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The development of a predictive method for the estimation of flux through polydimethylsiloxane membranes. II. Derivation of a diffusion parameter and its application to multisubstituted benzenes

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Summary

A substituent diffusion parameter, *Y*, was obtained from experimental diffusion data of a series of monosubstituted benzenes. This additive, constitutive parameter was correlated with the flux of 24 multisubstituted benzene derivatives consisting of *ortho*, *meta* and *para* disubstituted and several trisubstituted compounds. The correlation was significantly improved by the use of an indicator variable signifying the presence of intramolecular hydrogen bonding in some of the *ortho* compounds. The ability of the two models to predict flux was tested by application to a series of 20 benzene derivatives which were not part of the model data set.

Introduction

The rate of diffusion has been shown to be related to several linear free energy terms. These relationships have been useful in identifying critical parameters in the diffusion process. Factors that appear to influence the diffusion rate are hydrophobicity, polarizability, molecular size and electronic effects (Herzog and Swarbrick, 1971; Hung and Autian, 1972; Nasim et al., 1972; Lien and Tong, 1973; Lacey and Cowsar, 1974; Michaels et al., 1975; Lien and Wang, 1980; Khordagy et al., 1981; Lien, 1981; Shah et al., 1981; Bronaugh and Congdon, 1984).

It would be useful to be able to combine these critical factors into a single diffusion parameter, which would allow prediction of the flux of compounds based on their chemical structure through polydimethylsiloxane (PDMS) membranes. This concept is based on the fact that steady-state flux can be represented as the sum of additive, constitutive parameters (Moeckly and Matheson, 1991). Flux through PDMS membranes will not have the same values as those obtained in skin, however, a good correlation between them does exist and

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will eventually be useful for prediction of flux through skin (Moeckly, 1986).

Materials and Methods

The flux of multisubstituted benzene derivatives through supported PDMS sheeting (Silastic, Dow Corning Corp., Midland, MI) was measured using a previously described in vitro technique (Vayumhasuwan, 1988; Moeckly and Matheson, 1991). The diffusants listed in Table 2 were used as the model data set, while those in Tables 3 and 4 were used as the test data sets.

Conditions for solubility determination and the diffusion experiments were identical to those used in the preceding study of the monosubstituted benzenes (Moeckly and Matheson, 1991).

TABLE 1

Primary substituent diffusion parameters calculated from the flux of monosubstituted benzenes using Eqn 1

Substituent	Y	Substituent	Y
$-SO_2NH_2$	−3.14	$-(C{=}O)H$	−1.23
$-NH(C{=}O)NH_2$	−3.05	$-SCH_3$	−1.14
$-(C{=}O)NHOH$	−3.01	$-I$	−1.05
$-(C{=}O)NH_2$	−2.81	$-(C{=}O)OCH_3$	−1.20
$-COOH$	−2.06	$-O(CH_2)_3CH_3$	−0.997
$-CH_2CH_2C_6H_5$	−1.72	$-OCH_2CH_3$	−0.853
$-CH{=}CHCO_2CH_2CH_3$	−1.69	$-OCH_3$	−0.776
$-CH_2C_6H_5$	−1.69	$-(CH_2)_3CH_3$	−0.604
$-OC_6H_5$	−1.56	$-CH{=}CH_2$	−0.455
$-NH_2$	−1.49	$-CH_2CH_3$	−0.299
$-NO_2$	−1.47	$-Cl$	−0.284
$-O(C{=}O)CH_3$	−1.40	$-CF_3$	−0.255
$-(C{=}O)CH_3$	−1.38	$-CH_3$	−0.133
$-OH$	−1.31	$-H$	0.000
$-CN$	−1.30	$-F$	0.000

Results and Discussion

A diffusion parameter, Y, was defined in a manner analogous to the definition of other linear free energy relationships. This parameter was based on data collected in the preceding article for the monosubstituted benzene series (Moeckly and Matheson, 1991):

$$Y = \log J_{ss}^{R} - \log J_{ss}^{H} \quad (1)$$

where J_{ss} is the experimental steady-state flux and the superscripts R and H refer to the substituted and parent compound (benzene), respectively. The Y value for each of the substituents present on 30 monosubstituted benzenes is listed in Table 1.

