Solute Structure–Permeability Relationships in Human Stratum Corneum

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The permeability coefficients (k_p) of a series of methyl-substituted *p*-cresols were determined in human stratum corneum along with their partition coefficients (PC) between water and untreated stratum corneum, delipidized stratum corneum, octanol, and heptane. The PC values were identical in untreated and delipidized stratum corneum, suggesting that the stratum corneum/water PC data reflect the protein domain rather than the lipids. Although uptake into human stratum corneum was relatively insensitive to solute lipophilicity, reflecting the predominant role of proteins in the uptake, permeability coefficients were found to be more sensitive to lipophilicity, suggesting that transport is by a lipid pathway. A log–log plot of k_p versus stratum corneum/water PC within the phenol series is linear, but with a slope of 3.6, indicating that k_p is not directly proportional to PC. Functional group contributions to the free energy of the transfer process reflected in permeability or partitioning experiments were compared with group contribution data generated previously for the same substituents attached to the chain terminus of 21-esters of hydrocortisone. Within experimental error, a given functional group altered permeability by the same factor in either series of compounds. Group contributions of polar, hydrogen bonding substituents obtained from k_p data were similar to those from octanol/water PC data, suggesting that the barrier microenvironment resembles that of a hydrogen bonding organic solvent. Comparison of the k_p values of substituted *p*-cresols with those of hydrocortisone esters having similar lipophilicities also indicated a steep dependence of k_p on molecular weight (log k_p = constant + ψ log PC − n log MW, n = 4.6) similar to the dependence observed in other biomembranes and isolated lipid bilayers. *J Invest Dermatol 93:280–286, 1989*

Detailed knowledge of the influence of molecular structure on solute permeabilities and partition coefficients in human stratum corneum would be valuable from both a theoretical and a practical standpoint. Theoretically, such relationships are essential in understanding the mechanisms by which various solutes permeate through the skin and how various treatments may alter these transport pathways. From a practical standpoint, a quantitative data base relating chemical structure to skin partitioning and permeability would be useful in the design of drugs to be delivered transdermally. In spite of a recent intensified interest in dermal delivery, however, few systematic structure–transport studies have been reported.

The group contribution method [1–5] has been widely explored in the development of predictive relationships between solute structure and uptake into or transport through biologic membranes. This approach is not generally useful in transdermal delivery, however, because certain issues have not been resolved in sufficient detail to allow skin permeabilities to be predicted from solute structure. Among the central questions yet to be answered satisfactorily are the following: 1) Are lipophilicity scales based on partition coefficients (bulk solvent/water, lipid bilayer/water, stratum corneum/water) useful quantitative models for predicting skin transport? 2) Does a given functional group alter skin permeability by the same factor independent of the parent compound to which it is attached? 3) To what extent is molecular size, a parameter that is not explicitly considered in group contribution methods, important in determining permeabilities of solutes through the skin?

In this study, the permeability coefficients of a series of methyl-substituted *p*-cresols varying widely in lipophilicity were determined in human stratum corneum along with the partition coefficients of the same solutes between water and untreated or delipidized stratum corneum, octanol, and heptane. Functional group contributions to the free energy of the transfer process reflected in these experiments were calculated and compared with group contribution data generated previously [6,7] for the same substituents attached to the chain terminus of 21-esters of hydrocortisone varying in chain length. Such data from two series of compounds that differ substantially in molecular weight expand the knowledge base considerably, which is necessary to answer the questions posed above.

MATERIALS AND METHODS

Materials The following compounds (shown in Scheme I) were used in this study: 4-hydroxyphenylacetamide (1a); 4-hydroxybenzyl alcohol (1b); 4-hydroxyphenylacetic acid (1c); methyl 4-hydroxyphenylacetate (1d); *p*-cresol (1e); α-phenylacetamide (2a); benzyl alcohol (2b); phenylacetic acid (2c); methyl phenylacetate (2d); and toluene (2e). Compound 1a was obtained from Lancaster Synthesis Ltd. (Windham, NH), whereas the others were purchased from Aldrich Chemical Co. For some studies, compounds 1a and 2a

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Abbreviations:
D_m: diffusion coefficient
k_p: permeability coefficient
MSC: model selection criterion
PC: partition coefficient

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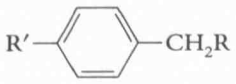

Scheme I

Compound	R'	R
1a	—OH	—$CONH_2$
1b	—OH	—OH
1c	—OH	—COOH
1d	—OH	—$COOCH_3$
1e	—OH	—H
2a	—H	—$CONH_2$
2b	—H	—OH
2c	—H	—COOH
2d	—H	—$COOCH_3$
2e	—H	—H

were synthesized from the corresponding methyl esters (1d and 2d) by reacting them with an excess of ammonia. The high performance liquid chromatography (HPLC) analyses of the reaction products versus the commercially obtained materials confirmed their identities and purities (>99% by HPLC).

