Algorithms for Skin Permeability Using Hydrogen Bond Descriptors: the Problem of Steroids*

MICHAEL H. ABRAHAM, FILOMENA MARTINS† AND ROBERT C. MITCHELL‡

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK, † Grupo de Estrutura e Reactividade Química, Department of Chemistry, University of Lisbon, Cc. Bento da Rocha Cabral 14, 1250 Lisboa, Portugal and ‡SB Pharmaceuticals, New Frontiers Science Park (North), 3rd Avenue, Harlow, Essex, UK

Abstract

Several algorithms that use hydrogen bond descriptors have been published for the permeation of compounds from aqueous solution through human stratum corneum. In the present work, all the skin permeability coefficients, Kp in cm s^{-1}, used in these algorithms for non-steroids have been correlated through the Abraham equation to give a new algorithm:

$$\log Kp = -5.241 + 0.437R_2 - 0.410\pi_2^H - 1.631\sum\alpha_2^H - 3.286\sum\beta_2^H + 2.012V_x \tag{1}$$

$$(n = 47, r^2 = 0.9567, \text{s.d.} = 0.197, F = 181)$$

where n is the number of solutes, r is the correlation coefficient, s.d. is the standard deviation, and F is the F-statistic. The solute descriptors are: R_2 an excess molar refraction, π_2^H the dipolarity/polarizability, $\sum\alpha_2^H$ and $\sum\beta_2^H$ the overall or effective hydrogen-bond acidity and basicity, and V_x the McGowan characteristic volume. Equation 1 is a reasonably good predictor of log Kp values for steroids as given by Johnson et al, but not for those given by Scheuplein.

There have been a rather large number of algorithms put forward for the estimation of permeability coefficients, Kp, for permeation of compounds from aqueous solution through human stratum corneum. Nearly all of these attempt to relate log Kp values to various properties of solutes, for example to functions of the water-octanol partition coefficient (P_{oct}), and molecular weight (MW). Five such functions (Brown & Rossi 1989; Fiserova-Bergerova et al 1990; McCone & Howd 1992; Guy & Potts 1993; Wilschut et al 1995; Robinson, personal communication) have recently been compared (Wilschut et al 1995). A large data base of 99 solutes was used, and it was concluded that two particular algorithms (McKone & Howd 1992; Robinson, personal communication) were the best predictors of log Kp values. Although algorithms based on functions of log P_{oct} and MW may be very useful for the estimation of log Kp values, they are purely empirical in nature and give little information as to the actual structural features of solutes that influence water-skin permeability. The same is true of algorithms that use group contributions (Pugh & Hadgraft 1994) or functions of log P_{oct}, MW and melting point (Barratt 1995).

One of the first attempts (Abraham et al 1995) to relate log Kp values to solute structure, using hydrogen bond descriptors, was through the linear free energy relationship:

$$\log SP = c + rR_2 + s\pi_2^H + a\sum\alpha_2^H + b\sum\beta_2^H + vV_x \tag{2}$$

Here, log SP is the dependent variable (i.e. log Kp in the present work), and the independent variables are solute descriptors as follows (Abraham 1993): R_2 is an excess molar

refraction, π_2^H is the dipolarity/polarizability, $\sum\alpha_2^H$ and $\sum\beta_2^H$ are the overall or effective hydrogen-bond acidity and basicity, and V_x is the McGowan characteristic volume (Abraham & McGowan 1987). Equation 2 was applied to a set of log Kp values, with Kp in units of cm s^{-1}, for 19 phenols, leading to:

$$\log Kp = -5.00 - 0.34\pi_2^H - 1.69\sum\alpha_2^H$$
$$- 2.69\sum\beta_2^H + 0.96V_x \tag{3}$$
$$(n = 19, r^2 = 0.9401, \text{s.d.} = -0.160, F = 55)$$

In this equation, and elsewhere, n is the number of data points, r is the correlation coefficient, s.d. is the standard deviation in the dependent variable, and F is the Fisher F-statistic. The R_2 descriptor was statistically not significant and so was discarded. Note that unless stated otherwise, all Kp values in this work are in units of cm s^{-1}. When data on another 25 solutes comprising aliphatic alcohols, diethylether, butanone, 2-ethoxyethanol, benzyl alcohol, 2-phenylethanol, and steroids were included, application of equation 2 gave the regression:

$$\log Kp = -5.05 - 0.59\pi_2^H$$
$$- 0.63\sum\alpha_2^H - 3.48\sum\beta_2^H + 1.79V_x \tag{4}$$
$$(n = 46, r^2 = 0.9582, \text{s.d.} = 0.249, F = 235)$$

Although the absolute values of the coefficients are not the same, equation 3 and equation 4 do show the structural features in the solute that influence permeability: if the solute is dipolar, or is a hydrogen-bond acid, then log Kp is slightly reduced; if the solute is a hydrogen-bond base, the value of log Kp is greatly reduced. The effect of increase in solute volume is to increase log Kp considerably. Thus unlike the various algorithms in log P_{oct} or MW, equations 3 and 4 lead to structural information on solute effects.

A similar data set to that used for equation 3 has been analysed (Lien & Gao 1995) to yield the algorithm:

$$\log Kp = -2 \cdot 17 - 0 \cdot 07 (\log P_{oct})^2 + 0 \cdot 835 \log P_{oct}$$
$$- 0 \cdot 265 H_b - 1 \cdot 844 \log MW \qquad (5)$$
$$(n = 22, r^2 = 0 \cdot 9564, s.d. = 0 \cdot 295, F = 94)$$

The parameter H_b is a general hydrogen-bond descriptor. In agreement with equation 3, solutes capable of hydrogen-bonding reduce the value of log Kp. Note that in equation 5, the original intercept has been adjusted to conform to Kp in units of $cm \, s^{-1}$.