The total diffusion parameter was calculated for each of the 24 multisubstituted benzene derivatives in the model data set by summing the Y values in Table 1 for each substituent present on the ring to yield the Y_T values listed in Table 2:

$$Y_T = \Sigma Y_i \quad (2)$$

These sums represent, to a first approximation, an estimation of flux, however, since they originated from monosubstituted benzene derivatives, they do not take into account any interaction among substituents on the benzene nucleus. These sums and their residuals along with the corresponding experimental log J_{ss} values are presented in Table 2.

The experimental flux values were regressed against Y_T and yielded the following equation:

$$\log J_{ss} = 0.851 Y_T - 0.363$$

$$r^2 = 0.910;\ \text{S.D.} = 0.340;\ n = 24;$$

$$F_{1,22} = 223.336 \quad (3)$$

This equation demonstrates that interaction between substituents is occurring, since the slope is not equal to unity and the intercept is not zero. The flux values calculated using Eqn 3 along with their residuals are given in Table 2.

While the ability to predict flux was improved overall by the use of Eqn 3 compared to merely using Y_T directly, it is still apparent that four of the *ortho* substituted compounds, namely, salicylic acid, 2-hydroxyacetophenone, methyl salicylate and 3-hydroxy-4-methoxybenzoic acid, have high residuals. All of these compounds, with the exception of 3-hydroxy-4-methoxybenzoic acid, are

capable of forming strong intramolecular hydrogen bonds. It is also interesting to note that the residuals for the three compounds capable of forming the intramolecular bonds are all positive while that of 3-hydroxy-4-methoxybenzoic acid is negative. This suggests that while the reason for the high residual for this material is unclear it does not appear to be the same as that for the other three compounds. The ability to form intramolecular hydrogen bonds effectively counters the hydrophilic effects of the adjacent polar substituents and increases the lipophilic character of the compounds, resulting in an experimental diffusion rate that is much greater than predicted by the values of the diffusion parameters. To take this factor into account, an indicator variable (IHB) was included in the equation and was set equal to unity for those compounds possessing intramolecular hydrogen bonding ability and to zero for all other compounds. The inclusion of the indicator variable resulted in an overall improvement in fit, as shown by the increase in correlation coefficient and decrease in the standard deviation in Eqn 4:

$$\log J_{ss} = 0.924Y_T + 0.952\text{IHB} - 0.346$$

$$r^2 = 0.986;\ \text{S.D.} = 0.140;\ n = 24;$$

$$F_{2,21} = 199.348 \qquad (4)$$

Eqn 4 indicates that log J_{ss} should be increased by 0.952 for those compounds having substituents with intramolecular hydrogen bonding ability. A significant decrease in residual values is achieved by the use of Eqn 4 except for 4-hydroxybenzamide and 3-chloro-4-methylaniline.

TABLE 2

Experimental and calculated steady-state flux for the model data set of multisubstituted benzenes

Compound	Experimental log J_{ss} (μM cm^{-2} s^{-1})	Y_T	Calculated log J_{ss} (μM cm^{-2} s^{-1})				
			Residual	Eqn 3	Residual	Eqn 4	Residual
Salicylic acid	−2.57	−3.28	0.71	−3.15	0.58	−2.42	−0.15
1-Fluoro-2-nitrobenzene	−1.84	−1.47	−0.37	−1.61	−0.23	−1.70	−0.14
2-Hydroxyacetophenone	−1.78	−2.69	0.91	−2.65	0.87	−1.88	0.10
Methyl salicylate	−1.67	−2.51	0.84	−2.50	0.83	−1.71	0.04
2-Chlorotoluene	−0.77	−0.42	−0.35	−0.72	−0.05	−0.73	−0.04
o-Xylene	−0.64	−0.27	−0.38	−0.59	−0.05	−0.59	−0.05
3-Hydroxybenzoic acid	−3.46	−3.28	−0.18	−3.15	−0.31	−3.38	−0.08
m-Anisaldehyde	−2.09	−2.00	−0.09	−2.07	−0.03	−2.19	0.10
3-Phenoxytoluene	−2.01	−1.69	−0.32	−1.80	−0.21	−1.91	−0.10
1-Fluoro-3-nitrobenzene	−1.62	−1.47	−0.15	−1.61	−0.01	−1.70	0.08
3-Chlorotoluene	−0.84	−0.42	−0.42	−0.72	−0.12	−0.73	−0.11
m-Xylene	−0.58	−0.27	−0.31	−0.59	0.01	−0.59	0.01
4-Hydroxybenzamide	−3.83	−4.12	0.29	−3.87	0.04	−4.15	0.32
4-Hydroxybenzoic acid	−3.31	−3.28	−0.03	−3.15	−0.16	−3.38	0.07
4′-Aminoacetophenone	−3.04	−2.87	−0.17	−2.81	−0.23	−3.00	−0.04
p-Anisaldehyde	−2.07	−2.01	−0.06	−2.07	0.00	−2.20	0.13
1-Fluoro-4-nitrobenzene	−1.60	−1.47	−0.13	−1.61	0.01	−1.70	0.10
4-Chlorotoluene	−0.69	−0.42	−0.28	−0.72	0.02	−0.73	0.04
p-Xylene	−0.46	−0.27	−0.19	−0.59	0.13	−0.59	0.13
3-Hydroxy-4-methoxybenzoic acid	−4.37	−4.06	−0.31	−3.82	−0.55	−4.10	−0.27
3′-Nitro-4′-chloroacetophenone	−3.33	−3.13	−0.20	−3.03	−0.30	−3.24	−0.09
3-Nitro-4-fluorotoluene	−2.03	−1.60	−0.43	−1.72	−0.31	−1.82	−0.21
3-Chloro-4-methylaniline	−1.96	−1.91	−0.05	−1.99	0.03	−2.11	0.15
1,2,4-Trimethylbenzene	−0.74	−0.40	−0.34	−0.70	−0.04	−0.71	−0.03