Human Stratum Corneum Preparations Stratum corneum was isolated from split-thickness human skin obtained from elective abdominoplastic surgery (Department of Dermatology, School of Medicine, University of Utah, Salt Lake City, UT) as described previously [6,7]. Delipidized stratum corneum was prepared by extraction with 2:1 chloroform-methanol [8,9].

Partition Coefficient Determinations Octanol/water and heptane/water partition coefficients were determined by the shake flask method [5]. Because the heptane/water partition coefficients of the substituted *p*-cresols were quite small in some cases, group contributions were determined from the partition coefficients of compounds 2a-2e that exhibited higher heptane/water partition coefficients due to the absence of the phenolic —OH group. In the heptane/water measurements, solute concentrations in the heptane phase at equilibrium were $< 10^{-3}$ ml/l to minimize solute self-association. Generally 10-15 ml of aqueous phase containing the solute of interest was equilibrated with 2-5 ml heptane in glass centrifuge tubes. The tubes were gently shaken for five min and allowed to equilibrate at 37°C for four h with intermittent mixing. The tubes were then centrifuged for two min and returned to the water bath for two additional h before the phases were separated and analyzed by HPLC. Octanol/water measurements were performed in a similar manner. Molar concentrations were used for partition coefficient calculations.

Partition coefficients between water and untreated or delipidized stratum corneum were measured at pH 4 and 37°C by monitoring solute depletion from bathing solutions as described previously [7]. Concentrations for these partition coefficient calculations were expressed on a wt/wt basis.

Permeability Coefficient Determinations Transport experiments with untreated or delipidized stratum corneum were carried out in two-chamber diffusion cells as described previously [6]. Donor solutions of substituted *p*-cresols were prepared in pH 4 succinate buffer (0.01 ionic strength) at concentrations of less than 0.1%, well below the threshold concentrations required for irreversible skin damage [10]. Before beginning the diffusion experiments, the isolated stratum corneum samples were hydrated in situ for 24 h, after which both chambers were emptied and the receiver side was filled with 2 ml of the receiver solution. The transport experiment was initiated by charging the donor chamber with the appropriate donor solution. Aliquots of the receiver solution were then analyzed at various times by HPLC and solute fluxes were calcuated from the slopes of plots of the amount penetrated versus time. Permeability coefficients (cm/h) were determined by dividing the solute flux by the donor phase concentration and the membrane surface area (0.65 cm^2).

RESULTS

Permeant Selection The solutes selected as permeants are shown in Scheme I (1a-e). In an earlier study of a series of hydrocortisone esters [6], group contributions were obtained from various functional groups attached to the end of a flexible 21-acyl chain. Intramolecular hydrogen bonding, which could not be precluded in the previous series, cannot occur in the substituted *p*-cresols chosen for this study. Also, the *p*-cresols are markedly different from the hydrocortisone series in size and molecular complexity, and thus appear to provide a means of exploring molecular size effects and rigorously determining the degree to which functional group contributions to skin transport are additive for substituents attached to a primary aliphatic carbon atom.

Partition Coefficients Shown in Table I are the octanol/water, heptane/water, and stratum corneum (untreated and delipidized)/water partition coefficients obtained in the partitioning experiments. A comparison of the partition coefficients of 1d and 1e in untreated and delipidized stratum corneum samples indicates that these tissues exhibit identical uptake properties for these solutes, suggesting that the stratum corneum/water partition coefficients of

Table I. Octanol/Water, Heptane/Water, and Stratum Corneum/Water Partition Coefficients of Various Substituted Toluenes or *p*-Cresols (Scheme 1)

