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Prediction of flux through polydimethylsiloxane membranes using atomic charge calculations

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Summary

A quantitative structure-transportability relationship (QSTR) for the prediction of flux of aromatic compounds through a polydimethylsiloxane (PDMS) membrane was developed using molecular modeling. A total of 103 compounds in 15 ring classes, including benzene, quinoline, naphthalene, pyridine, naphthyridine, furan, benzofuran, imidazole, benzimidazole, indole, thiophene, pyrrole, pyrazole, pyridazine and pyrazine, was studied. Maximum steady state flux was measured using isopropyl alcohol as solvent. Atomic charges in each molecule were computed using the Hückel-Gasteiger method. Flux was found to be significantly affected by atomic charge. Partial charge calculations combined with solubility and molecular weight provided a universal QSTR model for the estimation of flux for all 15 classes of compounds. The flux of the imidazoles was found to be systematically slower than expected while that of aliphatic amines was faster. An indicator variable for each of these two types of compounds was included in order to achieve the best predictive model. Crossvalidation, in which half of the data set is predicted by the other half, demonstrates that the model is robust and highly applicable.

Introduction

Passive absorption rates of substances through biological barriers can be related to the diffusion rates of the material through synthetic polymer membranes. Thus, the estimation of flux through a synthetic model membrane is potentially useful for the prediction of drug absorption through biological membranes. For example, it has been shown that the permeabilities of both excised and intact cornea could be related to the permeability of Pellethane membrane (Semla, 1987); the diffusion of non-electrolytes in the membrane system of *Chara ceratophylla* was similar to that in polymethylacrylate (Lieb and Stein, 1969); the flux of substituted benzenes through hairless mouse skin was related to their flux through PDMS membrane (Moeckly, 1986).

PDMS membrane has been frequently chosen as a model membrane for study (Garrett and Chemburker, 1968; Flynn and Yalkowsky, 1972; Twist and Zatz, 1986; Matheson et al., 1991). PDMS is a non-porous hydrophobic material through which polar compounds pass more slowly

