The Development of a Predictive Method for the Estimation of Flux Through Polydimethylsiloxane Membranes. III. Application to a Series of Substituted Pyridines

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The steady-state flux of 35 substituted pyridine derivatives was determined in polydimethylsiloxane membranes using isopropyl alcohol as the receiver solvent. These diffusants constituted a diverse group of compounds possessing a wide range of hydrophobic, steric, and electronic characteristics. Various parameters representing these physicochemical properties such as cyclohexane–water fragmental constants, molar refractivity, Hammett's σ constants, melting point, and mole fraction solubility were employed to develop empirical models capable of relating the flux to these characteristics of either the substituent on the pyridine ring or the compound itself.

KEY WORDS: membrane diffusion; linear free energy relationships; partition coefficient; molecular volume; diffusion prediction; pyridines.

INTRODUCTION

Theoretical as well as empirical relationships emphasize the importance of the effect of partition coefficient on flux. Based on this, many studies have been performed linking flux to a hydrophobic parameter (1–6).

Flux has also been shown to be affected by molecular size. Hung and Autian (7) reported the diffusivity of a series of aliphatic alcohols could be linearly related to molecular volume. It was noted that branching of an alcohol resulted in a decrease in the diffusion coefficient because of an increase in the molecular cross-sectional area.

Lacey and Cowsar (8) concluded from a study of steroid diffusion through polydimethylsiloxane (PDMS) membranes that diffusivity was a function of both the polarity and cross-sectional area of the molecule. Lien *et al.* (9–11) performed retrospective statistical analyses on numerous sets of percutaneous absorption data using various organic phase-water partition coefficients, molecular weight, molar refractivity, and solubility.

Empirical models were recently developed by Moeckly and Matheson (12) and Matheson *et al.* (13) which predicted the flux of a series of multisubstituted benzenes through polydimethylsiloxane membrane. Important parameters in the model included a hydrophobic term, a steric term represented by molar refractivity, an electronic term represented by Hammett's σ constants, and an indicator variable representing the ability to hydrogen bond intramolecularly.

The purpose of this study was to extend the earlier work on benzene derivatives to a series of substituted pyridines to develop a relationship between their flux through polydimethylsiloxane membrane and various physicochemical parameters which would allow prediction of flux.

MATERIALS AND METHODS

Solubility Determinations

The solubility of each solid diffusant was determined in triplicate by adding an excess of compound to 3 mL of isopropyl alcohol (Mallinckrodt Chemical Works, St. Louis, MO) contained in a screw-cap culture tube. The tubes were sealed, clamped to a submerged disk, and rotated by a stirrer (Stir Pak, Cole-Parmer, Chicago, IL) for at least 48 hr in a constant-temperature water bath (Haake Model ED, Saddle Brooke, NJ) maintained at 30°C. The tubes were placed upright for about 16 hr in the water bath to allow for settling of the solid material. Those solutions which were not clarified by standing were filtered into a vial using a 5-mL glass syringe (Micro-Mate, Popper and Sons, Inc. New Hyde Park, NY) with a disposable filter assembly (0.2-μm Nylon Syringe Filter Unit, Rainin Instrument Co., Inc., Woburn, MA) preheated to 30°C. An aliquot of the saturated solution was immediately diluted to an appropriate volume and analysed using a UV spectrophotometer (Model DB-G, Beckman Instruments, Inc., South Pasadena, CA). The density of the saturated solution was determined using a 2-mL pycnometer (Thomas Scientific, Swedesboro, NJ) in order to calculate the mole fraction of the solute in the saturated solution. The mole fraction solubility in isopropyl alcohol was calculated using the following equation:

$$MF = \frac{S/\mathrm{MW}}{S/\mathrm{MW} + (\rho - S)/60.1} \quad (1)$$

where MF is the mole fraction solubility, S is the solubility (g/L) of the solute, MW is the molecular weight of the solute, ρ is the density (g/L) of the solution, and 60.1 is the molecular weight of isopropyl alcohol.

Diffusion Studies

The steady-state flux of 35 substituted pyridines was determined. All compounds were used as received and are listed in Table 1. Positions on the pyridine ring are numbered, with the heteroatom being position number 1.

