Predicting Skin Permeability

Russell O. Potts[1,3] and Richard H. Guy[2]

Received May 20, 1991; accepted November 19, 1991

Published permeability coefficient (K_p) data for the transport of a large group of compounds through mammalian epidermis were analyzed by a simple model based upon permeant size [molecular volume (MV) or molecular weight (MW)] and octanol/water partition coefficient (K_{oct}). The analysis presented is a facile means to predict the percutaneous flux of pharmacological and toxic compounds solely on the basis of their physicochemical properties. Furthermore, the derived parameters of the model have assignable biophysical significance, and they provide insight into the mechanism of molecular transport through the stratum corneum (SC). For the very diverse group of chemicals considered, the results demonstrate that SC intercellular lipid properties alone are sufficient to account for the dependence of K_p upon MV (or MW) and K_{oct}. It is found that the existence of an "aqueous-polar (pore) pathway" across the SC is not necessary to explain the K_p values of small, polar nonelectrolytes. Rather, their small size, and consequently high diffusivity, accounts for their *apparently* larger-than-expected K_p. Finally, despite the size and breadth of the data set (more than 90 compounds with MW ranging from 18 to >750, and log K_{oct} ranging from −3 to +6), the postulated upper limiting value of K_p for permeants of very high lipophilicity cannot be determined. However, the analysis is able to define the physicochemical characteristics of molecules which should exhibit these maximal K_p values. Overall, then, we present a facile interpretation of a considerable body of skin permeability measurements that (a) very adequately describes the dependence of K_p upon permeant size and lipophilicity, (b) generates parameters of considerable physicochemical and mechanistic relevance, and (c) implies that the SC lipids alone can fully characterize the barrier properties of mammalian skin.

KEY WORDS: skin permeability; partition coefficient; molecular volume; lipid lamellae; stratum corneum.

INTRODUCTION

The skin's barrier function is important both to the transdermal delivery of drugs and to risk assessment following dermal exposure to toxic chemicals. A significant data base of transdermal delivery rates and associated physical properties has been compiled for a broad range of compounds. These data should, in theory, provide the means to develop predictive models of percutaneous absorption. Furthermore, such predictive models should be consistent with transport mechanisms. To date, skin transport data have often been explained using a model with distinct permeation behavior for compounds of specific polarities (1–4). For example, it has been postulated that very polar compounds traverse the lipophilic stratum corneum (SC) via "aqueous pores," while the transport of very nonpolar compounds is limited by their transfer from the SC into the aqueous, subadjacent tissue. For compounds of intermediate polarity, SC permeability appears to be linearly related to the membrane/water partition coefficient (K_m) of the permeant. While this model is consistent with experimental observation, there is no physical evidence supporting the existence of "aqueous pores," and there is no clear indication of where one regime ends and the next begins.

We have analyzed existing skin permeability data from a variety of sources using a simple model which depends only upon the size of the permeant and its octanol/water partition coefficient (K_{oct}). The compounds analyzed range in molecular weight from 18 to over 750, possess log K_{oct} values between −3 and +6, and encompass broad therapeutic and structural classes. Despite the profound structural and physicochemical diversity of these compounds, we believe that the simple model proposed is sufficient to explain the permeability behavior of the entire dataset. Further, the choice of parameters is based upon a mechanistic understanding of SC permeability. Thus, we suggest that the model is justified on the basis of simplicity, mechanistic relevance, and predictive ability.

THE MODEL AND APPLICATIONS

The steady-state transport of molecules through biological membranes is described as a solubility-diffusion process. The permeability coefficient (K_p), relating solute flux to the concentration gradient across the membrane, is expressed mathematically by Eq. (1),

$$K_p = K_m \cdot D_m/\partial \quad (1)$$

where K_m is the membrane/water partition coefficient of the permeant, D_m is the permeant diffusivity within the membrane, and ∂ is the diffusion pathlength. Because measurement of K_m is difficult, the more readily available octanol/water partition coefficient (K_{oct}) is often used instead. The use of K_{oct} in Eq. (1) predicts, most simplistically, that a plot of log K_p versus log K_{oct} should be linear with a slope of unity and intercept equal to log (D_m/∂). Data from Scheuplein and Blank for the transport of water and *n*-alkanols through human epidermis (5) are plotted in this way (i.e., as log K_p versus log K_{oct}) in Fig. 1. These results show that while log K_p of the larger, more lipophilic permeants increases linearly with increasing K_{oct}, the small, polar molecules deviate from this line. It is such an apparent independence of log K_p on log K_{oct} that has led to the hypothesis that these hydrophilic species transport via an "aqueous channel," in a manner independent of membrane partitioning (1–4).

Membrane transport as described above assumes that D_m remains constant for all permeants. However, even the simplest descriptions of diffusion predict an inverse relationship between D_m and permeant size (6). For SC (and other lipid membranes), it has been suggested that the functional dependence of D_m on molecular volume (MV) is exponential (7–10), i.e.,

[1] Cygnus Therapeutic Systems, 400 Penobscot Drive, Redwood City, California 94063.

[2] Departments of Pharmacy and Pharmaceutical Chemistry, University of California—San Francisco, San Francisco, California 94143.

[3] To whom correspondence should be addressed.