A number of equations for skin permeation, including an earlier and now outdated version of equation 2 (Kamlet et al 1986), for 24 simple monofunctional compounds have been compared (Roberts et al 1995). The best equations were:

$$\log Kp(cm \, h^{-1}) = -1 \cdot 35 - 1 \cdot 37\alpha - 4 \cdot 53\beta + 2 \cdot 05 V_I$$
$$(n = 24, r^2 = 0 \cdot 942, s.d. = - - -, F = 108) \qquad (6)$$

$$\log Kp(cm \, h^{-1}) = \log[0 \cdot 0434(10^{0 \cdot 187 \log P \, oct})$$
$$+ 0 \cdot 0434(10^{0 \cdot 437 \log P \, hex})] \qquad (7)$$
$$(n = 24, r^2 = 0 \cdot 950, s.d. = - - -, F = 90)$$

Kp is in units of $cm \, h^{-1}$ and log P_{hex} is the water-hexane partition coefficient. The π^*, α and β descriptors used before (Kamlet et al 1986) have the same meaning as π_2^H, $\sum \alpha_2^H$ and $\sum \beta_2^H$ in equation 2, although they are not equivalent, and V_I is the computer calculated intrinsic volume. Values of r^2, s.d. and F were not given (Roberts et al 1995); however we have converted their adjusted r_{adj}^2 values to the usual r^2 values, and have then calculated the corresponding F-statistic; for equation 7 the F-value was calculated with four variables. In equations 6 and 7 are given our calculated r^2 and F values.

A more general analysis has been carried out (Potts & Guy 1995) using data on 37 solutes including alcohols, acids, phenols, aromatic hydrocarbons, butanone and diethylether to obtain the algorithm:

$$\log Kp = -4 \cdot 85 + 0 \cdot 026 \, MV - 1 \cdot 72 H_d - 3 \cdot 93 H_a$$
$$(n = 37, r^2 = 0 \cdot 94, s.d. = - - -, F = 165) \qquad (8)$$

MV is the molar volume ($cm^3 \, mol^{-1}$), H_d is the hydrogen-bond acidity, and H_a is the hydrogen-bond basicity. On inspection, it turns out that H_d and H_a are exactly the $\sum \alpha_2^H$ and $\sum \beta_2^H$ descriptors (Abraham 1993), so that equation 8 can be written in the nomenclature generally accepted as:

$$\log Kp = -4 \cdot 85 + 0 \cdot 026 \, MV - 1 \cdot 72 \sum \alpha_2^H - 3 \cdot 93 \sum \beta_2^H$$
$$(9)$$

Equation 9 is thus a variant of the Abraham equation with V_x replaced by MV as the volume descriptor.

It is notable that in equations 8 and 9 no steroids were used in the solute data set. There is indeed a possible difficulty over these important compounds. Most data analyses (Wilschut et al 1995; El Tayar et al 1991; Abraham et al 1995) have used the Scheuplein set of log Kp values (Scheuplein et al 1969). However, recent work (Johnson et al 1995) has cast doubt on the Scheuplein values; these seem to be lower by factors of 5 to 80 than those reported (Johnson et al 1995). The purpose of the present work is to apply equation 2 to all the solutes used in

previous algorithms that included hydrogen-bond descriptors (Abraham et al 1995; Lien & Gao 1995; Potts & Guy 1995; Roberts et al 1995) in order to obtain a more general equation, and then to examine the two sets of log Kp values for steroids, viz. the Scheuplein set (Scheuplein et al 1969) and the recent set (Johnson et al 1995) to which we shall refer as the Johnson set.

Results and Discussion

The solutes and their descriptors in equation 2 are given in Table 1. Most of the values have been taken from previous compilations (Abraham 1993; Abraham et al 1995); where there are small differences the present updated values are to be preferred. We have omitted water from the list of solutes because on partition from bulk water to skin, it is not acting as a solute at all. The log Kp values are those compiled before (Abraham et al 1995), with additional data (Flynn 1990; Potts & Guy 1995). For the 47 non-steroid compounds in Table 1 we obtain the following regression:

$$\log Kp = -5 \cdot 241(0 \cdot 162) + 0 \cdot 437 R_2(0 \cdot 148)$$
$$- 0 \cdot 410 \pi_2^H(0 \cdot 183) - 1 \cdot 631 \sum \alpha_2^H(0 \cdot 148)$$
$$- 3 \cdot 286 \sum \beta_2^H(0 \cdot 235) + 2 \cdot 012 V_x(0 \cdot 113) \qquad (10)$$
$$(n = 47, r^2 = 0 \cdot 9567, s.d. = 0 \cdot 197, F = 181)$$

The s.d. values for the individual coefficients are given in parentheses. The t-test for the coefficient of π_2^H indicates a significance at the 97·0% level; all the other coefficients in equation 10, including that for R_2, are significant to 99·5% or better. This analysis suggests that equation 10 is statistically the best of the various algorithms that use hydrogen-bond descriptors (Abraham et al 1995; Lien & Gao 1995; Potts & Guy 1995; Roberts et al 1995) to describe log Kp values for solute sets that do not include steroids. The coefficients in equation 10 are close to those in equation 3, based on only 19 solutes, except for the b-coefficient. Interpretation of equation 10 in terms of the solute factors that influence skin permeation follows that of equation 3 and equation 4. The log Kp values used in the regression are in Table 2, together with those calculated on equation 10. A plot of log Kp observed vs log Kp calculated is shown in Fig. 1, and shows that points are randomly scattered about the line of identity.