Polydimethylsiloxane supported sheeting (Silastic NRV, Dow Corning Corp., Midland, MI) with nominal thicknesses of either 127, 508, or 1016 μm were utilized as model membranes. The material was cut into 2-in.-diameter circles and soaked in isopropyl alcohol for at least 24 hr before being used in the diffusion studies. Membrane thickness was measured with a micrometer (Craftsman Commercial, Sears and Roebuck, Chicago, IL) before each experiment at 12 predetermined points using a method described by Garrett *et al.* (14).

The diffusion cell (Medical Instruments, University of

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Table I. Various Physicochemical Parameters for the Substituted Pyridine Series

Compound	f_{oct}[a]	π_{oct}[b]	f_{chex}[a]	π_{chex}[a]	MR[b]	σ[b]	100/mp	log MF[c]
3-Pyridinecarboxaldehyde[d]	−0.38	−0.65	−0.85	−1.12	6.88	0.42	0.4653	0.0000
3,5-Lutidine[d]	1.22	1.12	1.06	0.96	10.27	−0.34	0.3788	0.0000
3-Hydroxypyridine[d]	−0.34	−0.67	−3.10	−3.43	2.85	−0.37	0.2500	−0.8477
5-Chloro-3-pyridinol[d]	0.40	0.04	−2.36	−2.72	7.85	−0.14	0.2304	−1.0605
3,5-Dichloropyridine[d]	1.66	1.42	1.50	1.26	11.03	0.46	0.2950	−0.9626
4-Butylpyridine[d]	2.25	1.98	2.09	1.82	19.60	−0.20	0.3648	0.0000
Nicotinic acid[d]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.1959	−2.3830
4-Picoline[d]	0.70	0.56	0.54	0.40	5.65	−0.17	0.3631	0.0000
3-Acetylpyridine[d]	−0.14	−0.55	−0.61	−1.02	11.20	0.50	0.3473	0.0000
3-Aminopyridine[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.3017	−0.2845
Pyridine[e]	0.18	0.00	0.02	−0.16	1.03	0.00	0.4329	0.0000
2-Aminopyridine[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.3008	−0.3099
2-Chloro-6-methoxypyridine[d]	1.01	0.69	0.74	0.42	12.87	−0.04	0.3736	0.0000
2-Ethylpyridine[d]	1.23	1.02	1.07	0.86	10.30	−0.15	0.4058	0.0000
2-Chloropyridine[d]	0.92	0.73	0.76	0.57	6.03	0.23	0.3902	0.0000
2-Butoxypyridine[d]	1.82	1.55	1.55	1.28	21.66	−0.32	0.3621	0.0000
2-Fluoropyridine[d]	0.40	0.14	0.24	−0.02	0.92	0.06	0.4292	0.0000
2-Methoxypyridine[d]	0.27	−0.02	0.00	−0.29	7.87	−0.27	0.4132	0.0000
2-Methoxy-5-nitropyridine[d]	0.01	−0.30	−0.71	−1.02	14.20	0.51	0.2621	−2.1175
2-Methyl-5-ethylpyridine[d]	1.75	1.58	1.59	1.42	9.27	−0.32	0.3802	0.0000
2-Methoxy-5-aminopyridine[d]	−0.76	−1.34	−2.21	−2.79	12.26	−0.93	0.3300	0.0000
2-Hydroxy-5-nitropyridine[d]	−0.60	0.95	−3.81	−4.16	9.18	0.41	0.2162	−2.2700
6-Hydroxynicotinic acid[d]	−0.61	−0.99	−6.24	−6.62	8.75	0.08	0.1745	−3.2757
2-Hydroxypyridine[d]	−0.34	−0.67	−3.10	−3.43	2.85	−0.37	0.2639	−0.8164
2,4-Dihydroxypyridine[d]	−0.86	−1.34	−6.22	−6.70	4.67	−0.74	0.1815	−2.4535
Picolinic acid[d]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.2439	−1.7594
2-Amino-4-methylpyridine[f]	−0.33	−0.76	−1.67	−2.10	10.04	−0.83	0.2688	−0.7206
6-Chloronicotinic acid[f]	0.65	0.41	−2.38	−2.62	11.93	0.68	0.2119	−1.5935
2-Amino-5-chloropyridine[f]	−0.11	−0.59	−1.45	−1.93	10.42	−0.43	0.2442	−1.4023
2-Amino-5-nitropyridine[g]	−1.11	−1.60	−2.90	−3.39	11.75	0.12	0.2174	−2.3819
2,5-Pyridinedicarboxylic acid[d]	−0.36	−0.64	−6.26	−6.54	12.83	0.90	0.1916	−3.2840
Ethyl nicotinate[d]	0.80	−0.01	0.33	−0.48	17.55	0.45	0.3340	0.0000
2-Methyl-5-butylpyridine[d]	2.11	2.69	1.95	2.53	24.22	−0.33	0.3589	0.0000
2,6-Dimethoxypyridine[d]	0.36	−0.04	0.09	−0.31	14.71	0.28	0.4113	0.0000
2-Amino-4,6-dimethylpyridine[d]	0.19	−0.20	−1.15	−1.54	14.66	−1.00	0.2972	−0.3534

