COMPUTATIONAL PARAMETERS IN CORRELATION ANALYSIS: GAS–WATER DISTRIBUTION COEFFICIENT

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday.

Theoretical linear solvation energy relationships (TLSER) combine computational molecular parameters with the linear solvation energy relationship (LSER) of Kamlet and Taft to characterize and predict properties of compounds. This paper examines the correlation of the gas–water equilibrium constant for 423 compounds with the TLSER parameters. Also, it describes new parameters designed to improve the TLSER information content.

Key words: Correlation analysis; QSAR; QSPR; LSER; LFER; Distribution coefficient; Henry's law; Molecular modeling.

Professor Exner has done much to promote the use of correlation analysis in chemistry and has written the most recent correlation analysis text[1]. This book contains a statement that explains our motivation for exploring relationships between properties and molecular properties: "..any regularity found in nature raises some kind of satisfaction". Our efforts to apply computational methods to LFER are due in large part to the encouragement of Otto Exner. It is a privilege to contribute to this special issue.

The equilibrium constant, L^W, for the gas–water phase distribution, X(g) → X(aq), is a measure of the interaction of the solute, X, and the solvent, water. The distribution coefficient is closely related to Henry's law constant, $K_h = L^W/RT$. Larger values of this distribution coefficient imply increased solubility in the aqueous phase which, in turn, implies increased solute/water molecular attraction. It would be convenient to be able to predict the value of L^W for a solute from its molecular structure as well as to be

able to characterize the molecular interactions in terms of molecular properties.

The relationship between the macroscopic (bulk) properties of chemical compounds and their microscopic (molecular) features is an inherent chemical concept. Quantitative structure activity/property (QSA/PR) relationships take this qualitative relationship further by quantifying, usually in the form of a linear regression, the relationship between structure and function.

As originally developed by Hansch, quantitative structure/activity relationships (QSAR), were designed to aid medicinal and pharmaceutical chemists in developing new drugs from biological activity data[2,3]. An obvious extension, QSPR, applies to toxicity and physical/chemical properties[4,5]. Prior to the development of QSAR in the medicinal chemistry arena, Burkhart and Hammett quantified a relationship between the structure of a series of substituted benzoic acid esters and their rates of hydrolysis[6,7]. Termed the linear free energy relationship, due to the underlying extrathermodynamic arguments relating these to the Gibbs free energy, the LFER construct has been used very successfully to correlate a wide range of physical and chemical properties[8].

Solute/solvent properties have generated a great deal of interest in the computational chemistry community in recent years[9,10]. In particular, the interaction between the solvent and the solute including the effect of solvent on solute molecular structure and therefore, the bulk properties of the solute is being studied through a wide variety of techniques. These techniques for modeling solute/solvent molecular interactions may be classified into three basic methods.

In the first method, the explicit model, solute and solvent molecules are treated individually[11]. This involves computation of all solute/solvent and solvent/solvent interactions; also, all solute and solvent molecule conformations need to be examined. Consequently, the calculations consume much time. Although there are cases of its use in quantum chemical studies, it has been used most frequently in molecular dynamics and Monte Carlo simulations. This method generates most information including structure deformities as well as solute/solvent and solvent/solvent bonding.

The second method is the implicit model, where solute molecules are treated explicitly, but a continuum model or potential is used for the solvent[12]. Because only solute molecule conformations are involved, this method is rapid enough to permit the use of *ab initio* or semiempirical methods. While this does not provide specific solute/solvent or solvent/

solvent bonding information, it does give Gibbs free energies of solvation. This model has generated most interest in the past several years.

The third method for studying solute/solvent interactions is the extension of the LFER/QSAR to the concept of solvation, and is the most empirical of the three methods[1,4,13–20]. A relatively large data set of empirical property data is required in order to generate a relationship. One advantage of this method is that relatively little information is needed about the correlated property/system. Often, very complex "solvent systems" such as receptors, may be characterized. For multiple solute/single solvent cases, a major disadvantage is that only inferences about the property in that particular solvent system can be made. Then too, the resulting correlation equation is valid for interpolation only, and may not be valid for the extrapolations outside of the data set region. Still, for complex systems such as receptor sites, where explicit or implicit methods cannot be used readily, the QSAR/QSPR/LFER methods can give useful insights into important features. This paper focuses on the use of this third method, with models based on LFER to study solute/solvent based interactions.

Often, this third method uses correlation analysis to relate some property to a set of molecular parameters. Kamlet and Taft provided a major step forward in applying LFER to solute/solvent interactions by developing an LFER subset, linear solvation energy relationships (LSER). This approach has used a set of empirical molecular parameters to characterize a wide range of physical, chemical and biological properties which involve solute/solvent interactions[21–24]. The generalized LSER approach is shown in Eq. (*1*), where any solute/solvent property may be divided into three separate effects.

$$\text{Property} = \text{cavity terms} + \text{dipolarity/polarizability terms} + \text{H-bond terms} + \text{intercept} \qquad (1)$$

Many solute/solvent properties follow this linear combination of terms. The bulk/cavity term models the energy required to break the solvent matrix and insert the solute. The dipolarity/polarizability term models interaction between the induced dipoles of the solute and solvent molecule. The hydrogen bonding terms model interactions involving the acidity and basicity of the solute and solvent. Abraham *et al.*, and Carr *et al.*, have extended the Kamlet–Taft sets of empirically based parameters to describe these interaction terms more adequately. These parameter sets have been

used to correlate, successfully, a wide variety of physical, chemical and biological properties.

