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A simple, predictive, structure-based skin permeability model

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Abstract

By an extension of our simple, molecular size-based model recently developed to describe octanol–water partition coefficients, we were able to obtain an entirely structure-based model that seems well suited to describe human skin permeability data. The corresponding equations not only eliminate the physicochemical interrelatedness of the parameters of the original Potts & Guy approach that was obtained from similar considerations, but also maintain its elegant simplicity and are consistent with a basic physicochemical model of the related phenomena. As the new model is structure based and fully computerized, it allows direct estimation of skin permeability for any molecule of known structure without the need to obtain octanol–water partition coefficients or other experimental data.

Introduction

Characterizing the ability of chemicals to penetrate through skin is of obvious interest for the pharmaceutical and cosmetic industries or for those studying the transdermal absorption of environmental pollutants. Understandably, considerable effort was channelled into developing quantitative predictive models for skin permeability, especially in the last decade as more experimental data became available (Flynn 1990; El-Tayar et al 1991; Kim et al 1992; Morimoto et al 1992; Potts & Guy 1992, 1995; Abraham et al 1995, 1997; Bunge & Cleek 1995; Lien & Gao 1995; Wilschut et al 1995; Pugh et al 1996, 2000; Johnson et al 1997; Kirchner et al 1997; Cronin et al 1999; McCarley & Bunge 2000; Poulin & Krishnan 2001). In fact, the modelling of skin permeability is one of the best-developed areas in the field of quantitative structure–permeability relationships, where the ultimate goal is to predict the rate of transport across any given biomembrane solely on the basis of the structure of the permeant and the composition of the membrane.

We have recently developed a unified, molecular size-based model to describe organic liquids (Buchwald & Bodor 1998a, 2000; Buchwald 2000), which, after introduction of a hydrogen-bonding-related parameter, resulted in a predictive method for octanol–water partition coefficients (Bodor & Buchwald 1997; Buchwald & Bodor 1998c). Since essentially all permeability models acknowledge the important role of permeant size and hydrogen-bonding ability, it was of obvious interest to test this molecular size-based concept for prediction of skin permeability.

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Background

Skin permeability

The mechanism of skin penetration has been studied by a variety of methods (Potts & Guy 1997; Bronaugh & Maibach 1999), yet there still is no universally accepted model of transdermal diffusion. According to current knowledge (Moghimi et al 1999), the main, rate-determining barrier of skin penetration is the stratum corneum, the outermost layer of the skin and a composite with a total thickness of about 10–15 μm (in dry state) containing around 15 layers of ordered stacks of flattened, nonviable, keratinized cells embedded in a lipid matrix. Solute penetration can occur both through an intercellular and a transcellular route. In addition, absorption that is not hindered by the barrier represented by the stratum corneum is also possible through sweat ducts and hair follicles. However, because this can only take place through a very small fractional area of the total skin surface, this route should not be very significant in most cases. Hydration of the stratum corneum may also influence absorption.

As the stratum corneum is an essentially dead layer even in living organisms, in-vitro permeability and partition determinations should be better predictors of the in-vivo behaviour than they usually are in other cases. Nevertheless, skin permeability is known to be subject to significant regional variety (Wester & Maibach 1999) and also to considerable interindividual variability.

Passive transport

For most chemicals of interest, the main transport mechanism through skin, as through most other biological membrane barriers of physiological or pharmaceutical relevance (e.g. blood–brain barrier, colon, cornea, small intestine, Caco-2, etc.), is passive diffusion. Active transport or biotransformation (metabolism) may significantly alter the fate of certain compounds, but these represent the exceptions from the general rule. Within the general theory of transport processes (Amidon et al 2000), a variety of models can be envisaged to describe such passive transports (Stein 1986; Camenisch et al 1996), but essentially all rely on size and partition properties as main predictors, and this is especially true for skin permeability.

If the distribution of particles is not uniform and a concentration gradient is present, random molecular motion results in redistribution. The mathematical and physical background of mass transfer phenomena is not especially difficult, but may be somewhat unfamiliar for most pharmaceutical scientists (Yu & Amidon 2000). For a given medium, the particle flux (J), the number of particles traversing through unit perpendicular area in unit time, is proportional to the concentration gradient (Fick's first law of diffusion) (Silbey & Alberty 2001):

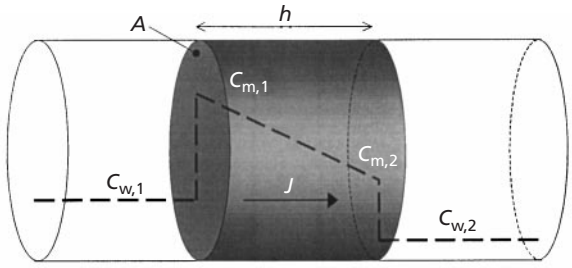

Figure 1 Donor and acceptor phases separated by a homologous membrane as the simplest possible model of passive transport through a biomembrane. The dashed line indicates a concentration-distribution at steady state, while J represents the particle flux through the membrane of thickness h and surface area A.

$$J = 1/A\ dn/dt/d/d = -D_m \delta C/\delta x \quad (1)$$

The proportionality constant in this equation is the diffusion coefficient (D_m) of the corresponding medium (measured in units of $m^2\ s^{-1}$), and the minus sign only indicates that the flow is directed toward smaller concentrations, a direction opposing the concentration gradient. Because, in the general case, particle distribution is a function of both time and spatial coordinates, we used partial derivatives (d). For a given membrane that separates two media containing different concentrations, the permeability coefficient of the membrane ($\mathscr{P}$) is defined in terms of the concentration difference at its two exterior sides:

$$J = 1/A\ dn/dt = \mathscr{P} \triangle C_{ext} \quad (2)$$

In the International System (SI, Système International d'Unités), $\mathscr{P}$ is measured in units of $m\ s^{-1}$; to maintain agreement with previous literature, here we will use cm s^{-1} throughout. The simplest possible arrangement relevant to the present case (permeability of a biological membrane such as skin) is a homogeneous (lipid) membrane surrounded by two similar (aqueous) phases as donor and acceptor compartments (Figure 1). The simplest possible assumption for such a case is that the main rate-limiting resistance to diffusion is the membrane proper (not the interface or the viscosity of the solution). At the donor–membrane and acceptor–membrane interface, concentrations are related to the exterior (aqueous) concentrations by the membrane–water partition coefficient ($P_{m/w}$):

$$P_{m/w} = C_{m,1}/C_{w,1} = C_{m,2}/C_{w,2} \quad (3)$$

At steady state ($dC/dt = 0$) in a homogenous membrane of thickness h, one can write:

$$J = D_m \times \triangle C_m/h = D_m P_{m/w}/h \times \triangle C_w \quad (4)$$

and a comparison with the definition of the permeability coefficient (equation 2) gives the frequently used:

$$\mathscr{P} = D_m P_{m/w}/h \quad (5)$$

Even the simplest descriptions of diffusion predict an inverse relationship between D_m and permeant size. For the particular case of a sphere of radius r moving within a continuous fluid of viscosity η we have the Stokes-Einstein equation:

