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USING THEORETICAL DESCRIPTORS IN STRUCTURE–ACTIVITY RELATIONSHIPS: SOLUBILITY IN SUPERCRITICAL CO_2

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The use of quantitative structure–activity relationships (QSAR) in correlating biological phenomena to chemical structure, and the use of linear free energy relationships (LFER) and linear solvation energy relationships (LSER) for correlating physical phenomena are becoming standard occurrences. In this work the empirical LSER solvatochromic descriptors were replaced with a computationally derived set to aid in *a priori* property prediction. This paper deals with the application of this descriptor set to correlating the solubilities of 22 compounds in super critical CO_2. A reasonable correlation, consistent with previous correlations by other researchers, was found.

INTRODUCTION

The solubility of aromatic compounds in supercritical fluids has been the topic of several recent studies.[1–3] Politzer *et al.*[4] found correlations when comparing the solubilities of nine indoles in supercritical CO_2, ethane, ethylene and trifluoromethane with two computational parameters. Politzer *et al.*[5] extended the initial dataset to include a total of 22 mostly aromatic compounds, correlating the solubility of these compounds in supercritical CO_2. They found a two-parameter equation, one describing the molecular volume and the other the variance in electrostatic potential, to provide the best correlative ability with the dataset examined. The conclusions arrived at were in complete accord with qualitative observations found previously, and with experimental evidence.

Quantitative structure–activity relationships (QSAR) have become widely used to correlate molecular structural features with their known biological, chemical and physical properties. QSAR assumes that there is a quantifiable relationship between microscopic (molecular) and macroscopic (empirical) properties in a compound or set of compounds. One such set of relationships applied to physical organic chemistry was the linear free energy relationship, reviewed first by Burkhardt[6] and Hammett,[7] and later quantified by Hammett.[8] A recent survey of LFER techniques and a discussion of the background was given by Exner.[9]

An enormous number of descriptors have been used by researchers to increase the ability to correlate a given property. A relatively new approach in the QSAR field has been an attempt to develop a single set of parameters for use with any data set, for any property. The advantage of this methodology is obvious: one is able immediately and directly to compare different data sets and different activities and have a base of reference. Taft, Kamlet and co-workers promulgated this philosophy with the solvatochromic parameters for use in the linear solvation energy relationship (LSER).[10–16] An extension of the LFER, the LSER, provides the basis for correlating any solute/solvent-based property with three distinct (and orthogonal) terms. The generalized LSER equation is

$$\log(\text{property}) = \text{bulk/cavity} + \text{polarizability/dipolarity} + \text{hydrogen bonding} \quad (1)$$

The strong point of the LSER methodology has been the ability to correlate a wide range and number of biological, physical and chemical properties involving solute–solvent interactions. By using the solva-

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tochromic descriptors, this has led to a much better understanding of the effects of solvent on many properties.[14,15,17,18]

However, the LSER parameters are limited in their ability to make *a priori* predictions because of their empirical nature. Although there are tables of LSER parameters and predictive relations to help in their estimation, LSER values complex molecules are not as easily found. Several attempts have been made to formulate 'rules-of-thumb' and to correlate the solvatochromic descriptors with computed descriptors.[19-23]

In the past, theoretical chemistry has been used to provide descriptors for QSAR and QSAR-like relationships.[24-31] Ford and Livingstone[32] pointed out the advantages of using computationally derived descriptors over extra-thermodynamically derived descriptors such as π and σ. Computational descriptors describe clearly defined molecular properties, making the interpretation of the QSAR equation generally more straightforward.