Abraham has recently extended the LSER by using gas chromatography instead of solvatochromic shifts to determine the LSER parameters, and added a dispersion term, which is modeled by the gas/hexadecane partition coefficient[25–28]. In addition, the LSER empirical solvation parameter (solute) set includes: the McGowan volume, a measure of the energy to separate solvent molecules to make space for a solute molecule; an excess molar refraction relative to hexadecane, related to dispersion interactions; dipolarity/polarizability; hydrogen bond basicity; hydrogen bond acidity.

Ford and Livingstone point out advantages for using computational parameters instead of empirical parameters. Parameters from molecular orbital based methods tend not to be class dependent as is often the case with group theoretical, topological or topographical indices[29]. MO-derived descriptors are readily computed, and can be selected in such a way as to nearly assure orthogonality of the parameter space[30,31]. There are currently a number of methods in the literature for examining physical, chemical and biological properties using computationally derived descriptors[19,31–34].

Following this philosophy, the theoretical linear solvation energy relationship (TLSER) was developed with the express aim at maintaining the function of the LSER, but using a one-for-one (as much as possible) replacement of empirical descriptors with computational ones. The resulting TLSER for some general property, *P*, is shown in Eq. (*2*).

$$\log P = a\, V_{mc} + b\, \pi_I + d\, \varepsilon_B + e\, q_- + c\, \varepsilon_A + f\, q_+ + g \qquad (2)$$

In this formalism, V_{mc} represents the molecular volume, and depicts the cavity size needed in the solvent matrix. The solvent Hildebrand solubility parameter multiplied by the solvent V_{mc} is a model of the energy needed to insert a solute molecule in the solvent matrix. The polarizability term, π_I, is obtained by dividing the polarization volume by the molecular volume. This results in a unitless term independent of volume and models the ease in which electrons may move throughout the molecule. The hydrogen bonding basicity term is modeled by covalent and electrostatic basicity terms. The covalent basicity (ε_B) is defined as a linear transformation of the E_{HOMO}, $0.30–0.01(E_{LUMO(water)} - E_{HOMO})$. This transformation provides a "zero point" reference for the scale, and corrects the scale to be positive for increasing basicity. The electrostatic basicity (q_-) is taken as the absolute

value of the most negative formal charge (nonhydrogen) in the molecule. Similarly, the hydrogen bond acidity is modeled by covalent and electrostatic terms. The covalent acidity (ε_A) is defined in the same manner as ε_B, but uses the HOMO energy of water and the LUMO energy of the substrate. The electrostatic acidity (q_+) is defined as the formal charge of the most positive hydrogen atom in the molecule. Table I contains a summary of these traditional TLSER parameters.

This methodology has been used successfully to develop correlation equations for a wide variety of properties[16,17,35–50]. The correlation equations have been useful in two ways. They can provide a means for estimating a property for some not yet measured compound; and they can serve as a probe into solute/solvent interactions. For example, if the solute hydrogen bonding basicity term, ε_B, is significant, it can suggest that the solvent hydrogen bonding acidity is involved.

It is of interest to consider why properties calculated for isolated molecules at 0 K should correlate well with experimental properties. This seems to suggest that molecular conformations under those conditions correlate reasonably well with those in more realistic situations.

Furthermore, most TLSER equations can be derived with sets of parameters that have small cross-correlation; that is to say, the descriptors are "pure", and reflect a particular microscopic property without "mixing" or contamination from other descriptors. This is in keeping with an assumption of most LFER/QSAR methods involving computationally derived descriptors.

TABLE I
TLSER descriptors

Symbol	Name	Definition	Units	Range
V_{mc}	molecular volume	molecular volume	100 A^3	0.3–3
π_I	polarizability index	polarizability/V_{mc}	none	0.07–0.16
ε_B	"covalent" HB basicity	0.30–0.01(E_{lw}–E_h)	heV	0.1–0.17
q_-	"electrostatic" HB basicity	maximum |(–) charge| on an atom	acu	0–0.8
ε_A	"covalent" HB acidity	0.30–0.01(E_l–E_{hw})	heV	0.14–0.2
q_+	"electrostatic" HB acidity	maximum (+) charge on an H atom	acu	0–0.8

Å, Angstrom; heV, hectoelectronvolt; acu, atomic charge unit; HB, hydrogen bond; E_l, LUMO energy; E_h, HOMO energy; E_{lw} and E_{hw} refer to E_l = 5.4428 eV and E_h = –12.1911 eV for water, respectively; || absolute value.

In an attempt to improve the quality of TLSER correlation equations, two new TLSER descriptors sets have been proposed: μ, made up of local dipole moments, and δ_{cv}, made up of charge variances. Debord[27] and colleagues have correctly pointed out that dipolarity is not directly accounted for in TLSER. However, some dipolar effects may be rationalized from q_+ and q_- coefficients while the induced dipolarity is accounted for in the π_I term. Consequently, there has been little need for a specific term for the dipolar effects. Early in the development of the TLSER parameters, Kamlet and Taft identified the molecular dipole moment as inadequate[23]. When far apart, a solute molecule with small dipole moment will not experience dipole interaction with a solvent molecule. However, when molecules are close, the local bond dipoles can interact. Because of its vector nature, molecules with strong bond dipoles and the appropriate geometry can have small dipole moments. Tetrachloromethane and 1,4-dinitrobenzene vividly demonstrate this; each has strong bond dipoles that cancel because of the geometry. Therefore, it is necessary to represent the dipole effects as a combination of local effects. To this end, three new descriptors were defined to represent local dipolar interactions[51].