[a] Calculated using the method in Ref. 16.
[b] Values obtained from Reference 17.
[c] Log mole fraction solubility.
[d] Aldrich Chemical Co., Milwaukee, WI.
[e] Sigma Chemical Co., St. Louis, MO.
[f] Fluka Chemical Co., Ronkonkoma, NY.
[g] Pfaltz and Bauer, Inc., Waterbury, CT.

Iowa, Iowa City) was composed of two chambers separated by the membrane, which was sealed by an O-ring when the cell was assembled by fastening four screws through the aluminum faceplate. Stainless-steel inlet and outlet ports allowed access to the inner solution compartments. Circular stirrers, with a cross-hair pattern on their surface, were held in place and away from the membrane surface by an O-ring. A hole bored diametrically into the stirrer contained a magnetic stirring bar. All materials which came into direct contact with either the donor or the receiving solution were made of Teflon or stainless steel. Rotation of the stirrers was accomplished by the use of externally mounted, rotating 48-lb magnets driven by DC motors (CYQM 23061-5-2, Barber-Colman, Rockford, IL) controlled by a variable-voltage transformer (Tech II, Model 2800, Model Rectifer Corp., Edison, NJ). The maximum voltage setting was used to maintain a stirring speed of 575 rpm for all experiments. The outer portion of the diffusion cell was a water jacket made of Plexiglas. Nylon inlet and outlet ports connected the water jacket to a water bath and constant-temperature circulator (Model IC-2, Brinkmann Instruments, Westbury, NY) in order to maintain the experimental temperature at 30°C.

The donor solution, which consisted of the neat liquid for the liquid diffusants or an isopropyl alcohol solution at 90% of saturation for the solid diffusants, was circulated through a 25-mL Erlenmeyer flask suspended in the 30°C water bath. The change in the donor concentration during the diffusion experiment was negligible. The receiver solution was externally circulated (Lab Pump, Jr., Model RHSY, Fluid Metering, Inc., Oyster Bay, NY) through Teflon tubing (1/16 × 1/8-in. PFA, Cole-Parmer Instrument Co., Chicago, IL) to a jacketed beaker at 30°C of either 100-, 200-, or 500-ml-capacity depending on the molar absorptivity of the diffusant and through a flow-through quartz cell of either 1-mm

(Type 44/B Quartz, Starna Cell Inc., Atascadero, CA) or 10-mm (Type 1 mm FO1A 6, Pye Unicam) pathlength mounted in a spectrophotometer. The receiver solution reservoir was stirred using a magnetic stirrer (Magnester II, Lab-Line Instruments, Inc., Melrose Park, IL). Both the donor and the receiver solutions were pumped at a constant flow rate of 9 mL/min.

Data were collected by a microcomputer (Apple IIe, Apple Computer, Inc., Cupertino, CA) connected to the spectrophotometer by an analog-to-digital converter (Adalab Interface Card, Interactive Microware, Inc., State College, PA) and reduced by means of a standard software package (Spectrochart, Interactive Microware, Inc. State College, PA).

The steady-state region of the cumulative amount of diffusant-versus-time curve was assumed to begin at a time greater than 2.7 times the lag time (15). The slope was calculated using the linear least-squares method and was converted to steady-state flux using the membrane thickness, the membrane area (8.04 cm^2), and for the solid diffusants, the percentage of saturation of the donor solution. Steady-state flux was normalized to a membrane thickness of 1016 μm.

