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A solubility equation for non-electrolytes in water

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Summary

A solubility equation is developed based on the steps: solid → super-cooled liquid → octanol → water. Estimating the standard Gibbs energy change for each step gives the following result:

$$\log C^{s}_{2,w} = 0.80 - 7.3 \times 10^{-4}[\Delta S^{f}(T_m - 298)] - 7.3 \times 10^{-4}[V_2(10.3 - \delta_2)^2] - \log PC$$

where $C^{s}_{2,w}$ is the molar aqueous solubility of the solute, ΔS^{f} its entropy of fusion, T_m its melting point, V_2 its molar volume, δ_2 its solubility parameter and PC its octanol–water partition coefficient. Comparison of this equation with a regression equation based on experimental data shows the derived result above to be nearly as good as the regression equation. The equation appears to provide good aqueous solubility estimates for solids and liquids.

Introduction

Recent reports (Yalkowsky and Valvani, 1980; Valvani et al., 1981) have developed an approach to estimating the aqueous solubility of non-electrolytes which appears to be remarkably successful. The development of the approach was based on both molecular and thermodynamic considerations. In this report we present a more

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complete thermodynamic framework for this approach based on the following steps:

$$\text{solid} \xrightarrow{\Delta g_1^0} \text{super-cooled liquid}$$

$$\text{super-cooled liquid} \xrightarrow{\Delta g_2^0} \text{octanol solution } (X^s_{2,oct})$$

$$\text{octanol solution } (X^s_{2,oct}) \xrightarrow{\Delta g_3^0} \text{aqueous solution } (X^s_{2,w})$$

$$\text{solid} \xrightarrow{\Delta g_T^0} \text{aqueous solution } (X^s_{2,w})$$

Scheme I

The resulting equation is slightly more general than the previously presented equations. Perhaps of more significance is the fact that if the observed solubility differs considerably from the estimated value, experimental determination of Gibbs energy for each step in Scheme I can be made and the factors responsible for the deviation determined.

Theoretical

From Scheme I:

$$\Delta g_T^0 = \Delta g_1^0 + \Delta g_2^0 + \Delta g_3^0 \tag{1}$$

where Δg^0 is the standard Gibbs energy change per mole. Consequently, estimation of the free energy change associated with each step will give Δg_T^0 and hence the solubility estimate. The equations used to estimate the free energy change associated with each step are generally available in the literature. We give only the brief discussion that follows: Fig. 1 presents a hypothetical composite graph of the fugacity vs composition. In Fig. 1, X_2 represents the solute mole fraction concentration in water or octanol as the solvent, $f_{2,solid}$ and $f_{2,scl}$ the fugacities of the pure solid and (hypothetical) super cooled liquid solute, $H_{2,oct}$ and $H_{2,w}$ the Henry's law constants for the solute in octanol and water, respectively, $X^s_{2,w}$ and $X^s_{2,oct}$ represent the solubility of the solute in water and octanol. The Henry's law constants are given by:

$$H_{2,w} = f_{2,solid}/X^s_{2,w} \tag{2}$$

$$H_{2,oct} = f_{2,solid}/X^s_{2,oct} \tag{3}$$

Henry's law for the solute

$$f_2 = H_2X_2 \tag{4}$$

is assumed to hold up to the solubility limit in both octanol and water.

The standard Gibbs energy per mole change for each step in Scheme I (see Fig. 1) are:

$$\Delta g_1^0 = RT\ln(f_{2,scl}/f_{2,solid}) \quad (5)$$

$$\Delta g_2^0 = RT\ln(H_{2,oct}/f_{2,scl}) \quad (6)$$

$$\Delta g_3^0 = RT\ln(H_{2,w}/H_{2,oct}) \quad (7)$$

Approximating expressions for estimating the standard molar Gibbs energy changes (Eqns. 5–7) can now be introduced. The first step may be approximated by:

$$\Delta g_1^0 = \Delta h^f(1 - T/Tm) \quad (8)$$

where Δh^f is the molar heat of fusion of the solute [1], T_m the melting point (°K) and T the temperature of interest (usually 298°K). The above equation is the ideal solubility equation if we assume that the difference in the heat capacities of the super-cooled liquid and crystalline forms of the solute is negligible. This has been shown to be a reasonable approximation (Yalkowsky and Valvani, 1980) when describing the aqueous solubility of a large number of organic non-electrolytes.