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TABLE 1

Selected parameters, experimental, calculated and predicted steady-state flux

Compounds	MW	log MF	Σe_H	Σe_P	Expt log J_{ss}	Calc. log J_{ss}	Residual	Pred. log J_{ss}	Residual
m-Nitrobenzaldehyde	151.12	−1.476	0.134	0.588	−2.520	−3.001	0.481	−3.073	0.554
2,5-Pyridinedicarboxylic acid	167.12	−3.284	0.508	0.970	−5.205	−4.763	−0.442	−4.725	−0.480
1-Fluoro-4-nitrobenzene	141.10	0.000	0.000	0.228	−1.600	−1.216	−0.384	−1.179	−0.421
4-Aminoquinaldine	158.20	−1.156	0.316	0.323	−3.481	−3.109	−0.372	−3.149	−0.332
2-Ethylimidazole	96.13	−0.219	0.237	0.339	−2.975	−2.609	−0.366	−2.506	−0.469
2-Thiophenemethanol	114.17	0.000	0.213	0.380	−2.179	−1.831	−0.348	−1.799	−0.380
3-Hydroxypyridine	95.10	−0.848	0.251	0.307	−2.685	−2.341	−0.344	−2.243	−0.442
6-Quinolinecarboxylic acid	173.13	−3.022	0.252	0.649	−4.672	−4.336	−0.336	−4.351	−0.321
Terephthalic acid	166.13	−3.454	0.504	0.710	−5.145	−4.815	−0.330	−5.136	−0.009
3,5-Dimethylpyrazole	96.13	−0.557	0.248	0.245	−1.791	−2.119	0.328	−2.045	0.251
1,2,5-Trimethylpyrrole	109.17	0.000	0.000	0.000	−0.918	−0.597	0.321	−0.665	−0.253
2-Methyl-5-nitroimidazole	127.10	−2.482	0.235	0.588	−4.024	−4.343	0.318	−4.358	0.334
2-Methyl-5-ethylpyridine	121.00	0.000	0.000	0.306	−0.868	−1.181	0.313	−1.231	0.363
Pyrrole	67.09	0.000	0.234	0.000	−0.891	−1.204	0.313	−1.254	0.363
4-Nitrobenzoic acid	167.12	−2.064	0.252	0.586	−3.358	−3.664	0.306	−3.767	0.410
Phenylether	170.21	0.000	0.000	0.258	−1.810	−1.513	−0.297	−1.460	−0.350
Quinoline	129.16	0.000	0.000	0.295	−1.490	−1.197	−0.293	−1.159	−0.331
2-Quinolinecarboxylic acid	173.17	−2.081	0.253	0.620	−3.552	−3.837	0.285	−3.784	0.232
7-Nitroindole	162.15	−1.565	0.000	0.230	−2.659	−2.375	−0.284	−2.283	−0.376
2-Methylimidazole	82.11	−0.545	0.237	0.339	−2.797	−2.519	−0.278	−2.599	−0.198
6′-Hydroxynicotinic acid	139.11	−3.276	0.507	0.625	−5.100	−4.826	−0.274	−4.835	−0.265
1-Naphthoic acid	172.18	−1.478	0.252	0.357	−2.985	−3.254	0.269	−3.332	0.337
4-Carboxybenzaldehyde	150.13	−2.069	0.387	0.715	−3.440	−3.698	0.258	−3.826	0.386
1-Methylpyrrole	81.12	0.000	0.000	0.000	−0.657	−0.402	−0.255	−0.397	−0.260