Another effect that has seemed to be inadequately accounted for is the possibility for multiple ligand sites. The electrostatic charge terms used in the TLSER are simple in nature, values of the most positive hydrogen and most negative atom (absolute value, so the number is positive and increasing with increasing strength). While these descriptors work well in most data sets we have examined, there have been cases where they do not adequately model a given interaction. In the vast majority of these cases, this is because either the solutes studied have multiple acidity or basicity sites that are separated by a large distance, or other charge effects are influencing the acidity or basicity. To this end, three new descriptors were defined to represent total charge descriptions, including multiple active sites, as opposed to just the "most active site".

RESULTS AND DISCUSSION

To account for the lack of a true dipole descriptor, three new dipole moment descriptors based on charge difference, $[q_i - q_j]$, and bond length, $[r_i - r_j]$, were defined. The maximum, total and average bond dipole moments are given, respectively, by

$$\mu_{max} = \text{maximum value for } |[q_i - q_j]\cdot[r_i - r_j]|/2 \ ;$$

$$\mu_{tot} = \Sigma\Sigma\ |[q_i - q_j]\cdot[r_i - r_j]|/2\ ;$$

and

$$\mu_{ave} = \mu_{tot}/n\ ,$$

where n is the number of bonds.

In an attempt to account for multiple ligand sites, we have used concepts based on the generalized integrated potential functions (GIPF) of Politzer and Murray[20]. They have published numerous studies using parameters based on electrostatic potential derived descriptors. In particular, we have used charge variance terms (total variance, positive charge variance, negative charges variance) with the electrostatic potential charges being replaced by (Coulson) formal charges. These three charge variance parameters are: positive, negative and total charge variances are given, respectively, by:

$$\delta_{cv_+} = \Sigma\ (q_{+i} - \langle q_+\rangle)^2/(n_+ - 1)$$

$$\delta_{cv_-} = \Sigma\ (q_{-i} - \langle q_-\rangle)^2/(n_- - 1);$$

and

$$\delta_{cv_t} = \Sigma\ (q_i - \langle q\rangle)^2/(n - 1) = \Sigma\ q_i^2\ /(n - 1)$$

because of the definition of formal charge for a neutral molecule. Table II summarizes these new parameter definitions. One would expect greater charge variance to accompany multiple ligand bonding possibilities.

TABLE II
"New" TLSER descriptors

Symbol	Name	Definition	Units	Range
μ_{tot}	total dipole moment	$\Sigma\Sigma\ \|[q_i - q_j]\cdot[r_i - r_j]\|/2$	acu · A	0–20
μ_{ave}	average dipole moment	μ_{tot}/n	acu · A	0–4
μ_{max}	maximum dipole moment	$\max\ \|[q_i - q_j]\cdot[r_i - r_j]\|/2$	acu · A	0–5
δ_{cv_-}	negative charge variance	$\Sigma\ (q_{-i} - \langle q_-\rangle)^2/(n_- - 1)$	acu	0–0.8
δ_{cv}	charge variance	$\Sigma(q_i)^2/(n - 1)$	acu	0–10
δ_{cv_+}	positive charge variance	$\Sigma\ (q_{+i} - \langle q_+\rangle)^2/(n_+ - 1)$	acu	0–5

[a] 2-Bromo-2-chloro-1,1,1-trifluoroethane; [b] 2-bromo-1,1,1,2-tetrafluoroethane; [c] 2,2-dichloro-1,1-difluoro-1-methoxyethane; [d] 1-chloro-1-(difluoromethoxy)-2,2,2-trifluoroethane. Note: http://webbook.nist.gov/chemistry/ is great source of chemical name/property information.

For the 423 compound set studied here, the relationship between the natural logarithm of the equilibrium constant, L^W, for the distribution of a compound between gaseous and aqueous phases and the original six TLSER descriptors is given by Eq. (*3*). Most of the statistical parameters listed with these correlation equations are commonly used. However, the less familiar variance inflation factor (VIF) is a measure of the cross correlation of a particular independent variable in terms of the others.

$$\log L^W = -0.766\ V_{mc2} + 29.02\ \pi_{I2} + 36.17\ \varepsilon_{B2} + 9.370\ q_{-2} + 12.39\ q_{+2} - 8.706 \qquad (3)$$

t-stat	4.8	6.1	6.6	21.4	15.7	14.2
P(2-tail)	0.000	0.000	0.000	0.000	0.000	0.000
VIF	2.20	2.20	1.30	1.48	1.14	

$N = 417$ $R = 0.900$ $\sigma = 0.939$ $F = 352$ $q^2 = 0.745$

Outliers: ethanenitrile, propanenitrile, butanenitrile, pentanenitrile, *N*-acetylpyrrolidine, 3-acetylpyridine

The corresponding equation with the new parameter set is given by Eq. (*4*).

$$\log L^W = -0.829 V_{mc2} + 34.06\pi_{I2} + 24.00\varepsilon_{B2} + 10.28q_{-2} + 13.17q_{+2} - 0.031\delta_{cv_{t2}} - 0.383\delta_{cv_{+2}} - 7.592 \qquad (4)$$

t-stat	5.1	7.0	4.1	19.4	15.0	2.6	5.5	13.2
P(2-tail)	0.000	0.000	0.000	0.000	0.000	0.010	0.000	0.000
VIF	1.17	2.35	2.53	1.85	1.50	1.25	1.43	