			Partition Coefficient			
Compound	R'	R	Octanol[a]/Water	Heptane[a]/Water	Untreated[b] SC/Water	Delipidized[b] SC/Water
1a	—OH	—$CONH_2$	0.82 ± 12%	1.05×10^{-5}[c]	5 ± 42% (6)	—
1b	—OH	—OH	2.10 ± 7%	4.9×10^{-5}[c]	9 ± 20% (6)	—
1c	—OH	—COOH	8.60 ± 3%	2.5×10^{-5}[c]	14 ± 12% (6)	—
1d	—OH	—$COOCH_3$	43.0 ± 8%	2.6×10^{-2}[c]	13 ± 29% (10)	13 ± 24% (10)
1e	—OH	—H	89.0 ± 4%	0.45[d]	22 ± 34% (10)	21 ± 36% (10)
2a	—H	—$CONH_2$	—	0.018 ± 23%	—	—
2b	—H	—OH	—	0.08 ± 6%	—	—
2c	—H	—COOH	—	0.04 ± 8%	—	—
2d	—H	—$COOCH_3$	—	43.0 ± 8%	—	—
2e	—H	—H	—	744 ± 11%	—	—

SC, stratum corneum.
[a] Expressed as mean ± CV of two determinations.
[b] Expressed as mean ± CV of the number of determinations (n).
[c] Estimated from group contributions obtained from 2a-2e heptane/water partitioning data.
[d] From Ref 5.

the methyl substituted *p*-cresols reflect uptake largely by the protein domain.

A useful concept in comparing partition coefficients in various solvent systems is that of selectivity, which refers to the relative abilities of solvents to discriminate between solutes varying in structure [11,12]. Selectivity in bulk solvent/water partitioning decreases with increasing polarity of the organic phase. Dramatic differences in the selectivities of octanol, heptane, and the stratum corneum solvent environment toward the substituted *p*-cresols (i.e., the sensitivity of the partition coefficients to solute structure) are clearly apparent from the range of partition coefficients in each partitioning system. The observed ratios (highest/lowest) vary from 4×10^4-fold in the heptane/water system to approximately 100-fold in the octanol/water system to only fourfold in stratum corneum/water. These tissue uptake data demonstrate that the stratum corneum is relatively insensitive to solute polarity over the range explored and, therefore, the solvent environment probed in these experiments is highly polar.

The selectivity of the stratum corneum protein domain can be related to that of octanol through a linear free energy relationship as described below:

$$\log PC_{pro} = \alpha \log PC(\text{octanol/water}) + \beta \qquad (1)$$

where PC_{pro} is the stratum corneum protein domain/water partition coefficient. The slope, α, reflects the relative selectivity of the stratum corneum to solute lipophilicity as measured by the octanol/water scale. Figure 1 shows a plot of log PC_{pro} versus log PC(octanol/water) for the methyl-substituted *p*-cresols examined along with the corresponding data for various 21-esters of hydrocortisone reported in a previous publication [7]. Both series fall on the same line, which has a slope, $\alpha = 0.27$, confirming the highly polar nature of the stratum corneum protein domain.

Permeability Coefficients Values for the permeability coefficients of the substituted *p*-cresols in untreated and chloroform/methanol extracted human stratum corneum are shown in Table II. Transport rates are much more sensitive than partition coefficients to solute structure, as evident in the 270-fold variation in permeability coefficients of solutes 1a–1e compared with a fourfold variation in stratum corneum/water partition coefficients for the same solutes.

The dramatic increases in the permeability coefficients in delipidized stratum corneum and the loss of selectivity to solute structure clearly show that delipidization destroys the transport barrier. A similar, high permeability value is also observed for toluene, 2e, in untreated stratum corneum. Because it is highly lipophilic, toluene would not be expected to be rate-limited by the lipid pathway of stratum corneum. Rather, the diffusion of substituted *p*-cresols through delipidized stratum corneum and toluene through untreated stratum corneum appear to be aqueous boundary layer controlled. Assuming an aqueous boundary layer thickness of 300 μm for the diffusion cell configuration [13] and an aqueous diffusivity of 1×10^{-5} cm²/sec yields a permeability coefficient estimate of 1.1 cm/h, very close to the highest values reported in Table II.