2-Methyl-1-phenyl-2-propanol	150.22	0.000	0.210	0.387	−1.820	−2.068	0.248	−2.117	0.297
2,4-Quinolinediol	161.16	−3.357	0.513	0.299	−5.469	−5.221	−0.248	−5.131	−0.338
2-Furaldehyde	96.09	0.000	0.238	0.370	−1.530	−1.775	0.245	−1.702	0.172
Pyridazine	80.09	0.000	0.210	0.454	−1.865	−1.623	−0.242	−1.555	−0.310
(2-Chloroethyl)benzene	140.61	0.000	0.000	0.123	−1.292	−1.055	−0.237	−1.047	−0.245
Butyrophenone	148.21	0.000	0.000	0.378	−1.719	−1.488	−0.231	−1.420	−0.299
8-Aminoquinoline	144.18	−1.070	0.153	0.295	−2.278	−2.506	0.228	−2.445	0.167
2,5-Dimethylfuran	96.13	0.000	0.000	0.000	−0.280	−0.501	0.221	−0.556	0.276
1-Methylimidazole	82.11	0.000	0.121	0.330	−1.813	−2.031	0.218	−2.027	0.214
Benzofuran	118.14	0.000	0.107	0.000	−0.948	−1.161	0.213	−1.172	0.224
Pyridine	79.10	0.000	0.000	0.296	−0.695	−0.901	0.206	−0.739	0.044
6-Chloronicotinic acid	157.56	−1.594	0.252	0.630	−3.098	−3.302	0.204	−3.404	0.306
Aniline	93.13	0.000	0.300	0.000	−1.750	−1.954	0.204	−1.799	0.045
Pyrazole	68.08	−0.261	0.258	0.221	−1.597	−1.789	0.192	−1.618	0.021
6-Methoxyquinoline	159.19	0.000	0.000	0.619	−2.097	−1.922	−0.175	−1.805	−0.292
Biphenyl	154.21	−1.408	0.000	0.000	−2.050	−1.875	−0.175	−1.951	−0.099
2-Thiopheneacetic acid	142.18	−0.286	0.251	0.364	−2.475	−2.303	−0.172	−2.301	−0.174
2-Thiophenemethylamine	113.19	0.000	0.242	0.317	−1.410	−1.240	−0.170	−1.185	−0.225
Phenol	94.11	−0.025	0.248	0.000	−1.570	−1.734	0.164	−1.596	0.026
3,5-Dichloropyridine	147.99	−0.963	0.000	0.296	−1.824	−1.988	0.164	−2.064	0.240
2-Furoic acid	112.08	−0.668	0.356	0.363	−2.476	−2.639	0.163	−2.652	0.176
Butyl phenyl ether	150.22	0.000	0.000	0.318	−1.250	−1.412	0.162	−1.494	0.244
Toluene	92.14	0.000	0.000	0.000	−0.388	−0.546	0.158	−0.490	0.102
4-Chlorobenzylalcohol	142.59	−0.504	0.213	0.382	−2.504	−2.349	−0.155	−2.357	−0.147
2,5-Dimethylpyrrole	95.15	0.000	0.229	0.000	−1.400	−1.554	0.154	−1.499	0.099
4-Aminophenol	109.13	−2.129	0.538	0.000	−3.910	−4.064	0.154	−4.184	0.274
2,5-Dimethylthiophene	112.19	0.000	0.000	0.000	−0.468	−0.619	0.151	−0.690	0.222
2-Aminobenzylalcohol	123.16	−1.024	0.296	0.385	−2.630	−2.777	0.147	−2.768	0.138
5-Nitro-8-hydroxyquinoline	190.16	−3.171	0.000	0.527	−4.220	−4.073	−0.147	−3.827	−0.393

