International Journal of Pharmaceutics, 16 (1983) 225–239
Elsevier

Correlations between alkane/water and octan-1-ol/water distribution coefficients and isocratic reversed-phase liquid chromatographic capacity factors of acids, bases and neutrals

T.L. Hafkenscheid and E. Tomlinson *

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

(Received January 21st, 1983)
(Modified version received March 3rd, 1983)
(Accepted March 10th, 1983)

Summary

For a large number of acid, base and neutral liquids and solids (including drugs) general relationships between both octan-1-ol/water distribution coefficients and isocratic reversed-phase liquid chromatography capacity factors and solute aqueous activity coefficients have been shown. These have lead to highly significant correlations being found between octan-1-ol/water distribution coefficients and isocratic chromatographic capacity factors determined using aqueous methanol/alkylsilica phase systems. In contrast, only for a series of neutral and basic solutes could a limited linear relationship be found between isocratic capacity factors and aliphatic alkane/water distribution coefficients, (with acids — and alcohols — being displaced irregularly from this relationship). It is suggested that capacity factors determined using methanol–water (volume fraction organic modifier = 0.50)/octadecylsilane could be used as a priori descriptors of solute physicochemical character in, for example, drug design and preformulation studies.

Introduction

Numerical descriptions of drug physicochemical character are much needed in pharmaceutical science. Consider the studies on quantitative structure–activity rela-

---

* To whom correspondence should be addressed.

tionships, the rational design of liquid–liquid extraction systems, or the trend towards selection of delivery systems based on preformulation studies. A particularly useful description has become the liquid/liquid distribution (or partition) coefficient, since it may be considered as (variously) a measure of solute hydrophobicity (sic) or lipophilicity, depending on the solvent pair used. Of all systems studied, solute distribution coefficients in octan-1-ol/water (Hansch and Leo, 1979) have the widest use. The complex nature of this system has caused it to be criticized as either a standard state (Rytting et al., 1970), or for studies of hydrophobic effects per se (Kinkel et al., 1981), though its use is indicated where both hydrophobic and hydrogen-bonding effects are required. Though much attention has been given to methods for the prediction of these coefficients, (e.g. Hansch and Leo, 1979; Rekker, 1977), often direct measurement is favoured, with simple shake-flask methods indicated for occasional determinations of values in the −2.5 to +2.5 log unit range. Although for titration-type studies automated methods such as the filter-probe technique (Tomlinson, 1982) are becoming increasingly used, it is apparent from the literature that reversed-phase liquid chromatographic methods provide a suitable alternative to the shake-flask method for the measurement of a large number of solute distribution coefficients.

Chromatographic systems employed for this purpose are of two types. First, liquid/liquid arrangements — where an adsorbed layer of, for example, octan-1-ol, acts as the stationary phase; and, second, liquid/solid systems — which generally have a chemically-bonded alkylsilica (typically octadecylsilane) as the nominal stationary phase, with aqueous methanol (or acetonitrile) as the eluent. To date, 55 such studies have been reported that relate oil/water distribution coefficients to reversed-phase liquid chromatographic retention, and although with the latter type of system early approaches (e.g. Tomlinson et al., 1981) found only reasonable correlations between chromatographic and shake-flask distribution coefficients, the use of additives which mask the effects of residual surface silanol (sic) groups on bases' chromatography (Wahlund and Sokolowski, 1978) leads to substantially improved correlations. Recognition of the effect of stationary phase silanol groups on the retention behaviour of basic solutes — and the addition of silanol group-masking agents to the eluent (Wahlund and Sokolowski, 1978) — has lead to substantially improved correlations (Unger and Chiang, 1981), which, in part, has lead to the increased use of reversed-phase liquid/solid chromatography for estimating drug distribution behaviour (Carlson et al., 1975; McCall, 1975; Twichett and Moffat, 1975; Henry et al., 1976; Hulshoff and Perrin, 1976; Yamana et al., 1977; Harrison et al., 1978; Baker et al., 1979; Könemann et al., 1979; Riley et al., 1979; Veith et al., 1979; Xu et al., 1979; Hearn and Hancock, 1980; Rittich et al., 1980; Braumann et al., 1981; Butte et al., 1981; Fujisawa et al., 1981a and b; McDuffie, 1981; Thyssen, 1981; Verbiese-Génard et al., 1981; Wells et al., 1981; Wilson et al., 1981; Xu et al., 1981; d'Amboise and Hanai, 1982; Barbato et al., 1982; Bieganowska, 1982; Hammers et al., 1982; Hanai and Hubert, 1982; Lebl, 1982; Lins et al., 1982).

The majority of these latter studies have been performed using solutes limited in their physicochemical character, and little work has been reported for compound series of very differing types and properties. In an attempt to elucidate a general retention index from reversed-phase liquid/solid chromatographic measurements for use in, for example, the above described areas, we have used (Hafkenscheid and Tomlinson, 1981) an extrapolated index, (κ_w), which is the logarithm of the solute's capacity factor at 100% aqueous eluent conditions, obtained via linear extrapolation of capacity factor values obtained using eluent organic modifier volume fractions, (ϕ), of $0.3 < \phi < 0.9$. This extrapolation technique has been reported by others (Yamana et al., 1977; Braumann and Grimme, 1981; Hammers et al., 1982). However, although we found for 32 model compounds that this index was significantly correlated with octan-1-ol/water distribution coefficients, (K_d^{oct}), during a recent study (Hafkenscheid and Tomlinson, 1983) we have shown that this linear extrapolation technique is inappropriate for many large organic molecules — in particular complex drug molecules.

