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Epidermal permeability — penetrant structure relationships: 3. The effect of hydrogen bonding interactions and molecular size on diffusion across the stratum corneum

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Abstract

The permeability coefficient, k_p, is the product of partition into (K_{SC}) and diffusion across (D/h) the stratum corneum (SC). From water, $\log K_{SC} = -0.024 + 0.59 \log K_{octanol}$. H-bonding between permeant and SC is a major negative determinant of D/h. SC is predominantly a H-bond donor (α), rather than acceptor (β), with α_{SC}:β_{SC} = 0.6:0.4. Chemical groups have characteristic H-bonding potentials to the SC which slow diffusion and are quantified as 'retardation coefficients' (RC). For penetrants of known α and β, $RC = 0.0024 + 1.36(\alpha - \beta) + 3.18\,\Sigma\beta$. For polyfunctionals of unknown α and β, an apparent retardation coefficient (RC*) is first estimated from $0.0024 + 1.36(\Sigma\alpha - \Sigma\beta) + 3.18\Sigma\beta$, where $\Sigma\alpha$, $\Sigma\beta$ are summed fragmental values, and RC calculated from $-0.0678 + 1.17RC^* - 0.0807(RC^*)^2$. The maximal diffusion (D_o/h) attainable by small, non-bonding molecules is about 0.03 cm/h, declining rapidly as H-bonding groups are introduced to a very low minimum (D_m/h) after about four groups. The D/h versus RC plot resembles an adsorption isotherm and the data can be fitted by Langmuir's equation. The effect of molecular weight on diffusion is lower than previously reported.

Keywords: Transdermal absorption; Stratum corneum; Diffusion; Hydrogen bonding; Solvatochromic; Adsorption isotherm

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Abbreviations: AIC, unweighted Akaike Information Criterion; α, β, scaled values of H-bond donor and receptor potentials; D, diffusion coefficient (cm^2/h); D_m, limiting minimal diffusion coefficient for powerfully H-bonding penetrant; D_o, maximal diffusion coefficient for small, non-H-bonding penetrant; F, Fisher's F-statistic; h, diffusional pathlength across stratum corneum (cm); k_p, permeability coefficient (cm^2/h); K_i, partition coefficient (phase i/water); N, number of data points; π^*, dipolarity/polarisability; r^2, coefficient of determination adjusted for degrees of freedom; RC, retardation coefficient; RC_o, minimal retardation coefficient for non H-bonding molecule; RC*, apparent retardation coefficient calculated from $0.0024 + 1.36(\alpha - \beta) + 3.18\,\beta$; SC, stratum corneum; S.D., standard deviation.

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1. Introduction

There is considerable continuing interest in the field of transdermal absorption following developments in topical and transdermal delivery systems and the need for risk assessment of absorption of xenobiotics. In vitro techniques have been developed and data analyses conducted to determine if simple physicochemical relationships can be found to predict absorption rate. Although there has been some success in this approach we feel that much greater progress can be made if the underlying determinants which control absorption at a molecular level are identified and quantified. The logical prediction of skin penetration and the insights gained into the underlying principles should ultimately predict likely penetrants, enhancers and retardants and suggest suitable polymeric materials for protective barrier materials.

Analyses of existing approaches to permeability prediction — and the extent to which they are successful — are given in previous papers in this series (Roberts et al., 1995; Roberts et al., 1996). In general two strategies have been employed using (a) properties of the whole molecule or (b) summation of molecular fragments. The former approach developed along two paths. The earlier semi-empirical line suggested by Lien and Tong, 1973 related the permeability coefficient, k_p, to an organic solvent/water partition coefficient, and Potts and Guy, 1992, using data for some 90 compounds, proposed the much quoted relationship:

$$\log k_p = -6.3 + 0.71 \log K_{oct} - 0.0061\ MW$$

$$r^2 = 0.69$$

between k_p and the octanol/water partition coefficient, K_{oct}.

The more fundamental solvatochromic approach, pioneered by Kamlet et al., 1983, related transfer properties in general to the size, electronic and bonding properties of the molecule:

$$\text{Effect} = f_1(\text{Size}) + f_2(\text{Polarity}) + f_3(\text{Intermolecular Bonding})$$

and, following this approach, Abraham et al., 1995 and Potts and Guy, 1995 were able to predict k_p in terms of the hydrogen bonding potential of the molecule.

The fragmental approach arises from the ideas of Hansch and Leo, 1979 although the importance of molecular features had long been recognised as a determinant of solute penetration through skin (Scheuplein and Blank, 1971), and Roberts, 1976 had already noted that permeability to phenolic compounds, alcohols and steroids, corrected for stratum corneum-water partitioning and size effects was inversely related to the number of H-bonding groups. However, this avenue was largely overlooked until Pugh and Hadgraft, 1994 applied a simple analysis based on a semi-empirical choice of groups to the same data set as Potts and Guy and obtained equally good regressions. Our present series of papers attempts to combine the simplicity of the fragmental group method with the underlying scientific nature of the solvatochromic method.

A major pitfall in prediction of k_p is that it is a composite of two more fundamental quantities representing the stages of transfer: partitioning into the outermost layer of the stratum corneum (SC) and subsequent diffusion across it.

$$k_p = K_{SC} \cdot (D/h)$$

where K_{SC} is the stratum corneum/solvent partition coefficient, and D the diffusion coefficient across pathlength h of the stratum corneum.

K_{SC} can be related to K_{oct} (see below) so the result of Potts and Guy at first sight implies overriding importance of the partition step. However, the mere fact that the partition coefficient is used as a predictor does not per se confine its effect to the partition step. Considering it highly probable that partition coefficients encode molecular properties such as hydrogen bonding parameters that are also highly significant determinants of the subsequent diffusion step, we estimated (D/h) separately and showed (Roberts et al., 1996) that it approximated to the number of H-bonding groups on the penetrant by a Langmuir (Michaelis-Menten) type equation. Here we extend the analysis to examine the effect of specific hydrogen bonding groups on (D/h), estimate the H-bonding potential of the stratum corneum and examine how far the technique is applicable to polyfunctional compounds.

2. Methods

k_p data are for human SC from the collection of Flynn, 1990; partition coefficients (log K) from the Medchem database (Biobyte Inc., Claremont, CA), K_{SC} values from Scheuplein and Blank, 1971, Lien and Tong, 1973, Anderson et al., 1976, 1988 and Roberts, 1976, solvatochromic parameters (α, β and π^*) from Abraham, 1993 and Abraham et al., 1995. The data are presented in Table 1. Regression analyses were performed using the Minitab package (Minitab Release 8.1, Minitab Inc., State College, PA 1991), and curve fitting was performed using unweighted logarithmic values (i.e. implicit logarithmic weighting) using Minim 3.0 (R. Purves, University of Otago, NZ). Regression statistics reported are: the coefficient of determination (r^2) adjusted for degrees of freedom, Fisher's F-value, unweighted Akaike Information Criterion (AIC) and probability values for significance of the regression coefficients (printed in italics beneath the coefficients).

3. Results and discussion

Abraham et al., 1995 calculated the effect of H-bonding on k_p, but this has the disadvantage of being a composite quantity, and its fundamental components, K_{SC} and (D/h), may be influenced by H-bonding (and other) properties to different extents. Our previous paper dealt with the effect of H-bonding groups on diffusion across the SC and we were able to demonstrate the dependency of log (D/h) on the number of H-bonding groups present and on the α and β values of the permeants.

