethylhexyl Phthalate	27.57	57.80						
Bis (2- ethylhexyl)phthalate	27.58	57.79						
Bis (ethoxyethyl) Phthalate	7.42	12.86	25.26	55.16				
Bis(2-n-butoxyethyl) Phthalate	20.69	41.74	94.76					
Bis(methoxyethyl) Phthalate	5.48	8.95	16.49	33.73	77.02			
Butyl 2-ethylhexyl Phthalate	27.54	57.63						
Butyl benzyl Phthalate	16.43	31.19	66.33					
Butyl cyclohexyl Phthalate	12.04		16.67	34.16				
Butyl decyl Phthalate	5.51	9.02	16.67	34.09	78.30			
Butyloctyl phthalate	16.08				78.26			
Dibutyl phthalate	5.54	9.05	16.74	34.19	78.65			
Dicapryl Phthalate	27.45	57.62						
Dicyclohexyl phthalate	27.80	55.11						
Diethyl Phthalate	2.43	3.26	4.87	8.09	14.99	31.27	73.88	
Diisobutyl phthalate	4.37				51.43			
Dimethyl Phthalate	1.93	2.39	3.24	4.90	8.12	15.32	32.27	
Di-octylphthalate		109.69						
Butyl oleate	18.24	36.70	83.71					
Butyl stearate	19.90	20.79	44.59					
Ethyl oleate	10.31	19.17	40.41	94.95				
Dibutyl succinate	2.14	2.81	4.13	6.79	12.56	26.42	63.06	
Diethyl adipate	1.60	1.91	2.48	3.55	5.67	10.37	21.65	52.34
Diethyl diethyl malonate	1.45	1.67	2.05	2.73	4.02	6.70	12.76	28.02
Diethyl sebacate	3.31	4.94	8.41	16.00	34.44			

Methyl abietate                      20.41   38.99   82.70

### High temperature retention data

#### HP-5

	RT 260 Ć	RT 280 Ć	RT 300 Ć
CH4	0.898	0.884	0.804
1,2,4,5-Tetrachlorobenzene	0.997	0.956	0.858
1,12-Dodecanediol	1.146	1.057	0.931
1-Acetonaphthone	1.113	1.031	0.908
2-Acetonaphthone	1.128	1.026	0.913
4-Acetylbiphenyl	1.273	1.133	0.977
1-Bromododecane	0.987	0.939	0.846
2(1-Naphthyl)ethanol	1.162	1.051	0.929
2,6-Dichloro-4-nitroaniline	1.196	1.072	0.946
4-Nitrobenzyl alcohol	1.071	1.024	0.888
Androsterone	3.248	2.225	1.693
Anthracene	1.293	1.144	0.988
Cholestane	5.449	3.344	2.334
Diphenyl ether	1.004	0.96	0.863
Methyl nonanoate	0.951		
N,N-Diethyldodecnamide	1.321	1.132	0.992
N,N-Dimethyldodecylamine	1.025	0.962	0.859
Nicotinamide	1.022	0.973	0.869
Phenylcyclohexane	0.998	0.947	0.856
Progesterone	5.503	3.414	2.385
trans-Stilbene	1.172	1.073	0.937
Tribenzylamine	2.1	1.592	1.272
Triisopropanolamine	1.015	0.964	0.861
Triphenylmethane	1.491	1.254	1.071
Dibenzyl ether	1.114	1.03	0.905
Cholesterol	9.219	5.109	3.292
Cholesteryl acetate	12.232	6.393	3.948
Chrysene	2.896	2.066	1.577
4-Cyanophenol	0.999	0.96	0.852
Dihydrocholesterol	9.358	5.168	3.359
Hexachlorobenzene	1.205	1.096	0.957
N,N-diethylcarbanilide	1.335	1.163	1.009
N,N-Diphenyl-4-phenylenediamine	3.895	2.542	1.837