In this present contribution we describe those relationships existing between isocratic capacity factors of acid, base and neutral molecules (including drugs) and liquid/liquid distribution coefficients determined using octan-1-ol/water and aliphatic alkane/water solvent pairs.

Experimental

Two isocratic chromatographic conditions have been studied, i.e. with $\phi = 0.50$ and $\phi = 0.75$ methanolic aqueous eluents. 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); (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). (N,N-dimethylaminododecane acts as a silanol group masking agent).

Procedures and other experimental details are as described previously (Hafkenscheid and Tomlinson, 1983).

Results and Discussion

The liquid–liquid distribution coefficient of a solute at low concentrations is generally defined in terms of equilibrium concentrations, (C), in the oil (o) and water (w), i.e.

$$K_d = C_o/C_w = (\gamma_w^\infty/\gamma_o^\infty)(\bar{V}_w/\bar{V}_o) \quad (1)$$

where γ^∞ and $\bar{V}$ are solute activity coefficient (at infinite dilution) and solvent molar volume, respectively. Expressing this in logarithmic form, then

$$\log K_d = \log \gamma_w^{\infty} - \log \gamma_o^{\infty} + a \tag{2}$$

where a is a constant equal to $\log(\bar{V}_w/\bar{V}_o)$. With aqueous eluents and alkylsilica stationary phases, γ_w^{∞} may be shown (Hafkenscheid and Tomlinson, 1981) to be expressed by a function of solute retention by

$$\log \gamma_w^{\infty} = \kappa_w - b \tag{3}$$

where κ is the logarithm of the capacity factor using aqueous eluents and b is a constant. Yalkowsky and Valvani (1980) have argued on the basis of similar solubility parameters for most drugs and octan-1-ol (sic), that for non-electrolytes $\gamma_w^{\infty} = 1$. Assuming this to be true, and combining Eqns. 2 and 3, it follows that:

$$\log K_d = \kappa_w + c \tag{4}$$

where c is a constant. We have shown previously that Eqn. 4 holds for octan-1-ol/water distribution coefficients when applied to simple aliphatics and aromatics (Hafkenscheid and Tomlinson, 1981), where κ_w values were calculated from k′ data using ($\log k' = \kappa_w + B\phi$), obtained with methanol–water eluents ($0.3 < \phi < 0.9$) and

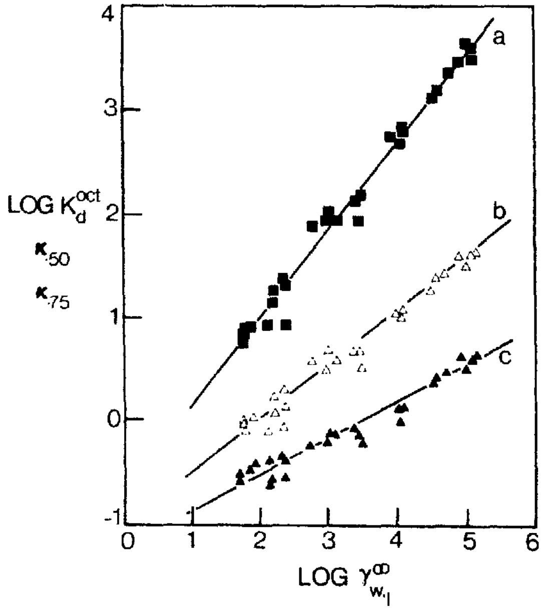

Fig. 1. Relationships between the logarithm of liquid solute–water activity coefficient at infinite dilution ($\log \gamma_{w,l}^{\infty}$) and: (a) the logarithm of solute octan-1-ol/water distribution coefficient, ($\log K_d^{oct}$); (b) the logarithm of solute isocratic chromatographic capacity factor at $\phi = 0.50$, ($\kappa_{0.50}$); and (c) logarithm of solute isocratic chromatographic capacity factor at $\phi = 0.75$, ($\kappa_{0.75}$). Drawn lines are regression lines according to: (a) Eqn. 6; (b) Eqn. 7; and (c) Eqn. 8, respectively.

where B is a constant for a given solute. Since B and κ_w are linearly related to one another (Hafkenscheid and Tomlinson, 1981; Hammers et al., 1982), it should follow from Eqn. 4 that there exist linear relationships between both $\log K_d^{oct}$ and $\log k'_{isocratic}$ and $\log \gamma_w^\infty$. Fig. 1 gives such relationships found for liquid solutes (at 20°C); where $\log \gamma_w^\infty$ has been obtained from

$$-\log X_w = \log \gamma_w^{sat} \cong \log \gamma_w^\infty \tag{5}$$

where X_w is the mole fraction aqueous solute solubility. (It has been shown (Hafkenscheid and Tomlinson, 1981) that for such compounds γ_w^∞ is a constant, independent of compound concentration.) From Fig. 1 it is seen for both distribution functions (and under both isocratic conditions) that these assumptions hold, such that

