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Epidermal permeability: penetrant structure relationships. 2. The effect of H-bonding groups in penetrants on their diffusion through the stratum corneum

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Abstract

The permeability coefficients of solutes through stratum corneum (SC) have previously been related to the presence of H-bonding groups on the penetrant. This study suggests that, whereas lipophilicity of a solute is the major determinant for solute partitioning into SC from aqueous solutions, the H-bonding of the solute is the main determinant of solute diffusion across SC. The diffusion is related to the number of H-bonding groups on the solute, with the presence of zero to two groups having the most pronounced effect on the magnitude of the diffusion coefficient. Diffusion was estimated from the permeability coefficient (k_p) and SC/water partition coefficient (K_{sc}) using the expression: $\log(D/h) = \log k_p - \log K_{sc}$ where D is the diffusion coefficient and h the path length for diffusion. For a set of 45 compounds the following regression is found: $\log(D/h) = -2.47 - 0.191\ \Sigma H - 0.0853\ \Sigma C^*$, $r^2 = 0.709$ where ΣH is the number of H-bonding groups present and ΣC^* the number of carbons not involved in a C=O bond in the penetrant. Better regressions are obtained when ΣC^* is used rather than size of the molecule as defined by molecular weight. An improved regression was obtained by using the solvatochromic parameters for individual H-bonding groups instead of ΣH: $\log(D/h) = -1.86 - 0.605\alpha - 2.09\beta$, $r^2 = 0.904$. Similar relationships between lag time, an independent estimate of diffusivity, and H-bonding parameters validate the dominant effect of H-bonding as a major determinant of diffusion coefficient.

Keywords: Epidermal permeability; Stratum corneum; Diffusion; Lag time; Solvatochromic; Hydrogen bonding

1. Introduction

The importance of molecular features has long been recognised as a determinant of solute penetration through skin (Scheuplein and Blank, 1971). The penetration of most compounds seems to be limited by the barrier function of the stratum corneum (SC) and, in particular, on the properties of the SC lipids (Potts and Guy, 1992; Surber et al., 1993). The mechanism(s) underlying this dependency remains unresolved. Almost 20 years ago Roberts (1976) noticed that permeability to phenolic compounds was inversely related

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to the number of H-bonding groups, and the role of H-bonding has recently been the subject of renewed interest following the development of the solvatochromic theory to explain partition phenomena (Kamlet et al., 1983) and most recently epidermal permeability (Abraham et al., 1995). Anderson and Raykar (1989) considered that the SC barrier could be modelled by a H-bonding organic solvent, and El Tayar et al. (1991) suggested the H-bond donor potential of the penetrant to be the main determinant of permeability. We have recently reviewed the various proposals relating permeability coefficient (k_p) of the SC to several penetrant properties (Roberts et al., 1995) and concluded that both the acceptor and donor properties of the penetrant H-bonding properties are important in determining k_p.

In this paper, we examine the dependence of the epidermal diffusion coefficient on the number of hydrogen bonding groups present on a penetrant molecule. The analysis is based on the assumption that the permeation through the stratum corneum is dependent on both a partition and diffusion process, the partition process being adequately defined by the stratum corneum-water partition coefficient in the first instance. The hypothesis that the epidermal diffusion coefficient is predominately related to the number of hydrogen bonding groups was then tested using lag times from the literature.

2. Methods

Data used in this study were extracted from the literature and are shown in Table 1. Log K_{sc} values are from Scheuplein and Blank (1971), Lien and Tong (1973), Anderson et al. (1976, 1988) and Roberts (1976). Log K_{oct} values are from the Medchem database (Biobyte Inc., Claremont, Ca), log k_p values from Flynn's database (Flynn, 1990) and lag times, τ, from Scheuplein et al. (1969), Roberts et al. (1977), and Siddiqui et al. (1989). Regression and most other statistical analyses were performed using the Minitab statistics package (Minitab Inc., State College, PA). Non-linear curve fitting was by the Minim package (R.D. Purves, University of Otago, Dunedin, New Zealand). Regressions are expressed in terms of N, the number of points in the regression; S.D., the standard deviation about regression; r^2, the coefficient of determination adjusted for degrees of freedom; F (Fisher's statistic), the regression mean square/error mean square; AIC, Akaike's information criterion (Yamaoka et al., 1978). Numbers in italics below coefficients are the p values. A high p value (traditionally > 0.05) indicates no significant difference between the coefficient and zero.