$N = 416$ $R = 0.899$ $\sigma = 0.935$ $F = 247$ $q^2 = 0.754$

Outliers: ethanenitrile, propanenitrile, butanenitrile, pentanenitrile, *N*-acetylpyrrrolidine, 3-acetylpyridine, triethyl phosphate

Equations (*3*) and (*4*) are statistically significant; examination of the statistical parameters shows that they meet the criteria in the procedure. Equation (*3*) is physically reasonable; all terms make physical sense. The negative volume coefficient sign indicates that increasing solute molecule size accompanies decreasing solute solubility in water. With increasing solute size more water–water H bonds need to broken to accommodate larger solute molecules. The π_I signs imply increasing solubility with increasing solute dipolarity/polarizability, as expected for this most polar solvent. The

ε_{B2} and q_{-2} signs imply increasing solubility with increasing basicity; water has strong hydrogen bond acidity. The q_{+2} sign implies increasing solubility with increasing acidity; water has strong hydrogen bond basicity. Increased polarizability and hydrogen bonding would accompany increased solubility. Except for the charge variance signs Eq. (*4*) is physically meaningful; increased charge variance might be expected to accompany increased L^W.

The R values indicate that each equation correlates the measured values with the TLSER parameters well. Also, the cross-validated correlation coefficient squared values, q^2, indicate that each equation predicts the solubility values quite well. The VIF values also indicate that the parameters have low cross-correlation.

The majority of the TLSER correlation outliers in Eqs (*3*) and (*4*) involve nitrogen-containing compounds including the first four alkanenitriles. A possible explanation is that their solution process might involve a different mechanism, *i.e.*, a chemical reaction such as hydrolysis. The number of outliers in the TLSER relations makes less than 2% of the number of compounds.

One of our null hypotheses has been supported for this compound set and property. The traditional TLSER descriptors have given a statistically and physically meaningful correlation equation (Eq. (*3*)) for the gas–water distribution equilibrium constant. However, the hypothesis that the new TLSER parameters would improve the correlation equation quality has not been supported for this compound set and property. While Eqs (*3*) and (*4*) are of comparable statistical quality, the two charge variance terms in Eq. (*4*) have counterintuitive signs. Occam's Razor Eq. (*3*) with five parameters would be preferred over Eq. (*4*) with seven.

Several possible explanations can be made for the lack of significance for the bond dipole parameters. One: the compounds in this list primarily involve single site interactions so that q_- and q_+ are good dipolarity descriptors. Two: the π_I descriptor adequately accounts for dipolarity when the data set is quite diverse. This suggests that the bond dipole parameters might be significant for compound sets with small change in polarizability index as sometimes occurs in some homologous series. Support for this idea is found in the correlation equations for the ester, alkane, haloalkane and *N*-ring compounds subsets listed below. Equations for phenols, alkylbenzenes, alkenes, aldehydes and ethers have $R^2 < 0.80$.

Esters

$$\log L^W = -18.57\ q_- - 20.00\ q_+ - 0.568\ \mu_{tot} + 28.48\ \mu_{max} - 15.38 \quad (5)$$

t-stat	5.6	10.5	7.9	12.8	8.0
P(2-tail)	0.000	0.0000.000	0.000	0.000	
VIF	1.19	3.41	1.88	4.57	

$N = 29$ $R = 0.936$ $\sigma = 0.130$ $F = 42.1$ $q^2 = 0.749$

Outliers: 2,2-dimethylpropanoate, methyl cyclopropanecarboxylate, isopropyl methanoate

Equation (*5*) indicates that ester solubility decreases with acidity, basicity and total bond dipole moment which seems counterintuitive. However, it seems reasonable that the solubility increases with the maximum bond dipole moment (which occurs near the carbonyl group). However, the standard TLSER descriptors provide a more statistically and physically significant correlation, Eq. (*6*).

$$\log L^W = -0.624\ V_{mc} + 99.09\ \varepsilon_A - 3.919\ q_+ - 13.96 \quad (6)$$

t-stat	10.1	18.3	6.1	15.6
P(2-tail)	0.000	0.000	0.000	0.000
VIF	1.21	1.07	1.18	

$N = 29$ $R = 0.968$ $\sigma = 0.083$ $F = 124$ $q^2 = 0.613$

Outliers: methyl cyclohexanecarboxylate, methyl cyclopropanecarboxylate, isobutyl 2-methylpropanoate

Alkanes

$$\log L^W = -1.384\ V_{mc} + 117.6\ \varepsilon_B - 6.996\ \mu_{ave} - 14.59 \quad (7)$$

t-stat	12.6	7.7	5.8	7.9
P(2-tail)	0.000	0.000	0.000	0.000
VIF	1.45	1.48	1.08	

$N = 35$ $R = 0.919$ $\sigma = 0.175$ $F = 55.8$ $q^2 = 0.754$

Outliers: methane

Equation (*7*) indicates that alkane solubility decreases with volume and increases with alkane basicity; these seem to fit intuition. However, it decreases with average bond dipole moment; this, in turn, seems counterintuitive. The standard TLSER descriptors give a less statistically significant relation, Eq. (*8*).