$$\log K_d^{oct} = 0.86(0.03) \log \gamma_{w,l}^\infty - 0.77(0.10) \tag{6}$$

$(n = 28;\ r = 0.985;\ F = 863)$

$$\kappa_{0.50} = 0.52(0.02) \log \gamma_{w,l}^\infty - 1.04(0.08) \tag{7}$$

$(n = 28;\ r = 0.975;\ F = 498)$

$$\kappa_{0.75} = 0.35(0.02) \log \gamma_{w,l}^\infty - 1.25(0.06) \tag{8}$$

$(n = 28;\ r = 0.965;\ F = 350)$

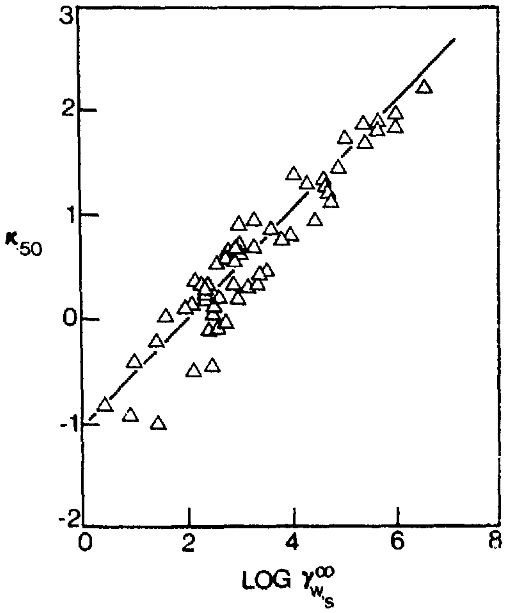

Fig. 2. Relation between the logarithm of solid solute-water activity coefficient at infinite dilution ($\log \gamma_{w,s}^\infty$) calculated using Eqn. 5, and the logarithm of solute isocratic chromatographic capacity factor at $\phi = 0.50$, ($\kappa_{0.50}$). The drawn line is the regression line for the same relationships for *liquid* solutes (Eqn. 7).

TABLE 1

LIQUID/LIQUID DISTRIBUTION COEFFICIENTS, EXTRAPOLATED CHROMATOGRAPHIC CAPACITY TERMS AND AQUEOUS ACTIVITY COEFFICIENTS

Solute	$\log K_d$ [a]		κ_{EX} [c]	γ_W^∞ [h]
	aliphatic alkane/ water [i]	octan-1-ol/ water		
1. dichloromethane		1.25	1.22	2.37 *
2. trichloromethane		1.95	1.90	2.98 *
3. tetrachloromethane	−0.02	2.73	2.83	4.02 *
4. butan-1-ol	−0.84	0.88	1.03	1.76 *
5. pentan-1-ol	−0.34	1.41	1.71	2.35 *
6. hexan-1-ol	0.45	2.03	2.41	2.99 *
7. cyclohexane	4.15	3.44	3.69	4.81 *
8. cyclohexanol		1.23	1.51	2.19 *
9. cyclohexanone		0.81	1.01	1.75 *
10. 2-chloropropane		1.90	1.95	3.14 *
11. 2-nitropropane	0.49	0.87	0.94	2.46 *
12. hexanoic acid		1.90	2.25 [f]	2.77 *
13. decanoic acid		4.09		4.68
14. ethoxyethane	0.93	0.83	0.99	1.84 *
15. ethylacetate		0.70	0.93	1.78 *
16. benzene	2.24	2.10	2.10	3.38 *
17. toluene	2.83	2.74	2.69	3.98 *
18. ethylbenzene	2.76	3.15	3.24	4.55 *
19. isopropylbenzene		3.66	3.75	4.94 *
20. propylbenzene		3.63	3.89	5.05 *
21. chlorobenzene	2.95	2.84	2.80	4.09 *
22. nitrobenzene	1.46	1.84	1.93	3.51 *
23. phenol	−0.84	1.48	1.26	1.62
24. aniline	−0.03	0.91	0.95 [g]	2.17 *
25. benzoic acid		1.87	1.81 [f]	2.29
26. methylbenzoate		2.18	2.31	3.48 *
27. ethylbenzoate		2.64	2.87	4.04 *
28. phenylmethanol	−0.72	1.10	1.28	2.19 *
29. para-xylene	3.09	3.15	3.29	4.51 *
30. para-chlorotoluene	3.30	3.33	3.42	4.71 *
31. para-nitrotoluene		2.39	2.45	3.78
32. para-cresol	−0.31	1.94	1.87	2.34
33. para-toluidine	0.44	1.40	1.49 [f]	2.61
34. para-toluic acid		2.27	2.34 [f]	2.68
35. para-dichlorobenzene	3.43	3.39	3.38	4.67
36. para-chloronitrobenzene		2.40	2.44	3.94
37. para-chlorophenol	−0.20	2.39	2.22	2.49
38. para-chloroaniline	0.60	1.83	1.83 [g]	2.88
39. para-chlorobenzoic acid		2.65	2.59 [f]	3.02
40. para-dinitrobenzene		1.48	1.73	3.51
41. para-nitrophenol	−1.96	1.92	1.65 [f]	2.37
42. para-nitroaniline		1.39	1.31	2.68
43. para-nitrobenzoicacid		1.89	1.89 [f]	2.16
44. hydroquinone		0.55	0.28	0.39
45. para-hydroxybenzoicacid		1.58	1.04 [f]	1.01
46. methylparaben		1.96	1.80	2.42
47. para-aminoethylbenzoate	−0.01		1.91	3.33
48. mesitylene		3.42	3.82	5.13 *
49. durene		4.00	4.19	5.73

TABLE 1 (continued)

