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The effect of structural QSAR parameters on skin penetration

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Abstract

The permeability coefficients (log k_p) of solutes through stratum corneum have been previously related to the octanol–water partition coefficients (log P_{oct}) and solvatochromic parameters. In this study, permeation coefficient data are related to the theoretical chemistry-derived structural parameters and also molecular connectivity and molecular shape indices. The results show that these parameters are comparable with the solvatochromic parameters in correlation with log k_p. Log P_{oct} can be corrected by the theoretical parameters to explain permeation coefficients and the equilibrium distribution of compounds between the stratum corneum and water (log K_m). Diffusion estimated from the expression $\log(D/h) = \log k_p - \log K_m$, where D is the diffusion coefficient and h is the path length for diffusion was also analyzed successfully by the structural parameters. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Percutaneous penetration; Epidermal permeability; Stratum corneum; Skin penetration; Theoretical QSAR

1. Introduction

Penetration of various materials is of interest to many industries and scientists. For example in formulation of topical drugs, assessment of toxicity of toxic materials and also environmental pollutants, it seems necessary to have correct information about the skin permeability of such compounds. Unfortunately, it is difficult to determine the absorption of chemicals into and through the skin and it can involve ethical difficulties with experiments on animals and human skin. Two experimental aspects of skin penetration, namely, water–skin partition coefficients (K_m) and solute permeation rates through skin (k_p), have been studied (Scheuplein, 1965; Scheuplein et al., 1969; Anderson et al., 1988) and the data produced by these studies have been analyzed by various workers to find a model capable of explaining the permeation process and to predict penetration without recourse to morally objectionable experiments (Tayar et al., 1991; Abraham et al., 1995; Roberts et al., 1996). In this study, the theoretical QSAR technique (TQSAR) has been employed in order to analyze the skin penetration results. The advantage of this method

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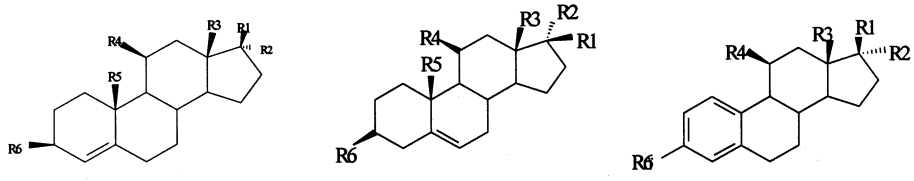
over the previous models is the convenience of obtaining the theoretical parameters. The results of this work have been compared with those of the previous models.

2. Materials and methods

Scheme 1 shows the structures of the various compounds used in this study. The biological data composed of log k_p (permeability coefficient) and log K_m (skin/water partition coefficient) are taken from the literature (Scheuplein, 1965; Scheuplein et al., 1969; Hadgraft and Ridout, 1987; Anderson et al., 1988; Raykar et al., 1988), and log(D/h) (logarithm of diffusion coefficient divided by the membrane thickness) is calculated by the expression: $\log(D/h) = \log k_p - \log K_m$.

In the present QSAR study, the calculated parameters generated by computer software have been used; the resulting equations will be termed TQSAR equations. The parameters included significant atomic charges, dipole moment, molecular weight, solvent accessible surface area (ASA),