Based on the LSER methodology, we have developed a new set of theoretically derived parameters for correlations in QSAR relationships.[33,34] Termed the theoretical linear solvation energy relationship (TLSER), this methodology has been applied to a number of diverse data sets correlating general toxicity, specific receptor-based toxicity, solute/solvent-based physical properties, and UV–visible absorption shifts.[35-40]

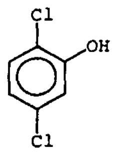
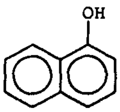
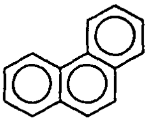
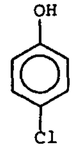
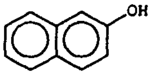
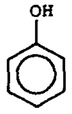
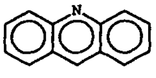
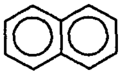
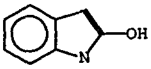
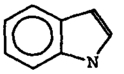
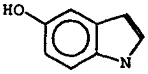
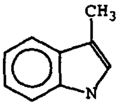
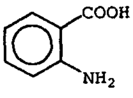
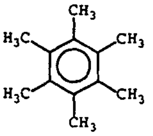
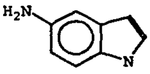
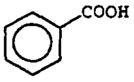
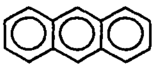
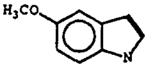
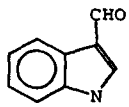
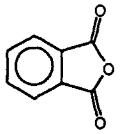
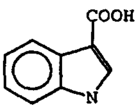
In this paper, we report our efforts to obtain the LSER correlation and predictive equations for the solubility of 22 solutes in supercritical carbon dioxide studied by Politzer *et al.*[5] In this way, a correlation different from, yet complementary to, the Politzer equation can be obtained. This will permit a further understanding and characterization of the processes which influence solubility in supercritical fluids. We also report the extension of the TLSER to compounds for which there are no measured solubility values, and compare these predictions to the predictions of Politzer *et al.*[41]

METHODS

All geometries were optimized using the MNDO algorithm as contained within MOPAC v6.0.[42,43] Table 1 lists the compounds used in this study. The solubility values in supercritical carbon dioxide were taken from several different sources, all at 308 K.[1-3,44,45] Visualization and structure entry were performed using the in-house developed Molecular Modeling Analysis and Display System and PC Model[46] (the program is marketed by Serena Software, Bloomington, IN, USA). All multiple regressions were performed using Minitab (the program is marketed by Minitab, State College, PA, USA).

The TLSER descriptors were taken directly from the MNDO calculations. These descriptors consist of six

Table 1. Compounds used

No.	Structure	No.	Structure
1		12	
2	$Cl_3C—CCl_3$	13	
3		14	
4		15	
5		16	
6		17	
7		18	
8		19	
9		20	
10		21	
11		22	

molecular parameters that attempt to describe the important features involved in solute–solvent interactions. These parameters were developed from and are modeled after the LSER methodology. The same generalized equation as the LSER, as shown in equation (1), is applicable to the TLSER.

The bulk/steric term of the TLSER is described by the molecular van der Waal's volume (V_{mc}), given in Å^3, and is computed by the method of Hopfinger.[47] The dipolarity/polarizability term uses the polarizability index (π_{i}) obtained by dividing the polarization volume[48,49] by the molecular volume to obtain a unitless quantity.[50] The resulting π_{i} is not generally correlated with V_{mc} and defines the ability of electron cloud to be polarized by an external field.

The hydrogen bonding term from equation (1) is divided into two effects in the LSER approach, a hydrogen bond acidity (HBA) and a hydrogen bond basicity (HBB). In the TLSER, the HBA and HBB effects are further subdivided into two contributions each, covalent acidity and basicity, and electrostatic acidity and basicity. The covalent HBB contribution is defined as the molecular orbital basicity (ε_β), and is computed by subtracting the energy of the highest occupied molecular orbital (HOMO) in the substrate from the energy of the lowest unoccupied molecular orbital (LUMO) of water. The covalent HBA contribution is the molecular orbital acidity (ε_α), and is computed in an analogous manner, with the energy of the HOMO of water being subtracted from the energy of the LUMO of the substrate. The electrostatic HBB, or the electrostatic basicity (q^-), is the magnitude of the most negative formal charge in the molecule. The electrostatic acidity (q^+) is the value of the most positive hydrogen. Both q^+ and q^- are derived directly from the Mulliken charges. The general form for this equation, then, is

$$\log P = P_0 + aV_{\mathrm{mc}} + b\pi_{\mathrm{i}} + c\varepsilon_\beta + dq^- + e\varepsilon_\alpha + fq^+ \quad (2)$$

P is the property of interest and P_0 is the intercept. It is important to note that although there are six descriptors in the generalized model, most correlations reduce to a 2–4-parameter equation.