Nicotine	1.007	0.955	0.859
Perylene	5.968	3.675	2.589
Trimethoprin	3.528	2.341	1.711
Triphenylamine	1.532	1.286	1.088
Amyl cinnamal	1.115	1.001	0.91
Anise alcohol	0.966		
Benzyl cinnamate	1.595		1.086
Benzyl salicylate	1.301		0.985
Cinnamal	0.985		
Eugenol	0.985		
Geraniol	0.954		
Hydroxycitronellal	0.9954		
$\alpha$ -Isomethyl ionone	1.039		0.885
Lilial	1.047		0.912
Methyleugenol	0.985		
Borneol	0.955		
Camphor	0.955		
Carvone	0.963		
Citronellal	0.94		
2-Methoxycinnamaldehyde	1.042		
Terpinen-4-ol	0.952		
Vanillin	1.005		
Dimethyl phthalate	1.023	0.969	0.866
Diethyl phthalate	1.072	1.011	0.887
Di-n-butyl phthalate	1.36	1.168	0.994
Di-capryl phthalate	2.872	1.948	1.484
Di-n-octyl phthalate	4.112	2.561	1.826
Dicyclohexyl phthalate	2.929	2.026	1.552
Di-isobutyl phthalate	1.28	1.115	0.967
Di-2-ethylhexyl phthalate	2.92	1.978	1.487
Di-2-octyl phthalate			
Butyl benzyl phthalate	2.205	1.643	1.292
Butyl cyclohexyl phthalate	1.85	1.46	1.19
Butyl decyl phthalate	1.34	1.2	1
Butyl octyl phthalate	2.11	1.168	1.263
Benzyl 2-ethylhexyl phthalate	2.9	1.98	1.47
Di-(2-methoxyethyl) phthalate	1.4	1.2	1.018
Di-(2-ethoxyethyl) phthalate	1.577	1.294	1.072
Di-(2-butoxyethyl) phthalate	2.591	1.803	1.385
Butyl oleate	2.101	1.555	1.232
Butyl stearate	2.16	1.58	1.244

Ethyl oleate	2.08	1.313	1.084
Methyl abietate	2.239	1.661	1.328
Diethyl adipate	1.098	0.939	0.845
Dibutyl succinate	1.042	0.969	0.868
Diethyl sebacate	1.154	1.046	0.924
Diethyl diethylmalonate	0.957	0.928	
Methacryloxypropyltrimethoxysilane	0.996	0.942	0.844
Glycidoxypropyltrimethoxysilane	1.007	0.961	0.849
Isocyanatopropyltriethoxysilane	0.975	0.94	0.885
3-Aminopropyltriethoxysilane	0.947		
Acenaphthene	1.055	0.992	0.893
Acenaphthylene	1.051	0.984	0.888
Fluoranthene	1.677	1.381	1.145
Fluorine	1.119	1.049	0.904
Resosinol	0.969	0.948	0.849
Quinoline	0.975	0.94	0.843
Tri-n-butyryn	1.202	1.08	0.936
Valerophenone	0.99	0.954	0.856
Carbazole	1.323	1.162	1.001
Octanophenone	1.129	1.024	0.917
Phenanthrene	1.282	1.148	0.987
2-Methoxynaphthalene	0.998	0.96	0.849
Benzenesulfonamide	1.08	1.024	0.902
m-Dinitrobenzene	1.044	0.986	0.876
Coumarin	1.043	0.993	0.891
n-Octyltriethoxy silane	0.994	0.955	0.847

**Rtx-440**

	RT	RT	RT
	260 C	280 C	300 C
CH4	2.504	2.573	2.64
1,2,4,5-Tetrachlorobenzene	3.181	3.082	3.007
1,12-Dodecanediol	4.413	3.81	3.494
1-Acetonaphthone	4.006	3.635	3.395
2-Acetonaphthone	4.184	3.734	3.455
4-Acetylbiphenyl	5.527	4.538	3.976
1-Bromododecane	3.049	2.975	2.92
2(1-Naphthyl)ethanol	4.51	3.939	3.61
2,6-Dichloro-4-nitroaniline	4.922	2.847	

