The factors that influence solubility in perfluoroalkane solvents

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ABSTRACT

Data on the solubility of neutral compounds in perfluoro-hexane, -heptane, and —octane have been obtained from the literature. It is shown that water-solvent and gas-solvent partition coefficients, P and K respectively, are effectively the same for all three perfluoroalkanes. Linear free energy relationships, LFERs, have been set up for these partition coefficients, as log P and log K. Comparison of the LFER coefficients in the log K equation for perfluoroheptane with those for a large number of other solvents shows that perfluoroheptane is an unusual solvent, in that small nonpolar solutes are more soluble than in other solvents. The comparative solubility of small nonpolar gaseous compounds in perfluoroheptane is due to a combination of cavity and interaction terms. Calculations using Pierotti's version of Scaled Particle Theory indicates that the solute-perfluoroheptane unfavourable cavity term is always smaller than that for solution in other solvents, which by itself would lead to enhanced solubilities in perfluoroheptane, as shown by small nonpolar solutes. As the solute becomes larger and more polar, the favourable interaction terms in other organic solvents become much larger than the corresponding interaction terms in perfluoroheptane. This results in the larger and/or more polar gaseous solutes being much more soluble in other organic solvents than in perfluoroheptane.

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1. Introduction

The perfluoroalkanes are interesting solvents; they are very insoluble in water, have low values of surface tension, viscosity and refractive index, and have remarkably high vapor pressures. They dissolve gases such as oxygen reasonably well [1], and have been suggested as oxygen-carriers for biological applications, and as components of drug and drug delivery systems [1]. Perfluoroalkanes, such as perfluorooctane, are also widely used in ophthalometry [2]. Although the solubility of permanent gases in perfluoroalkanes has been reviewed [3], there has been no general analysis of solubility in the perfluoroalkanes, and no general quantitative analysis of the factors involved. Duce et al. [4–6] have shown that fluoroalkanes interact weakly with themselves and with ethers and alkanes. Schwarz et al. [7] have combined ^{19}F NMR and ^{13}C NMR experiments on perfluorononane with quantum chemical modelling to show that perfluorononane has a quite rigid structure in which delocalised fluorine p-electrons cover the entire surface of the molecule. They suggest that this structure leads to large size cavities in the liquid which can retain high quantities of dissolved gases. However, the solubility of hydrogen, nitrogen and oxygen in perfluoroheptane is actually less than in hexane [8], in terms of the Ostwald solubility, so other factors must be at work. We therefore collected data on the solubility of compounds in the perfluoroalkanes [3–5,9–32], and then applied our linear free energy equations in order to deduce the general factors that influence solubility.

2. Methods

Our method of analysis is based on a cavity model of solvation, in which the solvation process is conceptually broken down into three steps. In the first step a cavity of suitable size and shape to accommodate the solute is created in the solvent. This requires breaking intermolecular interactions between the solvent molecules. In the second step, the solute occupies the cavity, and in the third step various solute-solvent interactions are set up between the solute and the surrounding solvent molecules. If we consider a situation in which the solvent remains constant and only the solute changes, we only need descriptors or properties of the solute in order to construct a mathematical model for this 'cavity approach'.

Symbols

Cs	solubility in a solvent
Cw	solubility in water
Ks	a gas-solvent partition coefficient
Kw	a gas-water partition coefficient
P	a water-solvent partition coefficient
$Poct$	the water-octanol partition coefficient
E	the solute excess molar refractivity in units of $(cm^3\ mol^{-1})/10$
S	the solute dipolarity/polarizability
A	overall or summation hydrogen bond acidity
B	overall or summation hydrogen bond basicity
V	the McGowan volume in units of $(cm^3\ mol^{-1})/100$
V_1	solvent molar volume
L	log $Khex$ where $Khex$ is the gas-hexadecane partition coefficient at 298 K
R_G	solute size parameter
y	reduced number density
σ	hard-sphere diameter
LFER	linear free energy relationship
PCA	principle component analysis
SPT	scaled particle theory

The work of creating a cavity will be proportional to the size of the cavity, and thus to the size of the solute. For processes that take place in solution we take the volume of the solute V, the McGowan volume in units of $(cm^3\ mol^{-1})/100$, as a suitable measure. In the case of gas to solvent processes we found that the logarithm of the solute gas to hexadecane partition coefficient at 298 K, L, yielded better statistical correlations.