0724-8741/92/0500-0663$06.50/0

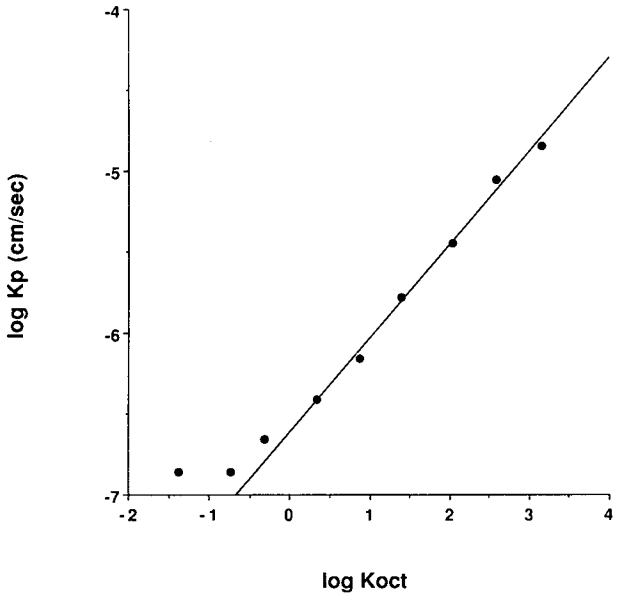

Fig. 1. A plot of log K_p versus log K_{oct} for water and *n*-alkanols (methanol through octanol). The data are from Scheuplein and Blank (5) for permeability through human epidermis. The line drawn is the best fit to the data from propanol to octanol.

$$D_m = D^0 \cdot \exp(-\beta \cdot MV) \quad (2)$$

where D^0 represents the diffusivity of a hypothetical molecule having zero molecular volume, and β is a constant. Substituting Eq. (2) into Eq. (1), followed by a logarithmic transformation and rearrangement, yields Eq. (3),

$$\log (K_p/K_{oct}) = \log (D^0/\partial) - \beta' \cdot MV \quad (3)$$

where $\beta' = \beta/2.303$. In Fig. 2, the data in Fig. 1 are replotted according to Eq. (3), using molecular volume values calculated by the method of Bondi (11). The linear correlation ($r^2 = 0.99$) is excellent, and values of 5×10^{-6} cm/sec and 0.03 mol/cm^3 are obtained for D^0/∂ and β', respectively.

The implication of the results presented in Fig. 2 is that the normalization of K_p by K_{oct} (i.e., $K_p/K_{oct} = D_m/\partial$) leads to an inverse dependence upon molecular volume for the compounds examined. Thus, the (apparently) anomalously high K_p for the smaller, more hydrophilic penetrants in Fig. 1 can be explained by their (relatively) high diffusivities, due to their small molecular volume.

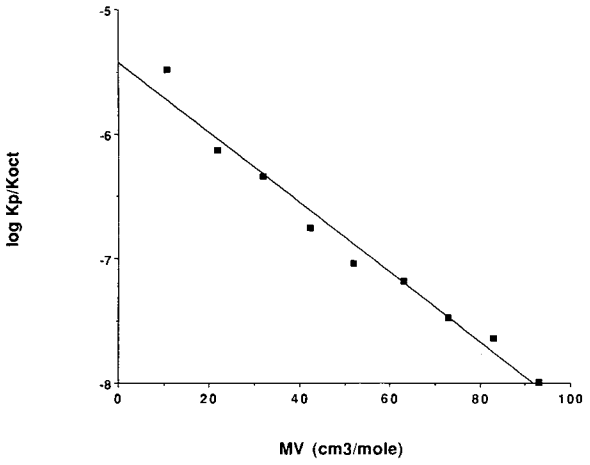

Fig. 2. The data from Fig. 1 replotted as log K_p/K_{oct} versus permeant molecular volume (MV).

The model, as expressed in Eq. (3), can be further refined. The implied equality between K_m and K_{oct} is an approximation which suffers from two flaws: (a) it assumes that the lipophilic environment of the SC is the same as that of octanol, and (b) it ignores the anisotropic nature of the SC lipid alkyl domains. The relationship between K_m and K_{oct} is better expressed, therefore, by Eq. (4) (12,13),

$$K_m = [K_{oct}]^f \quad (4)$$

where the coefficient f accounts for the difference between the partitioning domain presented by octanol and that presented by the SC lipids. It has been shown, for example, that a value of f less than unity implies that the partitioning domain of octanol is less polar than that of the membrane (13). Combination of Eqs. (1), (2) and (4) yields Eq. (5):

$$\log K_p = \log (D^0/\partial) + f \cdot \log K_{oct} - \beta' \cdot MV \quad (5)$$

It follows, then, that this model requires the multiple regression of log K_p upon log K_{oct} and MV. Such an analysis will provide values for f, β', and D^0/∂, all of which have assignable physicochemical significance.