Solute	log K_d [a]		κ_{EX} [e]	$\varkappa_w$ [h]
	aliphatic alkane/ water [i]	octan-1-ol/ water		
50. biphenyl		4.06	4.03	5.56
51. diphenylmethane		4.14	4.27	5.76
52. benzophenone	3.29	3.18	3.23	4.85
53. naphthalene	3.38	3.36	3.31	4.74
54. phenanthrene		4.46	4.43	6.12
55. anthracene		4.45	4.60	6.14
56. pyrene		4.88	4.89	6.52
57. barbitone	−1.95	0.69	1.01	1.45
58. allobarbitone		1.19	1.63	2.00
59. amobarbitone		2.07	2.63	3.02
60. butobarbitone		1.89	2.12	2.39
61. phenobarbitone		1.43	1.83	2.50
62. pentobarbitone	−1.30	2.03	2.59	3.29
63. secobarbitone		2.15	2.86	3.67
64. phenytoin		2.44	2.56	2.76
65. phenylbutazone	1.36	3.25	4.17 [f]	4.96
66. chlorothiazide		−0.27 [b]		1.40
67. hydroflumethiazide		−0.10 [b]		2.20
68. theobromine		−0.80	−0.10	0.91
69. sulfaphenazole		1.52	1.58 [f]	2.42
70. phenacetin		1.57	1.66	2.93
71. chloramphenicol	−1.48	1.14	1.74	2.54
72. meprobamate		0.70	2.03	2.18
73. progesterone	1.23	3.79	4.43	5.04
74. testosterone	0.37	3.31	3.67	4.38
75. cortisone	−0.55	1.56	2.60	2.88
76. hydrocortisone	−2.04	1.61	2.67	2.91
77. prednisolone		1.72	2.73	2.76
78. dexamethasone		1.99	3.29	2.95
79. triamcinolone acetonide		2.53	3.30	3.30
80. cocaine		2.09	1.54	3.56
81. strychnine		1.93	1.12	2.57
82. nialamide		0.87	1.48	2.48
83. droperidol		3.50 [d]	3.97	4.05
84. haloperidol		4.30	3.14	4.87
85. diazepam		2.85	3.43	4.52
86. chlorprothixene		3.37 [b,c]	4.04 [g]	5.37
87. chlortetracycline		−0.39	2.19	3.15

---

[a] Hansch and Leo (1979).

[b] For unionized species calculated using ion-correction equations.

[c] Frisk-Holmberg and van der Kleijn (1972).

[d] H.H. van Rooy (1980).

[e] At 20°C, calculated from k′ values given in Hafkenscheid and Tomlinson (1983), using chromatographic system I (Materials and Methods).

[f] Determined using eluent II.

[g] Determined using eluent III.

[h] For liquids (*) at 20°C calculated using Eqn. 5 and for solids using Eqn. 10 with values for $-\log X_w$ and T_m given in Hafkenscheid and Tomlinson (1983).

[i] Aliphatic alkane/water K_d values are averages of similar values for differing alkane/water systems (generally hexane/water; cyclohexane/water) (Hansch and Leo, 1979).

where n, r and F are the number of data points, linear regression correlation coefficient and variance-ratio coefficient, respectively; and where the values in parentheses are the standard deviations of the regression coefficients. κ is the logarithm of the capacity factor; subscripts 0.50 and 0.75 refer to volume fractions of methanol in the eluents used, and subscript 1 refers to liquids. Literature K_d values (Table 1) have been used in these correlations and κ values are as reported previously by us (Hafkenscheid and Tomlinson, 1983). Eqn. 2 gives that the constant a should equal $\log(\bar{V}_w/\bar{V}_o)$, which, if γ_{oct}^{∞} is assumed to be unity (Eqn. 4), has a value of about -0.80. This is in agreement with the intercept coefficient given in Eqn. 6. To obtain γ_w values for solids, we first need to recall the Hildebrand-Scott equation (1964) for describing the solubility of solids, i.e.

$$-\log X_w = \log \gamma_w^{sat} + \frac{\Delta S_f}{2.3R}\left[\frac{T_m}{T} - 1\right] - \frac{\Delta C_p}{2.3R}\left[\frac{T_m}{T} - 1\right] + \frac{\Delta C_p}{R}\log\frac{T_m}{T} \tag{9}$$

where ΔS_f, R and ΔC_p are 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. Assuming (Hollenbeck, 1980) that $\Delta C_p = 0$, and that ΔS_f is approximately constant, and for rigid molecules is 56.4 kJ · mol^{-1} (Yalkowsky, 1979), Eqn. 9 becomes

$$-\log X_{w,s} = \log \gamma_{w,s}^{sat} + 2.95[(T_m/T)\text{-}1] \tag{10}$$

where for poorly soluble compounds $\gamma_w^{sat} \cong \gamma_w^{\infty}$. Table 1 gives $\gamma_{w,s}^{\infty}$ values calculated in such a way using literature $-\log X_w$ and T_m values. Fig. 2 shows the relationship found between $\log \gamma_{w,s}^{\infty}$ and κ for $\phi = 0.50$. It is seen that there exists an excellent relationship between the two, such that for all liquids and solids studied we find that

$$\kappa_{0.50} = 0.50(0.02)\log \gamma_w^{\infty} - 1.03(0.07) \tag{11}$$

($n = 86$; $r = 0.946$; $F = 713$)

$$\kappa_{0.75}\text{-}0.35(0.01)\log \gamma_w^{\infty} - 1.36(0.05) \tag{12}$$

($n = 85$; $r = 0.944$; $F = 674$)

$$\log K_d^{oct} = 0.81(0.04)\log \gamma_w^{\infty} - 0.52(0.15) \tag{13}$$

($n = 86$; $r = 0.902$; $F = 365$).