For a description of the solute-solvent interactions we devised a number of solute descriptors. E the solute excess molar refractivity in units of $(cm^3\ mol^{-1})/10$ is a measure of the propensity of a solute to engage in general dispersion interactions, S the solute dipolarity/polarizability is a measure of the ability of a solute to take part in dipole-dipole and dipole-induced dipole interactions. A and B are the solute overall or summation hydrogen bond acidity and basicity that deal with solute (acid) − solvent (base) and solute (base) − solvent (acid) interactions.

These various solute descriptors were combined into two linear free energy relationships, LFERs, Eq. (1) and Eq. (2), for the analysis of properties of neutral molecules [33–35].

$$Log\ P_s = c + eE + sS + aA + bB + vV \qquad (1)$$

$$Log\ K_s = c + eE + sS + aA + bB + vL \qquad (2)$$

Eq. (1) is used for processes taking place in solution, and Eq. (2) is used for gas to solution processes. In Eq. (1) Ps is the partition coefficient from water to a given solvent for a series of solutes. In Eq. (2) Ks is the gas to solvent partition coefficient for a series of solutes in a given solvent. Throughout this work, solubilities are given on the molarity scale in mol dm^{-3} at 298 K, partition coefficients, Ps, refer to the same scale in both phases, and gas to solvent partition coefficients are given as the dimensionless quantity, Ks, with concentrations in the gas phase and in solution on the molarity scale.

The independent variables in Eq. (1) and Eq. (2) are obtained as follows. For pure liquid solutes, E can be calculated from the refractive index of the compound at 293 K [33]. In the case of gases and solids the refractive index can be estimated or E itself can be

calculated quite easily [36]. For neutral molecules, the descriptors S, A, B and L can be obtained from various chromatographic measurements and water to solvent partition measurements, as described before [33–35] and reviewed [33,37,38]. As an example, we show how we obtained the descriptors for hydromorphone (C17H19NO3, 5 rings, CAS 466-99-9), The McGowan volume, V, is easily calculated from the molecular formula and the number of rings in the molecule [33] as 2.0648 and the descriptor E was calculated by the ADME (Absolv) 5.0 suite to be 2.04 [36]. This leaves the descriptors S, A, B and L to be obtained. Experimental water-solvent partition coefficients were available for five solvents [39], and this would be enough to obtain values for the four descriptors through the solution of five simultaneous equations. However, we can convert all the five log Ps values into corresponding log Ks values through Eq. (3) where log Kw is the gas-water partition coefficient. We achieve this by taking log Kw as another unknown descriptor, making a total of five descriptors to be determined. But we now have equations in Eq. (1) for five log Ps values, equations in Eq. (2) for five log Ks values, and also two equations for log Kw [one in the form of Eq. (1) and one in the form of Eq. (2)] leading to no less than 12 simultaneous equations for five unknowns.

$$Log\ P_s = log\ K_s − log\ K_w \qquad (3)$$

The set of simultaneous equations were solved using the 'Solver' add-on to Microsoft Excel, leading to $E = 2.04$, $S = 1.60$, $A = 0.16$, $B = 1.95$. $V = 2.0648$, $L = 10.575$ and log $Kw = 12.53$; these then yield the calculated log Ps and log Ks values in Table 1. For the 12 observed and calculated values, the absolute error, AE = 0.04, the average absolute error, AAE = 0.16 and the standard deviation SD = 0.19 log units.

The coefficients c, e, s, a, b, v and l in Eq. (1) and Eq. (2) are the equation coefficients obtained by multiple linear regression analysis of the dependent variable against the independent variables in Eq. (1) and Eq. (2). These coefficients in Eq. (1) and Eq. (2) are not just fitting constants but reflect the chemistry of the system in question. In particular, the a-coefficient will reflect the hydrogen bond basicity of the system (because a hydrogen bond solute will interact with a system that is a hydrogen bond base) and the b-coefficient will reflect the hydrogen bond acidity of the system. Thus the coefficients in Eq. (1) and Eq. (2) serve to characterize particular systems.

3. Results

Values of log Ks and log Ps for solutes in perfluoro-hexane,

Table 1
Calculated and observed values of log P and log K for transfer of hydromorphone from water and the gas phase to various solvents.

Equations in log Ps	Calc	Obs
Octan-1-ol	0.68	0.92
Trichloromethane	1.49	1.69
1-Chlorobutane	−0.92	−1.00
Benzene	−0.09	−0.40
Diethyl ether	−0.73	−0.52
Gas-water	12.52	12.53

Equations in log Ks	Calc	Obs
Octan-1-ol	13.36	13.45
Trichloromethane	14.01	14.22
1-Chlorobutane	11.59	11.53
Benzene	12.34	12.13
Diethyl ether	11.13	11.35
Gas-water	12.55	12.53