The diffusion coefficients of the solutes were estimated by two methods. The first method is based on the assumption that equilibrium determined stratum corneum-water partition coefficients can be used to deduce diffusivity from epidermal permeability coefficients derived from steady-state fluxes. The second method is based on the direct relationship between lag time for steady-state penetration and diffusivity.

2.1. Permeability approach

The steady-state flux (J) of a solute across a membrane is given by Fick's first law as

$$J = K_{sc} AD(c_o - c_i)/h \quad (1)$$

where A is the area over which penetration occurs, D is the diffusion coefficient of the penetrant, h is the diffusional path length and c_o and c_i the concentrations at the outer and inner layers of the barrier.

If $c_i \ll c_o$ the flux per unit area is given by

$$J_A = K_{sc} A(D/h)c_o \quad (2)$$

The permeability coefficient (k_p) is defined as

$$k_p = K_{sc}(D/h)$$

or

$$\log k_p = \log K_{sc} + \log(D/h) \quad (3)$$

Log(D/h) was calculated from the re-arrangement of Eq. (3)

$$\log(D/h) = \log k_p - \log K_{sc} \quad (4)$$

Table 1
Data used in the analyses

	MW	log K_{oct}	log K_{sc}	log k_p	log(D/h)	ΣH	ΣC*	α	β	π*	τ
aldosterone	360.4	1.08	0.83	−5.52	−6.35	5	19	0.40	1.90	3.47	−*
benzyl alcohol	108.1	1.10	1.34	−2.22	−3.56	1	7	0.33	0.50	0.87	−*
benzyl alcohol	108.1	1.10	0.61	−2.22	−2.83	1	7	0.33	0.50	0.87	−*
butanoic acid	88.1	0.79	0.18	−3.00	−3.18	1	3	0.60	0.45	0.62	−*
butanol	74.1	0.88	0.40	−2.60	−3.00	1	4	0.37	0.48	0.42	−*
m-cresol	108.1	1.95	1.03	−1.82	−2.85	1	7	0.57	0.34	0.88	0.25
o-cresol	108.1	1.95	1.03	−1.80	−2.83	1	7	0.52	0.30	0.86	0.25
p-cresol	108.1	1.95	1.03	−1.75	−2.78	1	7	0.57	0.31	0.87	0.27
cortexolone	346.5	2.52	1.36	−4.13	−5.49	4	19	0.35	1.57	3.45	−*
cortexone	330.5	2.58	1.57	−3.35	−4.92	3	19	−*	−*	−*	−*
corticosterone	346.5	1.94	1.23	−4.22	−5.45	4	19	0.40	1.63	3.43	16.5
cortisone	360.5	1.47	0.93	−5.00	−5.93	5	18	0.35	1.84	3.50	−*
estradiol	272.4	4.01	1.66	−3.52	−5.18	2	18	0.88	0.95	3.30	−*
estradiol	272.4	4.01	1.66	−2.28	−3.94	2	18	0.88	0.95	3.30	−*
estriol	288.4	2.45	1.36	−4.40	−5.76	3	18	1.40	1.22	3.36	−*
estrone	270.4	3.13	1.66	−2.44	−4.10	2	17	0.56	0.91	3.10	−*
ethanol	46.1	−0.31	0.00	−3.10	−3.10	1	2	0.37	0.48	0.42	−*
heptanoic acid	130.2	2.72	1.78	−1.70	−3.48	1	6	0.60	0.45	0.60	−*
heptanol	116.2	2.72	1.48	−1.50	−2.98	1	7	0.37	0.48	0.42	−*
hexanoic acid	116.2	1.92	1.08	−1.85	−2.93	1	5	0.60	0.45	0.60	−*
hexanol	102.2	2.03	1.00	−1.89	−2.89	1	6	0.37	0.48	0.42	−*
hydrocortisone	362.5	1.61	0.85	−5.52	−6.37	5	19	0.70	1.87	3.49	14.9
hydrocortisone	362.5	1.61	0.85	−3.93	−4.78	5	19	0.70	1.87	3.49	14.9
hy-6-OH-hexanoate	476.6	2.79	1.58	−3.04	−4.62	6	24	−*	−*	−*	−*
hy-hemisuccinate	462.5	2.11	1.15	−3.20	−4.35	6	21	−*	−*	−*	−*
hy-hexanoate	460.6	4.48	3.20	−1.75	−4.95	5	24	−*	−*	−*	−*
hy-me-pimelate	518.6	3.70	2.72	−2.27	−4.99	6	25	−*	−*	−*	−*
hy-octanoate	488.7	5.49	4.20	−1.21	−5.41	5	26	−*	−*	−*	−*
hy-proprionate	418.5	3.00	1.84	−2.47	−4.31	5	21	−*	−*	−*	−*
hydroxyprogesterone	330.5	2.97	1.60	−3.22	−4.82	3	19	0.25	1.31	3.35	−*
methanol	32.0	−0.77	−0.22	−3.30	−3.08	1	1	0.43	0.47	0.44	−*
me-hydroxybenzoate	152.1	1.96	0.90	−2.04	−2.94	2	7	0.69	0.45	1.37	−*
2-naphthol	144.2	2.70	1.52	−1.55	−3.07	1	10	0.61	0.40	1.08	0.50
octanoic acid	144.2	3.05	2.15	−1.60	−3.75	1	7	−*	−*	−*	−*
octanol	130.2		3.00	1.70	−1.28	−2.98	1	8	0.37	0.48	0.42
pentanoic acid	102.1	1.39	0.48	−2.70	−3.18	1	4	0.60	0.45	0.60	−*
pentanol	88.2	1.56	0.70	−2.22	−2.92	1	5	0.37	0.48	0.42	−*
phenol	94.1	1.46	0.73	−2.09	−2.82	1	6	0.60	0.30	0.89	0.25
pregnenolone	316.5	3.54	1.70	−2.82	−4.52	2	20	0.32	1.18	3.29	−*
progesterone	314.5	3.05	2.02	−2.82	−4.84	2	19	0.00	1.14	3.29	−*
propanol	60.1	0.25	0.30	−2.85	−3.15	1	3	0.37	0.48	0.42	−*
resorcinol	110.1	0.08	0.25	−3.62	−3.87	2	6	1.10	0.58	1.00	1.33
testosterone	288.4	3.32	1.36	−3.40	−4.76	2	18	0.32	1.19	2.59	23.2
thymol	150.2	−*	3.30	1.86	−1.25	−3.11	1	10	0.52	0.44	0.79
3,4-xylenol	122.2	2.35	1.28	−1.44	−2.72	1	8	0.56	0.39	0.86	−*
ethyl benzene	−*	3.15	−*	0.08	−*	−*	−*	−*	−*	−*	−*
styrene	−*	2.95	−*	−0.19	−*	−*	−*	−*	−*	−*	−*
toluene	−*	2.73	−*	0.00	−*	−*	−*	−*	−*	−*	−*