The second step (super-cooled liquid solute → solute in octanol) is a mixing process which may be estimated by the well-known regular solution theory (Hildebrand et al., 1970) since only relatively non-polar substances are involved. Thus Eqn. 6 may be written as:

$$\Delta g_2^0 = V_2\phi_{oct}^2(\delta_{oct} - \delta_2)^2 \quad (9)$$

where V_2 is the solute molar volume, ϕ_{oct} the volume fraction of octanol in the solution (usually it is assumed that $\phi_{oct} = 1$) and δ_{oct} and δ_2 are, respectively, the octanol and solute solubility parameters.

The third step (solute in octanol → solute in water) involves the distribution of the solute between octanol and water and hence may be estimated by:

$$\Delta g_3^0 = RT\ln(PC_x) \quad (10)$$

where PC_x is the octanol–water partition coefficient of the solute on a mole fraction basis. We assume here that PC_x is concentration independent which is not unreasonable when one is dealing with non-electrolytes of low solubility.

Eqns. 1, 8, 9, and 10 combine to give:

$$\Delta g_T^0 = \Delta h^f(1 - T/T_m) + V_2\phi_{oct}^2(\delta_{oct} - \delta_2)^2 + RT\ln(PC_x) \quad (11)$$

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[1] Note that step one (Eqn. 8) is only needed for solids.

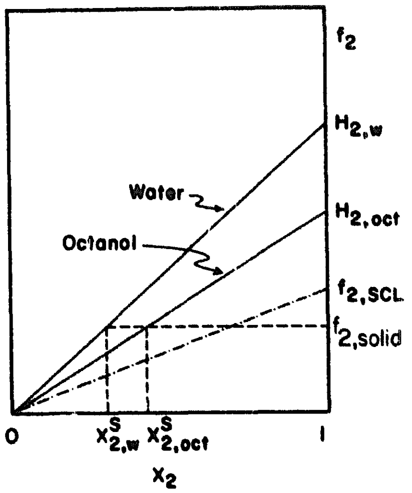

Fig. 1. Fugacity versus composition diagram.

Since

$$\Delta g^0_T = RT\ln(H_{2,w}/f_{2,solid}) \tag{12}$$

$$= -RT\ln X^s_{2,w} \tag{13}$$

From Eqn. 2 and Fig. 1, combining Eqns. 13 and 11 gives an expression for the mole fraction solubility of solute, $X^s_{2,w}$, in water

$$\ln X^s_{2,w} = \frac{-\Delta h^f}{RT}(1 - T/T_m) - \frac{V_2\phi^2_{oct}(\delta_{oct} - \delta_2)^2}{RT} - \ln PC_x \tag{14}$$

Using $T = 298°K$, $\phi_{oct} = 1$, $\Delta S^f = \Delta h^f/T_m$, $\delta_{oct} = 10.3$ and the fact that the commonly used molar partition coefficient, PC, is related approximately to PC_x by the equation:

$$\log PC_x = \log PC + 0.94 \tag{15}$$

$$\begin{aligned}\log X^s_{2,w} = &-0.94 - 7.3\times10^{-4}[\Delta S^f(T_m - 298)]\\ &-7.3\times10^{-4}[V_2(10.3 - \delta_2)^2] - \log PC\end{aligned} \tag{16}$$

