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Linear free energy relationship analysis of the solubility of solids in supercritical CO_2

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epoc ABSTRACT: Linear free energy relationship (LFER) methods were used to construct a model for the solubility of a species in supercritical CO_2. The final model was based on 64 molecules and 782 data points, employing a modified version of the Abraham LFER equation incorporating π^1, the dipolarity/polarizability of the CO_2 at a given density. This allowed us to model data ranging from 308 to 435 K and 74.3 to 410 bar, with an accuracy of ±0.65 log mole fraction units. The model shows that solubility in supercritical CO_2 is favoured by the presence of π and n electron pairs and hydrogen-bond basicity. Solute size and hydrogen-bond acidity are less important, whereas polarity/polarizability is statistically insignificant. Copyright © 2001 John Wiley & Sons, Ltd.
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KEYWORDS: supercritical carbon dioxide; LFER; hydrogen bonding

INTRODUCTION

Supercritical fluids, such as CO_2, have many distinct properties that make them highly important solvents in many industrial reactions. Examples of such processes are decaffeination of coffee,[1] extraction of hops,[2] spices[3] and seed oils.[4,5] Supercritical solvents are highly tuneable, so can be used to extract thermally sensitive material at low temperature.[6,7] The recovery of a solute from a supercritical solvent is easily achieved by simple changes in the operating conditions. Supercritical CO_2 is of particular interest industrially as it is non-flammable, inert, inexpensive, non-toxic and unregulated. The highly tuneable nature of supercritical CO_2 allows the solvating power of the solvent to be controlled, *i.e.* the solvating power of the CO_2 increases as its pressure is raised. Owing to these properties, supercritical CO_2 has been used industrially as a solvent for sensitive extracting/separating reactions where the purity of the extracted material must be of a very high standard.

The ability to predict accurately the solubility of a molecule in supercritical CO_2 is of great industrial importance. There have been many studies reported into the prediction of solubility. Famini and Wilson[8] used a theoretical linear solvation energy relationship (TLSER) to predict the solubility of 22 aromatic compounds in supercritical CO_2 at 14 MPa at 308 K and 20 MPa at 308 K. The TLSER method of Famini and Wilson[9] is a computational implementation of Kamlet and Taft's LSER approach. LSER models solvation properties as linear combinations of size, polarity, and hydrogen bonding terms: TLSER uses computed molecular properties for each of these terms.

Famini and Wilson's study of solubility in supercritical CO_2 produced the following equation for solvation at 14 MPa at 308 K:

$$\log S_{CO_2} = -6.037\pi_i + 10.440\varepsilon_\beta - 22.098q^- + 24.350q^+ - 8.370 \quad (1)$$

$$N = 19, R^2 = 0.928, SD = 0.477$$

where N is the number of data points in the model, R^2 is the square of the overall correlation coefficient and SD is the standard deviation. Although these statistics prove that the model is capable of predicting supercritical CO_2 solubility for a small set of similar molecules at the same temperature and pressure, it does not fully test the ability of the quantitative structure activity relationships (QSAR) predictive powers. Famini and Wilson's TLSER descriptors are calculated only for the most negative and positive formal charge in the molecule and, therefore, are only applicable to 1:1 complexes. This approach to calculation of the descriptors will cause the model to fail when there is multiple complexation.

Politzer *et al.*[10] initially used two computational

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parameters based on electrostatic potentials to find correlations when comparing the solubility of naphthalene and eight indoles in four supercritical fluids (C_2H_6, C_2H_4, CO_2 and CHF_3). They[11] then further defined three solute molecular properties: (a) surface area, (b) the sum of the variance between the positive and negative electrostatic potentials of the surface and (c) a balance term parameter, which indicates the extent to which a solute's positive and negative regions can interact. These three terms were used to model the solubility of 22 aromatic molecules in various supercritical fluids with impressive accuracy. Bush and Eckert[12] created a model of solubility in supercritical CO_2 based on the LFER developed by Kamlet *et al.*[13] The model was based on a data set of 35 molecules at a constant temperature and pressure of 308 K and 28.9 MPa. A model was produced with an average error of 65%.

A similar study has also been performed by Dongjin *et al.*[14] Here, the LFER approach of Abraham[15] was used to verify the proposed retention mechanism when performing supercritical fluid chromatography with CO_2, when an organic modifier is used with an octyldecylisilane-bonded phase in a packed capillary column. In that study the LFER equations were constructed for different concentrations of organic modifier, and it was shown that as the concentration of organic modifier increased the importance of a molecule size, polarizability and hydrogen-bond bascicity on solubility decreased.

