

Comparison of an Empirical and a Theoretical Linear Solvation Energy Relationship Applied to the Characterization of Solute Distribution in a Poly(ethylene) Glycol-Salt Aqueous Biphasic System

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A Linear Solvation Energy Relationship (LSER) developed by Abraham has been applied to the partition of organic solutes in an Aqueous Biphasic System (ABS) and to published values of their 1-octanol/water partition coefficients. The results are compared to the application of a conceptually similar Theoretical Linear Solvation Energy Relationship (TLSER) developed by Famini and co-workers. Differences and similarities in the molecular properties highlighted by each LSER are discussed. The theoretical relationship of Famini, although modeled on the approach of Abraham, seems not to encapsulate molecular properties in the same way as the Abraham's empirical relationship. However, this theoretical approach has the great merit of computational simplicity, and it is concluded that efforts directed toward its improvement could be rewarding.

INTRODUCTION

Aqueous biphasic systems (ABS) represent critical phenomena¹ occurring in aqueous solution when two or more polymers, or a polymer and salt, are mixed above critical concentrations or temperatures.² As a result, two immiscible liquid phases form without the involvement of any organic solvent but which may still be used for the differential partition and extraction of a wide variety of solutes. The range of solutes for which the technique is applicable is enormous. Solutes as varied in molecular size as inorganic ions, small organic molecules, biological macromolecules, colloidal inorganic particles, viruses, and even cells^{2–6} may all be successfully partitioned between the phases with the correct choice of ABS.

As is the case with conventional aqueous/organic biphasic systems, the phases differ in their solvent–solute interactions. These differences give to partition, the differential distribution of solutes between immiscible liquid phases, the power to separate substances of differing chemical nature. This has led to their widespread exploitation both in the laboratory and in large-scale liquid–liquid extraction processes and also in the characterization of solute properties, for example, in the measurement of log P, the 1-octanol/water partition coefficient.

There is considerable interest in being able to predict solute distribution between immiscible liquid phases. Many different approaches have been taken, including, to mention just a few, the correlative approach of Collander,⁷ group contribution approaches such as that of Leo and Hansch,⁸ and similar approaches based on phase equilibria due to Praus-

nitz.⁹ Such methods are generally grouped together as empirical approaches to understanding solvation that nevertheless continue to provide insight into the nature of solute–solvent interactions at the molecular scale. We recently published an approach to characterizing ABS partition¹⁰ based on the generalized solvation equation of Abraham.^{11,12} Using this approach we were able to compare the partitioning properties of ABS,¹⁰ some Room-Temperature Ionic Liquids,¹³ and a number of more conventional solvent/water partitioning systems.¹⁴

There has also been widespread interest in predicting molecular properties, including solvation, from theory.¹⁵ Again many different approaches have been taken, including *ab initio*, quantum mechanical methods, semiempirical methods, and chemometric methods. Such approaches have obvious attractions. Experimentation, which is costly and subject to random and human error, may be minimized. Recently the very real difficulties associated with the use of experimental determinations of log P for environmental modeling have come to the fore.¹⁶ Considerable uncertainty often attaches to published values for a variety of reasons but perhaps largely through lack of standardization of the methods employed.¹⁷ In addition, to these considerations, toxic and otherwise dangerous materials may be tackled easily, and there is no need to possess any of the substances under study and so costly and possibly redundant syntheses may be avoided.

One theoretical approach that attracted us, because of its resemblance to the LSER (Linear Solvation Energy Relationship) of Abraham, was the Theoretical Linear Solvation Energy Relationship (TLSER) of Famini and co-workers.^{18–22} A further advantage of this, and other similar methods, is the increasing availability of software for personal computers employing fast and accurate implementations of semiem-

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empirical molecular orbital theory for example MOPAC 2000 and Titan as used here.^{23,24} Both the LSER and TLSER assume that solute/solvent interactions are based on various additive properties of molecules that may be isolated as formal descriptors of the solvation process,¹⁹ e.g., as in eq 1.

$$\text{some property} = \text{cavity term(s)} + \text{polarity term(s)} + \text{hydrogen bonding terms} + \text{constant} \quad (1)$$

Many empirical descriptions of solvation are based on this formalism, for example, Kamlet and Taft's original solvatochromic LSER²⁵ and Hansen's solubility parameters.²⁶ Abraham's LSER, which is based on the empirical determination of Gibbs energy based descriptors by multiple regression of chromatographic data obtained from a variety of processes, is shown in eq 2.

$$\text{Log SP} = c + \nu V_x + rR_2 + b\Sigma\beta_2^H + s\pi_2^H \quad (2)$$

Here the log of some property, which may be as varied as the extent of solute penetration of membranes²⁷ or the distribution of solutes between immiscible liquid phases,²⁸ is related to the relative influence of the empirically determined solute descriptors.

The first solute descriptor is V_x , the solute volume, whose relative effect on the property SP, is given by the magnitude of the coefficient ν . The coefficient ν is thus analogous to the cavity term of eq 1 and related to the Hildebrand solubility parameter and the cohesive energy density²⁹ of the medium. However, in partition, as opposed to simple solubility, this is a relative measure of the difference in magnitude of this property between the two phases. For instance, for the distribution of a solute between an organic and an aqueous phase, the free energy of cavity formation in the aqueous phase will generally dominate because of the relatively cohesive hydrogen bonding interactions compared to energetically weaker dispersive interactions of the organic phase. In this case, for a solute that does not interact with water, ν will be positive and of a magnitude reflecting this difference in the free energy of cavity formation in the two phases. (Log P will conventionally take a positive sign for solvent phase preference and a negative sign for aqueous phase preference.)

The solute descriptor R_2 is the excess molar refraction i.e., the molar refraction of the solute minus that of an alkane of the same molecular volume.³⁰ This may be calculated from the refractive index and density of solutes liquid at 20 °C but may also be obtained from the summation of substructure fragments.³¹ It represents the strength of solute-solvent interactions involving nonbonding and π -bonding electrons of the solute. The sign and magnitude of the coefficient r reflects the relative strengths of these interactions in the two immiscible phases. Similarly, $\Sigma\beta_2^H$ represents the hydrogen bond acceptor strength of the solute, Σ indicating the fact that this term is the sum of the hydrogen bond basicity of the solute contributed by different hydrogen bonding groups. Since a hydrogen bond acceptor is expected to interact with a hydrogen bond donor the coefficient b represents the relative hydrogen bond donor strength of the two phases. A negative b coefficient of significant magnitude generally means that the hydrogen bond donor strength (Lewis acidity)

of the organic phase is small in comparison to water, a common situation. Similar arguments apply to $\Sigma\alpha_2^H$, the hydrogen bond donor acidity of the solute, and to the coefficient a , representing the relative acceptor strength of the phases.