As a first step to incorporating the steroids in any analysis, we can predict log Kp values using equation 10, and can compare them with the Scheuplein and Johnson values. Details are given in Table 3. The predicted values are in much better agreement with the Johnson set than with the Scheuplein set. If the discordant values for hydrocortisone are excluded, the average of log Kp(pred) − log Kp(obs) is 0·54 log units for five steroids, so that equation 10 predicts the log Kp values for the Johnson set reasonably well, considering that the descriptors for the steroids are way outside the range of values used to set up equation 10 (see Table 1). For the same five steroids this average difference is 1·61 log units for the Scheuplein set, and over all fourteen steroids is 1·39 log units for the Scheuplein set. Although these results do not show that the Johnson set of log Kp values is more correct than the Scheuplein set, they do show that the Johnson set is much more compatible with the log Kp values in Table 2 than is the Scheuplein set. We can

Table 1. Solute descriptors used in the analysis.

Solute	R_2	π_2^H	$\sum \alpha_2^H$	$\sum \beta_2^H$	V_x
Diethylether	0·041	0·25	0·00	0·45	0·7309
Butanone	0·166	0·70	0·00	0·51	0·6879
Formic acid	0·300	0·79	0·72	0·34	0·3239
Acetic acid	0·265	0·65	0·61	0·44	0·4648
Propanoic acid	0·233	0·65	0·60	0·45	0·6057
Butanoic acid	0·210	0·62	0·60	0·45	0·7466
Pentanoic acid	0·205	0·60	0·60	0·45	0·8875
Hexanoic acid	0·174	0·60	0·60	0·45	1·0284
Heptanoic acid	0·149	0·60	0·60	0·45	1·1693
Octanoic acid	0·150	0·60	0·60	0·45	1·3102
Methanol	0·278	0·44	0·43	0·47	0·3082
Ethanol	0·246	0·42	0·37	0·48	0·4491
Propan-1-ol	0·236	0·42	0·37	0·48	0·5900
Butan-1-ol	0·224	0·42	0·37	0·48	0·7309
Pentan-1-ol	0·219	0·42	0·37	0·48	0·8718
Hexan-1-ol	0·210	0·42	0·37	0·48	1·0127
Heptan-1-ol	0·211	0·42	0·37	0·48	1·1536
Octan-1-ol	0·199	0·42	0·37	0·48	1·2950
Nonan-1-ol	0·193	0·42	0·37	0·48	1·4354
Decan-1-ol	0·191	0·42	0·37	0·48	1·5763
2-Ethoxyethanol	0·237	0·50	0·30	0·83	0·7896
Benzene	0·610	0·52	0·00	0·14	0·7164
Toluene	0·601	0·52	0·00	0·14	0·8573
Ethylbenzene	0·613	0·51	0·00	0·15	0·9982
Styrene	0·849	0·65	0·00	0·16	0·9552
Phenol	0·805	0·89	0·60	0·30	0·7751
2-Methylphenol	0·840	0·86	0·52	0·30	0·9160
3-Methylphenol	0·822	0·88	0·57	0·34	0·9160
4-Methylphenol	0·820	0·87	0·57	0·31	0·9160
4-Ethylphenol	0·800	0·90	0·55	0·36	1·0569
3,4-Dimethylphenol	0·830	0·86	0·56	0·39	1·0569
2-Isopropyl-5-methylphenol	0·822	0·79	0·52	0·44	1·3387
2-Chlorophenol	0·853	0·88	0·32	0·31	0·8975
4-Chlorophenol	0·915	1·08	0·67	0·20	0·8975
4-Chloro-3-methylphenol	0·920	1·02	0·65	0·22	1·0384
4-Chloro-3,5-dimethylphenol	0·925	0·96	0·64	0·21	1·1793
2,4-Dichlorophenol	0·960	0·84	0·53	0·19	1·0199
2,4,6-Trichlorophenol	1·010	0·80	0·68	0·15	1·1423
4-Bromophenol	1·080	1·17	0·67	0·20	0·9501
2-Nitrophenol	1·015	1·05	0·05	0·37	0·9493
3-Nitrophenol	1·050	1·57	0·79	0·23	0·9493
4-Nitrophenol	1·070	1·72	0·82	0·26	0·9493
Methyl 4-hydroxybenzoate	0·900	1·37	0·69	0·45	1·1313
2-Naphthol	1·520	1·08	0·61	0·40	1·1441
Resorcinol	0·980	1·00	1·10	0·58	0·8338
Benzyl alcohol	0·803	0·87	0·39	0·56	0·9160
2-Phenylethanol	0·811	0·91	0·30	0·64	1·0569
Progesterone	1·450	3·29	0·00	1·14	2·6215
Pregnenolone	1·360	3·29	0·32	1·18	2·6645
Hydroxyprogesterone-17α	1·640	3·35	0·25	1·31	2·6802
Hydroxypregnenolone-17α	1·550	3·35	0·57	1·35	2·7232
Deoxycorticosterone	1·740	3·50	0·14	1·31	2·6802
Testosterone	1·540	2·59	0·32	1·19	2·3827
Cortexolone	1·910	3·45	0·36	1·60	2·7389
Corticosterone	1·860	3·43	0·40	1·63	2·7389
Cortisone	1·960	3·50	0·36	1·87	2·7546
Hydrocortisone	2·030	3·49	0·71	1·90	2·7976
Aldosterone	2·010	3·47	0·40	1·90	2·6890
Estrone	1·730	3·10	0·56	0·91	2·1558
Estradiol	1·800	3·30	0·88	0·95	2·1988
Estratriol	2·000	3·36	1·40	1·22	2·2575
Dexamethasone	2·040	3·51	0·71	1·92	2·9132
Lignocaine	1·010	1·49	0·11	1·27	2·0589