TABLE 1 (continued)

Compounds	MW	log MF	Σe_H	Σe_P	Expt log J_{ss}	Calc. log J_{ss}	Residual	Pred. log J_{ss}	Residual
2-Hydroxyquinoline	145.16	−2.211	0.256	0.279	−3.813	−3.667	−0.146	−3.661	−0.152
7-Amino-2,4-dimethyl-1,8-naphthyridine	173.22	−2.064	0.316	0.584	−3.663	−3.807	0.144	−3.922	0.259
Chlorobenzene	112.56	0.000	0.000	0.000	−0.540	−0.683	0.143	−0.693	0.153
Furfurylalcohol	98.10	0.000	0.213	0.380	−1.860	−1.723	−0.137	−1.684	−0.176
2-Methyl-5-nitrobenzimidazole	177.16	−1.875	0.229	0.555	−3.698	−3.563	−0.135	−3.676	−0.022
4,7-Dichloroquinoline	198.05	−1.567	0.000	0.296	−2.590	−2.716	0.126	−2.872	0.282
Imidazole	68.08	−0.386	0.362	0.330	−3.019	−2.894	−0.125	−2.945	−0.074
5-Chloro-8-hydroxyquinoline	179.61	−2.266	0.000	0.294	−3.166	−3.042	−0.124	−2.921	−0.245
6-Methoxyquinaldine	173.22	−0.515	0.000	0.626	−2.247	−2.360	0.113	−2.489	−0.242
Benzene	78.11	0.000	0.000	0.000	−0.256	−0.368	0.112	−0.404	0.148
2-Thiophenecarboxaldehyde	112.15	0.000	0.131	0.371	−1.685	−1.576	−0.109	−1.576	−0.109
Anisole	108.14	0.000	0.000	0.321	−1.030	−1.133	0.103	−1.014	−0.016
Aminopyrazine	95.11	−1.048	0.312	0.546	−2.587	−2.690	0.103	−2.643	0.056
Picolinic acid	123.11	−1.759	0.253	0.626	−3.282	−3.171	−0.111	−3.223	−0.059
6-Aminoquinoline	144.18	−1.001	0.302	0.301	−3.061	−2.961	−0.100	−2.889	−0.172
2-Naphthol	144.17	−0.556	0.249	0.000	−2.477	−2.377	−0.100	−2.335	−0.142
2-Methylthiophene	98.17	0.000	0.000	0.000	−0.426	−0.516	0.090	−0.541	0.115
Ethyl-2-methylbenzoate	164.21	0.000	0.000	0.361	−1.480	−1.570	0.090	−1.676	0.196
Isophthalic acid	166.13	−2.321	0.504	0.714	−3.987	−4.076	0.089	−4.466	0.479
Methylbenzoate	136.15	0.000	0.000	0.357	−1.460	−1.375	−0.085	−1.436	−0.024
t-Butylbenzene	134.22	0.000	0.000	0.000	−0.753	−0.837	0.084	−0.844	0.091
Methylparaben	152.15	−0.989	0.250	0.362	−2.740	−2.823	0.083	−2.833	0.093
3-Hydroxybenzoic acid	138.12	−0.880	0.500	0.357	−3.309	−3.230	−0.079	−3.467	0.158
4-Nitroimidazole	113.08	−3.478	0.351	0.540	−4.868	−4.945	0.077	−5.149	0.280
Phenylbutylamine	149.24	0.000	0.238	0.330	−1.397	−1.473	0.076	−1.516	0.119
Methylbenzylamine	121.18	0.000	0.213	0.382	−1.180	−1.252	0.072	−1.252	0.072
2-Chlorolepidine	177.63	−0.967	0.000	0.295	−2.300	−2.231	−0.069	−2.138	−0.162
Indole	117.15	−0.214	0.227	0.000	−1.846	−1.913	0.067	−1.774	−0.072
8-Nitroquinoline	174.16	−2.237	0.000	0.525	−3.395	−3.331	−0.064	−3.455	0.060
3-Quinolinecarboxylic acid	173.17	−2.851	0.252	0.647	−4.410	−4.349	−0.061	−4.249	−0.161
3-Chloroaniline	127.57	0.000	0.300	0.000	−2.015	−1.957	−0.058	−2.014	−0.001
Benzimidazole	118.14	−1.069	0.369	0.306	−2.944	−3.001	0.057	−2.976	0.032
6-Nitroquinoline	174.16	−2.593	0.000	0.525	−3.615	−3.563	−0.052	−3.349	−0.266
2-Hydroxy-4-methylquinoline	159.19	−2.545	0.256	0.291	−3.876	−3.826	−0.050	−3.824	−0.052
Benzoic acid	122.12	−0.698	0.252	0.357	−2.316	−2.364	0.048	−2.399	0.083
1,5-Dimethyl-2-pyrrole-carbonitrile	120.16	−0.720	0.000	0.366	−1.791	−1.748	−0.043	−1.781	−0.010
Furfurylamine	97.12	0.000	0.242	0.317	−1.116	−1.075	−0.041	−1.084	−0.032
5-Nitroquinoline	174.16	−1.465	0.000	0.521	−2.862	−2.825	−0.037	−2.950	−0.088
4-*t*-Butyltoluene	148.25	0.000	0.000	0.000	−0.915	−0.883	−0.032	−0.962	0.047
1-Methyl-2-phenoxyethylamine	151.21	0.000	0.238	0.641	−1.630	−1.603	−0.027	−1.656	0.026
Phenethylamine	121.18	0.000	0.236	0.328	−1.257	−1.278	0.021	−1.238	−0.019
2-Amino-5-nitropyridine	139.11	−2.382	0.300	0.529	−3.770	−3.763	−0.007	−3.673	0.097
4-Methoxy-2-quinolinic acid	203.20	−3.081	0.253	0.936	−4.617	−4.625	0.008	−4.893	0.276
p-Fluoro-α-methylbenzylamine	139.00	0.000	0.242	0.317	−1.420	−1.413	−0.007	−1.434	0.014
1,3-Diethylbenzene	134.22	0.000	0.000	0.000	−0.774	−0.780	0.006	−0.875	0.101
2,4-Dihydroxypyridine	111.10	−2.453	0.505	0.290	−4.289	−4.285	−0.004	−4.112	−0.177
1-Nitronaphthalene	173.17	−1.590	0.000	0.220	−2.447	−2.450	0.003	−2.378	−0.069
8-Hydroxyquinaldine	159.19	−1.449	0.000	0.299	−2.375	−2.378	0.003	−2.471	0.096
4-Aminoacetophenone	135.17	−1.276	0.304	0.385	−3.040	−3.042	0.002	−3.043	−0.003

than nonpolar compounds. In the extreme case, ionic compounds do not pass through the barrier (Garrett and Chemburkar, 1968).