The solute descriptor π_2^H , represents the polarity or polarizability of the solute and its coefficient, s , the relative intensity of these interactions in the two phases. Original works of Abraham should be consulted in order to understand how these descriptors are determined.²⁸

The TLSER of Famini and co-workers was expressly modeled on the success of the empirical LSER of Abraham.¹⁸⁻²² In eq 3 the property in question is defined as the partition coefficient Log P.

$$\text{Log P} = aV_{mv} + b\pi_1 + c\epsilon_B + dq_- + e\epsilon_A + fq_+ + \text{log } P_0 \quad (3)$$

The volume term, V_{mv} , is again molecular volume, but where Abraham employs the McGowan volume,³² Famini employs Hopfinger's molecular volume.³³ The coefficients a , b , c , d , e , and f , have the same relationship to the following property descriptors as corresponding coefficients in Abraham's LSER. The descriptors are derived from semiempirical molecular orbital theory, specifically MNDO. The descriptor π is derived from the molecular polarizable volume divided by the molecular volume. It is said to be a unitless, size independent quantity representing the ease with which the electron cloud may be moved or polarized. The molecular polarizable volume is found using the method of Kurtz and Korambath implemented in MOPAC 2000.²³

Hydrogen bonding terms as proposed in eq 1 have been subdivided in eq 3, not only into hydrogen bond acidity and hydrogen bond basicity, as in eq 2, but also further, into electrostatic and covalent aspects. Thus, ϵ_β represents the covalent basicity of the solute calculated from the HOMO (Highest Occupied Molecular Orbital) of the solute compared to the LUMO (Lowest Unoccupied Molecular Orbital) of water. This value is subtracted from a constant (0.3) so that the parameter is scaled and is intended to indicate that the greater the value, the greater the tendency to interact with water. The covalent acidity parameter, ϵ_a , is defined similarly, but the LUMO of the solute is compared to the HOMO of water.

Care has to be exercised when consulting earlier work of Famini, since values of covalent acidity and basicity have been redefined. Formerly a large magnitude of, e.g., basicity, implied that solute basicity was lower than would be required for interaction with water, but this has since been redefined by subtraction from a constant value of 0.3. The descriptor q represents the highest atomic charge on an atom of the solute. This is based on Mulliken charges and in the case of q_- , the highest formal negative charge of any atom in the molecule is used. In the case of q_+ , the highest positive charge on a proton is taken. These terms represent the molecular electrostatic basicity and electrostatic acidity.

In this paper we compare the application of Abraham's LSER and Famini's TLSER to the description of the partition of some small organic molecules in an ABS composed of a mixture of $(\text{NH}_4)_2\text{SO}_4$ and poly(ethylene glycol), MW = 2000 (PEG-2000). Differences and similarities in the molecular properties highlighted by each LSER are discussed.

METHODS

Partition coefficients of a series of small organic molecules were obtained by the distribution of picomolar quantities of radiochemical tracers in a PEG/salt ABS composed of 12.94% w/w ammonium sulfate and 19.29% w/w PEG-2000 having a tie line length of 44.92% w/w. Full details of the determination of radiochemical partition coefficients in ABS may be found in previous papers.^{10,34} Partition coefficients of dissociable solutes were determined under conditions assumed to guarantee neutrality.¹⁰ Abraham solute descriptors for the regression of the Abraham LSER were taken from published work of Abraham.^{28,31,35,36} Descriptors for the regression of Famini's TLSEr were obtained from semiempirical calculation (MNDO) using MOPAC 2000²³ following methods outlined by Famini.^{18–22} Accuracy in the estimation of these parameters was verified by comparison to published tables of descriptors.^{18–22} Molecular structure refinement was performed using Titan²⁴ and passed to MOPAC for further refinement and calculation of the Self-Consistent Field. Customized computer code was written in Pascal using Delphi 3³⁷ to parse the data from MOPAC output into a more convenient spreadsheet format. CPK volume was computed using Titan and McGowan volume³¹ by a compiled BASIC program supplied by Abraham.³⁶ Multiple linear regression of the various solute descriptors against measured or literature values of the partition coefficient to generate the LSERs and TLSErS was performed using StatBox-V2.³⁸

RESULTS

The development of an accurate and chemically reasonable description of any process based on solvation depends on examining the behavior of a wide range of solutes having different chemical properties. Since not all solutes can be examined in a finite time, selection has to be made. Recourse is usually associated with the development of a "well balanced" solute set of sufficient size and breadth of properties so that, for instance, an LSER would not change significantly with the inclusion of more solutes. In that sense, this study has been hampered by our election to determine partition coefficients radiochemically. The radiochemical technique has the advantage that ideal solution behavior, and thus concentration independent partition coefficients, can be assumed because of the extremely low concentrations employed. Unfortunately, the selection of solutes is determined by the availability of isotopes. Nevertheless, we have examined the partitioning of a wide range of organic solutes of varied functionality and believe the resulting free energy relationships give a convincing account of solute distribution in ABS.¹⁰ On the other hand, by using different methods and larger numbers of carefully selected solutes, improvements are certainly possible.

Table 1 shows the solutes selected for determination of theoretical descriptors for which published values of TLSEr descriptors were available.^{18–22} This small solute set allowed validation of the computational methods and a preliminary characterization of the various descriptors.

Solute Volume. The TLSEr of Famini uses the geometrical method of Hopfinger³³ to calculate van der Waals volumes (V_{mv}). This method was not available to us, and so the CPK volume and the McGowan volume³² were used. There was close, but not exact, correspondence between V_{mv}

Table 1. SoluteS Used in the Validation of TLSEr Descriptor Calculations

solute	Log P ^a	solute	Log P
1-propanol	0.25	phenol	1.46
acetic acid	−0.17	toluene	2.73
acetonitrile	−0.34	cyclohexane	3.44
acetophenone	1.58	decane	5.01
aniline	0.90	dichloromethane	1.25
benzene	2.13	dioxane	−0.27
1-butanol	0.88	ethane	1.81
chlorobenzene	2.84	ethene	1.13
1,2-dichloroethane	1.48	hexane	3.9
ethanol	−0.31	<i>N</i> -methylimidazole	−0.06
2-propanol	0.05	<i>N,N</i> -dimethylformamide	−1.01
methanol	−0.77	octane	5.18
1-octanol	3.00	pentane	3.39
1-pentanol	1.51	propylbenzene	3.69