K_{oct} = partition coefficient octanol/water; K_{SC} = partition coefficient stratum corneum/water; k_p = permeability coefficient (cm/h); D = diffusion oefficient through stratum corneum (cm^2/h); h = pathlength through stratum corneum (cm); ΣH = H-bonding groups per molecule; ΣC* = non-carbonyl carbons per molecule; τ = lag time (h); * = not available or not used in this paper.
Log K_{sc} values from Scheuplein and Blank (1971), Lien and Tong (1973), Anderson et al. (1976, (1988) and Roberts (1976); Log K_{oct} from the Medchem database (Biobyte Inc., Claremont, Ca); log k_p from Flynn's database (Flynn, 1990); lag times from Scheuplein et al. (1969), Roberts et al. (1977), and Siddiqui et al. (1989); α, β and π* from Abraham (1993) and Abraham et al. (1995).

2.2. Lag time approach

An independent estimate of diffusion across the SC is given by the lag time, τ (Crank, 1956; Siddiqui et al., 1989).

$$\log \tau = \log(6/h) + \log(D/h) \quad (5)$$

3. Results and discussion

3.1. Method based on Roberts

Roberts (1976) first suggested that the passage of a permeant through skin was related to its H-bonding capacity, expressed simply as the number of H-bonding groups present in the molecule, and the size of the molecule as defined by its molecular weight. He used a Stokes-Einstein model for diffusion in which the diffusivity is related to $MW^{0.5}$, appropriate when the penetrant molecule is much smaller than the free volume into which it may diffuse in the stratum corneum. In our initial analysis, we examined the effect of number of hydrogen bonding groups as a determinant of the diffusivity of solutes in the stratum corneum by a regression of $\log(D/h)$ against ΣH (the number of H-bonding groups in the permeant molecule). A correlation did exist but the r^2 was rather low at 0.624 (model M1). A plot of the data is shown in Fig. 1a.