3.1. Estimation of K_{SC}

An ideal model solvent to predict the initial partition step into SC should follow the relationship

$$K_{SC} = a\,(K_{model})^b$$

where $a = b = 1$, or

$$\log K_{SC} = \log a + b \log K_{model}$$

where $\log a = 0$ and $b = 1$. Most partition data are available for octanol, for which we have previously reported (Roberts et al., 1996):

$$\log k_{SC} = -0.024 + 0.59 \log K_{oct} \quad (1)$$

An extensive search through the Medchem database for a better model was unsuccessful. Results for some of the more common solvents are:

Octanol:	$a=-0.02$;	$b=0.59$;	$N=45$;	$r^2=84\%$
Butanol:	$a=-0.18$;	$b=0.70$;	$N=13$;	$r^2=84\%$
Chloroform:	$a=0.47$;	$b=0.47$;	$N=26$;	$r^2=85\%$
Heptane:	$a=1.03$;	$b=0.39$;	$N=24$;	$r^2=67\%$

In contrast to earlier results based on a smaller dataset (Roberts et al., 1977) MW is not a significant determinant:

$$\log K_{SC} = -0.078 + 0.543 \log K_{oct} + 0.00071\ \mathrm{MW}\ \ r^2 = 0.84$$

where the coefficient 0.00071 is not significantly different ($P = 0.10$) from zero.

Roberts et al., 1996 further suggested that a slope of the log K_{SC} versus log K_{oct} relationship less than unity indicates a SC environment similar in polarity to butanol. This work has found a slope of approximately 0.6, irrespective of the organic solvent used. Such a slope is more consistent with a partial desolvation of the solute polar groups, as advocated by Roberts et al., 1977 which could be caused by the water associated with ceramide polar head groups.

3.2. Studies on monofunctional permeants

3.2.1. Predictors of diffusion

To quantify H-bonding between permeant and SC we initially selected (from Flynn's dataset) the three examples of non-H-bonding hydrocarbons and the 26 monofunctional oxygenated compounds (alcohols, phenols, acids, ketones, ethers, esters) for which solvatochromic data were available. Replicate values for phenol were available from our laboratory.

Although the relationship between K_{SC} and K_{oct} is not ideal it does offer a way of splitting k_p into

Table 1
Data used in the analyses

Compound	MW	log k_p[a]	log K_{oct}[b]	log K_{hex}[b]	log D/h[c]	RC*[d]	α[e]	β	π*	RC[f]
Set 1a: compounds with zero or one H-bonding groups										
Benzyl alcohol	108.1	−2.22	1.10	−0.62	−2.85	1.51	0.33	0.50	0.87	1.36
Butanoic acid	88.1	−3.00	0.79	−0.96	−3.44	1.61	0.60	0.45	0.62	1.64
Butanol	74.1	−2.60	0.88	−0.70	−3.10	1.40	0.37	0.48	0.42	1.38
2-Butanone	72.1	−2.36	0.28	−0.25	−2.50	1.03	0.00	0.51	0.70	0.93
m-Cresol	108.1	−1.82	1.96	−0.35	−2.95	1.35	0.57	0.34	0.88	1.40
o-cresol	108.1	−1.80	1.95	0.25	−2.93	1.21	0.52	0.30	0.86	1.26
p-Cresol	108.1	−1.75	1.95	−0.19	−2.88	1.29	0.57	0.31	0.87	1.34
Decanol	158.3	−1.10	4.00	*	−3.44	1.40	0.37	0.48	0.42	1.38
Ethanol	46.1	−3.10	−0.31	−2.10	−2.89	1.40	0.37	0.48	0.42	1.38
Ethyl benzene	106.2	0.08	3.15	3.00	−1.75	0.31	0.00	0.15	0.51	0.28
Ethyl ether	74.1	−1.80	0.93	0.60	−2.32	0.91	0.00	0.45	0.25	0.82
4-Ethyl phenol	122.2	−1.46	2.40	0.23	−2.85	1.31	0.55	0.36	0.90	1.41
Heptanoic acid	130.2	−1.70	2.50	0.45	−3.15	1.61	0.60	0.45	0.60	1.64
Heptanol	116.2	−1.50	2.72	1.01	−3.08	1.40	0.37	0.48	0.42	1.38
Hexanoic acid	116.2	−1.85	1.92	0.24	−2.95	1.61	0.60	0.45	0.60	1.64
Hexanol	102.2	−1.89	2.03	0.45	−3.06	1.40	0.37	0.48	0.42	1.38
Methanol	32.0	−3.30	−0.77	−2.80	−2.82	1.45	0.43	0.47	0.44	1.44
2-Naphthol	144.2	−1.55	2.70	0.30	−3.20	1.52	0.61	0.40	1.08	1.56
Nonanol	144.3	−1.22	3.62	*	−3.33	1.40	0.37	0.48	0.42	1.38
Octanoic acid	144.2	−1.60	3.05	0.66	−3.38	1.61	0.60	0.45	0.60	1.64
Octanol	130.2	−1.28	3.00	*	−3.03	1.40	0.37	0.48	0.42	1.38
Pentanoic acid	102.1	−2.70	1.39	−0.92	−3.50	1.61	0.60	0.45	0.60	1.64
Pentanol	88.2	−2.22	1.56	−0.40	−3.12	1.40	0.37	0.48	0.42	1.38
Phenol	94.1	−2.09	1.46	−0.82	−2.93	1.31	0.60	0.30	0.89	1.36
Phenol	94.1	−1.72[g]	1.46	−0.82	−2.56	1.31	0.60	0.30	0.89	1.36
Phenol	94.1	−1.96[g]	1.46	−0.82	−2.80	1.31	0.60	0.30	0.89	1.36
Propanol	60.1	−2.85	0.25	−1.52	−2.97	1.61	0.37	0.48	0.42	1.38
Styrene	104.1	−0.19	2.95	0.44	−1.91	0.33	0.00	0.16	0.65	0.29
Thymol	150.2	−1.25	3.30	1.62	−3.17	1.5	0.52	0.44	0.79	1.51
Toluene	92.1	0.00	2.73	2.89	−1.59	0.29	0.00	0.14	0.52	0.26
3,4-Xylenol	122.2	−1.44	2.23	0.28	−2.73	1.35	0.56	0.39	0.86	1.47
Set 1b: polyfunctional compounds with α and β literature data										
Aldosterone	360.4	−5.52	1.08	*	−6.13	5.63	0.40	1.90	3.47	4.00
4-Bromophenol	173.0	−1.44	2.59	−0.20	−2.94	1.28	0.67	0.20	1.17	1.28
4-Chlorocresol	142.6	−1.26	3.10	0.36	−3.07	1.29	0.65	0.22	1.02	1.29
Chloroxylenol	156.6	−1.28	3.39	1.08	−3.26	1.28	0.64	0.21	0.96	1.26
4-Chlorophenol	128.6	−1.44	2.39	−0.12	−2.83	1.28	0.67	0.20	1.08	1.28
Cortexolone	346.5	−4.13	2.52	−1.00	−5.59	4.78	0.35	1.57	3.45	3.36
Cortexone	330.5	−3.35	2.88	0.48	−5.03	3.33	0.15	1.13	3.39	2.26
Corticosterone	346.5	−4.22	1.94	−1.62	−5.34	4.80	0.40	1.63	3.43	3.51
Cortisone	360.5	−5.00	1.42	−0.55	−5.81	5.80	0.35	1.84	3.50	3.83
Estradiol	272.4	−3.52	2.69	−0.20	−5.08	2.82	0.88	0.95	3.30	2.93
Estradiol	272.4	−2.28	2.69	−0.20	−3.84	2.82	0.88	0.95	3.30	2.93
Estriol	288.4	−4.40	2.47	−0.64	−5.83	4.31	1.40	1.22	3.36	4.13
Estrone	270.4	−2.44	2.76	0.48	−4.04	2.31	0.56	0.91	3.10	2.42
2-Ethoxy ethanol	90.1	−3.60	−0.54	*	−3.26	2.20	0.30	0.83	0.50	1.92
Hydrocortisone	362.5	−5.52	1.53	−2.04	−6.40	6.16	0.70	1.87	3.49	4.36
Hydroxyprogesterone	330.5	−3.22	2.74	0.40	−4.81	3.33	0.25	1.31	3.35	2.73
Me-4-hydroxy benzoate	152.1	−2.04	1.96	−0.53	−3.17	2.18	0.69	0.45	1.37	1.76
3-Nitrophenol	139.1	−2.25	2.00	−1.23	−3.41	1.50	0.79	0.23	1.57	1.50
4-Nitrophenol	139.1	−2.25	1.96	−2.15	−3.38	1.59	0.82	0.26	1.72	1.59