A *B* *C*

No.	NAME	R1	R2	R3	R4	R5	R6
1*A*	Progesterone	-$COCH_3$	-H	-CH_3	-H	-CH_3	=O
2*B*	Pregnenolone	-$COCH_3$	-H	-CH_3	-H	-CH_3	-OH
3*A*	Hydroxyprogesterone	-$COCH_3$	-OH	-CH_3	-H	-CH_3	=O
4*B*	Hydroxypregnenolone	-$COCH_3$	-OH	-CH_3	-H	-CH_3	-OH
5*A*	Deoxycorticosterone	-$COCH_2OH$	-H	-CH_3	-H	-CH_3	=O
6*A*	Testosterone	-OH	-H	-CH_3	-H	-CH_3	=O
7*A*	Cortexolone	-$COCH_2OH$	-OH	-CH_3	-H	-CH_3	=O
8*A*	Corticosterone	-$COCH_2OH$	-H	-CH_3	-OH	-CH_3	=O
9*A*	Cortisone	-$COCH_2OH$	-OH	-CH_3	=O	-CH_3	=O
10*A*	Hydrocortisone	-$COCH_2OH$	-OH	-CH_3	-OH	-CH_3	=O
11*A*	Aldosterone	-$COCH_2OH$	-H	-COH	-OH	-CH_3	=O
12*C*	Estrone	=O	-	-CH_3	-H	-	-OH
13*C*	Estradiol	-OH	-H	-CH_3	-H	-	-OH
14*C*	Estriol	-OH	-OH	-CH_3	-H	-	-OH
15*A*		-$COOCOCH_2CH_2CONH_2$	-OH	-CH_3	-OH	-CH_3	=O
16*A*		-$COOCOCH_2CH_2CON(CH_3)_2$	-OH	-CH_3	-OH	-CH_3	=O
17*A*		-$COOCOCH_2CH_2COOCH_3$	-OH	-CH_3	-OH	-CH_3	=O
18*A*		-$COOCOCH_2CH_2COOH$	-OH	-CH_3	-OH	-CH_3	=O
19*A*		-$COOCO(CH_2)_4CH2COOH$	-OH	-CH_3	-OH	-CH_3	=O
20*A*		-$COOCO(CH_2)_4CH_2CONH_2$	-OH	-CH_3	-OH	-CH_3	=O
21*A*		-$COOCO(CH_2)_4CH_2OH$	-OH	-CH_3	-OH	-CH_3	=O
22*A*		-$COOCOCH_2CH_3$	-OH	-CH_3	–OH	-CH_3	=O
23*A*		-$COOCO(CH_2)_4CH_2COOCH_3$	-OH	–CH_3	-OH	-CH_3	=O
24*A*		-$COOCO(CH_2)_4CH_3$	-OH	–CH_3	-OH	-CH_3	=O
25*A*		-$COOCO(CH_2)_6CH_3$	-OH	-CH_3	-OH	-CH_3	=O

Scheme 1. Structures of the compounds investigated

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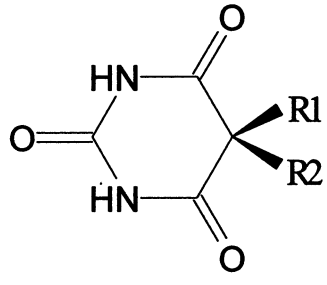
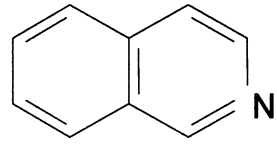
Number	Name
26	Methanol
27	Ethanol
28	1-Propanol
29	1-Butanol
30	1-Pentanol
31	1-Hexanol
32	1-Heptanol
33	1-Octanol
34	Barbital
35	Phenobarbital
36	Butabarbital
37	Amylobarbital
38	Isoquinoline
39	Salicylic acid





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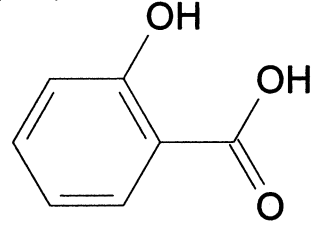
34. R1 = R2 = $-C_2H_5$
35. R1 = $-C_6H_5$, R2 = $-C_2H_5$
36. R1 = $-C_2H_5$, R2 = $-CH(CH_3)C_2H_5$
37. R1 = $-C_2H_5$, R2 = $-CH_2CH_2CH(CH_3)_2$



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Scheme 1. (*Continued*)

and the highest and the lowest electrostatic potentials on ASA, energies of the highest occupied and the lowest unoccupied molecular orbitals. These parameters were calculated by the AM1 semiempirical method and molecular mechanical programs. The molecular connectivity indices were

calculated by MOLCONN-Z software. Also, the solubility parameter and molar volume were calculated by a group contribution method (Fedors, 1974). Statistical analyses (multiple regression and step-wise regression) were performed using MINITAB statistical software to find the correlation between permeability data and structural parameters.

3. Results and discussion

According to the source of the biological data and also the structural similarities, different combinations of these compounds have been statistically analyzed; the results of which are as follows. Tables 1–3 contain the biological and calculated parameters which have been used in the following TQSAR equations.

3.1. Compounds **1–14** and **26–33**

The biological data for these compounds including steroids and alcohols are taken from Scheuplein (1965) and Scheuplein et al. (1969). The step-wise regression analyses resulted in the following equations:

$$\log k_p = 3.99 \log TA + 4.53 q_s^- - 0.762 OT - 11.364 \quad (1)$$

with $n = 22$, $r = 0.967$, $s = 0.316$ and $F = 87.5$.

$$\log k_p = -0.786 OT + 0.252\ {}^2\kappa - 1.617 q_s^+ - 5.767 \quad (2)$$

with $n = 22$, $r = 0.972$, $s = 0.296$ and $F = 101.3$.