The molar solubility $C^s_{2,w}$ is given by (approximately):

$$\log C^s_{2,w} = \log X^s_{2,w} + 1.74 \tag{17}$$

Thus, the molar solubility equation is:

$$\log C^s_{2,w} = 0.80 - 7.3 \times 10^{-4}\left[\Delta S^f(T_m - 298)\right]$$

$$-7.3 \times 10^{-4}\left[V_2(10.3 - \delta_2)^2\right] - \log PC \qquad (18)$$

Results and discussion

Eqns. 16 and 18 are identical with Eqns. 26 and 29 of Yalkowsky and Valvani (1980), except for the inclusion of the solubility parameter term. Regression analysis on rigid compounds gave (Yalkowsky and Valvani, 1980)

$$\log C^s_{2,w} = -1.05 \log PC - 0.012\ MP + 0.87 \qquad (19)$$

For rigid molecules ($\Delta S^f = 13.5$ eu) Eqn. 18 gives

$$\log C^s_{2,w} = 0.80 - 0.0099(MP - 25) - 7.3 \times 10^{-4}\left[V_2(10.3 - \delta_2)^2\right] - \log PC \qquad (20)$$

where MP is the melting point in °C and the temperature of interest is 25°C. Assuming $\delta_2 = 10.3$ for all compounds gives

$$\log C^s_{2,w} = 1.05 - 0.0099\ MP - \log PC \qquad (21)$$

Eqns. 21 and 19 are remarkably close. Note that the solubility parameter term in Eqn. 20 is always negative (i.e. lowers solubility). Neglecting this term is the likely reason for the coefficients of the log PC and MP terms being more negative in Eqn. 19 than expected from Eqns. 20 or 21. Since Eqn. 19 provided a remarkably good fit to the data (Yalkowsky and Valvani, 1980) it is expected that Eqn. 20 should also do so.

For liquids, the regression result is (Yalkowsky and Valvani, 1980)

$$\log X^s_{2,w} = -1.08 \log PC - 1.04 \qquad (22)$$

and Eqn. 16 gives

$$\log X^s_{2,w} = -\log PC - 0.94 \qquad (23)$$

assuming $\delta_2 = 10.3$. As expected, the agreement between Eqns. 22 and 23 is excellent.

To further assess the quality of Eqns. 16 and 18, we present in Table 1, the experimental and calculated (Eqn. 18) solubilities for liquids at room temperature, using literature data for all required parameters (V_2, δ_2 and log PC). Table 2 contains the results for solids and Table 3 gives the experimental data used for the solubility