2-Chlorophenol	2.716	2.731	2.761
4-Fluoroaniline	2.711	2.724	
4-Nitrobenzyl alcohol	3.771	3.447	3.226
Androsterone	25.437	15.806	10.687
Anthracene	5.627	4.66	4.101
Cholestane	42.186	24.069	15.034
Diphenyl ether	3.298	3.15	3.066
Methyl nonanoate	2.853	2.817	
N,N-Diethyldodecamide	5.546	4.49	3.918
N,N-Dimethyldodecylamine	3.245	3.086	3.006
Nicotinamide	3.317	3.161	3.083
Octan-2-ol	2.653	2.686	
Phenylcyclohexane	3.6	3.3	2.993
Progesterone		28.96	17.858
Styrene	2.622		
trans-Stilbene	4.611	4.003	3.631
Tribenzylamine	12.434	8.483	6.338
Triisopropanolamine	3.294	3.14	3.05
Triphenylmethane	7.13	5.483	4.526
Dibenzyl ether	4.202	3.677	2.76
Cholesterol			25.096
Cholesteryl acetate			30.683
Chrysene	21.534	13.839	9.653
4-Cyanophenol	3.247	3.069	3.036
Dihydrocholesterol		44.909	25.88
Hexachlorobenzene	4.773	4.125	3.725
N,N-diethylcarbanilide	5.741	4.68	4.092
N,N-Diphenyl-4-phenylenediamine	34	19.774	12.655
Nicotine	3.198	3.086	3.041
Perylene			20.157
Trimethoprin	28.886	16.859	10.888
Triphenylamine	7.467	5.721	4.7
Amyl cinnamal	4.029	3.596	3.366
Anise alcohol	3.035	2.966	
Benzyl cinnamate	8.601	6.277	5.021
Benzyl salicylate	5.751	4.671	4.064
Cinnamal	3.057	2.976	2.925
Eugenol	3.131	3.027	2.96
Farnesol (isomer 1)	4.012	3.56	
Farnesol (isomer 2)	4.142	3.64	
Geraniol	2.892	2.856	



Hydroxycitronellal	3.19		
$\alpha$ -Isomethyl ionone	3.393	3.186	3.079
Lilial	4.11	3.63	3.37
Limonene	2.7		
Linalool	2.726		
Methyleugenol	3.156	3.015	2.967
Borneol	2.905	2.868	
Camphor	2.88	2.856	
Carvone	2.984	2.929	2.903
Citronellal	2.788	2.772	
2-Methoxycinnamaldehyde	3.651	3.347	3.209
Vanillin	3.322	3.146	3.069
Dimethyl phthalate	3.347	3.156	3.077
Diethyl phthalate	3.724	3.419	3.233
Di-n-butyl phthalate	5.934	4.71	4.034
Di-capryl phthalate	18.545	11.253	7.638
Dicyclohexyl phthalate	19.892	12.401	8.485
Di-isobutyl phthalate	5.09	4.224	3.746
Di-2-ethylhexyl phthalate	20.01	11.3	7.692
Di-2-octyl phthalate	31.058	17.31	10.895
Butyl benzyl phthalate	13.691	9.011	6.565
Butyl cyclohexyl phthalate	10.29	7.18	4.04
Butyl decyl phthalate	5.92	4.7	4.03
Butyl octyl phthalate	5.91	4.707	4.05
Benzyl 2-ethylhexyl phthalate	3.701	3.417	9.9
Di-(2-methoxyethyl) phthalate	6.483	5.021	4.24
Di-(2-ethoxyethyl) phthalate	7.849	5.781	4.661
Di-(2-butoxyethyl) phthalate	16.985	10.484	7.29
Butyl oleate	12.05	7.9	5.86
Butyl stearate	12.56	8.01	5.96
Ethyl oleate	8.002	5.836	4.666
Methyl abietate	15.31	10.06	7.25
Diethyl adipate	3.03	2.941	2.921
Dibutyl succinate	3.426	3.205	3.078
Diethyl sebacate	4.355	3.757	3.441
Diethyl diethylmalonate	2.885	2.874	
Methacryloxypropyltrimethoxysilane	3.041	2.961	2.909
Glycidoxypropyltrimethoxysilane	3.142	3.037	2.959
Isocyanatopropyltriethoxysilane	2.911	2.875	2.854
3-Aminopropyltriethoxysilane	2.807	2.796	2.79
Acenaphthene	3.699	3.435	3.286