$$D = kT/6\pi\eta r \quad (6)$$

Since for near-spherical particles the volume (V) or even the molecular weight (MW) is related to the third power of r, this relationship is often used to justify an inverse proportionality between D and $V^{1/3}$ or $MW^{1/3}$, and slightly different powers (most frequently $MW^{1/2}$) are also commonly employed. Diffusion in polymers and within biological membranes and lipid bilayers is non-Stokesian (it does not obey the Stokes–Einstein equation). Nevertheless, a decrease with size still is a reasonable expectation, as the larger the diffusing molecule the more difficult its movement within the surrounding media will be. For example, if one assumes that molecular diffusion takes place by exploiting transient holes formed in the molecular structure of the diffusing media, the simplest statistical mechanical model suggests that the normalized probability p(V)dV of finding a hole with a volume between V and V + dV is given by a Boltzmann-type (Silbey & Alberty 2001) distribution:

$$p(V)dV = \frac{1}{V_0} e^{-\frac{V}{V_0}} dV \quad (7)$$

where V_0 is the mean hole volume. A diffusing molecule of volume V must find a hole $\geqslant V$ in its immediate neighborhood; the probability f(V) of this happening can be reasonably well estimated by simply integrating the above expression between V and infinity:

$$f(V) = \int_V^\infty p(V)dV = e^{-\frac{V}{V_0}} \quad (8)$$

For a given membrane and temperature, the total number of holes, their formation frequency, and their mean size are fixed; therefore, one can expect the diffusion coefficient to be proportional with f(V), and then:

$$D = D_0 e^{-aV} \quad (9)$$

Therefore, as long as all these simplifying assumptions are reasonable approximations, on the basis of equations 5 and 9 one can expect:

$$\log \mathscr{P} = \log (D_0/h) + \log P_{m/w} - a_v V \quad (10)$$

For most organic molecules of interest, usual measures of size (e.g. radius r, surface area A, volume V, molecular weight MW) tend to correlate strongly (Meyer 1986; Pearlman 1986; Camenisch et al 1996; Bodor & Buchwald 1997). Furthermore, because the molecular-size of these molecules usually varies over a relatively limited range (rarely significantly more than one order of magnitude), even the different powers or logarithms of these parameters are intercorrelated. Hence, almost any of them can be used (and have been used) in such relationships, and it is usually difficult to judge, based on performance alone, which one is more justified from a physicochemical perspective.

Potts & Guy-type approaches

Allowing for a Collander-type conversion (Collander 1951) to introduce the octanol–water partition coefficient, $\log P_{m/w} = a' + a'' \log P_{o/w}$, and using molecular weight (MW) instead of molecular volume as size descriptor, equation 10 is, in fact, the basis of the Potts & Guy (PG) approach (Potts & Guy 1992), which still is the most successful simple model for skin permeability:

$$\log \mathscr{P} = a_0 + a_1 \log P_{o/w} - a_2 MW \quad (11)$$

Stratum corneum–water partition coefficients ($P_{sc/w}$) have been measured and have been compared with other partition coefficients in an attempt to identify a good model partitioning system (e.g. see Pugh et al 1996 and references therein). Octanol seemed the best suited for conversions of this type involving $P_{sc/w}$ (Pugh et al 1996):

$$\log P_{sc/w} = -0.024 + 0.59 \log P_{o/w} \quad (12)$$
$$n = 45,\ r^2 = 0.84$$

Here, n represents the number of data used for regression, and r is the correlation coefficient. The basic assumption underlying such Collander-type conversions is that the free energies of transfer in two different solvent-pair systems (and, hence, the corresponding log Ps) are linearly related. However, this is not generally valid and only holds if the solutes show sufficient structural similarity (e.g. congener series). Therefore, the regression-derived coefficients used to relate two different partition coefficients by such conversions might strongly depend on the solute database used for regression. Nevertheless, the slope-coefficient relating log

$P_{sc/w}$ to log $P_{o/w}$ in this type of relationship is usually found to be in the 0.6–0.8 range (Pugh et al 1996; Johnson et al 1997). The original and much quoted Potts & Guy equation (Potts & Guy 1992) was obtained on a total of 93 compounds as:

$$\log \mathscr{P}_s \text{ (cm s}^{-1}) = -6.30 + 0.71 \log P_{o/w} - 0.0061 \text{ MW}$$
$$n = 93,\ r^2 = 0.67 \qquad (13)$$

A slightly modified version that uses $MW^{1/2}$ instead of MW also performed quite well in a comparison of five different models performed by Wilschut and co-workers (Wilschut et al 1995). Cronin et al (1999) examined the same problem on a set of 114 compounds using a total of 47 descriptors. They found the total number of lone pairs that can accept hydrogen bonds on the molecule (HA_{LP}) to be by far the most significant parameter. Nevertheless, after analysis of the data (and omission of seven outliers), they settled on the following PG-type equation:

$$\log \mathscr{P}_s \text{ (cm s}^{-1}) = -5.89 + 0.772 \log P_{o/w} - 0.0103 \text{ MW}$$
$$n = 107,\ r^2 = 0.859,\ \sigma = 0.394,\ F = 317 \qquad (14)$$

Here, σ represents the standard deviation of the regression, and F is Fisher's variance ratio. These results, however, as well as those of Kirchner et al (1997), are seriously compromised by the fact that for some strange reason they chose to use a log $\mathscr{P}$ dataset for 114 chemicals, of which 63 are calculated and not experimental values, obtained from the Occupational Safety and Health Association (Kirchner et al 1997). We found most of these values to give a perfect fit with the original PG equation (equation 13), and in the few cases where the fit was not perfect, obviously a different log $P_{o/w}$ value was used for the calculations. It is not surprising then that PG-type equations based on log $P_{o/w}$ and either MW (Cronin et al 1999) or V (Kirchner et al 1997) give good fits, and the obtained correlation coefficients are better than those of other, similar attempts.

A major drawback of the PG approach, despite the relatively easy accessibility of both of its parameters (log $P_{o/w}$, MW or V), is the strong physicochemical interrelatedness of its two parameters, as log $P_{o/w}$ is strongly size related (Buchwald & Bodor 1998c). Hence, this approach cannot reveal the basic mechanism and determinants of skin permeability. To overcome this difficulty, one obvious possibility was to use a solvatochromic-type approach in an attempt to identify the basic factors determining skin permeability. Studies of this type have been performed by Abraham and coworkers (Abraham et al 1995), by Potts & Guy themselves (Potts & Guy 1995) and by Pugh and co-workers (Pugh et al 1996). They all found size and hydrogen bonding (mostly hydrogen bond acceptor basicity) as clearly having the most important roles. El Tayar, Testa, Leo, and co-workers were the only ones to suggest otherwise in an earlier work (El-Tayar et al 1991), as they attributed an important (inhibiting) role to hydrogen bond donor acidity (measured by $\triangle\log P_{o/h} = \log P_{o/w} - \log P_{heptane/w}$). However, all other works (including this one), where all data were grouped together and not analysed separately for different subgroups, seem to indicate otherwise and are contrary to El-Tayar and co-workers' observation.