$$\log L^{W} = -1.139\ V_{mc} + 77.58\ \pi_{I} - 3.523\ q_{-} - 8.322 \qquad (8)$$

t-stat	10.5	7.6	3.3	8.3
P(2-tail)	0.000	0.000	0.002	0.000
VIF	1.21	1.46	1.11	

$N = 36$ $R = 0.895$ $\sigma = 0.195$ $F = 43.0$ $q^2 = 0.375$

Outliers: none

Haloalkanes

$$\log L^{W} = -0.710\ V_{mc} + 17.88\ \pi_{I} + 20.19\ q_{+} - 0.293\ \mu_{tot} - 1.449 \qquad (9)$$

t-stat	4.3	2.9	7.8	4.5	2.0
P(2-tail)	0.000	0.007	0.000	0.000	0.053
VIF	1.03	2.10	1.52	2.07	

$N = 45$ $R = 0.902$ $\sigma = 0.330$ $F = 43.8$ $q^2 = 0.702$

Outliers: 1,4-dichlorobutane, 1,3 -dichloropropane

Equation (*9*) suggests that haloalkane solubility increases with acidity and decreases with volume which seems to fit intuition. However, it increases with polarizability and decreases with total bond dipole moment which seems counterintuitive. The presence of π_I in the haloalkane Eq. (*9*) is reasonable since halogen atoms introduce considerable polarizability into a molecule. Consequently, the varied number of halogen atoms in the compounds provides considerable variation in their π_I values.

The standard TLSER descriptors give the much less statistically significant Eq. (*10*).

$$\log L^{W} = -0.723\ V_{mc} + 40.03\ \pi_{I} - 27.53\ \varepsilon_{A} + 19.28\ q_{+} + 0.501 \quad (10)$$

t-stat	3.5	6.7	2.0	5.1	0.23
P(2-tail)	0.001	0.000	0.050	0.000	0.820
VIF	1.03	1.22	2.22	2.02	

$N = 46$ $R = 0.843$ $\sigma = 0.416$ $F = 25.1$ $q^2 = 0.785$

Outlier: 1,4-dichlorobutane

N-Ring compounds

$$\log L^{W} = -26.83\ \varepsilon_{B} - 26.59\ q_{+} + 3.385\ \mu_{max} + 4.172 \quad (11)$$

t-stat	2.3	9.3	6.4	not sig.
P(2-tail)	0.030	0.000	0.000	not sig.
VIF	1.49	1.43	1.06	

$N = 35$ $R = 0.901$ $\sigma = 0.541$ $F = 44.8$ $q^2 = 0.883$

Outliers: *N*-acetylpyrrolidine

Equation (*11*) suggests that *N*-ring compound solubility decreases with basicity and acidity and seems counterintuitive. The suggested increase with maximum bond dipole moment seems reasonable. The standard TLSER descriptors give a less statistically significant relation, Eq. (*12*).

$$\log L^{W} = -54.78\ \varepsilon_{B} + 8.874\ q_{-} + 28.38\ q_{+} + 7.575 \quad (12)$$

t-stat	3.4	4.9	8.4	3.8
P(2-tail)	0.002	0.000	0.000	0.001
VIF	2.14	1.54	1.50	

$N = 35$ $R = 0.869$ $\sigma = 0.618$ $F = 31.8$ $q^2 = 0.683$

Outliers: *N*-acetylpyrrolidine

In conclusion, the standard TLSER parameters give an acceptable correlation equation for the gas–water distribution equilibrium constant for this overall data set. The new parameters give a correlation equation that is comparable statistically but less satisfactory physically. The suggestion that the bond dipole parameters might be significant in place of π_I in a homologous series is supported by three of the four (haloalkanes excepted) subset equations. The cross-validated correlation coefficient squared, q^2, values indicate that these correlation equations give good ($q^2 > 0.40$) predictive capabilities.

For some of the compound subsets, the new TLSER parameter set gives statistically significant relations with dipole moments; however, some of their terms seem to be counter to physical intuition. With the exception of the esters, the relations involving bond dipole moment parameters are more statistically significant and seem to be less physically significant than are the corresponding standard TLSER relations. Again, most of these subset equations also have good predictive capabilities. The dipole parameters seem to be significant when there is small π_I variation in the compound set. Further modifications of the TLSER parameter set along with applications of the current set to other properties seem appropriate.

PROCEDURE

Data for the 423 compounds was taken from tables compiled in a paper by Abraham and coworkers[52]. Table III lists these compounds with their natural log L^W values.

Molecular geometry description (Z-matrix) was done with PCMODEL (Serena Software, Bloomington, IN 47402-3076) and MMADS (in house developed)[53]. Each molecule was viewed to make sure the conformation was reasonable and likely a minimum. Theoretical calculations were done using MNDO in MOPAC6.0 (QCPE). MNDO has systematic errors which are greater than those in AM1 and PM3; consequently, this error "factors out" in the correlation equations.