Using a standard multiple linear regression program (RS1, BBN, Cambridge, MA), Eq. (5) was used to examine a number of different sets of percutaneous permeability data. It was first found that the data of Scheuplein and Blank (5) for water and *n*-alkanols are not well fit by the model. The reason is that, for this homologous series, K_{oct} and MV are codependent: each methylene group adds a (fairly) constant increment to both MV and log K_{oct}. To illustrate the potential of the model, therefore, we combined a number of data sets from Scheuplein and Blank (5) (water, *n*-alkanols, *n*-alkanoic acids, and alkanediols). The analysis of these data according to the model [Eq. (5)] yields the parameters presented in Table I and accounts for 89% of the variance in log K_p. Incorporation of data for 19 phenolic compounds [from a different source (14)] leads to only minor changes in the derived parameters (Table I) and maintains a very respectable correlation ($r^2 = 0.83$). Another data set, which has been cited as supportive of the existence of an "aqueous," polar pathway across the SC, is that of Ackermann *et al.* (3).

Table I. Multiple Regression Analysis of K_p Data Using Eq. (5): $\log\{K_p(\text{cm sec}^{-1})\} = \log(D_0/\partial) + f \cdot \log K_{oct} - \beta' \cdot MV$

Data	$\log(D_0/\partial)^a$	f^b	$10^3 \cdot \beta'^b$	r^2	n
A[c]	−5.9 ± 0.3	0.82 ± 0.13	17.6 ± 0.7	0.89	23
B[d]	−6.2 ± 0.2	0.74 ± 0.10	10.8 ± 0.6	0.83	42
C[e]	−5.7 ± 0.5	0.72 ± 0.07	9.5 ± 1.9	0.89	19

[a] D_0/∂ units are cm sec^{-1}.
[b] Value ± SD derived from multiple regression analysis.
[c] From Scheuplein and Blank (5).
[d] From Scheuplein and Blank (5); plus phenol data from Roberts *et al.* (14).
[e] From Ackermann *et al.* (3); values derived using K_{ether} were $\log(D_0/\partial) = -5.6 \pm 0.6$; $f = 0.50 \pm 0.06$; $\beta'' = -3.4\ (\pm 1.7) \times 10^{-3}$; $r^2 = 0.86$.

In this case, permeability through hairless mouse skin was measured, and the ether/water partition coefficient (K_{ether}) was used as the lipophilicity correlate (Fig. 3). It has been suggested previously that invoking a two-pathway explanation for these data is not justified on statistical grounds (15) and that a linear dependence of log K_p on log K_{ether} provides a perfectly adequate fit to the results for all compounds examined (*n*-alkanols, urea, thiourea, glycerol, glucose, and a series of hydrocortisone esters). Analysis of these data with Eq. (5) (replacing a K_{ether} by K_{oct}) also provides a statistically reasonable fit ($r^2 = 0.86$). In addition, the values of f and β' are very similar to those derived previously (Table I). Thus, the model, as described by Eq. (5), appears to apply equally well to human and mouse skin permeability data, for compounds spanning a broad range of physicochemical properties and structures.

For many compounds, molecular weight (MW) is often a reasonable approximation of molecular volume. We have analyzed the data above using Eq. (6) with MW in place of MV,

$$\log K_p = \log (D^0/\partial) + f \cdot \log K_{oct} - \beta'' \cdot MW \quad (6)$$

where β'' is a coefficient having significance similar to β' and includes a conversion factor for the substitution of MW for MV. These results are shown in Table II. Comparison of the coefficients in Tables I and II shows that analysis of the individual datasets by either Eq. (5) or Eq. (6) yields similar correlations; only the β'' and β' values differ because of the substitution of MW for MV.

Recently, Flynn has compiled an extensive data set of human epidermal permeability data, together with K_{oct} and MW, for about 90 chemicals (4). These compounds range in MW from 18 to over 750 and in log K_{oct} from -3 to $+6$. The plot of log K_p versus log K_{oct} (Fig. 4a) reveals no simple relation ($r^2 = 0.26$). However, a multiple regression on log K_{oct} and MW according to Eq. (6) provides a very reasonable fit ($r^2 = 0.67$) and values of the fitted parameters which are quite similar to the results obtained for the smaller data sets (see Table II).

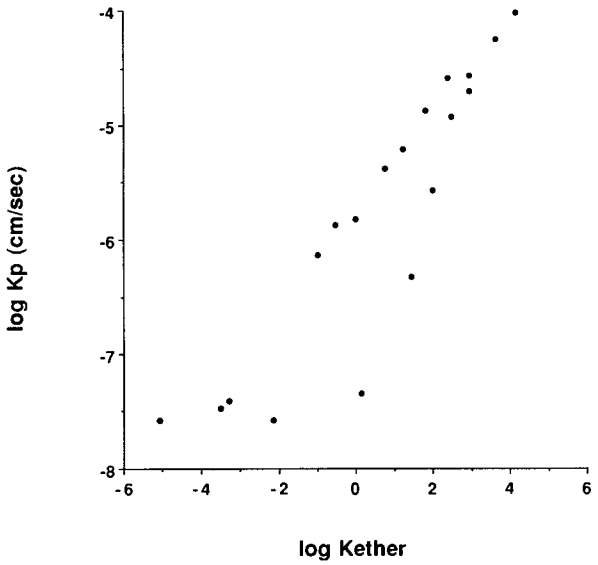

Fig. 3. A plot of log K_p versus log K_{ether} for *n*-alkanols, hydrocortisone alkyl esters, and other hydrophilic permeants. The data are from Ackermann *et al.* (3) using hairless mouse skin.