For Eqn. 13 omission of values for chlorprothixene, whose reported K_d value (Hansch and Leo, 1979) is in doubt when it is compared to an average value of 5.35 log units found for the closely related solute, chlorpromazine, and chlortetracycline (whose reported value, given in Table 1, is for the ionized species), leads to a significant improvement in the correlation, with statistics being found of ($n = 84$) $r = 0.924$; $F = 482$.

The correlations given by Eqns. 11–13 give us confidence in examining for relationships between log K_d^{oct} and isocratic κ values, and Eqns. 14 and 15 are those found, i.e.

$$\log K_d^{oct} = 1.55(0.05)\kappa_{0.50} + 1.16(0.05) \tag{14}$$

$$(n = 82;\ r = 0.963;\ F = 1009)$$

$$\log K_d^{oct} = 2.12(0.09)\kappa_{0.75} + 2.61(0.05) \tag{15}$$

$$(n = 81;\ r = 0.932;\ F = 520)$$

Here, in addition to chlorprothixene and chlortetracycline, haloperidol has been omitted from the regression analyses since: (a) it is chromatographed at pH = 7 in the ionized state; and (b) only one reference is available for its K_d^{oct} value. Both relationships given by Eqns. 14 and 15 are shown by Figs. 3a and b.

Although the use of both isocratic phase systems leads to significant correlations between log K_d^{oct} and κ (with k′ values determined using $\phi = 0.50$ giving better correlations), these do mask the fact that for some solute pairs (e.g. toluene and chlorobenzene, or aniline and paranitroaniline), there is a reversal in retention order when using highly modified eluents (a finding also of McDuffie et al. (1981) and Bieganowska (1982)). Since high concentrations of methanol ($\phi > 0.75$) also affect eluent pH, it is suggested that isocratic conditions of $\phi = 0.50$ are preferable for obtaining such correlations.

Interestingly, both isocratic k′ values may be combined to give an extrapolated chromatographic term, κ_{ex} (Table 1), which can be regarded as a measure of compound hydrophobicity (Hafkenscheid and Tomlinson, 1983) and which has good

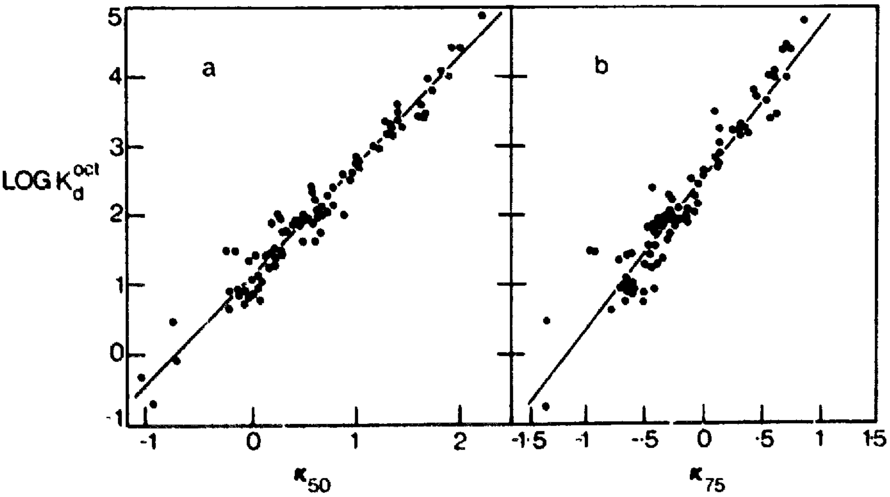

Fig. 3. Relationships between the logarithm of solute octan-1-ol/water distribution coefficients (log K_d^{oct}) and: (a) the logarithm of solute isocratic capacity factor at $\phi = 0.50$, ($\kappa_{0.50}$); and (b) the logarithm of solute isocratic capacity factor at $\phi = 0.75$ ($\kappa_{0.75}$).

correlation with log K_d^{oct}. Hence with

$$\kappa_{ex} = \kappa_{0.50} + 2(\kappa_{0.50} - \kappa_{0.75}) \tag{16}$$

then

$$\log K_d^{oct} = 0.92(0.04)\kappa_{ex} - 0.02(0.10) \tag{17}$$

$(n = 80;\ r = 0.940;\ F = 588)$

Solute types

When using either reversed-phase liquid chromatographic retention values or log K_d^{oct} values in general equations for estimating the aqueous solubilities of the compounds given in Table 1 (Hafkenscheid and Tomlinson, 1983), we have observed a marked difference in behaviour between acids and alcohols (including compounds able to undergo keto-enol tautomerism), and bases and neutrals. It is thus useful to examine for this behaviour in the present study. Omitting the outliers described previously, we obtain for

(i) neutral and bases:

$$\log K_d^{oct} = 1.66(0.05)\kappa_{0.50} + 1.06(0.06) \tag{18}$$

$(n = 42;\ r = 0.980;\ F = 951)$

$$\log K_d^{oct} = 2.42(0.10)\kappa_{0.75} + 2.50(0.05) \tag{19}$$

$(n = 42;\ r = 0.967;\ F = 570)$

(ii) acids and alcohols:

$$\log K_d^{oct} = 1.42(0.09)\kappa_{0.50} + 1.21(0.07) \tag{20}$$

$(n = 40;\ r = 0.928;\ F = 234)$

$$\log K_d^{oct} = 2.06(0.18)\kappa_{0.70} + 2.72(0.10) \tag{21}$$

$(n = 39;\ r = 0.885;\ F = 134)$

For all cases, use of $\kappa_{0.50}$ leads to higher correlation coefficients. Student t-tests on these correlations show that for Eqns. 19 and 21 ($\phi = 0.75$), the differences between slope and intercept coefficients are significant above the 90% confidence level, and with Eqns. 18 and 20 ($\phi = 0.50$), slope coefficients are significantly different at the 95% level, whereas the intercept values are significantly different at 80% level. These observed differences in correlations for the two solute groups appear to be manifestations of the effects of two solutes — hydroquinone and parahydroxybenzoic acid