Multiple linear regression analysis was done using standard statistical software packages (Minitab Data Analysis Software, Release 7, Minitab, Inc.; BMDP Statistical Software, Los Angeles, CA).

RESULTS AND DISCUSSION

Effect of Substituent Hydrophobicity. It is well-known that the partition coefficient plays an important role in the determination of the magnitude of flux. While the actual partition coefficient between the membrane and the bathing solution is the desired value to use in flux determinations, it is rarely utilized because of experimental difficulties in its determination. In this work, several hydrophobic parameters were used as estimates of partition coefficient as shown in Table I (16,17). Neither the hydrophobic fragment constant, f_{oct}, nor the hydrophobic substituent constant, π_{oct}, by themselves proved to be a good predictor for flux as shown by Models 1 and 2 in Table II. When these parameters were transformed to their corresponding parameters in the cyclohexane/water partitioning system, f_{chex} and π_{chex}, by using Seiler's l_h variable (18), it is apparent from Models 3 and 4 in Table II that this hydrophobic parameter was a better predictor of flux in this membrane system. The major reason for this would appear to be that the PDMS membrane, like cyclohexane, possesses little ability to hydrogen bond with the various diffusants. Octanol, however, can form hydrogen bonds with many of the penetrants used in this study.

Effect of Substituent Volume. Since cooperative movements of the molecules in the polymer chain and the penetrating molecule are needed for diffusion to take place, even in a partitioning membrane like PDMS (19), and because the diffusion coefficient is inversely related to the molecular radius, it was not surprising to find that flux was inversely proportional to the volume of the penetrating molecule. Several parameters, such as molecular weight, Verloop volume, and molar refractivity (MR), can be used to represent molar volume (20,21). Molar refractivity was chosen to represent molar volume because it provided a better fit than the other parameters (12). A substantially better model was obtained when a volume term was included as seen from the statistics of Model 5 in Table II.

Table II. Comparison of Models Regressed Against Various Physicochemical Parameters

Model	Predictor	R^2_{cv} [a]	s [b]
1	f_{oct} [c]	0.418	0.987
2	π_{oct} [d]	0.312	1.073
3	f_{chex} [e]	0.861	0.481
4	π_{chex} [f]	0.847	0.506
5	$f_{chex,MR}$ [g]	0.922	0.366
6	$f_{chex,MR,\sigma}$ [h]	0.940	0.327
7	$f_{chex,MR,\sigma,100/mp}$ [i]	0.964	0.257
8	$f_{chex,MR,\log MF}$ [j]	0.971	0.226

[a] Cross-validated correlation coefficient; $n = 35$.
[b] Estimated standard deviation of the regression.
[c] Hydrophobic fragmental constant for octanol/water system.
[d] Hydrophobic substituent constant for octanol/water system.
[e] Hydrophobic fragmental constant for cyclohexane/water system.
[f] Hydrophobic substituent constant for cyclohexane/water system.
[g] Molar refractivity (mL/*M*).
[h] Hammett's para electronic constant.
[i] Transformation of melting point in K.
[j] Logarithm of the solubility in isopropyl alcohol expressed as the mole fraction.

Effect of Substituent Electronic Behavior. Electronic properties of the substituents strongly affect the electron density around the aromatic ring. If a molecule contains an electron donating or withdrawing substituent, the partial charge distribution may be significantly different from that of pyridine. Electronic interaction between a substituent and the ring nitrogen through special resonance may further complicate the substituent effects (22,23). These may lead to both changes in the partition coefficient between the PDMS membrane and isopropyl alcohol and changes in the solubility of the penetrant in the isopropyl alcohol. Hammett's σ constants were added to the model (24). These constants are representative of the benzene system but were chosen because of a lack of availability of similar parameters for the pyridine nucleus. A somewhat better fit is obtained as shown by Model 6 in Table II.

It is interesting to compare the equation which relates flux of benzene derivatives (12) to the same physicochemical properties used in Model 6.