TABLE 3

Prediction of flux for the test data set using primary diffusion parameters

No.	Compound	Experimental log J_{ss} (μM cm^{-2} s^{-1})	Y_T	Calculated log J_{ss} (μM cm^{-2} s^{-1})				
				Residual	Eqn 3	Residual	Eqn 4	Residual
1	2′-Chloroacetophenone [a]	−1.83	−1.66	−0.17	−1.78	−0.05	−1.88	0.05
2	2-Chlorobenzaldehyde [a]	−1.58	−1.51	−0.07	−1.65	0.07	−1.74	0.16
3	Ethylparaben [a]	−2.69	−2.84	0.15	−2.78	0.09	−2.97	0.28
4	Ethyl 2-methylbenzoate [a]	−1.48	−1.47	−0.01	−1.61	0.13	−1.70	0.22
5	2′-Nitroacetophenone [a]	−2.80	−2.85	0.05	−2.79	−0.01	−2.98	0.18
6	1,3-Diethylbenzene [a]	−0.77	−0.60	−0.17	−0.87	0.10	−0.90	0.13
7	2-Nitrobenzoic acid [a]	−2.86	−3.53	0.67	−3.37	0.51	−2.66	−0.20
8	2-Chlorophenol [a]	−0.88	−1.59	0.71	−1.72	0.84	−0.86	−0.02

[a] Aldrich Chemical Co., Milwaukee, WI.
[b] Pfaltz and Bauer, Inc., Waterbury, CT.

Prediction of flux for the test data set containing primary substituents

In order to test the applicability of Eqns 3 and 4, the equations were used to predict the flux of a test data set of eight additional multisubstituted benzene derivatives as listed in Table 3 (Vayumhasuwan, 1988). For these compounds it was possible to use the diffusion substituent parameter values in Table 1 directly, since identical substituents appear in these compounds. The predictive ability of Eqn 3 for compounds 1–6 is quite good, since none of these compounds is able to hydrogen bond intramolecularly. However, for compounds 7 and 8 the residual values are considerable and for both of them the possibility of undergoing an intramolecular interaction is high.

The predictive ability of Eqn 4 for both of these compounds, when the indicator variable is given a value of unity, is much better and the residuals from Eqn 4 become much less than for Eqn 3. In general though, the residual values for compounds 1–6 are greater for Eqn 4 than for

TABLE 4

Prediction of flux for the test data set compounds using secondary diffusion parameters