— both of which are able to undergo association through intermolecular hydrogen-bonding in a hydrophobic environment. Without these solutes Eqns. 20 and 21 for acids and alcohols become, respectively:

$$\log K_d^{oct} = 1.52(0.09)\kappa_{0.50} + 1.13(0.06) \qquad (22)$$

$$(n = 38;\ r = 0.943;\ F = 289)$$

$$\log K_d^{oct} = 2.36(0.18)\kappa_{0.75} + 2.79(0.09) \qquad (23)$$

$$(n = 37;\ r = 0.913;\ F = 174)$$

Comparison of the slope and intercept coefficients of these latter equations with those of Eqns. 18 and 19, gives that the only statistically significant difference is between the intercept values of Eqns. 18 and 23 (which is significant above the 99% confidence level). Thus, these analyses show that for acids, bases and neutrals, a unique relationship exists between log K_d^{oct} and the isocratic κ parameter.

Aliphatic alkane / water distribution coefficients

Solute retention in methanol–water/alkylsilica chromatographic systems may be variously described in terms of a 'solvophobicity' model (Horváth et al., 1976), where mainly eluent contributions effect distribution to the stationary phase, or a 'partition' model (Lochmüller and Wilder, 1979), or a 'displacement adsorption' model (Hammers et al., 1982), for which adsorbed methanol forms (at least) a monolayer on the alkylsilica surface. In the context of these models, it is useful to

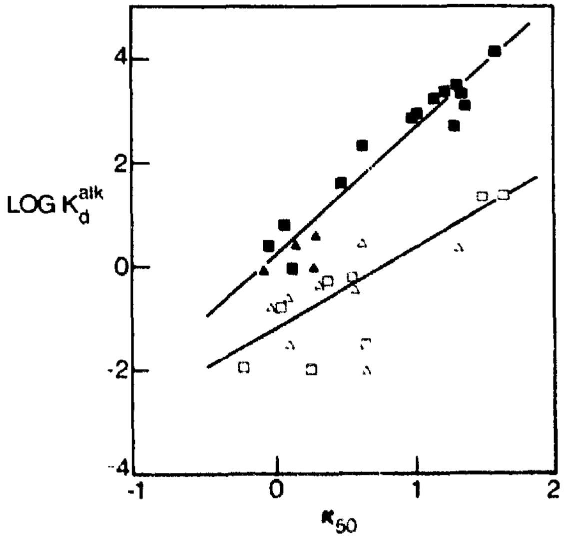

Fig. 4. Relationship between the logarithm of solute aliphatic alkane/water distribution coefficients (log K_d^{alk}) and the logarithm of solute isocratic capacity factor at $\phi = 0.50$ ($\kappa_{0.50}$), for neutrals (closed squares), bases (closed triangles), acids (open squares) and alcohols (open triangles). Drawn lines indicate the trend in the values and are not regression lines.

note that this present study does not find a general relationship between liquid/liquid distribution coefficients obtained in an aliphatic alkane/water system, (K_d^{alk}), and isocratic κ values.

Further insight can be gained by examination of the plot of log K_d^{alk} versus (for example) $\kappa_{0.50}$ (Fig. 4). A distinct relationship between these two parameters exists for most neutrals and bases studied (although some significant outliers exist); whereas all data points for alcohols and acids (including keto-enols), are irregularly displaced in a somewhat diffuse manner from this limited relationship. Thus, acids and alcohols appear to favour the aqueous phase of the alkane–water solvent pair to a greater extent than do basic and neutral solutes relative to effects demonstrated in either an octan-1-ol/water or a methanol–aqueous/alkylsilica system.

Conclusions

General relationships between both octan-1-ol/water distribution coefficients and isocratic chromatographic capacity factors, and solute aqueous activity coefficients (at infinite dilution) have been found for both liquid and solid neutral, acidic and basic solutes. Further, with the omission of compounds whose reported liquid/liquid distribution coefficients are subject to some criticism, highly significant correlations have been observed between shake-flask octan-1-ol/water distribution coefficients and isocratic chromatographic parameters. Based on arguments that at high concentrations of organic modifier: (a) large changes in eluent pH may occur; and that (b) the order of retention may be reversed due to specific effects of the modifier on retention, it is suggested that, using Hypersil octadecylsilane as stationary phase, an eluent of methanol–water of 0.50 volume fraction composition be used to obtain correlation of chromatographic parameters with log K_d^{oct} values. (The advantages of using chromatographic systems for estimating solute distribution coefficients, and the concordance found with (favoured) octan-1-ol/water K_d values, suggest to the present authors that rather than attempt to seek such correlations, it should be possible to use the $\kappa_{0.50}$ term directly as a descriptor of solute properties.)

The liquid/liquid distribution coefficients used in this study have been determined either in oil/water or oil/aqueous buffer solvent pairs (see Table 1). With the latter the given values are for the unionized form of the species as calculated using the usual ion-correction equations (Hansch and Leo, 1979). Since, in the chromatographic systems used in this present study, bases with a $pK_a > 6.5$ will be ionized to varying extents, the correlations between κ and log K_d^{oct} may indicate (as previously discussed by us — Hafkenscheid and Tomlinson, 1983) that: (i) the ionization of these solutes is suppressed by the methanol present in the eluent; and (ii) these bases are chromatographed as weak ion pairs with buffer phosphate ions.

