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Isocratic chromatographic retention data for estimating aqueous solubilities of acidic, basic and neutral drugs

T.L. Hafkenscheid and E. Tomlinson *

Physical Pharmacy Group, Department of Pharmacy, University of Amsterdam, Plantage Muidergracht 24, 1018 TV Amsterdam (The Netherlands)

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Summary

For 108 compounds of diverse chemical character (including drug molecules) isocratic reversed-phase liquid chromatographic retention parameters have been used in modifications of the Hildebrand-Scott equation to estimate compound aqueous solubility. The relationships found are valid for both liquids and crystalline solids, as well as for stronger ($pK_a > 6.5$) bases that are chromatographed in a partially ionized state. It is observed that there is a significant constant difference in behaviour between acid and alcohol molecules and neutral and base molecules. This difference can be empirically corrected for during solubility estimations. Comparison of the use of octan-1-ol/water distribution coefficients in these equations shows that the use of isocratic chromatograhic retention parameters lead to significantly better estimations of compound aqueous solubility.

Introduction

Since Yalkowsky and Valvani (1979, 1980) demonstrated a semi-empirical relationship between organic non-electrolyte aqueous solubility and a linear combination of solute octan-1-ol/water distribution coefficient and (for crystalline solids) melting point, a number of similar findings have been reported (Armstrong et al.,

* To whom correspondence should be addressed.

1979; Chiou et al., 1982; Mackay et al., 1980; Treiner et al., 1982). Recognized drawbacks in both determining or estimating liquid/liquid distribution coefficients have lead us to propose (Hafkenscheid and Tomlinson, 1981a and b) that the reversed-phase high-performance capacity factor using pure aqueous eluents, (k'_w)—since it is shown theoretically to be a measure of the non-ideal behaviour of a non-electrolyte in aqueous solution (as given by its activity coefficient, (γ_w))—can be used to replace the octan-1-ol/water distribution coefficient in the Yalkowsky-Valvani equation. Recently other workers (Whitehouse and Cooke, 1982) have supported this suggestion by publishing similar correlations relating hydrocarbon aqueous solubilities to reversed-phase HPLC retention data and (for the case of solids) melting points. In addition, Bruggeman et al. (1982) have shown that reversed-phase thin-layer chromatographic data can have a similar use.

Direct determination of k'_w is difficult due to excessive retention, and in most cases is estimated using extrapolation techniques. The simplest approach for doing so is that due to Snyder et al. (1979) where the logarithm of the solute capacity factor, κ, is related to eluent organic modifier volume fraction, ϕ, by

$$\kappa = \kappa_w - B\phi \tag{1}$$

where κ is the logarithmic form of the capacity factor; B is a constant, being characteristic of the organic modifier and solute under study. Using methanol–water mixtures as eluents, we have shown (Hafkenscheid and Tomlinson, 1981b) for $0.3 < \phi < 0.9$, with 32 solid and liquid aliphatic and aromatic model compounds, that Eqn. 1 describes retention well, and that derived κ_w values can be used successfully in the Yalkowsky-Valvani equation. Similar agreements with Eqn. 1 have been reported by Miyake et al. (1977) for a limited series of penicillins and cephalosporins, and recently by Hammers et al. (1982) for a variety of apolar aromatics. However, in attempting to extend the set of compounds studied to include complex drug molecules, we have found considerable deviations from linearity according to Eqn. 1. Although the quadratic relationship between κ and ϕ proposed by Schoenmakers et al. (1979), i.e.

$$\kappa = \kappa_w + a\phi^2 - b\phi \tag{2}$$

where a and b are constants depending on the solute and organic modifier, could be used to adequately fit the experimental data, such quadratic relationships used for extrapolation purposes require a larger number of κ values to be determined, particularly at low values of ϕ, since the uncertainty in κ_w becomes greatly increased. In view of this problem, and considering the reason for attempting to estimate aqueous solubilities using readily obtainable chromatographic data, we have now studied the possibility of using isocratic retention data in the Yalkowsky-Valvani equation. This present contribution reports our findings for 108 solids and liquid solutes of varying physicochemical character, having a large range of aqueous solubilities, and studied using two isocratic reversed-phase systems.

Materials and Methods

Materials

Solutes studied (Table 1) were obtained from various sources and were generally of analytical or synthetical grade purity. Other solutes were of the highest available purity and were used without further purification. N,N-Dimethylaminododecane was from Fluka (Buchs, Switzerland) and was of 95% purity. Stationary phase material was Hypersil ODS (5 μm) from Ahrin, Rijswijk, The Netherlands. Eluents were volumetrically made up from combinations of analytical grade methanol (from Baker, Deventer, The Netherlands) and, (depending on the type of solute chromatographed): (i) double-distilled water, (I); or (ii) pH 2.15 ammonium phosphate buffer containing 80 mmol $\cdot$ l^{-1} NH_4^+, (II); or (iii) pH 7.00 ammonium phosphate buffer containing 80 mmol $\cdot$ l^{-1} NH_4^+, (III); or (iv) pH 7.00 ammonium phosphate buffer containing 80 mmol $\cdot$ l^{-1} NH_4^+ and 0.8 mmol $\cdot$ l^{-1} N,N-dimethylaminododecane, (IV).

Procedures

Chromatographic equipment consisted of an Altex 110A single-piston pump, (Altex, Berkley, CA, U.S.A.) with additional dampening, a model 7125 injection valve (Rheodyne, Berkeley, CA, U.S.A.) and Waters 440 UV and R401 refractive index detectors (Waters, Milford, MA, U.S.A.) arranged in tandem. Peak recording was achieved with a Kipp BD 41 flatbed potentiometric recorder (Kipp and Son, Delft, The Netherlands). Eluent reservoir and the column were kept at 20.00 $\mp$ 0.01°C by immersion in a Hetotherm 02PT 623 thermostat waterbath (Heto, Birkerod, Denmark). The eluent reached the injection valve via a 1 ml coil immersed in the waterbath. Solutes were dissolved in eluent, generally in submillimolar amounts. Retention times were measured at 20.00 $\pm$ 0.01°C at a flow rate of 0.5 ml $\cdot$ min^{-1} using a microsplit stopwatch, and were corrected for residence times in end connections (except for very large retention times which were measured from a calibrated recorder output). Corrected retention times used for calculation of k′ were averaged from at least 5 determinations, and had a coefficient of variance of less than 0.4%. Column dead times were determined using a dilute solution of water in eluent, and were continuously monitored.