Acenaphthylene	3.627	3.373	3.231
Fluoranthene	9.217	6.83	5.51
Fluorine	4.129	3.703	3.455
Resosinol	2.99	2.93	2.906
Quinoline	3.065	2.985	2.963
Tri-n-butyrin	4.608	3.907	3.524
Valerophenone	3.141	3.029	2.999
Carbazole	6.018	4.885	4.233
Octanophenone	4.117		3.386
Phenanthrene	5.516	4.612	4.061
2-Methoxynaphthalene	3.173	3.046	2.993
Benzenesulfonamide	3.9	3.544	3.343
m-Dinitrobenzene	3.546	3.323	3.173
Coumarin	3.567	3.342	3.202
n-Octyltriethoxy silane	3.058	2.977	2.906

### Rtx-Opp

	RT
	300 Ć
CH4	0.99
1,2,4,5-Tetrachlorobenzene	1.059
1,12-Dodecanediol	1.169
2-Acetonaphthone	1.171
4-Acetylbiophenyl	1.245
1-Bromododecane	1.065
2(1-Naphthyl)ethanol	1.182
2,6-Dichloro-4-nitroaniline	1.264
Androsterone	2.456
Anthracene	1.225
Cholestane	2.141
Diphenyl ether	1.084
Methyl nonanoate	1.035
N,N-Diethyldodecamide	1.243
N,N-Dimethyldodecylamine	1.065
Nicotinamide	1.141
Phenylcyclohexane	1.063
Progesterone	4.447
trans-Stilbene	1.155
Tribenzylamine	1.45

Triisopropanolamine	1.103
Triphenylmethane	1.227
Dibenzyl ether	1.105
Cholesterol	3.191
Cholesteryl acetate	3.881
Chrysene	1.971
4-Cyanophenol	1.111
Dihydrocholesterol	3.34
Hexachlorobenzene	1.151
N,N-diethylcarbanilide	1.254
N,N-Diphenyl-4-phenylenediamine	2.055
Nicotine	1.066
Perylene	3.195
Trimethoprin	2.19
Triphenylamine	1.254
Amyl cinnamal	1.156
Benzyl cinnamate	1.367
Benzyl salicylate	1.234
$\alpha$ -Isomethyl ionone	1.121
Lilial	1.132
Camphor	1.061
2-Methoxycinnamaldehyde	1.163
Vanillin	1.104
Dimethyl phthalate	1.105
Diethyl phthalate	1.155
Di-n-butyl phthalate	1.287
Di-capryl phthalate	1.75
Di-n-octyl phthalate	2.111
Dicyclohexyl phthalate	1.925
Di-isobutyl phthalate	1.239
Di-2-ethylhexyl phthalate	1.774
Butyl benzyl phthalate	1.648
Butyl cyclohexyl phthalate	1.92
Butyl decyl phthalate	2.64
Butyl octyl phthalate	2.115
Benzyl 2-ethylhexyl phthalate	2.46
Di-(2-methoxyethyl) phthalate	1.331
Di-(2-ethoxyethyl) phthalate	1.395
Di-(2-butoxyethyl) phthalate	1.731
Butyl oleate	1.4
Butyl stearate	1.432

Ethyl oleate	1.285
Methyl abietate	1.499
Diethyl adipate	1.066
Dibutyl succinate	1.097
Diethyl sebacate	1.175
Diethyl diethylmalonate	1.047
Methacryloxypropyltrimethoxysilane	1.057
Glycidoxypropyltrimethoxysilane	1.074
Isocyanatopropyltriethoxysilane	1.038
Acenaphthene	1.116
Acenaphthylene	1.115
Fluoranthene	1.449
Fluorine	1.139
Resosinol	1.052
Quinoline	1.055
Tri-n-butyryn	1.217
Valerophenone	1.067
Carbazole	1.283
Octanophenone	1.133
Phenanthrene	1.242
2-Methoxynaphthalene	1.066
Benzenesulfonamide	1.224
m-Dinitrobenzene	1.161
Coumarin	1.156
n-Octyltriethoxy silane	1.044