Pregnenolone	316.5	−2.82	3.77	0.62	−5.02	2.40	0.32	1.18	3.29	2.59
Progesterone	314.5	−2.82	3.77	1.23	−5.02	1.95	0.00	1.14	3.29	2.08
Testosterone	288.4	−3.40	3.31	0.49	−5.33	2.48	0.32	1.19	2.59	2.60
Set 1c: polyfunctionals with no α and β literature data										
Atropine	289.4	−5.07	1.81	−3.25	−6.11	4.01	*	*	*	*
Chlorpheniramine	274.8	−2.66	3.39	0.24	−4.64	2.91	*	*	*	*
Codeine	299.4	−4.31	0.89	−1.37	−4.81	5.05	*	*	*	*
Etorphine	411.5	−2.44	1.86	0.15	−3.51	6.00	*	*	*	*
Fentanyl	336.5	−2.25	4.37	1.29	−4.80	3.49	*	*	*	*
Fentanyl	336.5	−2.00	4.37	1.29	−4.55	3.49	*	*	*	*
Hydrocortisone pimelamate	503.6	−3.05	2.31	*	−4.39	8.10	*	*	*	*
Hydrocortisone succinamate	461.6	−4.59	1.43	*	−5.41	8.10	*	*	*	*
Hydrocortisone *N,N*-diMe-succinamate	489.6	−4.17	2.03	−3.92	−5.34	7.70	*	*	*	*
Hydrocortisone 21-hemipimelate	504.6	−2.75	3.26	−4.09	−4.65	6.69	*	*	*	*
Hydrocortisone 21-hemisuccinate	462.5	−3.20	2.71	−5.70	−4.77	6.69	*	*	*	*
Hydrocortisone 21-hexanoate	460.6	−1.75	4.48	0.12	−4.37	6.11	*	*	*	*
Hydrocortisone 21-hexanoate-6-OH	476.6	−3.04	2.79	−4.05	−4.66	7.51	*	*	*	*
Hydrocortisone 21-Me-pimelate	518.6	−2.27	3.70	−1.16	−4.43	7.02	*	*	*	*
Hydrocortisone 21-succinate	476.6	−3.68	2.58	−2.33	−5.18	7.02	*	*	*	*
Hydrocortisone 21-octanoate	488.7	−1.21	5.49	1.30	−4.43	6.11	*	*	*	*
Hydrocortisone 21-propionate	418.5	−2.47	3.00	−1.50	−4.22	6.11	*	*	*	*
Hydromorphone	285.3	−4.82	1.25	−4.00	−5.53	5.17	*	*	*	*
Meperidine	247.0	−2.43	2.72	0.40	−4.01	2.32	*	*	*	*
Naproxen	230.3	−3.40	3.18	*	−5.25	2.93	*	*	*	*
Scopolamine (hyoscine)	303.4	−4.30	1.24	−1.83	−5.01	4.74	*	*	*	*

[a]Flynn (1990).
[b]Medchem database (Biobyte Inc., Claremont, CA).
[c]Calculated from log k_p − 0.59 log K_{oct} + 0.024.
[d]RC* calculated from sum of fragments. As a validation of the method, values in dataset 1b were calculated from suitable fragments as though the literature values were not known, e.g. chloroxylenol has 4-chlorophenol as the nearest equivalent. Aldosterone considered as cyclohexanone (α = 0, β = 0.56), cyclopentane (0, 0), 2 × cyclohexane (0, 0), ether (0, 0.45), ketone (0, 0.51), primary alcohol (0.37, 0.48) and secondary alcohol (0.32, 0.56) where the α and β values are from Abraham (1993) and Abraham et al. (1995). Thus $\Sigma\alpha$ = 0.69, $\Sigma\beta$ = 2.58. Substitution into RC* = 0.0024 + 1.36 ($\Sigma\alpha$ − $\Sigma\beta$) + 3.18 $\Sigma\beta$ gives RC* = 5.60. For polyfunctionals not in the literature RC is calculated from −0.0678 + 1.17 (RC*) − 0.0807 (RC*)^2.
[e]α, β and π^* from Abraham (1993) and Abraham et al. (1995).
[f]RC calculated from 0.0024 + 1.36 (α − β) + 3.18β
[g] Unpublished data.

partition and diffusion components. The validity of this approach is supported by the relationship between k_p, K_{oct} and the solvatochromic parameters:

$$\log k_p = \underset{0.000\ 0.010}{-1.26 + 0.51\ \log K_{oct}} \underset{0.000\ 0.002}{- 1.40\alpha - 2.64\beta} + \underset{0.551}{0.199\pi^*} + \underset{0.986(2)}{0.00013MW}$$

$N = 31$ S.D. = 0.1574 $r^2 = 96.3\%$ $F = 156$

AIC = −4.83

where the similarity in the log K_{oct} coefficients (0.59 and 0.51) suggests that the log K_{oct} term in eq. 2 represents SC/water partitioning. Note that π^* and MW are insignificant determinants compared with α and β. Their omission gives:

$$\log k_p = \underset{0.000\ 0.000}{-1.09 + 0.508\ \log K_{oct}} \underset{0.000\ 0.000}{- 1.26\alpha - 2.84\beta}$$

$N = 31$ S.D. = 0.1551 $r^2 = 96.4\%$ $F = 268$
AIC = −7.38

3.2.1.1. Solvatochromic parameters as predictors of diffusion. If we accept the implication of eq. 2 that log K_{oct} is the determinant of partitioning into SC,

then the remaining solvatochromic terms determine diffusion across it. Hence, calculating log K_{SC} from Eq. (1):

$$\log (D/h) =$$

$$-1.27-1.37\alpha-2.32\ \beta+0.324\pi^*-0.00313MW$$
$$0.000\quad 0.000\quad 0.000\quad 0.092\quad 0.005$$

$N = 31$ S.D. $= 0.1550$ $r^2 = 88.8\%$ $F = 60.3$
AIC $= -6.57$

α and β are the most important predictors, and π^* and MW may be removed with little effect on the regression:

$$\log (D/h) = -1.32-1.30\ \alpha-2.57\ \beta$$
$$0.000\quad 0.000\quad 0.000 \qquad (3)$$

$N = 31$ S.D. $= 0.1790$ $r^2 = 85.0\%$ $F = 86.3$

AIC $= 0.64$

3.2.1.2. Partition coefficients as predictors of diffusion. At first sight H-bonding capacity is probably best quantified by α and β. Whilst these are readily available or deducible for many monofunctional compounds we were not confident that they can be estimated for polyfunctionals by group contribution summation. (See section on polyfunctionals.) We therefore tried to estimate H-bonding from partition coefficients.