RESULTS AND DISCUSSION

The resulting TLSER regression correlating the solubility of the 22 solutes in Table 1 with the solubility in supercritical CO_2 at 14 MPa and 308 K is as follows, where all solubilities are in mole fraction:

$$\log S_{\mathrm{CO_2}}^{14\,\mathrm{MPa}} = -6{\cdot}037\pi_{\mathrm{i}} + 10{\cdot}440\varepsilon_\beta - 22{\cdot}098q^- + 24{\cdot}350q^+ - 8{\cdot}370 \quad (3)$$

$$N = 19,\ R = 0{\cdot}928,\ s = 0{\cdot}477,\ F = 22$$

Table 2 shows the significant TLSER parameters, and the observed solubilities, predicted solubilities, and the residuals. Three compounds were found to be outliners (residuals of greater than two standard deviations) and were removed from the regression. These were benzoic acid (**9**), phthalic anhydride (**11**), and acridine (**15**). All parameters were significant at the $t = 0{\cdot}95$ level.

An analogous relationship was developed for the

Table 2. TLSER descriptors and observed and predicted solubility in CO_2 at 14 MPa

					Log S^a		
No.	π_{i}	ε_β	q^-	q^+	Observed	Predicted	Residual
1	0·1348	14·8516	0·2352	0·2107	−1·201	−1·071	−0·130
2	0·1249	14·8524	0·0649	0·0000	−1·638	−1·839	0·201
3	0·1345	14·5857	0·2432	0·1968	−1·745	−1·845	0·100
4	0·1292	14·3309	0·2485	0·1926	−1·824	−2·011	0·187
5	0·1463	14·0169	0·0576	0·0599	−1·845	−2·384	0·539
6	0·1390	13·7806	0·2467	0·2049	−2·305	−2·838	0·533
7	0·1365	13·7436	0·2431	0·2062	−2·523	−2·614	0·091
8	0·1262	14·4734	0·0670	0·0004	−2·775	−2·350	−0·425
10	0·1366	13·8613	0·2355	0·1945	−2·804	−2·614	−0·190
12	0·1456	13·7997	0·2519	0·1940	−2·886	−3·596	0·710
13	0·1563	13·9208	0·0581	0·0613	−3·022	−3·065	0·042
14	0·1493	13·8593	0·2483	0·1923	−3·356	−3·719	0·363
16	0·1455	13·6153	0·2447	0·2183	−3·461	−3·032	−0·429
17	0·1462	13·7509	0·2527	0·1890	−3·943	−3·823	−0·120
18	0·1309	14·5949	0·3530	0·2137	−4·023	−3·633	−0·389
19	0·1464	13·7033	0·2292	0·1878	−4·071	−3·395	−0·676
20	0·1625	13·4916	0·0567	0·0600	−4·222	−3·888	−0·334
21	0·1427	14·1646	0·3275	0·2115	−4·921	−4·285	−0·636
22	0·1417	14·1644	0·3889	0·2123	−5·000	−5·562	0·562

[a] S is in units of mole fractions.

Table 3. TLSER descriptors and observed and predicted solubility in CO_2 at 20 MPa

No.	π_i	ε_β	q^-	q^+	Log S^a Observed	Log S^a Predicted	Residual
1	0·1348	14·8516	0·2352	0·2107	−1·004	−0·698	−0·306
2	0·1249	14·8524	0·0649	0·0000	−1·420	−1·614	0·194
3	0·1345	14·5857	0·2432	0·1968	−1·561	−1·591	0·030
4	0·1292	14·3309	0·2485	0·1926	−1·770	−1·966	0·197
5	0·1463	14·0169	0·0576	0·0599	−1·770	−2·318	0·549
6	0·1390	13·7806	0·2467	0·2049	−2·260	−2·934	0·675
7	0·1365	13·7436	0·2431	0·2062	−2·488	−2·778	0·290
8	0·1262	14·4734	0·0670	0·0004	−2·750	−2·300	−0·450
10	0·1366	13·8613	0·2355	0·1945	−2·745	−2·712	−0·033
11	0·1384	16·0102	0·2780	0·0861	−2·648	−2·821	0·173
13	0·1563	13·9208	0·0581	0·0613	−2·903	−2·884	−0·019
14	0·1493	13·8593	0·2483	0·1923	−3·254	−3·587	0·333
16	0·1455	13·6153	0·2447	0·2183	−3·367	−3·125	−0·241
17	0·1462	13·7509	0·2527	0·1890	−3·854	−3·790	−0·064
18	0·1309	14·5949	0·3530	0·2137	−3·947	−3·309	−0·638
19	0·1464	13·7033	0·2292	0·1878	−4·046	−3·412	−0·633
20	0·1625	13·4916	0·0567	0·0600	−4·161	−3·829	−0·332
22	0·1417	14·1644	0·3889	0·2123	−4·959	−5·235	0·276