^a Log *P* values obtained by database retrieval (*not* by estimation) using log K_{ow} .³⁹

and CPK volume as shown by eq 4, which also shows the regression coefficient (r^2) and the standard error of the estimate ($s(y)$). The scales differ since the V_{mv} parameter is scaled in 100 Å³ units.

$$V_{CPK} = 12.49 + 115.46V_{mv} \quad (4)$$

$$[r^2 = 0.995; s(y) = 3.03]$$

Comparison of the McGowan volume³² as used by Abraham and the V_{mv} parameter used by Famini, shown in eq 5, again gave a good, but not perfect, correspondence between the two scales.

$$V_{McG} = 0.055 + 0.796V_{mv} \quad (5)$$

$$[r^2 = 0.996; s(y) = 0.019]$$

It is interesting to note that the McGowan volume is somewhat smaller than Hopfinger's molecular volume. Later, in the application of the MNDO-based TLSEr, the use of different volume parameters affects the calculation of the polarizability descriptor since it is used in its calculation. The V_{mv} parameter may give a better geometrical account of the overlap of atomic van der Waals volumes compared to a simple summation of individual atomic volumes.³³

Solute Acidity and Basicity. Calculations of Electrostatic Basicity using MOPAC 2000 and published MNDO TLSEr descriptors^{18–22} calculated using MOPAC 6.0 showed excellent correspondence, as indicated in eq 6, albeit with some minor individual differences.

$$q_{+(MOPAC\ 2000)} = 0.0007 + 1.001q_{+(Famini)} \quad (6)$$

$$[r^2 = 0.9989; s(y) = 0.005]$$

Differences could have been due to different levels of accuracy being adopted for the convergence of the SCF or slight differences in final geometry. The differences were not judged to be of major concern.

MOPAC 2000 calculated values of Electrostatic Acidity, and those taken from the literature showed almost complete correspondence (eq 7) but with similar minor deviations as for the calculation of electrostatic basicity and likely for similar reasons.

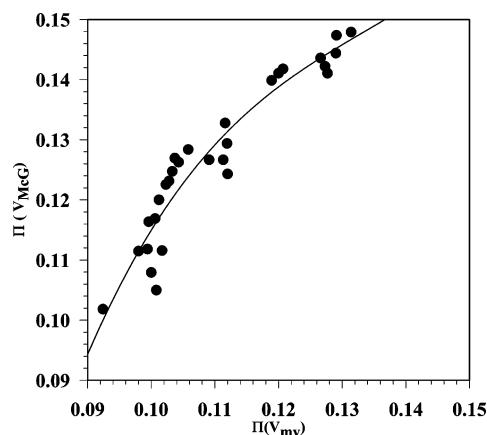


Figure 1. Polarity calculated using McGowan volume compared to polarity calculated using Hopfinger's molecular volume.

$$q_{-(\text{MOPAC 2000})} = 0.00002 + 0.9956q_{-(\text{Famini})} \quad (7)$$

$$[r^2 = 0.9999; s(y) = 0.001]$$

Estimates of covalent basicity using HOMO and LUMO values from Titan compared to Famini's published values were also satisfactory with the significant exception of dichloroethane which was omitted from the regression (eq 8) and from further consideration.

$$\epsilon_{\text{B(Titan)}} = 0.0003 + 0.9987\epsilon_{\text{B(Famini)}} \quad (8)$$

$$[r^2 = 0.9965; s(y) = 0.001]$$

Results for the calculation of covalent acidity were similar, and again dichloroethane was an outlier and not included in the regression shown as eq 9.

$$\epsilon_{\text{A(Titan)}} = 0.0019 + 0.9888\epsilon_{\text{A(Famini)}} \quad (9)$$

$$[r^2 = 0.9994; s(y) = 0.001]$$

Molecular Polarizability. Figure 1 shows the effect of calculating solute polarizability using the McGowan volume in comparison to the use of Hopfinger's molecular volume. The effect is dramatic, and it is apparent that the molecular volume and McGowan volumes do not increase at the same rate and this has a profound effect on the estimation of molecular polarizability. If the V_{mv} method is used, Figure 1 becomes a straight line with slope one (data not shown). The McGowan method is a simple summation based on atom type, whereas Hopfinger's method may take more account of the overlap of van der Waals radii.

The method used to estimate molecular volume may be more important than is customarily assumed. It is an important feature of LSERs, often accounting for more than 50% of the variance of the regression. In turn, this reflects the importance of cavity formation and the importance of the cohesive energy density of liquids in determining solvation. In view of this, accurate estimation would seem important. The method of Hopfinger is widely used in QSAR, where geometrical requirements may be crucial, e.g., in molecular recognition. The issue may be worthy of further careful investigation.

Relationship of TLSEr Descriptors to Abraham Descriptors. The formalism of Abraham's generalized solvation

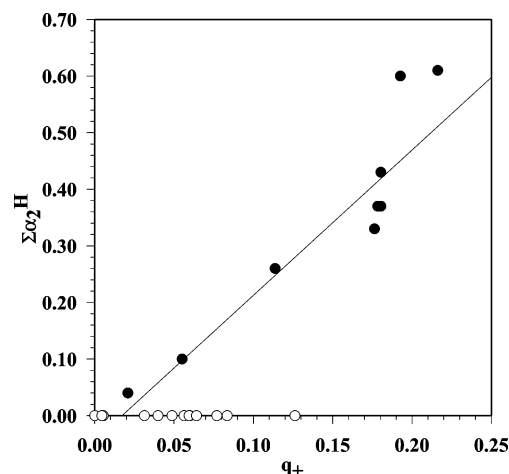


Figure 2. Relationship between Abraham's hydrogen bond acidity ($\Sigma\alpha_2^H$) and Famini's electrostatic acidity (q_+). Closed symbols were included in the regression, open symbols were not.

equation is seductive because the limited numbers of terms have easily understood chemical meanings and the descriptions reflect the known physical chemistry. As with all LSER there is concern regarding the independence of the descriptors. However, in this context it is of interest to compare the relationship of the TLSEr descriptors to the LSER descriptors upon which they are explicitly modeled. Only relatively limited comparisons between TLSEr and LSER seem to have been published previously.⁴⁰ MNDO-derived TLSEr descriptors have been used to apparently good effect to describe a number of physicochemical processes and seem to have highlighted differences which would have been inaccessible via the generalized solvation equation.^{18–22}

It is not clear how chemically meaningful these studies are. The relationship between the volume terms of the two LSERs has already been examined above. Relationships between the other descriptors are presented below.

