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Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids

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The aqueous solubility data of aliphatic alcohols, alkyl substituted benzoates and steroids was regressed against physico-chemical properties of the solutes. The solubility parameter, molar volume and melting point were used as independent parameters. Three parameter approach yielded good correlations. The contribution of melting point to the overall correlations is marginal. It indicates that when functional groups exhibit stronger interactions with water, the influence of melting point on the aqueous solubility may be reduced.

INTRODUCTION

The aqueous solubility of drugs has attracted the attention of pharmacists because of its importance in the design of dosage forms, absorption and toxicity. Water solubility (S_w) of organic nonelectrolytes was well correlated with solvatochromic parameters[1, 2] and partition coefficients[3, 4]. The solubility parameter, δ, is an intrinsic physico-chemical property of a substance. Though δ is known as cohesive energy density, it has been used to describe the solute-solvent interactions and the behaviour of solutions[5]. Some efforts were made to use δ to explain the aqueous behaviour of nonelectrolytes, although the final result was expressed in terms of PC[6]. Appropriate thermodynamic treatment (theoretic) gave an expression which contains five independent variables.

In the present work, we report the usefulness of solubility parameter, δ_2, and molar volume, V_2, in predicting aqueous solubility. Aliphatic alcohols, alkyl-*p*-substituted benzoates and steroids were chosen for the regression analysis. Most of the compounds were used as adjuvants and drugs in pharmacy. We have chosen an empirical approach in order to use fewer variabales.

EXPERIMENTAL

The solubility parameter and molar volume of the compounds were estimated based on Fedors fragmental constants[7] using the software developed in this laboratory. The melting points of the liquid solutes are considered as 25°C. The aqueous solubility data was expressed as molar solubility and was taken from the literature[3]. Quick-Fox PC/AT was used. Multiple regression analysis of the data was performed using Lotus 1–2–3 (3.0) package. Fisher F ratio was calculated using standard statistical procedure[8].

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RESULTS AND DISCUSSION

Aqueous solubility predictions—Aliphatic alcohols

The aqueous solubility data including physico-chemical properties of several aliphatic alcohols were recorded (Table-1). This series was used earlier to correlate aqueous solubility with partition coefficient[3].

TABLE-1
SOLUBILITY DATA FOR SOME ALIPHATIC ALCOHOLS

S. No.	Name of the compound	δ_2 (H^{a})	V_2 (cc/mole)^{a}	log S_w (observed)^{b}
1.	1-Butanol	11.33	91.5	–0.01
2.	2-Methyl-1-propanol	11.11	92.1	0.06
3.	2-Butanol	11.11	92.1	0.39
4.	1-Pentanol	10.96	107.9	–0.61
5.	2-Methyl-1-butanol	10.77	108.2	–0.48
6.	3-Methyl-1-butanol	10.77	108.2	–0.51
7.	2,2-Dimethyl-1-propanol	10.58	107.4	–0.42
8.	2-Pentanol	10.77	108.2	–0.31
9.	3-Pentanol	10.77	108.2	–0.24
10.	3-Methyl-2-butanol	10.58	108.5	–0.21
11.	2-Methyl-2-butanol	10.59	107.2	0.09
12.	1-Hexanol	10.66	124.5	–1.24
13.	2-Methyl-1-pentanol	10.51	124.3	–1.11
14.	4-Methyl-1-pentanol	10.51	124.3	–1.14
15.	2,2-Dimethyl-1-butanol	10.34	123.5	–1.04
16.	3,3-Dimethyl-1-butanol	10.34	123.5	–0.50
17.	2-Ethyl-1-butanol	10.51	124.3	–1.17
18.	2-Hexanol	10.51	124.3	–0.88
19.	3-Hexanol	10.51	124.3	–0.82
20.	3-Methyl-2-pentanol	10.34	124.6	–0.74
21.	4-Methyl-2-pentanol	10.34	124.6	–0.81
22.	2-Methyl-2-pentanol	10.34	124.6	–0.71
23.	3,3-Dimethyl-2-butanol	10.16	123.8	–0.64
24.	Cyclohexanol	11.56	105.5	–0.45
25.	2-Methyl-2-pentanol	10.34	124.6	–0.51
26.	3-Methyl-3-pentanol	10.34	124.6	–0.39
27.	2,3-Dimethyl-2-butanol	10.16	123.8	–0.41
28.	2,4-Dimethyl-2-pentanol	9.99	139.9	–0.96
29.	1-Heptanol	10.46	140.1	–1.83
30.	2,2-Dimethyl-1-pentanol	10.15	139.6	–1.52