In Eqs. (1) and (2), log TA is the logarithm of total solvent accessible surface area calculated using a probe of 1.4 Å radius (Connolly, 1983), q_s^- is the sum of atomic charges on the hydrogen bonding heteroatoms calculated by a classical method (Abraham et al., 1991) which is used as the H-bonding acceptor ability (Dearden and Ghafourian, 1999), OT is the number of hydrogen bonding heteroatoms (in this series of compounds only the oxygen atom was present), ${}^2\kappa$ is the second-order molecular shape index and q_s^+ is the sum of the atomic charges on the hydrogen bonding hydrogen atoms calculated by the AM1 method. These equations are comparable with the equation resulting from the LSER approach of Abraham et al. (1995) in which the solvatochromic parameters have been used:

$$\log k_p = -5.33 - 0.62\pi_2^H - 0.38\Sigma\alpha_2^H - 3.34\Sigma\beta_2^H + 1.85 V_X \quad (3)$$

with $n = 22$, $r = 0.978$, $s = 0.268$ and $F = 93.7$

Considering the reduced numbers of the parameters used in the TQSAR equations, the calculated parameters work well enough in predicting the permeability coefficient, and they have the advantage of being readily accessible. The two methods agree in that the most important factors in controlling the permeability of compounds are hydrogen bonding basicity (OT and q_s^- in TQSAR equations and $\Sigma\beta_2^H$ in the LSER equation) and the size of the compounds, which are presented by log TA (Eq. (1)) and ${}^2\kappa$ (Eq. (2)) in TQSAR equation and V_X in LSER equation. The molecular shape index, ${}^2\kappa$, can also be regarded as the degree of linear graph-likeness, with the larger normal alcohols and steroids having the higher ${}^2\kappa$ values. q_s^+ is used as a hydrogen bonding donor ability parameter (Dearden and Ghafourian, 1999) and has a negative effect on the permeation coefficient (Eq. (2)). Standardization of the parameters in Eq. (2) results in -1.13, 0.438 and -0.201 as the coefficients of OT, ${}^2\kappa$ and q_s^+, respectively, which shows the lower importance of the hydrogen bonding donor ability in the permeation process, in comparison with the other two parameters.

log K_m is correlated with the octanol/water partition coefficient (Tayar et al., 1991) and also with the solvatochromic parameters of π_2^H and $\Sigma\beta_2^H$ (with negative coefficients) and $\Sigma\alpha_2^H$ and V_X (with positive coefficients) (Abraham et al., 1995). It has been shown that the octanol/water partition coefficient needs to be corrected by hydrogen bonding parameters in order to model membrane/water partitioning (Vaes et al., 2000). For the stratum corneum partition coefficient, the correcting parameter selected by step-wise regression analysis is energy of the highest occupied molecular orbital, E_{HOMO}, calculated by the AM1

method (Eq. (4)). The E_{HOMO} is a hydrogen bonding acceptor ability parameter (Dearden and Ghafourian, 1995) and according to Eq. (4) has a positive effect on log K_m, indicating the more H-bond acceptor preference of stratum corneum in comparison with the octanol phase.

$$\log K_m = 0.471 \log P_{oct} + 0.122E_{HOMO} + 1.42 \quad (4)$$

with $n = 22$, $r = 0.976$, $s = 0.142$ and $F = 194$.

Table 1
Values of water–skin partition coefficients as log K_m, permeability coefficients as log k_p, log D/h, log P_{oct}, OT and log TA