**Rxi-5Sil MS**

	RT	RT
	300 Ć	320 Ć
CH4	0.854	0.841
1,2,4,5-Tetrachlorobenzene	0.974	0.932
1,12-Dodecanediol	1.102	1.004
1-Acetonaphthone	1.068	1.036
2-Acetonaphthone	1.08	1.032
4-Acetylbiphenyl	1.214	1.096
1-Bromododecane	0.966	0.91
2(1-Naphthyl)ethanol	1.123	1.042
2,6-Dichloro-4-nitroaniline	1.148	1.051
2-Chlorophenol	0.899	

4-Nitrobenzyl alcohol	1.034	0.999
Androsterone	2.683	2.023
Anthracene	1.238	1.139
Cholestane	3.93	2.683
Diphenyl ether	0.996	0.949
Methyl nonanoate	0.919	0.902
N,N-Diethyldodecamide	1.225	1.101
N,N-Dimethyldodecylamine	1.008	0.944
Nicotinamide	0.983	0.948
Phenylcyclohexane	0.981	0.926
Progesterone	4.087	2.777
trans-Stilbene	1.132	1.044
Tribenzylamine	1.806	1.445
Triisopropanolamine	0.976	0.938
Triphenylmethane	1.396	1.194
Dibenzyl ether	1.073	0.997
Cholesterol	5.981	3.772
Cholesteryl acetate	7.202	4.316
Chrysene	2.482	1.882
4-Cyanophenol	0.964	0.941
Dihydrocholesterol	6.141	3.841
Hexachlorobenzene	1.179	1.078
N,N-diethylcarbanilide	1.25	1.129
N,N-Diphenyl-4-phenylenediamine	3.004	2.156
Nicotine	0.976	0.953
Perylene	4.596	3.108
Trimethoprin	2.668	1.938
Triphenylamine	1.408	1.214
Amyl cinnamal	1.059	1.01
Anise alcohol	0.95	0.921
Benzyl cinnamate	1.457	1.258
Benzyl salicylate	1.233	1.109
Cinnamal	0.943	0.937
Eugenol	0.975	0.929
Geraniol	0.926	0.909
Hydroxycitronellal	0.96	0.931
$\alpha$ -Isomethyl ionone	0.986	0.956
Lilial	1.021	0.958
Linalool	0.929	
Methyleugenol	0.969	0.918
Borneol	0.923	0.918

Camphor	0.942	0.892
Carvone	0.926	0.918
Citronellal	0.926	
2-Methoxycinnamaldehyde	1.02	0.961
Terpinen-4-ol	0.912	0.904
Vanillin	0.999	0.954
Dimethyl phthalate	0.99	0.945
Diethyl phthalate	1.015	0.979
Di-n-butyl phthalate	1.24	1.096
Di-capryl phthalate	2.143	1.639
Di-n-octyl phthalate	2.874	2.022
Dicyclohexyl phthalate	2.331	1.747
Di-isobutyl phthalate	1.182	1.075
Di-2-ethylhexyl phthalate	2.19	1.657
Butyl benzyl phthalate	1.828	1.473
Butyl cyclohexyl phthalate	1.62	1.34
Butyl decyl phthalate	1.2	1.108
Butyl octyl phthalate	1.74	1.42
Benzyl 2-ethylhexyl phthalate	2.1	1.9
Di-(2-methoxyethyl) phthalate	1.27	1.138
Di-(2-ethoxyethyl) phthalate	1.399	1.185
Di-(2-butoxyethyl) phthalate	2.009	1.542
Butyl oleate	1.713	1.401
Butyl stearate	1.77	1.39
Ethyl oleate	1.443	1.194
Methyl abietate	1.871	1.488
Diethyl adipate	0.955	0.903
Dibutyl succinate	0.993	0.94
Diethyl sebacate	1.095	1.009
Diethyl diethylmalonate	0.927	0.904
Methacryloxypropyltrimethoxysilane	0.968	0.936
Glycidoxypropyltrimethoxysilane	0.949	0.939
Isocyanatopropyltriethoxysilane	0.929	0.908
3-Aminopropyltriethoxysilane	0.915	
Acenaphthene	1.021	0.976
Acenaphthylene	1.014	0.967
Fluoranthene	1.597	1.343
Fluorine	1.08	1.018
Resosinol	0.942	0.933
Quinoline	0.948	0.929
Tri-n-butyryn	1.094	1.021

