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The Factors that Influence Skin Penetration of Solutes*

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Abstract

In this study, human skin permeation data are analysed using a number of physicochemical descriptors.

It is shown that the equilibrium distribution of compounds between the stratum corneum and water ($\log K_m$) can be correlated with either water-octanol partition coefficients ($\log P_{oct}$) or Abraham solute descriptors. The latter reveals that partitioning of compounds is governed by solute size and hydrogen-bond acidity that favour the stratum corneum, and solute dipolarity/polarizability, and hydrogen-bond basicity that favour water.

For water-skin permeation coefficient ($\log k_p$) data it is demonstrated that $\log P_{oct}$ cannot be used as a descriptor across a wide range of chemical families, but that $\log k_p$ can be correlated using Abraham solute descriptors. These disclose that $\log k_p$ values are increased by solute size and decreased by solute dipolarity/polarizability, hydrogen-bond acidity and hydrogen-bond basicity. It is suggested that different solutes travel through the stratum corneum by the same route, which cannot be distinguished as an intercellular or transcellular mechanism.

Backward skin permeation is examined and it is demonstrated that factors governing this process can be rationalized. Furthermore, it is shown that using the Abraham analysis, $\log P_{oct}$ can be corrected to correlate $\log k_p$ over a wide range of compounds.

The determination of solute descriptors is also described, indicating that Abraham solute descriptors can be obtained by substructure summation and partition coefficient measurements, so that dermatological properties can be predicted for solutes without the necessity for synthesis.

An area of increasing interest to many important industries is the penetration of chemicals through the skin. For example, in the pharmaceutical industry, not only is the interest in skin for the traditional topical applications, such as anti-inflammatory agents, but also as an alternative drug delivery mechanism, which has some biopharmaceutical benefits such as bypassing hepatic first-pass elimination and improving compliance (Kai et al 1992). To the cosmetic industry, skin penetration is important where penetrative agents are employed to alter skin quality (Barry 1988). Skin penetration by environmental pollutants is another concern especially to occupational toxicology, as transdermal absorption of noxious solutes is acknowledged to be an important uptake route (Houk & Guy 1988). However, measurement of the penetration of chemicals into and through skin is laborious and can involve ethical difficulties with either human or animal experiments. Hence there is a need for a method which is capable of predicting and explaining the physicochemical factors that determine percutaneous penetration. An important starting point for the development of such a method is an understanding of the structure of skin.

Skin is composed of three principal layers, the epidermis, the dermis and subcutaneous fat. The subcutaneous fat is located below the dermis and functions as a fat storage layer, with insulating and protecting (shock-absorbing) properties. It does not have a role in percutaneous penetration because it is below the vascular system, which is located in the dermis (Singh & Singh 1993). The dermis (2 mm) is an acellular connective tissue which supports blood vessels and nerves. Hair follicles, sebaceous glands and sweat glands stem from here to reach the skin surface. Transport of solutes in this area is rapid, moving via microvascular blood vessels into the systemic circulation. Above the dermis is the epidermis, which is essentially divided into two parts. The inner part is viable epidermis (150 μm) (Houk & Guy 1988) in which the cells proliferate and then change to form the dead cells of the stratum corneum. The stratum corneum (10–15 μm) forms the outermost part and is of great importance to the study of skin penetration because it is the principal barrier, the main rate-determining step in solute penetration. The cells of the stratum corneum are cornified, containing dense crystallized keratin, which are often described as being hydrophilic as they contain very little lipid. The cells are flat, elongated and closely packed. They are surrounded by an intercellular lipid matrix, the exact nature of which has, until recently, been rather unclear. Currently it is understood that the matrix is composed of lipid and aqueous regions, arranged in layers (Elias 1981). This intercellular matrix makes up between 10 and 30% of the total volume (Grayson & Elias 1982). A particularly important property of the stratum corneum, in the context of this study, is its ability to become heavily hydrated. Under hydrating conditions, Raykar et al (1988) report water uptake of as much as 4·76 mg of water per mg of dry abdominal skin. Values around 2·5 mg mg^{-1} are more common, suggesting that hydrated stratum corneum is typically about 70% w/w water.

Three possible mechanisms have been suggested for solute permeation through the stratum corneum. The first can be

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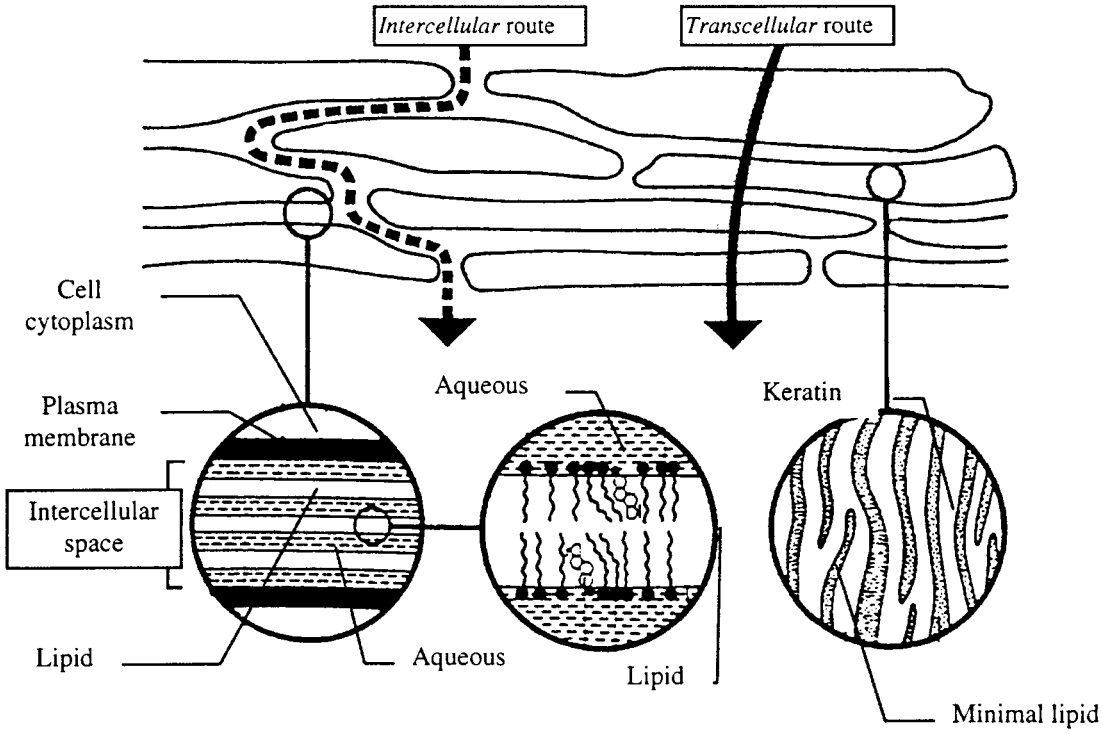

FIG. 1. A depiction of the currently suggested intercellular and transcellular micro routes for solute entry into the stratum corneum.

described as the shunt route, which provides a parallel pathway by which solutes can be absorbed by sweat ducts and hair follicles without hindrance by the stratum corneum. This mechanism is minimized by having only a very small fractional area (10^{-2}–10^{-3} of total skin area). The second and third mechanisms are the intercellular and transcellular routes (Scheuplein 1965, 1978; Barry 1988) (Fig. 1). For the transcellular route, solutes pass directly through the corneal cells and intermediary intercellular lipid matrix, whilst for the intercellular route, solutes diffuse around the corneal cells in a tortuous manner, remaining constantly in the intercellular matrix.