Table II. Multiple Regression Analysis of K_p Data Using Eq. (6): $\log\{K_p(\text{cm sec}^{-1})\} = \log(D_0/\partial) + f \cdot \log K_{oct} - \beta'' \cdot MW$

Data	$\log(D_0/\partial)^a$	f^b	$10^3 \cdot \beta''^b$	r^2	n
A[c]	-5.8 ± 0.3	0.81 ± 0.10	13.0 ± 4.0	0.90	23
B[d]	-6.0 ± 0.2	0.70 ± 0.09	5.0 ± 0.3	0.82	42
C[e]	-5.8 ± 0.4	0.62 ± 0.06	4.2 ± 0.1	0.89	19
D[f]	-6.3 ± 0.8	0.71 ± 0.06	6.1 ± 0.6	0.67	93

[a] D_0/∂ units are cm sec^{-1}.
[b] Value ± SD derived from multiple regression analysis.
[c] From Scheuplein and Blank (5).
[d] From Scheuplein and Blank (5), plus phenol data from Roberts *et al.* (14).
[e] From Ackermann *et al.* (3); values derived using K_{ether} were $\log(D_0/\partial) = -5.6 \pm 0.5$; $f = 0.48 \pm 0.05$; $\beta'' = -1.9 \pm 0.8 \times 10^{-3}$; $r^2 = 0.87$.
[f] Data from Flynn (4).

DISCUSSION

Equations (5) and (6) describe a simple model with which to predict skin permeability. Data obtained in different laboratories and with a broad range of compounds are

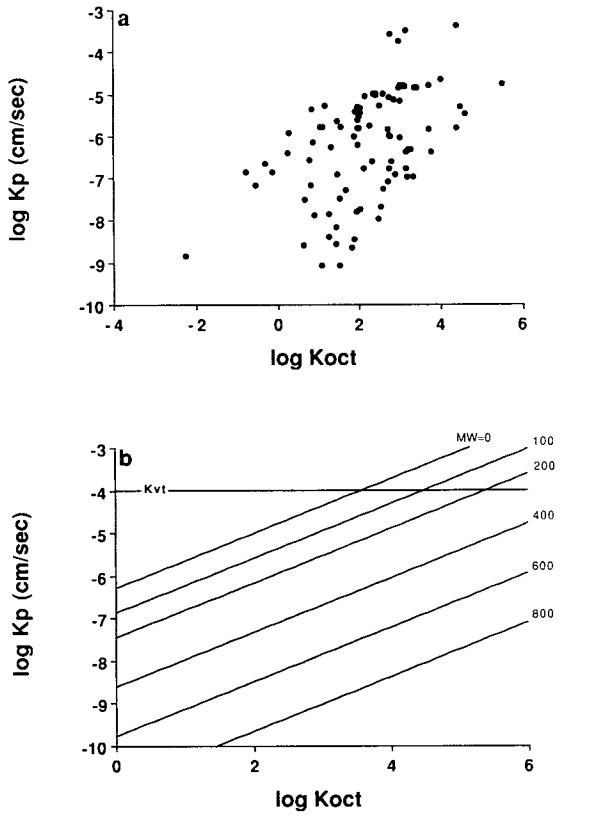

Fig. 4. (a) A plot of log K_p versus log K_{oct} for data compiled by Flynn (4). The permeability coefficients were measured through human epidermis. (b) A contour plot of the dependence of log K_p on log K_{oct} according to Eq. (6). The (constant) molecular weight for each contour is noted. The horizontal line represents a hypothetical upper limiting value of K_{vt} of 10^{-4} cm sec^{-1}.

well described by the model. In the most rigorous test of the model, data compiled by Flynn on ~90 compounds (4) were analyzed using MW instead of MV. The results of that analysis showed that 67% of the variability in the data is explained by the model. Further, there is no systematic variation in measured versus predicted K_p and no apparent relationship between those compounds showing the greatest positive (toluene and etorpine) and negative deviation (naproxen, estradiol, atropine, and aldosterone). Comparable results have been reported by Kasting *et al.* (9) using a similar model and over 30 compounds (different from those analyzed here). Given that 30% experimental variation in permeability data is not uncommon (15), the analysis suggests that the model completely describes the data. Analysis of data from individual laboratories [e.g., Scheuplein and Blank (5), and Ackermann *et al.* (3); see Table II] shows that more than 82% of the variation can be accounted for by the model. In addition, these results (compare Tables I and II) show that the substitution of MW for MV provides an equivalent fit. Kasting *et al.* similarly found that replacement of MV with MW reduced r^2 values by only about 0.05 (9). Thus, for compounds ranging in molecular weight from 18 to >750 and in log K_{oct} from −3 to +6, the permeability through human skin can be predicted by Eq. (7).

$$\log K_p\ (\text{cm sec}^{-1}) = -6.3 + 0.71 \cdot \log K_{oct} - 0.0061 \cdot \text{MW} \quad (7)$$

A contour plot of this dependence of log K_p upon log K_{oct} and MW is shown in Fig. 4b.

