A Predictive Algorithm for Skin Permeability: The Effects of Molecular Size and Hydrogen Bond Activity

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Purpose. To develop a predictive algorithm of nonelectrolyte transport through skin based upon a partitioning-diffusion model.
Methods. Drug permeability is described by a partitioning-diffusion equation. Through free-energy relationships, partitioning is related to the drug's molecular volume (MV), and hydrogen bond donor (H_d) and acceptor (H_a) activity. Diffusion is related to the drug's MV using a theory of diffusion through lipid lamellae based on free-volume fluctuations within the lipid domain. These two explicit descriptions are combined to give an equation describing permeability in terms of the permeant's physical properties. The aqueous permeability coefficients of 37 nonelectrolytes through human epidermis were evaluated as a function of these physical properties using a multiple regression analysis.
Result. The results of the regression analysis show that 94% of the variability in the data can be explained by a model which includes only the permeant's MV, H_d and H_a. These results further provide an algorithm to predict skin permeability based upon the values of these parameters. In addition, the relative contribution of various chemical functional groups (e.g., -COOH) is derived, and can be used to predict skin transport from drug structure alone.
Conclusions. A biophysically relevant model of drug transport through human skin is derived based solely on the physical properties of the drug. The model provides an algorithm to predict permeability from the drug's structure and/or physical properties. Moreover, the model is applicable to a number of lipid barrier membranes, suggesting a common transport mechanism in all.

KEY WORDS: percutaneous absorption; skin permeability; membrane transport; membrane-water partitioning.

INTRODUCTION

The barrier function of human skin is important both to the transdermal administration of drugs and to the uptake of toxic chemicals following dermal exposure. As a result, several models to predict molecular transport through human skin have been developed (1–7). While some of these models are empirical, and predict transdermal flux without providing mechanistic insight, others (e.g., 2,3) describe partitioning into, and permeation through human stratum corneum (SC) in a physicochemically rigorous fashion to derive a model consistent with transport through the extracellular lipid domain. Such analyses lead one to conclude that the free energy of solute transfer into SC lipids is a function of the size, polarity and hydrogen bonding ability of the permeant; group contribution terms for several molecular substituents can be derived. In a different approach (8), a solubility-diffusion model has been used to describe percutaneous penetration, approximating the partitioning (solubility) of drug into SC lipids by the linear sum of the partition coefficients for the same compound between pure organic phases and water. It was then deduced that transport was independent of permeant size (as judged by molecular weight), a finding which is inconsistent with diffusion theory. Previously, we extended the solubility-diffusion model of Kasting *et al.* (1) and approximated the partitioning term with the permeant octanol-water partition coefficient (K_{oct}) (6). We derived an explicit dependence of diffusivity, and hence permeability, on the molecular size of the permeant, consistent with results obtained in other lipid-based membranes. While the resulting model provided satisfactory predictive capability, the use of K_{oct} disguised specific molecular details important to drug transport through the skin.

Molecular partitioning between an organic phase and water has been explained in terms of physical chemistry (8,10–14); for example, partitioning between an organic phase and water, and between lipid membrane phases and water, can be very accurately described by a transfer free energy model (10–14). Here, we incorporate such a model into a solubility-diffusion description of drug transport through human SC to derive a new algorithm which [A] provides an even more accurate description of permeability, and [B] yields insight into the molecular details of drug-lipid interactions during transport through the SC.

MODEL AND METHODS

For nonelectrolyte transport through lipid membranes (bounded on both sides by an aqueous milieu), the permeability coefficient (P) is defined by Equation 1

$$P = K_m \cdot D/\delta \quad (1)$$

where K_m is the membrane-water partition coefficient of the solute, D is its diffusivity through the membrane, and δ is the diffusion pathlength. The membrane-water partition coefficient is difficult to measure directly, and often it is approximated by an organic phase-water partition coefficient (K_{org}). Empirically K_m is related to K_{org} by Equation 2

$$\log K_m = \alpha \cdot \log K_{org} + \gamma \quad (2)$$

where α and γ are constants. If α is close to unity, and γ negligible, then the organic phase chosen may be considered to be an adequate partitioning model for the membrane of interest (2,3,15).