Figure 2 shows the relationship between the electrostatic acidity descriptors of Famini (as calculated by us) and published values of the hydrogen bond α parameter of Abraham for the solutes in Table 1. There is clearly a sense in which q_+ (electrostatic acidity) encapsulates $\Sigma\alpha_2^H$. However, many solutes having zero values of $\Sigma\alpha_2^H$ are assigned finite and significant acidity, as q_+ , in the TLSEr (distinguished by open symbols in Figure 2). In other words, the semiempirical computational approach assigns significant positive charge to molecular species which manifest zero acidity in the empirical approach of Abraham. Even worse from a predictive point of view, finite values of Abraham's $\Sigma\alpha_2^H$ fall within this range, precluding a simple threshold method of exclusion.

Figure 3 shows the relationship between covalent acidity (ϵ_A) and Abraham's $\Sigma\alpha_2^H$. It is hard to discern any relationship. Covalent acidity seems not to be encapsulated in Abraham's term. It seems surprising that aspects of the HOMO/LUMO-based acidity/basicity terms have seemed useful in correlating, for instance, the solvatochromic responses of polarity indicating chromophores and modeling dissociation equilibria.^{18–22}

Multiple regression of electrostatic acidity and covalent acidity on Abraham's $\Sigma\alpha_2^H$ was performed to examine whether Abraham's $\Sigma\alpha_2^H$ is a composite of both electrostatic

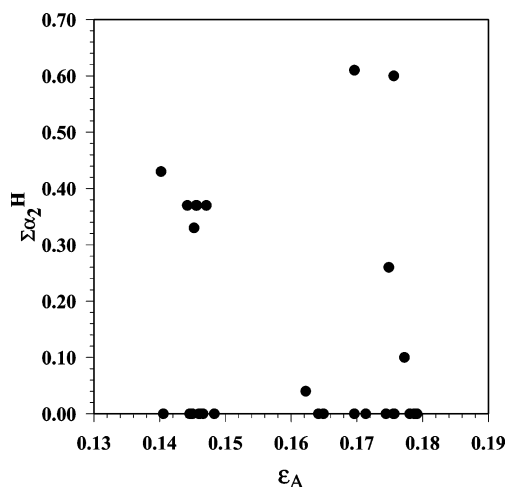


Figure 3. Relationship between Abraham's hydrogen bond acidity ($\Sigma\alpha_2^H$) and the covalent acidity (ϵ_A) of Famini.

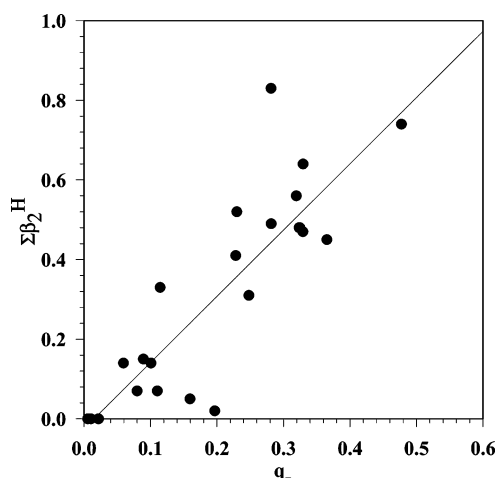


Figure 4. Relationship between Abraham's hydrogen bond basicity ($\Sigma\beta_2^H$) and Famini's electrostatic basicity (q_-).

and covalent acidity. The relationship found is represented in eq 10:

$$\Sigma\alpha_2^H = 2.594q_+ - 0.549\epsilon_a \quad (10)$$

$$[R^2 = 0.83; s(y) = 0.087; \text{VIF } q_+ = 1.002; \epsilon_a = 1.002]$$

Eq 10 clearly indicates that only electrostatic acidity is significantly related to Abrahams' $\Sigma\alpha_2^H$, and there is little relationship to ϵ_A . The influence of electrostatic acidity is greater than covalent acidity in absolute terms, and the influence of covalent acidity is negative in eq 10.

The relationship between solute electrostatic basicity (q_-) and Abraham's hydrogen bond basicity ($\Sigma\beta_2^H$) was found to be similar to that between q_+ and Abraham's $\Sigma\alpha_2^H$. Thus, Figure 4 shows that there is a relationship between the electrostatic basicity of Famini (q_-) and the parameter $\Sigma\beta_2^H$ of Abraham. The relationship is not close, but there is less tendency for theoretical electrostatic basicity to assign basicity where empirical methods find none.

As with covalent acidity, Figure 5 shows that any relationship between the covalent basicity of Famini (ϵ_B) and the β parameter of Abraham ($\Sigma\beta_2^H$) is quite nebulous. There is no relationship. Multiple regression of the data for the solutes in Table 1 also showed that covalent basicity was not a

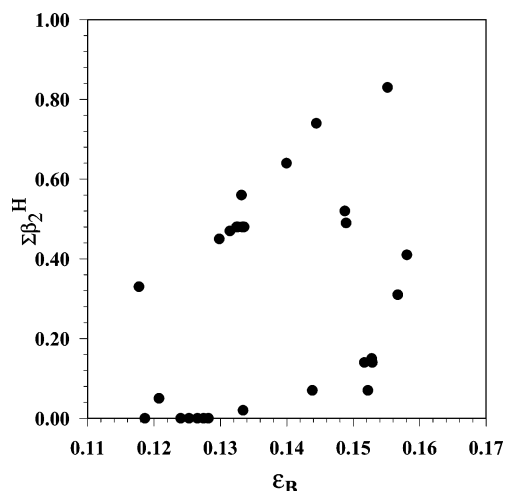


Figure 5. Relationship between Abraham's hydrogen bond basicity ($\Sigma\beta_2^H$) and the covalent basicity (ϵ_B) of Famini.