The equations are

$$\log J_{ss} = -0.289 + 0.456 f_{chex} - 0.0898\ MR - 0.389\ \sigma \quad (2)$$

$$r^2 = 0.963, \quad SD = 0.177, \quad F = 196.457, \quad n = 31$$

for the benzene series and

$$\log J_{ss} = -0.936 + 0.56 f_{chex} - 0.0596\ MR - 0.349\ \sigma \quad (3)$$

$$r^2 = 0.940, \quad SD = 0.327, \quad F = 161.165, \quad n = 35$$

for the pyridine series.

While there are some similarities in the sign and magnitude of the coefficients, the benzene and pyridine models are not interchangeable. This is not surprising since one of the limitations of QSAR relationships is that they are chemical class limited, i.e., a predicted property of one class of compounds cannot be predicted by the relationship from another class of compounds.

Effect of Penetrant Melting Point. It was observed that compounds with a higher melting point had a lower steady-state flux. Most of these compounds not only are more polar, which would create a less favorable partition coefficient, but also have a higher molecular weight and therefore a larger molecular volume. Melting point (mp) becomes an indirect indicator of both partition coefficient and molecular volume. On these bases, it should be expected to be correlated with steady-state flux. The use of the nonlinear transformation, 100/mp, in which melting point is expressed as absolute temperature, produced better results than the use of melting point directly and improved the model as shown by Model 7 in Table II. The group size was set at 5 for the cross-validation process.

Model 7 is given by Eq. (4).

$$\log J_{ss} = -2.684 + 0.416\, f_{chex} - 0.040\ \mathrm{MR} - 0.339\ \sigma + 4.449\ (100/\mathrm{mp}) \quad (4)$$

$$r^2_{cv} = 0.964, \quad \mathrm{SD} = 0.2573, \quad F = 200.79, \quad n = 35$$

The critical value for the significance of the regression test is $F_{0.05}(4,30) = 4.62$. Since the F value is much greater than the critical value, the significance of the regression equation is accepted.

The technique of cross-validation (25) was used in order to generate a predictive r^2 value. This technique produces a predicted value for each diffusant, and not just a fitted or calculated value as is obtained by ordinary linear regression. The flux values predicted using Model 7 are given in Table III. The average compound is predicted within 1.81 times the experimental flux. The advantage of using Model 7 is that all of its parameters are available by calculations or from tables. The relative contributions of the normalized coefficients are given in Table IV.

Table III. Predicted Flux Using Models 7 and 8 (Group = 5)

Compound	Expt log J_{ss} (mmol/cm²/sec)	Predicted logJ_{ss} (mmol/cm²/sec)			
		Model 7	Residual	Model 8	Residual
3-Pyridinecarboxaldehyde	−1.823	−1.225	−0.598	−1.520	−0.303
3,5 Lutidine	−0.949	−0.882	−0.067	−0.938	−0.011
3-Hydroxypyridine	−2.685	−2.852	0.167	−2.577	−0.108
5-Chloro-3-pyridinol	−2.621	−2.909	0.288	−2.631	0.010
3,5-Dichloropyridine	−1.482	−1.383	−0.099	−1.240	−0.242
4-tert-Butylpyridine	−1.227	−0.856	−0.371	−0.936	−0.291
Nicotinic acid	−3.760	−3.488	−0.271	−3.512	−0.247
4-Picoline	−0.845	−1.023	0.178	−0.993	0.148
3-Acetylpyridine	−1.992	−2.039	0.048	−1.579	−0.413
3-Aminopyridine	−2.682	−2.178	−0.504	−2.054	−0.628
Pyridine	−0.695	−0.745	0.050	−0.972	0.277
2-Aminopyridine	−1.895	−2.261	0.367	−2.138	0.244
2-Chloro-6-methoxypyridine	−1.211	−1.212	0.001	−1.186	0.025
2-Ethylpyridine	−0.718	−0.740	0.022	−0.972	0.254
2-Chloropyridine	−1.081	−0.935	−0.146	−0.857	−0.223
2-Butoxypyridine	−1.155	−1.192	0.037	−1.240	0.084
2-Fluoropyridine	−0.878	−0.694	−0.184	−0.913	0.035
2-Methoxypyridine	−0.809	−1.067	0.258	−1.281	0.472
2-Methoxy-5-nitropyridine	−2.653	−2.554	−0.098	−2.952	0.299
2-Methyl-5-ethylpyridine	−0.868	−0.572	−0.297	−0.745	−0.123
2-Methoxy-5-aminopyridine	−2.230	−2.441	0.211	−2.167	−0.063
2-Hydroxy-5-nitropyridine	−3.747	−3.877	0.130	−3.895	0.148
6-Hydroxynicotinic acid	−5.400	−4.812	−0.588	−5.143	−0.258
2-Hydroxypyridine	−2.499	−2.795	0.296	−2.623	0.124
2,4-Dihydroxypyridine	−4.289	−4.474	0.186	−4.598	0.309
Picolinic acid	−3.282	−3.320	0.039	−3.218	−0.063
2-Amino-4-methylpyridine	−2.228	−2.244	0.016	−2.325	0.097
6-Chloronicotinic acid	−3.098	−3.502	0.404	−3.088	−0.010
2-Amino-5-chloropyridine	−2.625	−2.482	−0.143	−2.642	0.017
2-Amino-5-nitropyridine	−3.770	−3.445	−0.325	−3.622	−0.149
2,5-Pyridinedicarboxylic acid	−5.205	−5.359	0.155	−5.457	0.252
Ethyl nicotinate	−1.527	−2.006	0.480	−1.511	−0.016
2-Methyl-5-butylpyridine	−1.113	−1.120	0.007	−1.223	0.111
2,6-Dimethoxypyridine	−1.129	−1.597	0.468	−1.519	0.390
2-Amino-4,6-dimethylpyridine	−2.253	−2.060	0.193	−2.148	−0.105