Two experimental aspects of skin penetration have been studied and are of particular interest. Firstly, water-skin partition coefficients (K_m) have been determined, in which excised human skin has been treated as a partitioning phase (Scheuplein 1965; Scheuplein et al 1969). Secondly, solute permeation rates through skin (k_p) have been determined (Scheuplein 1965; Scheuplein et al 1969; Roberts et al 1977), in which the stratum corneum is used as a membrane between an aqueous donor half-cell and an aqueous acceptor half-cell. Although all these experiments have been done in-vitro, they do not suffer from the often pronounced differences between in-vivo and in-vitro experiments of other biological systems, because the principal barrier, the stratum corneum, is in essence a dead layer in the living organism (Marks et al 1988).

The data produced by these studies have been analysed by various workers to find a model capable of explaining the permeation process and to predict penetration without recourse to morally objectionable experiments. However, an issue often neglected by workers concerning these studies, is that they are conducted in aqueous solution. This has a profound effect on skin properties and under these conditions the skin becomes hydrated (Scheuplein et al 1969). Therefore, any deductions from these studies do not directly pertain to the skin in-vivo, but rather to heavily hydrated skin. Nevertheless the results are still very useful, because under normal in-vivo conditions the skin becomes hydrated easily, and more so under therapeutic conditions, because drugs are normally administered either in solution (water/gel solvent vehicle) or with the skin occluded (using a bandage or patch) which also has a pronounced hydration effect.

In this paper, we analyse the results from the above studies in terms of the methodology outlined below, and, additionally, we compare the results of our analysis with those of previous analyses.

Methodology

The methodology is based on the general solvation equation (Abraham 1993a):

$$\log SP = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + vVx \quad (1)$$

In this equation, SP is some property of a series of solutes in a given system, and the explanatory variables, or descriptors, are solute properties as follows.

R_2 is an excess molar refraction that can be determined simply from a knowledge of the compound refractive index (Abraham et al 1990a). Since R_2 is almost an additive property, it is quite straightforward to deduce values for compounds that are solid at room temperature. The R_2

descriptor represents the tendency of a solute to interact with a phase through π or n electron pairs.

π_2^H is the solute dipolarity/polarizability (Abraham et al 1991), it being not possible to devise descriptors for these properties separately. At present some 1000 values of π_2^H are known, and it is possible to obtain further values by use of various water-solvent partition coefficients (Abraham 1993b).

$\Sigma\alpha_2^H$ is the solute effective or overall hydrogen-bond acidity. For mono-acids, this descriptor was originally obtained directly from hydrogen-bond complexation constants (Abraham et al 1989), as α_2^H, and in this way values were found for many types of solutes such as carboxylic acids, alcohols, and phenols (Abraham 1993b). Now that the acid scale is established, further values of $\Sigma\alpha_2^H$ can be obtained by use of partition coefficients.

$\Sigma\beta_2^H$ is the solute effective or overall hydrogen-bond basicity. Again, for mono-bases, this was first obtained from hydrogen-bond complexation constants, as β_2^H, (Abraham et al 1990b) and modified and extended through water-solvent partition coeffients. Leahy et al (1992) have examined partition in four water-solvent systems using an equation that resembles equation 1, but with rather different descriptors. There were a number of solutes investigated by Leahy et al (1992) for which no constant β-value could be found. In other words, for these solutes the relative effective hydrogen-bond basicity varies with the solvent system. Abraham (1993b) later showed that this was also the case with equation 1, but as it happens, none of these solutes are included in any of the datasets examined in this work.

Vx is the McGowan characteristic volume that can be calculated for any solute simply from molecular structure, using a table of atomic constants (Abraham & McGowan 1987).

The coefficients in equation 1 are found by the method of multiple linear regression analysis and serve to characterize the phase in question as follows: the r-constant is a measure of the propensity of the phase to interact with solute π and n electron pairs; the s-constant describes the phase dipolarity/polarizability; the a-constant is a measure of the phase hydrogen-bond basicity; the b-constant measures the phase hydrogen-bond acidity; and the v-constant is a measure of the phase lipophilicity. For cases where log SP refers to distribution between phases, these constants will reflect the difference in properties of the two phases.

Two particular applications (Abraham et al 1994a) of equation 1 are of importance in this work. Firstly, water-octanol partition coefficients, as $\log P_{oct}$, were shown to follow equation 2:

$$\log P_{oct} = 0{\cdot}088 + 0{\cdot}562R_2 - 1{\cdot}054\pi_2^H + 0{\cdot}034\Sigma\alpha_2^H - 3{\cdot}460\Sigma\beta_2^H + 3{\cdot}814Vx \quad (2)$$

$$n = 613 \qquad \rho = 0{\cdot}9974 \qquad \text{s.d.} = 0{\cdot}116 \qquad F = 23161{\cdot}6$$

Here, n is the number of data points, ρ is the correlation coefficient, s.d. is the regression standard deviation and F is the Fisher F-statistic.

This equation is important in that it shows that the main factors influencing water-octanol partitions are solute dipolarity and basicity that favour water, and solute size that favours octanol. Solute acidity plays a negligible part because water and wet octanol have very similar hydrogen-bond basicities. Secondly, the $\Delta\log P$ parameter of Seiler (1974), defined as $\Delta\log P_{16} = \log P_{oct} - \log P_{16}$, where the latter refers to the water-hexadecane system, was shown to follow equation 3:

$$\Delta\log P_{16} = -0{\cdot}072 - 0{\cdot}093R_2 + 0{\cdot}528\pi_2^H + 3{\cdot}655\Sigma\alpha_2^H + 1{\cdot}396\Sigma\beta_2^H - 0{\cdot}521Vx \quad (3)$$

$$n = 288 \qquad \rho = 0{\cdot}9833 \qquad \text{s.d.} = 0{\cdot}173 \qquad F = 1646{\cdot}3$$

This shows, for the first time, that the $\Delta\log P$ parameter reflects not only solute acidity but also solute dipolarity, basicity and size.