El Tayar et al., 1991 (examined in detail in paper 1 of this series, Roberts et al., 1995), suggested that α could be estimated by ($\log K_{oct} - \log K_{hexane}$) for prediction of k_p. We obtained better regressions when $\log K_{oct}$ and $\log K_{hexane}$ were included separately since they had different coefficients. The H-bonding ability of a compound might be related to its relative affinities for strongly H-bonding (water) and non-H-bonding (hexane) liquids. On this argument $\log K_{hexane}$ is an (inverse) measure of H-bonding. For the monofunctional compounds (set 1a, Table 1), log K_{hexane} is indeed related to the solvatochromic parameters:

$$\log K_{hexane} =$$

$$-0.108-2.59\ \alpha-3.93\ \beta-1.98\ \pi^*+0.0399MW$$
$$0.860\quad 0.000\quad 0.001\quad 0.003\quad 0.000$$

$N = 28$ S.D. $= 0.4657$ $r^2 = 86.2\%$ $F = 43.0$

AIC $= 53.0$

The constant (-0.108) is not significantly different from zero. The difference in the coefficients of α and β in the hexane regressions might reflect the predominant H-bond donor property of water (Abraham, 1993). This difference problem is inherent in the use of partition coefficients to estimate H-bonding to SC. The strength of H-bonding of a penetrant to SC depends on its own α,β values and those of the SC. For example in the extreme case, if the SC had a β value of zero then α of the penetrant would be irrelevant. It is likely, therefore, that a partitioning solvent used to model H-bonding must have similar α and β properties to SC (see later).

Log K_{oct} is also well related to solvatochromic parameters:

$$\log K_{oct}$$
$$= 0.434-0.348\alpha-3.74\beta-1.49\ \pi^*+0.0388MW$$
$$0.057\quad 0.098\quad 0.000\quad 0.000\quad 0.000$$

$N = 31$ S.D. $= 0.1700$ $r^2 = 97.8\%$ $F = 339$

AIC $= -0.86$

but the dependency on α is much lower, presumably because the basicity values of octanol and water are more similar than their acidities.

However, when log K_{oct} and log K_{hexane} were used as predictors of log (D/h) the regressions were poor:

$$\log (D/h) =$$
$$-1.31 + 0.328 \log K_{oct} + 0.224 \log K_{hexane}$$
$$-0.0208\ \text{MW}\quad r^2 = 62.9\%$$

In summary: K_{SC} may be estimated from K_{oct}. The most powerful determinant of diffusion across the SC is the H-bonding capability of the penetrant, measured by α and β. MW is of minor importance and π is insignificant. Log K_{oct} and log K_{hexane} are poor predictors even for simple monofunctional compounds. It is unlikely that they will prove useful in prediction of log (D/h) of polyfunctionals as we had hoped.

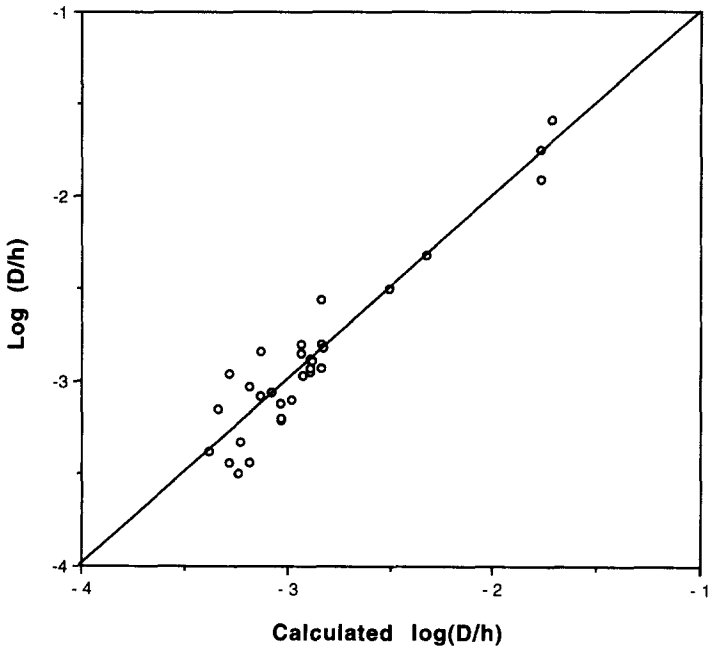

Fig. 1. Log (D/h) values calculated by fragmental method (Eq. 4).

3.2.1.3. Functional groups as predictors of diffusion. Log (D/h) values were calculated from Eq. (3) and regressed against the number (1 or 0) of each group present.

$$\log(D/h) = -1.36 - 1.67\,\text{acid} - 1.41\,\text{alcohol} - 1.17\,\text{phenol} - 0.986\,\text{carbonyl} - 0.759\,\text{ether} - 0.0502\,\text{C}^* \quad (4)$$

$N = 31$ S.D. $= 0.1651$ $r^2 = 87.3\%$ $F = 35.3$

AIC $= -1.16$ All P values < 0.003

where 'acid' is the integer number (0 or 1) of acid groups present and C* is the number of carbons atoms not involved in H-bonding (non-carbonyl carbons).

Log (D/h) values from Eq. (4) are plotted against observed values in Fig. 1. The predictor coefficients are all negative and larger for strong H-bonding groups like acid and alcohol. These 'retardation coefficients' (RCs) are listed in Table 2.

3.2.2. Estimation of the H-bonding properties of the SC: α_{SC} and β_{SC}

This was attempted in two ways.

3.2.2.1. (a) Direct calculation based of analysis of SC lipids. The mole fraction of each lipid group in the SC was calculated using the lipid composition (Table 3) as reported by Wertz, 1992, and its α and β values taken from Abraham, 1993. The

Table 2
Retardation coefficients calculated from regression Eq. 4

Group	α[a]	β	RC[b]	N	S.D.
Alcohols (primary)	0.37	0.48	1.41	11	0.11
Phenols	0.57	0.32	1.17	10	0.11
Acids	0.60	0.45	1.67	5	0.13
Ether	0.00	0.45	0.759	1	*
Ketone	0.00	0.51	0.986	1	*
C*	0.00	0.00	0.050	31	0.015

[a]α and β values are representative values for the groups from Abraham (1993).
[b]Retardation coefficients are the coefficients in the regression Eq. 4.

Table 3
Composition and H-bonding properties of stratum corneum lipids

Lipid	% by weight[a]	MW	Number of groups per molecule (n)					H-bonding[b]	
			Primary alcohol	Secondary alcohol	Secondary amide	Ester	Acid	α	β
			α[c] 0.37 β 0.45	α 0.33 β 0.56	α 0.40 β 0.71	α 0.00 β 0.45	α 0.60 β 0.45		
Ceramide 1	2.96	970	1	1	1	1	0	0.34	0.66
Ceramide 2	8.25	680	1	2	1	0	0	1.73	2.77
Ceramide 3	4.52	668	1	2	1	0	0	0.97	1.54
Ceramide 4	5.62	665	1	2	1	0	0	1.21	1.93
Ceramide 5	5.28	554	1	2	1	0	0	1.36	2.17
Ceramide 6	11.36	684	1	3	1	0	0	2.92	4.72
Cholesterol	21.60	387	0	1	0	0	0	1.84	3.13
Cholesterol esters[d]	9.30	651	0	0	0	1	0	0.00	0.64
Fatty acids[e]	23.00	349	0	0	0	0	1	3.96	2.97
Triglycerides[e]	8.10	1083	0	0	0	3	0	0.00	1.01
								14.33	21.54

[a]Data from Wertz (1992).
[b]α H-bonding effect calculated by 100 · (% by weight) · $\Sigma n\alpha$/MW.
[c]α and β values from Abraham (1993).
[d]Based on oleate.
[e]Based on C_{23} $H_{47}COOH$.