Table II. Permeability Coefficients, k_p (cm/h), of Various Substituted *p*-Cresols Through Untreated and Delipidized Human Stratum Corneum at 37°C

Solute[a]	k_p[b] Untreated	Delipidized
1a	$4.5 \times 10^{-4} \pm 35\%$ (4)	$0.79 \pm 4\%$ (2)
1b	$2.0 \times 10^{-3} \pm 30\%$ (6)	$0.78 \pm 4\%$ (2)
1c	$2.5 \times 10^{-3} \pm 3\%$ (4)	—
1d	$2.0 \times 10^{-2} \pm 4\%$ (4)	—
1e	$1.2 \times 10^{-1} \pm 8\%$ (6)	$0.80 \pm 1\%$ (2)
2e	$0.83 \pm 3\%$ (2)	—

[a] See Scheme I.
[b] Expressed as mean ± CV of the number of determinations (n).

Permeability–Partition Coefficient Relationships: Shown in Figure 2 is a log–log plot of the substituted *p*-cresol permeability coefficients versus the corresponding stratum corneum/water partition coefficients. Although this log–log plot is linear, the slope of the line is approximately 3.6, much higher than the value of 1.0 implied in homogeneous membrane models where the permeability coefficient is directly proportional to the membrane/vehicle partition coefficient.

Also depicted in Figure 2 is a similar log–log plot of data from a previous study for a series of hydrocortisone esters [6]. Over the same lipophilicity range spanned by the substituted *p*-cresols, the lines appear to be parallel. At higher lipophilicities in the hydrocortisone series, distinct downward curvature appears in the plot. This has been attributed to a change in the mechanism of uptake with increasing hydrocortisone ester lipophilicity from protein domain to lipid domain dominated [6]. Both sets of data in Figure 2 clearly suggest that the solvent nature of the barrier microenvironment of the stratum corneum does not resemble the microenvironment governing solute distribution into the skin.

Least squares regression analyses of the logarithms of k_p versus the logarithms of octanol/water or heptane/water partition coeffi-

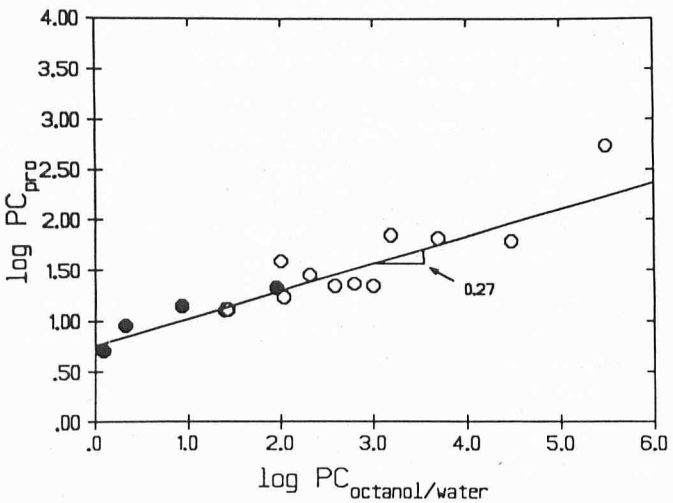

Figure 1. Plot of log PC_{pro} versus log $PC_{octanol/water}$ for various methyl substituted *p*-cresols (●) and 21-esters of hydrocortisone (○). PC_{pro} is the stratum corneum protein domain/water partition coefficient.

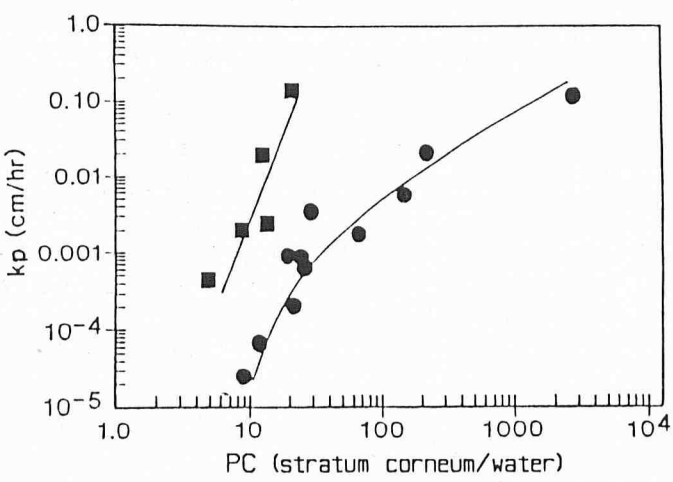

Figure 2. Log–log plots of the observed permeability coefficients, k_p, of various methyl substituted p-cresols (■) and 21-esters of hydrocortisone (●) versus their stratum corneum/water partition coefficients.