Finally, it is shown that although reversed-phase liquid chromatography using aqueous methanol eluents and alkylsilica stationary phases may be used to obtain terms which correlate well with octan-1-ol/water distribution coefficients, the approach cannot be regarded as an analogue of an aliphatic alkane/water solvent system — in which distribution coefficients reflect a purely hydrophobic solute property (Kinkel et al., 1981). It is probable that this is due to the presence of an adsorbed (structured) methanol layer being present on the surface of the alkylsilica.

References

d'Amboise, M. and Hanai, T., Hydrophobicity and retention in reversed phase liquid chromatography. J. Liq. Chromatogr., 5 (1982) 229–244.

Baker, J.K., Rauls, D.O. and Borne, R.F., Correlation of biological activity and high-pressure liquid chromatographic retention index for a series of propranolol, barbiturate, and anthranilic acid analogues. J. Med. Chem., 22 (1979) 1301–1306.

Barbato, F., Recanatini, M., Silippo, C. and Vittoria, A., Hydrophobic constants and quantitative structure activity relationships (QSAR) in sets of phenothiazine drugs. Eur. J Med. Chem., 17 (1982) 229–234.

Bieganowska, M.L., Relationships between biological activity of N-phenylamides of benzoylacetic acid and their capacity ratios in reversed-phase systems. J. Liq. Chromatogr. 5 (1982) 39–48.

Braumann, T. and Grimme, L.H., Determination of hydrophobic parameters for pyridazinone herbicides by liquid-liquid partition and reversed-phase high-performance liquid chromatography. J. Chromatogr. 206 (1981) 7–15.

Butte, W., Fooken, C., Klussmann, R. and Schuller, D., Evaluation of lipophilic properties for a series of phenols, using reversed-phase high performance liquid chromatography and high-performance thin-layer chromatography. J. Chromatogr., 214 (1981) 59–67.

Carlson, R.M., Carlson, R.E. and Kopperman, H.L., Determination of partition coefficients by liquid chromatography. J. Chromatogr., 107 (1975) 219–223.

Ellgehausen, H., d'Hondt, C. and Fuerer, R., Reversed-phase chromatography as a general method for determining octan-1-ol/water partition coefficients. Pesticide Sci., 12 (1981) 219–227.

Frisk-Holmberg, M. and van der Kleyn, E., The relationship between the lipophilic nature of tricyclic neuroleptics and antidepressants, and histamine release. Eur. J. Pharmacol. 18 (1972) 139–147.

Fujisawa, S. and Masuhara, E., Determination of partition coefficients of acrylates, methacrylates, and vinylmonomers using high performance liquid chromatography (HPLC). J. Biomed. Res. Mater. 15 (1981a) 787–793.

Fujisawa, S. and Masuhara, E., Determination of hydrophobic parameters (log P_{HPLC}) for methacrylates, initiators and miscellaneous compounds used in dentistry by high-performance liquid chromatography (HPLC). Shika Rikogaku Zasshi, 22 (1981b) 277–284.

Hafkenscheid, T.L. and Tomlinson, E., Estimation of aqueous solubilities of organic non-electrolytes using liquid chromatographic retention data. J. Chromatogr., 218 (1981) 409–425.

Hafkenscheid, T.L. and Tomlinson, E., Isocratic chromatographic retention data for estimating aqueous solubilities, of acidic, basic and neutral drugs. Int. J. Pharm. (1983) submitted for publication.

Hammers, W.E., Meurs, G.J. and de Ligny, C.L., Correlations between liquid chromatographic capacity ratio data on LiChrosorb RP-18 and partition coefficients in the octanol-water system. J. Chromatogr., 247 (1982) 1–13.

Hanai, T. and Hubert, J., Hydrophobicity and chromatographic behaviour of aromatic acids found in urine. J. Chromatogr., 239 (1982) 527–536.

Hansch, C. and Leo, A., Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley Interscience, New York, 1979.

Harrison, I.T., Kurz, W., Massey, I.J. and Unger, S.H., Antibacterial activity of N-(β-styryl) formamides related to tuberin. J. Med. Chem., 21 (1978) 588–591.

Hearn, M.T.W. and Hancock, W.S., Hydrophobicity parameter capacity factor relationships of iodoaminoacids, J. Chromatogr. Sci., 18 (1980) 288–292.

Henry, D., Block, J.H., Anderson, J.L. and Carlson, G.R., Use of high-pressure liquid chromatography for quantitative structure-activity relationship studies of sulfonamides and barbiturates. J. Med. Chem., 19 (1976) 619–626.

Hildebrand, J. and Scott, R.L., The Solubility of Non-Electrolytes, Dover Publishing, New York, 1964.

Hollenbeck, G.R., Determination of differential heat of solution in real solutions from variation in solubility with temperature. J. Pharm. Sci., 69 (1980) 1241–1242.

Horváth, C., Melander, W. and Molnár, I., Solvophobic interactions in liquid chromatography with nonpolar stationary phases. J. Chromatogr., 125 (1976) 129–156.

Hulshoff, A. and Perrin, J.H., A comparison of the determination of partition coefficients of 1,4-benzodiazepines by high-performance liquid chromatography and thin-layer chromatography. J. Chromatogr., 129 (1976) 263–276.