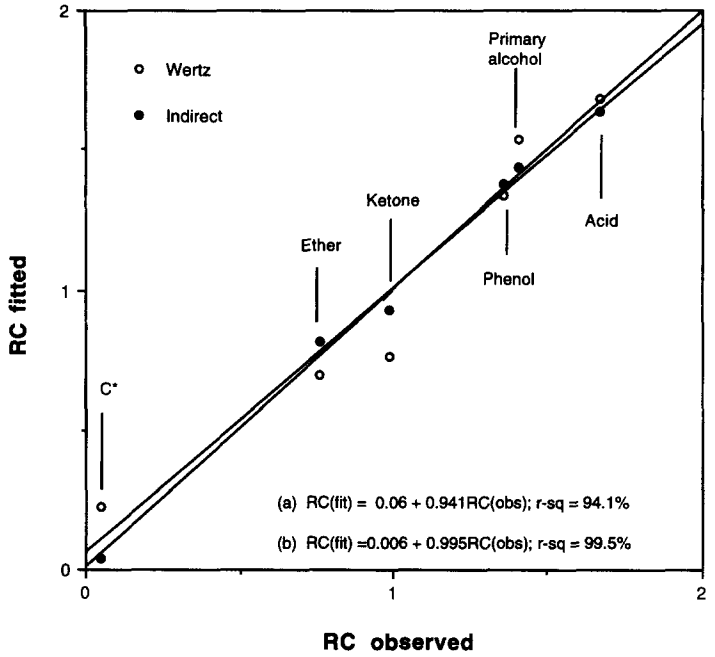

Fig. 2. RC values calculated (a) from SC lipid analysis of Wertz (b) by indirect method (Eq. (5)).

total α effect of the SC lipids was calculated as 14.33 and the β effect as 21.54. The relative strengths of H-bond acidity and basicity of the SC are therefore α_{SC}:β_{SC} = 0.40:0.60 in contrast to the implication of Eq. (3) that acidic H-bonding properties predominate. H-bonding of each penetrant (H_p) was calculated as $\{(\alpha_g \cdot \beta_{SC}) + (\beta_g \cdot \alpha_{SC})\}$, where the suffix, $_g$, denotes a functional group. For phenol this was the mean value for the eight phenols (α_{phenol} = 0.57, β_{phenol} = 0.36), and for C* the mean values for ethyl benzene, toluene and styrene divided by 7.3, i.e. the mean number of C* atoms (α_{C*} = 0.00, β_{C*} = 0.02). There should be a monotonic relationship between H_p and RC, passing through the origin. For the six functional groups in dataset 1a the regression is:

$$RC = 0.205 + 2.73H_p$$
$$\quad\; 0.174 \quad 0.001$$

$N = 6$ S.D. $= 0.1588$ $r^2 = 92.6\%$ $F = 63.3$

AIC = 8.24

The high intercept of 0.205 along with the magnitudes of α_{SC} and β_{SC} being the reverse of those predicted by Eq. (3) makes these values of α_{SC} and β_{SC} dubious. The assumptions that (i) SC lipid polar head groups are solely responsible for the H-bonding effect, and that (ii) α and β can be summed for polyfunctionals, may not be justified.

3.2.2.2. (b) Indirect calculation based on RCs. In the simplest case RC would be directly related to H-bonding between penetrant and SC:

$$RC = X + Y[(\alpha_p \times \beta_{SC}) + (\beta_p \times \alpha_{SC})]$$

Since $\alpha_{SC} = (1 - \beta_{SC})$:

$$RC = X + Y\beta_{SC}(\alpha_p - \beta_p) + Y\beta_p$$

The regression (Fig. 2) is:

$$RC = 0.0024 + 1.36(\alpha_p - \beta p) + 3.18\beta_p \qquad (5)$$
$$\quad\; 0.969 \quad 0.001 \qquad\quad 0.000$$

$N = 6$ S.D. $= 0.055$ $r^2 = 99.1\%$ $F = 280$

AIC = -24

Note that:

(1) r^2 is higher.

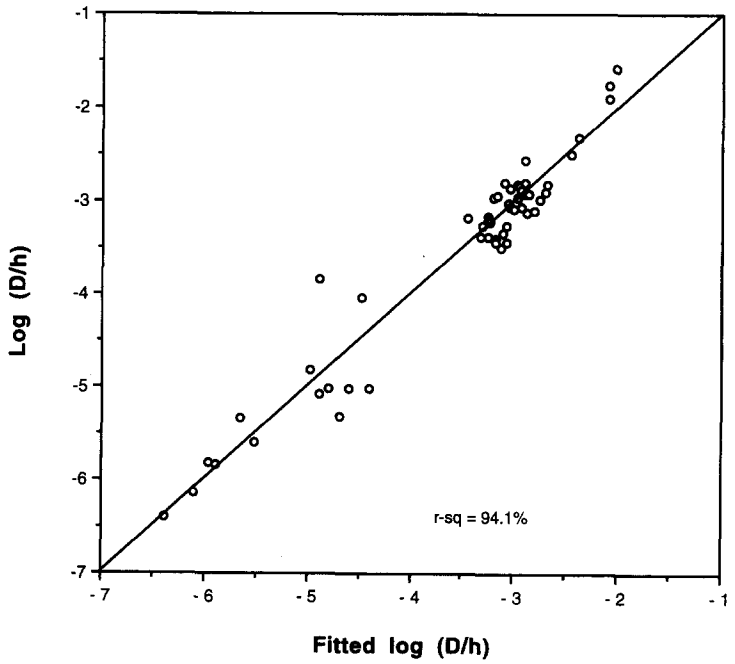

Fig. 3. Log (D/h) fitted from log (D/h) = −1.42 − 0.785 RC − 0.00428 MW (Eq. (7)).

(2) Solving $Y\beta_{SC} = 1.36$, $Y = 3.18$ gives $\alpha_{SC} = 0.573$ and $\beta_{SC} = 0.427$ in agreement with Eq. (3).
(3) The intercept is not significantly different from zero.

3.3. Studies on polyfunctional permeants

Several approaches to the prediction of D/h for compounds with multiple H-bonding groups were examined.

3.3.1. Estimation of D/h from RC values

The effectiveness of Eq. (4) was checked by calculating D/h for aldosterone, cortisone, progesterone and testosterone. Confidence intervals are high as the predictor values are removed from the values (zero or one) that determine the regression. D/h estimates were (cm/h):

Aldosterone:	1.3×10^{-8}	(1.3×10^{-8})
Cortisone:	8.7×10^{-9}	(3.5×10^{-8})
Testosterone:	2.1×10^{-5}	(5.3×10^{-7})
Progesterone:	5.1×10^{-5}	(4.3×10^{-7}).