Valerophenone	0.955	0.927
Carbazole	1.274	1.156
Octanophenone	1.073	1.003
Phenanthrene	1.235	1.111
2-Methoxynaphthalene	0.958	0.952
Benzenesulfonamide	1.046	1.003
m-Dinitrobenzene	1.009	0.955
Coumarin	1.019	0.97
n-Octyltriethoxy silane	0.946	0.908

### SPB-Octyl

	RT
	260 °C
CH4	0.974
1,2,4,5-Tetrachlorobenzene	1.687
1,12-Dodecanediol	2.332
1-Acetonaphthone	2.221
2-Acetonaphthone	2.376
4-Acetylbiphenyl	3.365
1-Bromododecane	1.507
2(1-Naphthyl)ethanol	2.579
2,6-Dichloro-4-nitroaniline	2.799
2-Chlorophenol	1.172
4-Fluoroaniline	1.133
Androsterone	4.056
Anthracene	3.906
Diphenyl ether	1.688
Methyl nonanoate	1.252
N,N-Diethyldodecamide	3.476
N,N-Dimethyldodecylamine	1.724
Nicotinamide	1.46
Octan-2-ol	1.119
Phenylcyclohexane	1.96
Styrene	1.104
trans-Stilbene	2.866
Tribenzylamine	9.727
Triisopropanolamine	1.5
Triphenylmethane	5.02
Dibenzyl ether	2.415

Chrysene	18.575
4-Cyanophenol	1.398
Hexachlorobenzene	3.41
N,N.diethylcarbanilide	3.496
N,N-Diphenyl-4-phenylenediamine	23.48
Nicotine	1.59
Trimethoprin	14.974
Triphenylamine	5.279
Amyl cinnamal	2.228
Anise alcohol	1.372
Benzyl alcohol	
Benzyl cinnamate	5.632
Benzyl salicylate	3.65
Cinnamal	1.408
Eugenol	1.477
Farnesol (isomer 1)	2.208
Farnesol (isomer 2)	2.305
Geraniol	1.294
Hydroxycitronellal	1.445
$\alpha$ -Isomethyl ionone	1.748
Lilial	1.876
Limonene	1.195
Linalool	1.177
Methyleugenol	1.503
Borneol	1.342
Camphor	1.304
Carvone	1.38
Citronellal	1.285
2-Methoxycinnamaldehyde	1.83
$\alpha$ -Pinene	1.134
$\beta$ -Pinene	1.172
Terpinen-4-ol	1.327
Vanillin	1.547
Dimethyl phthalate	1.564
Diethyl phthalate	1.843
Di-n-butyl phthalate	3.487
Di-capryl phthalate	13.36
Di-n-octyl phthalate	22.473
Dicyclohexyl phthalate	14.21
Di-isobutyl phthalate	2.897
Di-2-ethylhexyl phthalate	12.1



Butyl benzyl phthalate	8.849
Butyl cyclohexyl phthalate	6.76
Butyl decyl phthalate	3.48
Butyl octyl phthalate	3.47
Benzyl 2-ethylhexyl phthalate	2.079
Di-(2-methoxyethyl) phthalate	3.455
Di-(2-ethoxyethyl) phthalate	4.385
Di-(2-butoxyethyl) phthalate	10.517
Butyl oleate	9.3
Butyl stearate	10.01
Ethyl oleate	5.692
Methyl abietate	10.84
Diethyl adipate	1.352
Dibutyl succinate	1.663
Diethyl sebacate	2.289
Diethyl diethylmalonate	1.275
Methacryloxypropyltrimethoxysilane	1.368
Glycidoxypropyltrimethoxysilane	1.423
Isocyanatopropyltriethoxysilane	1.301
3-Aminopropyltriethoxysilane	1.221
Acenaphthene	2.125
Acenaphthylene	2.018
Fluoranthene	7.234
Fluorine	2.49
Resosinol	1.263
Quinoline	1.462
Tri-n-butyryn	2.363
Valerophenone	1.516
Carbazole	3.657
Octanophenone	2.312
Phenanthrene	3.8
2-Methoxynaphthalene	1.589
Benzenesulfonamide	1.743
m-Dinitrobenzene	1.671
Coumarin	1.753
n-Octyltriethoxy silane	1.474