Kinkel, J.F.M., Tomlinson, E. and Smit, P., Thermodynamics and extrathermodynamics of organic solute liquid-liquid distribution between water and 2,2,4-trimethylpentane. Int. J. Pharm., 9 (1981) 121–136.

Könemann, H., Zelle, R., Busser, F. and Hammers, W.E., Determination of log P_{oct} values of chloro-substituted benzenes, toluenes and anilines by high-performance liquid-chromatography on ODS-silica. J. Chromatogr., 178 (1979) 559–565.

Lebl, M., Amino acids and peptides. CLXXVIII. Correlation between the hydrophobicity of substituents in the phenylalanine moiety of oxytoxin carbaanalogues and reversed-phase-chromatographic k′-values. J. Chromatogr., 242 (1982) 342–345.

Lochmüller, C.H. and Wilder, D.R., The sorption behaviour of alkyl bonded phases in reverse-phase, high performance liquid chromatography. J. Chromatogr. Sci., 17 (1979) 574–579.

Lins, C.L.K., Block, J.H. Doerge, R.F. and Barnes, G.J., Determination of octanol–water equivalent partition coefficients of indolizine and substituted 2-phenylindolizines by reversed-phase high-pressure liquid chromatography and fragmentation values. J. Pharm. Sci., 71 (1982) 614–617.

McCall, J.M., Liquid-liquid partition coefficients by high-pressure liquid chromatography. J. Med. Chem., 18 (1975) 549–552.

McDuffie, B., Estimation of octanol/water partition coefficients for organic pollutants using reverse-phase HPLC. Chemosphere, 10 (1981) 73–83.

Rekker, R.F., The Hydrophobic Fragmental Constant, Elsevier, Amsterdam, 1977.

Riley, C.M., Tomlinson, E. and Jefferies, T.M., Functional group behaviour in ion-pair reversed-phase high-performance liquid chromatography using surface-active pairing ions. J. Chromatogr., 185 (1979) 197–224.

Rittich, B., Polster, M. and Králik, O., Reversed-phase high-performance liquid chromatography I. Relationship between R_M values and Hansch's π parameters for a series of phenols. J. Chromatogr., 197 (1980) 43–50.

van Rooy, H.H., The analysis of centrally-acting drugs in body fluids by GC and HPLC, Doctoral Thesis, University of Amsterdam, 1980, p. 90.

Rytting, J.H., Davis, S.S. and Higuchi, T., Suggested thermodynamic standard state for comparing drug molecules in structure–activity studies. J. Pharm Sci., 61 (1970) 816–818.

Thyssen, H.H.W., The relationship between log P, R_m, log k′, and the constants π and f; a study on penicillins. Eur. J. Med. Chem., 16 (1981) 449–452.

Tomlinson, E., Poppe, H. and Kraak, J.C., Thermodynamics of functional groups in reversed-phase high performance liquid-solid chromatography. Int. J. Pharm., 7 (1981) 225–243.

Tomlinson, E., Filter-probe extractor: a tool for the rapid determination of oil- water partition coefficients. J. Pharm. Sci., 71 (1982) 602–604.

Twichett, P.J. and Moffat, A.C., High-pressure liquid chromatography of drugs. An evaluation of an octadecylsilane stationary phase. J. Chromatogr., 111 (1975) 149–157.

Unger, S.H. and Chiang, G.H., Octanol-physiological buffer distribution coefficients of lipophilic amines by reversed-phase high-performance LC and their correlation with biological activity. J. Med. Chem., 24 (1981) 262–270.

Veith, G.D., Austin, N.M. and Morris, R.T., A rapid method for estimating log P for organic chemicals. Water Res., 13 (1979) 43–47.

Verbiese-Génard, N., Hanocq, M., van Damme, M. and Molle, L., High-performance liquid chromatographic capacity factor and partition coefficient relationship in a benzamide series. Int. J. Pharm., 9 (1981) 295–303.

Wells, M.J.M., Clark, C.R. and Patterson, R.M., Correlation of reversed-phase capacity factors for barbiturates with biological activities, partition coefficients and molecular connectivity indices. J. Chromatogr. Sci., 19 (1981) 573–582.

Wilson, J.J., Honegger, A., Stötzel, R.P. and Hughes, G.J., The behaviour of peptides on reverse-phase supports during high pressure liquid chromatography. Biochem. J., 199 (1981) 31–41.

Xu, X., Xu, H., Lu, Y.A. and Chen, J., Determination of partition coefficients by high-pressure liquid chromatography I. Determination of the partition coefficient of cinnamic acids and related compounds by reversed-phase high pressure liquid chromatography. Yao Hsueh Hsueh Pao, 14 (1979) 246–252.

Xu, X., Xu, H., Chen, J. and Tang, Q.M., Determination of partition coefficient by high pressure liquid chromatography III. Comparison of determination of partition coefficient using different kinds of bonded octadecylsilane support. Yao Hsueh Hsueh Pao, 16 (1981) 177–181.

Yalkowsky, S.H., Estimation of entropies of fusion of organic compounds. Ind. Eng. Chem. Fundam., 18 (1979) 108–111.

Yalkowsky, S.H. and Valvani, S.C., Solubility and partitioning I. Solubility of nonelectrolytes in water. J. Pharm. Sci., 69 (1980) 912–922.

Yamana, T., Tsuji, A., Miyamoto, E. and Kubo, O., Novel method for determination of partition coefficients of penicillins and cephalosporins by high-pressure liquid chromatography. J. Pharm. Sci., 66 (1977) 747–749.