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The *E* and *C* model for predicting the solubility of drugs in pure solvents

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Abstract

The *E* and *C* model for hydrogen bonding is used together with nonspecific solubility parameters to predict the solubility of a Lewis base solute in a series of solvents of several chemical classes. A linear relationship between enthalpies of hydrogen bonding calculated from the Drago model and entropies obtained from a few experimental solubilities allows the prediction of the entropy contribution for the other solvents. Correct orders of magnitude are predicted in solvents of all polarities (from benzene to glycerin) which were not used to obtain the empirical relationships. The results suggest that the *E* and *C* model may be useful to reduce the experimental work usually needed for predicting solubility of drugs in pure solvents of different acid-base characteristics.

Keywords: Solubility prediction; *E* and *C* numbers; Solubility parameters; Hydrogen bonding; Enthalpy calculation

The *E* and *C* model (Drago and Wayland, 1965)

$$-\Delta H^{AB}\ (\mathrm{kcal/mol}) = (E_A E_B + C_A C_B) \qquad (1)$$

where *C* and *E* express the tendency of acids (A) and bases (B) to form covalent and electrostatic bonds, has been used by several workers (Fowkes et al., 1984; Hô, 1994), but it has not been applied to solubility prediction. A model similar to that of Fowkes et al. (1984) may be written for the solubility (mole fraction X_2) of a solid drug:

$$-RT \ln X_2 = -\ln X_2^{i} + V_2 \phi_1^2 (\delta_1^{NS} - \delta_2^{NS})^2 + RT\left(\ln\frac{V_2}{V_1} + 1 - \frac{V_2}{V_1}\right) + \sum \Delta H_2^{AB} - T\sum \Delta S_2^{AB} \qquad (2)$$

where $\ln X_2^{i}$ is the logarithm of the ideal mole fraction solubility, *V* is the molar volume and ϕ is the volume fraction (Hildebrand et al., 1970). The subscripts, 1 and 2 refer to the solvent and the drug, respectively. 'Nonspecific solubility parameters' δ^{NS} are calculated from the dispersion δ_{1d} and polar δ_{1p} solubility parameters of Hansen (Barton, 1983):

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Table 1
Experimental and predicted mole fraction solubilities of (I) in weakly polar and basic solvents

Solvent	X_2	X_2 (calc)[a]	$\Delta H^{AB(b)}$ (cal/mol)	δ_1 (cal/cm^3)$^{1/2}$	$\delta_1^{NS(c)}$ (cal/cm^3)$^{1/2}$
Butylacetate	7.89×10^{-4}	5.64×10^{-4}	−2990	8.5	7.9
Toluene	0.79×10^{-3}	1.86×10^{-3}	−1443	8.9	8.8
Ethylacetate	1.99×10^{-3}	1.99×10^{-3}	−2990	9.0	7.8
Benzene	0.78×10^{-3}	3.02×10^{-3}	−1443	9.1	9.0
Chloroform	1.15×10^{-3}	2.64×10^{-3}	−4443	9.3	8.8
Acetone	8.51×10^{-3}	8.58×10^{-3}	−3194	9.8	9.1
Dioxane	1.97×10^{-2}	1.02×10^{-2}	−3471	10.0	9.3
Pyridine	1.90×10^{-2}	1.91×10^{-2}	−4860	10.7	10.2
Aniline	5.50×10^{-2}	2.91×10^{-2}	−3856	11.0	9.8
Dimethylacetamide	2.75×10^{-2}	2.98×10^{-2}	−4114	11.1	9.9
Dimethylformamide	6.17×10^{-2}	6.48×10^{-2}	−3856	12.1	10.8
Dimethylsulfoxide	1.90×10^{-1}	0.69×10^{-1}	−4244	13.0	12.0
Methylformamide	2.46×10^{-1}	0.44×10^{-1}	−3856	14.5	13.1

[a] Eqs. (2) and (7); $X_2^i = 8.495 \times 10^{-3}$; $V_2 = 156.6$ cm^3 mol^{-1}, $\delta_2 = 12.7$ (cal/cm^3)$^{1/2}$.
[b] Eq. (4) and Table 3.
[c] Eq. (3).

$$\delta^{NS} = (\delta_d^2 + \delta_p^2)^{1/2} \tag{3}$$

The net enthalpy of hydrogen bonding (Eq. (2)) is the algebraic sum of exothermic solute–solvent hydrogen bonding and endothermic breaking of solvent–solvent hydrogen bonds:

$$\sum \Delta H_2^{AB} \text{ (kcal/mol)}$$

$$= -\sum (E_A E_B + C_A C_B)_{2-1}$$

$$+ \sum (E_A E_B + C_A C_B)_{1-1} \tag{4}$$

Therefore, the sign of the net enthalpy may be negative or positive depending on whether exothermic or endothermic effects predominate. Hydrogen bonding self-association of the solute is disregarded since the solvent is in large excess.