**Stx-500**

	RT	RT
	260 Ć	280 Ć
CH4	0.869	0.859
1,2,4,5-Tetrachlorobenzene	0.955	0.917
1,12-Dodecanediol	1.114	1.01
1-Acetonaphthone	1.075	1.011
2-Acetonaphthone	1.128	1.037
4-Acetylbiphenyl	1.282	1.135
1-Bromododecane	0.938	
2(1-Naphthyl)ethanol	1.138	1.045
2,6-Dichloro-4-nitroaniline	1.228	1.097
4-Nitrobenzyl alcohol	1.043	0.986
Androsterone	4.359	2.816
Anthracene	1.298	1.154
Cholestane	6.343	3.767
Diphenyl ether	0.954	0.939
N,N-Diethyldodecamide	1.308	1.13
N,N-Dimethyldodecylamine	0.951	0.91
Nicotinamide	0.987	0.933
Phenylcyclohexane	0.961	0.923
Progesterone	9.71	5.483
trans-Stilbene	1.145	1.051
Tribenzylamine	2.086	1.565
Triisopropanolamine	0.967	0.945
Triphenylmethane	1.41	1.195
Dibenzyl ether	1.078	1.012
Cholesterol	11.928	6.486
Cholesteryl acetate	15.478	7.924
Chrysene	3.554	2.44
4-Cyanophenol	0.965	0.938
Dihydrocholesterol	12.33	6.665
Hexachlorobenzene	1.173	1.075
N,N-diethylcarbanilide	1.297	1.142
N,N-Diphenyl-4-phenylenediamine	4.482	2.843
Nicotine	0.97	0.92
Perylene	8.974	5.195
Trimethoprin	3.742	2.413
Triphenylamine	1.453	1.22
Amyl cinnamal	1.086	0.993

Benzyl cinnamate	1.59	1.318
Benzyl salicylate	1.277	1.131
$\alpha$ -Isomethyl ionone	1	0.941
Lilial	1.06	0.968
Carvone		0.913
2-Methoxycinnamaldehyde	1.05	0.965
Vanillin	0.975	
Dimethyl phthalate	0.97	0.942
Diethyl phthalate	1.04	0.959
Di-n-butyl phthalate	1.326	1.14
Di-capryl phthalate	2.905	1.96
Di-n-octyl phthalate	4.489	2.685
Dicyclohexyl phthalate	3.231	2.185
Di-isobutyl phthalate	1.19	1.076
Di-2-ethylhexyl phthalate	2.928	1.966
Butyl benzyl phthalate	2.291	1.652
Butyl cyclohexyl phthalate	1.92	1.457
Butyl decyl phthalate	2.54	1.13
Butyl octyl phthalate	1.32	1.13
Benzyl 2-ethylhexyl phthalate	2.93	1.96
Di-(2-methoxyethyl) phthalate	1.37	1.165
Di-(2-ethoxyethyl) phthalate	1.527	1.256
Di-(2-butoxyethyl) phthalate	2.61	1.792
Butyl oleate	1.98	1.47
Butyl stearate	2.087	1.5
Ethyl oleate	1.5	1.244
Methyl abietate	2.259	1.652
Diethyl adipate	0.935	0.907
Dibutyl succinate	0.977	0.952
Diethyl sebacate	1.08	1.017
Methacryloxypropyltrimethoxysilane	0.928	
Glycidoxypropyltrimethoxysilane	0.943	
Isocyanatopropyltriethoxysilane	0.933	0.95
Acenaphthene	1.04	0.982
Acenaphthylene	1.03	0.959
Fluoranthene	1.829	1.477
Fluorine	1.096	1.022
Resosinol	0.928	0.904
Quinoline	0.933	0.908
Tri-n-butylin	1.111	1.029
Valerophenone	0.948	0.929