TABLE 1

SOLUBILITY ESTIMATES FOR LIQUIDS

Compound	log PC [a]	V_2 [b]	δ_2 [b]	7.3×10^{-4} $V_2(10.3 - \delta_2)^2$	log $C^s_{2,w}$ Calculated	Experimental [a]
Carbon tetrachloride (CCl_4)	2.83	97.10	8.55	0.2171	−2.25	−2.22
Chloroform ($CHCl_3$)	1.96	80.64	9.16	0.0765	−1.24	−1.12
Dichloromethane (CH_2Cl_2)	1.25	64.51	9.88	0.0083	−0.46	−0.66
Acrylonitrile (C_3H_3N)	−0.92	66.28	10.56	0.0033	1.72	0.15
Methyl acetate ($C_3H_6O_2$)	0.18	79.88	9.46	0.0412	0.58	0.61
Chloropropane (C_3H_7Cl)	2.04	88.74	8.39	0.2363	−1.48	−1.46
Ethyl acetate ($C_4H_8O_2$)	0.70	99.53	8.91	0.1404	−0.04	−0.06
2-Butanol ($C_4H_{10}O$)	0.61	92.41	11.08	0.0410	0.15	0.39
1-Pentanol ($C_5H_{12}O$)	1.48	108.7	11.12	0.0534	−0.73	−0.60
3-Pentanol ($C_5H_{12}O$)	1.21	108.0	10.16	0.0015	−0.41	−0.24
1,2-Dichlorobenzene ($C_6H_4Cl_2$)	3.38	113.1	10.04	0.0056	−2.59	−3.13
Benzene (C_6H_6)	2.01	89.41	9.16	0.0848	−1.65	−1.29
Cyclohexanone ($C_6H_{10}O$)	0.81	104.2	10.42	0.0011	−0.01	−0.05
Cyclohexane (C_6H_{12})	3.44	108.8	8.19	0.3535	−2.99	−3.07
2-Hexanone ($C_6H_{12}O$)	1.38	124.2	8.63	0.2528	−0.83	−0.84
Hexanoic acid ($C_6H_{12}O_2$)	1.90	125.9	11.68	0.1750	−1.27	−1.07
2,2-Dimethylbutane (C_6H_{14})	3.82	133.7	6.71	1.258	−4.28	−3.61
2,3-Dimethylbutane (C_6H_{14})	3.85	131.1	6.97	1.062	−4.11	−3.62
3,3-Dimethyl-2-butanol ($C_6H_{14}O$)	1.48	125.4	9.51	0.0572	−0.74	−0.65
Dipropylamine ($C_6H_{15}N$)	1.70	138.2	7.97	0.5475	−1.45	−0.54
Triethylamine ($C_6H_{15}N$)	1.45	139.9	7.42	0.8473	−1.50	−0.83
Benzyl alcohol (C_7H_8O)	1.02	103.8	12.05	0.2321	−0.45	−0.45
Methyl benzoate ($C_8H_8O_2$)	2.12	125.9	10.19	0.0011	−1.32	−1.81
Ethyl benzene (C_8H_{10})	3.15	123.1	8.84	0.1916	−2.54	−2.81
Dibutylamine ($C_8H_{19}N$)	2.75	170.7	8.15	0.5758	−2.53	−1.44
Ethyl benzoate ($C_9H_{10}O_2$)	2.64	144.2	9.75	0.0318	−1.87	−2.22
n-Propyl benzene (C_9H_{12})	3.63	140.1	8.64	0.2818	−3.11	−3.14
Isopropyl benzene (C_9H_{12})	3.66	140.2	8.60	0.2958	−3.16	−3.33
1,3,5-Trimethylbenzene (C_9H_{12})	3.42	139.6	8.88	0.2054	−2.83	−3.25
Diphenylether ($C_{12}H_{12}O$)	4.28	160.4	10.10	0.0047	−3.48	−2.60
1-Dodecanol ($C_{12}H_{26}O$)	5.13	224.6	9.78	0.0443	−4.37	−4.80
Diphenyl methane ($C_{13}H_{12}$)	4.14	167.9	9.57	0.0653	−3.40	−4.07

[a] From Valvani et al. (1981).

[b] From Hoy (1970).

TABLE 2

SOLUBILITY ESTIMATES FOR SOLIDS

Compound	7.3×10^{-4} $[\Delta S^f(T_m - 298)]$	log PC[a]	7.3×10^{-4} V_2 $(10.3 - \delta_2)^2$	log $C^s_{2,w}$	
				Calculated	Experimental
p-Dichlorobenzene ($C_6H_4Cl_2$)	0.269	3.39	0.030	−2.89	−3.21[b]
Benzoic acid ($C_7H_6O_2$)	0.744	2.0	0.426	−2.37	−1.55[c]
Phenylacetic acid ($C_8H_8O_2$)	0.374	1.46	0.041	−1.07	−0.896[c]
Naphthalene ($C_{10}H_8$)	0.513	3.30	0.000	−3.01	−3.61[b]
2-Naphthol ($C_{10}H_8O$)	0.801	2.86	0.035	−2.89	−2.29[c]
Anthracene ($C_{14}H_{10}$)	1.97	4.45	0.025	−5.65	−6.19[b]
Phenanthrene ($C_{14}H_{10}$)	0.628	4.46	0.362	−4.65	−5.11[b]

[a] From Hansch and Leo (1979).