cients established that octanol/water partition coefficients correlate better with transport than heptane/water partition coefficients. Plots of log k_p for both the hydrocortisone esters and the substituted *p*-cresols versus the logarithms of their heptane/water or octanol/water partition coefficients are shown in Figures 3 and 4, respectively. Although the coefficients of determination obtained from the regression analyses of log k_p with log PC (octanol/water) were larger than with log PC (heptane/water), the conclusion that octanol/water partition coefficients are better correlated with stratum corneum permeabilities comes primarily from the slopes of these plots (shown in the Figures), which are much closer to one for the correlations of log k_p with log PC (octanol/water).

Molecular Weight Effects: Although octanol appears to best mimic the chemical nature of the barrier microenvironment of the stratum corneum, two widely separated lines are necessary to fit the *p*-cresol series and the hydrocortisone series in Figure 4, suggesting that factors other than lipophilicity, as measured by octanol/water partition coefficients, must be considered to account for the variance in permeabilities. Because these two series also differ by nearly fivefold in molecular weight, molecular size effects were assumed to account for this disparity.

An empirical relationship used to examine the dependence of the observed diffusion constant on solute molecular weight is shown in Equation (2)

$$D_m = D_m^{\circ} MW^{-n} \qquad (2)$$

where MW is the solute molcular weight and n and D_m° are constants characteristic of the membrane at a given temperature. This relationship is based on the Stokes-Einstein equation governing the diffusion of spherical particles in a continuous medium [14]. Lieb and Stein [15,16] refer to the parameter n as the mass selectivity coefficient.

Incorporating into the regression model the dependence of log k_p on both the diffusivity, D_m, which varies with molecular weight, and the octanol/water partition coefficient leads to Equation (3)

$$\log k_p = \text{constant} + \psi \log PC \text{ (octanol/water)} - n \log MW \qquad (3)$$

According to Equation (3) the permeability coefficient of a solute across the stratum corneum is directly proportional to log PC and inversely proportional to the nth power of its molecular weight. Table III presents results of least squares regression analyses of the log k_p values versus the logarithm of octanol/water partition coefficients with and without the molecular weight term. Data for the hydrocortisone esters and *p*-cresols were first considered separately and then combined. Within each series, the inclusion of a molecular weight term did not significantly improve the fits as determined by the model selction criterion, MSC (MSC gives the same rankings

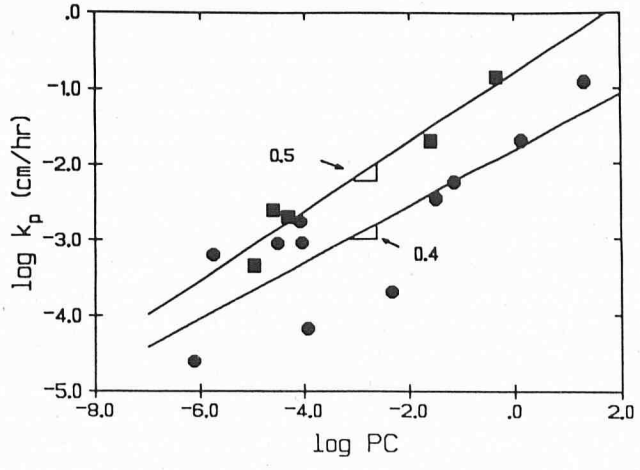

Figure 3. Plots of log k_p versus the logarithms of the heptane/water partition coefficients of various 21-esters of hydrocortisone (●) and methyl-substituted *p*-cresols (■).