The experimental solubility of 1-(*p*-chlorophenyl)-*N*-(4-chloro-2-pyrimidil) cyclopropane carboxamide (I) was measured at 25 ± 0.2°C in pure solvents (analytical or chromatographic grade, Merck and Probus, Table 1 and Table 2). The synthesis of this insecticide is detailed elsewhere (Jiménez-Durán, 1989). The melting point (233.85 K) and heat of fusion (9015 cal/mol) of (I) were determined by DSC (Metler TA 3000). Saturated solutions were prepared by equilibrating an excess of solute with the solvents in a constant temperature shaker bath. After separation of the solid phase (centrifugation and filtration through UltiporTM66 Nylon 66 membranes, pore size 0.45 μm), samples were analyzed using the gas chromatography technique (Perkin Elmer 8300) described by Zweig and Sherma (1979). Volume of the samples injected, 5 μl, temperature of the detector and injector, 300°C, nitrogen flux, 40 ml/min. The column was 3% SE-30 on Chromosorb WHP 80/100 (2 m, 1/8 in.) at 230°C. The densities were determined in 10-ml picnometers. The results are the average of at least four measurements.

Model compounds containing the key functional group (Table 3) are used whenever *E* and *C* are unknown. Only the first term on the right-hand side of Eq. (4) is needed to calculate the net enthalpy of (I) in basic solvents (Table 1). Alcohols and glycols may behave as acids and bases:

$$\begin{aligned} \sum \Delta H_2^{AB} = & -(E_A E_B + C_A C_B)_{2-1}(\text{NH} - \text{OH}) \\ & -(E_A E_B - C_A C_B)_{2-1}(\text{C} = \text{O} - \text{H}) \\ & +(E_A E_B + C_A C_B)_{1-1}(\text{H} - \text{OH}) \end{aligned} \tag{5}$$

Table 2
Experimental and predicted mole fraction solubilities of (I)[a] in alcohols and glycols

Solvent	X_2	X_2 (calc)[b]	X_2 (calc)[c]	ΔH^{AB}[d] (cal/mol)	δ_1 $(\mathrm{cal/cm^3})^{1/2}$	δ_1^{NS}[e] $(\mathrm{cal/cm^3})^{1/2}$
1-Octanol	5.62×10^{-4}	6.78×10^{-4}	16×10^{-4}	-1524.5	10.3	8.5
1-Pentanol	7.59×10^{-4}	3.05×10^{-4}	8.81×10^{-4}	-1831.4	10.6	8.1
Cyclohexanol	0.80×10^{-3}	1.19×10^{-3}	4.37×10^{-3}	-2235.7	10.9	8.7
Isobutanol	1.01×10^{-3}	0.23×10^{-3}	0.46×10^{-3}	-1231.5	11.1	7.9
Butanol	1.91×10^{-3}	0.56×10^{-3}	1.25×10^{-3}	-1398.4	11.3	8.3
Isopropanol	2.34×10^{-3}	0.56×10^{-3}	1.72×10^{-3}	-1931.5	11.5	8.3
Benzyl alcohol	1.29×10^{-2}	0.54×10^{-2}	1.93×10^{-2}	-2189.0	11.6	9.5
Propanol	5.89×10^{-3}	1.02×10^{-3}	2.30×10^{-3}	-1427.1	12.0	8.5
Ethanol	5.49×10^{-3}	2.13×10^{-3}	14.6×10^{-3}	-3255.0	13.0	8.8
1,3-Butanediol	4.68×10^{-2}	0.46×10^{-2}	2.76×10^{-2}	-3047.4	14.1	9.5
Methanol	3.89×10^{-2}	1.56×10^{-2}	17×10^{-2}	-4036.5	14.5	9.5
Diethylene glycol	2.00×10^{-1}	0.36×10^{-1}	0.68×10^{-1}	-928.0	14.7	10.7
1,2-Propanediol	9.77×10^{-3}	14.8×10^{-3}	2.67×10^{-3}	2725.0	14.8	9.4
Ethylene glycol	5.25×10^{-3}	43.6×10^{-3}	12.1×10^{-3}	2021.6	16.0	9.9
1,4-Butanediol	5.00×10^{-3}	24.2×10^{-3}	10.4×10^{-3}	5068.9	16.4	11.5
Glycerin	1.60×10^{-3}	174×10^{-3}	1.18×10^{-3}	8115.6	17.7	10.3

[a] $X_2^{\mathrm{i}} = 8.495 \times 10^{-3}$; $V_2 = 156.6\ \mathrm{cm^3\ mol^{-1}}$; $\delta_2 = 12.2\ \mathrm{cal^{1/2}\ cm^{-3/2}}$

[b] Eqs. (2) and (7).

[c] Eqs. (2) and (8).

[d] Methanol and ethanol, Eq. (5) and Table 3; other alcohols and glycols, Eq. (6).

[e] Eq. (3).