Materials and Methods

Three-dimensional molecular structures were built and optimized using the Alchemy package (Tripos Assoc., St Louis, MO). Experimental skin-permeability data were collected from the literature mainly based on the recent compilations of Johnson et al (1997) and Wilschut et al (1995) (Table 1). Whenever more permeability data were available for the same compound, we used their average. To illustrate the variability of the experimental data, for such cases, together with the logarithm of the average, we also included the standard deviation of the corresponding log values under the s.d. heading of Table 1. Even if the logarithmic values are not expected to have Gaussian (normal) distribution, $\exp\{-(x-\mu)^2/2\sigma^2\}/(\sigma\sqrt{2\pi})$, these values are still descriptive of the spread of the experimental log $\mathscr{P}$ values. Following Johnson et al (1997), steroid permeabilities originally measured by Scheuplein and co-workers in 1969 (Scheuplein et al 1969) were omitted, because of apparent discrepancies compared with those measured by other groups. Whenever corrected permeabilities representing the permeabilities of the non-ionized form of partially ionized compounds were significantly different from the non-corrected values, we used the corrected values as given by Johnson et al (1997). Experimental octanol–water partition coefficients were recommended values from the recent compilation of Hansch et al (1995). For the few cases where no such values were available, we used the values from the original publications.

The effective van der Waals molecular volume (V_e) and the hydrogen bonding-related N parameter of the QLogP model were calculated using our program as previously described (Bodor & Buchwald 1997; Buchwald & Bodor 1998c). Volumes were computed with a fast, essentially analytical algorithm that requires

Table 1 Experimental and calculated skin-permeability for 98 compounds with data available in the literature

Compound	Formula	V_e[a] ($Å^3$)	N[a]	QlogP[a] (cm s^{-1})	MW	log $P_{o/w}$[b]	ref.[c]	log $\mathscr{P}_s$[d]	s.d.[e]	Ref.[c]	Eqn 19[f]	Eqn 20[f]	PG[f] Eqn 13	Rob.[f] Eqn 17
Aldosterone	$C_{21}H_{28}O_5$	279.44	10	1.67	360.45	1.08	H	−7.82	0.05	J	−7.27	−7.67	−7.73	−7.58
Amobarbital	$C_{11}H_{18}N_2O_3$	176.50	5	2.00	226.27	2.07	H	−6.20		J	−6.14	−6.19	−6.21	−6.31
Aniline	$C_6H_7N_1$	77.41	2	1.02	93.13	0.91	W	−5.21		W	−5.93	−6.09	−6.22	−6.05
Anisole	$C_7H_8O_1$	88.78	1	2.10	108.14	2.11	H	−4.69		J	−5.29	−5.13	−5.46	−5.47
Atropine	$C_{17}H_{23}N_1O_3$	231.10	6	2.03	289.37	1.83	H	−6.81		P	−5.93	−5.78	−6.77	−6.80
Barbital	$C_8H_{12}N_2O_3$	134.39	5	0.66	184.19	0.65	H	−7.51		J	−6.67	−7.07	−6.96	−6.90
Benzaldehyde	$C_7H_6O_1$	83.84	1	1.94	106.12	1.48	H	−4.77		J	−5.36	−5.23	−5.90	−5.83
Benzene	C_6H_6	68.03	0	2.16	78.11	2.13	H	−4.42	0.11	J	−5.07	−4.84	−5.26	−5.20
Benzyl alcohol	$C_7H_8O_1$	88.81	2	1.38	108.14	1.10	H	−5.33		J	−5.79	−5.85	−6.18	−6.07
Butanol	$C_4H_{10}O_1$	71.53	2	0.83	74.12	0.88	H	−6.15	0.07	J	−6.01	−6.21	−6.13	−5.89
Butanone	$C_4H_8O_1$	65.79	2	0.65	72.11	0.29	H	−5.90		J	−6.08	−6.33	−6.53	−6.22
Butobarbital	$C_{10}H_{16}N_2O_3$	162.54	5	1.56	212.25	1.73	H	−7.27		J	−6.31	−6.48	−6.37	−6.43
Caffeine	$C_8H_{10}N_4O_2$	132.51	7	−0.84	194.19	−0.07	H	−7.56		J	−7.68	−8.55	−7.53	−7.38
Chlorpheniramine	$C_{16}H_{19}Cl_1N_2$	220.83	4	4.14	274.79	3.39	H	−6.21		W	−5.08	−4.55	−5.57	−5.79
Codeine	$C_{18}H_{21}N_1O_3$	228.30	6	1.95	299.37	1.14	H	−7.09		Jc	−5.96	−5.84	−7.32	−7.26
Corticosterone	$C_{21}H_{30}O_4$	279.45	8	2.21	346.47	1.94	H	−7.05	0.38	J	−6.29	−6.22	−7.04	−7.01
Cresol, 4-chloro	$C_7H_7Cl_1O_1$	105.39	1	2.63	142.58	3.10	H	−4.79		J	−5.08	−4.78	−4.97	−5.18
Cresol, *m*-	$C_7H_8O_1$	88.24	1	2.08	108.14	1.96	H	−5.37		J	−5.30	−5.14	−5.57	−5.56
Cresol, *o*-	$C_7H_8O_1$	88.20	1	2.08	108.14	1.95	H	−5.36		J	−5.30	−5.14	−5.58	−5.57
Cresol, *p*-	$C_7H_8O_1$	88.21	1	2.08	108.14	1.94	H	−5.31		J	−5.30	−5.14	−5.58	−5.57
Cecanol	$C_{10}H_{22}O_1$	155.30	2	3.50	158.28	4.57	H	−4.44	0.25	J	−4.93	−4.47	−4.02	−4.60
Dexamethasone	$C_{22}H_{29}F_1O_5$	298.01	10	2.26	392.47	1.83	H	−7.75		J	−7.04	−7.28	−7.39	−7.29
Diclofenac	$C_{14}H_{11}Cl_2N_1O_2$	206.60	3	4.40	296.15	4.40	H	−5.30		J	−4.77	−4.12	−4.98	−5.33
Diethylcarbamazine	$C_{10}H_{21}N_3O_1$	171.31	6	1.12	199.30	1.75	P	−7.44		W	−6.69	−7.02	−6.27	−6.34
Digitoxin	$C_{41}H_{64}O_{13}$	593.13	21	3.70	764.95	2.83	H	−8.44		W	−8.66	−9.10	−8.96	−8.02
Ephedrine	$C_{10}H_{15}N_1O_1$	141.48	4	1.61	165.23	0.93	H	−5.78		J	−6.09	−6.20	−6.65	−6.61
Estradiol	$C_{18}H_{24}O_2$	224.62	3	3.05	272.39	4.01	H	−5.94	0.10	J	−4.54	−3.75	−5.11	−5.43
Ethane, 1,1,1-trichloro	$C_2H_3Cl_3$	70.80	0	2.25	133.40	2.49	H	−5.90		W	−5.03	−4.78	−5.35	−5.45
Ethanol	$C_2H_6O_1$	43.33	2	−0.07	46.07	−0.31	H	−6.60	0.07	W	−6.37	−6.79	−6.80	−6.28
Ethanol, 2-ethoxy	$C_4H_{10}O_2$	78.93	4	−0.38	90.12	−0.32	H	−7.16		J	−6.89	−7.50	−7.08	−6.76
Ethanol, 2-phenyl	$C_8H_{10}O_1$	103.06	2	1.83	122.17	1.36	H	−5.44		J	−5.60	−5.55	−6.08	−6.03
Ethyl ether	$C_4H_{10}O_1$	71.96	2	0.84	74.12	0.89	H	−6.35		J	−6.00	−6.20	−6.12	−5.88
Ethylbenzene	C_8H_{10}	96.00	0	3.05	106.17	3.15	H	−3.47		J	−4.71	−4.25	−4.71	−4.89
Etorphine	$C_{25}H_{33}N_1O_4$	325.57	8	3.53	411.54	1.86	W	−6.00		W	−5.70	−5.26	−7.49	−7.35
Fentanyl	$C_{22}H_{28}N_2O_1$	280.54	6	4.59	336.48	4.05	H	−5.76	0.26	W	−5.30	−4.75	−5.48	−5.71
Fluocinonide	$C_{26}H_{32}F_2O_7$	358.78	11	3.47	494.53	3.19	H	−6.33		J	−6.75	−6.74	−7.05	−6.90
Heptanol	$C_7H_{16}O_1$	113.36	2	2.16	116.20	2.72	H	−5.01	0.05	J	−5.47	−5.34	−5.08	−5.19
Hexanol	$C_6H_{14}O_1$	99.50	2	1.72	102.18	2.03	H	−5.25	0.16	J	−5.65	−5.63	−5.48	−5.47
Hydrocortisone	$C_{21}H_{30}O_5$	286.00	10	1.87	362.47	1.61	H	−7.73	0.62	J	−7.19	−7.53	−7.37	−7.28
Hydrocortisone, 21-(6-hydroxy)hexanoate	$C_{27}H_{40}O_7$	379.29	12	3.40	476.61	2.79	J	−6.60		J	−6.98	−7.04	−7.23	−7.07
Hydrocortisone 21-(*N*,*N*-dimethyl)succinamate	$C_{27}H_{39}N_1O_7$	382.76	14	2.06	489.61	2.03	J	−7.73		J	−7.91	−8.41	−7.85	−7.57
Hydrocortisone 21-hemipimelate	$C_{28}H_{40}O_8$	394.18	12	3.87	504.62	3.26	J	−6.30		J	−6.79	−6.73	−7.06	−6.90
Hydrocortisone 21-hemisuccinate	$C_{25}H_{34}O_8$	352.09	12	2.53	462.54	2.11	J	−6.76		J	−7.33	−7.60	−7.62	−7.41
Hydrocortisone 21-hexanoate	$C_{27}H_{40}O_6$	372.31	10	3.66	460.61	3.70	H	−5.30		J	−6.08	−5.74	−6.48	−6.46
Hydrocortisone 21-methylpimelate	$C_{29}H_{42}O_8$	408.62	12	4.33	518.65	3.30	J	−5.82		J	−6.60	−6.43	−7.12	−6.93
Hydrocortisone 21-methylsuccinate	$C_{26}H_{36}O_8$	366.57	12	2.99	476.57	2.58	J	−7.23		J	−7.14	−7.30	−7.38	−7.20
Hydrocortisone 21-octanoate	$C_{29}H_{44}O_6$	400.28	10	4.48	488.66	5.49	J	−4.76		J	−5.73	−5.15	−5.38	−5.53
Hydrocortisone 21-pimelamate	$C_{28}H_{41}N_1O_7$	396.99	14	2.52	503.63	2.30	J	−6.61		J	−7.73	−8.11	−7.74	−7.46
Hydrocortisone 21-propionate														