illustrate this in Fig. 2, where the log Kp values for the Johnson set are not far from the line of identity for equation 10, but those for the Scheuplein set consistently lie well away. Possible reasons for the discrepancies between the two sets of log Kp values have been discussed (Johnson et al 1995). Our analysis supports their suggestion that in correlations to predict human skin permeabilities, the Johnson set of log Kp values should be used. The permeation of corticosterone through

human epidermal membrane at 27°C and 39°C has recently been studied (Peck et al 1995); from their results, a value of about −6·82 may be deduced for log Kp at 27°C. This is in good agreement with our calculated value from equation 10, and with the observed value in the Johnson set.

Log Kp values from saline to human skin for the five compounds listed in Table 4 have also been determined (Johnson et al 1996). Three of these are steroids common to the

Table 2. Observed and calculated values of log Kp for permeation of solutes through human skin.

Solute	LogKp (cm s^1)		
	Observed[a]	Calculated[b]	Calculated[c]
Diethylether	−5·35	−5·33	−5·37
Butanone	−5·90	−5·75	−5·82
Formic acid	−7·08[d]	−7·07	−6·99
Acetic acid	−7·01[d]	−6·90	−6·85
Propanoic acid	−7·01[d]	−6·64	−6·61
Butanoic acid	−6·46[d,e]	−6·36	−6·33
Pentanoic acid	−6·14[d,e]	−6·07	−6·05
Hexanoic acid	−5·42[d,e]	−5·80	−5·79
Heptanoic acid	−5·27[d,e]	−5·53	−5·53
Octanoic acid	−5·18[d,e]	−5·24	−5·25
Methanol	−6·56	−6·93	−6·88
Ethanol	−6·56	−6·58	−6·56
Propan-1-ol	−6·41	−6·30	−6·29
Butan-1-ol	−6·16	−6·03	−6·02
Pentan-1-ol	−5·78	−5·74	−5·75
Hexan-1-ol	−5·44	5·46	−5·48
Heptan-1-ol	−5·05	−5·18	−5·20
Octan-1-ol	−4·84[d]	−4·90	−4·94
Nonan-1-ol	−4·78[d,e]	−4·62	−4·67
Decan-1-ol	−4·66[d]	−4·34	−4·39
2-Ethoxyethanol	−7·16	−6·97	−7·04
Benzene	−4·51[d]	−4·21	−4·21
Toluene	−3·56[d]	−3·93	−3·94
Ethylbenzene	−3·48[d]	−3·67	−3·69
Styrene	−3·75[d]	−3·74	−3·77
Phenol	−5·64	−5·66	−5·63
2-Methylphenol	−5·36	−5·22	−5·21
3-Methylphenol	−5·37	−5·45	−5·44
4-Methylphenol	−5·31	−5·34	−5·33
3,4-Dimethylphenol	−5·00	−5·30	−5·31
4-Ethylphenol	−5·01	−5·21	−5·22
2-Isopropyl-5-methylphenol	−4·83	−4·81	−4·84
2-Chlorophenol	−5·04	−4·96	−4·99
4-Chlorophenol	−5·00	−5·23	−5·20
4-Chloro-3-methylphenol	−4·82	−4·95	−4·93
4-Chloro-3,5-dimethylphenol	−4·79	−4·59	−4·58
2,4-Dichlorophenol	−4·78	−4·60	−4·58
2,4,6-Trichlorophenol	−4·78	−4·43	−4·39
4-Bromophenol	−5·00	−5·09	−5·06
2-Nitrophenol	−4·56[d]	−4·62	−4·70
3-Nitrophenol	−5·81	−5·56	−5·56
4-Nitrophenol	−5·81	−5·76	−5·77
Methyl 4-hydroxybenzoate	−5·60	−5·74	−5·78
2-Naphthol	−5·11	−5·03	−5·05
Resorcinol	−7·18	−7·25	−7·19
Benzyl alcohol	−5·78	−5·88	−5·93
2-Phenylethanol	−5·68	−5·73	−5·82

[a]Previous data (Abraham et al 1995) unless shown otherwise. [b]Equation 10. [c]Equation 11. [d]Previous data (Potts & Guy 1995). [e]Previous data (Flynn 1990).

Johnson and Scheuplein sets. The log Kp values for testosterone and estradiol are close to the original Johnson values, but that for corticosterone is closer to the Scheuplein value. The two other compounds studied are lignocaine and the steroid dexamethasone. Descriptors for these additional two compounds are in Table 1, and enable predictions of log Kp to be made through equation 10. There is reasonable agreement between log Kp(pred) and log Kp(obs) (Table 4). However, the observed value for lignocaine relates to both neutral and charged species in the aqueous buffer solution (pH 7·4).