Data for the TLSER parameters were extracted from the MOPAC files and calculated with MADCAP (in house developed)[54]. The formal charges are based on the Coulson formalism. Correlation equation coefficients and statistical parameters were obtained by multilinear correlation analysis (SYSTAT, MYSTAT, Course Technology, Cambridge, MA 02142). The cross-validated R squared, $R(\mathrm{cv})^2$ or q^2, were obtained with CODESSA (Semichem, Shawnee, KS 66216). Terms were retained if significant at the 0.95 level [P(2-tail) < 0.05] and if the variance inflation factor (VIF), a mea-

TABLE III
Compounds with log L^W values at 25 °C

Compound	log L^W	Compound	log L^W
Methane	–1.46	Propene	–0.97
Ethane	–1.34	Butene	–1.01
Propane	–1.44	Pentene	–1.23
Butane	–1.52	Pent-2-ene	–0.96
2-Methylpropane	–1.70	3-Methylbut-1-ene	–1.34
Pentane	–1.70	2-Methybutl-2-ene	–0.96
2-Methylbutane	–1.75	Hexene	–1.16
2,2-Dimethylpropane	–1.84	2-Methylpentene	–1.08
Hexane	–1.82	Heptene	–1.22
2-Methylpentane	–1.84	Hept-2-ene	–1.23
3-Methylpentane	–1.84	Octene	–1.41
2,2-Dimethylbutane	–1.84	Non-1-ene	–1.51
2,3-Dimethylbutane	–1.72	Buta-1,3-diene	–0.45
Heptane	–1.96	2-Methylbuta-1,3-diene	–0.50
2-Methylhexane	–2.15	2,3-Dimethylbuta-1,3-diene	–0.29
3-Methylhexane	–1.99	Penta-1,4-diene	–0.68
2,2-Dimethylpentane	–2.11	Hexa-1,5-diene	–0.74
2,3-Dimethylpentane	–1.85	Cyclopentene	–0.41
2,4-Dimethylpentane	–2.08	Cyclohexene	–0.27
3,3-Dimethylpentane	–1.88	1-Methylcyclohex-1-ene	–0.49
Octane	–2.11	Cyclohepta-1,3,5-triene	0.73
3-Methylheptane	–2.18	Propyne	0.35
2,2,4-Trimethylpentane	–2.12	But-1-yne	0.12
2,3,4-Trimethylpentane	–1.88	Pentyne	–0.01
Nonane	–2.30	Hex-1-yne	–0.21
2,2,5-Trimethylhexane	–2.15	Hept-1-yne	–0.44
Decane	–2.32	Oct-1-yne	–0.52
Cyclopropane	–0.55	Tetrafluoromethane	–2.29
Cyclopentane	–0.88	Chloromethane	0.40
Methylcyclopentane	–1.17	Dichloromethane	0.96
Propylcyclopentane	–1.56	Trichloromethane	0.79
Pentylcyclopentane	–1.87	Tetrachloromethane	–0.06
Cyclohexane	–0.90	Chloroethane	0.46
Methylcyclohexane	–1.25	1,1-Dichloroethane	0.62
cis-1,2-Dimethylcyclohexane	–1.16	1,2-Dichloroethane	1.31
trans-1,4-Dimethylcyclohexane	–1.55	1,1,1-Trichloroethane	0.14
Ethene	–0.94	1,1,2-Trichloroethane	1.46

TABLE III
(*Continued*)

Compound	log L^W	Compound	log L^W
1,1,2,2-Tetrachloroethane	1.81	(*Z*)-1,2-Dichloroethene	0.86
1,1,1,2-Tetrachloroethane	0.94	(*E*)-1,2-Dichloroethene	0.57
Pentachloroethane	1.02	Trichloroethene	0.32
1-Chloropropane	0.24	Tetrachloroethene	–0.07
2-Chloropropane	0.18	1-Chloroprop-2-ene	0.42
1,2-Dichloropropane	0.93	Ethoxyethane	1.17
1,3-Dichloropropane	1.39	Propoxypropane	0.85
1-Chlorobutane	0.12	Diisopropyl ether	0.39
2-Chlorobutane	0.00	Butoxybutane	0.61
2-Chloro-2-methylpropane	–0.80	Methoxyflurane[c]	0.82
1,4-Dichlorobutane	1.70	Isoflurane[d]	–0.07
1-Chloropentane	0.05	Tetrahydrofuran	2.55
1-Chlorohexane	0.00	2-Methyltetrahydrofuran	2.42
1-Chloroheptane	–0.21	2,5-Dimethyltetrahydrofuran	2.14
Bromomethane	0.60	Tetrahydropyran	2.29
Dibromomethane	1.44	1,4-Dioxane	3.71
Tribromomethane	1.56	Methoxymethane	1.40
Bromoethane	0.54	Methoxyethane	1.54
1,2-Dibromoethane	1.71	2-Methoxy-2-methylbutane	1.62
1-Bromopropane	0.41	Methanal	2.02
2-Bromopropane	0.35	Ethanal	2.57
1-Bromobutane	0.29	Propanal	2.52
1-Bromo-2-methylpropane	0.02	Butanal	2.33
2-Bromo-2-methylpropane	–0.62	2-methylpropanal	2.10
1-Bromopentane	0.07	Pentanal	2.22
1-Bromohexane	–0.13	Hexanal	2.06
1-Bromoheptane	–0.25	Heptanal	1.96
1-Bromooctane	–0.38	Octanal	1.68
Iodomethane	0.65	Nonanal	1.52
Iodoethane	0.54	Buten-2-al	3.10
1-Iodopropane	0.39	Hexen-2-al	2.70
1-Iodobutane	0.18	Octen-2-al	2.52
1-Iodopentane	0.10	Propanone	2.79
1-Iodohexane	–0.06	Butanone	2.72
1-Iodoheptane	–0.20	Pentan-2-one	2.58
Halothane[a]	0.08	Pentan-3-one	2.50
Teflurane[b]	–0.37	3-Methylbutan-2-one	2.38

TABLE III
(*Continued*)