$$(\log k_p - \log K_{sc}) = \log(D/h)$$

$$= -2.80 - 0.500 \sum H$$

$$< 0.001 \quad < 0.001 \quad \text{(M1)}$$

$N = 45$; S.D. = 0.680; $r^2 = 62.4\%$; $F = 73.9$; AIC = 137

The r^2 figure suggests that little more than 60% of the value of $\log k_p$ can be accounted for by this very simple measure of H-bonding capacity noted by Roberts (1976). Inclusion of MW as a determinant of diffusivity as suggested by Roberts (1976) and more recently by Potts and Guy (1992) improved r^2 slightly to 0.672, but the p value of ΣH increased to an unacceptable level of 0.404 (model M2).

$$(\log k_p - \log K_{sc})$$

$$= \log(D/h) = -2.56 - 0.125 \sum H - 0.00501\ MW$$

$$< 0.001 \quad 0.404 \quad 0.009 \quad \text{(M2)}$$

$N = 45$; S.D. = 0.635; $r^2 = 67.2\%$; $F = 46.2$; AIC = 131

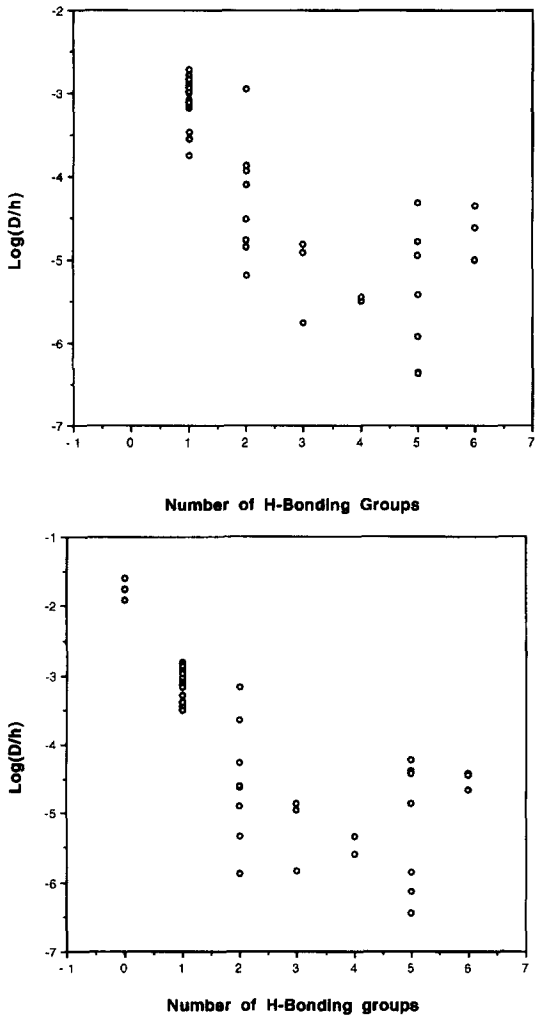

Fig. 1. Log(D/h) values plotted against number of H-bonding groups per penetrant molecule. (D/h) units are cm h^{-1}. Log(D/h) is calculated from $\log k_p - \log K_{sc}$. In (a) experimental $\log K_{sc}$ are used; in (b) they are calculated from $-0.025 + 0.59 \log K_{octanol}$.