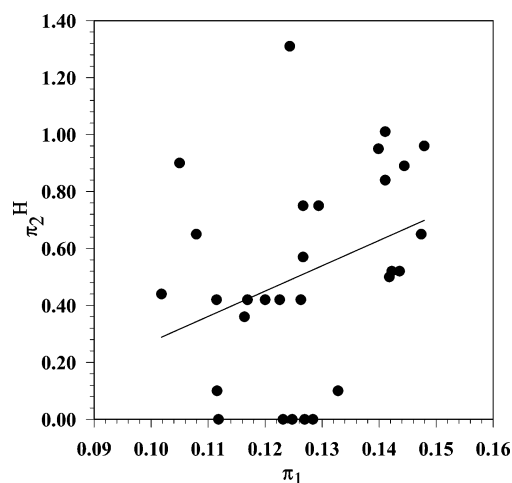


Figure 6. Relationship between Abraham's polarity term (π_2^H) and Famini's theoretical polarity (π_1).

significant component of Abraham's $\Sigma\beta_2^H$ parameter. The influence of covalent basicity on β is opposite in sign to that of electrostatic basicity and contributes less by an order of magnitude as shown in eq 11:

$$\Sigma\beta_2^H = 1.63q_- - 0.114\epsilon_b \quad (11)$$

$$[R^2 = 0.79; s(y) = 0.121; \text{VIF } q_- = 1.05; \epsilon_b = 1.05]$$

The theoretical polarity parameter (π_1) is examined in Figure 6 in relation to Abraham's π_2^H . However, any relationship between these parameters is not close and is subject to great scatter.

By contrast Figure 7 shows that there is a closer relationship between the theoretical polarity parameter, π_1 , and Abraham's molar refractivity (R_2^H) than there is with Abraham's π_2^H (Figure 6). However, this is not particularly useful since Abraham's molar refractivity may already be calculated, rather than empirically estimated. It is also interesting to note that there is a relationship between π_2^H and the molecular dipole moment (μ) as calculated by MNDO methods using MOPAC 2000 and as shown in Figure 8. Molecular dipole moment is not featured in either Famini's TLSER or Abraham's empirical LSER.

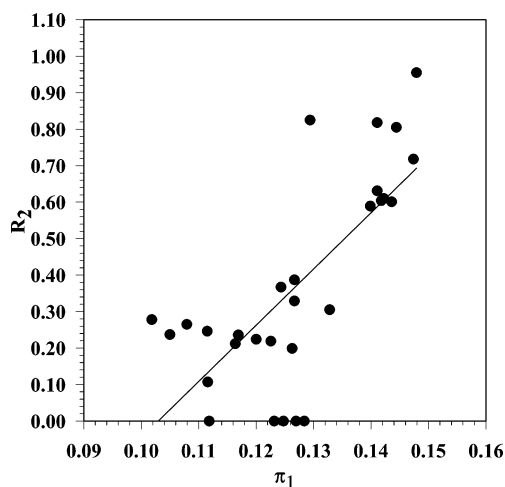


Figure 7. Relationship between Abraham's excess molar refraction (R_2) and Famini's theoretical polarity π_1 .

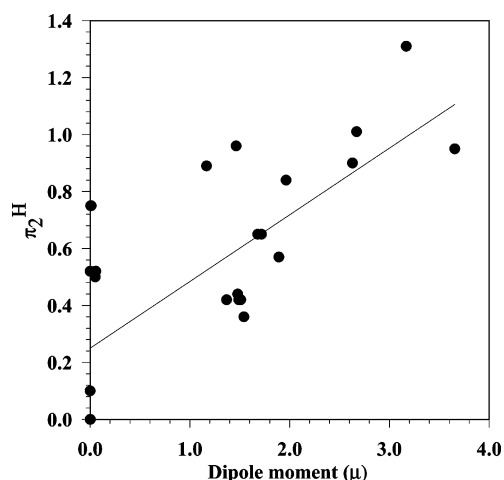


Figure 8. Relationship between Abraham's polarity parameter (π_2^H) and the calculated molecular dipole moment (μ).

The Description of Partition by TLSEr and Empirical LSER. For the prediction of partition in the 1-octanol/water system Abraham's published generalized solvation equation for a large selected solute set is given in eq 12:²⁸

$$\text{Log } P = 0.088 + 0.56R_2 - 1.054\pi_2^H + 0.032\Sigma\alpha_2^H - 3.460\Sigma\beta_2^H + 3.814V_x \quad (12)$$

$$[r^2 = 0.995; s(y) = 0.116]$$

Using published Abraham solute descriptors and 1-octanol/water partition coefficients for the solutes shown in Table 1, the regression obtained is shown as in eq 13:

$$\text{Log } P = 0.32 + 0.49R_2 - 1.52\pi_2^H - 0.51\Sigma\alpha_2^H - 2.48\Sigma\beta_2^H + 3.50V_x \quad (13)$$

$$[r^2 = 0.95; s(y) = 0.433; F = 81.75]$$

The probabilities associated with eq 13 and given in Table 2 show that only variables relating to volume and solute basicity, and perhaps polarity, make a significant contribution to the regression. Descriptors making little contribution to the regression, the excess molar refraction, and the solute acidity show little significance at the 95% confidence level.

Table 2. Significance of the Solvent Coefficients of Abraham's Generalized Solvation Equation in Fitting Eq 13^a

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$s(\pi_2^H)$	-1.52	-0.6129	2.7994	22	0.0105	5.44
$a(\Sigma\alpha_2^H)$	-0.51	-0.4105	1.0634	22	0.2991	1.40
$b(\Sigma\beta_2^H)$	-2.48	-0.7447	4.4153	22	0.0002	3.05
$v(V_x)$	3.50	0.7783	11.5041	22	8.9E-11	1.18
$r(R_2)$	0.49	-0.1862	0.9407	22	0.3571	3.17
constant =	0.32					

^a Distribution of solutes in Table 1 in 1-octanol/water from published data.

Table 3. Significance of Solvent Coefficients of Famini's TLSEr to Fitting Eq 14^a

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$d(q_-)$	-8.70	-0.7575	9.7324	24	8.33E-10	2.36
$f(q_+)$	3.60	-0.5172	2.1628	24	0.0407	2.30
$v(V_{mv})$	2.94	0.7890	12.9859	24	2.4E-12	1.08
constant =	0.39					

^a Distribution of solutes in Table 1 in 1-octanol/water from published data.

Table 4. Significance of Solvent Coefficients of Famini's TLSEr to Fitting Eq 15^a

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$d(q_-)$	-8.99	-0.7575	9.4249	24	1.54E-09	2.34
$f(q_+)$	4.23	-0.5172	2.3683	24	0.0263	2.31
$v(V_{McG})$	3.63	0.7783	11.9981	24	1.25E-11	1.09
constant =	0.21					

^a Distribution of solutes in Table 1 in 1-octanol/water from published data.

Thus, eqs 12 and 13 are essentially the same. Considering the limited and rather arbitrarily selected set of solutes comprising Table 1 chosen to test the LSER, the result may be considered good.