Compound	log k_p	log K_m	log P_{oct}[e]	log D/h	log TA	OT
1A[a]	−6.38	2.01	3.70	−8.39	2.497	2
2B[a]	−6.38	1.70	3.13	−8.08	2.498	2
3A[a]	−6.78	1.60	2.47	−8.38	2.502	3
4B[a]	−6.78	1.63	3.00	−8.41	2.506	3
5A[a]	−6.90	1.57	2.88	−8.47	2.512	3
6A[a]	−6.95	1.36	3.31	−8.31	2.462	2
7A[a]	−7.68	1.36	2.52	−9.04	2.515	4
8A[a]	−7.78	1.23	1.94	−9.01	2.524	4
9A[a]	−8.56	0.93	1.42	−9.49	2.520	5
10A[a]	−9.08	0.85	1.53	−9.93	2.527	5
11A[a]	−9.08	0.83	1.08	−9.91	2.516	5
12C[a]	−6.00	1.66	2.76	−7.66	2.448	2
13C[a]	−7.08	1.66	2.69	−8.74	2.465	2
14C[a]	−7.95	1.36	2.47	−9.31	2.461	3
15A[b]	−8.14	0.95	1.43	−9.09	2.604	7
16A[b]	−7.73	1.08	2.03	−8.81	2.642	7
17A[b]	−7.23	1.34	2.60	−8.57	2.625	7
18A[b]	−6.76	1.04	2.11	−7.80	2.613	8
19A[b]	−6.30	1.83	3.26	−8.13	2.662	8
20A[b]	−6.61	1.40	2.30	−8.01	2.675	7
21A[b]	−6.60	1.30	2.79	−7.90	2.654	7
22A[b]	−6.02	1.48	3.00	−7.50	2.571	6
23A[b]	−5.82	2.12	3.70	−7.94	2.684	8
24A[b]	−5.30	2.32	4.48	−7.62	2.627	6
25A[b]	−4.76	3.56	5.49	−8.32	2.662	6
26[c]	−6.56	−0.22	−0.77	−6.34	1.808	1
27[c]	−6.56	−0.22	−0.31	−6.34	1.923	1
28[c]	−6.41	0.30	0.25	−6.71	2.009	1
29[c]	−6.16	0.40	0.88	−6.56	2.059	1
30[c]	−5.78	0.70	1.56	−6.48	2.154	1
31[c]	−5.44	1.00	2.03	−6.44	2.192	1
32[c]	−5.05	1.48	2.72	−6.53	2.252	1
33[c]	−4.84	1.70	2.97	−6.54	2.283	1
34[d]	−7.51	–	0.65	–	2.277	3
35[d]	−6.90	–	1.47	–	2.343	3
36[d]	−7.27	–	1.89	–	2.332	3
37[d]	−6.20	–	1.96	–	2.374	3
38[d]	−5.33	–	2.08	–	2.186	0
39[d]	−5.76	–	2.26	–	2.180	3

[a] Log K_m and log k_p values from Scheuplein et al. (1969).
[b] Log K_m and log k_p values from Anderson et al. (1988).
[c] Log K_m and log k_p values from Scheuplein (1965).
[d] Log k_p values from Hadgraft and Ridout (1987).
[e] Log P_{oct} values from Tayar et al. (1991).