Analysis of Skin Penetration

Determination of solute descriptors

To construct an equation for skin penetration data which is similar to equations 2 and 3, it is necessary to obtain the five solute descriptors in the general equation (eqn 1). For the alcohols (Scheuplein 1965; Roberts 1976) and phenols (Roberts et al 1977) solute descriptors were readily available from previous studies. However, for the steroids (Scheuplein et al 1969) new solute descriptors had to be determined. Since Vx can be obtained by simple arithmetic, we are essentially left with four descriptors—R_2, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ and π_2^H—that need to be determined.

R_2, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ were determined by summing the values for the appropriate fragments shown in Table 1. The values for these fragments were obtained from partition coefficients (Abraham et al 1994b). In the case of R_2, a value of 1·15 was used for the unsubstituted hydrocarbon four-ring steroid system, and the ΔR_2 values are the additional fragment values. Thus for testosterone $R_2 = 1{\cdot}15 + 0{\cdot}261$ (3-carbonyl 4-ene) $+ 0{\cdot}127$ (17-α-hydroxy) $= 1{\cdot}538$, $\Sigma\alpha_2^H = 0{\cdot}32$ (17-β-hydroxy) and $\Sigma\beta_2^H = 0{\cdot}63$ (3-carbonyl-4-ene) $+ 0{\cdot}56$ (17-α-hydroxy) $= 1{\cdot}19$.

Table 1. Fragment values of R_2, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ for steroids.

Substructure	ΔR_2[a]	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$
3-Carbonyl	0·045	0·00	0·56
3-Carbonyl-4-ene	0·261	0·00	0·63
3-Carbonyl-1,4-diene	0·445	0·00	0·63
3-β-Hydroxy	0·115	0·32	0·57
5-Ene	0·055	0·00	0·10
11-Carbonyl	0·045	0·00	0·27
11-β-Hydroxy	0·115	0·25	0·30
17-Carbonyl	0·057	0·00	0·52
17-β-Hydroxy	0·127	0·32	0·56
17-β-$COCH_3$	0·037	0·00	0·51
17-β-$COCH_2OH$	0·332	0·15	0·70
17-α-Methyl-17-β-hydroxy	0·077	0·30	0·60
17-α-Hydroxy-17-β-$COCH_3$	0·234	0·25	0·68
17-α-Hydroxy-17-β-$COCH_2OH$	0·500	0·35	0·94
3-Hydroxy-1,3,5-triene	0·525	0·56	0·39
11,18-CH-OH[b]	0·267	0·25	0·57
16-α-Hydroxy-17-β-hydroxy	0·324	0·84	0·83

[a] The given ΔR_2 values are to be added to 1·15 for the hydrocarbon four-ring steroid system. [b] In aldosterone.

Table 2. Coefficients of equation 1 for various water-solvent partitioning systems.

Solvent	c	r	s	a	b	v
Isobutanol[a]	0·249	0·480	−0·639	−0·050	−2·284	2·758
Octanol[b]	0·088	0·562	−1·054	−0·034	−3·460	3·814
Diethyl ether[a]	0·462	0·571	−1·035	−0·024	−5·508	4·346
Benzene[a]	0·017	0·490	−0·604	−3·013	−4·628	4·587
Cyclohexane[a]	0·124	0·844	−1·800	−3·727	−4·923	4·692
Alkane[a]	0·281	0·647	−1·687	−3·520	−4·848	4·326
Hexadecane[b]	0·087	0·667	−1·617	−3·587	−4·869	4·433

[a] Abraham (1993a). [b] Abraham et al (1994a).

π_2^H cannot be easily obtained from fragments unless they are large and non-interacting (Abraham et al 1994b). However, since we now only had this one descriptor to determine (after R_2, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ and Vx had been obtained), we used available partition coefficients of the steroids to back-calculate it, using established partition coefficient regression equations (Table 2). In several cases, more than one partition coefficient had been reported, and then the back-calculations served to confirm the total assigned set of descriptors. Partition coefficients of many of the steroids have been determined in the water-amylcaproate system (Scheuplein 1965; Scheuplein et al 1969). However, there were not enough data to obtain a regression equation for this system, but we used the log P values as a check on the comparison between the steroids.

Application to water-skin partition coefficients

Scheuplein (1965) and Scheuplein et al (1969) determined water-skin (human abdominal stratum corneum) partition coefficients—denoted as K_m and defined by equation 4—for eight alcohols and fourteen steroids, listed in Table 3.

$$K_m = \frac{[\text{mols of solute absorbed per unit mass dry tissue}]}{[\text{mols of solute in solution per unit mass of water}]} \quad (4)$$

It was noted by Scheuplein et al (1969) that measured water-amylcaproate partition coefficients gave a guide to permeability, and were more suitable than water-hexadecane partition coefficients as a model. They, therefore, suggested that the stratum corneum was a more polar phase than had been previously understood. More recently, Tayar et al (1991) have re-examined the data of Scheuplein (1965) and Scheuplein et al (1969) and showed that there is a reasonable correlation between $\log K_m$ and $\log P_{oct}$:

$$\log K_m = 0{\cdot}51 \log P_{oct} + 0{\cdot}10 \quad (5)$$

$$n = 22 \qquad \rho = 0{\cdot}971 \qquad \text{s.d.} = 0{\cdot}156$$

Three values of $\log P_{oct}$ used in equation 5 were estimated; if these are excluded, equation 6 results:

$$\log K_m = 0{\cdot}514 \log P_{oct} + 0{\cdot}104 \quad (6)$$

$$n = 19 \qquad \rho = 0{\cdot}9694 \qquad \text{s.d.} = 0{\cdot}163 \qquad F = 265{\cdot}5$$

Although equation 6 is quite good, it yields no information as to the factors that influence the partitioning process. Application of equation 1, with the descriptors given in Table 3, leads to equation 7:

$$\log K_m = -0{\cdot}027 - 0{\cdot}374\pi_2^H + 0{\cdot}334\Sigma\alpha_2^H - 1{\cdot}674\Sigma\beta_2^H + 1{\cdot}869\text{Vx} \quad (7)$$

$$n = 22 \qquad \rho = 0{\cdot}9710 \qquad \text{s.d.} = 0{\cdot}166 \qquad F = 70{\cdot}2$$

Table 3. Values of water-skin partition coefficients, as $\log K_m$, and permeability coefficients, as $\log k_p$. $\log k_{P_{back}}$ values are also given.