The MNDO TLSEr approach was then applied to the same data set, using calculated values for Famini's descriptors, but using published values of molecular volume,^{18,22} and not the McGowan Volume. Note that π_1 was also estimated using the molecular volume descriptor. Table 3 shows the significance of the parameters exceeding the 95% confidence level, and the regression equation is shown in eq 14:

$$\text{Log } P = 0.39 - 8.70q_- + 3.60q_+ + 2.94V_{mv} \quad (14)$$

$$[r^2 = 0.94; s(y) = 0.42; F = 144.89]$$

Only three parameters, electrostatic basicity (q_-), volume (V_{mv}), and electrostatic acidity (q_+), are of any significance in accounting for the variance of the regression.

This agrees very closely with a published TLSEr by Famini.¹⁸ The overall effect of Famini's basicity and volume parameters on the partition coefficient is substantially the same, although there is no polarity term, as in the Abraham solvation equation, but the effect of acidity is quite different and rather contrary to accepted opinion. It is generally accepted that the phases of the octanol/water system are not

Table 5. Part a Solutes Used in ABS Partitioning; Abraham Parameters, Measured and Predicted Values of Log D (ABS Partition Coefficient), Log P (Octanol/Water Partition Coefficient), and Relative Errors of the Predictions and Part b Solutes Used in ABS Partitioning; Farnini Parameters, Measured and Predicted Values of Log D (ABS Partition Coefficient), Log P (Octanol/Water Partition Coefficient), and Relative Errors of the Predictions

Part a												
solute	π_2^H	α_2^H	β_2^H	V_{McG}	R_2	log D (ABS)	log D pred	Log D error	log P (o/w)	log P pred	Log P error	
1,4-dichlorobenzene	0.75	0.00	0.02	0.96	0.83	2.12	1.94	0.18	3.44	3.42	0.02	
1-propanol	0.42	0.37	0.48	0.59	0.24	0.49	0.47	0.02	0.25	0.28	-0.03	
4,4-dichlorobiphenyl	1.31	0.00	0.20	1.57	1.64	3.14	3.15	-0.01	5.23	5.10	0.13	
acetic acid	0.65	0.61	0.45	0.46	0.27	0.23	0.32	-0.09	-0.17	-0.28	0.11	
acetonitrile	0.90	0.04	0.33	0.40	0.24	0.23	0.18	0.05	-0.34	-0.40	0.06	
acetophenone	1.01	0.00	0.49	1.01	0.82	1.38	1.36	0.02	1.58	1.66	-0.08	
aniline	0.96	0.26	0.50	0.82	0.96	1.08	1.16	-0.08	0.90	1.00	-0.10	
anisole	0.74	0.00	0.29	0.92	0.71	1.53	1.44	0.09	2.11	2.20	-0.09	
benzamide	1.50	0.49	0.67	0.97	0.99	1.24	1.16	0.08	0.64	0.52	0.12	
benzene	0.52	0.00	0.14	0.72	0.61	1.48	1.28	0.20	2.13	2.11	0.02	
benzoic acid	0.90	0.59	0.40	0.93	0.73	1.45	1.43	0.02	1.87	1.78	0.09	
benzyl alcohol	0.87	0.33	0.56	0.92	0.80	1.16	1.19	-0.03	1.10	1.18	-0.08	
1-butanol	0.42	0.37	0.48	0.73	0.22	0.68	0.70	-0.02	0.88	0.83	0.05	
4-chloroaniline	1.13	0.30	0.35	0.94	1.06	1.44	1.61	-0.17	1.83	1.93	-0.10	
chlorobenzene	0.65	0.00	0.07	0.84	0.72	1.81	1.62	0.19	2.84	2.78	0.06	
1, 2-dichloroethane	0.64	0.10	0.11	0.64	0.42	0.90	1.05	-0.15	1.48	1.68	-0.20	
ethanol	0.42	0.37	0.48	0.45	0.25	0.25	0.24	0.01	-0.31	-0.27	-0.04	
ethyl acetate	0.62	0.00	0.45	0.75	0.11	0.57	0.58	-0.01	0.73	0.71	0.02	
4-hydroxybenzoic acid	0.90	0.81	0.56	0.99	0.93	1.63	1.49	0.14	1.58	1.56	0.02	
2-propanol	0.36	0.33	0.56	0.59	0.21	0.40	0.36	0.04	0.05	0.03	0.02	
methanol	0.44	0.43	0.47	0.31	0.28	0.10	0.04	0.06	-0.77	-0.78	0.01	
methyl iodide	0.43	0.00	0.13	0.51	0.68	0.75	0.99	-0.24	1.51	1.44	0.07	
nitrobenzene	1.11	0.00	0.28	0.89	0.87	1.36	1.44	-0.08	1.85	1.87	-0.02	
1-octanol	0.42	0.37	0.48	1.30	0.20	1.54	1.65	-0.11	3.00	3.05	-0.05	
1-pentanol	0.42	0.37	0.48	0.87	0.22	0.92	0.94	-0.02	1.51	1.39	0.12	
phenol	0.89	0.60	0.31	0.78	0.81	1.32	1.33	-0.01	1.46	1.54	-0.08	
p-toluic acid	0.90	0.60	0.38	1.07	0.73	1.69	1.70	-0.01	2.27	2.41	-0.14	
toluene	0.52	0.00	0.14	0.86	0.60	1.55	1.51	0.04	2.73	2.66	0.07	
1,2,4-trichlorobenzene	0.81	0.00	0.00	1.08	0.98	2.14	2.26	-0.12	4.02	4.01	0.01	
Part b												
solute	q_-	q_+	ϵ_A	ϵ_B	π_1	V_{McG}	Log D (ABS)	Log D pred	Log D error	Log P (o/w)	Log P pred	Log P error
1,4-dichlorobenzene	-0.0995	0.0841	0.1521	0.1834	0.1520	0.9612	2.12	1.90	0.22	3.44	3.05	0.39
1-propanol	-0.3238	0.1786	0.1333	0.1455	0.1169	0.5900	0.49	0.44	0.05	0.25	0.24	0.01
4,4-dichlorobiphenyl	-0.0948	0.0792	0.1571	0.1873	0.1709	1.5690	3.14	3.03	0.11	5.23	5.45	-0.22
acetic acid	-0.3652	0.2162	0.1298	0.1696	0.1079	0.4648	0.23	0.32	-0.09	-0.17	-0.38	0.21
acetonitrile	-0.1146	0.0209	0.1177	0.1622	0.1050	0.4042	0.23	0.33	-0.10	-0.34	0.54	-0.88
acetophenone	-0.2814	0.0642	0.1489	0.1787	0.1411	1.0139	1.38	1.43	-0.05	1.58	1.91	-0.33
aniline	-0.2282	0.1137	0.1581	0.1749	0.1479	0.8162	1.08	1.37	-0.29	0.90	1.64	-0.74
anisole	-0.2859	0.0752	0.1571	0.1752	0.1471	0.9160	1.53	1.32	0.21	2.11	1.53	0.58
benzamide	-0.3388	0.1539	0.1482	0.1778	0.1430	0.9728	1.24	1.39	-0.15	0.64	1.72	-1.08
benzene	-0.0594	0.0595	0.1517	0.1744	0.1422	0.7164	1.48	1.45	0.03	2.13	2.18	-0.05
benzoic acid	-0.3783	0.2167	0.1479	0.1833	0.1418	0.9317	1.45	1.38	0.07	1.87	1.51	0.36
benzyl alcohol	-0.3235	0.1801	0.1505	0.1772	0.1408	0.9160	1.16	1.38	-0.22	1.10	1.60	-0.50
1-butanol	-0.3241	0.1786	0.1334	0.1456	0.1200	0.7309	0.68	0.69	-0.01	0.88	0.78	0.10
4-chloroaniline	-0.2302	0.1195	0.1574	0.1793	0.1529	0.9386	1.44	1.62	-0.18	1.83	2.19	-0.36
chlorobenzene	-0.1102	0.0770	0.1522	0.1791	0.1474	0.8388	1.81	1.62	0.19	2.84	2.45	0.39
1,2-dichloroethane	-0.1967	0.0487	0.1350	0.1713	0.1294	0.6352	0.90	0.81	0.09	1.48	1.09	0.39
ethanol	-0.3235	0.1783	0.1324	0.1442	0.1115	0.4491	0.25	0.18	0.07	-0.31	-0.33	0.02
ethyl acetate	-0.2863	0.0308	0.1388	0.1712	0.1185	0.6879	0.57	0.62	-0.05	0.73	0.40	0.33
4-hydroxybenzoic acid	-0.3817	0.2163	0.1521	0.1834	0.1454	0.9904	1.63	1.50	0.13	1.58	1.68	-0.10
2-propanol	-0.3192	0.1763	0.1332	0.1452	0.1164	0.5900	0.40	0.44	-0.04	0.05	0.26	-0.21
methanol	-0.3291	0.1803	0.1314	0.1402	0.1018	0.3082	0.10	-0.14	0.24	-0.77	-1.03	0.26
methyl iodide	-0.1090	0.0266	0.1371	0.1727	0.1499	0.5077	0.75	0.88	-0.13	1.51	1.50	0.01
nitrobenzene	-0.3419	0.0953	0.1425	0.1903	0.1493	0.8906	1.36	1.22	0.14	1.85	1.52	0.33
1-octanol	-0.3241	0.1786	0.1336	0.1471	0.1263	1.2945	1.54	1.64	-0.10	3.00	2.84	0.16
1-pentanol	-0.3247	0.1804	0.1326	0.1456	0.1226	0.8718	0.92	0.92	0.00	1.51	1.34	0.17
phenol	-0.2480	0.1926	0.1567	0.1756	0.1444	0.7751	1.32	1.39	-0.07	1.46	1.56	-0.10
p-toluic acid	-0.3773	0.2167	0.1482	0.1841	0.1442	1.0726	1.69	1.63	0.06	2.27	2.04	0.23
toluene	-0.1007	0.0601	0.1529	0.1757	0.1436	0.8573	1.55	1.60	-0.05	2.73	2.42	0.31
1,2,4-trichlorobenzene	-0.0811	0.0989	0.1511	0.1864	0.1549	1.0836	2.14	2.20	-0.06	4.02	3.71	0.31