We will use the LFER approach of Abraham,[15] in which the important solute–solvent interactions are separated out into five physiochemical properties or descriptors. In order to predict the properties of a series of solutes in a given solvent system (SP) the descriptors are combined to give the following LFER.

$$\log \mathrm{SP} = c + eE + sS + aA + bB + vV \qquad (2)$$

The descriptors are defined as follows:[15,16] *E* is the excess molar refraction, *i.e.* the molar refraction of the solute minus the molar refraction of an alkane of equivalent volume; *S* is a combined dipolarity/polarizability descriptor showing how polar or polarizable the species is; *A* is the total solute hydrogen bond acidity for the molecule; *B* is the total solute hydrogen bond basicity for the molecule; *V* is the Mcgowan characteristic volume.[17]

This equation has been developed for transfer processes involving two or more solutions, liquid or solid phases. These descriptors refer to particular physiochemical properties of the molecule, and are constant for a given molecule. The coefficients in Eqn. (2) (*e, s, a, b* and *v*) can be regarded as constants for a given system. It is these coefficients that contain the complimentary effects of the phase on the interactions for a given system.

The *e* coefficient indicates the ability of the phase to interact with solutes *via* π and *n* electron pairs. The *s* coefficient gives the tendency of the phase to interact with dipolar/polarizable solutes. The *s* coefficient also indicates how well the electrons in the solute will be polarized. The *a* and *b* coefficients are the hydrogen-bond basicity and the acidity of the phase respectively. The *v* coefficient is a combination of positive exoergic dispersion forces and a negative endoergic cavity term.

The relative size of these coefficients will allow us to determine the importance and influence of each descriptor for a given solute system. For example, the LFER model quoted by Abraham *et al.*[18] for octanol/water partition. This equation has a large positive *v*, such that larger molecules prefer octanol to water, and a large negative *b*, showing that water is much more H-bond acidic than octanol. *E* and *S* are less important, whereas *A* is insignificant in this treatment, which implies that water and octanol are of almost equal H-bond basicity.

Although this approach of Abraham has proven reliable in modelling many solvent systems, such as octanol, it does not allow for large changes in the density of the solvent. The highly tuneable nature of supercritical CO_2 and the range of temperatures and pressures in our dataset are accounted for by the addition of a sixth descriptor, π^1, to the LFER equation, as suggested by Lagalante and Bruno.[19] π^1 describes the polar/polarizability of the solvent at a specific density; it also gives a measure of the solvent's ability to induce dipolar phenomena in the solute, and is analogous to the *S* term of Abraham, except that it describes the chemical properties of the solvent and not the solute. Only *S* requires an analogous solvent term, as the other descriptor values for supercritical CO_2 have been proven constant over the gas/liquid density range, *via* measurement made using UV–visible solvatochromatic methods.[20]

The values for the Abraham descriptors were not observed, they were computationally derived using the group contribution approach of Platts *et al.*[16] In the method of Platts *et al.* the molecules are broken down by the computer into their substituent fragments; each of these fragments carries an associated value for Abraham's descriptor values. Each of these separate fragment values is then summed to give molecular descriptor values. It should be stated that this method of generating the descriptors is only an estimate of these descriptors, and, as such, could lead to cumulative errors for a large molecule. However, the main test of the errors involved in this process comes from its ability to reproduce experimental observation, as demonstrated by Platts *et al.*[21] for several large water/solvent data sets.

Solubility values (used here as $\log S_{CO_2}$, where *S* is the mole fraction) for molecules in CO_2 can be measured using numerous techniques.[22] There are four main categories into which all of these techniques fall, namely: (i) flow or dynamic, (ii) static, (iii) chromatographic, (iv) spectroscopic. The easiest and most common method for obtaining $\log S_{CO_2}$ values is *via* the flow dynamic method. As flow dynamic is the easiest and most reliable the vast majority of data used in this study was obtained from literature that used this method.

METHODS

A data set of solubility in supercritical CO_2 for 67 molecules at varying temperature and pressure was compiled from various references.[23–51] Nearly all of these values were acquired through the online solubility database.[52] These data were acquired from the references in the form of mole fraction, which was converted to log S_{CO_2}. The temperature range for these data was between 308 K and 433 K with a pressure range of between 74.3 and 410 bar.