Solute	$\log K_m$	$\log k_p$[de] ($\log k_1^{obs}$)	$\log k_{P_{back}}$[fg] ($\log k_2^{obs}$)	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	Vx
Methanol[a]	−0·22	−6·56	−6·34	0·278	0·44	0·43	0·47	0·308
Ethanol[a]	−0·22	−6·56	−6·34	0·246	0·42	0·37	0·48	0·449
Propan-1-ol[a]	0·30	−6·41	−6·71	0·236	0·42	0·37	0·48	0·590
Butan-1-ol[a]	0·40	−6·16	−6·56	0·224	0·42	0·37	0·48	0·731
Pentan-1-ol[a]	0·70	−5·78	−6·48	0·219	0·42	0·37	0·48	0·872
Hexan-1-ol[a]	1·00	−5·44	−6·44	0·210	0·42	0·37	0·48	1·013
Heptan-1-ol[a]	1·48	−5·05	−6·53	0·211	0·42	0·37	0·48	1·154
Octan-1-ol[a]	1·70	−4·84	−6·54	0·199	0·42	0·37	0·48	1·295
Progesterone[b]	2·01	−6·38	−8·39	1·450	3·29	0·00	1·14	2·622
Pregnenolone[b]	1·70	−6·38	−8·08	1·360	3·29	0·32	1·18	2·665
17α-Hydroxypregnenolone[b]	1·63	−6·78	−8·41	1·550	3·35	0·57	1·35	2·723
17α-Hydroxyprogesterone[b]	1·60	−6·78	−8·38	1·640	3·35	0·25	1·31	2·680
Deoxycorticosterone[b]	1·57	−6·90	−8·47	1·674	3·39	0·15	1·13	2·680
Testosterone[b]	1·36	−6·95	−8·31	1·540	2·59	0·32	1·19	2·383
Cortexolone[b]	1·36	−7·68	−9·04	1·910	3·45	0·35	1·57	2·739
Corticosterone[b]	1·23	−7·78	−9·01	1·860	3·43	0·40	1·63	2·739
Cortisone[b]	0·93	−8·56	−9·49	1·960	3·50	0·35	1·84	2·755
Hydrocortisone[b]	0·85	−9·08	−9·93	2·030	3·49	0·70	1·87	2·798
Aldosterone[b]	0·83	−9·08	−9·91	2·010	3·47	0·40	1·90	2·689
Oestrone[b]	1·66	−6·00	−7·66	1.730	3·10	0·56	0·91	2·156
Oestradiol[b]	1·66	−7·08	−8·74	1·800	3·30	0·88	0·95	2·199
Oestriol[b]	1·36	−7·95	−9·31	2·000	3·36	1·40	1·22	2·258
Diethylether[c]	–	−5.35	–	0·041	0·25	0·00	0·45	0·731
Butanone[c]	–	−5·90	–	0·166	0·70	0·00	0·51	0·688
2-Ethoxyethanol[c]	–	−7·16	–	0·237	0·50	0·30	0·83	0·790

[a] $\log K_m$ and $\log k_p$ values from Scheuplein (1965); [b] $\log K_m$ and $\log k_p$ values from Scheuplein et al (1969); [c] $\log k_p$ values from Scheuplein & Blank (1971). [d] This is the inward permeation rate and could be described as $\log k_{P_{in}}$, but is denoted $\log k_p$ for consistency. [e] Equivalent to k_1 rate constant. [f] Calculated from equation 19. [g] Equivalent to k_2 rate constant.

Equation 7 is not as good statistically as equation 6, judging by the F-statistic, but it is much more informative. It shows that the main factors that influence the water-stratum corneum partitioning process are solute basicity that favours water and solute size that favours the stratum corneum. Minor factors are solute dipolarity that favours water and solute acidity that favours the stratum corneum. Hence the stratum corneum behaves as though it is slightly less dipolar, slightly more basic, less acidic and more lipophilic than water. Comparison with equation 2 shows also that the stratum corneum is much less lipophilic than wet octanol (v = 1·869 in eqn 7; v = 3·814 in eqn 2). Indeed, the stratum corneum is even less lipophilic than wet isobutanol (v = 2·758, see Table 2), even though the solubility of water in isobutanol is 16·9% w/w at 25°C (Riddick & Bunger 1970) corresponding to 0·49 mol fraction. The most likely explanation for this is that the stratum corneum in equilibrium with water is highly hydrated. This agrees with suggestions by Elias (1981), Raykar et al (1988) and Barry (1988). This might also explain why solute basicity affects water-stratum corneum partition much less than it does water-octanol partition (b = −1·674 in eqn 7; b = −3·460 in eqn 2); i.e. the presence of a considerable quantity of water in the stratum corneum confers substantial acidity that partly counterbalances the very acidic aqueous phase. The stratum corneum, of course, is not a homogeneous phase, but equation 7 does suggest that not only the keratin-filled cells, but also the intercellular lipid phase contains water, in agreement with current knowledge. The water in the lipid phase is probably bound to the basic end-groups which will not, therefore, function so effectively as hydrogen-bond bases towards (hydrated) solute molecules.

Application to water-skin permeability coefficients

Permeability coefficients were also obtained by Scheuplein (1965) and Scheuplein et al (1969), given in Table 3 as $\log k_p$ with k_p in units of $cm\,s^{-1}$. For the 22 solutes, Tayar et al (1991), using the three estimated $\log P_{oct}$ values, found:

$$\log k_p = 0{\cdot}16 \log P_{oct} - 7{\cdot}15 \qquad (8)$$

$$n = 22 \qquad \rho = 0{\cdot}164 \qquad \text{s.d.} = 1{\cdot}170$$

Using the 19 measured values only, a similarly very poor correlation, equation 9, is given:

$$\log k_p = 0{\cdot}174 \log P_{oct} - 7{\cdot}121 \qquad (9)$$

$$n = 19 \qquad \rho = 0{\cdot}176 \qquad \text{s.d.} = 1{\cdot}232 \qquad F = 0{\cdot}5$$

This very poor correlation is due to the values for the alcohols and the steroids lying on two distinct lines (Fig. 2).

A much better correlation was obtained by Tayar et al (1991) with the $\Delta \log P$ parameter, if cortisone was omitted:

$$\log k_p = -1{\cdot}36 \Delta \log P - 3{\cdot}38 \qquad (10)$$

$$n = 21 \qquad r = 0{\cdot}901 \qquad \text{s.d.} = 0{\cdot}498$$

Tayar et al (1991) explained this correlation on the basis that the $\Delta \log P$ parameter mainly reflects solute hydrogen-bond acidity and that this has a retarding effect on permeability through interactions of the acidic groups in the solute with basic groups in the lipid phase during an intercellular route.

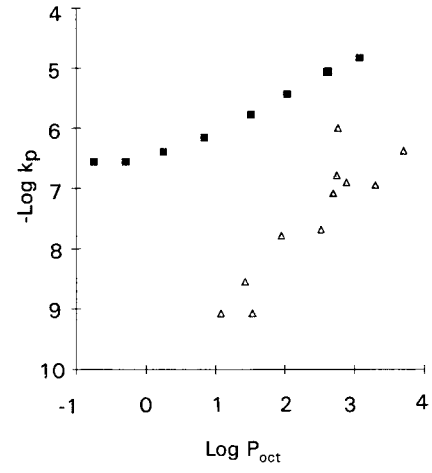

FIG. 2. Log plot of permeability coefficient vs P_{oct} for 19 alcohols (■) and steroids (△) (excluding pregnenolone, 17α-hydroxypregnenolone and oestriol for which measured P_{oct} values were not available).