Table 1 (*cont.*)

Compound	Formula	V_e[a] (Å^3)	N[a]	QlogP[a] (cm s^{-1})	MW	log $P_{o/w}$[b]	ref.[c]	log $\mathscr{P}_s$[d]	s.d.[e]	Ref.[c]	Eqn 19[f]	Eqn 20[f]	PG[f] Eqn 13	Rob.[f] Eqn 17
Hydrocortisone 21-succinamate														
	$C_{25}H_{35}N_1O_7$	354.72	14	1.17	461.55	1.43	J	−8.14		J	−8.27	−8.99	−8.10	−7.79
Hydromorphone	$C_{17}H_{19}N_1O_3$	213.13	6	1.53	285.34	0.89	J	−7.63		Jc	−6.16	−6.15	−7.41	−7.33
	$C_{24}H_{34}O_6$	330.34	10	3.29	418.53	3.00	J	−6.02		J	−6.62	−6.61	−6.72	−6.70
Hyoscine	$C_{17}H_{21}N_1O_4$	232.63	8	1.62	303.36	1.24	H	−7.86		J	−6.89	−7.20	−7.27	−7.22
Indometacin	$C_{19}H_{16}Cl_1N_1O_4$	253.65	7	3.01	357.79	4.27	H	−5.39		J	−6.13	−6.04	−5.45	−5.68
Isoquinoline	$C_9H_7N_1$	100.65	2	1.76	129.16	2.08	H	−5.33		J	−5.63	−5.60	−5.61	−5.66
Lidocaine	$C_{14}H_{22}N_2O_1$	201.12	5	2.79	234.34	2.26	H	−5.34		J	−5.82	−5.68	−6.12	−6.24
Methanol	$C_1H_4O_1$	29.28	2	−0.51	32.04	−0.77	H	−6.86		J	−6.55	−7.09	−7.04	−6.36
Methyl 4-OH benzoate	$C_8H_8O_3$	110.90	3	1.36	152.15	1.96	H	−5.60		J	−5.99	−6.11	−5.84	−5.90
Morphine	$C_{17}H_{19}N_1O_3$	213.69	6	1.55	285.34	0.76	H	−7.81		Jc	−6.15	−6.14	−7.50	−7.41
Naphthol, 2-	$C_{10}H_8O_1$	110.60	1	2.80	144.17	2.70	H	−5.13	0.03	J	−5.02	−4.67	−5.26	−5.41
Naproxen	$C_{14}H_{14}O_3$	174.92	3	3.40	230.26	3.34	H	−4.97		J	−5.17	−4.78	−5.33	−5.58
Nicotine	$C_{10}H_{14}N_2$	136.06	4	1.44	162.23	1.17	H	−5.50	0.54	J, P	−6.16	−6.31	−6.46	−6.44
Nitroglycerin	$C_3H_5N_3O_9$	127.15	3	1.88	227.09	1.62	H	−5.51		W	−5.79	−5.77	−6.54	−6.58
Nonanol	$C_9H_{20}O_1$	141.28	2	3.05	144.26	4.26	H	−4.78		J	−5.11	−4.76	−4.16	−4.65
Octanol	$C_8H_{18}O_1$	127.53	2	2.61	130.23	3.00	H	−4.65	0.23	J	−5.29	−5.04	−4.96	−5.15
Ouabain	$C_{29}H_{44}O_{12}$	438.01	18	0.93	584.66	−2.11	J	−9.66		W	−9.17	−10.15	−11.36	−8.75
Pentanol	$C_5H_{12}O_1$	85.53	2	1.28	88.15	1.56	H	−5.78		J	−5.83	−5.92	−5.73	−5.62
Pethidine	$C_{15}H_{21}N_1O_2$	204.35	4	3.61	247.34	2.45	H	−5.99		W	−5.29	−4.89	−6.07	−6.20
Phenobarbital	$C_{12}H_{12}N_2O_3$	165.98	5	1.67	232.24	1.47	H	−5.90		J	−6.27	−6.41	−6.67	−6.70
Phenol	$C_6H_6O_1$	74.21	1	1.64	94.11	1.46	H	−5.53	0.14	J	−5.48	−5.43	−5.84	−5.74
Phenol, 2,4,6-trichloro	$C_6H_3Cl_3O_1$	125.57	1	3.27	197.45	3.69	H	−4.78		J	−4.82	−4.36	−4.88	−5.20
Phenol, 2,4-dichloro	$C_6H_4Cl_2O_1$	108.54	1	2.73	163.00	3.06	H	−4.78		J	−5.04	−4.72	−5.12	−5.34
Phenol, 2-amino-4-nitro	$C_6H_6N_2O_3$	100.99	3	1.05	154.13	1.53	H	−6.74		W	−6.12	−6.32	−6.15	−6.17
Phenol, 2-chloro	$C_6H_5Cl_1O_1$	91.37	1	2.18	128.56	2.15	H	−5.04		J	−5.26	−5.07	−5.56	−5.61
Phenol, 3-nitro	$C_6H_5N_1O_3$	91.89	2	1.48	139.11	2.00	H	−5.81		J	−5.75	−5.78	−5.73	−5.78
Phenol, 4-amino-2-nitro	$C_6H_6N_2O_3$	101.16	3	1.05	154.12	0.96	H	−6.11		W	−6.12	−6.31	−6.56	−6.51
Phenol, 4-bromo	$C_6H_5Br_1O_1$	99.51	1	2.44	173.01	2.59	H	−5.00		J	−5.16	−4.90	−5.52	−5.67
Phenol, 4-chloro	$C_6H_5Cl_1O_1$	91.32	1	2.18	128.56	2.39	H	−5.00		J	−5.26	−5.07	−5.39	−5.47
Phenol, 4-chloro-3,5-dimethyl (chloroxylenol)														
	$C_8H_9Cl_1O_1$	119.05	1	3.06	156.61	3.39	J	−4.83		J	−4.91	−4.50	−4.85	−5.11
Phenol, 4-ethyl	$C_8H_{10}O_1$	102.28	1	2.53	122.17	2.58	H	−5.01		J	−5.12	−4.85	−5.21	−5.32
Phenol, 4-nitro	$C_6H_5N_1O_3$	91.89	2	1.48	139.11	1.91	H	−5.81		J	−5.75	−5.78	−5.79	−5.83
Phenylenediamine, *m*-, 4-chloro	$C_6H_7Cl_1N_2$	103.62	4	0.41	142.59	0.85	H	−6.23		J	−6.58	−6.99	−6.57	−6.49
Phenylenediamine, *o*-	$C_6H_8N_2$	86.82	4	−0.13	108.14	0.15	H	−6.90		J	−6.79	−7.34	−6.85	−6.64