Solute diffusivity through a lipid membrane can be predicted theoretically from statistical fluctuation considerations (16,17), and has been shown experimentally (18,19) to conform to Equation 3,

$$D = D_0 \exp(-\beta' \cdot MV) \quad (3)$$

where β' is a constant, and D_0 is the diffusivity of a hypothetical molecule having MV = 0. Substitution of Equations 2 and 3 into Equation 1 gives, upon rearrangement, Equation 4, which describes P in terms of the permeant's size and organic-water partitioning,

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$$\log P = \alpha \cdot \log K_{org} - \beta \cdot MV + \log D_0/\delta \quad (4)$$

where $\beta = \beta'/2.303$, and we have assumed (based on our earlier analyses (6)) that $\gamma \ll \log D_0/\delta$ and can therefore be ignored.

The organic phase-water partition coefficient can be more explicitly represented (8,10–13) in terms of the solute's MV and dipolarity/polarizability (π), hydrogen bond donor (H_d) and acceptor activity (H_a), and molar refractivity (R_2).

$$\log K_{org} = a_1 \cdot MV + a_2 \cdot \pi + a_3 \cdot H_d + a_4 \cdot H_a + a_5 \cdot R_2 \quad (5)$$

The R_2 and π terms reflect the polarity of the solute, while H_d and H_a reflect its hydrogen bonding activity. The molecular volume term combines effects which both favor and diminish partitioning into the organic phase. The effects favoring partitioning are solute-solvent interactions (van der Waals and dispersion forces), which involve (induced) dipole-dipole interactions and therefore, increase with the size of the molecule. The unfavorable term is due to the free energy cost associated with the formation of a free-volume "cavity" within the solvent of sufficient size to accommodate the solute. Equation 5 is a general relationship for any organic phase; different values of the coefficients ($a_1 \ldots a_5$) reflect the physicochemical properties of the organic phase. Solute partitioning into lipid membranes is considered to be different from that into bulk hydrocarbon (20–22) primarily due to the requirement for configurational disordering of the lipid alkyl chains in "cavity" formation. Nevertheless, Equation 5 has been used empirically to predict membrane associated processes such as anesthetic potency (8,13), and drug transport across the blood-brain barrier (14).

Substitution of Equation 5 into Equation 4 yields an expression for the permeability coefficient independent of an arbitrarily selected organic phase-water partition coefficient and dependent only on the permeant's physical properties.

$$\log P = [a_1 - \beta] \cdot MV + a_2 \cdot \pi + a_3 \cdot H_d + a_4 \cdot H_a + a_5 \cdot R_2 + \log (D_0/\delta) \quad (6)$$

Equations 4, 5, and 6 have been used to evaluate, by multiple linear regression (Statworks), published permeability data for 37 chemicals transporting through human epidermis. The results are presented as the regression coefficient and the associated standard error, the coefficient of determination (r^2), and the F-statistic. Only those terms which resulted in the maximal value of F were included in the regression analysis; all other terms were omitted. The studies, from which the experimental permeability values were obtained (4), were performed at temperatures close to 25°C using nonelectrolyte permeants applied to the epidermal surface in an aqueous solution. Values of MV (23), H_d, H_a, π, R_2 (13), K_{oct}, K_{hep} and K_{hex} (5,8) were also obtained from the literature, and are shown in Table 1.

RESULTS AND DISCUSSION

The permeability coefficients analyzed are presented in Table 1. The Table also includes the octanol-water (K_{oct}), heptane-water (K_{hep}) and hexadecane-water (K_{hex}) partition coefficients, the dipolarity/polarizability values (π), the hydrogen bond donor (H_d) and acceptor (H_a) activities, and the molar refractivity (R_2) and molecular volume (MV) of each permeant. The chemicals comprise a subset of those previously considered (6), and were chosen because all of the desired physical properties were available. These compounds cover a reasonably broad range of structure, physical properties and size ($10.6 < MV\ (cm3/mol) < 114$; $-1.4 < \log K_{oct} < 4.24$). Nevertheless, it should be said that further effort needs to be undertaken to expand the complement of chemicals included. In particular, the calculations must be extended to polyfunctional species, and to datasets in which collinearity between certain physicochemical parameters (e.g., K_{oct} and MV) is eliminated or minimized. Furthermore, although a case can be made for eliminating some of the P values in Table 1 on the grounds that their values may be questionable, we have chosen, in this initial examination, not to do so (preferring rather to weight all published results equally).