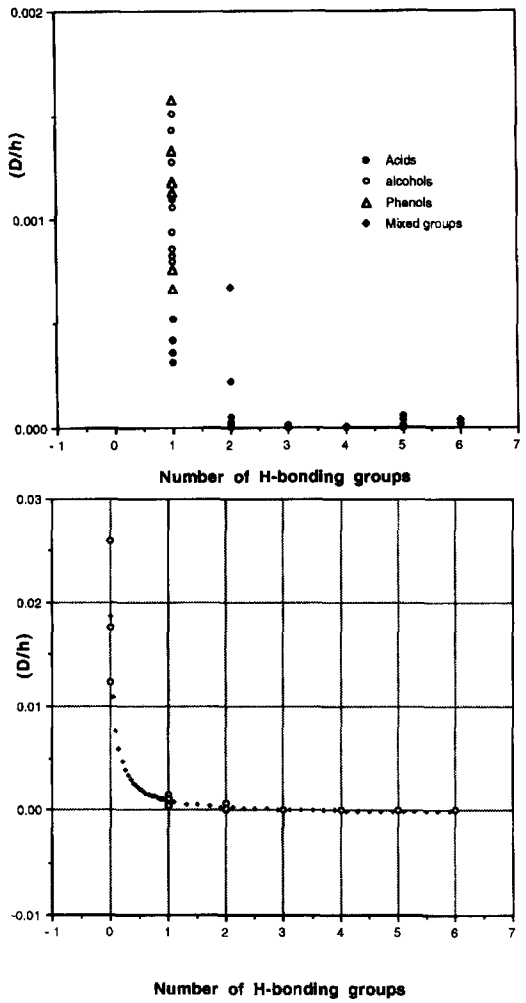

Fig. 2. (D/h) values plotted against number of H-bonding groups per penetrant molecule. (D/h) units are cm h^{-1}. (D/h) is calculated from k_p/K_{sc}. In (a) experimental K_{sc} are used; in (b) they are calculated from $\log K_{sc} = -0.024 + 0.59 \log K_{octanol}$. The theroretical plot in (b) is that of Eq. (M8) using the parameter values $(D_o/h) = 0.0186$ cm h^{-1}, $(D_M/h) = -3.5 \times 10 - 4$ cm h^{-1} and $K = 0.073$.

The plot of (D/h) against ΣH is shown in Fig. 2a. H-bonding capacity is plotted simply as the number of groups, irrespective of their strengths, and of molecular size, so that the plotting of mean values and standard deviation error bars may not be appropriate in terms of a statistical analysis. Nevertheless Fig. 2a shows that the introduction of one H-bonding group brings about a dramatic reduction in diffusivity; second and third groups cause further reductions although the effect is non-linear, and further groups have no effect on the minimal value. Generally acids seem to diffuse more slowly than alcohols or phenols. To extend the plot to compounds with no H-bonding groups we included ethyl benzene, styrene and toluene in the dataset. Log K_{sc} values are not reported for these so were calculated from the relationship (see later):

$$\log K_{sc} = -0.024 + 0.590(\log K_{oct}) \quad (6)$$

The plot in Fig. 2b shows the effect of H-bonding groups on diffusion even more dramatically. The curve shape suggests that the diffusion coefficient is dependent in terms of a maximal adsorption of a solute to polar groups in the transport pathway of solutes through the stratum corneum. Accordingly, the diffusion coefficient of a solute decreases as the solute becomes bound to polar groups in the pathway until these groups are unable to associate with any additional H-bonding groups on the solute. Above this saturable number of groups, the diffusion coefficient of the solute appears to be relatively constant.

The diffusivity of a solute can then be related to a saturable adsorption process for a given solute in a form analogous to the Langmuir's isotherm which has the general form:

$$\text{Amount adsorbed} = \frac{\text{Maximal amount adsorbed}}{(K/\text{concentration of adsorbent}) + 1} \quad (7)$$

where the equilibrium constant, K, is the ratio of rate constants for the desorption and adsorption processes. Recognising that the maximal diffusion coefficient is related to the minimal adsorption, Eq. (7) is re-expressed in the form:

$$(D_n - D_o)/h = [(D_M - D_o)/h]/[(K/n) + 1]$$

or

$$(D_n/h) = \{[(D_M - D_o)/h][n/(K+n)]\} + (D_o)/h \quad (8)$$

so that the effect of introducing n H-bonding groups is the difference in diffusion from a maximal value, (D_o/h), corresponding to zero H-bonding groups, and D_M is the maximal effect, theoretically at $n = \infty$.

This relationship between D_n/h and n was plotted using the Minim fitting program, giving $(D_o/h) = 0.0186$ cm h^{-1}, $(D_M/h) = -3.5 \times 10^{-4}$ cm h^{-1} and $K = 0.073$. $N = 48$; $r^2 = 91\%$

The data fit Eq. (8) reasonably well, as may be seen from Fig. 2b where values of (D_n/h) calculated using the Minim results are plotted along with the observed values. The equation is consistent with a dramatic reduction of diffusion when one or two H-bonding groups are added to a hydrocarbon skeleton. A plateau diffusion coefficient is predicted for the introduction of more than two groups. The reciprocal of the K value (13.7) suggests the effect of attraction to binding sites is an order of magnitude greater than the entropic tendency for molecules to leave these sites. The effect of H-bonding is therefore such a dominant feature that it would quickly reach a maximum value as successive H-bonding groups are added to a penetrant molecule. This analysis clearly shows that the effect of H-bonding on permeability is not a linear additive effect as implied by one of us earlier (Roberts, 1976) and later assumed by Lien and Gao (1995).