Solubility values were generally taken from the literature (sources being: Breon and Paruta, 1970; Kabasakalian et al, 1966; Martindale, 1979; The Merck Index, 1976; Stephen and Stephen, 1963; The United States Pharmacopeia, 1980; Valvani et al., 1981; Yalkowsky and Valvani, 1980; Yalkowsky and Morozowich, 1980), or were determined by us at 20°C, (duplicated 72 h shake-flask equilibration, followed by filtration, centrifugation and analysis).

Data processing was carried out using a standard computer program for multivariate data handling.

TABLE I

CHROMATOGRAPHIC RETENTION DATA AND RELEVANT PHYSICOCHEMICAL PARAMETERS

Solute	character [a]	log $k'_{0.75}$	log $k'_{0.50}$	log K_d [b]	$-\log X_w$ [g] (mole fraction)	$[(T_m/T)-1]$	$\log(T_m/T)$
1. dichloromethane	N	−0.420	0.129	1.25	2.37		
2. trichloromethane	N	−0.235	0.480	1.95	2.98		
3. tetrachloromethane	N	0.145	1.044	2.73	4.02		
4. *n*-butanol	Alc.	−0.600	−0.054	0.88	1.76		
5. *n*-pentanol	Alc.	−0.380	0.314	1.41	2.35		
6. *n*-hexanol	Alc.	−0.163	0.694	2.03	2.99		
7. cyclohexane	N	0.602	1.633	3.44	4.81		
8. cyclohexanol	Alc.	−0.390	0.244	1.23	2.19		
9. cyclohexanone		−0.530	−0.022	0.81	1.75		
10. 2-chloropropane	N	−0.118	0.570	1.90	3.14		
11. 2-nitropropane	N	−0.610	−0.089	0.87	2.46		
12. 2-methylpropanoic acid	Ac.	−0.680 [c]	−0.120 [c]	–	1.44		
13. 2-methylbutanoic acid	Ac.	−0.490 [c]	0.185 [c]	–	2.13		
14. hexanoic acid	Ac.	−0.240 [c]	0.588 [c]	1.90	2.77		
15. octanoic acid	Ac.	0.177 [c]	1.288 [c]	–	4.07		
16. decanoic acid	Ac.	0.600 [c]	–	4.09	4.80	0.039	0.017
17. ethoxyethane	N	−0.410	0.055	0.83	1.84		
18. ethylacetate	N	−0.500	−0.075	0.70	1.78		
19. benzene	N	−0.062	0.663	2.10	3.38		
20. toluene	N	0.154	1.001	2.74	3.98		
21. ethyl-benzene	N	0.330	1.302	3.15	4.55		
22. iso-propyl-benzene	N	0.476	1.566	3.66	4.94		
23. propyl-benzene	N	0.530	1.648	3.63	5.05		
24. secbutyl-benzene	N	0.662	1.893	–	5.47		
25. chloro-benzene	N	0 114	1.011	2.84	4.09		
26. nitro-benzene	N	−0.259	0.471	1.84	3.51		
27. phenol	Ac.	−0.600	0.020	1.48	1.83	0.071	0.030
28. aniline	Ba	−0.700 [d]	−0.146 [d]	0.91	2.17		
29. benzoic acid	Ac	−0.490 [c]	0.276 [c]	1.87	3.32	0.348	0.130
30. methyl benzoate	N	−0.158	0.663	2.18	3.48		
31. ethyl benzoate	N	0.025	0.973	2.64	4.04		

32. propyl benzoate	N	0.221	1.300	–	4.56 [f]		
33. phenylmethanol	Alc	−0.61	0.023	1.10	2.19		
34. *p*-xylene	N	0.375	1.346	3.15	4.51		
35. *p*-chlorotoluene	N	0.329	1.359	3.33	4.71 [f]		
36. *p*-nitrotoluene	N	−0.070	0.770	2.39	4.13	0.118	0.048
37. *p*-cresol	Ac	−0.410	0.347	1.94	2.49	0.051	0.021
38. *p*-toluidine	Ba	−0.500 [d]	0.165 [d]	1.40	2.85	0.081	0.034
39. *p*-toluic acid	Ac	−0.287 [c]	0.591 [c]	2.27	4.32	0.553	0.191
40. *p*-dichlorobenzene	N	0.311	1.337	3.39	5.00	0.113	0.046
41. *p*-chloronitrobenzene	N	−0.054	0.779	2.40	4.59 [f]	0.217	0.085
42. *p*-chlorophenol	Ac	−0.308	0.538	2.39	2.73 [f]	0.080	0.033
43. *p*-chloroaniline	Ba	−0.450 [d]	0.310 [d]	1.83	3.41 [f]	0.179	0.072
44. *p*-chlorobenzoic acid	Ac	−0.150 [c]	0.763 [c]	2.65	5.27	0.761	0.246
45. *p*-dinitrobenzene	N	−0.380	0.323	1.48	5.07	0.526	0.183
46. *p*-nitrophenol	Ac	−0.490 [c]	0.218 [c]	1.92	3.33	0.324	0.122
47. *p*-nitroaniline	Ba	−0.760	−0.069	1.59	3.98	0.440	0.158
48. *p*-nitrobenzoic acid	Ac	−0.450 [c]	0.334 [c]	1.89	4.40	0.758	0.245
49. hydroquinone	Ac	−1.420	−0.840	0.55	1.94	0.526	0.183
50. *p*-hydroxybenzoic acid	Ac	−1.010 [c]	−0.330 [c]	1.58	2.98	0.666	0.221
51. methylparaben	Ac	−0.550	0.230	1.96	3.54	0.379	0.139
52. methyl-*p*-aminobenzoate	Ba	−0.720	−0.021	–	3.63	0.321	0.121
53. ethyl-*p*-aminobenzoate	Ba	−0.520	0.288	–	4.06	0.246	0.096
54. mesitylene	N	0.593	1.669	3.42	5.13		
55. 1,3,5-trichlorobenzene	N	0.891	2.098	–	6.18	0.148	0.060
56. durene	N	0.753	1.901	4.00	6.33	0.202	0.080
57. pentamethylbenzene	N	0.914	2.120	–	5.73	0.117	0.048
58. biphenyl	N	0.483	1.666	4.06	6.08	0.174	0.070
59. diphenylmethane	N	0.564	1.800	4.14	5.81	0.018	0.008
60. benzophenone	N	0.093	1.140	3.18	5.13 [f]	0.096	0.040
61. naphthalene	N	0.279	1.288	3.36	5.35	0.205	0.081
62. phenanthrene	N	0.655	1.904	4.46	6.89	0.260	0.100
63. anthracene	N	0.686	1.989	4.45	8.12	0.669	0.222
64. pyrene	N	0.848	2.195	4.88	7.89	0.464	0.165
65. triphenylene	N	0.980	2.440	–	8.74	0.611	0.207
66. perylene	N	1.225	2.830	–	10.54	0.881	0.274
67. barbitone	Ac	−0.840	−0.222	0.69	3.16	0.580	0.199
68. allobarbitone	Ac	−.680	0.093	1.19	3.54	0.519	0.182
69. amobarbitone	Ac	−0.296	0.679	2.07	4.41	0.468	0.167
70. butobarbitone	Ac	−0.440	0.410	1.89	3.47	0.365	0.135