S. No.	Name of the compound	δ_2 (H[a])	V_2 (cc/mole)[a]	log S_w (observed)[b]
31.	2,4-Dimethyl-1-pentanol	10.15	140.7	−1.60
32.	4,4-Dimethyl-1-pentanol	10.15	139.6	−1.55
33.	2-Heptanol	10.31	140.4	−1.55
34.	3-Heptanol	10.31	140.4	−1.44
35.	4-Heptanol	10.31	140.4	−1.40
36.	5-Methyl-2-hexanol	10.15	140.7	−1.38
37.	2-Methyl-2-hexanol	10.15	140.7	−1.32
38.	2,2-Dimethyl-3-pentanol	9.99	139.9	−1.36
39.	2,4-Dimethyl-3-pentanol	9.99	141.0	−1.23
40.	2-Methyl-2-hexanol	10.15	139.6	−1.09
41.	3-Methyl-3-hexanol	10.15	139.6	−1.00
42.	2,3-Dimethyl-2-pentanol	9.99	139.9	−0.91
43.	2,3-Dimethyl-3-pentanol	9.99	139.9	−0.86
44.	3-Ethyl-3-pentanol	10.15	139.6	−0.87
45.	2,3,3-Trimethyl-2-butanol	9.83	139.1	−0.72
46.	1-Octanol	10.28	156.2	−2.37
47.	2-Ethyl-1-hexanol	10.14	156.5	−2.11
48.	2-Octanol	10.14	156.5	−2.09
49.	2-Methyl-2-heptanol	10.00	155.7	−1.72
50.	3-Methyl-3-heptanol	10.00	155.7	−1.60
51.	2,2,3-Trimethyl-3-pentanol	9.71	155.2	−1.27
52.	1-Nonanol	10.13	172.3	−3.01
53.	7-Methyl-1-octanol	10.00	172.6	−2.49
54.	2,2-Diethyl-1-pentanol	9.87	171.8	−2.42
55.	2-Nonanol	10.00	172.6	−2.74
56.	3-Nonanol	10.00	172.6	−2.66
57.	4-Nonanol	10.00	172.6	−2.59
58.	5-Nonanol	10.00	172.6	−2.49
59.	2,6-Dimethyl-4-heptanol	9.74	173.2	−2.51
60.	3,5-Dimethyl-4-heptanol	9.74	173.2	−2.51
61.	1-Decanol	10.01	188.4	−3.60
62.	2-Undecanol	9.79	204.8	−2.94
63.	1-Dodecanol	9.81	220.6	−4.80
64.	1-Tetradecanol	9.66	252.8	−5.84
65.	1-Pentadecanol	9.60	268.9	−6.35
66.	1-Hexadecanol	9.54	285.0	−7.00
67.	1-Octadecanol	9.45	317.2	−8.40

[a] Calculated by Fedors constants (Fedors, 1974)
[b] Yalkowsky and Valvani, (1980)

The bases for the selection of parameters are:

(i) Solubility parameter to denote the interactions of solute-solvents.

(ii) Molar volume to denote the cavity desirable in the solvent environment to accommodate the solute molecule. The advantage is that molar volume can also be estimated by the Fedors fragmental constants[7].

(iii) Entropy of fusion (ΔS_f) and melting point (m.p.) to denote the entropy of mixing. The variables were represented in the ideal solubility equation[5]. The alcohols recorded here are liquids (except 4) and ΔS_f is fairly constant for liquids (13.5 eu). Hence ΔS_f term was dropped in the analysis. However, m.p. term is retained in the regression analysis because it was included in the analysis proposed by solvatochromic parameter approach and partition coeffcients approach respectively[4, 9]. These three parameters were employed in the regression model. The equation is

$$\log S_w = 0.005\,(\text{m.p.}-25) - 0.986\delta_2 - 0.0453V_2 + 15.1582 \qquad (1)$$

$$n = 67;\ s = 0.4849;\ r^2 = 0.9225$$

$$F = 249.97;\ F(3, 63, 0.01) = 4.10$$

The correlations are fairly high ($r^2 = 0.9225$). The error in the predicted solubility is approximately ± 8% for most of the compounds. The coefficient of δ_2 is nearly one indicating that the δ_2 has greater influence in the predictions. The sign of V_2 is in tune with fundamental principles. The coefficient of (m.p.-25) is less than the approximated value of Yalkowsky and Valvani[3] *i.e.* 0.01. Since m.p.