Our earlier paper (Roberts et al., 1995) argued on the basis of solvatochromic theory that molecular size is generally correlated to the lipophilic nature of the permeant, which is the underlying main determinant. This seems to be substantiated by the substitution of the number of carbon atoms (ΣC), or, better, ΣC* (the number of C atoms not involved in H-bonding C=O groups) for MW, which give superior regressions (Models M3, M4).

$$(\log k_p - \log K_{sc}) = \log(D/h) = -2.53 - 0.165 \sum H - 0.0789 \sum C$$

$$< 0.001 \quad 0.146 \quad 0.002 \quad \text{(M3)}$$

$N = 45$; S.D. = 0.610; $r^2 = 69.7\%$; $F = 51.7$; AIC = 128.

$$(\log k_p - \log K_{sc}) = \log(D/h) = -2.47 - 0.191\ \Sigma H - 0.0853\ \Sigma C^*$$

$$< 0.001 \quad < 0.001 \quad < 0.001 \quad \text{(M4)}$$

$N = 45$; S.D. = 0.599; $r^2 = 70.9\%$; $F = 54.5$; AIC = 126

It is noteworthy that Scheuplein and Blank (1971, 1973) have related the permeability of alcohols to number of carbon atoms rather than size.

A possible limitation in deriving Eqs. (M1) to (M4) is the use of equilibrium-derived stratum corneum-water partition coefficients in deducing diffusion coefficients from dynamic epidermal permeability coefficient data. We therefore also examined K_{sc} as an independent variable to confirm its significance as a determinant of epidermal permeability coefficients and to ascertain whether its coefficient was approximately unity. A coefficient other than unity would be indicative of a partition process into an environment with a polarity different from that defined by an equilibrium-derived stratum corneum-water partition coefficient. The following regression was obtained:

$$\log k_p = -2.72 + 0.911 \log K_{sc} - 0.484\ \Sigma H$$

$$< 0.001 \quad < 0.001 \quad < 0.001 \quad \text{(M5)}$$

$N = 45$; S.D. = 0.685; $r^2 = 61.3\%$; $F = 35.8$; AIC = 138

Thus, $\log k_p$ is significantly related to $\log K_{sc}$ and the coefficient (0.911) is not significantly different ($p = 0.903$) from unity.

3.2. Method based on individual H-bonding group contributions

Whilst our initial analysis suggests that the presence and number of H-bonding groups is a determinant of diffusivity within the stratum

corneum, the use of an arbitrary number of hydrogen bonding groups does not provide an optimal regression for diffusivity predictions. It is to be expected that the different groups (alcohol, acid, etc.) would have different H-bonding capacities and hence different efficacies in retarding diffusion.

The use of defined H-bond contributions for individual groups, as defined by the solvatochromic parameters α and β, (Abraham et al., 1995) led to an excellent regression:

$$(\log k_p - \log K_{sc}) = \log(D/h) = -1.86 - 0.605\alpha - 2.09\beta$$
$$< 0.001 \quad 0.016 \quad < 0.001$$
$$N = 37; \quad \text{S.D.} = 0.358; \quad r^2 = 90.4\%; \quad F = 170; \quad \text{AIC} = 58.5 \qquad \text{(M6)}$$

A plot of $\log(D/h)$ values fitted by model (M6) is shown in Fig. 3.

Inclusion of π^* or MW does not improve the regression:

$$(\log k_p - \log K_{sc}) = \log(D/h) = -1.95 - 0.484\alpha - 1.67\beta - 0.186\pi^*$$
$$< 0.001 \quad 0.053 \quad < 0.001 \quad 0.089$$

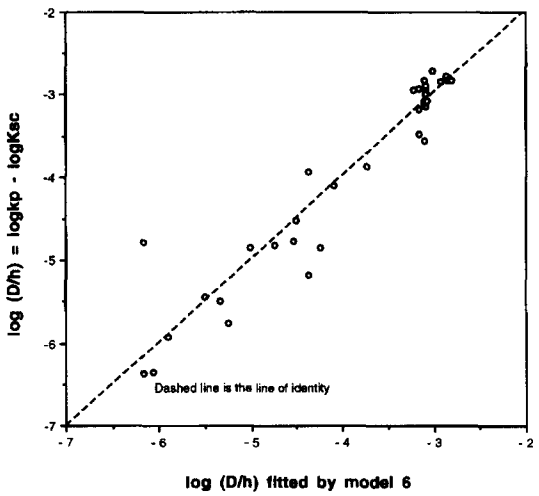

Fig. 3. Experimental log (D/h) values compared with fitted values calculated from α and β (model (M6)).

$$N = 37; \quad \text{S.D.} = 0.348; \quad r^2 = 90.9\%; \quad F = 121; \quad \text{AIC} = 57.2 \qquad \text{(M7)}$$

$$(\log k_p - \log K_{sc}) = \log(D/h) = -1.83 - 0.573\alpha - 1.73\beta - 0.0018\ \text{MW}$$
$$< 0.001 \quad 0.022 \quad < 0.001 \quad 0.243$$
$$N = 37; \quad \text{S.D.} = 0.356; \quad r^2 = 90.5\%; \quad F = 115; \quad \text{AIC} = 58.9 \qquad \text{(M8)}$$