TABLE 1 (continued)

Solute	character [a]	log $k'_{0.75}$	log $k'_{0.50}$	log K_d [b]	$-\log X_w$ [g] (mole fraction)	$[(T_m/T)-1]$	$\log(T_m/T)$
71. phenobarbitone	Ac	−0.680	0.159	1.43	4.07	0.532	0.185
72. metharbitone	Ac	−0.530	0.158	–	3.74	0.461	0.165
73. pentobarbitone	Ac	−0.277	0.679	2.03	4.40	0.375	0.139
74. secobarbitone	Ac	−0.203	0.820	2.15	5.16	0.505	0.178
75. mesantoin	Ac	−0.460	0.371	–	4.23	0.399	0.146
76. phenytoin	Ac	−0.460	0.544	2.44	5.56	0.949	0.290
77. phensuximide	Ba	−0.650	0.051	–	3.34	0.177	0.071
78. methsuximide	Ba	−0.440	0.358	–	3.60	0.113	0.046
79. primidone	Ac	−0.780	−0.050	–	4.38	0.891	0.277
80. acenocoumarin	Ac	−0.079 [c]	1.245 [c]	–	6.12	0.611	0.207
81. phenylbutazone	Ac	0.094 [c]	1.454 [c]	3.25	5.82 [f]	0.290	0.111
82. chlorothiazide	Ac	–	−1.060	−0.27	4.78	1.143	0.331
83. hydroflumethiazide	Ac	–	−0.680	−0.10	4.75	0.863	0.270
84. theobromine	Ac	−1.360 [c]	−0.940 [c]	−0.80	4.30	1.150	0.333
85. sulfaphenazole	Ac	−0.990 [c]	−0.137 [c]	1.55	4.07	0.556	0.192
86. phenacetin	Ba	−0.500	0.219	1.57	4.11	0.399	0.146
87. chloramphenicol		−0.710	0.107	1.14	3.86	0.447	0.161
88. meprobamate	N	−0.720	0.195	0.70	3.50	0.447	0.161
89. benziodarone	Ac	0.925 [c]	–	–	6.69 [f]	0.502	0.177
90. progesterone		0.400	1.743	3.79	6.16	0.379	0.139

91. testosterone	Alc	0.123	1.304	3.31	5.74	0.461	0.165
92. cortisone	Alc	−0.440	0.575	1.56	4.91	0.689	0.228
93. hydrocortisone	Alc	−0.310	0.686	1.61	4.85	0.659	0.220
94. prednisolone	Alc	−0.320	0.694	1.72	4.95	0.744	0.241
95. dexamethasone	Alc	−0.199	0.965	1.99	5.40	0.029	0.262
96. triamcinolone acetonide	Alc	−0.172	0.986	2.53	6.05	0.932	0.286
97. codeine		−0.420 [d]	0.217 [d]	-	3.31	0.454	0.162
98. cocaine	B	−0.035 [e]	0.490 [e]	2.09	4.34	0.266	0.102
99. strychnine	B	−0.340 [e]	0.145 [e]	1.93	5.07	0.846	0.266
100. nialamide	B	−0.620	0.079	0.87	3.82	0.454	0.162
101. methaqualone	B	−0.202	0.728	-	4.66	0.341	0.128
102. cyclizine	B	0.352 [e]	1.230 [e]	-	5.21	0.300	0.114
103. droperidol		0.077 [e]	1.375 [e]	3.50	5.32	0.430	0.155
104. haloperidol		0.068 [e]	1.091 [e]	4.30	6.17	0.440	0.158
105. diazepam	B	0.067	1.186	2.85	5.59	0.362	0.134
106. chlorprothixene	B	0.846 [e]	1.911 [e]	3.37	6.15 [f]	0.266	0.102
107. chlortetracycline	B	−0.690 [d]	0.271 [d]	−0.39	4.65	0.509	0.178
108. cimetidine	B	−1.120 [d]	−0.330 [d]	-	3.09	0.416	0.151

[a] Alc. = alcohol; Ac = acid; Ba = Base; N = neutral.
[b] Octan-1-ol/water distribution coefficient (Hansch and Leo, 1979).
[c] Determined using eluent II.
[d] Determined using eluent III.
[e] Determined using eluent IV.
[f] Determined in this present study.
[g] Solubility in pure water at room temperature (see Materials and Methods), except where determined by us (20°C).

Results and Discussion

Model

Hildebrand and Scott (1964) have argued that for regular solutions, solubility may be given by

$$-\log X = \log \gamma^{sat} + \frac{\Delta S_f}{2.3R}\left[\frac{T_m}{T} - 1\right] - \frac{\Delta C_p}{2.3R}\left[\frac{T_m}{T} - 1\right] + \frac{\Delta C_p}{R}\log\frac{T_m}{T} \quad (3)$$

where X is the mole fraction solubility; γ^{sat} the solute activity coefficient in saturated solution; ΔS_f, R and ΔC_p the entropy of fusion, gas constant and difference in heat capacity (at constant pressure) of solid and supercooled liquid solute; and T_m and T are the solute melting point and temperature, respectively. Hollenbeck (1980) has proposed two methods for simplifying Eqn. 3 for use with real solutions. That is:

(i) $\Delta C_p = 0$, which gives

$$-\log X = \log \gamma^{sat} + \frac{\Delta S_f}{2.3R}\left[\frac{T_m}{T} - 1\right] \quad (4)$$

Yalkowsky (1979) has suggested ΔS_f to be approximately constant, so that Eqn. 4 becomes

$$-\log X = \log \gamma^{sat} + C\left[\frac{T_m}{T} - 1\right] \quad (5)$$

where C is a constant

(ii) $\Delta S_f = \Delta C_p$; from which Eqn. 3 becomes

$$-\log X = \log \gamma^{sat} + \frac{\Delta C_p}{R} \cdot \log\frac{T_m}{T} \quad (6)$$

Assuming ΔC_p to be approximately constant then Eqn. 6 becomes

$$-\log X = \log \gamma^{sat} + D \log\frac{T_m}{T} \quad (7)$$

where D is constant.