The results presented in Table II provide a quantitative estimate of the error associated with each parameter in the model. In particular, they show that both f and β'' in Eq. (7) have associated standard deviations of less than 10%. In addition, f and β'' have t values of 11.1 and −10.7, respectively, demonstrating that the probability of these results occurring due to random chance is less than 10^{-4} for each parameter. In addition, the upper and lower 95% confidence intervals of the predicted values of log K_p span an average value of 0.5 over the entire distribution. The predicted log K_p versus log K_{oct}, together with the 95% confidence intervals for chemicals of constant (400) MW, is shown in Fig. 5. These combined results demonstrate that the model fits the experimental data to a high level of statistical significance and predicts values of log K_p within rather narrow confidence limits.

In addition to its predictive ability, the model also provides mechanistic insight into the skin's barrier function. For example, the molecular volume dependence explicit in this model is consistent with transport through lipid lamellae (8). Lieb and Stein analyzed the permeability of a number of simple membranes (human and dog red blood cells, *Chara ceratophylla,* and black lipid membranes) (8) using Eq. (3) and derived values of β' which are in good agreement with the values derived here, suggesting a common mechanism of transport through all membranes. Cohen and Turnbull derived Eq. (2) from a statistical analysis of free-volume fluctuations in the diffusing medium (7). Stein and others have carried this argument further to suggest that the free-volume fluctuations originate from rotational isomerization along the lipid alkyl chains (8). Furthermore, several investigators

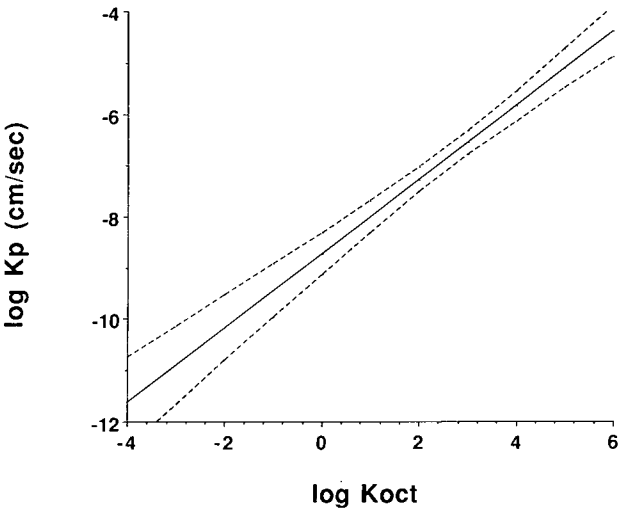

Fig. 5. A plot of log K_p versus log K_{oct} for compounds of constant (400) MW. The solid line is that predicted by Eq. (6); the dashed lines are the upper and lower 95% confidence intervals, which were determined from the statistics of the multiple regression analysis of the data in Ref. 4.

have pointed out that the reciprocal value of β' is a measure of the average free-volume available for diffusion. The β' values determined here suggest an average free volume of about 30 cm^3/mol. This value takes on particular significance in light of recent experimental results which show that water permeability through the SC is correlated with increased free volume within the lipid alkyl chains due to rotational isomerization (17). Interestingly, a value of 30 cm^3/mol is consistent with those calculated for the incremental free volume formed during rotational isomerization of the lipid alkyl chains (18). Thus, the molecular-volume dependence of SC permeability is (a) similar to that seen in other lipid membranes (8), (b) consistent with a lipid free-volume fluctuation model of permeant transport (7), and (c) supported by the results of experiments performed using mammalian SC (17).

Others have analyzed the molecular weight dependence of SC permeability using a power function (i.e., $D_m \sim \text{MW}^{\Phi}$) (19). While these analyses provide a reasonable statistical fit to the data, there is no physical significance to the exponent ϕ. In contrast, the choice of an exponential MV dependence [Eq. (2)] is justified on both experimental and theoretical bases. Also, the derived coefficient (β') has physical meaning. Thus, the use of Eq. (2) has physical and mechanistic relevance, as well as providing a statistically significant fit to the data.

While the dependence of log K_p on MV is very similar between SC and simpler lipid membranes, the value extrapolated to zero MV (D^0/∂) differs significantly. Whereas for simple membranes, D^0/∂ values near 10 cm sec^{-1} are obtained (8), those for SC are of the order of 10^{-6} cm sec^{-1}. In simple membranes, ∂ is equal to the bilayer thickness (i.e., about 50 Å), while D^0 is approximately 10^{-6} cm^2 sec^{-1}. Since the transport mechanism through the SC appears to be similar to that through simple membranes, it seems unlikely that D^0 for the SC will be significantly less than 10^{-7} cm^2 sec^{-1}. Consequently, the low value of D^0/∂ derived from the data presented here is most likely due to a very large ∂ rather

than a small D^0. Given the relative values of D^0/∂ for SC and for simple biomembranes, we estimate $\partial = 500$ μm. Such a result has been obtained from a variety of independent experiments (20, and references therein). In other words, while the SC and simpler membranes share a common mechanism of transport through lipid lamellae, the extracellular lipid domain in the SC provides a substantially longer diffusion pathlength and, consequently, a significantly lower permeability.