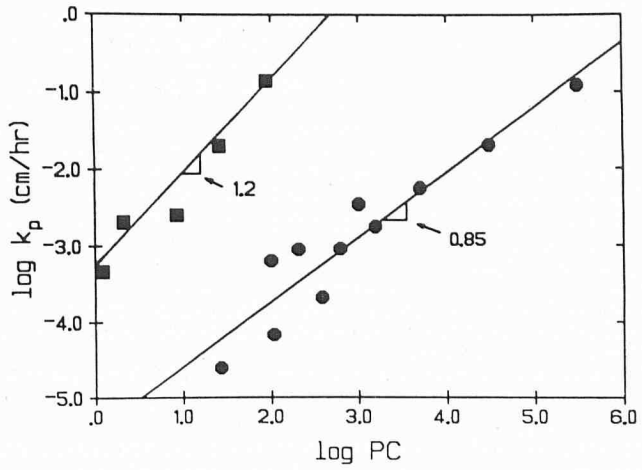

Figure 4. Plots of log k_p versus the logarithms of the octanol/water partition coefficients of various 21-esters of hydrocortisone (●) and methyl-substituted *p*-cresols (■).

between models as the Akaike Information Criterion [17] but has been normalized so that it is independent of the scaling of the data points [18]). This was not unexpected, as the changes in molecular weights within each series were small (<20% for the hydrocortisone esters and <35% for the substituted *p*-cresols).

The inclusion of molecular weight in the regression analysis was essential for the combined data, however, as shown by the statistics reported in Table III. A plot of log k_p (observed) vs. log k_p (predicted) when the molecular weight term is included is shown in Figure 5. Only when molecular weight diferences are included in the model is it possible to account for the permeability coefficients of both series with a single line. The value of the mass selectivity coefficient obtained in this analysis, n = 4.6, is comparable to the values reported previously in other biologic membranes [15,16,19].

Functional Group Contributions From the permeability data reported in Table II, thermodynamic group contributions to the free energy of transfer of various functional groups from water to the stratum corneum barrier microenvironment, $\Delta(\Delta G\ddagger)_{-X}$, can be calculated using the following relationship:

$$\Delta(\Delta G\ddagger)_{-X} = -2.303RT \log(k_p[RX]/k_p[RH]) \qquad (4)$$

Functional group contributions to the standard free energy of transfer from water to heptane, octanol, and the stratum corneum protein domain were also calculated from equilibrium partition coefficients according to Equation (5):

$$\Delta(\Delta G^{\circ})_{-X} = -2.303RT \log(PC_{RX}/PC_{RH}) \qquad (5)$$

Group contributions obtained from the substituted *p*-cresol permeability and partitioning data are reported in Table IV along with data for the same functional groups obtained in a previous study of hydrocortisone esters. The ± values reported in parentheses reflect the coefficients of variation of the averages obtained for the two sets of parent compounds.

DISCUSSION

Utility of Model Partitioning Systems in Predicting Barrier Properties Nearly a century ago Overton [20,21] observed that the permeability of nonelectrolytes through biologic membranes correlated well with their bulk lipid/water partition coefficients. These observations have since been confirmed in studies of a variety of biomembranes [22-24], isolated cells [25-27], and isolated lipid bilayer membranes [11,28-30]. Close scrutiny of the data in Table IV and the plots in Figures 2 to 4 is useful in ascertaining which partitioning system of those examined (heptane, octanol, or stratum corneum) best mimics the barrier properties of stratum corneum.

Table III. Comparison of the Results of Least Squares Regression Analyses of Log k_p Versus Logarithm of Octanol/Water Partition Coefficients With and Without a Molecular Weight Term

	(Without Molecular Weight)[a]			(With Molecular Weight)[b]			
Parent Series	Slope (ψ)	COD[c]	MSC[d]	Slope[d] (ψ)	COD[c]	MSC[d]	n
Hydrocortisone esters	0.85 ± 0.1	0.89	1.85	0.86 ± 0.1	0.90	1.73	3.1 ± 4.8
Substituted *p*-cresols	1.2 ± 0.2	0.94	1.94	1.06 ± 0.2	0.97	2.15	2.7 ± 1.8
Combined data of hydrocortisone esters and *p*-cresols	0.33 ± 0.2	0.2	−0.03	0.87 ± 0.1	0.91	2.10	4.6 ± 0.5

[a] Slope, ψ, expressed as the estimate ± SD according to Equation (3) with n = 0.
[b] Slope, ψ, and mass selectivity parameter, n, expressed as the estimate ± SD according to Equation (3) with n ≠ 0.
[c] Coefficient of determination.
[d] Model selection criterion (a larger value indicates the preferred model, Ref 18).