However, we know from equation 3 that the $\Delta \log P$ parameter is not just a measure of solute hydrogen-bond acidity but is a composite parameter involving lipophilicity, basicity and dipolarity, as well as acidity. $\Delta \log P$ may be useful as a descriptor for the prediction of further permeability values, but it is of little value in the interpretation of the permeability process.

We have applied equation 1 to the 22 solutes used by Tayar et al (1991) to arrive at an alternative equation to equation 10, equation 11. We have also used a further three values given by Scheuplein & Blank (1971)—those for diethylether, 2-ethoxyethanol and butanone (denoted the Extra-S set, listed in Table 3)—to yield equation 12:

$$\log k_p = -5{\cdot}333 - 0{\cdot}622\pi_2^H - 0{\cdot}378\Sigma\alpha_2^H - 3{\cdot}342\Sigma\beta_2^H + 1{\cdot}851Vx \qquad (11)$$

$$n = 22 \qquad \rho = 0{\cdot}9781 \qquad \text{s.d.} = 0{\cdot}268 \qquad F = 93{\cdot}7$$

$$\log k_p = -5{\cdot}194 - 0{\cdot}567\pi_2^H - 0{\cdot}506\Sigma\alpha_2^H - 3{\cdot}368\Sigma\beta_2^H + 1{\cdot}767Vx \qquad (12)$$

$$n = 25 \qquad \rho = 0{\cdot}9780 \qquad \text{s.d.} = 0{\cdot}260 \qquad F = 110{\cdot}1$$

There is a profound difference between an analysis based on equation 11 and the analysis of Tayar et al (1991) based on equation 10. The former shows that the two main factors that influence permeability are solute hydrogen-bond basicity that reduces permeability and solute size (or lipophilicity) that increases permeability. A less important factor is solute dipolarity that reduces permeability. In striking contrast to the analysis of Tayar et al (1991), solute acidity plays little part. This is understandable on the basis that the large amounts of water in the stratum corneum (as deduced from the above partition studies) render it sufficiently acidic to retard the passage of basic compounds but not acidic compounds. It should be noted that although water has basic as well as acidic properties, monomeric water is no more basic than simple alcohols, and bulk water is even less basic than are bulk alcohols (Kamlet et al 1983).

Table 4. Values of permeability coefficients, as $\log k_p$, and solute descriptors, for phenols[a] and alcohols[b].

Solute	$\log k_p$	R_2	π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^H$	Vx
Resorcinol	−7·18	0·980	1·00	1·10	0·58	0·834
4-Nitrophenol	−5·81	1·070	1·72	0·82	0·26	0·949
3-Nitrophenol	−5·81	1·050	1·57	0·79	0·23	0·949
Phenol	−5·64	0·805	0·89	0·60	0·30	0·775
Methyl 4-hydroxy-benzoate	−5·60	0·900	1·37	0·69	0·45	1·132
m-Cresol	−5·37	0·822	0·88	0·57	0·34	0·916
o-Cresol	−5·36	0·840	0·86	0·52	0·30	0·916
p-Cresol	−5·31	0·820	0·87	0·57	0·31	0·916
2-Naphthol	−5·11	1·520	1·08	0·61	0·40	1·144
2-Chlorophenol	−5·04	0·853	0·88	0·32	0·31	0·898
4-Ethylphenol	−5.01	0·800	0·90	0·55	0·36	1·057
3,4-Dimethylphenol	−5·00	0·830	0·86	0·56	0·39	1·057
4-Bromophenol	−5·00	1·080	1·17	0·67	0·20	0·950
4-Chlorophenol	−5.00	0·915	1·08	0·67	0·20	0·898
2-Isopropyl-5-ethylphenol	−4·83	0·822	0·79	0·52	0·44	1·339
4-Chloro-3-methylphenol	−4·82	0·920	1·02	0·65	0·22	1·038
4-Chloro-3,5-dimethyl-phenol	−4·79	0·925	0·96	0·64	0·21	1·179
2,4,6-Trichlorophenol	−4·78	1·010	1·01	0·82	0·08	1·142
2,4-Dichlorophenol	−4·78	0·960	0·99	0·58	0·14	1·020
Benzyl alcohol	−5·78	0·083	0·87	0·33	0·50	0·916
2-Phenylethanol	−5·68	0·811	0·91	0·30	0·64	1·057

[a] $\log k_p$ values from Roberts et al (1977) and [b] Roberts (1976).

Another dataset that is suitable for analysis through equation 1, is that of Roberts et al (1977) (Table 4). Tayar et al (1991) found only a poor correlation with the $\Delta \log P$ parameter for this set of phenols:

$$\log k_p = -0{\cdot}37\Delta \log P - 4{\cdot}43 \qquad (13)$$

$$n = 18 \qquad \rho = 0{\cdot}675 \qquad \text{s.d.} = 0{\cdot}441$$

They suggested that possibly the phenols permeate by two different routes, depending on their lipophilicities. However, we do not find any such distinction as indicated in equation 14:

$$\log k_p = -4{\cdot}994 - 0{\cdot}341\pi_2^H - 1{\cdot}691\Sigma\alpha_2^H - 2{\cdot}689\Sigma\beta_2^H + 1{\cdot}965Vx \qquad (14)$$

$$n = 19 \qquad \rho = 0{\cdot}9696 \qquad \text{s.d.} = 0{\cdot}160 \qquad F = 54{\cdot}9$$

Note that in equation 14 we have one extra datapoint, compared with equation 13; this corresponds to a phenol which was ambiguously described as chloroxylenol by Roberts et al (1977) and which we identified as 4-chloro-3,5-dimethylphenol.

Comparison of equations 14 and 11 shows that for the phenols there is a significant term in solute acidity, whereas for the alcohols and steroids there is no such term. It is likely that this reflects the particular solute sets, and is not necessarily due to a fundamental difference in permeation mechanism.

An extension of the analysis is to combine the two datasets. This can be done because both research groups used the same methodology and the same skin type (human abdominal). Furthermore, the combined dataset can be extended by two datapoints—those for benzyl alcohol and 2-phenylethanol (denoted the Extra-R set)—obtained by Roberts (1976). This leads to equation 15:

$$\log k_p = -5{\cdot}048 - 0{\cdot}586\pi_2^H - 0{\cdot}633\Sigma\alpha_2^H - 3{\cdot}481\Sigma\beta_2^H + 1{\cdot}787Vx \qquad (15)$$

$$n = 46 \qquad \rho = 0{\cdot}9789 \qquad \text{s.d.} = 0{\cdot}249 \qquad F = 235{\cdot}0$$

Clearly, the equation has not collapsed on combination of the two datasets. We suggest, therefore, that as well as being the best equation for the alcohols, steroids and phenols, it is also the best general equation available for application to new compounds. On this basis, there is no dual mechanism within these classes of compounds. Indeed, any division into intercellular and transcellular routes is arbitrary, bearing in mind that the intercellular phase, and the cells themselves, both contain lipids and both will be to some extent hydrated. The interpretation of equation 15 follows closely that of equation 12, except that it appears that solute acidity retards permeation to a small extent.