Often K_{oct} is used as an estimate of K_m since the latter is experimentally difficult to determine. As shown in Eq. (4), these two partition coefficients are related, with the parameter f serving as a measure of the similarity between the two lipophilic phases. Specifically, the finding that f is less than 1 suggests that the partitioning domain of octanol is less polar than the membrane. Recently, Kasting *et al.* (10) have analyzed K_p results using Eq. (6). However, they chose to fix $f = 1$, arguing that other values were not statistically justified. In contrast, we find that the values derived here for f (Table II) are all significantly less than 1. We conclude, therefore, that the partitioning domain of human SC lipids is more polar than octanol. Similar analyses to that used here have led to the same conclusion for the partitioning behavior of lecithin bilayers relative to octanol (13). Consistent with this conclusion are analyses of the data of Ackermann *et al.* (3) using both K_{ether} and K_{oct} values. The f value with K_{ether} (0.50 ± 0.06) is significantly lower than that with K_{oct} (0.72 ± 0.07), and both are less than 1, reflecting the fact that both organic phases are less polar than the partitioning domain of the SC. Anderson *et al.* (21) measured the SC/water partitioning of a number of hydrocortisone esters and compared the results to the corresponding K_{oct}. Analysis of these results with Eq. (4) led to a value of the exponent of 0.85, similar to that obtained here, and supportive of the deduction that the partitioning domain of SC lipids is more polar than octanol.

The model presented here provides a simple mechanistic description of SC permeability. A number of investigators have interpreted log K_p vs log K_{oct} data, such as those shown in Fig. 1, by a more complex model in which the transport mechanism changes for permeants of differing polarity. In particular, the apparent independence of log K_p upon log K_{oct} for small, polar compounds has led to the hypothesis that these molecules traverse the SC via "aqueous pores" (1–4). The permeability of these small, polar compounds, however, is explained on the basis of their molecular volume (Fig. 2). Thus, it is not necessary to invoke the existence of an "aqueous pore" to account for the permeability of these compounds. Significantly, sucrose and glucose are among the compounds analyzed here. The very low permeabilities (K_p values near 10^{-8} cm sec^{-1}) of these highly polar and relatively large compounds are adequately described by the model, with differences between predicted and experimental K_p values that are well within the range shown by other compounds.

The form of Eq. (6) indicates that the increase in K_p with increasing K_{oct} is offset somewhat by increasing molecular size. However, it has been suggested that skin permeability does not progressively increase with increasing lipophilicity but, instead, reaches a limiting value. Perhaps the most persuasive evidence to support this contention is that skin stripped of its SC does not have an infinite permeability (22). There is a residual resistance which remains due, at least in part, to the diffusional barrier of the aqueous, viable epidermis and upper dermis. Other interpretations of skin transport have also suggested that, for compounds of very high lipophilicity, the rate-determining step becomes the slow transfer rate from the lipophilic SC to the aqueous, viable tissue. However, analysis of the large data base presented here does not require a rate-limiting K_p value in order to explain fully the dependence of K_p on K_{oct} and MW, despite the relatively high lipophilicities of some of the compounds studied. Why is this the case? To answer the question it is instructive to define reasonable values for the two alternative rate-limiting processes defined above.

The permeability coefficient (K_{vt}) of a reasonably sized nonelectrolyte through the viable tissue between the SC and the dermal microvasculature is given by

$$K_{vt} = D_{vt}/\partial_{vt} \tag{8}$$

where D_{vt} is the diffusion coefficient [typically in the range of 10^{-6}–10^{-5} cm^2 sec^{-1} (23)], and ∂_{vt} is the diffusion pathlength (of the order of 100 μm). It follows then that K_{vt} is about 10^{-4} cm sec^{-1} (or about 0.1 to 1.0 cm/hr). Values for lipid–water interfacial transfer coefficients have been reported for a variety of small, nonelectrolytes (24), and are of comparable magnitude to the K_{vt} calculated above. To include a limiting value of permeability into the model as described requires that the definition of K_p be extended to account for the existence of two potential resistances in series.

$$K_p^{-1} = \partial/K_m \cdot D_m + K_{vt}^{-1} \tag{9}$$

If the above expanded form of K_p is substituted into Eq. (6) and the regression analysis is repeated using values of K_{vt} of 10^{-4} cm sec^{-1} or greater, no statistically significant improvement in the fit of the data can be achieved. Indeed, the quality of the fit often decreases because there are no data which require a limiting regime of K_p. Nevertheless, this conclusion does not rule out the possibility that a change in the rate-determining step will ultimately occur. In fact, Eq. (9) permits us to identify the physicochemical properties of those compounds which will illustrate the phenomenon. Substitution of Eq. (9) into Eq. (7) gives

$$\log \{K_p^{-1} - K_{vt}^{-1}\} = 6.3 - 0.71 \cdot \log K_{oct} + 0.00061 \cdot MW \tag{10}$$

For the resistance associated with either transfer into, or transfer through, the viable tissue to become rate-limiting (i.e., $K_{vt}^{-1} \gg K_p^{-1}$), it follows that

$$\log (K_{vt}^{-1}) \gg 6.3 - 0.71 \cdot \log K_{oct} + 0.0061 \cdot MW \tag{11}$$

