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

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The steady-state flux of 33 substituted quinoline 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, intramolecular hydrogen bonding ability, melting point, and mole fraction solubility were employed to develop empirical models capable of relating the rate of diffusion to these characteristics of either the substituent on the quinoline ring or the compound itself.

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

INTRODUCTION

Moeckly and Matheson (1) and Matheson *et al.* (2) recently developed empirical models which predicted the flux of a series of multisubstituted benzenes through a polydimethylsiloxane (PDMS) 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. Hu and Matheson (3) extended this work to a series of substituted pyridines which included, in addition to the terms above, a contribution from the melting point and the solubility of the penetrant.

The purpose of this study was to extend the earlier concept to a series of substituted quinolines to develop a relationship between their flux through polydimethylsiloxane membranes and various physicochemical parameters, thereby allowing prediction of their flux.

MATERIALS AND METHODS

The 33 compounds were used in this study as received and are listed in Table I. The methods of determination of their solubility and flux were described earlier as were the data analysis techniques (3). The quinoline structure is numbered using the definitive rules for nomenclature of organic chemistry (4).

In this paper, as in the others in this series, the models are built stepwise to show the influence of a subsequent parameter on the model. Fick's law indicates that the partition coefficient, the molar volume, a factor determining the magnitude of the diffusion coefficient, and the concentration gradient are the most important parameters controlling the magnitude of flux for a given compound. These parameters are included in this series of models and are the most significant contributors, but as molecular structures become more complicated, it is necessary to introduce additional factors to account for these complexities. Consequently, a parameter which acts as a partition coefficient correction term for a given structure with the ability to bond intramolecularly, must be added to the model.

RESULTS AND DISCUSSION

Effect of Substituent Hydrophobicity. Several hydrophobic parameters were used as estimates of partition coefficient as shown in Table I (5,6). Neither the hydrophobic fragment constant, f_{oct}, nor the hydrophobic substituent constant, π_{oct}, by itself proved to be a good predictor for flux as shown in Models 1 and 2 in Table II. Just as for the benzene (1) and pyridine derivatives (3), transformation of these parameters from the octanol/water partitioning system to the cyclohexane/water partitioning system, f_{chex} and π_{chex} (7), provided better predictions of flux in this membrane system as shown by Models 3 and 4 in Table II. The major reason for this would appear to be that neither the PDMS membrane nor cyclohexane possesses the ability to hydrogen bond with the diffusant, while octanol can form hydrogen bonds with many of the penetrants used in this study, thereby yielding a partition coefficient that is estimated to be too high for this membrane system.

Effect of Substituent Volume. It was not surprising to find the flux was inversely proportional to the volume of the penetrating molecule. Hung *et al.* (8) reported that 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 due to an increase in the molecular cross-sectional area. Lacey and Cowsar (9) concluded from a study of steroid diffusion through polydimethylsiloxane (PDMS) membranes that diffusivity was a function of both the polarity and the cross-sectional area of the molecule. Several parameters, such as molecular weight, Verloop volume, and molar refractivity (MR), can be used to represent molar volume (10). Molar refractivity was chosen to represent molar volume because it provided a better fit than the other parameters (1). A substantially better model can be obtained when the molar refractivity term is included as seen from the statistics of Model 5 in Table II.

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

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Table I. Various Physicochemical Parameters for the Substituted Quinoline Series