Analysis of the permeability coefficient data in Table 1 using the solubility-diffusion model (Equation 4), which was described in our original paper (6), is presented in Table 2. The results with octanol are similar to those obtained previously (6) and show that 84% of the variability in P can be described by this simple model of lipid-lamella limited transport through the SC. The regression coefficient associated with K_{oct} is ~1, suggesting that the octanol is a reasonable model for solute partitioning into SC lipids, in agreement with experimental findings (2). These results also show that epidermal transport decreases exponentially with increasing permeant volume, again consistent with a lipid lamella-based route of penetration through the SC. Repeating the regression analysis (again, using Equation 4) with either K_{hep} or K_{hex} (instead of K_{oct}) also results in statistically significant fits to the data; however, a clear physical interpretation of the outcome is lacking. In particular, these regressions yielded no MV-dependence, and the regression coefficient α was significantly less than unity for both solvents, suggesting that neither was an adequate partitioning model for SC lipids. It is possible, therefore, that previous studies, which have reported no dependence of P on MV (5,24), reached this conclusion because of an inappropriate choice of the organic phase-water partition coefficient.

To better examine and define the role of partitioning in membrane transport, the K_{org} values were subjected to a multiple regression analysis using Equation 5. The results are shown in Table 3. For each dataset, (a) there was significant correlation ($r > 0.80$) between π and R_2, and (b) inclusion of both π and R_2 in the analysis had no effect on the statistical significance of the F-value. Consequently, the R_2 term was omitted in the final analysis. Similarly, the π term in the K_{oct} regression was not significantly different from zero, and was omitted in the analysis of these partition coefficients. Previously published results (8), using a larger group of compounds (for which collinearity is not a significant problem), are essentially indistinguishable from those presented here. Similarly, our analyses mirror those of Abraham (13) with the exceptions (i) that we omitted the R_2 term, and (ii) that we calculated MV in a slightly different way. Nevertheless, Abraham (13) also showed, for octanol and hexadecane, that the regression coefficient for the R_2 term is much smaller than the other coefficients, and that its sign is inconsistent. Overall, these findings suggest that organic-

Table 1. Values of P (cm/s), MV (cm^3/mol), H_d, H_a, π, R_2, K_{oct}, K_{hep} and K_{hex} for a Series of Nonelectrolyte Compounds

Compound	log P	Π	H_d	H_a	MV	R_2	log K_{oct}	log K_{hex}	log K_{hep}
water	−6.85	0.45	0.82	0.35	10.6	0.00	−1.38	−4.38	
methanol	−6.68	0.44	0.43	0.47	21.7	0.28	−0.73	−2.42	−2.80
methanoic acid	−7.08	0.60	0.75	0.38	22.3	0.30	−0.54	−3.93	−3.63
ethanol	−6.66	0.42	0.37	0.48	31.9	0.25	−0.32	−2.24	−2.10
ethanoic acid	−7.01	0.65	0.61	0.45	33.4	0.27	−0.31	−3.28	−2.90
n-propanol	−6.41	0.42	0.37	0.48	42.2	0.24	0.34	−1.48	−1.52
n-propanoic acid	−7.01	0.65	0.60	0.45	43.6	0.23	0.26	−2.64	−2.14
butane-2-one	−5.90	0.70	0.00	0.51	49.4	0.17	0.28	−0.25	−0.25
benzene	−4.51	0.52	0.00	0.14	50.0	0.61	2.00	2.29	
diethyl ether	−5.35	0.25	0.00	0.45	52.0	0.04	0.83	0.66	
n-butanol	−6.16	0.42	0.37	0.48	52.4	0.22	0.88	−1.08	−0.70
n-butanoic acid	−6.36	0.62	0.60	0.45	53.9	0.21	0.79	−1.92	−0.96
phenol	−5.64	0.89	0.52	0.30	53.9	0.81	1.46	−0.70	−0.82
toluene	−3.56	0.52	0.00	0.14	60.0	0.60	2.70	2.89	
styrene	−3.75	0.65	0.00	0.16	60.2	0.85	2.95		
n-pentanol	−5.78	0.42	0.37	0.48	62.6	0.22	1.40	−0.39	
benzyl-OH	−5.78	0.87	0.33	0.56	64.0	0.80	1.10	−0.62	
n-pentanoic acid	−6.01	0.60	0.60	0.45	64.1	0.21	1.33	−1.31	0.44
2-chlorophenol	−5.04	0.88	0.32	0.31	66.0	0.85	2.15		
4-chlorophenol	−5.00	1.08	0.67	0.20	66.0	0.92	2.39	−1.31	−0.12
m-cresol	−5.38	0.88	0.57	0.34	67.6	0.82	1.96		
o-cresol	−5.36	0.86	0.52	0.30	67.6	0.84	1.95		
p-cresol	−5.29	0.87	0.57	0.31	67.6	0.82	1.96		
4-bromophenol	−5.00	1.17	0.67	0.20	70.0	1.08	2.59	−0.11	−0.20
4-nitrophenol	−5.81	1.72	0.82	0.26	71.0	1.07	1.96	−2.0	−2.15
3-nitrophenol	−5.81	1.57	0.79	0.23	71.0	1.05	2.00	−1.4	−1.23
2-nitrophenol	−4.56	1.05	0.05	0.37	71.0	1.02	1.80	−1.4	1.04
ethylbenzene	−3.48	0.51	0.00	0.15	72.3	0.60	3.15		
n-hexanol	−5.45	0.42	0.37	0.48	72.9	0.21	2.03	0.11	0.45
n-hexanoic acid	−5.44	0.60	0.60	0.45	74.3	0.17	1.89	−0.85	0.24
β-naphthol	−5.11	1.08	0.61	0.40	79.5	1.52	2.84	1.77	0.30
n-heptanol	−5.05	0.42	0.37	0.48	83.1	0.21	2.49	0.77	1.01
n-heptanoic acid	−5.28	0.60	0.60	0.45	84.6	0.15	2.33	−0.29	1.16
n-octanol	−4.84	0.42	0.37	0.48	93.3	0.20	3.15	1.62	1.65
n-octanoic acid	−5.21	0.60	0.60	0.45	94.8	0.15	2.83	0.41	1.95
n-nonanol	−4.77	0.42	0.37	0.48	104	0.19	3.68	1.97	2.28
n-decanol	−4.66	0.42	0.37	0.48	114	0.19	4.24	2.56	2.91