Table 2
Values of atomic charge parameters, ESP^-, and E_{HOMO}

Compound	q_s^{+a}	q^{-a}	q_s^{-a}	q_s^{-b}	q^{-b}	ESP^-	E_{HOMO}
1A	0.1027	−0.2849	−0.5698	−0.710	−0.341	−39.926	−10.007
2B	0.3064	−0.2956	−0.6186	−0.786	−0.341	−35.002	−9.486
3A	0.2089	−0.2838	−0.5638	−0.677	−0.337	−34.691	−9.522
4B	0.4179	−0.3073	−0.6299	−0.782	−0.337	−31.120	−9.465
5A	0.2078	−0.2963	−0.5931	−0.808	−0.439	−40.088	−10.020
6A	0.1983	−0.3181	−0.6009	−0.813	−0.444	−39.480	−10.063
7A	0.2147	−0.3181	−0.6138	−0.808	−0.439	−40.130	−10.004
8A	0.4162	−0.2773	−0.5668	−0.808	−0.439	−39.280	−9.992
9A	0.2157	−0.3174	−0.6148	−0.808	−0.439	−40.058	−10.046
10A	0.4131	−0.3099	−0.6325	−0.808	−0.439	−39.349	−10.020
11A	0.4092	−0.3094	−0.6094	−0.808	−0.439	−46.230	−9.966
12C	−0.0602	−0.2802	−0.5323	−0.724	−0.340	−34.91	−8.894
13C	0.4389	−0.3253	−0.6157	−0.828	−0.444	−31.565	−9.070
14C	0.4181	−0.3352	−0.5896	−0.784	−0.400	−33.628	−9.209
15A	0.4401	−0.4340	−0.7324	−0.790	−0.421	−38.941	−10.052
16A	0.4210	−0.3266	−0.6240	−0.789	−0.420	−39.503	−10.034
17A	0.4144	−0.3362	−0.6336	−0.741	−0.372	−39.678	−10.084
18A	0.4538	−0.3341	−0.6182	−0.742	−0.373	−39.051	−10.079
19A	0.4399	−0.3564	−0.6580	−0.737	−0.368	−39.637	−10.051
20A	0.4306	−0.4373	−0.7380	−0.790	−0.421	−41.058	−10.022
21A	0.4202	−0.3302	−0.5151	−0.821	−0.452	−39.850	−7.241
22A	0.4220	−0.3515	−0.6507	−0.738	−0.369	−39.589	−9.983
23A	0.4083	−0.3482	−0.6466	−0.741	−0.372	−39.615	−10.108
24A	0.4197	−0.3196	−0.6131	−0.738	−0.369	−39.692	−10.042
25A	0.4220	−0.3168	−0.6468	−0.737	−0.368	−39.637	−9.957
26	0.1956	−0.3252	−0.3252	−0.458	−0.458	−32.074	−11.135
27	0.1964	−0.3295	−0.3295	−0.452	−0.452	−32.943	−10.876
28	0.1964	−0.3289	−0.3289	−0.452	−0.452	−32.572	−10.892
29	0.1954	−0.3279	−0.3279	−0.452	−0.452	−32.221	−10.751
30	0.1954	−0.3259	−0.3259	−0.452	−0.452	−32.711	−10.863
31	0.1961	−0.3261	−0.3261	−0.452	−0.452	−32.379	−10.959
32	0.1958	−0.3262	−0.3262	−0.452	−0.452	−32.444	−10.953
33	0.1960	−0.3251	−0.3251	−0.452	−0.452	−32.403	−10.945
34	0.2736	−0.3437	−0.3437	−0.442	−0.442	−29.822	−11.265
35	0.2723	−0.3394	−0.3394	−0.442	−0.442	−29.728	−9.9624
36	0.2722	−0.3287	−0.3287	−0.442	−0.442	−33.286	−11.197
37	0.2724	−0.3442	−0.3442	−0.442	−0.442	−29.771	−11.156
38	0.1592	−0.1384	−0.1384	−0.351	−0.351	−30.186	−9.028
39	0.2434	−0.3410	−0.3410	−0.380	−0.380	−44.678	−9.501

[a] Calculated by the AM1 method.
[b] Calculated by the classical method (Abraham et al., 1991).

On the other hand, using only the theoretical descriptors in step-wise regression analysis showed that only two parameters of log TA and OT is enough to obtain a good correlation which, considering the F-statistic is more significant than is the correlation with the solvatochromic parameters reported by Abraham et al. (1995).

$$\log K_m = -7.03 + 3.84 \log TA - 0.349OT \quad (5)$$

with $n = 22$, $r = 0.967$, $s = 0.166$ and $F = 140$.

The correlation shows that the main factors that influence the stratum corneum partitioning process are solute basicity that favors water and solute size that favors the stratum corneum. This was also concluded from the correlation with the

solvatochromic parameters which showed that the stratum corneum is less basic and more lipophilic than water with polarity/polarizability and hydrogen bond donor ability having much smaller influences (Abraham et al., 1995). From the observation of correlation of log P_{oct} with the two parameters of OT and log TA (Eq. (6)), it can be deduced that partitioning from water into stratum corneum, in comparison with the partitioning from water to octanol, is less affected by solute size and hydrogen bonding acceptor ability.

$$\log P_{oct} = -13.7 + 7.47 \log TA - 0.751 OT \quad (6)$$

with $n = 22$, $r = 0.975$, $s = 0.277$ and $F = 184$.