Compound	log L^W	Compound	log L^W
Hexan-2-one	2.41	Methyl pentanoate	1.88
4-Methylpentan-2-one	2.24	Ethyl pentanoate	1.83
Heptan-2-one	2.23	Methyl hexanoate	1.83
Heptan-4-one	2.13	Ethyl hexanoate	1.64
Octan-2-one	2.11	Isobutyl 2-methylpropanoate	1.24
Nonan-2-one	1.83	Methyl 2,2-dimethylpropanoate	1.76
Nonan-5-one	1.94	Methyl cyclopropanecarboxylate	3.01
Decan-2-one	1.72	Methyl cyclohexanecarboxylate	2.42
Undecan-2-one	1.58	Ethanenitrile	2.85
Cyclopentanone	3.45	Propanenitrile	2.82
Cyclohexanone	3.60	Butanenitril	2.67
3,3-Dimethylbutan-2-one	2.28	Pentanenitril	2.58
2,4-Dimethylpentan-3-one	2.01	Ammonia	3.15
Cyclopropyl methyl ketone	3.38	Methylamine	3.34
Cyclohexyl methyl ketone	2.86	Ethylamine	3.30
Methyl methanoate	2.04	Propylamine	3.22
Ethyl methanoate	1.88	Butylamine	3.11
Propyl methanoate	1.82	Pentylamine	3.00
Isopropyl methanoate	1.48	Hexylamine	2.90
Isobutyl methanoate	1.63	Heptylamine	2.78
Isopentyl methanoate	1.56	Octylamine	2.68
Methyl ethanoate	2.30	Cyclohexylamine	3.37
Ethyl ethanoate	2.16	Dimethylamine	3.15
Propyl ethanoate	2.05	Diethylamine	2.99
Isopropyl ethanoate	1.94	Dipropylamine	2.68
Butyl ethanoate	1.94	Diisopropylamine	2.36
Isobutyl ethanoate	1.73	Dibutylamine	2.38
Pentyl ethanoate	1.84	Trimethylamine	2.35
Isopentyl ethanoate	1.62	Triethylamine	2.36
Hexyl ethanoate	1.66	Nitromethane	2.95
Methyl propanoate	2.15	Nitroethane	2.72
Ethyl propanoate	1.97	1-Nitropropane	2.45
Propyl propanoate	1.79	2-Nitropropane	2.30
Pentyl propanoate	1.55	1-Nitrobutane	2.27
Methyl butanoate	2.08	1-Nitropentane	2.07
Ethyl butanoate	1.83	*N*-Butylacetamide	6.83
Propyl butanoate	1.67	*N*,*N*-Dimethylformamide	5.73

TABLE III
(*Continued*)

Compound	log L^W	Compound	log L^W
Ethanoic Acid	4.91	2-Butoxyethanol	4.59
Propanoic Acid	4.74	2,2,2-Trifluoroethanol	3.16
Butanoic Acid	4.66	Ethanethiol	0.84
Pentanoic Acid	4.52	Propane-1-thiol	0.78
3-Methylbutanoic Acid	4.47	Butane-1-thiol	0.73
Hexanoic Acid	4.56	Diethyl sulfide	1.07
Water	4.64	Dipropyl sulfide	0.94
Methanol	3.74	Diisopropyl sulfide	0.89
Ethanol	3.67	Diethyl disulfide	1.20
Propan-1-ol	3.56	Sulfur hexafluoride	–2.23
Propan-2-ol	3.48	Dimethyl sulfide	1.18
Butan-1-ol	3.46	Ethyl methyl sulfide	1.10
2-Methylpropan-1-ol	3.30	Dimethyl sulfoxide	7.41
Butan-2-ol	3.39	*N*-Acetylpyrrolidine	7.19
2-Methylpropan-2-ol	3.28	*N*-Methylpiperidine	2.85
Pentan-1-ol	3.35	Morpholine	5.26
Pentan-2-ol	3.22	*N*-Methylmorpholine	4.64
Pentan-3-ol	3.19	Pyridine	3.44
2-Methylbutan-1-ol	3.24	2-Methylpyridine	3.40
3-Methylbutan-1-ol	3.24	3-Methylpyridine	3.50
2-Methylbutan-2-ol	3.25	4-Methylpyridine	3.62
Hexan-1-ol	3.23	2,3-Dimethylpyridine	3.54
Hexan-3-ol	2.98	2,4-Dimethylpyridine	3.57
2-Methylpentan-2-ol	2.88	2,5-Dimethylpyridine	3.46
4-Methylpentan-2-ol	2.74	2,6-Dimethylpyridine	3.37
2-Methylpentan-3-ol	2.85	3,4-Dimethylpyridine	3.83
Heptan-1-ol	3.09	3,5-Dimethylpyridine	3.55
Octan-1-ol	3.00	2-Ethylpyridine	3.18
Nonan-1-ol	2.85	3-Ethylpyridine	3.37
Decan-1-ol	2.67	4-Ethylpyridine	3.47
Cyclopentanol	4.03	2-Chloropyridine	3.22
Cyclohexanol	4.01	3-Chloropyridine	2.94
Cycloheptanol	4.02	Pyridine-3-carbonitrile	4.95
Prop-2-en-1-ol	3.69	Pyridine-4-carbonitrile	4.42
2-Methoxyethanol	4.96	Pyridine-3-carbaldehyde	5.21
2-Ethoxyethanol	4.91	Pyridine-4-carbaldehyde	5.14
2-Propoxyethanol	4.70	3-Acetylpyridine	6.06

TABLE III
(*Continued*)