water partitioning depends only marginally, if at all, on the solute's molar refractivity.

The regression results show that nonelectrolyte partitioning from an aqueous solution increases with increasing solute size, reflecting increased van der Waals and dispersion attractive forces between the solute and the organic phase relative to those between the solute and water. These attractive terms dominate the unfavorable energy associated with the formation of a free-volume "cavity" within the organic phase; hence, the positive coefficient. The MV effect is greatest for alkanes, indicating greater hydrophobic attractive forces in these solvents relative to octanol.

Table 2. A Multiple Regression Analysis of the Permeability Coefficient Data in Table 1 Using Equation 4: $\log P = \alpha \cdot \log K_{org} - \beta \cdot MV + \log D_0/\delta$

Solvent	$10^2 \cdot \beta$ (cm^3/mol)	α	log D_0/δ	r^2	F	n
Octanol	3.80	1.19	−5.06	0.84	88	37
	(0.73)	(0.13)	(0.29)			
Heptane	nsd[a]	0.43	−5.53	0.79	113	33
		(0.04)	(0.67)			
Hexadecane	nsd[a]	0.38	−5.42	0.70	59	27
		(0.05)	(0.95)			

[a] nsd Not statistically different from zero.

The hydrogen bonding terms show that increased solute hydrogen bond acceptor and donor activity resulted in decreased partitioning into the organic phase due to the free energy cost associated with the disruption of hydrogen bonds in the aqueous phase. In each case, however, a smaller decrease was seen for octanol due to the finite hydrogen bonding ability of, and water solubility in, this solvent. In other words, hydrogen bonding solutes are better accommodated in octanol than in alkanes. The H_d regression coefficients show that solutes with hydrogen-bond donating ability partition least well into alkanes. This expected result is, of course, completely consistent with the relative hydrogen bond acceptor activity of the solvent phases involved and their respective H_a values: octanol (0.48) *versus* alkane (0). The regression on K_{oct}, however, showed only a weak inverse dependence on the solute hydrogen bond acceptor activity (H_a), whereas partitioning into the two alkane

Table 3. A Multiple Regression Analysis of the Organic-Water Partition Coefficients in Table 1 Using Equation 5: $\log K_{org} = a_1 \cdot MV + a_2 \cdot \pi + a_3 \cdot H_d + a_4 \cdot H_a$ (also shown are comparable results obtained elsewhere (8))

Solvent	$10^2 \cdot a_1$ (cm^3/mole)	a_2	a_3	a_4	r^2	F	n
Octanol	5.63	nsd[a]	−4.09	−0.51	0.98	478	37
	(0.14)		(0.20)	(0.09)			
Heptane	6.50	−2.90	−4.80	−1.49	0.95	124	33
	(0.32)	(0.39)	(0.48)	(0.24)			
Hexadecane	5.84	−2.65	−5.17	−1.51	0.85	31	27
	(0.60)	(0.69)	(0.91)	(0.47)			
From reference 8:							
Octanol	5.83	0.15	−3.51	−0.74	0.99	249	78
	(0.53)	(0.23)	(0.38)	(0.31)			
Heptane	6.78	−3.45	−5.35	−1.02	0.99	438	75
	(0.69)	(0.30)	(0.50)	(0.39)			