The estimation of flux of various classes of compounds through PDMS membrane has been studied extensively by both conventional QSAR and molecular modeling approaches. Linear free energy relationships and other QSAR models involving electronic, steric and physico-chemical parameters were established for the flux of substituted benzenes (Matheson et al., 1991; Moeckly and Matheson, 1991), pyridines and quinolines (Hu, 1990) and aliphatic compounds (Narayanaswamy, 1992). More general models for different classes of aromatic compounds were also developed using a fragmental approach (Laoratthaphong, 1989; Hu, 1990) and by molecular modeling (Liu, 1991).

Classical QSAR relationships, such as the one relating chain length to activity (Yalkowsky and Flynn, 1973), apply only to homologs with different alkyl carbon numbers, while the other functional groups remain the same. This limitation makes it difficult to compare target parameters among different classes of compounds. For this reason, a general model is needed. Computer-aided three-dimensional QSAR, has been able to extract and relate the common 'field' properties to activities of noncongeneric compounds by comparative field analysis (Cramer et al., 1988; Liu, 1991). This suggests a general model for the prediction of the target parameters of various classes of compounds is possible.

It is well known that electronic structure is one of the most important factors in the determination of chemical and physical properties. Atomic charge has been used to estimate both the chromatographic retention indices of polyhalogenated biphenyls (Hasan and Jurs, 1990) and the aqueous solubility of various of organic compounds (Bodor and Huang, 1992). The Hammett substituent constant, σ, has been found to significantly influence flux (Moeckly and Matheson, 1991). Polarity of compounds may be measured as dipole moment, which was found to be significantly correlated to flux (Hu, 1990). Measurement of dipole moment, however, is a tedious procedure in which the dielectric constant is determined at different temperatures (Atkins, 1990). With the advancement of computational methods, it is possible to obtain molecular atomic charges from quantum mechanical calculations to compute the dipole moment. Since the dipole moment is a measurement of charge separation in the molecule, one of the most important factors influencing flux may be the charge distribution itself within a molecule. All the compounds, under the experimental conditions, of this study are in the non-ionized form so the overall charge of each molecule is zero; however, the electron distribution in an electrically neutral molecule is not the same everywhere.

The exact mechanism for a diffusant passing through a polymer barrier is not yet clear, but there is no doubt that the diffusion process involves a series of interactions between the diffusant and the barrier (Matheson et al., 1979, 1980). It is assumed that one of the most important modes of interaction is the atomic electronic field interaction. The overall effect of those interactions is the sum of the effects of the local interaction of each functional group or atom with the polymer. If the local interaction can be estimated, the overall effects on flux can also be quantified.

The purpose of this study is to test the effect of atomic charge on flux and to develop a general model for prediction of flux.

Materials and Methods

Determination of flux

The flux of 103 compounds including six imidazoles, five pyrroles, six thiophenes, two pyrazoles, one pyridazine, one pyrazine, two benzimidazoles, one naphthyridine, one benzofuran, 10 pyridines, four naphthalenes, 21 quinolines, 36 benzenes, five furans and two indoles through PDMS membrane (Silastic® Medical Grade NRV, Dow Corning Corp., Midland, MI) and their solubilities in isopropyl alcohol were measured using previously described methods (Hu, 1990; Moeckly and Matheson, 1991; Yang, 1992). All the compounds along with their molecular weight, solubility and experimental flux are listed in Table 1.