We can now add the five steroids (Johnson et al 1996) to the 47 compounds in Table 1; we have not included hydrocortisone because of the very large spread of reported log Kp values, see Table 3. If we also include dexamethasone but not lignocaine, because of the neutral/charged species problem, our final equation becomes:

$$\log Kp = -5 \cdot 132(0 \cdot 098) + 0 \cdot 439 R_2(0 \cdot 133)$$
$$- 0 \cdot 489 \pi_2^H(0 \cdot 118) - 1 \cdot 478 \sum \alpha_2^H(0 \cdot 126)$$
$$- 3 \cdot 442 \sum \beta_2^H(0 \cdot 157) + 1 \cdot 941 V_x(0 \cdot 112) \quad (11)$$
$$(n = 53, r^2 = 0 \cdot 9577, \text{s.d.} = 0 \cdot 213, F = 213)$$

The data set for equation 11 thus comprises the 47 non-steroids in Table 1, five steroids of the Johnson set in Table 3 (progesterone, testosterone, corticosterone with log Kp = −7·08, aldosterone and estradiol) and dexamethasone (Table 4). The statistical goodness-of-fit has hardly altered from that of equation 10, and the coefficients are but marginally changed. All the coefficients in equation 11 are significant to 99·6% or better. A plot of log Kp(obs) vs log Kp(calc) on equation 11 is shown in Fig. 3; the five steroids of the Johnson set and dexamethasone are randomly scattered about the line of identity.
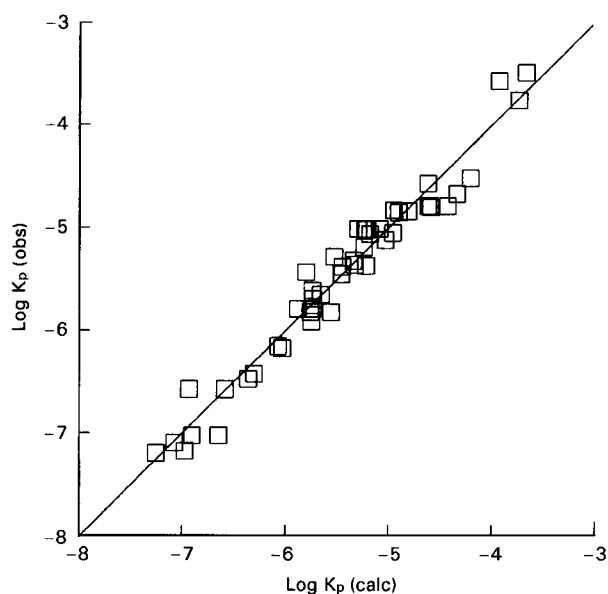
FIG. 1.   Plot of log Kp(obs) vs log Kp(calc) on equation 10 for 47 non steroid compounds.

Equation 11 is our preferred algorithm for skin permeability, because it is much more general than equation 10. Not only does it include steroids, but the spread of all the descriptors has been increased considerably.

This means that interpolative predictions of log Kp can be made for a huge number of additional compounds, with descriptor values that fall within the extra range. The calculated log Kp values on equation 11 are in Table 2 for the non steroid compounds, and in Table 3 for the steroids used in the regression. Recent work (Johnson et al 1995) has now resolved the difficulty over the different coefficients in equation 3 and equation 4; this can be seen to be due entirely to the use of the Scheuplein data set in equation 4. When the Johnson set is used, there is almost no change in the regression coefficients.
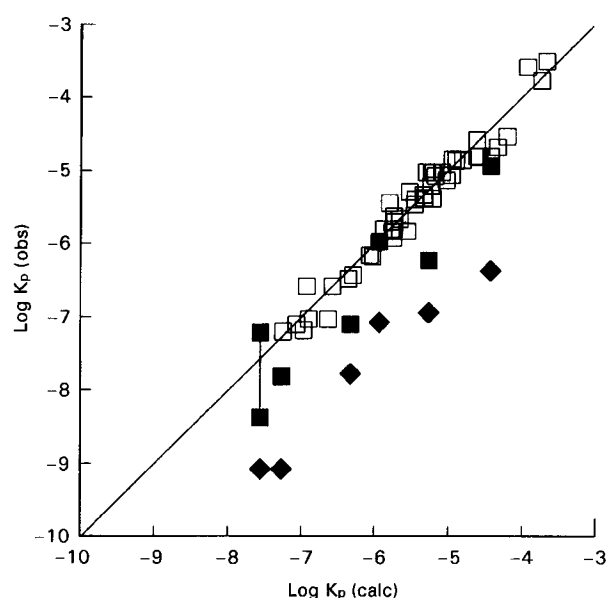

FIG. 2.   Plot of log Kp(obs) vs log Kp(calc) on equation 10 ($\square$) showing the observed and predicted values for the six steroids common to the Johnson ($\blacksquare$) and Scheuplein ($\blacklozenge$) set. The range of observed values for hydrocortisone is indicated.

This has considerable implications as regards the mechanism of permeation. The final algorithm, equation 11, includes a very wide range of solute type, from hydrophilic solutes such as methanol (log $P_{oct} = -0.74$) and formic acid (log $P_{oct} = -0.54$) to lipophilic solutes such as progesterone (log $P_{oct} = 3.70$) and decan-1-ol (log $P_{oct} = 4.18$). Since these varied solutes can all be accommodated by the same algorithm, we suggest a permeation mechanism in which a one-route process is the dominant feature, as already advocated (Guy & Potts 1993; Potts & Guy 1995). However, for very hydrophilic compounds with log P_{oct} values lower than those of methanol and formic acid, it is possible that an aqueous-pore pathway exists (Flynn 1990). Hence equation 11 should not be used to

Table 3.   Values of Log Kp for the Johnson and Scheuplein steroid sets.