different in terms of their relative basicity.²⁸ However, the electrostatic acidity descriptor is on the margins of significance.

The MNDO TLSEr was then applied to the description of octanol/water partition using the solutes of Table 1 but using the McGowan volume in place of the molecular

Table 6. Significance of the Coefficients of Abraham's LSER Applied to Partitioning in an ABS of the Solutes Shown in Table 5 and Fitted to Eq 16

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$b(\Sigma\beta_2^H)$	-1.22	-0.4792	8.9473	25	2.88E-09	1.10
$\nu(V_x)$	1.70	0.8887	14.2791	25	1.59E-13	1.83
$r(R_2)$	0.50	0.8075	5.4260	25	1.24E-05	1.96
constant =	-0.09					

volume directly in the TLSER and in the computation of the polarity descriptor. The relative significance of the parameters for this TLSER are as shown in Table 4, and the minimum subset equation, significant at the 95% level, is shown as eq 15:

$$\text{Log } P = 0.21 - 8.99q_- + 4.23q_+ + 3.63V_{\text{McG}} \quad (15)$$

$$[r^2 = 0.932; s(y) = 0.45; F = 125.302]$$

The correlation is very much the same, and the relative contribution of the parameters is hardly affected. There is an effect on the volume coefficient, but as noted above, V_{mv} is larger than V_{McG} and so this is expected. Again solute electrostatic acidity features in the regression, but it is of low significance.

Having verified the computational methods and the statistical procedures using parameters and data for the well-known 1-octanol/water system, Famini's TLSER and Abraham's LSER were then applied to the partition of solutes in a PEG/(NH₄)₂SO₄ ABS. The solutes for which we obtained partitioning data, and for which Abraham solute descriptors were available, are shown in Table 5a. The MNDO descriptors for this solute set are shown in Table 5b. When the Abraham LSER approach is used to analyze the ABS partitioning data, the relative importance of the parameters of the regression that emerge is shown in Table 6. Again the number of variables has been reduced until all are significant at the 95% level.

In many respects, this LSER is very similar to the results for partitioning in the 1-octanol/water system but instead of π_2^H emerging as the additional parameter along with solute basicity and volume, it is the molar refractivity (R_2^H) which emerges as important. This implies a role for nonbonding electrons in directing the partition in this system, in turn implying an increased partition coefficient for aryl and halogenated species. The simplest equation significant at the 95% level is eq 16:

$$\text{Log } D = -0.09 + 0.50R_2 - 1.22\Sigma\beta_2^H + 1.70V_x \quad (16)$$

$$[r^2 = 0.97; s(y) = 0.126; F = 265.31]$$

When the same partitioning data is analyzed by MNDO-based TLSER (method of Famini, see Table 5b), a slightly different picture emerges, as it did for the 1-octanol/water system. The TLSER equation for this is given by eq 17:

$$\text{Log } D = -1.83 - 2.69q_- + 2.21q_+ + 11.36\epsilon_A + 1.81V_{\text{McG}} \quad (17)$$

$$[r^2 \text{ is } 0.95; s(y) = 0.158; F = 127.75]$$

Table 7. Significance of the Coefficients of the TLSER Applied to ABS Partitioning Data