Compound	f_{oct}[a]	π_{oct}[b]	f_{chex}[a]	π_{chex}[a]	MR[b]	σ[b]	100/mp	log MF[c]
Quinoline[d]	0.18	0.00	0.02	−0.16	1.03	0.00	0.3883	0.0000
4-Methylquinoline[d]	0.70	0.56	0.54	0.40	5.65	−0.17	0.3540	0.0000
6-Methoxyquinoline[d]	0.27	−0.02	0.00	−0.29	7.87	−0.27	0.3425	0.0000
3-Quinolinecarboxylic acid[d]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.1813	−2.8508
4,7-Dichloroquinoline[d]	1.66	1.42	1.50	1.14	11.03	0.46	0.2793	−1.5670
2-Methyl-8-hydroxyquinoline[d]	0.18	−0.05	−2.58	−2.97	7.47	−0.54	0.2894	−1.4485
6-Methylquinoline[d]	0.70	0.56	0.54	0.40	5.65	−0.17	0.3390	0.0000
8-Nitroquinoline[d]	−0.08	−0.28	−0.69	−0.89	7.36	0.78	0.2755	−2.2366
8-Hydroxyquinoline[d]	−0.34	−0.61	−3.10	−3.37	2.85	−0.37	0.2890	−1.5171
8-Aminoquinoline[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.2941	−1.0701
2-Chloro-4-methylquinoline[d]	1.44	1.29	1.28	0.97	10.65	0.06	0.3030	−0.9666
2-Methyl-8-nitroquinoline[d]	0.44	0.28	−0.17	−0.49	11.98	0.61	0.2421	−2.6840
5-Chloro-8-hydroxyquinoline[d]	0.40	0.12	−2.36	−2.80	7.85	−0.14	0.2525	−2.2660
2-Methyl-4-aminoquinoline[d]	−0.33	−0.76	−1.67	−2.26	10.04	−0.83	0.2268	−1.1561
5-Nitro-8-hydroxyquinoline[d]	−0.60	−0.89	−3.81	−4.26	9.18	0.41	0.2198	−3.1713
2-Methyl-6-methoxyquinoline[d]	0.79	0.54	0.52	0.11	12.49	−0.44	0.2976	−0.5146
2-Methylquinoline[d]	0.70	0.56	0.54	0.40	5.65	−0.17	0.3690	0.0000
6-Quinolinecarboxylic acid[e]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.1771	−3.0223
4-Methoxy-2-quinolinecarboxylic acid[d]	0.00	−0.34	−3.14	−3.64	13.77	0.18	0.2128	−3.0809
2-Quinolinecarboxylic acid[e]	−1.19	−0.32	−4.22	−3.35	6.93	0.45	0.2320	−2.0809
6-Isopropylquinoline[d]	1.64	1.53	1.48	1.37	14.96	−0.15	0.3173	0.0000
2-Hydroxy-4-methylquinoline[d]	0.18	−0.05	−2.58	−2.97	7.47	−0.54	0.2020	−2.4547
2,4-Quinolinediol[d]	−0.86	−1.22	−6.22	−6.74	4.67	−0.74	0.1592	−3.3565
6-Aminoquinoline[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.2558	−1.0013
5-Aminoquinoline[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.2625	−1.0867
3-Aminoquinoline[d]	−0.85	−1.32	−2.19	−2.66	5.42	−0.66	0.2743	−0.6925
2-Hydroxyquinoline[d]	−0.34	−0.61	−3.10	−3.37	2.85	−0.37	0.2121	−2.2111
4-Hydroxyquinoline[d]	−0.34	−0.61	−3.10	−3.37	2.85	−0.37	0.2110	−1.5316
6-Nitroquinoline[d]	−0.08	−0.28	−0.69	−0.89	7.36	0.78	0.2353	−2.5935
8-Quinolinecarboxylic acid[e]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.2174	−2.9393
4-Quinolinecarboxylic acid[d]	−0.09	−0.32	−3.12	−3.35	6.93	0.45	0.1898	−2.8268
5-Nitroquinoline[d]	−0.08	−0.28	−0.69	−0.89	7.36	0.78	0.2899	−1.4647
6-Methoxy-8-nitroquinoline[d]	0.01	−0.30	−0.71	−1.02	14.20	0.38	0.2315	−3.1675

[a] Calculated using the method in Ref. 4.
[b] Values obtained from Ref. 5.
[c] Log mole fraction solubility.
[d] Aldrich Chemical Co., Milwaukee, WI.
[e] Pfaltz and Bauer, Inc., Waterbury, CT.

quinoline. Electronic interaction between a substituent and the ring nitrogen through special resonance may further complicate the substituent effects (11,12). These may lead to changes in both the partition coefficient and the solubility of the penetrant in the isopropyl alcohol. Hammett's σ constants were added to the model (13). These constants are representative of the benzene system but were chosen because of a lack of availability of similar parameters for the quinoline nucleus. A somewhat better model is obtained as shown by Model 6 in Table II. Swain and Lupton's field-inducing and resonance effect parameters (14) were also tried instead of the σ constants in the regression analysis, but neither provided a significant improvement over Model 6.