Further Analysis of the $\log P_{oct}$ Model

Fig. 2 shows, for the alcohols and steroids, that when $\log k_p$ is plotted against $\log P_{oct}$ the data splits into two distinct groups, one for the alcohols and one for the steroids. Our analysis shows that this is mainly due to the difference in the volume term in the $\log k_p$ and $\log P_{oct}$ regressions (compare eqns 2 and 12). In order to extend our analysis, we have correlated the phenolic $\log k_p$ values of Roberts et al (1977) with $\log P_{oct}$, equation 16. The correlation is much better than for equation 8 because the dataset covers a congeneric series within which the volume does not vary very much.

$$\log k_p = 0{\cdot}689 \log P_{oct} - 6{\cdot}915 \qquad (16)$$

$$n = 19 \qquad \rho = 0{\cdot}8509 \qquad \text{s.d.} = 0{\cdot}311 \qquad F = 44{\cdot}6$$

Thus for congeneric series—such as alcohols, steroids and phenols taken separately—reasonable correlations are obtained between $\log P_{oct}$ and $\log k_p$. The reason for this is not that there are different mechanisms but is simply due to the lack of variation of the solute descriptors within each of the series (see Tables 3, 4). The alcohol series best illustrates this, where the π_2^H, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ values remain the same and only the Vx descriptor varies. However, if all of the $\log k_p$ data used in this work are taken as a whole, $\log P_{oct}$ provides only a very poor correlation, illustrated by equation 17 and Fig. 3.

$$\log k_p = 0{\cdot}386 \log P_{oct} - 6{\cdot}787 \qquad (17)$$

$$n = 43 \qquad r = 0{\cdot}3609 \qquad \text{s.d.} = 1{\cdot}094 \qquad F = 6{\cdot}1$$

The reason for the very poor correlation of $\log k_p$ against $\log P_{oct}$ can be understood by comparing the equations 2 and 15. The main difference is that the coefficient in Vx is much larger for the $\log P_{oct}$ regression (3·814) than for the $\log k_p$ regression (1·787). This suggests that if the regression of $\log k_p$ against $\log P_{oct}$ were adjusted by the incorporation of a corrective term in Vx, a much better regression would be obtained:

$$\log k_p = 0{\cdot}812 \log P_{oct} - 1{\cdot}474Vx - 5{\cdot}631 \qquad (18)$$

$$n = 43 \qquad \rho = 0{\cdot}9581 \qquad \text{s.d.} = 0{\cdot}340 \qquad F = 223{\cdot}9$$

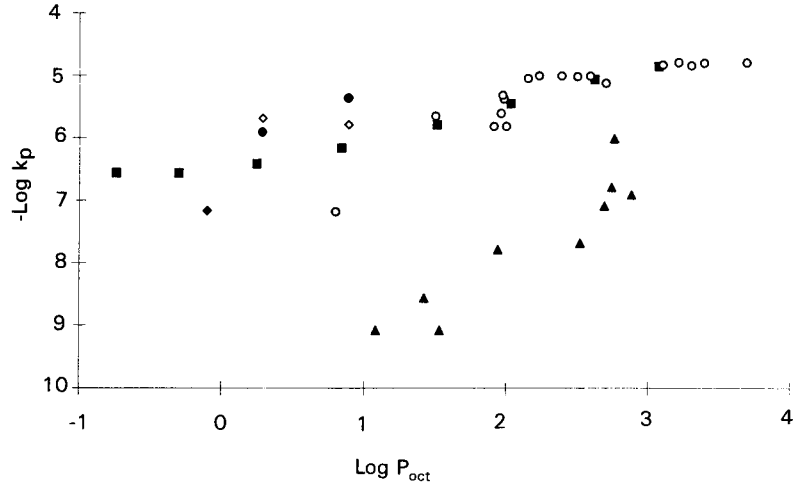

FIG. 3. Log plot of permeability coefficient vs P_{oct} for all 43 available compounds. ■ Alcohols, ▲ steroids, ◆ Extra-S, ○ phenols, ◇ Extra-R.

This simple volume correction to $\log P_{oct}$ transforms the scatter diagram in Fig. 3 to a reasonably linear relationship shown in Fig. 4. Conversely, the scatter plot of $\log k_p$ against $\log P_{oct}$, that has always been held as evidence of a two-route mechanism of permeation, is shown to be no more than an artefact due to the use of a model solvent that is too lipophilic compared with the stratum corneum.

The relationship between equations 15 and 18 explains how Takahashi et al (1993) were able to correct $\log P_{oct}$ by a mol. wt descriptor in order to correlate $\log k_p$ values for six narcotic analgesics, since mol. wt is roughly proportional to volume. It explains also how Potts & Guy (1992) were earlier able to set out equations 19 and 20 for the prediction of $\log k_p$ values using a similar data set to the one we have used:

$$\log k_p = -6{\cdot}2 + 0{\cdot}74 \log P_{oct} - 0{\cdot}0108MV \qquad (19)$$

$$n = 42 \qquad \rho = 0{\cdot}91$$

$$\log k_p = -6{\cdot}0 + 0{\cdot}70 \log P_{oct} - 0{\cdot}0050MW \qquad (20)$$

$$n = 42 \qquad \rho = 0{\cdot}91$$

For a much larger data set, a similar equation to equation 20 had n = 89 and $\rho = 0{\cdot}82$ (Guy & Potts 1993). In the above equations, MV is the calculated molar volume and MW is the mol. wt. Our own version of equation 20 is:

$$\log k_p = -5{\cdot}740 + 0{\cdot}851 \log P_{oct} - 0{\cdot}012MW \qquad (21)$$

$$n = 43 \qquad \rho = 0{\cdot}9628 \qquad \text{s.d.} = 0{\cdot}321 \qquad F = 253{\cdot}6$$

Modification of the $\log P_{oct}$ descriptor by either a volume term or the mol. wt thus provides a useful predictive equation (Potts & Guy 1992). However, our analysis through equations 15 and 18 well illustrates the theoretical reason for the success of such predictive equations. In practical terms, our own equations using the modified $\log P_{oct}$ descriptor, equations 18 and 21 yield standard