The values of Scheuplein and Blank, 1971, shown in parentheses, are estimated from a diffusional pathlength of 300 μm (Lieckfeldt and Lee, 1995). The agreement with experimental estimates is poor, possibly because groups do not exert their full effects independently in polyfunctional compounds.

3.3.2. Estimation of D/h from partition coefficients

The section on monofunctionals had already suggested that this approach was unlikely to succeed. Nevertheless various partition coefficients were tried as predictors. The dataset comprised all compounds in Table 1 and the following regression illustrates the lack of success:

$$\log (D/h) = \underset{0.00}{-2.69} + \underset{0.111}{0.218} \log K_{oct} + \underset{0.902}{0.0106} \log K_{hexane} - \underset{0.000}{0.00726}\, MW$$

$N = 66$ S.D. $= 0.703$ $r^2 = 62.7\%$ $F = 37.5$

AIC $= -1690$

Note that, in contrast to the monofunctional study, MW is the most significant predictor —

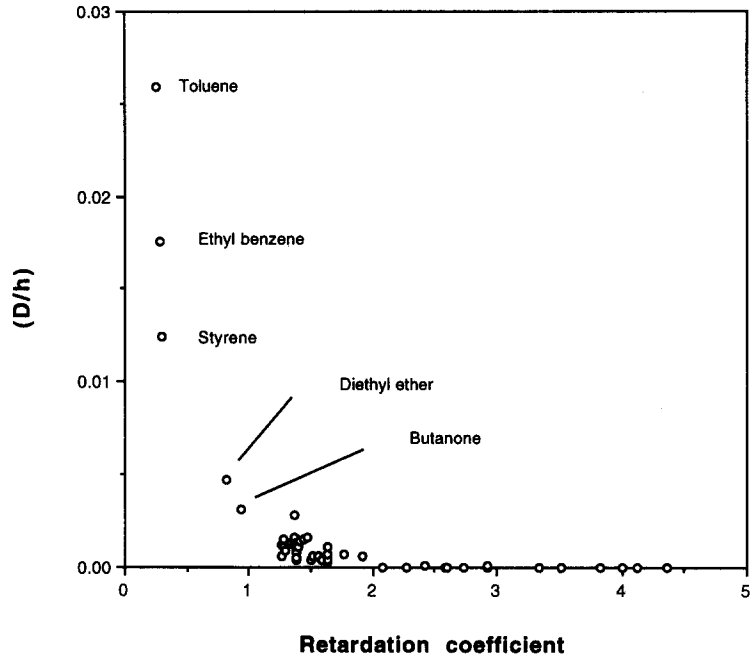

Fig. 4. Relationship between D/h and RC calculated from Eq. (5).

probably because large molecules tend to have several H-bonding groups.

3.3.3. Compounds for which solvatochromic parameters are available

Fifty-three compounds (combined datasets 1a and 1b in Table 1) were identified for which α, β and π^* are reported by Abraham et al., 1995.

3.3.3.1. Estimation of D/h from solvatochromic parameters.

$$\log (D/h) = -1.43 - 0.955\ \alpha - 1.60\ \beta + 0.101\ \pi^* - 0.00474\ MW$$
$$\text{(0.000)}\quad \text{(0.000)}\quad \text{(0.000)}\quad \text{(0.399)}\quad \text{(0.003)}$$

$N = 53$ S.D. $= 0.2813$ $r^2 = 94.0\%$ $F = 204$

AIC $= -1565$

π^* is thus an insignificant predictor and may be removed from the regression:

$$\log (D/h) = -1.50 - 0.911\alpha - 1.58\beta - 0.00367\ MW$$
$$\text{(0.000)}\quad \text{(0.000)}\quad \text{(0.000)}\quad \text{(0.000)}$$

$N = 53$ S.D. $= 0.2805$ $r^2 = 94.0\%$ $F = 273$

AIC $= -1567$

The intercept, -1.50, represents an intrinsic diffusion term, D_o/h, describing the maximum possible diffusion rate of an infinitely small, non-bonding molecule.

$$\log (D_o/h) = -1.50$$

(95% confidence interval: -1.70 to -1.30)

$$D_o/h = 0.0316\ (0.0200 \text{ to } 0.0501)\ \text{cm/h} \qquad (6)$$

3.3.3.2. Estimation of D/h from RC values. Eq. 5 showed that RC was related to α and β of the penetrant:

$$\text{RC} = 0.0024 + 1.36\ (\alpha - \beta) + 3.18\ \beta$$

RC values for the compounds in the combined datasets 1a and 1b were calculated from this equation.

3.3.3.2.1. Empirical approach. Regression of $\log(D/h)$ against RC and MW is reasonably good (Fig. 3):

$$\log (D/h) = -1.42 - 0.785\ RC - 0.00428\ MW \qquad (7)$$
$$\text{(0.000)}\quad \text{(0.000)}$$

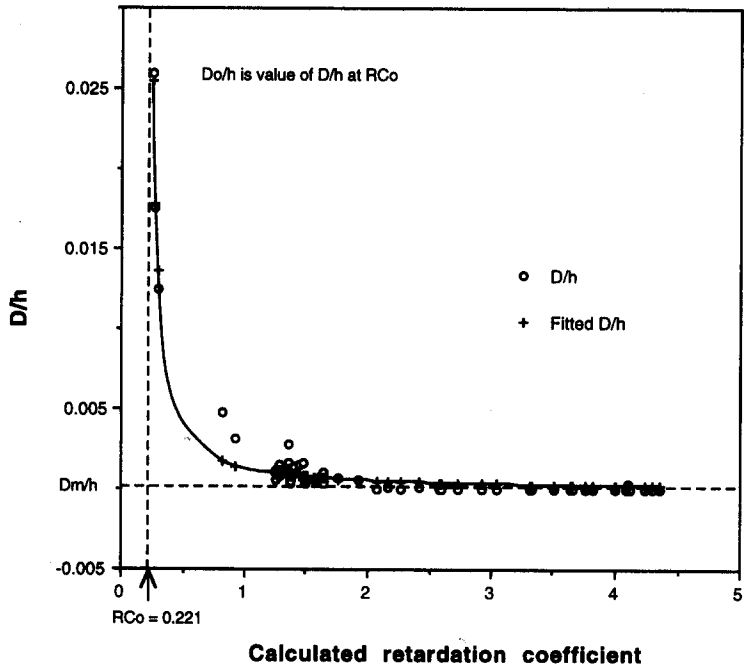

Fig. 5. D/h values fitted to all data points by Langmuir equation (Eq. (8)).

$N = 53$ S.D. $= 0.2839$ $r^2 = 93.9\%$ $F = 398$

AIC $= 77.9$

$Do/h = 0.0380$ (0.0257 to 0.0562) cm/h.

3.3.3.2.2. Adsorption isotherm approach. The plot of (D/h) against RC (Fig. 4) resembles the shapes of Langmuir adsorption isotherms applied to enzyme kinetics (Michaelis-Menten), and drug receptor theory (see for example Boulton, 1991). Attempts were made to fit the data to equations of this form using the Minim program.

The reduction in the diffusion term $(D_o - D)/h$ is analogous to the amount adsorbed; the saturation effect is $(D_o - D_m)/h$, where D_m is the minimum diffusion coefficient of an infinitely hindered penetrant; $(RC - RC_o)$ — the force driving adsorption — is analogous to concentration (see Fig. 5).

(a) Freundlich isotherm

This is the simplest empirical approach:

$$(D_o - D)/h = d\,(RC - RC_o)^e$$

Convergence of this equation was not achieved using Minim.