Both simplifications (i.e. Eqns. 5 and 7) have been compared in this present study by substituting for $\log \gamma^{sat}$ a term of the form $(A \cdot \kappa + E)$.

Chromatography

As described in Materials, different methanolic aqueous eluents have been used (I–IV), dependent upon the physicochemical character (mainly pK_a) of the solute(s)

studied. These were evaluated by observing the solutes' chromatographic characteristics (peak shape and dependence of k′ on the amount of solute injected). Non-ionizable solutes (e.g. benzene), very weak acids (e.g. phenol, barbitone) or very weak bases (e.g. *p*-nitroaniline, phenacetin) were readily chromatographed using non-buffered eluent (I). Weak acids (e.g. benzoic acid, phenylbutazone) were chromatographed in their undissociated form using eluent made with buffer of pH 2.15 (II), and weak bases (aniline, codeine) were chromatographed using eluent with buffer of pH 7.00 (III). For some of the bases, addition of N,N-dimethylaminododecane to the eluent (IV) was found to be necessary to obtain good peak shape and to minimize the dependency of k′ on the amount of solute injected. (As discussed by Wahlund and Sokolowski (1978) the effect of this aliphatic hydrophobic amine appears to be due to the elimination of the effect of stationary phase residual silanol groups).

Results obtained for all solutes are presented in Table 1, together with their relevant physicochemical parameters; solutes 1–66 are model compounds, solutes 67–108 are drugs. The absence of some k′ values is due to the fact the they were either too high for proper detection (e.g. benziodarone or decanoic acid at $\phi = 0.50$) or too low (e.g. chlorothiazide at $\phi = 0.75$) to be measured with certainty.

Estimation of aqueous solubility

(a) All solutes

Estimations of solute aqueous solubility (i.e. $-\log X_w$, where the subscript w refers to water as the solvent) have been obtained using multiple linear regression analysis of the data given in Table 1. For liquids, where $T_m < T$ a dummy value of 0.000 was used for $[(T_m/T) - 1]$ and $\log(T_m/T)$. Eqns. 8–11 are the found relationships according to Eqns. 5 and 7 viz:

$$-\log X_w = \underset{(0.06)}{3.70} + \underset{(0.09)}{2.53}\,\kappa_{0.75} + \underset{(0.16)}{3.46}\,[(T_m/T) - 1] \quad (8)$$

($n = 106$; $r = 0.956$; $F = 547$)

$$-\log X_w = \underset{(0.07)}{3.62} + \underset{(0.08)}{2.51}\,\kappa_{0.75} + \underset{(0.49)}{10.7}\,\log(T_m/T) \quad (9)$$

($n = 106$; $r = 0.958$; $F = 574$)

$$-\log X_w = \underset{(0.07)}{2.13} + \underset{(0.05)}{1.79}\,\kappa_{0.50} + \underset{(0.14)}{3.08}\,[(T_m/T) - 1] \quad (10)$$

($n = 106$; $r = 0.964$; $F = 671$)

$$-\log X_w = \underset{(0.08)}{2.08} + \underset{(0.06)}{1.77}\,\kappa_{0.50} + \underset{(0.44)}{9.62}\,\log(T_m/T) \quad (11)$$

($n = 106$; $r = 0.962$; $F = 645$)

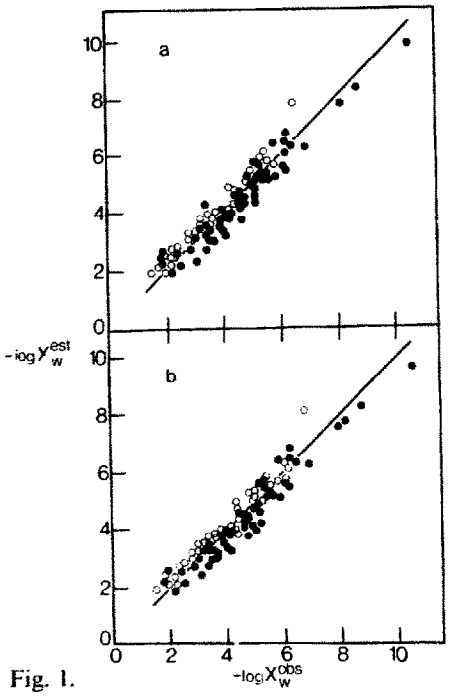

Fig. 1.

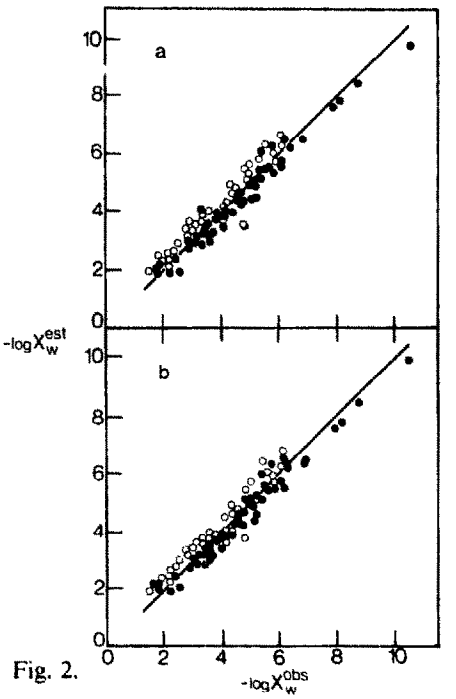

Fig. 2.

Fig. 1. Relationship between observed aqueous solubilities, $-\log X_w^{obs}$, and those estimated, $(-\log X_w^{est})$, using isocratic ($\phi_m = 0.75$) capacity factors and the: (a) $[(T_m/T)-1]$—Eqn. 8; and (b) $\log(T_m/T)$—Eqn. 9—approximations for all solutes studied. Key: closed datum points neutrals and bases, open datum points acids and alcohols.