If we choose the calculated value of 10^{-4} cm sec^{-1} for K_{vt}, then Eq. (11) requires that

$$0.71 \cdot \log K_{oct} + 0.0061 \cdot MW \ll 2.3 \tag{12}$$

The inequality in Eq. (12) predicts, for example, that for a permeant of MW = 100, log K_{oct} must be greater than 4.1 if the viable tissue transfer process (K_{vt}) is to be rate-limiting. For MW = 200, Eq. (12) implies that a permeant must have log $K_{oct} \gg 5.0$ for the switch in rate-controlling processes to

occur. This relationship is shown graphically in Fig. 4b. To the best of our knowledge, no experiments have been performed with such small and highly lipophilic compounds, under experimental conditions amenable to this analysis. It is physicochemically unreasonable, in some cases, to expect that the necessary conditions of lipophilicity and size can be achieved. Thus, the reason why the data base cannot be used to establish a limiting value for K_{vt} is that it does not contain any chemicals whose properties fit the criteria necessary to define the regime. Practically speaking, this finding is perhaps not surprising since such compounds would be expected to be extremely water-insoluble and difficult to work with under the experimental conditions required to establish steady-state penetration kinetics across skin from an aqueous donor phase into an aqueous receptor phase.

Saturated hydrocarbons represent a group of chemicals which have small molecular sizes and high lipophilicities [e.g., *n*-decane has MW = 142 and log K_{oct} = 6.2 (25)]. The alkanes have physicochemical properties, therefore, that would seem appropriate to test the predicted limiting value of K_p. For a molecule of the size of *n*-decane, Eq. (12) would be satisfied by log $K_{oct} \gg 4.5$, a criterion clearly met by this hydrocarbon. Scheuplein and Blank reported the permeability coefficients of several *n*-alkanes, in the vapor phase, through dry human SC (23). These permeability coefficients [$K_p(v)$] are related to the conventional K_p values (determined using aqueous donor and receiver solutions and employed in all analyses presented in this paper) by Eq. 13,

$$K_p = K_p(v) \cdot [C_v/C_w] \quad (13)$$

where C_w is the saturation solubility of the alkane in water and C_v is the saturation vapor concentration. Using values of C_w and C_v from the literature (23,26), alkane K_p were calculated from the published $K_p(v)$ values (see Table III). Regression of the derived log K_p values against log K_{oct} yields a remarkably straight line (r^2 = 0.99) with no evidence of a limiting regime. As with the *n*-alkanol data (see above), analysis of the *n*-alkane results using Eq. (6) was not possible since log K_{oct} and MW are codependent in these homologous series. However, analysis using Eq. (3) (substituting MW for MV) yields a very reasonable correlation (r^2 = 0.80) and values for log (D^0/∂) and β'' which are identical, within error, to values obtained using other datasets. It is interesting to note, therefore, that despite the apparent suitability of the alkanes for probing the high-lipophilicity regime, they do not define a limiting K_p value. One reason is that the $K_p(v)$ values were obtained using dry SC without an aqueous receptor medium. In fact, the receptor phase provided a gaseous sink. Thus, the derived K_p values are calculated on this basis and reflect the permeant interaction with a membrane in contact with a perfect sink on its downstream face. Under these conditions, therefore, the mechanisms which are predicted to result in a change in the rate-limiting step (e.g., K_{vt} above), cannot operate. Of note is the fact that under these conditions the SC continues to behave as an ideal lipophilic biomembrane and that log K_p continues to increase with increasing log K_{oct}.

In conclusion, the apparently sigmiodal dependence of log K_p upon log K_{oct} inferred for data such as those shown in Fig. 1 suggests a nonlinear relationship between these parameters. However, when MV is taken into account, the data lie on a three-dimensional surface defined by log K_p, log K_{oct}, and MV. Overall, then, skin permeability can be described by a simple, mechanistically based model of excellent predictive capacity. Furthermore, the model does not require the existence of either "aqueous pores" or a high-lipophilicity limiting value of K_{vt} to account for a very wide spectrum of data. In addition, the model agrees with a lipid free-volume description of SC transport based on independent biophysical data. Finally, the model is consistent with transport through lipid lamellae in general and suggests that lipid properties alone are sufficient to explain SC permeability.

Table III. Alkane K_p Values Derived from Vapor Phase Permeability Coefficients [$K_p(v)$] Using Eq. (13)

Alkane	log[$K_p(v)$][a]	logK_p[b]	logK_{oct}[c]
n-Pentane	−5.76	−3.92	3.62
n-Hexane	−5.54	−3.62	4.00
n-Heptane	−5.20	−3.20	4.66
n-Octane	−4.80	−2.60	5.16
n-Nonane	−4.54	−2.13	5.7[d]
n-Decane	−4.46	−1.94	6.2[d]

[a] From Ref. 23 [$K_p(v)$ units are cm sec^{-1}].
[b] Calculated using Eq. (13) (K_p units are cm sec^{-1}).
[c] From Ref. 26.
[d] Extrapolated from values for lower homologues.

ACKNOWLEDGMENTS

This research was supported in part by a grant from the National Institutes of Health (HD-23010), a cooperative agreement with the Environmental Protection Agency (CR-816785), and a research contract with Sandia National Laboratories (#69-5518). We would like to thank our colleagues at Cygnus and UCSF for many valuable discussions. The intellectual input of Brad Anderson, Annette Bunge, Gordon Flynn, Mike Francoeur, Jonathan Hadgraft, Kim Hoang, Gerry Kasting, and Ron Smith has greatly facilitated the writing of this paper.