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$d(q_-)$	2.69	0.4039	6.2094	24	2.04E-06	2.44
$f(q_+)$	2.21	-0.1721	3.0343	24	0.0057	2.55
$e(\epsilon_a)$	11.36	0.6947	4.6888	24	9.16E-05	1.60
$\nu(V_x)$	1.81	0.8932	13.6287	24	8.59E-13	1.46
constant =	-1.83					

Table 8. Significance of the Coefficients of Abraham's LSER Applied to the Prediction of Log P (Octanol/Water) for the ABS Data Set Significant at the 95% Level

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$s(\pi_2^H)$	-0.98	0.2927	8.8782	24	4.76E-09	3.50
$b(\Sigma\beta_2^H)$	-3.54	-0.6264	30.8404	24	8.06E-21	1.45
$\nu(V_x)$	3.95	0.8353	45.2448	24	9.5E-5	1.84
$r(R_2)$	0.60	0.6507	5.6512	24	8.08E-06	4.85
constant =	-0.08					

Table 9. Significance of the Parameters of the TLSER for the Prediction of Log P (Octanol/Water) from the Data of Table 5

variable	coeff	correlation/ Y	Student's <i>t</i>	dof	probability	VIF
$d(q_-)$	5.60	0.5115	6.9454	26	2.25E-07	1.01
$\nu(V_x)$	4.01	0.8376	12.5570	26	1.52E-12	1.01
constant =	-0.31					

The significance of the coefficients is shown in Table 7. Because relevant parameters were not available for the whole of this data set, the McGowan volume was used in both the LSER and the TLSER.

As was the case with the description of 1-octanol/water partitioning, volume emerges as an important parameter, as do electrostatic basicity and acidity, but the third most significant parameter is covalent acidity. The remaining parameters are relatively unimportant (including electrostatic acidity). It is far from clear whether these differences are chemically significant. The fact that the coefficient for the covalent acidity is so large is undoubtedly due to the scaling of this descriptor and implies nothing about its significance. The minimum equation at the 95% level is as in eq 17.

The two LSERs have not been compared in the prediction of log P (1-octanol/water partition) using the solutes contained in the ABS data set (Table 5a,b). This is remedied in the following regressions. Table 8 shows the parameters significant at the 95% level for the prediction of log P using Abrahams LSER which is given in eq 18:

$$\text{Log } P = -0.08 - 0.98\pi_2^H - 3.54\Sigma\beta_2^H + 3.95V_x + 0.60R_2 \quad (18)$$

$$[r^2 = 0.99; s(y) = 0.092; F = 1516.157]$$

For the prediction of log P using the ABS data set of Table 5b and Famini's TLSER, the results (significant at the 95% level) are shown in Table 9 with the minimum multiple regression equation given by eq 19:

$$\text{Log } P = -0.312 - 5.60q_- + 4.01V \quad (19)$$

$$[r^2 = 0.89; s(y) = 0.456; F = 111.38]$$

For the TLSEr of Famini applied to the description of Log P using the ABS data set, only two parameters are significant at the minimum 95% level. Thus, although we have used a somewhat different solute set, it has not changed the 1-octanol/water regression to any significant extent.

Several significant features of these comparisons may be highlighted. The TLSEr approach clearly picks up the most important features of the solvation process, i.e., those highlighted also by the empirical regression. These features are the importance of the solvent parameters related to volume and basicity. The basicity of significance is clearly that of Lewis basicity, and any covalent basicity is of little importance. Beyond this, if it is assumed that the Abraham LSER is a reasonable description of the distribution process in these systems, the TLSEr does not highlight the smaller contributions to the observed distribution, these being the solute polarity in the case of the 1-octanol/water system and the excess molar refractivity in the ABS. Some parameters of the TLSEr, dealing with the remaining variability of the regression, are difficult to understand. Thus, in the case of the 1-octanol/water system, solute electrostatic acidity appears as a significant parameter. Similarly, in the ABS, covalent acidity seems to be assigned a role in the description of the partitioning process by the TLSEr which is assigned to other parameters in the empirical LSER.

CONCLUSIONS

There seems to be general agreement that the LSER of Abraham represents a powerful technique for the prediction and understanding of solution properties of solutes and of solvation-dominated chemical and physical processes. The present paper provides no additional evidence to support this. However the parameters are derived empirically and Gibbs energy related, and from this point of view their success is perhaps understandable. If this is accepted, it is not clear from the above analysis that the theoretical solute property parameters developed by Famini and co-workers are equally applicable. In the present study, the parameters for covalent acidity and basicity seem not to have proved particularly useful. In addition, the polarity of solutes hardly seems to have been captured. On the other hand, the electrostatic basicity and acidity seem to have been captured to a large degree, although, even here, it appears that there is considerable room for refinement. These conclusions may also be understood to follow from the fact that the quantum chemical approach is based on gas-phase structures.

One respect in which refinement is certainly required is the development of summed terms analogous to those of Abraham which can encapsulate and quantify the existence of multiple hydrogen bonding sites within a molecule. Abraham has recently begun to develop a group contribution scheme⁴¹ applicable to his generalized solvation equation which will no doubt assist in its application and generalization since descriptors may no longer need to be determined but may be estimated instead. Tables of hydrogen bond structural group constants have recently been made available.⁴² Nevertheless, there is likely to remain considerable interest in a simple, but meaningful, method for the prediction of solvation and partition from a theoretical or semitheoretical point of view.

A number of issues emerge from the present study. Many properties can be predicted with considerable accuracy using

molecular models. Dimensional descriptors of volume, surface area, shape, and so on are easy to produce, and a study of the correct selection of these for solvation prediction could be rewarding. Some molecular properties used by Abraham to describe nonbonding electron interactions and polarity driven interactions seem also easily available directly from molecular structure. The biggest challenge seems to be to accurately encapsulate potential hydrogen bonding structures in a mathematical format directly from molecular structure. For example, a much larger study, employing the screening charge density approach of COSMO⁴³ to generate descriptors related to polarity and hydrogen bonding, found close correspondence with Abraham parameters only for descriptors related to molecular volume. The approach taken in the TLSEr of Famini has imperfections, but it is attractively simple, particularly in comparison to the latter approach, and could be profitably improved upon. Improvements in relation to the elimination of spurious nonzero values of hydrogen bonding parameters and the implementation of methods capable of handling the occurrence of multiple hydrogen bonding sites in a single molecule might prove relatively simple and rewarding to implement.

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