Effect of Intramolecular Bonding. Intramolecular hydrogen bonding has been observed in quinolines in which the ring nitrogen acts as a hydrogen bond acceptor and the substituents, such as hydroxy, carboxylic acid, or amino at the 2 or 8 position, act as hydrogen bond donors. Intramolecular hydrogen bonding between a properly positioned substituent and the aromatic ring nitrogen increases the hydrophobicity of the diffusant. This results in an experimental diffusion rate much faster than the predicted value. In order to account for this effect, an indicator variable, IHB, was assigned a value of 1 for those compounds that can intramolecularly hydrogen bond and 0 for all other compounds as indicated in Table I. Inclusion of this predictor in Model 7 had a significant effect on the ability of the model to predict flux as shown in Table II.

Effect of Penetrant Melting Point. The effect of melting point on the flux of the quinoline derivatives was similar to its effect on the pyridine derivatives (3). The use of the nonlinear transformation, 100/mp, in which melting point is expressed as absolute temperature, produced better results than the use of the melting point itself and improved the fit as shown in Model 8 in Table II. The flux values predicted using Model 8 are presented in Table III. The group size was set at five for the cross-validation process.

Model 8 is given by Eq. (1).

Table II. Comparison of Models Regressed Against Various Physicochemical Parameters

Model	Predictor(s)	R^2_{CV}[a]	s[b]
1	f_{oct}[c]	0.232	0.929
2	π_{oct}[d]	0.225	0.933
3	f_{chex}[e]	0.539	0.720
4	π_{chex}[f]	0.391	0.827
5	f_{chex}, MR[g]	0.708	0.582
6	f_{chex}, MR, σ[h]	0.791	0.501
7	f_{chex}, MR, σ, IHB[i]	0.930	0.296
8	f_{chex}, MR, σ, IHB, 100/mp[j]	0.956	0.237
9	f_{chex}, MR, IHB, log MF[k]	0.973	0.182

[a] Cross-validated correlation coefficient; $n = 33$.
[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 constant.
[i] Indicator variable for intramolecular hydrogen bonding.
[j] Transformation of melting point (K).
[k] Logarithm of the solubility expressed as mole fraction.

$$\log J_{SS} = -4.307 + 0.357 f_{chex} - 0.075\ MR - 0.473\sigma + 8.022\ (100/mp) + 0.597\ IHB \quad (1)$$
$$s = 0.237,\quad r^2_{CV} = 0.956,\quad F = 118.54,\quad n = 33$$

The critical value for the significance of the regression test is $F_{0.05}(5,27) = 2.57$. Since the F value is much greater than the critical value, the significance of the regression equation is accepted. The average compound is predicted within 1.73 times the experimental flux.

Effect of Penetrant Solubility. More soluble quinoline derivatives were found to have higher diffusion rates. This effect is easily seen by examination of the flux of isomeric compounds. For example, the solubility of 2-quinolinecarboxylic acid is 18.4 mg/mL ($\log J_{ss} = -3.5523$), while that of 4-quinolinecarboxylic acid is 3.3 mg/mL ($\log J_{ss} = -4.5178$); and the solubility of 5-nitroquinoline is 78.7 mg/mL ($\log J_{ss} = -2.8620$), while that of 6-nitroquinoline is 5.7 mg/mL ($\log J_{ss} = -3.6146$). This is not unexpected because of the inverse relationship between melting point and solubility. The logarithmic transformation of the solubility of the penetrant in isopropyl alcohol expressed on the mole fraction scale was added to the predictors in Model 8. After this was done, both σ and the melting point transformation (100/mp)

Table III. Predicted Flux Using Models 8 and 9 (Group = 5)