Fig. 2. Relationship between observed aqueous solubilities, $-\log X_w^{obs}$, and those estimated, $(-\log X_w^{est})$, using isocratic ($\phi_m = 0.50$) capacity factors and the: (a) $[(T_m/T)-1]$—Eqn. 10; and (b) $\log(T_m/T)$—Eqn. 11—approximations. Key as for Fig. 1.

where the values in parentheses beneath the regression coefficients are observed standard deviations values for the coefficient; and n, r and F are the number of data values used, the multiple correlation coefficient and the variance ratio value, respectively. Figs. 1 and 2 are representations of Eqns. 8–11 in which estimated $-\log X_w$ values are plotted against observed solubility values. It is demonstrated by these Eqns. and figures that non-ionic solute aqueous solubilities can be well estimated using isocratic reversed-phase HPLC retention data incorporated in the simplified forms of the Hildebrand-Scott relationship, with between 91% and 93% of the variance in the solubility data being accounted for by the models used (all coefficients are significant above the 99.9% confidence level). However, no significant difference can be observed between the two models where either $[(T_mT) - 1]$ or $\log[(T_m/T)]$ have been used to account for intermolecular forces in the crystalline state. Thus either of the two simplifications described in Model can be used with equal success.

(b) Bases

Since pH 7 is close to the upper pH limit attainable with silica-based chemically-

bonded stationary phases, higher eluent pHs have not been used in this present study, which means that using eluent III, bases with a $pK_a > 6.5$ have been chromatographed in a partially dissociated form. For relatively insoluble ($-\log X_w > 2$) monoprotic bases, (B), the degree of ionization in a saturated aqueous solution, (I_w), is given by:

$$I_w = [BH^+]/(1000/18)X_w \tag{12}$$

where $[BH^+]$ is the concentration of the protonated base. Since

$$\frac{[BH^+]^2}{\frac{1000}{18} \cdot X_w - [BH^+]} = K_b = 10^{-14}/K_a \tag{13}$$

where K_b and K_a are the ionization constants of the base, then I_w may be expressed as (Hafkenscheid and Tomlinson, 1983)

$$I_w = \frac{10^{-14}}{K_a}\left[\frac{(1 + 222 \cdot 10^{14}K_aX_w)^{1/2} - 1}{111X_w}\right] \tag{14}$$

For bases with a pK_a less than 10 and with reasonable solubilities ($-\log X_w$ less than 6.5), I_w will be considerably lower than the degree of solute ionisation at pH = 7.0, ($I_{pH=7}$), which is given by

$$I_{pH=7} = \left(1 + \frac{K_a}{10^{-7}}\right)^{-1} \tag{15}$$

These general effects are graphically represented by Fig. 3, which shows both I_w for different values of X_w, and I at pH = 7 as a function of solute pH_a. It is seen that these bases are generally more dissociated at pH 7 than in a saturated aqueous

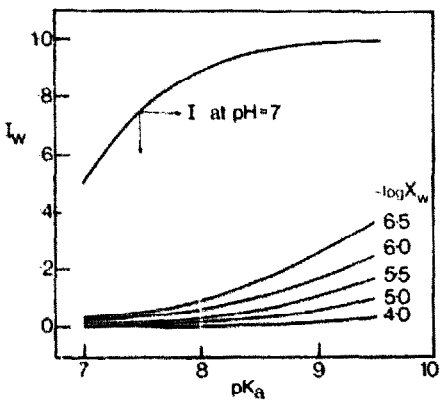

Fig. 3. Relationships between the degree of ionization in a saturated aqueous solution, I_w, (Eqn. 12), as a function of solute pK_a (Eqn. 14) for monoprotic bases of different aqueous solubilities, and the solute fraction ionized, (I), at pH = 7 versus pK_a.

solution, and, for the present study, should lead to log k′ values that give rise to estimate $-\log X_w$ values being lower than observed values. However, application of Eqns. 8–11 reveals that estimated $-\log X_w$ values for 'stronger' bases such as cyclizine ($pK_a = 8.16$; Perrin, 1972) and chlorprothixene ($pK_a = 7.6$, Hansch and Leo, 1979) are in good agreement with observed values. This may be explained by the influence of methanol on ionic equilibria in the mobile phase, and by the fact that phosphate anions present in the buffered eluents can act as pairing ions for the solute cations, which will thus be chromatographed as the more hydrophobic ion pair.

(c) Liquids

For solutes that are liquid at 20°C, using 0.000 as a dummy value for either $[(T_m/T) - 1]$ or $\log(T_m/T)$, then Eqns. 5 and 7 will reduce to

$$-\log X_w = A \cdot \kappa + E \tag{16}$$

and where the values of A and E should approximate to those found in Eqns. 8–11. For the 33 liquids here (Table 1), linear regression of the data shows this to be true, as given by Eqns. 17 and 18, i.e.

$$-\log X_w^l = 2.75(0.23)\kappa_{0.75} + 3.58(0.05) \tag{17}$$

$(n = 33;\ r = 0.972;\ F = 532)$

and

$$-\log X_w^l = 1.85(0.07)\kappa_{0.50} + 2.03(0.07) \tag{18}$$

$(n = 33;\ r = 0.977;\ F = 651)$

where superscript l denotes liquids; r is the correlation coefficient and the values in parentheses next to the regression coefficients are their standard deviations. Thus, for liquids there is a direct relationship between $\log X_w$ and log k′ obtained using isocratic reversed-phase systems.

(d) Acids and alcohols

Whilst examining differences between estimated (Eqns. 8–11) and observed solubility values (i.e. $\Delta(-\log X_w)$), it has been found that acidic solutes generally yield a positive value. For example, application of Eqn. 10 yields positive $\Delta(-\log X_w)$ values for 25 out of 32 acids, with a Sign-test showing this number of positive deviations to be significant above the 99% confidence-level.

The same phenomenon may be observed also for alcohols, (including hydroxy steroids); application of Eqn. 10 yielding a positive $\Delta(-\log X_w)$ value for 10 out of 11 alcohols—which is significant at the 98% level. This collective deviation in acid and alcohol solubility estimation can also be observed in the recent study by

Amidon and Williams (1982), who used an extended form of the Yalkowsky-Valvani equation to estimate solubility.