(b) Langmuir (Michaelis-Menten) isotherm

This considers adsorption as equilibrium between adsorptive and desorptive processes.

Arranging the equation as

$$(D/h) = D_o/h - [(D_o/h - D_m/h)(RC - RC_o) /(K + RC - RC_o)] \quad (8)$$

the following values were fitted:

Parameter	Final value	S.D.	
D_o/h	0.192	9.12E-03	
D_m/h	6.57E-05	1.24E-04	large S.D.
RC_o	0.222	4.02E-03	
K	5.31E-03	2.54E-04	
$N = 53$	$r^2 = 97.7\%$	AIC $= -558$	

S.D. of residuals $= 6.84$E-4

K is the equilibrium constant for desorption. Its low value shows that H-bonding is a powerful determinant of diffusion.

Several attempts were made to incorporate MW as a size term in the equation. The simplest treats retardation as the sum of the H-bonding and size effects. This leads to equations of the type:

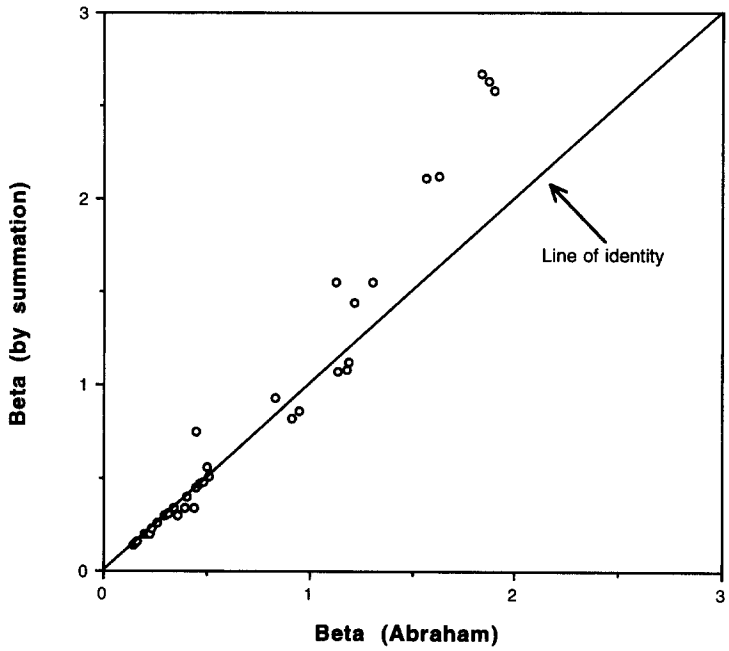

Fig. 6. β calculated by sum of fragmental values compared with literature values for combined datasets 1a and 1b.

$$(D/h) = D_o/h - \{[(D_o - D_m/h)(RC - RC_o) \times /(K + RC - RC_o)] + j\ MW^n\}$$

All attempts at fitting these equations were unsuccessful. The higher MW compounds invariably have several H-bonding groups which probably obscures the smaller size effect.

3.3.4. Estimation of RC when α and β values are unavailable

3.3.4.1. Validation of method. Validation estimations were made for compounds of known α and β (datasets 1a, 1b). The previous section shows a degree of success in estimating diffusion from RC values calculated from α and β. The next step is to see if α and β can be estimated by a fragmental approach, e.g. whether aldosterone can be considered as cyclohexanone, cyclopentane, ether, ketone, primary alcohol, secondary alcohol and two cyclohexane fragments. Corresponding α and β values (Abraham, 1993) give $\Sigma\alpha = 0.69$ and $\Sigma\beta = 2.58$. Compounds such as chloroxylenol were treated as 'unknowns', and α and β taken as those of the nearest monofunctional compound (chlorophenol). Comparison of $\Sigma\beta$ with literature β values (Abraham et al., 1995) is shown in Fig. 6. Apparent RC values (RC*) were calculated from $RC^* = 0.0024 + 1.36\ (\Sigma\alpha - \Sigma\beta) + 3.18\Sigma\beta$ (Eq. 5). The validity of this fragmental approach was tested by substitution into the most successful regressions of the previous section.

3.3.4.1.1. Estimation of D/h from solvatochromic parameters.

$$\log D/h = \underset{0.000}{-1.67} \underset{0.000}{-0.756\ \Sigma\alpha} \underset{0.000}{-0.741\ \Sigma\beta} \underset{0.000}{-0.00578 MW}$$

$N = 53$ S.D. $= 0.2531$ $r^2 = 90.5\%$ $F = 166$

AIC $= 102$

$D_o/h = 0.0214$ (0.0120 to 0.0380) cm/h.

3.3.4.1.2. Estimation of D/h from RC values. Calculation of RC

The success of this approach was examined by plotting RC against RC* for the combined datasets 1a and 1b. The regression is:

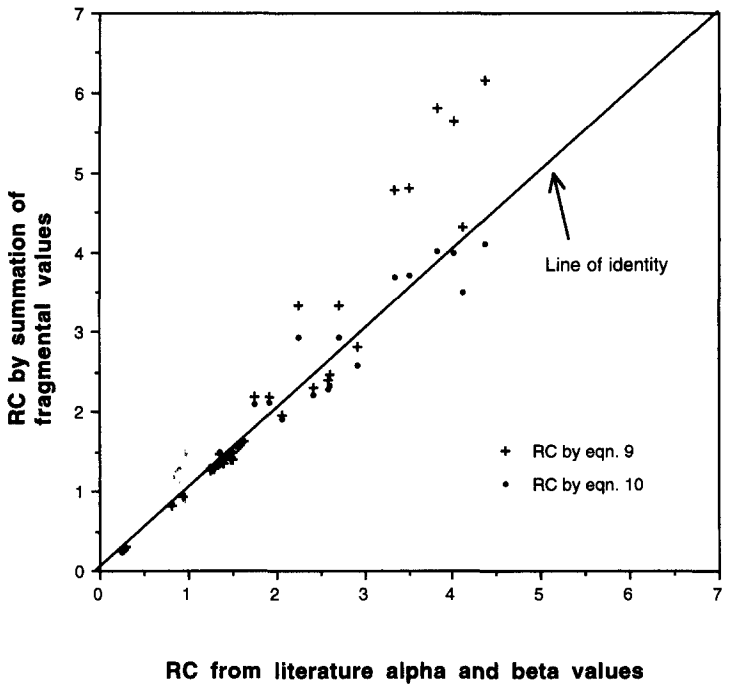

Fig. 7. Comparison of methods for calculating retardation coefficients of polyfunctionals.

$$RC = 0.475 + 0.668\ RC^*$$
$$\textit{0.000}\quad\textit{0.000} \qquad (9)$$

$N = 53$ S.D. $= 0.2546$ $r^2 = 92.5\%$ $F = 646$

AIC $= 65.4$

Despite the reasonably high value of $r^2 = 92.5\%$ the regression is unsatisfactory: the plot is curved (Fig. 7) and it should have coefficients of 0 and 1 for the two predictor terms.

The regression

$$RC = -0.0678 + 1.17\ RC^* - 0.0807\ RC^{*2}$$
$$\textit{0.492}\quad\textit{0.000}\quad\textit{0.000} \qquad (10)$$

$N = 53$ S.D. $= 0.1915$ $r^2 = 95.8\%$ $F = 591$

AIC $= 36.2$

is better. The constant term is not significantly different from zero and the plot of fitted values is close to the line of identity (Fig. 7). These RC values are good predictors of D/h:

$$\log (D/h) = -1.30 - 0.761\ RC - 0.00463\ MW$$
$$\textit{0.000}\ \textit{0.000}\quad\textit{0.000}$$

$N = 53$ S.D. $= 0.3105$ $r^2 = 92.7\%$ $F = 329$

AIC $= 87.4$

$(D_o/h) = 0.0501$ (0.0309 to 0.0794) cm/h.