In order to be consistent with our earlier analysis on the significance of the equilibrium-derived stratum corneum partition coefficients in determining dynamically derived permeability coefficients, we repeated the analysis for models (M6)–(M8) with K_{sc} as an independent variable. The regressions obtained, (M9)–(M11), confirm the significance of K_{sc} as a determinant for permeability coefficient which again has a coefficient not too different from unity:

$$\log k_p = -1.72 + 0.851 \log K_{sc} - 0.625\alpha - 2.06\beta$$
$$< 0.001 \quad < 0.001 \quad 0.012 \quad < 0.001$$
$$N = 37; \quad \text{S.D.} = 0.353; \quad r^2 = 90.6\%; \quad F = 117; \quad \text{AIC} = 58.3 \qquad \text{(M9)}$$

The inclusion of π^* or MW also did not significantly affect the regression as shown in Eqs. (M10) and (M11):

$$\log k_p = -1.88 + 0.943 \log K_{sc}$$
$$< 0.001 \quad < 0.001$$
$$-0.514\alpha - 1.74\beta - 0.151\pi^* \qquad \text{(M10)}$$
$$0.052 \quad < 0.001 \quad 0.276$$
$$N = 37; \quad \text{S.D.} = 0.352; \quad r^2 = 90.7\%; \quad F = 88.3; \quad \text{AIC} = 59.0$$

$$\log k_p = -1.71 + 0.845 \log K_{sc}$$
$$< 0.001 \quad < 0.001$$
$$-0.628\alpha - 2.08\beta + 0.00010\ \text{MW}$$
$$0.019 \quad 0.002 \quad 0.974 \qquad \text{(M11)}$$

$N = 37$; S.D. = 0.359; $r^2 = 90.3\%$; $F = 84.8$;

AIC = 60.3

3.3. Methods based on calculation of D from lag time, τ

Lag time values (τ) although often of limited reliability, offer an independent estimate of diffusion coefficient (Eq. (5)). We therefore examined the relationship between τ and the number of H-bonding groups on a solute as a validation of our hypothesis. A good positive correlation between log τ and ΣH is obtained:

$$\log \tau = -0.860 + 0.488 \sum H \qquad \text{(M12)}$$

$N = 10$; $S.D. = 496$; $r^2 = 65.8\%$; $F = 18.3$;

AIC = 8.8.

The plot is shown in Fig. 4a. It is of interest that the slope from this relationship is almost identical to that (0.500) derived from $\log(D/h)$ vs. ΣH using permeability data (model M1). The regression is improved (Fig. 4b) when log τ is predicted from the solvatochromic parameters α and β:

$$\log \tau = -0.796 - 0.173\alpha + 1.31\beta \qquad \text{(M13)}$$

$$0.078 \quad 0.759 \quad < 0.001$$

$N = 10$; S.D. = 0.336; $r^2 = 84.3\%$; $F = 25.2$;

AIC = 1.6.

It is interesting that the main determinant in M13 of τ is β. β is the H-acceptor power of the solute, and a similar high dependence of log k_p on β was noted by Abraham et al. (1995) when working on a similar dataset of phenols and steroids. When their results were incorporated into a larger dataset α assumed a greater significance. The high significance of β probably reflects the emphasis on the hydroxyl group as a determinant in this small data set. The separation of α and β is more likely when there are a number of differing H-bonding groups in a data set and discrimination between the types of H-bonding present is facilitated.