This method was also successful in modeling the $\log(D/h)$:

Table 3
Values of molecular weight, HT, solubility parameter, molar volume, molecular shape indices and $^4\chi^v_{pc}$

Compound	MW	HT	δ	V	$^2\kappa$	$^0\kappa_\alpha$	$^4\chi^v_{pc}$
1A	314.5	0	10.912	44.3	5.50	31.32	5.53
2B	316.5	1	10.912	44.3	5.50	31.32	5.57
3A	330.5	1	10.912	44.3	5.50	33.13	6.12
4B	332.5	2	10.912	44.3	5.50	33.13	6.17
5A	330.5	1	18.368	36.9	6.02	33.13	5.49
6A	288.4	1	20.038	13.0	4.75	27.77	5.18
7A	346.5	2	18.368	36.9	6.00	34.95	6.04
8A	346.5	2	18.368	36.9	6.27	34.95	5.46
9A	360.5	2	18.368	36.9	6.25	36.79	5.84
10A	362.5	3	18.368	36.9	6.25	36.79	6.02
11A	360.4	2	18.368	36.9	6.81	36.79	5.02
12C	270.4	1	14.510	3.8	4.75	26.02	3.47
13C	272.4	2	20.038	13.0	4.75	26.02	3.71
14C	288.4	3	20.038	13.0	4.75	27.16	4.10
15A	447.5	2	16.904	75.1	8.90	48.16	6.02
16A	475.6	2	12.215	126.4	9.71	51.47	6.39
17A	462.5	2	12.441	109.1	9.47	50.11	6.06
18A	448.5	3	14.483	86.1	8.90	48.16	6.01
19A	490.6	3	12.677	134.4	10.64	54.04	6.01
20A	428.6	2	14.234	123.4	9.81	50.11	6.02
21A	462.6	3	13.815	115.9	9.81	50.11	5.96
22A	404.5	2	12.332	75.0	7.55	42.41	5.98
23A	504.6	2	11.391	157.4	11.24	56.03	6.06
24A	424.6	2	11.010	123.3	9.22	48.16	5.96
25A	430.6	2	10.549	155.5	10.40	52.07	5.96
26	32.0	0	13.767	43.5	0.00	0.60	0.00
27	46.0	0	12.575	59.6	2.00	1.43	0.00
28	60.0	0	11.836	75.7	3.00	2.41	0.00
29	74.0	0	11.330	91.8	4.00	3.49	0.00
30	88.0	0	10.962	107.9	5.00	4.67	0.00
31	102.2	0	10.681	124.0	6.00	5.92	0.00
32	116.2	0	10.463	140.0	7.00	7.22	0.00
33	130.2	0	10.283	156.1	8.00	8.59	0.00
34	184.2	0	14.198	125.8	4.02	11.47	1.52
35	232.2	0	14.419	147.6	5.33	17.91	1.49
36	212.2	0	13.134	158.3	4.89	15.84	2.08
37	226.3	0	12.273	191.5	5.56	16.86	1.71
38	129.2	0	11.530	109.5	2.94	10.00	0.37
39	138.1	2	13.125	112.9	3.41	10.00	0.33

$$\log (D/h) = -3.706 - 0.0037MW - 0.609HT + 0.077ESP^{-} \quad (7)$$

with $n = 22$, $r = 0.987$, $s = 0.22$ and $F = 224$.

$$\log (D/h) = -4.223 - 0.0356\ {}^{0}\kappa_{\alpha} - 0.602HT + 0.065ESP^{-} \quad (8)$$

with $n = 22$, $r = 0.988$, $s = 0.22$ and $F = 224$.

In Eqs. (7) and (8), MW is the molecular weight, HT is the number of hydrogen bonding hydrogens (those connected to the oxygen or nitrogen atoms) and ESP^{-} is the most negative electrostatic potential on the solvent accessible surface of molecules which can be considered as the hydrogen bonding basicity parameter (Dearden and Ghafourian, 1999). The equations show that hydrogen-bonding ability of compounds reduces the diffusion coefficient. MW is a parameter, which can be considered as a size parameter. On the other hand in the series studied, MW can be regarded as an indicator of presence of oxygen atoms, as oxygen atoms that replace the carbon atoms in the structure lead to a higher molecular weight for the same molecular volume. In the latter case, it can be concluded that the higher density of oxygen atoms in the structure lowers the log (D/h). ${}^{0}\kappa_{\alpha}$ is the alpha-modified zero-order molecular shape index which is highly correlated with MW ($r = 0.998$). Using the solvatochromic parameters leads to the following equation with similar values of statistical parameters:

$$\log (D/h) = -5.45 - 0.626R_2 - 0.503\Sigma\alpha_2^{H} - 1.47\Sigma\beta_2^{H} \quad (9)$$

with $n = 22$, $r = 0.986$, $s = 0.22$ and $F = 217$.

In this equation, R_2 is the excess molar refraction, which represents the tendency of a solute to interact with a phase through π or n electron pairs. In other words, R_2 shows the presence of more oxygen atoms in this series, which reduces the log (D/h). This equation is in agreement with Eqs. (7) and (8).