In order to use the group contribution method of Platts *et al.*[21] the chemical structures of the molecule were converted to SMILES strings (simplified molecular input line entry system).[53] Abraham descriptors were then obtained for all of the molecules in our data set on an SGI O^2 computer. The remaining sixth descriptor, π^1, was calculated according to the following relation.[19,20]

$$\rho_r = \frac{\rho}{\rho_c} \tag{3a}$$

$$\pi^1 = 1.15\rho_r - 0.98 \quad (\rho_r < 0.7) \tag{3b}$$

$$\pi^1 = 0.173\rho_r - 0.37 \quad (\rho_r > 0.7) \tag{3c}$$

where ρ_r is the reduced density, ρ_c is the critical density of CO_2, and ρ is the density of supercritical CO_2. Values for CO_2 density and supercritical density were obtained from the NIST on-line Chemistry web book.[54]

Using these descriptors, coefficients were calculated for the solvation equation *via* multiple linear regression analysis (MLRA). The MLRA was carried out using the JMP statistical package published by SAS software. Once the descriptors and coefficients were calculated, the accuracy and validity of the model was checked using the following statistics: R^2 indicates how much of the variance of the original data set was being modelled successfully. The SD tests the accuracy of the predicted values generated by the model. The significance of individual coefficients was evaluated using the *t* ratio, *i.e.* the ratio of the regression coefficient to its standard error, which tests the significance of each coefficient. The cross-validated, or leave-one-out R^2 value (R^2_{cv}) was used as an indicator of internal self-consistency. The ability to combine data of different temperature and pressure *via* the sixth descriptor π^1 was tested by the remodelling of the final data without the π^1 descriptor.

RESULTS

A series of 830 log S_{CO_2} values was modelled successfully. The following LFER equation was obtained:

$$\log S_{CO_2} = 1.059 - 1.903E + 0.254S - 0.768A - 0.826B - 0.342V + 4.100\pi^1 \tag{4}$$

$$N = 830, R^2 = 0.718, \mathrm{RMS} = 0.777, R^2_{cv} = 0.715$$

Analysis of this model showed three main outliers whose predicted log S_{CO_2} values were more than two log units from that of the observed log S_{CO_2} values. The presence of these molecules clearly affects the accuracy and validity of the model. With the removal of these outliers from the regression the following equation was given:

$$\log S_{CO_2} = 1.124 - 1.796E + 0.09S - 0.661A - 1.116B - 0.220V + 4.292\pi^1 \tag{5}$$

$$N = 782, R^2 = 0.782, \mathrm{SD} = 0.659, R^2_{cv} = 0.779$$

The R^2 and R^2_{cv} show an increase of 0.06 upon removal of the outliers, whereas the SD shows a decrease of 0.12 log units from 0.78 log units to 0.66 log units. Although these statistics are inferior to those offered by the supercritical CO_2 model of Famini and Wilson[8] ($R^2 = 0.928$, SD = 0.477), our equation covers a wider range of values (−7.347 to −0.762 log units), a spread of over 6.5 log units). Our model also contains a wider range of molecules, many of which were multifunctional, and consists of values at different temperature and pressure.

A list of the outliers removed from Eqn. (4) is shown in Table 1. The calculated descriptor values for these outliers were checked by comparing the partition coefficient (log *P*) values calculated using the generated descriptors against the observed log *P* values for a number of different solvent systems. Observed log *P* values were obtained from the MedChem2000 database[55] the results are shown in Table 2. The log *P* values for *β*-carotene were not available from the MedChem database and could, therefore, not be analysed in this manner.

The large difference in observed and calculated values for piroxicam shows clearly that the error in predicting log S_{CO_2} values in our model for this molecule was caused by incorrect calculation of the descriptors. Piroxicam is a zwitterionic molecule, which may account for the errors in its calculation as the method used for obtaining descriptor values does not take this into account. For this reason piroxicam was removed from the model. By contrast, calculated descriptors give reasonable predic-

Table 1. Outliers removed from Eqn. (1)

Name	No. of points
β-Carotene	9
2,4-D	23
Piroxicam	16

Table 2. Observed and calculated log *P* values for outliers

	Piroxicam			2,4-D		
Solvent	Obs.[a]	Calc.	Error	Obs.[a]	Calc.	Error
Octanol	1.795	−0.647	2.442	2.729	2.656	0.073
Hexadecane	−1.52	−6.178	4.658			
PGDP	−0.07	2.752	−2.822			
CHCl3				1.2	2.301	−1.101
Air				7.75	6.499	1.251