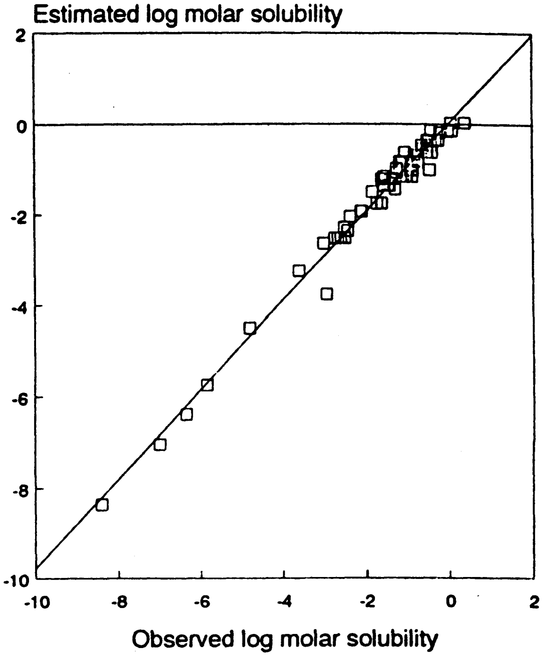

Fig. 1. Relationship between the estimated and observed log molar aqueous solubility of aliphatic alcohols, Eq. (2).

is taken as 25°C for alcohols, the first term in the Eq. (1) will be reduced to zero. Its sign is positive, but, in general, it is expected to be negative. Hence the m.p. term was dropped from the analysis. The regression equation for other parameters is:

$$\log S_w = -0.954\ \delta_2 - 0.0445\ V_2 + 14.726 \qquad (2)$$

$$n = 67;\ s = 0.4813;\ r^2 = 0.9224$$

The correlations are same in equations (1) and (2). In other words, melting point has no or marginal contribution to predict the aqueous solubility of alcohols.

A good linear relationship was observed between the estimated and observed solubility (Fig. 1). A scattergram (Fig. 2) was constructed by plotting estimated log S_w along Y-axis and residuals along the X-axis. The scattering of points is random and most of the residuals are within 2 SD units. Thus Eq. (2) can be used to predict the aqueous solubility of aliphatic alcohols.

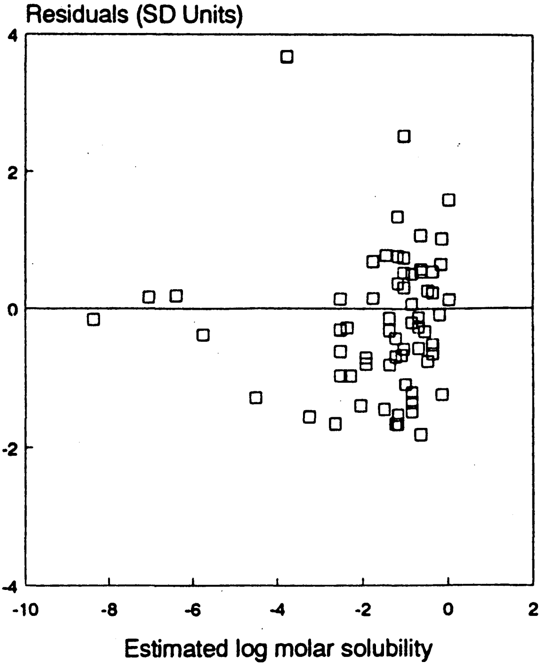

Fig. 2. Scattergram for aqueous solubility predictions for aliphatic alcohols, Eq. (2). Standardised residuals are expressed in standard deviation (SD) units.