3.2. Hydrocortisone esters

The log k_p values for compounds **15**–**25** were obtained from Anderson et al. (1988). Stepwise regression analyses led to the following equations:

$$\log k_p = 0.80 \log P_{oct} - 8.883 \quad (10)$$

with $n = 11$, $r = 0.936$, $s = 0.371$ and $F = 63.7$.

$$\log k_p = -0.428\delta - 4.80\ {}^{4}\chi_{pc}^{v} + 28.06 \quad (11)$$

with $n = 11$, $r = 0.946$, $s = 0.362$ and $F = 34.2$.

In Eq. (11), δ is the solubility parameter calculated by a group contribution method (Fedors, 1974), ${}^{4}\chi_{pc}^{v}$ is the fourth-order valence-corrected path-cluster molecular connectivity index. The correlation with δ shows that polarity of compounds has a lowering effect on the permeation coefficient of the esters. The ${}^{4}\chi_{pc}^{v}$ index in this series carries information about branching in the R1 substituent, which is not favored for the permeation process. In addition, the index is valence corrected and therefore, distinguishing between graphs containing different atoms indicates the preference of oxygen and nitrogen atoms over carbon atom. This could be explained by the observation of Roberts et al. (1996) that one H-bonding group brings about a dramatic reduction in diffusivity; second and third groups cause further reductions although the effect is non-linear, and further groups have no effect on the minimal value.

17A is an outlier from Eq. (11) and its exclusion leads to Eq. (12) with improved statistics.

$$\log k_p = -0.441\delta - 4.66\ {}^{4}\chi_{pc}^{v} + 27.5 \quad (12)$$

with $n = 10$, $r = 0.986$, $s = 0.193$ and $F = 122.6$.

The correlation of log K_m (Raykar et al., 1988) with log P_{oct} is as follows.

$$\log K_m = 0.656 \log P_{oct} - 2.39q_s^{-} - 1.843 \quad (13)$$

with $n = 11$, $r = 0.983$, $s = 0.158$ and $F = 114$.

In Eq. (13), q_s^{-} is the sum of atomic charges on the hydrogen bonding heteroatoms calculated by the AM1 method which is used as the hydrogen bonding acceptor ability and has a negative coefficient. In other words for hydrocortisone esters, stratum corneum seems to prefer compounds with higher hydrogen bond acceptor ability than does

octanol. Abraham et al. has shown for the 22 steroids and alcohols (Abraham et al., 1995) that solute basicity has a less negative effect in partitioning from water into stratum corneum than it has for partitioning from water into octanol. This could be due to the heterogeneous nature of the stratum corneum and the differing characteristics of the compartments to which compounds partition. Anderson et al. have reported the stratum corneum protein domain/water and stratum corneum lipid domain/water partition coefficients of some hydrocortisone 21-esters. Statistical analyses yielded the following equations for these data:

$$\log K_m \text{ (protein)} = 0.398 \log P_{oct} + 11.4q_s^+ - 4.474 \quad (14)$$

with $n = 11$, $r = 0.942$, $s = 0.169$ and $F = 31.6$.

$$\log K_m \text{ (lipid)} = 0.968 \log P_{oct} - 7.57q^- - 3.552 \quad (15)$$

with $n = 7$, $r = 0.996$, $s = 0.120$ and $F = 278$.

In these equations q_s^+ is the sum of atomic charges on hydrogen bonding hydrogen atoms calculated by the AM1 method and q^- is the most negative atomic charge on the hydrogen bond accepting heteroatoms calculated by the AM1 method. The equations suggest that, in comparison with octanol, the protein domain favors solutes with higher H-bond donor groups and the lipid domain favors stronger H-bond acceptors. The following equation is the result of stepwise regression analysis using the theoretical parameters from which **20A** is an outlier and its deletion leads to the significantly improved Eq. (17).

$$\log K_m = 0.026\ V - 15.6 \log MW + 39.9 \quad (16)$$

with $n = 11$, $r = 0.867$, $s = 0.426$ and $F = 12$.

$$\log K_m = 0.0288V - 19.7 \log MW + 50.6 \quad (17)$$

with $n = 10$, $r = 0.944$, $s = 0.298$ and $F = 29$.