[a] Taken from Ref. 48, averaged where several data reported.

tion of three log *P* values for 2,4-D. We omit this molecule from our final model, since it appears there might be some problem with the experimental values used. Although we could not analyse β-carotene using the same method to determine error we still removed it from the model. One possible explanation for the erroneous predicted values of β-carotene may be due to the fact that our model's descriptor values do not discriminate between *cis* and *trans* double bonds. The highly conjugated nature of β-carotene could magnify this effect and generate substantial errors in the calculated descriptors.

Analysis of the *t*-ratio for each individual coefficient in Eqn. (5) indicates that the *s* coefficient of the *S* descriptor is insignificant. All other descriptors are >99% significant. For this reason the *S* descriptor is omitted from the model, resulting in Eqn. (6) and the plot of observed versus calculated log S_{CO_2} shown in Fig. 1.

$$\log S_{CO_2} = 1.128 - 1.753E - 0.642A - 1.054B - 0.22V + 4.323\pi^1 \quad (6)$$

$$N = 782, R^2 = 0.782, SD = 0.659, R^2_{cv} = 0.780$$

To test the importance of the π^1 descriptor, and to see whether its use is warranted in this model, the data set was remodelled with the exclusion of the outliers, but this time the π^1 descriptor was omitted from the model to give us Eqn. (7):

$$\log S_{CO_2} = -0.088 - 1.7E - 0.38A - 1.21B + 0.268S - 0.08V \quad (7)$$

$$N = 782, R^2 = 0.694, SD = 0.782, R^2_{cv} = 0.689$$

From these statistics it can be seen clearly that the inclusion of π^1 significantly improves the quality of the results. With the removal of the π^1 descriptor we see a drop in R^2 of 0.088, and a drop in $R_{cv}{}^2$ of 0.091 compared with the statistics given by Eqn. (6). An increase of 0.123 is seen in the SD when compared with that of Eqn. (6).

The statistics of Eqn. (6) suggest that we can now predict new solubilities with an accuracy of around 0.65 log mole fraction units. This claim can be checked by splitting the data into training and test sets, constructed by the random removal of ~5% (31 data points), followed by remodelling of the remaining 751 data points. The new model was then used to predict the value of the test set, resulting in an SD of 0.649 log units. This supports our assertion that Eqn. (6) should be able to predict values of log S_{CO_2} for new molecules with an accuracy of approximately 0.65 log units.

Direct comparison of the coefficients in Eqn. (6) is hampered because values of π^1 cover a much lower range than the other descriptors. Instead, the relative importance of each descriptor in Eqn. (6) was assessed by analysis of the *t*-ratios, as listed in Table 3. The most significant term is *E*, with the largest *t*-ratio value and a large negative coefficient, implying that supercritical CO_2 is highly opposed to interacting with the substrate with a high density of π-and *n*-electron pairs. The *t*-ratios

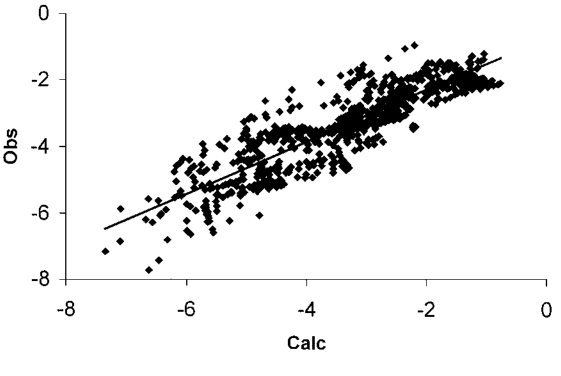

Figure 1. Observed versus, calculated log S_{CO_2} from Eqn. (6)

Table 3. Coefficients and *t*-ratios for Eqn. (6)

Term	Coefficient	S.E.	*t*-ratio
Intercept	1.128	0.108	10.428
E	−1.753	0.040	−44.148
A	−0.642	0.097	−6.628
B	−1.054	0.068	−15.576
V	−0.220	0.024	−8.975
π^1	4.323	0.239	18.071

show that the next most significant descriptor is π^1, which has a large positive coefficient, showing that the higher the density of the supercritical CO_2 the more the solute will be dissolved. Negative coefficient values are also given for A and B. A larger negative t-ratio is given by B with respect to A, indicating that the stronger a substrate's hydrogen bond basicity the less it will be solvated by the supercritical CO_2.