The chemical similarity of a given solvent environment to the stratum corneum barrier can be assessed in a qualitative way from the slopes of plots of log k_p versus log PC as shown in Figures 2 to 4, with slopes closer to one indicating greater similarity. By this criterion, octanol appears to be superior to heptane or to the stratum corneum environment probed in partitioning studies as a model solvent of the barrier. A more detailed evaluation is possible by examining the group contribution data in Table IV.

Group contributions generated from transport data are much larger than those obtained from partition coefficients between water and the stratum corneum (Table IV) revealing that the domains probed in transport and distribution experiments are quite different. In previous studies of hydrocortisone esters [6,7], the stratum corneum uptake of those esters having a log PC (octanol/water) < 3 were found to be governed by the protein domain, whereas their transport was by a lipid pathway. The uptake of the substituted *p*-cresols examined in this work would also be expected to be governed solely by the protein domain as the most lipophilic compound in the series, *p*-cresol (1e), has a log PC (octanol/water) of less than 2. This prediction is confirmed by the finding that the untreated stratum corneum/water partition coefficients of both 1d and 1e are identical to the values obtained using delipidized stratum corneum (Table I). The highly polar behavior of the stratum corneum in uptake studies (Fig 1) also supports the view that the stratum corneum partition coefficients of the *p*-cresols are governed by the protein domain, whereas the barrier to their transport is more lipidlike (i.e., more sensitive to permeant lipophilicity). Further evidence that the transport barrier involves a lipid domain is seen in the dramatic increases in permeability coefficients upon delipidization (Table II).

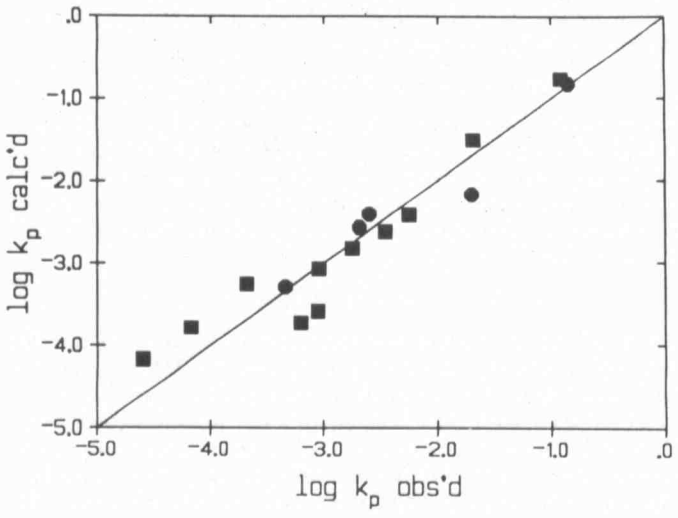

Figure 5. Plots of log k_p predicted by Equation (3) versus the observed log k_p data for various 21-esters of hydrocortisone (■) and methyl-substituted *p*-cresols (●).

Comparisons of group contributions generated from permeabilities with those from partition coefficients of the various solutes between water and the bulk solvents heptane or octanol indicate that the conclusion as to which bulk solvent best approximates the barrier properties depends to some extent on the functional group examined. The superiority of octanol/water partition coefficients is clearly evident in comparing values for polar, hydrogen bonding functional groups, implying that hydrogen bonds are not completely broken in the rate-limiting step for solute transport through stratum corneum as one might expect if the rate-limiting region were more hydrocarbon-like as, for example, in the interior of lipid bilayers. Hydrogen acceptor functional group contributions obtained from the transport data appear to lie between those observed in octanol/water and heptane/water partitioning. On the other hand, the methylene group contribution to transport suggests that the stratum corneum barrier is much more polar than either heptane or octanol. Thus, structure–biomembrane permeability studies of homologous series may not give a clear picture of the selectivity of biomembranes to solutes varying more diversely in structure.

These more detailed comparisons suggest that no single bulk solvent precisely mimics the solvent properties of the stratum corneum transport barrier.

Molecular Size Effects Although octanol/water partition coefficients appear to be the most useful among those partitioning systems explored in correlating chemical structure and skin permeability, the need for two distinct lines in Figure 4 to describe both the substituted *p*-cresol and the hydrocortisone ester data clearly indicates that lipophilicity alone, regardless of the lipophilicity scale employed, cannot account for the relative permeabilities of structurally diverse sets of compounds. Previous studies by Cooper and Kasting [32,33] concluded that molecular size (or molecular weight) is one of the most important factors governing transport across skin.