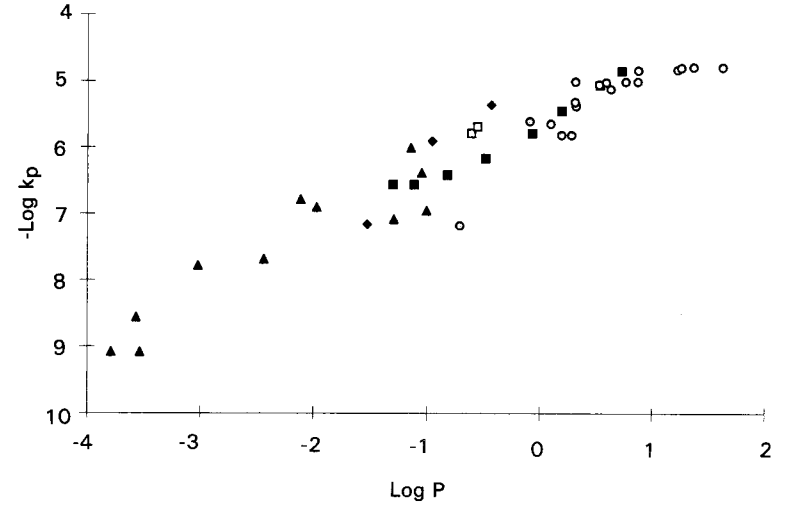

FIG. 4. Log plot of permeability coefficient vs volume adjusted P_{oct} for all 43 available values. ■ Alcohols, ▲ steroids, ◆ Extra-S, ○ phenols, □ Extra-R.

deviations of around 0·33 log units in $\log k_p$, as compared with an s.d. value of 0·25 for the full equation (eqn 15). Thus, provided it is not too difficult to determine or estimate the descriptors in equation 15, it still seems worthwhile to use the full equation to estimate any value in $\log k_p$.

Comparison of Equilibrium ($\log K_m$) and Kinetic Measurements ($\log k_p$)

The Scheuplein dataset of Table 3 contains the results of two different types of measurement: the equilibrium water-stratum corneum partition ($\log K_m$) and the permeation rate ($\log k_p$) from water through the skin. If the stratum corneum is the principal barrier to permeation from water through the skin, i.e. the forward direction, it will also be the principal barrier to permeation in the reverse direction, i.e. through the stratum corneum back into the water. We refer to the rate of the reverse direction as $k_{p_{back}}$. This quantity can be obtained from the equilibrium partition and the forward permeation through equations 22 and 23.

$$\log K_m = \log k_p / k_{p_{back}} \quad (22)$$

$$\log k_{p_{back}} = \log k_p - \log K_m \quad (23)$$

The regression equation for $\log k_{p_{back}}$, based on equation 1 and using the dataset in Table 3, is given by equation 24, which is very different to the $\log k_p$ equation (eqn 11).

$$\log k_{p_{back}} = -5{\cdot}304 - 0{\cdot}247\pi_2^H - 0{\cdot}716\Sigma\alpha_2^H - 1{\cdot}670\Sigma\beta_2^H - 0{\cdot}018Vx \quad (24)$$

$$n = 22 \qquad \rho = 0{\cdot}9849 \qquad \text{s.d.} = 0{\cdot}242 \qquad F = 137{\cdot}5$$

A possible explanation for this can be found in the work of van de Waterbeemd et al (1981), who compared the rate constants for solutes going into, k_1^{obs}, and out of, k_2^{obs}, octanol at the interface of a water-octanol system (also see discussion by Dearden (1990)) with the equilibrium constant $\log P_{oct}$. They suggested that when the inward rate constant k_1^{obs} is proportional to the equilibrium constant $\log P_{oct}$ then the rate controlling step is k_1 (see Fig. 5) and that the backward rate constant k_2^{obs} is diffusion-controlled at the stagnant organic layer (k_2'' in Fig. 5). Since in our work we find that the regression equations for $\log k_p$ (inward rate constant) and $\log K_m$ (equilibrium constant) are similar whilst that for $\log k_{p_{back}}$ (backward rate constant) is very different then this suggests, following on from the ideas of van de Waterbeemd et al (1981), that $\log k_{p_{back}}$ could be entirely or partially diffusion controlled. This is supported by the fact that the coefficients in equation 24 (except that for the small acidity term) are smaller than those in equation 11, implying that structural effects have a smaller effect on $\log k_{p_{back}}$ than on $\log k_p$.

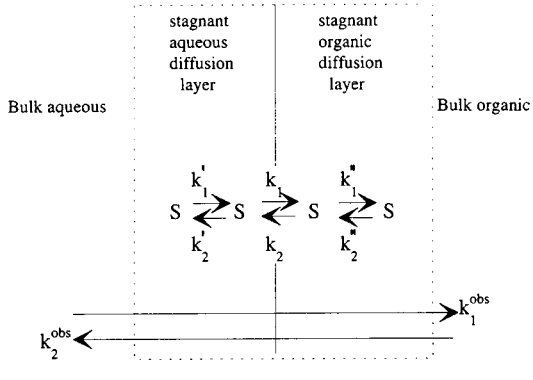

FIG. 5. The interfacial transfer of a solute, S, described by a three-step mechanism for the water-octanol system. Adapted from van de Waterbeemd et al (1981).

Conclusions

Analysis of water-skin partition coefficients, $\log K_m$, by the solvation equation (eqn 1) shows that the main factors involved are solute basicity that favours water, and solute size or lipophilicity that favours the stratum corneum. These results can be rationalized if stratum corneum is highly aqueous (as would be expected under hydrating conditions), and hence is somewhat acidic but still less acidic than bulk water. A similar analysis of stratum corneum permeability coefficients ($\log k_p$) for alcohols, steroids, and phenols shows that $\log k_p$ is greatly retarded by solute basicity, slightly retarded by solute dipolarity and acidity, and greatly increased by solute lipophilicity. These permeability results can be rationalized on the same basis as the water-skin partition coefficients.

Unlike previously published models, it has been demonstrated that skin permeability coefficients can be accounted for by a single high quality regression equation covering a wide and disparate set of chemical functionality. This indicates that it is likely there is only a single penetration mechanism rather than several mechanisms. This conclusion is very important, particularly in the context of the absorption of toxic chemicals where predictions of dermal absorption and dermal toxicity depend crucially on whether a two-route (Fiserova-Bergerova et al 1990) or a one-route mechanism applies (Guy & Potts 1993). Our findings support the conclusions of the latter workers.

Comparison of the regression equations for $\log K_m$, $\log k_p$ and $\log k_{p_{back}}$ suggests that the physicochemical factors controlling $\log k_{p_{back}}$ are very different to those controlling $\log K_m$ and $\log k_p$. This can be rationalized on the basis that $\log k_{p_{back}}$ is largely diffusion controlled.

Although there is a reasonable correlation of water-stratum corneum partition coefficients with $\log P_{oct}$, the latter cannot be used to correlate water-stratum corneum permeation coefficients for different families of solute. However, if $\log P_{oct}$ is corrected by a solute volume term, a good correlation is found between $\log k_p$ and the corrected $\log P_{oct}$ term, which could be used to estimate further $\log k_p$ values. Our analysis also explains the success of the correlations based on $\log P_{oct}$ and mol. wt.