Table IV. Relative Contributions of the Independent Variables for Models 7 and 8

Independent variable	Fraction	
	Model 7	Model 8
f_{chex}	0.560	0.528
MR	0.129	0.137
σ	0.096	—
100/mp	0.215	—
log*MF*	—	0.335

Effect of Penetrant Solubility. Under sink conditions, steady-state flux should be directly proportional to the donor concentration. Therefore, for two compounds with the same partition coefficient, the one possessing the higher solubility will have the higher steady-state flux if both are at the same fraction of saturation in the donor solution. The logarithmic transformation of the solubility of the penetrant in isopropyl alcohol expressed using the mole fraction scale was added to form Model 8 in Table II. After this was done the regression procedure removed both σ and 100/mp from the equation. The correlation and the standard deviation of the predictive line were improved again. As before, the group size was set at five for the cross-validation process.

Model 8 is given by Eq. (5).

$$\log J_{ss} = -0.943 + 0.362 f_{chex} - 0.040\ \mathrm{MR} + 0.500 \log MF \quad (5)$$

$$r^2_{cv} = 0.971, \quad \mathrm{SD} = 0.2264, \quad F = 348.52, \quad n = 35$$

The critical value for the significance of the regression test is $F_{0.05}(3,31) = 2.911$.

Flux values predicted using Model 8 are given in Table III. The prediction of flux using Model 8 is somewhat better than the predictions of Model 7. The average compound is predicted within 1.68 times the experimental flux. The relative contributions of the normalized coefficients are given in Table IV.

A potential disadvantage of this model is that the solubility of the penetrant has to be determined in isopropyl alcohol. However, once solubilities were determined, a fragmental model for solubility prediction was developed and could be utilized in future work (26).