Phenylenediamine, *p*-	$C_6H_8N_2$	86.90	4	−0.13	108.14	−0.30	H	−7.18		J	−6.79	−7.33	−7.17	−6.91
Phenylenediamine, *p*-, 2-nitro	$C_6H_7N_3O_2$	104.34	5	−0.29	153.14	0.53	H	−6.86		J	−7.06	−7.69	−6.86	−6.76
Piroxicam	$C_{15}H_{13}N_3O_4S_1$	212.87	10	−0.45	331.35	3.06	H	−7.37		W	−8.13	−9.05	−6.15	−6.27
Progesterone	$C_{21}H_{30}O_2$	265.98	4	3.86	314.47	3.87	H	−5.22	0.26	J	−4.50	−3.61	−5.47	−5.71
Styrene	C_8H_8	91.16	0	2.90	104.15	2.95	H	−3.75		J	−4.77	−4.35	−4.84	−4.98
Sucrose	$C_{12}H_{22}O_{11}$	238.46	12	−1.08	342.30	−3.70	H	−8.84		W	−8.78	−9.97	−11.02	−8.64
Sufentanyl	$C_{22}H_{30}N_2O_2S_1$	309.25	8	4.06	386.55	3.95	H	−5.61	0.24	W	−5.91	−5.60	−5.85	−6.00
Testosterone	$C_{19}H_{28}O_2$	243.62	4	3.30	288.43	3.32	H	−5.98	0.27	J	−4.79	−4.07	−5.70	−5.90
Thymol	$C_{10}H_{14}O_1$	130.23	1	3.42	150.22	3.30	H	−4.82		J	−4.76	−4.26	−4.87	−5.12

Table 1 (*cont.*)

Compound	Formula	V_e[a] (Å^3)	N[a]	QlogP[a] (cm s^{-1})	MW	log $P_{o/w}$[b]	ref.[c]	log $\mathscr{P}_s$[d]	s.d.[e]	Ref.[c]	Eqn 19[f]	Eqn 20[f]	PG[f] Eqn 13	Rob.[f] Eqn 17
Propanol	$C_3H_8O_1$	57.44	2	0.38	60.10	0.25	H	−6.39	0.11	J	−6.19	−6.50	−6.49	−6.12
Resorcinol	$C_6H_6O_2$	80.46	2	1.11	110.11	0.80	H	−7.18		J	−5.89	−6.02	−6.40	−6.27
Salicylic acid	$C_7H_6O_3$	96.02	1	2.33	138.12	2.26	H	−5.22	0.27	Jc	−5.20	−4.98	−5.54	−5.62
Toluene	C_7H_8	82.00	0	2.61	92.14	2.73	H	−3.56		J	−4.89	−4.54	−4.92	−5.00
Urea	$C_1H_4N_2O_1$	42.24	4	−1.55	60.06	−2.11	H	−7.39		W	−7.36	−8.26	−8.16	−7.48
Water	H_2O_1	14.60	2	−0.98	18.02	−1.38	H	−6.46	0.28	J	−6.74	−7.39	−7.39	−6.47
Xylenol, 3,4-	$C_8H_{10}O_1$	102.37	1	2.53	122.17	2.35	H	−5.00		J	−5.12	−4.84	−5.38	−5.45

[a]Molecular volumes (V_e), N-parameters (N), and calculated log octanol–water partition coefficients (QLogP) obtained using our QLogP software. [b]Experimental log octanol–water partition coefficients. [c]Reference for experimental data: H, Hansch et al (1995); J, Johnson et al (1997); P, Pugh et al (2000); W, Wilschut et al (1995). Jc denotes corrected permeability for the non-ionized form from Johnson et al (1997). [d]Experimental log human skin permeability coefficients. [e]Values represent the standard deviation of the log values when more than one experimental skin permeability data were available. [f]Calculated log skin permeabilities (in cm s^{-1}) using the present (equations 19 and 20), the Potts & Guy (equation 13) and the Robinson (equation 17) models.

only 3D structure-files as input and is based on differential geometry's global Gauss-Bonnet formula and a method described by Rowlinson for the volume of triple overlaps (Bodor & Buchwald 1997). The N-contributions were also assigned in a fully automated manner by the QLogP program based on the same structure-files. As already described previously (Buchwald & Bodor 1998c), these N-contributions were corrected with 1 for every hydroxyl group present in glucose-type rings for oubain (3) and sucrose (8). To obtain more accurate calculated log $P_{o/w}$ values, the N-contribution of phenylenediamines was readjusted with N = 2, as the original version of QLogP consistently over-predicted their log $P_{o/w}$, and the N-contribution of the $-ONO_2$ group was set to 1 on the basis of the log $P_{o/w}$ data of nitroglycerin. All statistical analyses, including multiple linear regressions, were performed using a standard spreadsheet program (Microsoft Excel 97).