Eq. (5) is used with the E and C of methanol, ethanol and (I) (Table 3). Methanol is the model of the interaction $\Sigma\Delta H_{(2-1)}^{\mathrm{AB}}$ for the other alcohols and glycols, and self-association of these solvents, $\Delta H_2^{\mathrm{AB}}(\mathrm{H-OH})_{1-1}$, is approximated by $V_1\delta_{1\mathrm{h}}^2$ (cal/mol), where δ_{h} is the hydrogen bonding parameter (Barton, 1983):

$$\Delta H_2^{\mathrm{AB}}\ (\mathrm{cal/mol}) = -6853.1 + V_1\delta_{1\mathrm{h}}^2 \tag{6}$$

Calculated net enthalpies are listed in Table 2.

The second term of Eq. (2) is obtained by iteration as described by James (1986), beginning with $\phi_1 = 1$. Nonspecific solubility parameters are used for alcohols and glycols and total solubility parameters δ_1 for the other solvents. This is a reasonable choice; for solvents of Table 1, δ_1^{NS} is close to δ_1. The solubility parameter of (I) ($\delta_2 = 12.7$) was determined in dioxane–water mixtures ($\delta_2 = 12.7$).

The entropy term of Eq. (2) cannot be calculated from properties of the pure compounds and a linear relationship between ΔH_2^{AB} (from the Drago model) and ΔS_2^{AB}, formally analogous to enthalpy–entropy compensation (Boots and de Bokx, 1989), is suggested. Whether this assumption is reasonable will be shown if the predicted ΔS_2^{AB} give reasonable solubilities for other solvents not used to obtain the equation. It is intended to use Eq. (7) as a predictive relationship and consequently it is only based on a minimum number of experiments, i.e. the solubilities of (I) in three Lewis base solvents, acetone, ethyl acetate and pyridine ($\Delta S_2^{\mathrm{AB}} = -6.90$, -6.11 and -13.11 cal/(mol K)):

$$\sum\Delta H_2{}^{\mathrm{AB}} = -1351.83 + 267.55\sum\Delta S_2{}^{\mathrm{AB}},$$
$$r = 0.999, n = 3 \tag{7}$$

Unlike regression, prediction with Eq. (7) does not imply any fit of the data, being a better test for a model (Yalkowsky and Banerjee, 1992). To estimate the solubility of (I) in another solvent, say DMA, $\Sigma\Delta H_2^{\mathrm{AB}} = -4.114$ kcal/mol (Table 3 and Eq. (4)), $\Sigma\Delta S_2^{\mathrm{AB}}(\mathrm{calc}) = -10.32$ cal/(mol K) (Eq. (7)) and $X_2(\mathrm{calc}) = 0.0298$ (Eq. (2)). The experimental value is $X_2 = 0.0275$. Eqs. (2) and (7)

Table 3
E and C of solvents and model compounds

Solvent	E_A	C_A	Model Compound of
Pyrrole[a]	2.54	0.295	NH of (I) and aniline
Chloroform[a]	3.02	0.159	
Methanol[b]	3.41	0.14	Alcohols and glycols
Ethanol[a]	3.88	0.451	
	E_B	C_B	
Pyridine[c]	1.17	6.40	
N,N-Dimethylformamide[c]	1.23	2.48	C = 0 of (I)
N,N-Dimethylacetamide[c]	1.32	2.58	
Ethyl acetate[c]	0.975	1.74	Butyl acetate
Acetone[c]	0.987	2.33	
Dioxane[c]	1.09	2.38	
Dimethylsulfoxide[c]	1.34	2.85	
Benzene[a]	0.525	0.681	Toluene
Methanol[b]	0.78	1.12	Alcohols and glycols
Ethanol[a]	1.84	1.09	

[a] Drago (1980).
[b] Drago and Wayland (1965).
[c] Drago et al. (1971).

predict correct orders of magnitude for the solubility of (I) in most solvents (Tables 1 and 2). The large errors obtained for some of the glycols (Table 2) suggest that the coefficients of Eq. (7) may differ for glycols. Using the experimental solubilities of (I) in glycerin, ethylene glycol and 1,3-butanediol:

$$\sum \Delta H_2{}^{AB} = -1955.14 + 395.58 \sum \Delta S_2{}^{AB}, \quad (7)$$

$$r = 0.990, n = 3 \quad (8)$$

Eq. (8) gives better predictions than Eq. (7) for glycols (Table 2).

Eqs. (7) and (8) calculate reasonable solubilities in other solvents of wide polarity range that were not used to obtain these relationships. Using all the data set ($n = 29$ solvents), $r = 0.94$; for the separate sets, $r = 0.97$ (glycols) and $r = 0.93$ (other solvents). This does not demonstrate an actual enthalpy–entropy compensation; however, the formal analogy (Eqs. (7) and (8)) serves as truly predictive to calculate solubility from a few experimental measurements.

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