A small negative coefficient is also displayed by the size term V, revealing that for supercritical CO_2 the exoergic dispersion forces are dominated by the endoergic cavity term. From this it can be concluded that solubility in supercritical CO_2 is favoured if the volume/size of the substrate is small. As has already been stated the s coefficient of S was omitted from the equation, indicating that the polarity/polarizability of the substrate has no effect on its solubility. This is to be expected, as CO_2 has no permanent dipole for polar interaction.

The negative coefficients for E, A, and B can be rationalized by comparing the LFER equation given in this study to that of the LFER equation for the prediction of melting point given by Saunders and Platts.[56] The LFER for melting point shows a large positive coefficient for these descriptors, where a positive coefficient value indicates an increase in solid-state stability. Most of the molecules used to construct Eqn. (6) are solids in the conditions used, such that the stabilizing solid-state interactions must be disrupted before solvation in CO_2 can occur. Although this is not equivalent to melting, the similarity of the two equations strongly suggests that solid-state effects are an important factor in determining the solubility of solids in supercritical CO_2.

The two equations can be compared quantitatively by treating them as vectors and calculating the angle between them:[57] in this case, we calculate an angle of 137° between the LFERs for solubility in CO_2 and melting point. Thus there is clearly some relationship between these two processes, although there are also substantial differences between them. The main difference in the angle between vectors for these equations is due to the difference in a coefficient values. In contrast to Eqn. (3), the LFER equation for melting point shows a distinctively higher value for A than B. The contrast between these two equations implies that supercritical CO_2 has some H-bond basicity.

We can compare the properties we have proposed for the solubility in supercritical CO_2 to those proposed by Famini and Wilson.[8] Absolute comparisons cannot be drawn between our equation and that of Famini and Wilson as their descriptors are calculated using a different method, and also our model includes the sixth descriptor π^1 to account for the effects of temperature and pressure. Famini and Wilson's electrostatic basicity term, analogous to our B, also has a large negative coefficient. Famini and Wilson's equation shows a negative value for the dipolar/polarizability term, analogous to our S term. The value of the coefficients for Famini and Wilson's polar descriptor is much less than that of the electrostatic basicity. Famini and Wilson also report a positive electrostatic acidity term, suggesting that an increase in hydrogen-bonding acidity in the substrate would increase its solubility, again implying that supercritical CO_2 has hydrogen bond basic properties.

Famini and Wilson state that these values are due to the fact that CO_2 is harder 'non-polarizable' rather than soft 'polarizable' and that harder solutes are more soluble than soft solutes. This is consistent with both the Pearson[58] and the Vogel and Drago[59] models of acidity and basicity. They also show that the significance of the harder terms, electrostatic acidity and basicity, is far higher than those of the soft terms, such as polarizability. These conclusions are consistent with our findings.

Abraham's descriptors for hydrogen-bond acidity and basicity are composites of both hard and soft terms, unlike those of Famini and Wilson, and we therefore cannot conclude anything about hardness and softness. However, the non-significance of the S term shows that polarity of a species is insignificant to its solubility in supercritical CO_2, consistent with the conclusions of Famini and Wilson.

CONCLUSIONS

We have developed a model for the prediction of solubility in supercritical CO_2 based on 64 molecules and 782 data points. The model had a temperature range from 308 to 435 K and a pressure range of 74.3 to 410 bar. A good correlation between observed and calculated results is seen, with an R^2 value of 0.782 and an SD value of 0.659 log units. The predictive power of the model was further tested by the development of a test set of data. This indicates that our model can predict log S_{CO_2} values to ± 0.65 log units.

The LFER equation given by our model has a very large positive coefficient value for the π^1 descriptor. The equation also showed relatively large negative coefficient values for the hydrogen-bond basicity B and the excess molar refraction E, with smaller negative terms for hydrogen-bond acidity and volume. The polarity/polarizability descriptor S was insignificant in the regression. From these coefficient values it was determined that solubility in supercritical CO_2 is increased if the density of the CO_2 is increased. The solubility of a species in CO_2 will therefore be favoured if its π- and n-electron density and hydrogen-bond basicity is low. To a lesser extent the solubility in supercritical CO_2 is favoured if the molecule is small and if its hydrogen-bond acidity is low.

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