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References

Abraham, M. H. (1993a) Scales of hydrogen bonding: their construction and application to physicochemical and biochemical processes. Chem. Soc. Rev. 22: 73–83

Abraham, M. H. (1993b) Hydrogen-bonding 31. Construction of a scale of solute effective or summation hydrogen bond basicity. J. Phys. Org. Chem. 6: 660–684

Abraham, M. H., McGowan, J. C. (1987) The use of characteristic volumes to measure cavity terms in reversed phase liquid chromatography. Chromatographia 23: 243–246

Abraham, M. H., Grellier, P. L., Prior, D. V., Duce, P. P., Morris, J. J., Taylor, P. J. (1989) Hydrogen bonding 7. A scale of hydrogen bond acidity based on log K values for complexation in tetrachloromethane. J. Chem. Soc., Perkin Trans. 2: 699–711

Abraham, M. H., Whiting, G. S., Doherty, R. M., Shuely, W. J. (1990a) Hydrogen-bonding part 13. A new method for characterisation of GLC stationary phases—the Laffort dataset. J. Chem. Soc., Perkin Trans. 2: 1451–1460

Abraham, M. H., Grellier, P. L., Prior, D. V., Morris, J. J., Taylor, P. J. (1990b) Hydrogen-bonding part 10. A scale of solute hydrogen bond basicity using log K values for complexation in tetrachloromethane. J. Chem. Soc., Perkin Trans. 2: 521–529

Abraham, M. H., Whiting, G. S., Doherty, R. M., Shuely, W. J. (1991) Hydrogen-bonding 16. A new solute solvation parameter pi-h2 from gas chromatographic data. J. Chromatogr. 587: 213–228

Abraham, M. H., Chadha, H. S., Whiting, G. S., Mitchell, R. C. (1994a) Hydrogen bonding part 32. An analysis of water-octanol and water-alkane partitioning and the $\Delta \log P$ parameter of Seiler. J. Pharm. Sci. 83: 1085–1100

Abraham, M. H., Chadha, H. S., Mitchell, R. C. (1994b) Hydrogen bonding part 33. The factors that influence the distribution of solutes between blood and brain. J. Pharm. Sci. 83: 1257–1266

Barry, B. W. (1988) Action of skin penetration enhancers—the lipid protein partitioning theory. Int. J. Cosm. Sci. 10: 281–293

Dearden, J. C. (1990) Molecular structure and drug transport. In: Hansch, C. (ed.) Comprehensive Medicinal Chemistry. Vol. 4, Pergamon Press, Oxford, pp 375–411

Elias, P. M. (1981) Epidermal lipids, membranes and keratinisation. Int. J. Dermatol. 20: 1–19

Fiserova-Bergerova, V., Pierce, J. T., Drot, P. O. (1990) Dermal absorption potential of industrial chemicals across the skin: criteria for skin notation. Am. J. Ind. Med. 17: 617–635

Grayson, S., Elias, P. M. (1982) Isolation and lipid biochemical characterisation of the stratum corneum call membrane complexes: implications for the cutaneous permeability barrier. J. Invest. Dermatol. 78: 128–135

Guy, R. H., Potts, R. O. (1993) Penetration of industrial chemical across the skin: a predictive model. Am. J. Ind. Med. 23: 711–719

Houk, J., Guy, R. H. (1988) Membrane models for skin penetration studies. Chem. Rev. 88: 455–471

Kai, T., Isami, T., Kotabata, K., Kurosaki, Y., Nakayama, T., Kimura, T. (1992) Keratinised epithelial transport of β-blocking agents. I. Relationship between physicochemical properties of drugs and the flux across rat skin and hamster cheek pouch. Chem. Pharm. Bull. 40: 2498–2504

Kamlet, M. J., Abboud, J.-L. M., Abraham, M. H., Taft, R. W. (1983) Linear solvation energy relationships. 23. A comprehensive collection of solvatochromic parameters, π^*, α and β and some methods for simplifying the generalised solvatochromic equation. J. Org. Chem. 48: 2877–2887

Leahy, D. E., Morris, J. J., Taylor, P. J., Wait, A. R. (1992) Model solvent systems for QSAR, Part 3. An LSER analysis of the critical quartet. New light on hydrogen bonding strength and directionality. J. Chem. Soc., Perkin Trans. 2: 705–722

Marks, R. M., Barton, S. P., Edwards, C. (1988) The physical nature of skin. MTP Press Ltd, Lancaster

Potts, R. O., Guy, R. H. (1992) Predicting skin permeability. Pharm. Res. 9: 663–669

Raykar, P. V., Fung, M. C., Anderson, B. D. (1988) The role of protein and lipid domains in the uptake of solutes by human stratum corneum. Pharm. Res. 5: 140–150

Riddick, J. A., Bunger, W. B. (1970) Organic Solvents. Wiley Interscience, New York

Roberts, M. S. (1976) Percutaneous Absorption of Phenolic Compounds. PhD Thesis, University of Sydney

Roberts, M. S., Anderson, R. A., Swarbrick, J. (1977) Permeability of human epidermis to phenolic compounds. J. Pharm. Pharmacol. 29: 677–683

Scheuplein, R. J. (1965) Mechanisms of percutaneous adsorption. I. Routes of penetration and the influence of solubility. J. Invest. Dermatol. 45: 334–346

Scheuplein, R. J. (1978) The skin as a barrier. In: Jarrett, A. J. (ed.) The Physiology and Pathophysiology of the Skin. Academic Press, London, pp 1669–1751

Scheuplein, R. J., Blank, I. H. (1971) Permeability of the skin. Physiol. Rev. 51: 702–747

Scheuplein, R. J., Blank, I. H., Brauner, M. D., MacFarlane, D. J. (1969) Percutaneous absorption of steroids. J. Invest. Dermatol. 52: 63–70

Seiler, P. (1974) Interconversion of lipophilicities from hydrocarbon/water systems into octanol/water systems. Eur. J. Med. Chem-. Chim. Therap. 9: 473–479

Singh, S., Singh, J. (1993) Transdermal drug delivery by positive diffusion and iontophoresis: a review. Med. Res. Rev. 13: 519–521

Takahashi, K., Tamagawa, S., Katagi, T., Rytting, J. H., Nishihata, T., Mizuno, N. (1993) Percutaneous permeation of basic compounds through shed snake skin as a model membrane. J. Pharm. Pharmacol. 45: 882–886

Tayar, N. E., Tsai, R. S., Testa, B., Carrupt, P. A., Hansch, C., Leo, A. (1991) Percutaneous penetration of drugs: a quantitative structure permeability relationship study. J. Pharm. Sci. 80: 744–749

van de Waterbeemd, H., Boekel, C. C. A. A., De Sevaux, R. L. F. M., Jansen, A. C. A., Gerritsma, K. W. (1981) Transport in QSAR IV. The interfacial drug transfer model. Relationships between partition coefficients and rate constants in drug partitioning. Pharm. Weekbl. [Sci.] 3: 224–236