Steroid	log Kp (cm s^{-1})			
	Predicted[a]	Predicted[b]	Observed[c]	Observed[d]
Progesterone	−4·43	−4·94[e]	−4·92	−6·38
Pregnelone	−5·03	−5·51	–	−6·38
Hydroxyprogesterone-17α	−5·22	−5·73	–	−6·78
Hydroxypregnenolone-17α	−5·82	−6·29	–	−6·78
Deoxycorticosterone	−5·05	−5·59	–	−6·90
Testosterone	−5·27	−5·67[e]	−6·21	−6·95
Cortexolone	−6·15	−6·70	–	−7·68
Corticosterone	−6·33	−6·88[e]	−7·08 −6·82[f]	−7·78
Cortisone	−7·01	−7·61	–	−8·56
Hydrocortisone	−7·56	−8·11	−8·35 −7·48 −7·19	−9·08
Aldosterone	−7·27	−7·86[e]	−7·79	−9·08
Estrone	−5·32	−5·66	–	−6·00
Estradiol	−5·94	−6·26[e]	−5·95	−7·08
Estratriol	−7·50	−7·78	–	−7·95

[a]Predicted values on equation 10 with descriptors in Table 1. [b]Predicted values on equation 10 with descriptors in Table 1. [c]The Johnson set (Johnson et al 1995). [d]The Scheuplein set (Scheuplein et al 1969). [e]These are calculated, not predicted, because the values were used to generate equation 11. [f]An observed value for corticosterone (Peck et al 1995).

Table 4. Values of log Kp for steroids (Johnson et al 1995).

Compound	log Kp (cm s⁻¹) Predicted[a]	Calculated[b]	Observed
Testosterone	−5·27	−5·67	−5·83
Corticosterone	−6·33	−6·88	−7·56
Estradiol	−5·94	−6·26	−5·94
Dexamethasone	−7·39	−7·96	−7·75
Lignocaine	−5·62	−5·95[c]	−5·96

[a]Predicted values on equation 10 with descriptors in Table 1.
[b]Calculated values on equation 11 with descriptors in Table 1.
[c]Predicted value on equation 11.
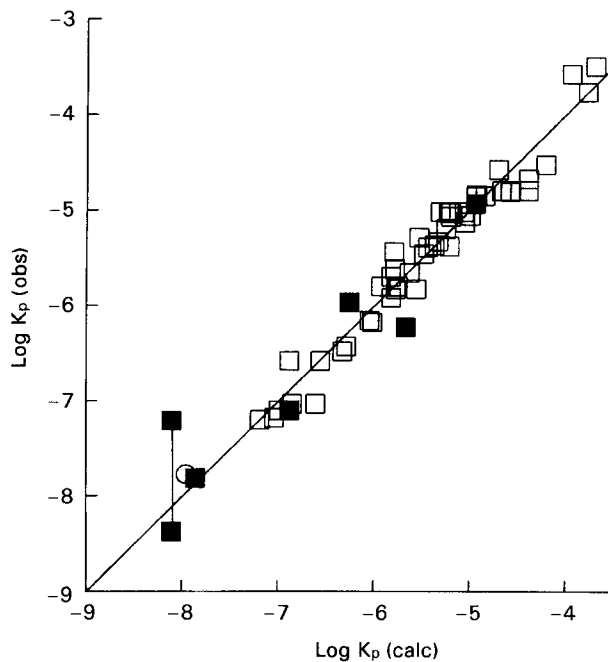
FIG. 3. Plot of log Kp(obs) vs log Kp(calc) on equation 11 (□), showing the points for the five included steroids of the Johnson set (■) and the included point for dexamethasone (○). The range of observed values for hydrocortisone, not included in the regression, is also given.

predict log Kp values for compounds with log P_{oct} less than about −1, at least for the time being.

We now turn to the quite different data set on steroid ester permeability (Anderson et al 1988), for the eleven esters of hydrocortisone shown in Table 5. We have calculated descriptors for these steroids as explained before (Abraham & Chadha 1996), and list them in Table 6. In brief, descriptors were assigned by the summation of values for fragments (or substructures) that are as large as possible in order to include intramolecular effects within the fragment. The obtained set of descriptors was then verified or modified through the calculation of partition coefficients using known equations (Abraham & Chadha 1996). The calculated log P values were compared with water-octanol, P_{oct}, and water-heptane, P_{alk}, values (Anderson et al 1988), and in a few cases with water-ether, P_{ether}, values (Flynn 1971; Ackermann et al 1987). Details of observed and calculated log P values are in Table 7; it is clear that is possible to assign descriptors that can reproduce the observed log P values reasonably well. Once the steroid

Table 5. The hydrocortisone esters (Anderson et al 1988).

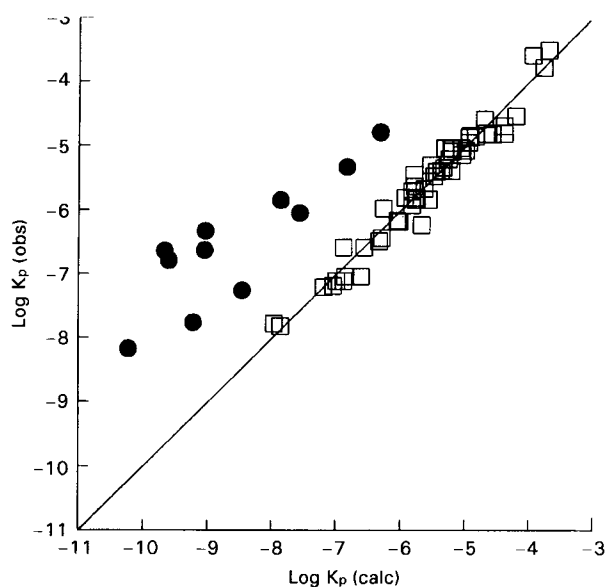| Compound	R
1a	−CH₂CH₂CONH₂
1b	−CH₂CH₂CONMe₂
1c	−CH₂CH₂CO₂Me
1d	−CH₂CH₂CO₂H
1e	−(CH₂)₅CO₂H
1f	−(CH₂)₅CONH₂
1g	−(CH₂)₅OH
1h	−CH₂CH₃
1i	−(CH₂)₅CO₂Me
1j	−(CH₂)₄CH₃
1k	−(CH₂)₆CH₃