Aqueous Solubility Predictions—Alkyl-*p*-Subsitituted Benzoates

Table-2 contains the aqueous solubility data and related physico-chemical constants. The three-parameter approach gave the Eq. (3).

$$\log S_w = -0.00922\ (\text{m.p.}-25) - 0.243\ \delta_2 - 0.039\ V_2 + 6.8188 \qquad (3)$$

$$n = 14;\ s = 0.0765;\ r^2 = 0.9988$$

$$F = 2377.62,\ F(3, 10, 0.01) = 6.55$$

TABLE-2
SOLUBILITY DATA OF ALKYL *p*-SUBSTITUTED BENZOATES

Sl. No.	Name of the compound	δ_2 (H)	V_2 (cc/mole)	log Sw^b (observed)
1.	Methyl *p*-aminobenzoate	11.42	123.1	−1.60
2.	Ethyl *p*-aminobenzoate	11.13	139.2	−1.99
3.	Propyl *p*-aminobenzoate	10.89	155.3	−2.33
4.	Butyl *p*-aminobenzoate	10.69	171.4	−2.76
5.	Pentyl *p*-aminobenzoate	10.53	187.5	−3.35
6.	Hexyl *p*-aminobenzoate	10.38	203.6	−3.95
7.	Heptyl *p*-aminobenzoate	10.26	219.7	−4.60
8.	Octyl *p*-aminobenzoate	10.16	235.8	−5.40
9.	Nonyl *p*-aminobenzoate	10.06	251.9	−6.00
10.	Dodecyl *p*-aminobenzoate	9.84	300.2	−7.80
11.	Methyl *p*-hydroxybenzoate	13.31	113.9	−1.84
12.	Ethyl *p*-hydroxybenzoate	12.82	130.0	−2.22
13.	Propyl *p*-hydroxybenzoate	12.42	146.1	−2.59
14.	Butyl *p*-hydroxybenzoate	12.09	162.2	−2.89

[a]Calculated by Fedors constants (Fedors, 1974)
[b]Yalkowsky and Valvani (1980)

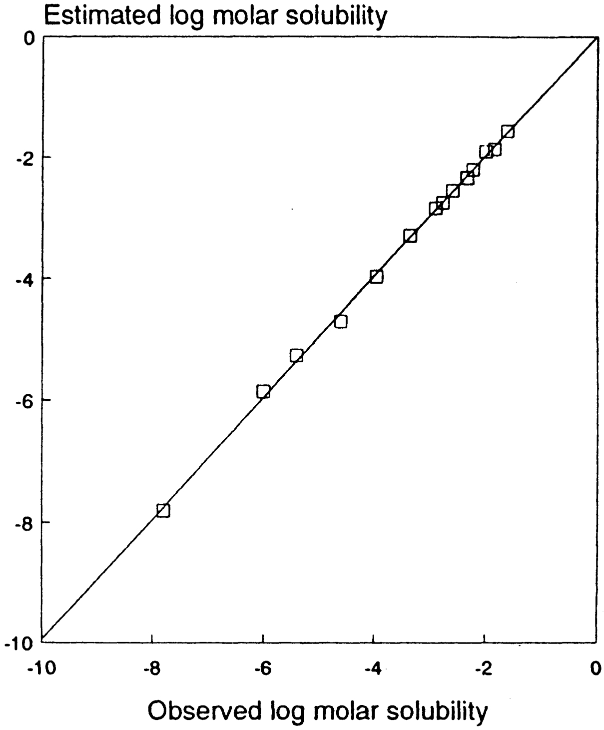

Fig. 3. Relationship between the estimated and observed log molar aqueous solubility of alkyl substituted benzoates, Eq. (3).

The correlations are significantly high ($r^2 = 0.9982$). The error in the predicted solubility is ± 4%. It is worth noting the coefficient of (m.p.-25) term and its sign, because this value is nearly 0.01 as estimated[3], in the context of regression equations with partition coefficients. *p*-Substituted benzoates can strongly interact with water through hydrogen bonding. The equation should reflect these types of interactions. Since the coefficient of (m.p.-25) is same as expected value, the coefficients of other parameters were reduced. However, their signs are same as in Eq. (1). The correlation coefficient was found to be 0.9923, when the m.p. term was dropped in the regression analysis. In general, the aim of regression analysis is to get $r^2 = 1$. In such cases, it is possible to include m.p. term, since such data is readily available in the literature or can be easily obtained experimentally. Therefore three-parameter approach is useful to predict the aqueous solubility.

Good linear relationship was obtained between the observed and estimated solubility values (Fig. 3). Scattergram indicated random distribution of points and the errors are within 2 standard deviation units (Fig. 4).