[a] S is in units of mole fraction.

solubility at 20 MPa, with the same descriptors being significant (again, at the $t = 0{\cdot}95$ level). This correlation is

$$\log S^{20\,\mathrm{MPa}}_{\mathrm{CO_2}} = -4{\cdot}374\pi_i + 15{\cdot}674\varepsilon_\beta - 20{\cdot}783q^- + 23{\cdot}207q^+ - 18{\cdot}083 \quad (4)$$

$$N = 18,\ R = 0{\cdot}939,\ s = 0{\cdot}431,\ F = 24$$

The TLSER descriptors, observed and predicted solubilities, and residuals are shown for this regression are shown in Table 3. Solubilities at 20 MPa were not available for naphthol (**12**) and the indole-3-carbaldehyde (**21**), and therefore could not be included in the regression. Further, acridine was again found to be an outlier and was deleted from the regression.

It is not readily apparent why acridine, benzoic acid and phthalic anhydride are outliers. Acridine and phthalic anhydride were predicted to be less soluble than they were. Benzoic acid was predicted to be two standard deviations more soluble. Decreasing the electrostatic basicity of the former and decreasing the electrostatic acidity of the latter would bring them into line. It is possible that adding the hydrogen bonding gaussians by deriving the TLSER descriptors from either AM1 or PM3 would alleviate these descriptors, although initial indications on an unrelated data set do not suggest this.[51]

By examining the coefficients and t-scores of each variable in the regression, it is possible to speculate about important aspects of the solubility in supercritical carbon dioxide. The electrostatic basicity term, q^-, is negative, suggesting an inverse relationship between basicity and solubility. Likewise, the molecular orbital basicity is positive, indicating a similar inverse relationship. It is not readily apparent why the basicity terms are significant in this equation, as CO_2 cannot act as a hydrogen bonding acid (or as a Lewis acid). Because of the inverse relationship between basicity and solubility, one possible explanation is that in actuality the acidity of the substrate is being accounted for. The electrostatic acidity term, q^+, is positive, suggesting increasing that the hydrogen bonding acidity of the substrate would increase the solubility. The coefficient of the final term in the regression, π_i, is negative, indicating that an increase in polarizability of the solute decreases solubility. This would imply that less polarizable, or 'harder,' solutes would be more soluble than more polarizable, or 'softer,' solutes. If one assumes carbon dioxide to be more 'hard' than 'soft', this is entirely consistent with both the Pearson[52] and Drago[53] models of acidity and basicity.

The t-score, as given in Table 4 for both equations, gives the relative rankings of each of the descriptors. As

Table 4. t-Scores for equations (3) and (4)

Equation	π	ε_β	q^-	q^+
3	−3·38	2·43	−7·64	6·24
4	−3·44	5·76	−8·01	6·67

expected, the 'hard' terms, q^+ and q^-, are the most significant, followed by π_i and ε_β. This is entirely consistent with arguments given above.

In order to determine the cross-correlations of the independent variables for each equation, the variance inflation factors (VIF) were calculated, and are given in Table 5. The VIF is the correlation of how well a given independent variable correlates against all other independent variables and is usually displayed as $1/(1-R^2)$, where R is the correlation coefficient for the regression.[54] A VIF of 1·0 indicates no correlation between the examined independent variable and all others. Cut-offs for acceptable values of the VIF vary, but are typically between 8 and 10. As is evident in Table 5, the maximum value is 7·1 (for q^+), coming close to the cut-off, but still within acceptable limits.