In Eqs. (16) and (17), V is molar volume calculated by group contribution method (Fedors, 1974) and log MW is the logarithm of molecular weight. As discussed before, molecular weight could be considered as an indicator of presence of oxygen and nitrogen atoms. Indeed the log MW for this series of compounds is correlated with the number of oxygen atoms (OT) ($r = 0.790$). Coefficients of these parameters in correlation with log P_{oct} (Eq. (18)) show that octanol is more lipophilic than stratum corneum and that solute basicity affects water–stratum corneum partition much less than it does water–octanol partition.

$$\log P_{oct} = 0.044V - 31.9 \log MW + 82.7 \quad (18)$$

with $n = 10$, $r = 0.958$, $s = 0.395$ and $F = 39$.

Correlations of these parameters with log K_m(lipid) and log K_m(protein) show that, considering the coefficients of the parameters, the lipid domain is more lipophilic and less polar than the protein domain. Coefficients of both parameters in Eq. (17) are higher than those in Eq. (19) and lower than those in Eq. (20), indicating that the compounds probably partition to both compartments in the unchanged stratum corneum. Comparing the correlations of log P_{oct} and log K_m(lipid) (Eqs. (18) and (20)), it seems that octanol is even more lipophilic than the lipid domain of stratum corneum. This could be due to the presence of a high amount of water even in the lipid domain of stratum corneum.

$$\log K_m(\text{protein}) = 0.0156V - 9.27 \log MW + 24.4 \quad (19)$$

with $n = 10$, $r = 0.856$, $s = 0.277$ and $F = 9.6$.

$$\log K_m \text{ (lipid)} = 0.0362V - 23.6 \log MW + 60.6 \quad (20)$$

with $n = 7$, $r = 0.982$, $s = 0.267$ and $F = 54$.

3.3. Compounds **34–39**

Biological data for these miscellaneous compounds were obtained from Hadgraft and Ridout (1987). For this series, the log K_m values are not available and log k_p shows the following correlation with the theoretical parameters:

$$\log k_p = 28.4q^- + 0.018V + 2.824 \quad (21)$$

with $n = 6$, $r = 0.967$, $s = 0.284$ and $F = 22$.

In this equation q^- is the most negative atomic charge on the molecule calculated by the classical method (Abraham et al., 1991). The equation is in accordance with previous equations and indicates

the opposing effect of hydrogen bonding acceptor ability and the favorable effect of solute size on the permeation coefficient. Correlation with log P_{oct} is not good and incorporation of any other parameter in order to improve the correlation is not statistically significant.

$$\log k_p = 1.13 \log P_{oct} - 8.44 \quad (22)$$

with $n = 6$, $r = 0.763$, $s = 0.628$ and $F = 5.6$.

4. Conclusion

It was concluded from this study that the main limiting factor in skin penetration of the chemicals was the hydrogen bonding basicity, which reduces both k_p and K_m. Increasing the size of the molecules increased the k_p values, which was due to the collinearity of the size parameter and hydrophobicity in this series of compounds. The resulting TQSAR equations were of comparable statistics with the equations resulting from the solvatochromic parameters (LSER equations). The advantage of calculated parameters over the solvatochromic parameters is that they are readily accessible without any experimental procedure.

Appendix A. List of the symbols and their definitions

ASA	solvent accessible surface area
$\Sigma\alpha_2^H$	hydrogen bonding donor ability
$\Sigma\beta_2^H$	hydrogen bonding acceptor ability
D	diffusion coefficient
δ	solubility parameter
E_{HOMO}	energy of the highest occupied molecular orbital
ESP^-	the most negative electrostatic potential on the solvent accessible surface of molecules
h	membrane thickness
HT	number of hydrogen bonding hydrogens
K_m	skin/water partition coefficient
k_p	permeability coefficient
${}^2\kappa$	second-order molecular shape index
${}^0\kappa_\alpha$	alpha-modified zero-order molecular shape index
log P_{oct}	octanol/water partition coefficient
MW	molecular weight
OT	number of hydrogen bonding heteroatoms
κ_2^H	polarity/polarizability
q^-	the most negative atomic charge on the hydrogen bond accepting heteroatoms
q_s^-	sum of atomic charges on the hydrogen bonding heteroatoms
q_s^+	sum of atomic charges on the hydrogen bonding hydrogen atoms
R_2	the excess molar refraction
TA	total area
V	molar volume
${}^4\chi_{pc}^v$	fourth-order valence-corrected path-cluster molecular connectivity index

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