The mass selectivity coefficient, n, defined by Equation (2), is a useful parameter for characterizing the sensitivity of a given membrane to permeant molecular weight [15,16]. Its value is typically one third to one half for diffusion in water and other bulk solvents [14,15], whereas values of n > 3 have been observed for diffusion in polymer membranes [15,16,19], biologic membranes [15,16,19], and lipid bilayers [15,34–36]. The value of n for stratum corneum obtained from this study is 4.6, which is comparable to the values reported for other biologic membranes. This steep dependence of diffusion constant on solute molecular weight highlights another major difference between the rate-limiting barrier microenvironment of the stratum corneum and model bulk solvents (where n is typically one third to one half).

Additivity in Functional Group Free Energies No significant differences can be seen in Table IV between the group contributions obtained from studies of substituted *p*-cresols and those determined from hydrocortisone ester permeabilities suggesting that, within the experimental errors typically attainable in such determinations, functional group free energy contributions to solute transport through human stratum corneum are approximately additive.

Table IV. Thermodynamic Group Contributions (cal/mol) to the Free Energy of Transfer of Various Functional Groups from Water to Hydrocarbon, Octanol, Stratum Corneum or the Stratum Corneum Barrier Microenvironment at 37°C.

					Stratum Corneum				
	Heptane		Octanol		Protein Domain		Lipid Domain	Transport Barrier	
Functional Group	HC[a] Esters	*p*-Methyl Phenols	HC[a] Esters	*p*-Methyl Phenols	HC[a] Esters	*p*-Methyl Phenols	HC[a] Esters	HC[a] Esters	*p*-Methyl Phenols
$-CH_2-$	−800	—	−710	—	−210	—	−680	−440	—
$-CONH_2$	6600	6600	2700	2900	410	910	1000	2700	3400
	(6600 ± 0%)[b]		(2800 ± 5%)		(660 ± 53%)			(3050 ± 16%)	
$-CON(CH_3)_2$	3500	—	1400	—	160	—	—	2600	—
$-COOCH_3$	1500	1800	850	770	~0	320	670	1400	1100
	(1650 ± 13%)		(810 ± 7%)		(160 ± 140%)			(1250 ± 17%)	
$-COOH$	6000	6100	1600	1400	−220	280	1000	1500	2400
	(6050 ± 1%)		(1500 ± 9%)		(30 ± 560%)			(1950 ± 33%)	
$-OH$	5900	5600	2400	2300	610	550	2300	2400	2500
	(5750 ± 4%)		(2350 ± 3%)		(580 ± 7%)			(2450 ± 3%)	

[a] Hydrocortisone ester data are from Refs 6 and 7.
[b] Values in parentheses are mean values of the hydrocortisone ester and *p*-cresol data ± coefficient of variation.

Within the degree of precision indicated by the reported coefficients of variation, these quantities may be quite useful in predicting changes in permeability coefficients of a solute upon chemical modification.

Consider, for example, the effect of increasing chain length in a molecule by a single methylene group. As shown in Table IV, the value obtained in this study, −440 cal/mol, agrees quite well with the estimate of −460 cal/mol reported by Scheuplein and Blank [31] for the effect of each additional $-CH_2-$ group on the permeabilities of n-alkanols in human stratum corneum. These data indicate that the incorporation of an additional $-CH_2-$ group into a molecule increases its permeability in stratum corneum by approximately twofold (calculated from Equation 4) when the lipid pathway governs transport rate. Comparing the —COOH group contribution with that of $-COOCH_3$ demonstrates that methyl ester formation should increase the permeability coefficient through the skin by more than threefold. Converting a carboxylic acid to an unsubstituted amide decreases permeability by fivefold. Replacing a primary —OH with —H increases permeability by 55-fold, and so on. Different group contributions would be expected when the same functional groups are attached to more sterically hindered sites such as secondary or tertiary carbon atoms [1–5]. Likewise, locating polar, hydrogen bonding functional groups in close proximity to other interactive functional groups would be expected to reduce the values for these groups, as seen in bulk partitioning experiments [1–5]. Furthermore, the above values would be applicable only when transport is governed by the lipid pathway.

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