Molecular modeling

A molecular modeling software package (SYBYL 5.4, Tripos Associates, Inc., St. Louis, MO) installed on a mainframe computer (Silicon-Graphics 4D 120GTX, Silicon Graphics, Inc., Mountain View, CA) was used to generate molecular models and minimize their configurational energy. Charges on each atom were computed using the Hückel-Gasteiger method in the SYBYL package in which the Hückel method (Streitwieser, 1961) was used to calculate the π component and the Gasteiger-Marsili (1980) method was used to calculate the σ component of the atomic charge. The net charge is the sum of the charges calculated by the two methods. The charge on the hydrogen atoms is represented by the term e_H and the charge on the heteroatoms is represented by e_P.

Regression analysis

Effects of the computed atomic charges and other physico-chemical properties, including solubility and molecular weight, on flux were then examined using the partial least-square (PLS) regression method in the SYBYL software package. Results were evaluated using the crossvalidation method in the SYBYL package. Calculated and predicted flux values are listed in Table 1.

Results and Discussion

The hydrogen atom(s) in polar groups such as carboxylic acid, hydroxy, amino, aldehyde, and at certain positions in ring systems like imidazole, pyrrole, pyrazole and furan possesses a significantly higher positive charge value than other hydrogen atoms. These compounds diffuse more slowly. If, however, the molecule can form intramolecular hydrogen bonds, flux is not correlated to the charge of that particular hydrogen. On this basis, these charge values were removed from consideration, which improved the model. Compounds shown to be capable of intramolecular hydrogen bonding (Liu, 1991) included 2-aminobenzylalcohol, 7-nitroindole, 8-carboxyquinoline, 8-hydroxyquinaldine, 8-aminoquinoline, 5-nitro-8-hydroxyquinoline and 5-chloro-8-hydroxyquinoline.

Oxygen and nitrogen atoms were negatively charged, but the charge related to flux only if all the unshared electron pairs of these atoms were unconjugated. An unconjugated electron pair(s) is defined as the unshared electron pair(s) in the outer electron layer of the atom and must not form a hyperconjugated system with a neighboring π system. By this definition, the unshared electron pair(s) of nitrogen in aliphatic amines, the cyanide group and the double-bonded nitrogen in the aromatic ring systems of pyridine, naphthyridine, quinoline, imidazole, pyrazole, pyrazine and pyridazine can be classed as unconjugated. In addition, the unshared electron pairs of aliphatic halogen and the oxygen in ketone, alcohol, ether, nitro, the double-bonded oxygen in the carboxy group of carboxylic acids plus the oxygen in phenolic ethers and esters can also be classified as unconjugated. Due to steric effects, the C-O bonds of phenolic ethers and esters (and the same bond directly attached to any heteroaromatic ring system) were rotated in their energy-favored conformation so that the unshared electron pairs on oxygen were not in the same plane as the aromatic ring. Consequently, these *p*-electron pairs are classified as unconjugated. In all other situations, the unshared electron pair(s) of nitrogen, oxygen and halogen was classified as conjugated.

If any of the unshared electron pairs of a heteroatom were conjugated, such as those in thiophene, furan, benzofuran, chlorobenzene, and 1-methylpyrrole, no significant relationship between charge and flux was observed and the charge of this atom was not included in the calculation.

The basis for the hydrogen-polymer and the heteroatom-polymer interactions may be different although the resultant effect on flux is the same. It has been shown that the *p*-electron pairs of the oxygen in the polymer backbone can hydrogen bond (West et al., 1961). Thus, a possible interaction mechanism for a highly charged hydrogen in the diffusant may be hydrogen bonding with the oxygen in the polymer backbone, while heteroatoms with an unconjugated electron pair

in the diffusant may be subject to charge repulsion by this oxygen. This may result in less solubility in the membrane. Both potential mechanisms will hinder diffusion. Since the same type of polymer was used for all diffusion experiments, the difference in the strength of the polymer-diffusant interaction is determined by the electric field of the diffusants. Assuming the atomic charge is localized at a point, the electric field of a charged atom is proportional to its charge (Levine, 1988). Charge from same type of atom will have the same effect and will be additive, but the extent of the effect on the flux of the charges on other types of atoms may differ due to differences in both charge density and the possible mechanism of interaction with the polymer.