REFERENCES

1. B. Idson and C. R. Behl. Drug structure vs. penetration. In *Transdermal Delivery of Drugs, Vol III*, A. F. Kydonieus and B. Berner (eds.), CRC Press, Boca Raton, FL, 1987, pp. 85–151.
2. G. L. Flynn and B. Stewart. Percutaneous drug penetration; Choosing candidates for transdermal development. *Drug Dev. Res.* 13:169–185 (1988).
3. C. Ackermann, G. L. Flynn, and W. M. Smith. Ether-water partitioning and permeability through hairless mouse skin in vitro. II. Hydrocortisone 21-n-alkyl esters, alkanols and hydrophilic compounds. *Int. J. Pharm.* 36:67–71 (1987).
4. G. L. Flynn. Physicochemical determinants of skin absorption. In *Principles of Route-to-Route Extrapolation for Risk Assessment*, T. R. Gerrity and C. J. Henry (eds.), Elsevier, New York, 1990, pp. 93–127.
5. R. J. Scheuplein and I. H. Blank. Molecular structure and diffusional processes across intact skin. Report to the US Army Chemical R&D Laboratories, Edgewood Arsenal, MD 1967.
6. W. R. Lieb and W. D. Stein. Implications of two different types

of diffusion for biological membranes. *Nature* 234:219–222 (1971).
7. M. H. Cohen and D. Turnbull. Molecular transport in liquids and gases. *J. Chem. Phys.* 31:1164–1169 (1959).
8. W. R. Lieb and W. D. Stein. Non-Stokesian nature of transverse diffusion within human red cell membranes. *J. Membr. Biol.* 92:111–119 (1986).
9. G. B. Kasting, R. L. Smith, and E. R. Cooper. Effect of lipid solubility and molecular size on percutaneous absorption. In *Skin Pharmacokinetics,* B. Shroot and H. Schaefer (eds.), Karger, Basel, 1987, pp. 138–153.
10. G. B. Kasting, R. L. Smith, and B. D. Anderson. Prodrugs for dermal delivery: Solubility, molecular size and functional group effects. In *Prodrugs and Their Topical Use,* K. B. Sloan (ed.), Marcel Dekker, New York, 1992 (in press).
11. A. Bondi. van der Waals volumes and radii. *J. Phys. Chem.* 68:441–452 (1964).
12. W. R. Lieb and W. D. Stein. Biological membranes behave as non-porous polymer sheets with respect to diffusion of non-electrolytes. *Nature* 224:240–243 (1967).
13. J. M. Diamond and Y. Katz. Interpretation of nonelectrolyte partition coefficients between dimyristoyl lecithin and water. *J. Membr. Biol.* 17:127–154 (1974).
14. M. S. Roberts, R. A. Anderson, and J. Swarbrick. Permeability of human epidermis to phenolic compounds. *J. Pharm. Pharmacol.* 29:677–683 (1977).
15. R. H. Guy and J. Hadgraft. Physicochemical aspects of percutaneous penetration and its enhancement. *Pharm. Res.* 5:753–758 (1988).
16. D. Southwell, B. W. Barry, and R. Woodford. Variations in permeability of human skin and between specimens. *Int. J. Pharm.* 18:299–309 (1984).
17. R. O. Potts and M. L. Francoeur. Lipid biophysics of water loss through the skin. *Proc. Natl. Acad. Sci. USA* 87:3871–3873 (1990).
18. H. Trauble and D. H. Haynes. The volume change in lipid bilayer lamellae at the crystalline-liquid crystalline phase transition. *Chem. Phys. Lipids* 7:324–335 (1971).
19. B. D. Anderson and P. V. Raykar. Solute structure-permeability relationships in human stratum corneum. *J. Invest. Dermatol.* 93:280–286 (1989).
20. R. O. Potts and M. L. Francoeur. The influence of stratum corneum morphology on water permeability. *J. Invest. Dermatol.* 96:495–499 (1991).
21. B. D. Anderson, W. I. Higuchi, and P. V. Raykar. Heterogeneity effects on permeability-partition coefficient relationships in human stratum corneum. *Pharm. Res.* 5:566–573 (1988).
22. G. L. Flynn, H. Durrheim, and W. I. Higuchi. Permeation of hairless mouse skin. II. Membrane sectioning and influence on alkanol permeabilities. *J. Pharm. Sci.* 70:52–56 (1981).
23. R. J. Scheuplein and I. H. Blank. Permeability of the skin. *Physiol. Rev.* 51:702–747 (1971).
24. R. H. Guy, R. S. Hinz, and M. Amantea. Solute transport and penetration at liquid/liquid interfaces. *Faraday Disc. Chem. Soc.* 77:127–137 (1984).
25. Pomona College Medicinal Chemistry (MEDCHEM) database. Pomona College, Claremont, CA, 1984.
26. D. A. Haydon, B. M. Hendry, S. R. Levinson, and J. Requena. A comparative study of nerve impulse blockage and the properties of black lipid membranes. *Biochim. Biophys. Acta* 470:17–34 (1977).