[a] nsd Not statistically different from zero.

phases was emphatically inversely related to H_a. This result implies that hydrogen bond acceptors are not well-accommodated in alkanes as compared to octanol. Whereas octanol is capable of donating a hydrogen bond via the hydroxyl group, heptane and hexadecane cannot do so. Partitioning decreased in the hydrocarbon solvents with increasing solute polarity (π); no significant dependence on π was found for octanol, however, presumably reflecting the finite solubility of water in this phase. Thus, aqueous-organic partitioning can be described in terms of the free energy of solute transfer between phases and can ultimately be related to the physical properties of both phases.

A multiple regression analysis of the epidermal permeability data in Table 1 was performed using Equation 6. A statistically improved fit of these data was obtained (see Table 4) by *omitting* the π and R_2 terms. The implication, therefore, is that the transport of permeants across the SC (when 'delivered' from aqueous solution) is primarily controlled by the molecular size and hydrogen bond activity. Comparison of Tables 2 and 4 shows that the extended relationship involving H_a and H_d (Equation 6) significantly improves the fit of the data to the model (which is now independent of the organic phase considered). The a_3 and a_4 coefficients in Table 4 are negative, confirming that stratum corneum permeability is inversely related to the permeant's hydrogen bonding ability (as measured by H_a and H_d). However, these values clearly differ from the corresponding coefficients associated with organic phase-water partitioning (Table 3). The permeability regression implies that the SC is better able to accept H-bonds than octanol (a_3 for the K_{oct} regression is -4.09 ± 0.20), whereas octanol better accommodates H-bond acceptors (a_4 for the K_{oct} regression is -0.51 ± 0.09). In the latter situation, the SC lipids behave more like a pure hydrocarbon (a_4 for the K_{hep} and K_{hex} regressions are *ca.* -1.5). Thus, while octanol-water mimics some of the characteristics of stratum corneum lipid-water partitioning, it fails to account for all relevant features.

Overall, the a_3 and a_4 values in Table 3 suggest that the organic solvents accommodate hydrogen bond acceptors better than H-bond donors, and that octanol is the most "forgiving" environment for such polar molecules (further emphasized by the lack of significant dependence upon solute π). The results in Table 4, on the other hand, imply that the SC lipids accept hydrogen bonds better than they donate but that, like octanol, polar species can be accommodated more easily in the SC than in alkane solvents (*vi.* the absence of π dependence again). These conclusions may be compare with those of a previous study (3), which reported the free energies of partitioning of various solutes into SC, octanol and heptane. Solutes containing substituents which could both donate an accept hydrogen bonds (e.g., $-CONH_2$, -COOH, and -OH) partition similarly into SC and octanol, but less favorably into heptane. Conversely, when these substances were replaced by groups which could only *accept* hydrogen bonds (e.g., $-CON(CH_3)_2$) and $-COOCH_3$), the free energies of partitioning into the SC were more similar to those into heptane than those into octanol. It follows, then, that the most appropriate partitioning model for stratum corneum lipids is neither octanol-water nor hydrocarbon-water; rather, the "correct" model depends upon the properties of the solute.

Next, we turn to the dependence of the permeability upon molecular size (i.e., MV). The original solubility-diffusion model (Equation 4, Table 2) indicated the expected inverse dependence of P upon MV (characterized by the negative regression coefficient $\beta = -3.80(\pm 0.73) \times 10^{-2}$ cm^3/mol). Quantitatively, this result was consistent with our previous examination of a larger dataset of P values using molecular weight (as opposed to MV) to characterize permeant size. However, multiple regression analysis with the extended model (Equation 6, Table 4) results a MV-coefficient which is positive ($2.50(\pm 0.18) \times 10^{-2}$ cm^3/mol).