Since data for acids and alcohols have been incorporated in the original regressions, this will lead to some error in the estimation of $-\log X_w$ for other solute types using the regression coefficients of Eqns. 8–11. To examine in more detail the possibility of a relative variance in acid and alcohol behaviour, and in an attempt to adjust for any such effect, data for 38 neutral model compounds (Table 1) have been used to obtain $\log X_w^n$ (sic) as a function of κ and $[(T_m/T) - 1]$ or $\log(T_m/T)$, and then to use obtained regression coefficients for estimating the solubilities of other solute groups. Thus:

$$-\log X_w^n = \underset{(0.07)}{3.71} + \underset{(0.14)}{2.50}\kappa_{0.75} + \underset{(0.29)}{4.34}[(T_m/T) - 1] \quad (19)$$

$(n = 38; r = 0.984; F = 523)$

$$-\log X_w^n = \underset{(0.07)}{3.67} + \underset{(0.14)}{2.49}\kappa_{0.75} + \underset{(0.87)}{12.9}\log(T_m/T) \quad (20)$$

$(n = 38; r = 0.984; F = 522)$

$$-\log X_w^n = \underset{(0.08)}{2.31} + \underset{(0.06)}{1.68}\kappa_{0.50} + \underset{(0.21)}{3.96}[(T_m/T) - 1] \quad (21)$$

$(n = 38; r = 0.992; F = 1056)$

$$-\log X_w^n = \underset{(0.09)}{2.28} + \underset{(0.07)}{1.69}\kappa_{0.50} + \underset{(0.73)}{11.6}\log(T_m/T) \quad (22)$$

$(n = 38; r = 0.992; F = 1050)$

Fig. 4a and b illustrate the very highly significant relationships given between observed solubilities and isocratic chromatographic retention data for neutral model compounds, these are slightly more significant than shown previously (Hafkenscheid and Tomlinson, 1981b) for similar regressions performed using κ_w data (by extrapolation using Eqn. 1) for methyl, chloro and nitro mono- and disubstituted benzenes.

Taking Eqn. 21 as the most significant correlation found for the neutral model solutes, solubilities have been estimated for the 43 acids and alcohols and for 56 neutrals and bases given in Table 1; thus for (i) acids and alcohols:

$$-\log X_w^{obs} = \underset{(0.04)}{-0.85}\log X_w^{est} - \underset{(0.21)}{0.11} \quad (23)$$

$(n = 43; r = 0.952; F = 400)$

(ii) neutrals and bases:

$$-\log X_w^{obs} = -0.98(0.02) \log X_w^{est} + 0.04(0.10) \quad (24)$$

$(n = 56; r = 0.988; F = 2192)$

Statistical analysis reveals that the slope coefficients for Eqns. 23 and 24 differ significantly from unity at the 99.9% confidence level and the 50% confidence level, respectively, and that the intercepts do not differ from zero at the 50% confidence level. Although both intercepts are not dissimilar (at the 50% confidence level), the slope coefficients for Eqns. 23 and 24 are found to be significantly different from one another (at the 99% confidence level). These features are illustrated by Fig. 5a and b.

Such an exercise confirms the observations suggested by the Sign-tests that acids and alcohols behave significantly differently from other solute groups, and it can be suggested that, for example, using Eqn. 21 as the basic regression equation, then for acids and alcohols a simple multiplication factor, (i.e. $\times 0.85$), can be used to correct estimated solubility values.

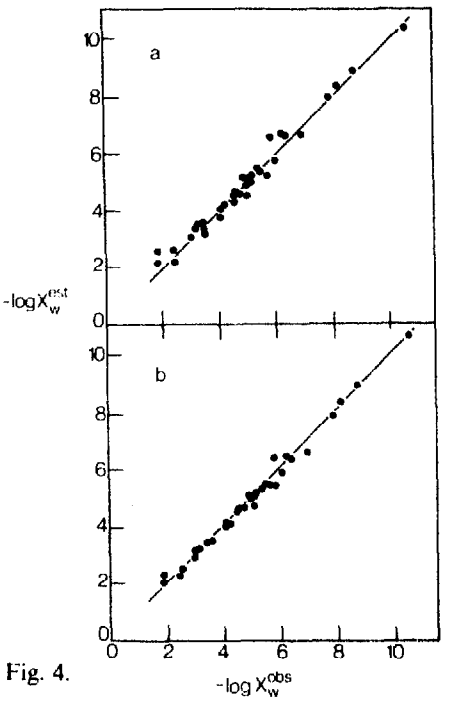

Fig. 4.

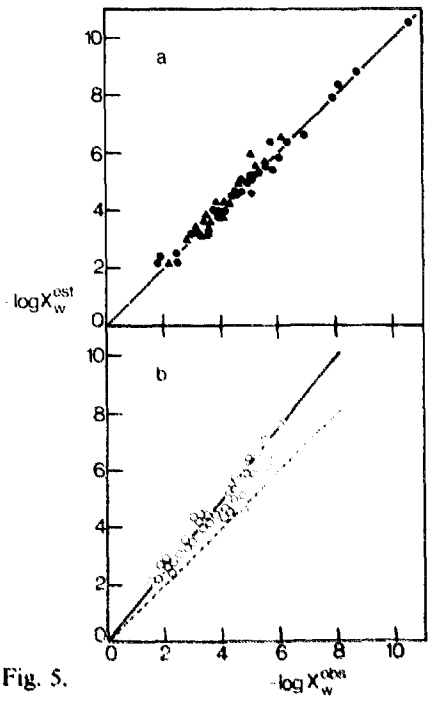

Fig. 5.

Fig. 4. For neutral model compounds (Table 1) relationships between observed aqueous solubilities and those estimated using: (a) isocratic κ ($\phi_m = 0.75$) and $\log(T_m/T)$ terms—Eqn. 20; and (b) isocratic κ ($\phi_m = 0.50$) and $[(T_m/T) - 1]$ terms—Eqn. 21.

Fig. 5. Solubility estimations using the regression coefficients of Eqn. 21 for: (a) all neutral and basic solutes—Eqn. 24; and (b) all acids and alcohols—Eqn. 23 (Table 1). The dashed line of Fig. 5b has a slope equal to unity and intercept of zero. (Key: bases are indicated by triangles).

(e) Specific solutes

The differentiation between various solutes according to their physicochemistry used in this paper has included monofunctional and multifunctional solutes with one strongly dominating function. However, some compounds (Table 1) are not readily classified because they either have a particular structural peculiarity or do not have a clearly dominant functionality. The solutes falling into these groups (Fig. 6) are now treated in more detail.

(i) Cyclohexanone. Using Eqns. 19–22, cyclohexanone yields $-\log X_w$ values considerably higher (2.24–2.39) than that observed (1.75). However, cyclohexanone is not a neutral compound since it is known to be weakly acidic due to keto–enol tautomerism ($pK_a = 11.3$).