In summary, although $\Sigma\alpha$ and $\Sigma\beta$ deviate from literature values, they may be used as predictors of D/h.

3.3.4.2. Application to compounds with unknown α, β values. $\Sigma\alpha$ and $\Sigma\beta$ values were calculated for the full dataset in Table 1. These were used in the previously successful regressions.

3.3.4.2.1. Estimation of D/h from solvatochromic parameters.

$$Log\ (D/h) =$$
$$-2.50 + 0.247\ \Sigma\alpha + 0.052\ \Sigma\beta - 0.00682\ MW$$
$$\textit{0.000}\ \textit{0.434}\quad\textit{0.846}\quad\textit{0.000}$$

$N = 74$ S.D. $= 0.7464$ $r^2 = 58.2\%$ $F = 34.9$

AIC $= 277$

A poor result — note the low significance of $\Sigma\alpha$ and $\Sigma\beta$.

3.3.4.2.2. Estimation of D/h from RC values calculated from Eq. 10. (a) Empirical approach

$$\log (D/h) =$$

$$-0.625 - 2.16\ RC + 0.272\ RC^2 - 0.00048\ MW \quad (11)$$
$$0.043 \quad 0.000 \quad 0.000 \quad 0.696$$

$N = 74$ S.D. $= 0.5283$ $r^2 = 79.1\%$ $F = 93.0$

AIC $= 226$

$D_o/h = 0.237$ (0.0588 to 0.965) cm/h.

MW is not a significant predictor.

(*b*) *Adsorption isotherm approach* (12)

Parameter	Final value	S.D.	
D_o/h	0.196	7.86E-03	
D_m/h	−6.72E-05	8.98E-05	Large S.D.
RC_o	0.221	3.61E-03	
K	5.48E-03	2.22E-04	

$N = 74$ $r^2 = 97.7\%$ AIC $= -777$

S.D. of residuals = 5.93E-04

Again although $\Sigma\alpha$ and $\Sigma\beta$ deviate from literature values of α and β it is possible to use RC values based on them as predictors of D/h.

3.3.4.2.3. Comparison of D/h with literature values. The estimates of Scheuplein and Blank, 1971 for D/h of aldosterone, cortisone, progesterone, testosterone and ethanol are 4, 12, 144, 175 and 16 650 cm/h $\times 10^{-7}$, respectively. Values calculated by Eq. 1 (7, 15, 95, 47 and 12 800), Eq. /11 (82, 83, 815, 268 and 7784), and Eq. (12) (18, 18, 139, 161 and 5060), are in broad agreement, given the extent to which sequential estimations must be used.

3.4. Estimation of D_o

Estimation of diffusion coefficients is problematical. They are usually calculated from lag times, which are difficult to determine with any precision and require the pathlength across the SC to be known. Our three estimates of the maximal diffusion term (D_o/h) using α and β literature values are 0.0316, 0.038 and 0.192 cm/h (Eqs. 6, 7 and 8). SC thickness 15 μm with tortuosity factor 20 (Lieckfeldt and Lee, 1995) gives D_o values of 2.6, 3.2 and 16 $\times 10^{-7}$ cm^2/s. No literature values exist for D_o, but, as expected, these are higher than the values of about 8 $\times 10^{-9}$ cm^2/s for higher alcohols calculated from the data of Scheuplein and Blank, 1971.

3.5. Effect of penetrant size on D

Several authors (see for example Kasting et al., 1992) used equations based on

$$D = D_o(\mathrm{MW})^b$$

to relate diffusion to size. For Stokes diffusion through a fluid medium, b is between $-1/2$ and $-1/3$, and Scheuplein and Blank, 1971 and Roberts, 1976 assumed that this applied to the SC. For diffusion across membranes, apparent values of b from -3 to -5 indicate a strong dependence of diffusion on MW. These cases, however, use some other penetration parameter, such as k_p, rather than D. Anderson and Raykar, 1989 using cresols and hydrocortisone esters ($N = 16$) found:

$$k_p = \text{constant}.(K_{oct})^a.\ (\mathrm{MW})^b$$

where $b = -4.6$. The data from Pugh and Hadgraft, 1994 ($N = 87$) on which the Potts and Guy, 1992 model is based give $b = -3.3$.

We propose that K_{oct}, which Anderson and Raykar, 1989 implicitly used as a measure of the partition step, also encodes binding to the SC. Diffusion should then be more accurately written as

$$D = \text{constant}.(\text{binding})^a.(\mathrm{MW})^b$$

and we suggest that RC measures the binding term. Hence using datasets 1a, 1b:

$$\log (D/h) = 1.62 - 2.59 \log RC - 2.16 \log MW$$
$$0.010 \quad 0.000 \quad 0.000$$

$N = 53$ S.D. $= 0.4079$ $r^2 = 87.3\%$ $F = 180$

AIC $= -767$

where the MW dependency ($b = -2.59$) is much less than that of Anderson and Raykar, 1989. It is likely that their size effect is further complicated by the different bonding properties of their steroids.

The size dependence for diffusion can also be examined using the free volume approach of Potts and Guy, 1992. Using datasets 1a, 1b:

$$\log (D/h) = \underset{}{-1.97} \underset{0.000}{-2.01 \log RC} \underset{0.000}{-0.00708\ MW}$$

$$N = 53 \text{ S.D.} = 0.3053\ r^2 = 92.9\%\ F = 341$$

$$\text{AIC} = 85.6$$

The coefficient is similar to the value of -0.0061 found by Potts and Guy, confirming that size is a determinant of solute penetration.

4. Conclusion

Octanol is the best of the common solvents for modelling partitioning of penetrant into SC:

$$\log K_{SC} = -0.024 + 0.59 \log K_{oct}.$$

Diffusion across SC may then be calculated using $\log (D/h) = \log k_p - \log K_{SC}$. (D/h) depends on H-bonding groups in the penetrant and its molecular weight. For monofunctional compounds

$$\log (D/h) =$$

$$-1.03 - 1.25\ \alpha - 2.53\ \beta - 0.00326\ \text{MW}$$

The characteristic α and β values of the various chemical groups implies that each group has a characteristic retardant effect on diffusion. This was termed the retardation coefficient (RC).

RC depends on interaction of the H-bonding groups of the penetrant with those of the SC. Thus, knowing RC and α and β for the penetrant the (relative) H-bonding properties of the SC can be estimated. These are in the proportion α_{SC}:β_{SC} = 0.57:0.43.

For polyfunctional compounds the analysis is more problematical. (D/h) falls sharply to low levels when more than two H-bonding groups are present in the molecule. (D/h) cannot be related to H-bonding estimated by differential partitioning into H-bonding and inert solvents. Calculation of solvatochromic parameters and RC values using a fragmental approach is more successful. Plots of (D/h) against RC are reminiscent of Langmuir (Michaelis-Menten) adsorption. Equations analogous to adsorption isotherm fit the data remarkably well. The maximum rate of diffusion (D_o/h) of an infinitely small, non-bonding molecule is about 0.03 cm/h. The effect of penetrant size on diffusion is lower than previously reported, probably because bonding to the SC was overlooked.

Acknowledgements

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