Compound	log L^W	Compound	log L^W
4-Acetylpyridine	5.59	Nitrobenzene	3.02
Quinoline	4.20	1-Methyl-2-nitrobenzene	2.63
2-Methylpyrazine	4.04	1-Methyl-3-nitrobenzene	2.53
2-Ethylpyrazine	4.00	Benzamide	8.07
2-Isobutylpyrazine	3.70	Phenylmethanol	4.86
Thiophene	1.04	2-Phenylethan-1-ol	4.98
2-Methylthiophene	1.01	3-Phenylpropan-1-ol	5.08
Benzene	0.63	Methoxybenzene	1.80
Toluene	0.65	Ethoxybenzene	1.63
Ethylbenzene	0.58	Methyl phenyl sulfide	2.00
o-xylene	0.66	2-Methylaniline	4.06
m-xylene	0.61	4-Methylaniline	4.09
p-xylene	0.59	2,6-Dimethylaniline	3.82
Propylbenzene	0.39	2-Chloroaniline	3.60
Isopropylbenzene	0.22	3-Chloroaniline	4.27
1,2,3-Trimethylbenzene	0.89	4-Chloroaniline	4.33
1,2,4-Trimethylbenzene	0.63	2-Methoxyaniline	4.49
1,3,5-Trimethylbenzene	0.66	3-Methoxyaniline	5.35
1-Ethyl-2-methylbenzene	0.76	4-Methoxyaniline	5.49
1-Ethyl-4-methylbenzene	0.70	2-Nitroaniline	5.41
Butylbenzene	0.29	3-Nitroaniline	6.49
Isobutylbenzene	–0.12	4-Nitroaniline	7.54
sec-Butylbenzene	0.33	*N*-Methylaniline	3.44
tert-Butylbenzene	0.32	*N*,*N*-Dimethylaniline	2.53
1-Isopropyl4-methylbenzene	0.50	Phenol	4.85
Pentylbenzene	0.17	2-Methylphenol	4.31
Hexylbenzene	0.03	4-Methylphenol	4.50
Styrene	0.91	2,3-Dimethylphenol	4.52
2-Phenyl-1-propene	0.91	2,4-Dimethylphenol	4.41
Benzaldehyde	2.95	2,5-Dimethylphenol	4.34
4-Methylbenzaldehyde	3.13	2,6-Dimethylphenol	3.86
Acetophenone	3.36	3,4-Dimethylphenol	4.77
4-Methylacetophenone	3.45	3,5-Dimethylphenol	4.60
4-Methoxyacetophenone	3.23	3-Ethylphenol	4.59
Methyl benzoate	2.88	4-Ethylphenol	4.50
Ethyl benzoate	2.67	4Propylphenol	4.33
Benzonitrile	3.09	4-*tert*-Butylphenol	4.34

TABLE III
(*Continued*)

Compound	log L^W	Compound	log L^W
2-Fluorophenol	3.88	1,2,4,5-Tetrachlorobenzene	0.98
4-Fluorophenol	4.54	1,2,3,5-tetrachlorobenzene	1.19
2-Chlorophenol	3.34	1,2,4,5-Tetrachlorobenzene	0.98
3-Chlorophenol	4.85	2-Chloro-1-mrthylbenzene	0.84
4-Chlorophenol	5.16	Bromobenzene	1.07
4-Chloro-3-methylphenol	4.98	4-Bromo-1-methylbenzene	1.02
4-Bromophenol	5.23	Iodobenzene	1.28
2-Iodophenol	4.55	Biphenyl	1.95
2-Methoxyphenol	4.09	Naphthalene	1.76
3-Methoxyphenol	5.62	1-Methylnaphthalene	1.79
3-Hydroxybenzaldehyde	6.97	1,3-Dimethylnaphthalene	1.81
4-Hydroxybenzaldehyde	6.48	1,4-Dimethylnaphthalene	2.07
3-Hydroxybenzonitrile	7.08	2,3-Dimethylnaphthalene	2.04
4-Hydroxybenzonitrile	7.46	2,6-Dimethylnaphthalene	1.93
2-Nitrophenol	3.36	1-Ethylnaphthalene	1.76
3-Nitrophenol	7.06	Indane	1.07
4-Nitrophenol	7.81	1,2-Dihydroacenaphthylene	2.31
Benzenethiol	1.87	Fluorene	2.46
Fluorobenzene	0.59	1-Naphthylamine	5.34
(Trifluoromethyl)benzene	0.18	2-Naphthylamine	5.48
Chlorobenzene	0.82	1-Naphthol	5.63
1,2-Dichlorobenzene	1.00	2-Naphthol	5.95
1,3-Dichlorobenzene	0.72	Anthracene	2.90
1,4-Dichlorobenzene	0.74	Phenanthrene	2.85
1,2,3-Trichlorobenzene	0.91	Pyrene	3.32
1,2,4-Trichlorobenzene	0.82	Triethyl phosphate	5.53
1,3,5-Trichlorobenzene	0.57		

[a] 2-Bromo-2-chloro-1,1,1-trifluoroethane; [b] 2-Bromo-1,1,1,2-tetrafluoroethane; [c] 2,2-Dichloro-1,1-difluoro-1-methoxyethane; [d] 1-Chloro-1-(difluoromethoxy)-2,2,2-trifluoroethane. Note: http://webbook.nist.gov/chemistry is great source of chemical name/property information.

sure of the cross correlation, satisfied, VIF < 5. Outliers were compounds with residuals ≥3 standard deviation.

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