Table 4. A Multiple Regression Analysis of the Permeability Coefficient Data in Table 1 Using Equation 6: $\log P = [a_1 - \beta] \cdot MV + a_3 \cdot H_d + a_4 \cdot H_a + \log (D_0/\delta)$

$10^2 \cdot [a_1 - \beta]$ (cm^3/mole)	a_3	a_4	$\log (D_0/\delta)$	r^2	F	n
2.56	−1.72	−3.93	−4.85	0.94	165	37
(0.16)	(0.16)	(0.33)	(0.18)			

Table 5. Incremental Permeabilities (Δ log P) of Various Functional Groups Calculated from the Regression Coefficients in Table 4 and Equation 7: Δ log P = 0.0256 (±0.0018) · ΔMV − 1.72(±0.16) · ΔH_d − 3.93 (±0.33) · ΔH_a, Where MV (23) ΔH_a and ΔH_d (25) Values were Obtained from the Literature (the Error Associated with Each Value is Shown in Parentheses)

Functional Group	ΔH_a	ΔH_d	ΔMV (cm^3/mole)	Δ log P	
				Equation 7	Refs. 2,3
-OH	0.48	0.32	8.0	−2.23 (0.22)	−1.70
-COOH	0.45	0.55	19.7	−2.21 (0.29)	−1.06
$-CONH_2$	0.78	0.25	22.2	−2.93 (0.25)	−1.90
$-COOCH_3$	0.45	0.00	30.6	−0.99 (0.13)	−1.06
$-CON(CH_3)_2$	0.78	0.00	43.4	−1.95 (0.20)	−1.84
$-CH_2-$	0.00	0.00	10.2	0.26 (0.02)	0.31

This is because this coefficient now represents a combination of physical phenomena: the impact of molecular size on partitioning *and* diffusion. Intuition dictates that increasing MV increases the hydrophobic surface area and that this will increase partitioning into (and hence, permeability through) a lipid membrane. Conversely, larger molecules diffuse more slowly since they require more "space" to be created in the medium, and this in turn leads to diminished permeability. The positive value of the MV-coefficient in Table 4 (a_1-β) argues that partitioning effects dominate.

In addition to providing mechanistic insight into skin transport, the results described here allow prediction of steady-state skin permeability coefficients based solely upon the permeant's size and hydrogen bonding activity. The predicted values are more accurate than those obtained using the simpler model (6), and the roles of both the solute's MV and hydrogen bonding activity in the determination of permeability can be deduced. Given that MV can be calculated from the molecular structure (23), and that H_d and H_a values for various chemical substituents have been compiled (25), it is also possible to calculate the contribution of different functional groups to the incremental permeability (Δ log P) using Equation 7 and the regression coefficient values in Table 4.

$$\Delta \log P = 0.0256 \cdot \Delta MV - 1.72 \cdot \Delta H_d - 3.93 \cdot \Delta H_a \quad (7)$$

This analysis (Table 5) shows, for example, that the addition of a $-CH_2-$ group results in a two-fold increase in P, similar to experimental measurements of the permeabilities of n-alkanols through human skin (26). In contrast, the addition of a carboxyl group decreases P by about 40-fold, due to the free energy cost associated with disruption of hydrogen bonds. Anderson *et al.* (2,3) calculated the functional group contributions to skin transport for series of hydrocortisone and p-methyl phenol analogs containing these same substituents. The results of this alternative analysis are also shown in Table 5, and compare very well with the values derived here, suggesting that size- and hydrogen bond-dependent partitioning is the physical basis for predicted changes in permeability. Similarly, Pugh & Hadgraft (7) have analyzed the effect of functional substituents on drug transport through human skin and found generally similar results. However, it should be stated that, while functional group contributions are valuable for predicting drug flux, their utility is limited to substituents with no interactions. For example, the skin permeability coefficient of 2-nitrophenol is ~20-times greater than those of 3-nitrophenol and 4-nitrophenol (Table 1) due to the formation of an intramolecular hydrogen bond between the hydrogen bond donor ($-NO_2$) and acceptor (-OH) groups when they are situated adjacent to each other on the ring (an effect which increases the net lipophilicity of the molecule).

In conclusion, drug permeation through human skin can be accurately described by a simple model based on transport through stratum corneum lipid domains. [Self-evidently, this conclusion holds only for those compounds for which the SC is the rate-limiting barrier. As pointed out elsewhere (e.g., 4,27,28), our analysis is inadequate in its present form to predict the P of very lipophilic chemicals whose penetration is determined by the underlying, aqueous, viable skin tissue]. The results provide mechanistic insight into the biophysical aspects of transport and yield a facile and accurate means to predict transport. Finally, the conclusions derived here may be generally applied to transport through other lipid membranes, e.g., the blood-brain-barrier (14). Thus, the general nature of the approach holds promise for similar predictive paradigms in other medically relevant barrier membranes.

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NOTE ADDED IN PROOF

A similar approach was recently published by Abraham *et al.* (29).

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