[b] From Yalkowsky and Valvani (1980).

[c] From Seidell (1941).

estimate of the solids. Fig. 2 presents a graph of the error, log $C^s_{2,w}$ (observed) − log $C^s_{2,w}$(predicted), versus log PC for both Eqn. 18 of this work and the regression equation of Yalkowsky and Valvani (1980) (Eqn. 19) for liquids. The standard error of the estimate using Eqn. 18 is 0.51 while that using the regression equation is 0.46. These results indicate that the derived equation (Eqn. 18) does nearly as well as the regression equation. The error terms in Fig. 2 are comparable in all cases. There is a slight trend evident in Fig. 2 for the error term to increase with increasing partition coefficient, but the trend is similar for both approaches. The error term for the solid compounds is also presented in Fig. 2. The result for the solids appears to be similar to that for liquids.

TABLE 3

LITERATURE DATA FOR SOLIDS

Compound	ΔS^f(e.u.)[a]	T_m (°K)[a]	V_2[a]	δ_2
p-Dichlorobenzene	13.1	326.1	117.8	9.71[b]
Benzoic acid	10.47	395.4	96.47	12.76[c]
Phenylacetic acid	9.91	349.7	124.8	10.97[c]
Naphthalene	12.72	353.2	126.1	10.24[b]
2-Naphthol	11.47	393.6	112.7	10.95[c]
Anthracene	14.09	489.5	138.9	10.80[c]
Phenanthrene	12.07	369.3	181.9	8.65[c]

[a] From Handbook of Physics and Chemistry, 54th Edn., C.R.C. Press, 1974.

[b] Calculated from enthalpies of vaporization obtained from Dreisbach (1955).

[c] Calculated from enthalpies of vaporization obtained from vapor pressure data in ref. (a) above.

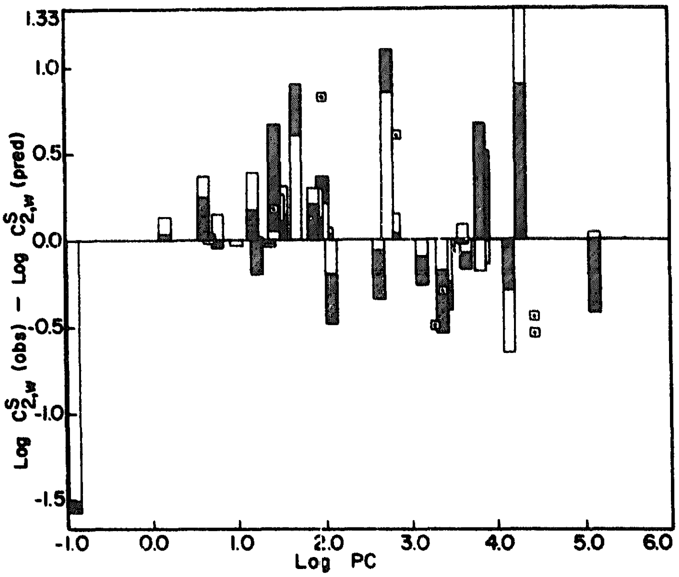

Fig. 2. Graph of log $C^s_{2,w}$(observed) − log $C^s_{2,w}$(predicted) versus log partition coefficient. Open bars: □, obtained from data in Valvani et al. (1981); closed bars: ▨, this work; ⊡, solids.

The individual terms in Eqn. 18 are given in Tables 1 and 2. For both liquids and solids the log PC term is the dominating term. For solids the entropy of fusion term (ideal solubility based on $\Delta Cp = 0$) also makes a substantial contribution. The solubility parameter term is usually small. Consequently the assumption of ideal solubility (made by Yalkowsky and Valvani, 1980) of all compounds in octanol ($\delta_2 = \delta_{oct} = 10.3$ in Eqn. 18) appears to be a reasonable approximation to make especially when the required data are not available.

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