Comparison of the TLSER-derived correlation with the Politzer-derived equation (4) is possible. First, the correlation coefficients are fairly close, for the 14 MPa case the Politzer equation gives 0·948, and with the 20 MPa regression a correlation coeficient of 0·931 is achieved. Second, the TLSER correlations indicate the same conclusions as reached by Politzer *et al.* The TLSER parameters may be viewed as having the further advantage, however, of being able to separate the acidity and basicity effects, and to separate the covalent from the electrostatic interactions.

Politzer *et al.*[41] also reported the use of their equation for predicting the solubility of several highly toxic organosulfur and organophosphorus compounds. In addition, they predicted the solubility of several simulants. A simulant is defined as a chemical compound (or mixture) that exhibits the same activities or properties of interest as the agent, but is non-toxic. It is useful to compare the Politzer-derived predictions for these compounds against the TLSER predictions.

Table 6 displays the predicted values from the Politzer equation and the TLSER equation for three compounds, bis(2-chloroethyl) sulfide (HD, mustard), isopropyl methylphosphonofluoridate (GB, Sarin) and *O*-ethyl *S*-(diisopropylaminoethyl) methylphosphonothiolate (VX). In addition, the solubilities for five simulants have also been predicted, dichloropentane (HD simulant), hydroxyethyl ethyl sulfide (HD simulant), diethyl methylphosphonate (GB simulant), *p*-fluorobenzyl alcohol (GB simulant) and diisopropylaminoethanol (VX simulant). Except for two cases (VX, diethyl methylphosphonate), the agreement between the two methodologies is fairly good. This is surprising given the difference in molecular orbital techniques (*ab initio* versus semi-empirical) and the methodology (electrostatic potential versus charges and molecular orbital energies).

Table 5. Variance inflation factors for equations (3) and (4)

Equation	π	ε_β	q^-	q^+
3	2·4	2·6	7·0	7·1
4	1·5	1·6	6·5	6·9

Table 6. Predicted solubilities of compounds and simulants in supercritical CO_2 (14 MPa)

	Solubilities (mole fraction)	
Compound	Politzer equation	This work
HD	$2{\cdot}02\times10^{-2}$	$6{\cdot}62\times10^{-3}$
GB	$1{\cdot}85\times10^{-11}$	$1{\cdot}41\times10^{-10}$
VX	$7{\cdot}10\times10^{-8}$	$2{\cdot}24\times10^{-13}$
Dichloropentane	$1{\cdot}33\times10^{-2}$	$1{\cdot}78\times10^{-1}$
Hydroxyethyl ethyl sulfide	$1{\cdot}64\times10^{-3}$	$3{\cdot}60\times10^{-2}$
Diethyl methylphosphonate	$2{\cdot}80\times10^{-8}$	$1{\cdot}593\times10^{-12}$
p-Fluorobenzyl alcohol	$5{\cdot}51\times10^{-4}$	$8{\cdot}10\times10^{-4}$
Diisopropylaminoethanol	$8{\cdot}53\times10^{-6}$	$4{\cdot}54\times10^{-6}$

CONCLUSION

The TLSER descriptors provide a very good correlation for solubility in supercritical carbon dioxide. The dataset used in this correlation is admittedly small and fairly limited. The correlations described here are nearly as accurate as the higher level, *ab initio* quantum chemical, dual-parameter relationships derived by Politzer *et al.* Further, the TLSER relationship developed here is readily comparable to other TLSER derived relationships. Both the TLSER and the Politzer equation prediced similar values for three compounds and six simulants, with two exceptions.

It should also be noted that the TLSER descriptors represent additional effects other than those strictly accounted for in the generalized LSER sense. Indeed, taken separately, such phenomena as charge transfer and Lewis acidity could be readily parameterized to these descriptors. However, this consistent set of descriptors was developed within the context of the LSER method, and within this framework can be used to describe solute–solvent interactions. Because most of the compounds considered in past regressions have been monofunctional, no attempt has been made to consider multiple acceptor or donor sites.

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