Compound	Expt. $\log J_{SS}$ (μmol/cm^2/sec)	Predicted $\log J_{SS}$ (μmol/cm^2/sec)			
		Model 8	Residual	Model 9	Residual
Quinoline	−1.4903	−1.190	−0.301	−1.548	0.057
4-Methylquinoline	−1.8529	−1.625	−0.228	−1.605	−0.248
6-Methoxyquinoline	−2.0969	−2.052	−0.045	−1.964	−0.133
3-Quinolinecarboxylic acid	−4.4101	−4.690	0.280	−4.536	0.126
4,7-Dichloroquinoline	−2.3913	−2.538	0.146	−2.641	0.249
2-Methyl-8-hydroxyquinoline	−2.3752	−2.688	0.313	−2.867	0.492
6-Methylquinoline	−1.7474	−1.755	0.008	−1.641	−0.106
8-Nitroquinoline	−3.3947	−3.207	−0.187	−3.421	0.026
8-Hydroxyquinoline	−2.3583	−2.637	0.278	−2.728	0.369
8-Aminoquinoline	−2.2781	−2.214	−0.064	−2.346	0.068
2-Chloro-4-methylquinoline	−2.2996	−2.244	−0.055	−2.277	−0.023
2-Methyl-8-nitroquinoline	−3.8269	−3.577	−0.250	−3.786	−0.041
5-Chloro-8-hydroxyquinoline	−3.1655	−2.989	−0.176	−3.167	0.001
2-Methyl-4-aminoquinoline	−3.4809	−3.526	0.045	−3.294	−0.187
5-Nitro-8-hydroxyquinoline	−4.2195	−4.191	−0.028	−4.340	0.120
2-Methyl-6-methoxyquinoline	−2.2467	−2.476	0.229	−2.411	0.164
2-Methylquinoline	−1.6215	−1.526	−0.096	−1.623	0.002
6-Quinolinecarboxylic acid	−4.6724	−4.757	0.085	−4.557	−0.115
4-Methoxy-2-quinolinecarboxylic acid	−4.6171	−4.050	−0.568	−4.213	−0.404
2-Quinolinecarboxylic acid	−3.5523	−4.232	0.680	−3.712	0.160
6-Isopropylquinoline	−1.8972	−2.429	0.532	−1.991	0.094
2-Hydroxy-4-methylquinoline	−3.8755	−3.920	0.045	−4.146	0.270
2,4-Quinolinediol	−5.4693	−5.136	−0.333	−5.707	0.237
6-Aminoquinoline	−3.0606	−3.157	0.097	−3.090	0.029
5-Aminoquinoline	−3.1130	−3.051	−0.062	−3.089	−0.024
3-Aminoquinoline	−2.9338	−3.011	0.077	−2.881	−0.052
2-Hydroxyquinoline	−3.8125	−3.696	−0.117	−3.822	0.010
4-Hydroxyquinoline	−3.6878	−3.795	0.107	−3.442	−0.245
6-Nitroquinoline	−3.6146	−3.555	−0.059	−3.596	−0.019
8-Quinolinecarboxylic acid	−4.2129	−3.720	−0.493	−3.661	−0.552
4-Quinolinecarboxylic acid	−4.5178	−4.680	0.162	−4.474	−0.044
5-Nitroquinoline	−2.8620	−3.191	0.329	−2.961	0.099
6-Methoxy-8-nitroquinoline	−4.3323	−3.883	−0.450	−4.393	0.061

Table IV. Relative Contributions of the Independent Variables for Models 8 and 9

Independent variable	Fraction	
	Model 8	Model 9
f_{chex}	0.354	0.331
MR	0.134	0.127
σ	0.126	—
100/mp	0.247	—
logMF	—	0.349
IHB	0.230	0.193

were removed from the equation by the regression procedure to produce Model 9 as seen in Table II. Again, the group size was set at five for the cross-validation process.

It is interesting that addition of the solubility term causes the terms σ and melting point to be removed. This is not unexpected because of the well-known relationship between solubility and melting point. The correlation coefficient and the standard deviation of the predicted line again improved in this model.

Model 9 is given by Eq. (2).

$$\log J_{SS} = -1.418 + 0.318 f_{chex} - 0.069\ MR + 0.563 \log MF + 0.802\ IHB \quad (2)$$

$$s = 0.182, \quad r^2_{CV} = 0.973, \quad F = 256.41, \quad n = 33$$

The flux values predicted using Model 9 are presented in Table III. Prediction of flux using Model 9 is somewhat better than the predictions of Model 8. The average compound is predicted within 1.52 times the experimental flux. The relative contributions of the normalized coefficients are given in Table IV.

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