FIG. 4. Plot of log Kp(obs) vs log Kp(calc) for the total 53 compounds on equation 11 (□), showing the observed and predicted values for the steroids in the Anderson data set (●).

descriptors are to hand, the log Kp values can be calculated through equation 10 (or equation 11) and compared with the observed values (Anderson et al 1988). There is no agreement at all between observed and calculated values; on average the former are 2·0 log units larger. This is not the result of random variation, as can be seen from Fig. 4, but is a systematic difference. As pointed out before (Johnson et al 1995), differences in temperature of experimental measurements are not very critical, and this can be eliminated as a major source of variation. Another possibility might be that the Anderson steroid set is more lipophilic than the compounds used to set up equation 11, and undergoes permeation by a different route. However, log P_{oct} varies from 1·43 to 5·49 for the Anderson

Table 6. Calculated descriptors and observed log Kp values for the Anderson steroid ester data set.

Solute	R_2	π_2^H	$\sum \alpha_2^H$	$\sum \beta_2^H$	V_x	log Kp (cm s^{-1})
Ia	2·31	3·35	1·00	2·84	3·4924	−8·14
Ib	2·21	3·75	0·48	2·86	3·7742	−7·73
Ic	1·99	3·10	0·46	2·61	3·5922	−7·23
Id	2·10	3·15	1·06	2·61	3·4513	−6·76
Ie	2·02	3·59	1·06	2·61	3·8740	−6·30
If	2·21	3·90	0·96	2·84	3·9151	−6·61
Ig	2·03	3·49	0·83	2·64	3·7174	−6·60
Ih	1·87	2·90	0·46	2·16	3·2360	−6·02
Ii	1·93	3·48	0·46	2·61	4·0149	−5·82
Ij	1·81	3·02	0·46	2·16	3·6587	−5·30
Ik	1·77	3·05	0·46	2·16	3·9404	−4·76

Table 7. Observed and calculated partition coefficients for the Anderson steroid data set.

Solute	Observed[a]			Calculated[b]		
	logP$_{oct}$	logP$_{alk}$	logP$_{ether}$	logP$_{oct}$	logP$_{alk}$	logP$_{ether}$
Ia	1·43			1·38	−6·00	−1·03
Ib	2·03	−3·92		1·89	−3·80	−0·36
Ic	2·58	−2·33		2·62	−2·34	0·69
Id	2·11			2·12	−5·09	0·02
Ie	3·26	−4·09		3·22	−4·06	1·32
If	2·30			2·36	−5·03	0·14
Ig	2·79	−4·05		2·62	−3·89	0·63
Ih	3·00	−1·49	1·98	2·97	−1·47	1·52
Ii	3·70	−1·15		3·80	−1·23	2·07
Ij	4·42	0·12	3·58	4·42	0·10	3·20
Ik	5·49[c]	1·30	4·67	5·44	1·23	4·37

[a]Log P$_{oct}$ and log P$_{alk}$ (Anderson et al 1988); log P$_{ether}$ (Flynn 1971; Ackermann et al 1987). [b]Using the descriptors in Table 6, and equations for partition coefficients (Abraham & Chadha 1996). [c]This is an extrapolated value (Anderson et al 1988).
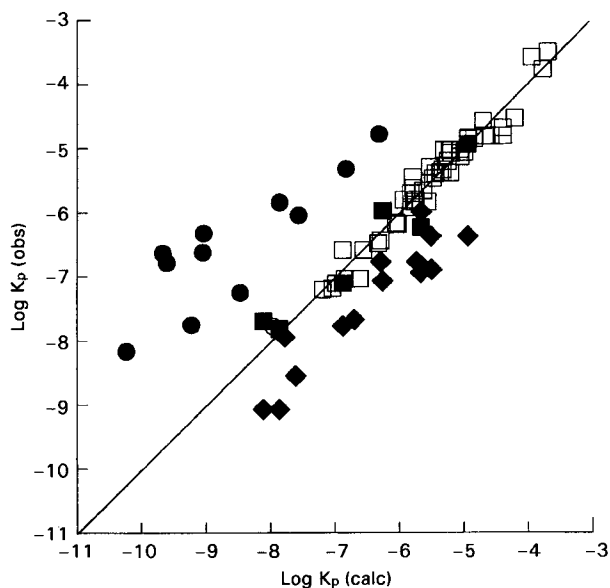

FIG. 5. Plot of log Kp(obs) vs log Kp(calc) on equation 11, for the non-steroid compounds (□), the steroids in the Johnson set including an average observed value for hydrocortisone (■), the steroids in the Anderson set (●), the steroids in the Scheuplein set (◆), and the point for dexamethasone (○).