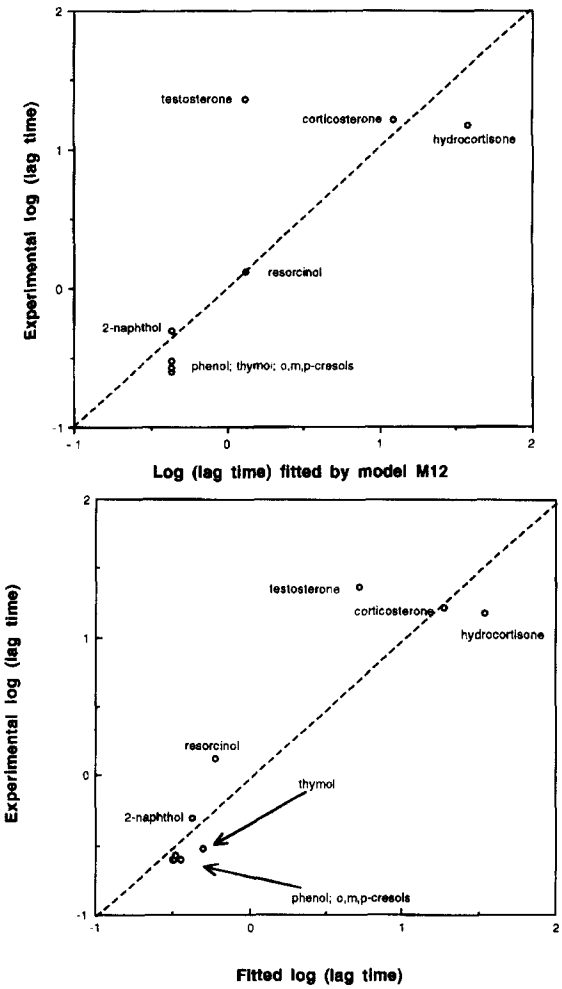

Fig. 4. Log (lag time) values compared with fitted values. Lag times in hours. Dashed lines are the lines of identity. Fitted values calculated from H-bond group numbers (model M12) in (a) and from α and β values (model (M13)) in (b).

The addition of other independent variables such as π^* and MW leads to ill-defined regressions, as may be anticipated when only ten data points are used:

$$\log \tau = -1.24 + 0.275\alpha + 0.038\beta + 0.708\pi^* \qquad \text{(M14)}$$

$$0.133 \quad 0.748 \quad 0.985 \quad 0.481$$

$N = 10$; S.D. = 0.347; $r^2 = 83.3\%$; $F = 15.9$;

AIC = 2.8

$$\log \tau = -1.63 + 0.51\alpha + 0.04\beta + 0.0075\,\mathrm{MW}$$
$$0.270 \quad 0.683 \quad 0.983 \quad 0.538 \qquad \text{(M15)}$$
$$N = 10; \quad \text{S.D.} = 0.351; \quad r^2 = 82.9\%; \quad F = 15.5;$$
$$\text{AIC} = 3.0$$

Although lag time data are imprecise, this correlation of $\log \tau$ with the number of H-bonding groups on a solute is a validation of the importance of H-bonding as a determination of diffusivity. The analysis also yields an interesting conclusion in that the constant term should theoretically represent the fastest penetration possible by a solute. The value of -0.796 corresponds to this 'minimum lag time' of 10 min, a lag time similar to that reported for most of the phenols by Roberts et al. (1977). Of course we make no claim for the accuracy of this result based on the available data.

3.4. H-bonding versus lipophilicity as a determinant of epidermal permeability

Whilst this analysis suggests that H-bonding is the major determinant of solute diffusivity in the stratum corneum, it should be emphasised that the partition process will appear to be the dominant determinant of epidermal transport for most solutes. The inter-relationship of this work with our earlier work (Roberts et al., 1995) and that of Abraham et al. (1995) can be deduced by integration of the relationships between K_{sc} and its determinants. K_{sc} is correlated to the corresponding octanol-water partition coefficient for a given solute as shown for this data set of 45 solutes (Eq. (6)):

$$\log K_{sc} = -0.024 + 0.590(\log K_{oct}) \qquad (9)$$
$$N = 45; \quad \text{S.D.} = 0.323; \quad r^2 = 83.9\%; \quad F = 230;$$
$$\text{AIC} = 69.5$$

The slope obtained is similar to that reported between $\log k_p$ and $\log K_{oct}$ by Roberts et al. (1977), Potts and Guy (1992) and others and reflects the greater variability in partition coefficients for the solute set relative to the limited H-bonding or diffusivity variation. The coefficient of $\log K_{oct}$ is much less than unity suggesting a more polar environment than octanol. This was interpreted previously by Roberts (1976) as a solute only being partially desolvated in moving from water into the stratum corneum environment.

4. Conclusion

The solvatochromic parameters, particularly the H-bonding properties, of a penetrant have a dominant effect on the diffusion across the SC, but a smaller influence on the partitioning, where lipophilicity might be an important factor. The present analysis suggests that future work needs to be undertaken on a more accurate calculation of the effects that individual groups have on diffusion, and in particular accounting for the contribution of more than one H-bonding group on a given penetrant molecule. We are currently examining methods of describing the role of H-bonding in solute structure-epidermal permeability relationships more accurately.

Similar relationships between lag time, an independent estimate of diffusivity, and H-bonding parameters validate the dominant effect of H-bonding as a determinant of diffusion coefficient.

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