Results and Discussion

The acceptable predictive ability and relative success of the Potts & Guy (PG) approach (Potts & Guy 1992) is a good indication that even the considerably simplified permeation model that has been briefly summarized here in the Background section can give a reasonable description of skin permeability. Figure 2, which illustrates human skin permeability ($\mathscr{P}_s$) as a function of the log octanol–water partition coefficient (log $P_{o/w}$) with compounds grouped according to increasing molecular size, is included to illustrate the applicability of this model here. The good linear correlation between log $\mathscr{P}_s$ and log $P_{o/w}$ that is clearly present within each size subgroup (Figure 2) is much less obvious if one looks at the overall data, because there is an additional size dependence that keeps shifting the more-or-less parallel trend-lines of each subgroup further down as size increases.

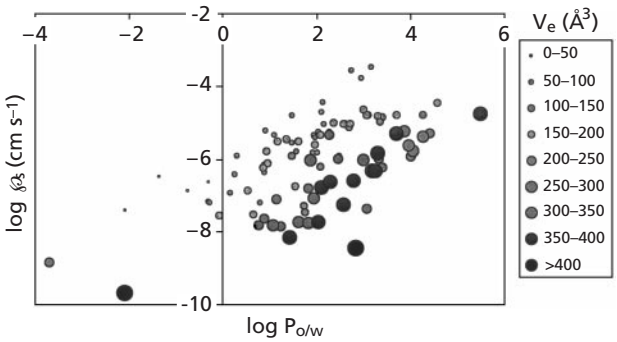

Figure 2 Human skin permeability as a function of the log octanol–water partition coefficient. Molecules are grouped according to increasing molecular size (as measured by V_e). Larger and darker symbols indicate larger molecules.

$$\log \mathscr{P}_s(\text{cm s}^{-1}) = -6.93(\pm 0.16) + 0.46(\pm 0.06) \log P_{o/w}$$
$$n = 98,\ r^2 = 0.344,\ \sigma = 0.953,\ F = 50 \qquad (15)$$

Figure 3 is included to further illustrate that the (log $\mathscr{P}_s$, log $P_{o/w}$, V_e) data are essentially two-dimensional, meaning that the data points are not randomly distributed within this space, but mainly scattered around an inclined planar surface. Since the surface around which

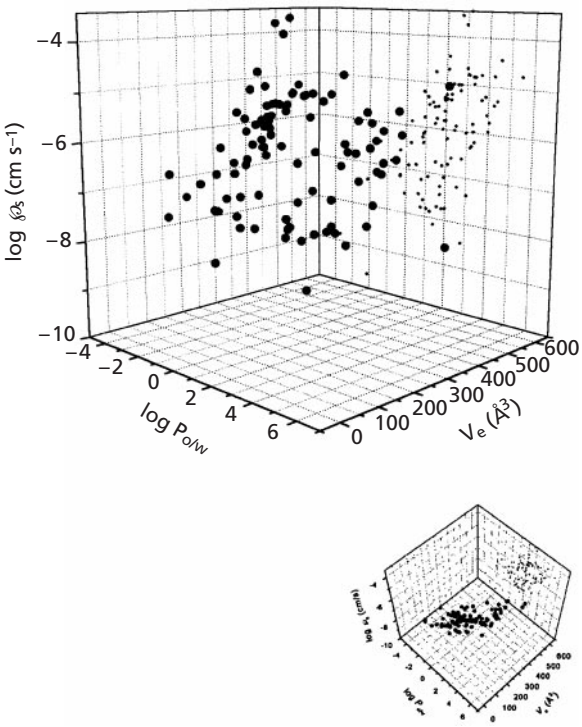

Figure 3 Three-dimensional scatter plot illustrating the dependence of log human skin permeability (log $\mathscr{P}_s$, vertical axis) on log $P_{o/w}$ and size (measured by V_e). The data are essentially two-dimensional meaning that the data points placed in the 3D space of the corresponding cube are scattered around an inclined planar surface in the XYZ space of the graphics. The larger view (left) is from under this plane as it rises from the origin in the lower back corner toward the upper, front corner. The smaller gray dots represent projections on the (log $P_{o/w}$, log $\mathscr{P}_s$) plane (right-hand, backside wall), and this 2D projection corresponds to Figure 2. The smaller inset gives a more tilted view of the very same scatter plot. This time, however, the point of view is within the plane around which most data points are distributed. This view makes it obvious that most of the 3D space is empty, because points are distributed around a 2D surface.

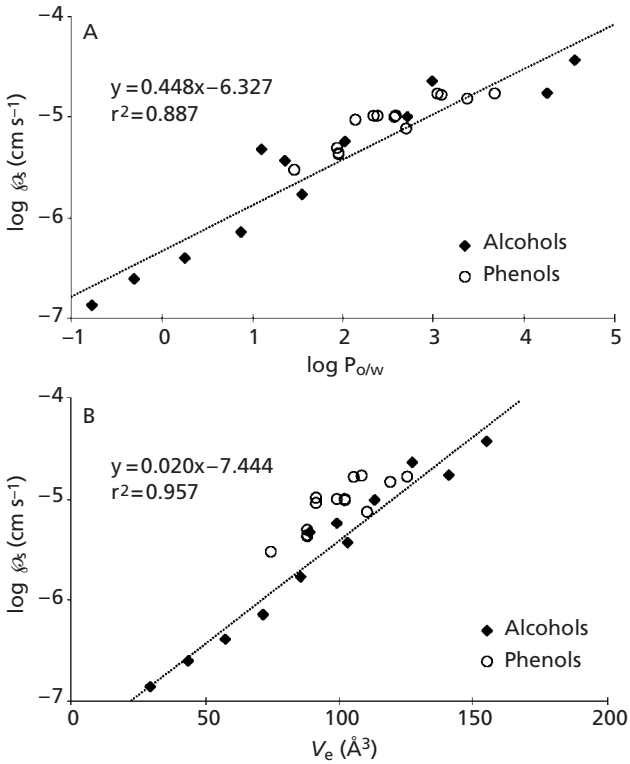

Figure 4 Logarithmic human skin permeability (log $\mathscr{P}_s$) of monofunctionalized alcohols and phenols as a function of lipophilicity (log $P_{o/w}$; A) and molecular size (V_e; B). The line represents the linear trend-line of alcohols only.

the data are scattered is not perpendicular to any of the walls, neither log $P_{o/w}$ nor size alone can give adequate linear description, only their combination. For the present data, linear regression gives slightly modified coefficients as compared with the original PG equation (Potts & Guy 1992) (equation 13):

$$\log \mathscr{P}_s(\text{cm s}^{-1}) = -6.02(\pm 0.12) + 0.60(\pm 0.04) \log P_{o/w} - 0.0052(\pm 0.0042)\text{MW} \quad (16)$$

$$n = 98,\ r^2 = 0.752,\ \sigma = 0.589,\ F = 144$$

Nevertheless, values calculated with the original equation (equation 13) give the very same correlation coefficient ($r^2 = 0.752$), proving again that the two parameters are interrelated, and therefore their regression coefficients with opposing signs cannot be considered as rigorously determined, a problem common to any regression-derived model that has intercorrelated parameters.