set, and hence overlaps considerably with log P$_{oct}$ values for the compounds in equation 11 (−0·74 to 4·18), so this possibility can hardly be correct. Another possibility is that we have assigned completely incorrect values to our descriptors. However, since they reproduce log P values that cover a very wide range, see Table 7, it is difficult to see how the same descriptors will yield log Kp values that are in error by two log units. Just as there is little explanation of why the Johnson data set is not compatible with the Scheuplein data set (Johnson et al 1995), we have no explanation as to why the Anderson data set seems incompatible with either of the other two sets. We can illustrate the dilemma by a plot of log Kp(obs) against log Kp(calc) on equation 11, including the 47 non-steroids, and the steroids in the three separate data sets, as well as dexamethasone, see Fig. 5. For simplicity we show an average observed log Kp value for hydrocortisone in the Johnson set, rather than the range shown in Fig. 3. It seems reasonably clear that Fig. 5 indicates three mutually incompatible steroid data sets: firstly, the Johnson set (Johnson et al 1995) plus dexamethasone, that is consistent with the data for the non-steroids in Table 1; secondly, the set of Scheuplein; and thirdly, the steroid ester set of Anderson.

It seems quite pointless to combine the log Kp values for all the steroids in the various data sets into one equation, and so we suggest that equation 11 be used as the most general

algorithm for the prediction of log Kp values, certainly for non-steroids. Whether or not equation 11, or some other algorithm, can be used for the prediction of log Kp values for steroids in general will depend on further work to resolve the problem of incompatible data sets (Johnson et al 1995). Our study shows also how little can be deduced about the generality and the predictive usefulness of an algorithm if it is based on a data set limited in number and limited in compound type.

Unlike other workers (Potts & Guy 1995), we have not attempted to obtain mechanistic information on skin permeation through a comparison of our algorithm for skin permeation with algorithms for water-solvent partition (Abraham & Chadha 1996). As pointed out before (Abraham et al 1995), the solute factors that influence a rate of transfer from one phase to another, such as skin permeation, need not quantitatively be the same as the factors that influence the equilibrium partition between the two phases. Hence very little can be deduced by comparisons of skin permeation, a rate process in one system, with water-solvent partition, an equilibrium process in another system.

References

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

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., Chadha, H. S., Mitchell, R. C. (1995) The factors that influence skin penetration of solutes. J. Pharm. Pharmacol. 47: 8–16

Abraham, M. H., Chadha, H. S. (1996) Applications of a solvation equation to drug transport properties. In: Pliska, V., Testa, B., van de Waterbeemd, H. (eds) Lipophilicity in Drug Action and Toxicology. VCH, Weinheim, Germany, pp 311–337

Ackermann, C., Flynn, G. L., Smith, W. M. (1987) Ether-water partitioning and permeability through nude mouse skin in vitro. II. Hydrocortisone 21 *n*-alkyl esters, alkanols, and hydrophilic compounds. Int. J. Pharm. 36: 67–71

Anderson, B. D., Higuchi, W. I., Raykar, P. V. (1988). Heterogeneity effects on permeability-partition coefficient relationships in human stratum corneum. Pharm. Res. 5: 566–573

Barratt, M. D. (1995) Quantitative structure-activity relationships for skin permeability. Toxic. In Vitro 9: 27–37

Brown, S. L., Rossi, J. E. (1989) A simple method for estimating dermal absorption of chemicals in water. Chemosphere 19: 1989–2001

El Tayar, N., 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

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

Flynn, G. L. (1971) Structural approach to partitioning: estimation of steroid partition coefficients based upon molecular constitution. J. Pharm. Sci. 60: 345–353

Flynn, G. L. (1990) Physicochemical determinants of skin absorption. In: Gerrity, T. R, Henry, C. J. (eds) Principles of Route-to-Route Extrapolation for Risk Assessment. Elsevier, New York, pp 93–127

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

Johnson, M. E., Blankschtein, D., Langer, R. (1995) Permeation of steroids through human skin. J. Pharm. Sci. 84: 1144–1146

Johnson, M. E., Mitragotri, S., Patel, A., Blankschtein, D., Langer, R. (1996) Synergestic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery. J. Pharm. Sci. 85: 670–679

Kamlet, M. J., Doherty, R. M., Abboud, J.-L. M., Abraham, M. H., Taft, R. W. (1986) Solubility: a new look. CHEMTECH 16: 566–576

Lien, E. J., Gao, H. (1995) QSAR Analysis of skin permeability of various drugs in man as compared to in vivo and in vitro studies in rodents. Pharm. Res. 12: 583–587

McKone, T. E., Howd, R. A. (1992) Estimating dermal uptake of nonionic organic chemicals from water and soil: I. unified fugacity-based models for risk assessments. Risk. Anal. 12: 543–557

Peck, K. D., Ghanen, A.-H., Higuchi, W. I. (1995) The effect of temperature upon the permeation of polar and ionic solutes through human epidermal membrane. J. Pharm. Sci. 84: 975–982

Potts, R. O., Guy, R. H. (1995). A predictive algorithm for skin permeability: the effects of molecular size and hydrogen bond activity. Pharm. Res. 12: 1628–1633

Pugh, W. J., Hadgraft, J. (1994) *Ab initio* prediction of human skin permeability coefficients. Int. J. Pharm. 103: 163–178

Roberts, M. S., Pugh, W. J., Hadgraft, J., Watkinson, A. C. (1995) Epidermal permeability-penetrant structure relationships: I. An analysis of methods of predicting penetration of monofunctional solutes from aqueous solution. Int. J. Pharm. 126: 219–233

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

Wilschut, A., ten Berge, W. F., Robinson, P. J., McKone, T. E. (1995) Estimating skin permeation. The validation of five mathematical models. Chemosphere 30: 1275–1296