Carbazole	1.334	1.171
Octanophenone	1.071	1.008
Phenanthrene	1.291	1.135
2-Methoxynaphthalene	0.951	0.915
m-Dinitrobenzene	1.017	0.978
Coumarin	1.037	0.98
n-Octyltriethoxy silane	0.949	

**ABSTRACT****DETERMINATION OF DESCRIPTORS BY LIQUID-LIQUID PARTITION AND CHROMATOGRAPHIC METHODS**

by

**THUSHARA KARUNASEKARA**

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**Advisor:** Prof. Colin F. Poole**Major:** Chemistry (Analytical)**Degree:** Doctor of Philosophy

Partition coefficients for varied compounds were determined for several totally organic biphasic systems using formamide, propylene carbonate, ethylene glycol or dimethyl sulfoxide as the base solvent and n-heptane, 1,2-dichloroethane, 1-octanol or isopentyl ether as the counter solvent. These partition coefficient databases are analyzed using the solvation parameter model facilitating a quantitative comparison of these systems with other totally organic and water-based partition systems. These totally organic biphasic solvent systems offer a complementary approach to water-based partition systems for sample preparation and the determination of descriptors for compounds virtually insoluble in water or unstable in water.

A new method of solvent classification is proposed based on the five system constants of the solvation parameter model for transfer of neutral compounds from the gas phase to solvent and hierarchical cluster analysis for identifying solvents with similar properties and for organizing them into selectivity groups. This method resulted in the classification of 36 common solvents used in chromatography into seven selectivity groups with four solvents (2,2,2-trifluoroethanol, *N,N*-dimethylformamide, dimethyl sulfoxide and water) behaving independently. The classification scheme provides a logical approach for solvent selection as the first step in

chromatographic method development. A similar approach for the transfer of neutral compounds between condensed phases and hierarchical cluster analysis was used to classify 19 aqueous and 17 totally organic biphasic partition systems for liquid-liquid extraction. The totally organic biphasic partition systems exhibit an almost continuous range of properties with minimal group formation demonstrating a wider and complementary range of selectivity to the aqueous biphasic systems. The classification of the liquid-liquid partition systems provides a suitable method of identifying suitable systems for sample preparation based on liquid-liquid extraction and for the simulation of extractions for target compound isolation.

Retention factors on a minimum of eight stationary phases at various temperatures by gas-liquid chromatography and liquid-liquid partition coefficients for eight totally organic biphasic systems were combined to estimate descriptors for 28 fragrance compounds with an emphasis on compounds that are known or potential allergens. Similar approach with additional liquid chromatographic measurements was used to estimate descriptors for 24 esters widely used as plasticizers and solvents in industry. The descriptors facilitated the estimation of several properties of biological and environmental interest (sensory irritation threshold, odor detection threshold, nasal pungency threshold, skin permeability from water, skin-water partition coefficients, octanol-water partition coefficients, absorption by air particles, adsorption by diesel soot particles, air-water partition coefficients, and adsorption by film water).

A combination of gas chromatography and liquid-liquid partition in totally organic biphasic systems is used to determine descriptor values for compounds of low volatility suitable for characterizing open tubular columns at high temperatures. The descriptor database of varied compounds includes several difficult to determine by conventional techniques due to their low water solubility or stability. The descriptor database facilitates an expansion of the descriptor space and compound variation for characterizing separation systems. As an application the

descriptor database is used to determine the system constants for SPB-Octyl, HP-5, Rxi-5Sil MS, Rtx-440, and Rtx-OPP for the temperature range 200-300°C. As an example of the broader affect of temperature on column selectivity the variation of the system constants for Rtx-440 over the temperature range 60-300°C is described in detail. These studies demonstrate the persistence of polar interactions to the highest temperature studied and that at high temperatures selectivity differences persist for moderately polar stationary phases.

## AUTOBIOGRAPHICAL STATEMENT

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### Selected Publications

- **T. Karunasekara**, C.F. Poole. “Compounds for expanding the descriptor space for characterizing separation systems”, J. Chromatography A, **2012** (submitted).
- **T. Karunasekara**, S.N. Atapattu, C.F. Poole. “Determination of Descriptors for Plasticizers by Chromatography and Liquid-Liquid Partition”. Chromatographia, **2012** (in press).
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