As data on monofunctionalized alcohols (the largest amount of skin permeability data available for a congener series) indicate (Figure 4), the assumption of linearity between human skin log $\mathscr{P}$ and log $P_{o/w}$ or V_e may not be entirely accurate, but represents a reasonable approximation. We certainly do not intend to advocate over-simplification of the problem for the sake of maintaining linearity. Data from Figure 2 and Figure 4 may indicate a slight tendency toward a sigmoidal dependence (Camenisch et al 1996), and limiting permeability values may very well exist. Nevertheless, for the range of compounds considered here, linearity seems a very good approximation, and since there is no sufficient evidence clearly favouring any particular nonlinear model, there is no compelling reason yet to deviate from linearity and use more complex models. Even as obviously special

permeants as methanol ($\log P_{o/w} = -0.77$) at one end or decanol ($\log P_{o/w} = 4.57$) at the other end do not deviate strongly from linearity as illustrated by Figure 4 or by the size-subgroups of Figure 2. Nonetheless, for comparison purposes, we also included the predictions of the more complex Robinson model (Wilschut et al 1995), which assumes parallel permeation ($\mathscr{P} = \mathscr{P}_1 + \mathscr{P}_2$) through the lipid and protein fractions of the stratum corneum followed by a serial permeation ($1/\mathscr{P} = 1/\mathscr{P}_1 + 1/\mathscr{P}_2$) through a watery epidermal layer. A mathematically somewhat similar model, which was obtained by assuming parallel permeation through lipoidal and pore pathways in the stratum corneum, followed by a serial permeation through the dermis–epidermis, was also proposed by Higuchi and coworkers (Kim et al 1992). Assuming a PG-like dependence for the permeation coefficient of the lipid fraction of the stratum corneum ($\mathscr{P}_{lf}$) and a simple inverse dependence on the square root of MW for the other two permeation coefficients ($\mathscr{P}_{pf}$, $\mathscr{P}_{aq}$), the Robinson model results in (Wilschut et al 1995):

$$\mathscr{P} = \frac{1}{\dfrac{1}{\mathscr{P}_{lf} + \mathscr{P}_{pf}} + \dfrac{1}{\mathscr{P}_{aq}}} = \frac{1}{\dfrac{1}{10^{-1.326+0.6097\log P_{o/w}-0.1786\sqrt{MW}} + \dfrac{0.0001519}{\sqrt{MW}}} + \dfrac{1}{\dfrac{2.5}{\sqrt{MW}}}} \quad (\text{cm h}^{-1}) \tag{17}$$

Calculated values obtained from this equation (Table 1) correlate slightly better with the present experimental data than those obtained from equations 13 or 16 ($r^2 = 0.788$ vs 0.752). The root mean squared error (MSE) of this approach (0.592), which provides a more direct measurement of the predictive error, is smaller than that of the original PG approach (equation 13, 0.663), but is no smaller than that of the readjusted equation 16 (0.580). Hence, there still is no significant difference clearly indicating the adequacy of this more complex model that contains two more adjustable parameters, and the linear approach should represent a good approximation.

Using the two parameters (V_e, N) of our QLogP approach (Bodor & Buchwald 1997; Buchwald & Bodor 1998c) developed to predict log octanol–water partition coefficients, we can maintain the simplicity, elegance, and reasonable performance of the original PG approach, and also obtain an entirely structure-based predictive method with parameters that are clearly related to the basic factors determining skin permeability. The QLogP model uses:

$$\log P_{o/w} = 0.032V_e - 0.723N \tag{18}$$

to predict the octanol–water partition coefficient, and has been shown to provide good prediction for a large variety of structures (Bodor & Buchwald 1997; Buchwald & Bodor 1998b, 1998c). The effective van der Waals molecular volume (V_e) used here is a better measure of size than MW. N represents a novel parameter introduced with this model and, because of the nature of the octanol–water partitioning, it is mainly related to the hydrogen bonds formed at the acceptor sites of the solute molecule when it is transferred from octanol to water (Bodor & Buchwald 1997; Buchwald & Bodor 1998c; Edward 1998; Buchwald 2000). On the basis of the detailed analysis of a large number of partition data of mono- and multi-substituted compounds (Bodor & Buchwald 1997; Buchwald & Bodor 1998c), use of a quantified parameter that has only integer values seems justified. Essentially all polar, oxygen- and nitrogen-containing simple functions increase N by 2 units, while those in an aromatic environment increase its value by 1. After the corresponding rules have been established, the assignment procedure has been fully automated and integrated within the QLogP program. Values used for some commonly encountered functions are as follows: 2 for —OH, —O—, —NH_2, —NH—, —N<, —CN, —NO_2, —CO—, —COOH, —COO—, —CH=NOH, —N=N—; 4 for —CON<, —CONH—. For those attached to an aromatic ring: 1 for Ar–OH, Ar–O—, Ar–NO_2, Ar–CN, Ar–COOH; 2 for Ar–NH_2, Ar–NH–, Ar–COO—; 3 for Ar–CONH—; and 4 for Ar–SO_2NH_2. The contribution of each function is fixed, and for most molecules the assumption of simple additivity of N values (essentially H-bond formation) works well. The assumption of additivity (and, hence, of independence of substituent contributions) may be even less rigorous for transport properties than it is for partition or solubility properties, but it provides a convenient estimate and has some experimental support (Pugh et al 1996; Mayer et al 2000).

It may also be questionable whether the N parameter derived from octanol–water partitioning can be applied, as is, without any modification in the skin permeability case. In this work, we maintained its value unaltered because of the apparently close relationship between log $P_{o/w}$ and log $\mathscr{P}_s$, and because presently available data on log $\mathscr{P}_s$ do not allow the deduction of as clear rules as it was possible from the considerably larger experimental data on log $P_{o/w}$. N is related only to the hydrogen bond

accepting ability, but solvatochromic-based approaches indicate that for skin permeability/partition hydrogen bond donor ability might also play some (albeit not a very significant) role (Abraham et al 1995; Potts & Guy 1995). For the limited number of acids (diclofenac, indometacin, naproxen, salicylic acid) or phenols present in this database, where hydrogen bond donor ability may be most relevant, we found calculated values using the unmodified N values of the QLogP model to agree reasonably well with the experimental log $\mathscr{P}_s$ data (Table 1). Indometacin is one of the strongest deviants, but its log $P_{o/w}$ is also mispredicted.