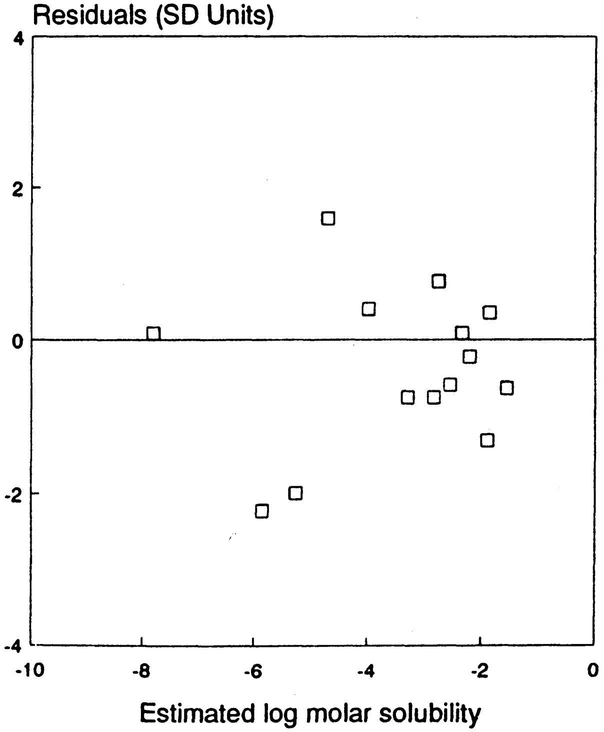

Fig. 4. Scattergram obtained from Eqn (3) for aqueous solubility predictions for alkyl substituted benzoates Eq. (3).

Aqueous solubility predictions—Steroids

Partition coefficient and melting point data were used by Yalkowsky and Valvani to correlate the aqueous solubility of steroids[3]. In their method, experimental PC values were employed because the estimated log PC values gave poor correlations. In the present study, the aqueous solubility data were extracted from literature[3] and used for regression analysis. The relevant parameters and observed solubility are given in Table-3. The three-parameter regression equation is:

$$\log S_w = -0.004\,(\text{m.p.}-25) + 0.2626\,\delta_2 - 0.01V_2 - 3.5851 \qquad (4)$$

$$n = 19;\ s = 0.3634;\ r^2 = 0.6561$$

$$F = 9.54;\ F(3, 15, 0.01 = 5.42$$

TABLE-3
SOLUBILITY DATA FOR SOME STEROIDS

Sl. No.	Name of the compound	δ_2 (H^a)	V_2 (cc/moles)^a	log S_w (observed)^b
1.	Hydrocortisone	13.75	257.8	–2.97
2.	Corticosterone	12.43	267.0	–3.24
3.	Deoxycorticosterone	11.37	273.1	–3.45
4.	Cortisone	13.16	259.6	–3.27
5.	Hydrocortisone acetate	12.54	299.3	–4.34
6.	Cortisone acetate	11.98	301.1	–4.21
7.	Deoxycorticosterone acetate	10.34	314.6	–4.63
8.	11-β-Hydroxyprogesterone	11.30	273.4	–3.82
9.	Progesterone	10.01	280.5	–4.42
10.	Testosterone	11.04	246.2	–4.08
11.	Prednisolone	13.85	256.6	–3.18
12.	Prednisolone acetate	12.61	294.1	–4.37
13.	Triamicinolone	14.38	251.3	–3.68
14.	Triamcinolone acetonide	12.44	296.7	–4.31
15.	Triamcinolone diacetate	11.65	336.5	–4.13
16.	Dexamethasone	13.60	268.8	–3.59
17.	Betamethasone	13.60	268.8	–3.77
18.	Dexamethasone acetate	12.44	310.3	–4.90
19.	Betamethasone-17-valerate	11.99	358.6	–4.71

[a]Calculated by Fedors constants (Fedors, 1974)
[b]Yalkowsky and Valvani, (1980)

The correlation coefficient is appreciable ($r^2 = 0.6561$). The F ratio is higher than the statistical table value (5.42). It indicates that the parameters in the equations (4) are significant. The errors in the predicted values are ± 10%. Equation (4) yielded poor correlation because these parameters were obtained by fragmental constants method[7]. This is not surprising since the addition of group contributions cannot account for nonadditive properties. Geometric features are nonadditive and can alter the solubility behaviour of the drugs. Similar conclusions were obtained for steroids with partition coefficients[3]. The coefficients and their signs in the equation (4) are not agreeing with the equations (1) and (3). It is understandable because each series will interact with water differently.

The results obtained in the present study indicated that the three-parameter-regression equation can provide a reasonable estimate of water solubility of different compounds. Whenever stronger interaction between different functional groups and water is possible, two parameter approach involving solubility parameter and molar volume adequate to predict the aqueous solubility.

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