REFERENCES

1. R. L. Bronaugh and E. R. Congdon. Percutaneous absorption of hair dyes: Correlation with partition coefficient. *J. Invest. Dermatol.* **83**:124–127 (1984).
2. K. A. Herzog and J. Swarbrick. Drug permeation through thin-model membranes. III. Correlations between *in vitro* transfer, *in vivo* absorption, and physicochemical parameters of substituted benzoic acids. *J. Pharm. Sci.* **60**:1666–1668 (1971).
3. L. Khordagy, N. Khalafallah, and S. Khalif. *In vitro* transport of substituted benzoic acids across liquid and solid barriers and its correlation to *in vivo* data. *Pharm. Acta Helv.* **56**:222–224 (1981).
4. A. S. Michaels, S. K. Chandrasekaran, and J. E. Shaw. Drug permeation through human skin: Theory and *in vitro* experimental measurement. *AlChE* **21**:986–996 (1975).
5. K. Nasim, M. C. Meyer, and J. Autian. Permeation of aromatic organic compounds from aqueous solutions through polyethylene. *J. Pharm. Sci.* **61**:1775–1780 (1972).
6. P. V. Shah, R. J. Monroe, and F. E. Guthrie. Comparative rates of dermal penetration of insecticides in mice. *Toxicol. Appl. Pharm.* 59:414–423 (1981).
7. G. W. C. Hung, and J. Autian. Use of thermal gravimetric analysis in sorption studies. II. Evaluation of diffusivity and solubility of a series of aliphatic alcohols in polyurethane. *J. Pharm. Sci.* **61**:1094–1098 (1972).
8. R. E. Lacey and D. R. Cowsar. Factors affecting the release of steroids from silicones. In A. C. Tanquary and R. E. Lacey (eds.), *Controlled Release of Biologically Active Agents, Adv. Exp. Med. Biol.* 47:117–144 (1974).
9. E. J. Lien and G. L. Tong. Physico-chemical properties and percutaneous absorption of drugs. *J. Soc. Cosmet. Chem.* 24:371–384 (1973).
10. E. J. Lien and P. H. Wang. Lipophilicity, molecular weight, and drug action: Reexamination of parabolic and bilinear models. *J. Pharm. Sci.* 69:648–650 (1980).
11. E. J. Lien. Structure activity relationships and drug disposition. In R. George, R. Okun, and A. K. Cho (eds.), *Annu. Rev. Pharmacol. Toxicol.* **21**:31–61 (1981).
12. D. M. Moeckly and L. E. Matheson. The development of a predictive model for the estimation of diffusion rates through polydimethylsiloxane membranes. I. Identification of critical variables for a series of substituted benzenes. *Int. J. Pharm.* 77:151–162 (1991).
13. L. E. Matheson, P. Vayumhasuwan, and D. M. Moeckly. The development of a predictive method for the estimation of diffusion rates through polydimethylsiloxane membranes. II. Derivation of a diffusion parameter and its application to multisubstituted benzenes. *Int. J. Pharm.* 77:163–168 (1991).
14. E. R. Garrett and P. B. Chemburkar. Evaluation, control, and prediction of drug diffusion through polymeric membranes. I. Methods and reproducibility of steady-state diffusion studies. *J. Pharm. Sci.* 57:944–948 (1968).
15. J. Crank. *The Mathematics of Diffusion,* Oxford Press, London, 1956, p. 48.
16. R. F. Rekker. *The Hydrophobic Fragmental Constant, Its Derivation and Application. A Means of Characterizing Membrane Systems,* Pharmaco Chemistry Library, Elsevier, New York, 1977, Vol. 1.
17. C. Hansch and A. Leo. Pomona College Medicinal Chemistry Project, Issue 23, 1983.
18. P. Seiler. Interconversion of lipophilicities from hydrocarbon/water systems into the octanol/water system. *Eur. J. Med. Chem.* 9:473–479 (1974).
19. W. R. Lieb and W. D. Stein. Implications of two different types of diffusion for biological membranes. *Nature New Biol.* 234:220–222 (1971).
20. A. Verloop, W. Hoogenstraaten, and J. Tipker. Development and application of new steric parameters in drug design. In E. J. Ariens (ed.), *Drug Design,* Academic Press, New York, Vol. 7, 1976, pp. 165–319.
21. C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien. "Aromatic" substituent constants for structure-activity correlations. *J. Med. Chem.* **16**:1207–1222 (1973).
22. R. A. Barnes. Properties and reactions of pyridine and its hydrogenated derivatives. In E. Klingsberg (ed.), *Pyridine and Its Derivatives,* Part I, Interscience, New York, 1960, Chap. 1.
23. T. E. Peacock. *Electronic Properties of Aromatic and Heterocyclic Molecules,* Academic Press, New York, 1965.
24. D. D. Perrin. In S. H. Yalkowsky, A. A. Sinkula, and S. C. Valvani (eds.), *Physical Chemical Properties of Drugs,* 1980. p. 1.
25. R. H. Myers. *Classical and Modern Regression with Applications,* 2nd ed., 1990, p. 167.
26. M.-W. Hu. *Prediction of the Diffusion Rate of Aromatic and Heteroaromatic Compounds in Polydimethylsiloxane Membranes,* Ph.D. thesis, University of Iowa, Iowa City, 1990.