Using the two parameters of the QLogP approach for a linear regression, we obtained:

$$\log \mathscr{P}_s(\text{cm s}^{-1}) = -5.94(\pm 0.12) + 0.0127(\pm 0.0014)\,V_e - 0.491(\pm 0.036)\,N \quad (19)$$

$n = 98$, $r^2 = 0.723$, $\sigma = 0.623$, $F = 124$

The performance of this fully predictive method that uses no experimental data is only marginally worse than that of the PG approach (equation 16) that is based on experimental log P values and uses two parameters that are clearly interrelated. To verify the stability, consistency, and the predictive ability of this model, a "leave one group out"-type test was also performed. First, the 98 data were divided into five almost equal subsets by putting every fifth compound of the alphabetical list into a separate subgroup, as this seemed to provide sufficiently random groups from a chemical perspective. Then, 80 data from four of these groups (plus the first or the first two compounds of the fifth group if needed) were used for linear regression, and the remaining 18 data were used to test the predictive ability of the obtained equations. Not surprisingly (considering the very low number of adjustable parameters), the model proved to be very stable: in the five different equations obtained, no regression coefficient varied with more than 7% of its value as compared with equation 19. The regression coefficient of V_e ranged from 0.0122 to 0.0136 and that of N from -0.482 to -0.518. The predictive ability, as tested by this method, was also reasonable: the root mean squared errors (MSE) for the 18 compounds used for prediction were in the range 0.500–0.716, and were not very different from the MSEs of the corresponding "training" sets (0.590–0.637).

From a predictive perspective alone this is already good enough, but from a physicochemical perspective there still are two somewhat troubling aspects regarding the coefficients of this equation. First, the value of the coefficient of V_e is only about half of that describing the size dependence obtained for alcohols (0.020, Figure 4), whereas within a physicochemically consistent approach

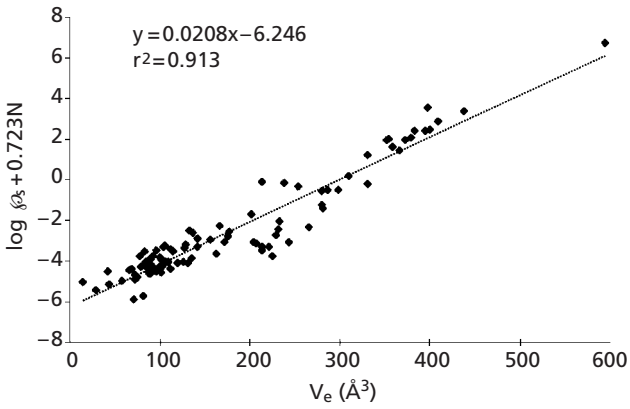

Figure 5 Size dependence of the N-corrected log $\mathscr{P}_s$ values. The dashed line represents the trend-line described by equation 20.

one would expect it to be in the same range. Second, if N is indeed related to hydrogen-bonding changes during the transfer between the two phases, the coefficient of N is related to the free energy of hydrogen bonds, and therefore its value should be closer to the statistically much better defined value of 0.723 obtained for log $P_{o/w}$. While this 0.723 value has been verified by now on close to a thousand quite reliable log P data including those of many simple monofunctionalized molecules, the present set contains less than a hundred log $\mathscr{P}_s$ data and mostly for multifunctionalized molecules, where intramolecular interactions can overshadow many effects. The number of affected hydrogen bonds (and hence N) may not be exactly the same for octanol–water transport as for stratum corneum–water transport, but the corresponding free energies per H-bond should not be very different. Hence, we built in this expected N-dependence into the regression by using log $\mathscr{P}_s + 0.723$N, and indeed obtained an excellent linear dependence on size (Figure 5):

$$\log \mathscr{P}_s(\text{cm s}^{-1}) + 0.723\text{N} = -6.25(\pm 0.14) + 0.0208(\pm 0.0007)\text{V}_e \quad (20)$$

$n = 98$, $r^2 = 0.913$, $\sigma = 0.743$, $F = 1010$

Fortunately, the obtained slope is essentially identical with that obtained earlier for monofunctionalized alcohols, proving the consistency of this approach and the applicability of the N parameter for this type of modelling (Figure 5). Furthermore, we investigated how the correlation coefficient between size (V_e) and the N-corrected log permeability coefficient (log $\mathscr{P}_s + aN$) depends on the value of the N coefficient (a). As Figure 6 illustrates, there is a broad maximum around $a \approx 0.8$. This might represent further evidence supporting the idea that the value of this coefficient, which is assumed

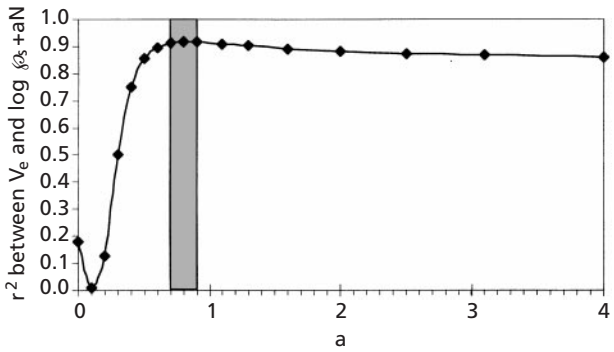

Figure 6 The correlation coefficient between size (V_e) and the N-corrected permeability coefficient ($\log \mathscr{P} + aN$) has a broad maximum around $a \approx 0.8$ (within the shaded area), in good agreement with the expectation that a should be around 0.723. The value at $a = 0$ corresponds to the correlation coefficient (r^2) between V_e and $\log \mathscr{P}$ (0.179), and at $a \to \infty$ to the correlation coefficient between V_e and N (0.838).

to be related to the free energy of H-bonding, should be in the 0.7–0.8 range, as suggested by our previous octanol–water partition studies. As mentioned in our previous publications (Bodor & Buchwald 1997; Buchwald & Bodor 1998b, c), this value of the N-coefficient ($a = 0.723$) gives a free energy change corresponding to a change of $\triangle N = 1$ ($\triangle G_N{}^0 = 0.723RT \ln 10 = 4.2$ kJ mol^{-1}) that is in excellent agreement with the generally accepted free energy of hydrogen bonds in water (4–5 kJ mol^{-1}) (Grant & Higuchi 1990; Jeffrey & Saenger 1994).

Even if V and N are clearly unrelated from a physicochemical perspective, they are intercorrelated, especially for drug-like compounds (more hydrogen bonding sites also mean bigger size). As already mentioned in relation to equation 16, since these parameters have opposing effects on permeability, there is some freedom in choosing their exact contributions without significantly altering the quality of the correlation. In fact, because of the highly biased, drug-like nature of the present dataset, V_e and N are unusually strongly intercorrelated here (Figure 6), but this is not the case for more general datasets.

When directly comparing experimental and calculated values, the two models based on equations 19 and 20 give a similar description of the data (r^2 of 0.723 and 0.707, respectively). Equation 19 obtained by direct linear regression, obviously, gives a somewhat better correlation with the experimental data, but the slope and the intercept are better for equation 20. At present, we would recommend the use of equation 19 for prediction purposes, as it gives smaller standard deviation. However, if further evidence from the permeability of other biomembranes also supports the correctness of a 0.7–0.8 N-coefficient, equation 20 might give a more accurate picture of the phenomena.

Conclusions

The present, entirely structure-based predictive method (equations 19 and 20) seems well suited for skin permeability prediction. The corresponding equations not only decouple the parameters of the original Potts & Guy approach, but also maintain its elegant simplicity and are consistent with a basic physicochemical model of the related phenomena.

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