(ii) Progesterone. Progesterone behaves not as a neutral compound (Fig. 6) but in a manner similar to the other 'alcoholic' steroids studied; (estimated $-\log X_w$ values (Eqns. 19–22) being 6.35–6.88). Progesterone exhibits keto–enol tautomerism which makes it behave as a weak acid. (Although this could be influenced by the presence of silanol groups on the surface of the stationary phase, with a large molecule like progesterone this is unlikely due to steric effects.)

(iii) Chloramphenicol. Using Eqns. 19–22, $-\log X_w$ values of 3.88–4.37 are calculated compared to an observed value of 3.86. Since chloramphenicol is an essentially neutral solute with 'alcoholic' functionalities, it appears that in such circumstances one can use the neutral model compound regression equation (Eqn. 21) with the correction term for acids or alcohols.

(iv) Haloperidol. Although haloperidol is a relatively strong base, ($pK_a = 8.66$), and has a hydroxy moiety (Fig. 6), it does not behave like chloramphenicol, rather it has estimated $-\log X_w$ values that are lower (5.79–5.99) than is observed (6.17). This may be explained by Fig. 3 which, as discussed above, shows that k′ values lower than expected will arise unless the protonated form of the base tends to form ion pairs with eluent phosphate anions.

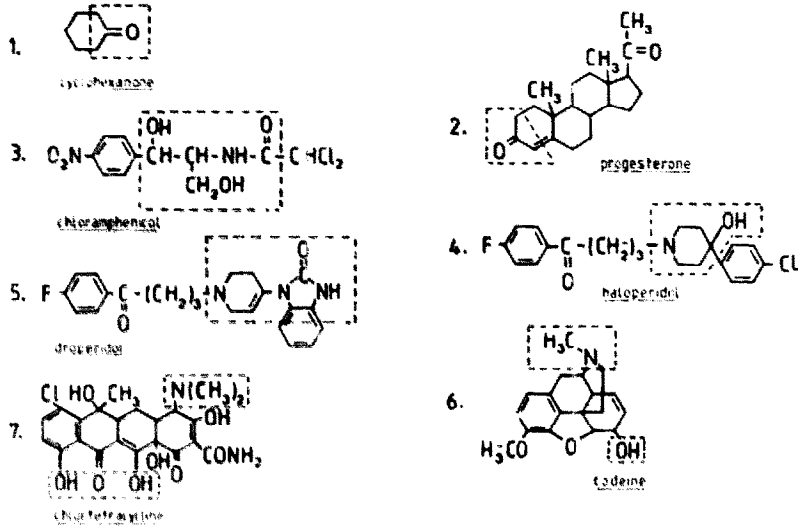

Fig. 6. Solute structures.

(v) Droperidol. Unlike its analogue, droperidol behaves as an 'acidic' compound, with its estimated $-\log X_w$ values (5.77–6.43) being considerably higher than the observed value of 5.32. Such behaviour is explained by –CO–NH– keto–enol tautomerism in the benzimidazol-2-one ring system (similar to its thione analogue—pK_a 9.18—Serjeant and Dempsey, 1979). Droperidol as a base has a lower pK_a (7.64) than haloperidol, which may partly explain the large difference in behaviour due to less ionization at pH 7.00 (Eqns. 14 and 15).

(vi) Codeine. This compound introduces a further degree of complexity, since, apart from being a relatively strong base ($pK_a = 8.21$) with a hydroxyl moiety, it is known to exist (Böhme and Hartke, 1976) as a hydrate with $T_m \approx 333°K$. This form will lead to a decrease in intermolecular forces in the crystalline state (anhydrous codeine has a T_m of 426°K). Interestingly, although using a T_m value of 426°K yields $-\log X_w$ values of 4.47–4.72, use of the lower hydrate T_m value of 333°K yields values of 3.23–3.34,which are close to the observed value of 3.31 (notwithstanding the presence of a hydroxyl-group).

(vii) Chlortetracycline. This antibiotic is a relatively strong base ($pK_a = 9.31$) with both acidic and alcoholic functionalities. At a pH of 7.00, the basic group will be fully ionized, whereas the acidic phenol ($pK_a = 7.47$) will be only partly ionized. At a pH = 7.00 chlortetracycline may thus be chromatographed in a number of states (ie. cation, zwitterion and/or ion pair). Although the $-\log X_w$ estimated using the regression coefficients derived using the neutral model solutes (Eqn. 21) is 4.78, (compared to an observed value of 4.65), it may not be concluded that chlortetracycline is chromatographed in a 'neutral' state, since it is uncertain from the literature as to the form in which this drug's solubility was obtained.

Extrapolated κ values

It has been an aim of a number of groups, including ourselves, to determine whether a chromatographic retention scale to describe solute hydrophobicity (sic) could be developed, and which would be as useful as the Pomona liquid/liquid distribution coefficient data base (Hansch and Leo, 1979). Early attempts (Tomlinson, 1975) to use thin-layer chromatography data were thwarted by low reproducibility of values, and initial use of HPLC techniques were unsuccessful due to the, then, usage of reversed-phase silica-based stationary phases having high residual silanol groups (Tomlinson et al., 1981). Arguing that only stationary phases with low residual silanol groups can be used in such studies, we have developed (Hafkenscheid and Tomlinson, 1981b) a chromatographic retention term, κ_w, using extrapolation of k′ data (using Eqn. 1) with $0.3 < \phi_m < 0.9$ eluent compositions and Hypersil ODS as the stationary support. Although this approach resulted in an excellent correlation between κ_w and octan-1-ol/water distribution coefficients using 32 model compounds, this present study indicated that this approach is not possible when drugs are considered. However, the excellent reproducibility of isocratic data $\kappa_{0.50}$ and $\kappa_{0.75}$ and the similarity in significance of, for example, Eqns. 19 and 21, etc., indicate that these two values could be combined to generate an extrapolated chromatographic term which may be used in such approaches as the Yalkowsky-Valvani

equation. Defining such a term as

$$\kappa_{ex} = \kappa_{0.50} + 2(\kappa_{0.50} - \kappa_{0.75}) \tag{25}$$

then replacing $\kappa_{0.50}$ and $\kappa_{0.75}$ values in the appropriate significant Eqns. described above (i.e. Eqns. 8–11, 17, 18, 19–22, and 23, 24), we obtain, respectively:

$$-\log X_w = \underset{(0.11)}{0.78} + \underset{(0.04)}{1.11}\kappa_{ex} + \underset{(0.48)}{7.42}\log(T_m/T) \tag{26}$$

$(n = 104;\ r = 0.958;\ F = 558)$

$$-\log X_w^1 = 1.09(0.05)\kappa_{ex} + 0.81(0.13) \tag{27}$$

$(n = 33;\ r = 0.968;\ F = 461)$

$$-\log X_w^n = \underset{(0.10)}{1.22} + \underset{(0.03)}{1.01}\kappa_{ex} + \underset{(0.19)}{3.72}\left[(T_m/T) - 1\right] \tag{28}$$

$(n = 38;\ r = 0.994;\ F = 1385)$

and using the coefficients of Eqn. 28 we further obtain for
(i) acids and alcohols:

$$-\log X_w^{obs} = -0.81(0.03)\log X_w^{est} - 0.13(0.17) \tag{29}$$

$(n = 41;\ r = 0.970;\ F = 611)$:

(ii) neutrals and bases:

$$-\log X_w^{obs} = -1.00(0.02)\log X_w^{est} - 0.08(0.12) \tag{30}$$

$(n = 56;\ r = 0.986;\ F = 1832)$.