No.	Compound	Experimental log J_{ss} (μM cm^{-2} s^{-1})	Y_T	Calculated log J_{ss} (μM cm^{-2} s^{-1})				
				Residual	Eqn 3	Residual	Eqn 4	Residual
1	Ethyl salicylate [a]	−1.61	−2.64	1.03	−2.61	1.00	−1.83	0.22
2	DL-2-(2-Chlorophenoxy)propionic acid [a]	−2.53	−3.25	0.72	−3.13	0.60	−2.40	−0.13
3	4-Isopropylbenzaldehyde [a]	−1.64	−1.63	−0.01	−1.75	0.11	−1.85	0.21
4	2-Chlorophenoxyacetic acid [a]	−2.83	−3.12	0.29	−3.02	0.19	−3.23	0.40
5	4-*tert*-Butylphenol [a]	−1.90	−1.84	−0.06	−1.93	0.03	−2.05	0.15
6	Methyl 4-*tert*-butylbenzoate [a]	−1.71	−1.73	0.02	−1.84	0.13	−1.94	0.23
7	4-*tert*-Butylbenzoic acid [a]	−2.53	−2.59	−0.06	−2.57	0.04	−2.74	0.21
8	4-*tert*-Butyltoluene [a]	−0.92	−0.67	−0.25	−0.93	0.01	−0.97	0.05
9	2-Chloro-4′-fluoroacetophenone [a]	−1.64	−1.66	0.02	−1.78	0.14	−1.88	0.24
10	2-Aminobenzyl alcohol [a]	−2.63	−2.93	0.30	−2.60	−0.03	−2.78	0.15
11	2-(*m*-Hydroxyphenoxy)ethanol [b]	−3.54	−3.47	−0.07	−3.32	−0.22	−3.55	0.01
12	4-Methoxybenzyl acetate [b]	−2.13	−2.31	0.18	−2.33	0.20	−2.48	0.35

[a] Aldrich Chemical Co., Milwaukee, WI.
[b] Pfaltz and Bauer, Inc., Waterbury, CT.

Eqn 3. This appears to indicate that Eqn 3 is better able to predict the flux for those compounds not able to form intramolecular hydrogen bonds, but that Eqn 4 is a much better predictor for those that possess the ability for an intramolecular interaction.

Prediction of flux for the test data set containing secondary fragments

The diffusion substituent parameters in Table 1 cannot be applied directly to the compounds in Table 4, but it is interesting to attempt to extend their application to them, since the fragments in these compounds are fairly similar in structure to the substituents in Table 1. For example, the $-(C{=}O)OCH_2-$ fragment in ethyl salicylate is similar in structure to the acetate group in Table 1, so, at least, to a first approximation, the Y value of -1.20 is chosen for this fragment and added to the values of -1.31 for $-OH$ and -0.133 for $-CH_3$ to yield a value for Y_T of -2.64 shown in Table 4. The secondary fragment diffusion parameters based on the values of the primary substituent diffusion parameters in Table 1 are listed in Table 5.

Eqn 3 again predicts the flux quite well for all but the first two compounds in Table 4, which have the ability to hydrogen bond intramolecularly and again are better predicted by Eqn 4. Overall, except for compounds 1 and 2, the residuals are somewhat less for Eqn 3 than for Eqn 4. The residuals in Table 4 are somewhat higher than those in Table 3, but this is to be expected, since the secondary fragmental values do not take into account the effects of branching for the isopropyl and *t*-butyl groups. In addition, the substituents in all the compounds in Tables 3 and 4, except for compounds 4 and 12 in Table 4, are bonded directly to the benzene ring just as they were in the monosubstituted benzenes from which they were derived. The residuals for both of these compounds are fairly high. Unpublished observations (Vayumhasuwan, 1988) indicate that, when the primary substituent of a polar functionality is displaced by one or more methylene groups from the ring, the flux is increased and that prediction will be low if the primary substituent diffusion parameters are used directly.

This report is based on relationships similar to those found by others between flux and physicochemical properties (Lien and Tong, 1973), but many more classes of compounds were studied and included in the same model in this work. The relationships obtained were broader in scope and application than previously. In addition, it is demonstrated that the dependency of flux on several physico-chemical properties could be reduced to a single diffusion parameter capable of predicting the flux of compounds not in the data set. This has led us to the conclusion that it is possible to develop a fragmental model for prediction of flux. Work on these models has been completed and is being prepared for publication.

TABLE 5

Secondary fragmental diffusion parameters estimated from primary substituent diffusion parameters from Table 1 used to estimate Y_T for compounds in Table 4

Secondary fragment	Primary substituent	Y
$-(C{=}O)CH_2-$	$-(C{=}O)CH_3$	-1.38
$-(C{=}O)OCH_2-$	$-(C{=}O)OCH_3$	-1.20
$-OCH_2CH_2-$	$-OCH_2CH_3$	-0.853
$-OCH_2-$	$-OCH_3$	-0.776
$-OCH-$	$-OCH_3$	-0.776
$-CH(CH_3)_3$	$-(CH_2)_3CH_3$	-0.604
$-CH(CH_3)_2$	$3\times-CH_3$	-0.399
$-CH_2-$	$-CH_3$	-0.133

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