(Eqns. 29 and 30 have slope coefficients which are significantly different from each other above the 99.99% confidence level.)

In all cases (Eqns. 26–30) it is seen that the use of the κ_{ex}-term does not alter the statistical significance of the corresponding relationships derived using $\kappa_{0.50}$ and $\kappa_{0.75}$ data, and hence can be used successfully in the Yalkowsky-Valvani equation. Of particular interest is that the magnitude of the κ_{ex} coefficient approximates to unity, which may suggest a physical relevance of κ_{ex} and which requires further study. Further, use of κ_{ex} leads to similar observations of the difference in behaviour between neutral and basic compounds and acidic and alcoholic solute.

Solubility estimation using octan-1-ol/water distribution coefficients—a comparison

Yalkowsky and Valvani (1979) have argued that since the solubility parameter of

most drugs is similar to that for octan-1-ol, then solute liquid/liquid distribution coefficients between water and octan-1-ol can be used to replace the γ^{sat} term of the Hildebrand-Scott equation (Eqn. 3). Our arguments (Hafkenscheid and Tomlinson, 1983) and those of others (Hammers et al., 1982), are that RP-HPLC retention data mimic aliphatic alcohol/water distribution coefficients more than those determined using alkane/water systems.

Considering the finding of this present study that use of RP-HPLC values in the Yalkowsky-Valvani equation reveals significant differences in behaviour of acids and alcohols and neutrals and bases, then it should follow that similar behaviour shows when octan-1-ol/water solute distribution coefficients, (K_d), are used. Hence, for those compounds for which K_d data are available (Table 1), we find

$$-\log X_w = \underset{(0.16)}{1.22} + \underset{(0.05)}{0.99} \log K_d + \underset{(0.21)}{2.84}\left[(T_m/T) - 1\right] \qquad (31)$$

$(n = 86;\ r = 0.912;\ F = 206)$

(for which the corresponding equation using RP-HPLC data has the legend)

$(n = 86;\ r = 0.955;\ F = 424).$

$(n = 86;\ r = 0.955;\ F = 424).$

$$-\log X_w^n = \underset{(0.09)}{1.24} + \underset{(0.03)}{1.04} \log K_d + \underset{(0.21)}{3.69}\left[(T_m/T) - 1\right] \qquad (32)$$

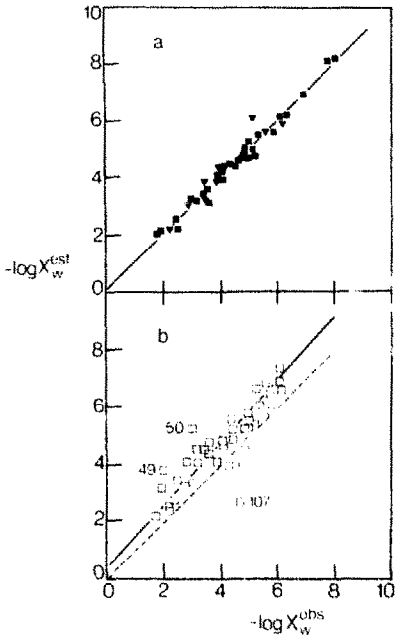

Fig. 7. Solubility estimates using octan-1-ol/water distribution coefficients (Eqn. 32) for: (a) neutral and basic solutes—Eqn. 34; and (b) acidic and alcoholic solutes—Eqn. 33. The dashed line of Fig. 7b has a slope equal to unity and intercept of zero. (Key as for Fig. 5; compound numbers are as Table 1).

Using Eqn. 32 in a similar manner to Eqns. 21 and 28 we obtain for (i) acids and alcohols:

$$-\log X_w^{obs} = -0.86(0.07) \log X_w^{est} - 0.16(0.33) \quad (33)$$

$(n = 37; r = 0.907; F = 162)$;

(ii) neutrals and bases

$$-\log X_w^{obs} = -0.98(0.03) \log X_w^{est} + 0.06(0.14) \quad (34)$$

$(n = 43; r = 0.981; F = 1048)$.

For Eqns. 33 and 34 slope coefficients are significantly different from each other above the 80% confidence level, and the slope coefficient of Eqn. 33 is shown to be significantly different from unity above the 90% level. The relationships embodied in Eqns. 33 and 34 are illustrated by Figs. 7a and b, which, together with the statistical relevances of Eqns. 31–34 show that although in all cases use of K_d values lead to poorer correlations, the difference in behaviour of these two groups of solutes is again in evidence.

Conclusions

For over 100 compounds, including simple mono- and polyfunctional solute and drug molecules of different physicochemical type, the use of isocratic RP-HPLC capacity factors in the Yalkowsky-Valvani simplification of the Hildebrand-Scott equation for describing aqueous solubilities has been shown to give excellent estimations over a wide solubility range ($1.4 < -\log X_w < 10.5$). In addition, the correlations obtained have a higher statistical significance than those obtained using octan-1-ol/water distribution coefficients. Although we have argued that due to ionization and buffer effects (Eqns. 12–15; Fig. 3), k′ values of bases should lead to lower estimations of their solubilities, this is found not to be the case (which may indicate that during chromatography protonated bases are either eluted as weakly formed ion pairs, or that there is salting out effect taking place—both of which lead to higher k′ values).

Finally, a significant finding of this study is that using isocratic k′ values there is a significant difference in behaviour between acids and alcohols, and neutrals and bases, with a constant overestimation of solubility for the former group which may be easily corrected for. These effects are also shown when octan-1-ol/water distribution coefficients are used (though at a less significant level), and appear to be inherent in the use of the Yalkowski-Valvani equation—an effect which requires further study.

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