Based on the above analysis and the experimental results, the following rules were determined for the selection of which computed charges were correlated to flux:

(1) The charge on a hydrogen atom must be higher than 0.1 and the hydrogen atom is not involved in intramolecular hydrogen bonding.

(2) The charge on heteroatoms which contain unshared electron pairs all of which are unconjugated.

The charge of most atoms in a molecule was not used according to these selection rules and for some compounds, such as benzene, chlorobenzene, 1,3-diethylbenzene, *t*-butylbenzene, toluene, 4-*t*-butyltoluene, biphenyl, 2-methylthiophene, 1-methylpyrrole, 2,5-dimethylthiophene, 1,2,5-trimethylpyrrole and 2,5-dimethylfuran, atomic charge was completely excluded. Charge values are listed in Table 1.

A model with five predictors, including charges selected according to the previously stated rules, solubility and molecular weight, was generated by PLS to fit the flux of 15 ring systems and is given by Eqn 1.

$$\log J_{ss} = -0.249 - 3.69\Sigma e_H - 1.48\Sigma e_P + 3.87(\Sigma e_H \times \Sigma e_P) + 0.769 \log MF - 0.004\ MW \quad (1)$$

$s = 0.309$; $r^2 = 0.939$; $n = 103$; $F = 313.59$

where J_{ss} is the maximum steady-state flux (μmol/s per cm^2), e_H denotes the charge value of hydrogen atoms with a charge higher than 0.1, e_P is the absolute charge value of heteroatoms which contain unshared electron pairs all of which are unconjugated, $\Sigma e_H \times \Sigma e_P$ represents the product of the two types of charges in the same molecule, MF is the mole fraction solubility and MW denotes molecular weight.

Considering the number of classes of compounds and the number of different functional groups in each class, the fitted results from Eqn 1 are very satisfactory. The signs of Σe_H and Σe_P are negative, which indicates flux is inversely proportional to charge. According to the selection rules and computed results, the charge values of hydrogen atoms included in the Σe_H term are those in the amino, hydroxy, aldehyde and carboxylic acid groups as well as those on the ring nitrogen in imidazole and pyrrole. These atoms are hydrogen bonding donors.

Some compounds have both highly charged hydrogen atoms and heteroatoms with an unconjugated electron pair. Consequently, these contribute to both the e_H and e_P terms. This type of compound may self-associate by intermolecular hydrogen bonding, which will reduce the ability of these atoms to interact with the polymer. Since the self-association occurs between oppositely charged atoms, the strength of association may be estimated by the Coulomb force which is proportional to the product of the two different types of charge (Levine, 1988). Thus, a cross term of the opposite charge values occurring in the same molecule, $\Sigma e_H \times \Sigma e_P$, was used as a correction for intermolecular hydrogen bonding. The coefficient for this correction term is positive, indicating that intermolecular hydrogen bonding reduces the charge effect on flux.

The driving force for diffusion is the concentration gradient in the direction of diffusion. Ideally, when the receiver side is maintained at 'sink' conditions, steady state flux should be directly proportional to concentration on the donor side (Crank, 1986). The maximum flux was measured using either the neat liquid, or a solution at 90% saturation if the diffusant was a solid, on the donor side. The mole fraction solubility was cho-

sen as one of the predictors and was found directly related to the flux (Hu, 1990). The positive sign of log MF indicates the donor concentration is the driving force for flux.

Size of diffusant will also affect flux by influencing diffusion coefficient (Jacobs, 1967). Flux of substituted benzenes was shown to be related to molar refractivity (Moeckly and Matheson, 1991). Permeability in *Chara ceratophylla* membrane was related to relative molecular weight (Lieb and Stein, 1969). In this experiment, molecular weight was used to estimate size and was found to function as well as more sophisticated measurments of molecular size. Results show the expected inverse relationship between molecular weight and flux. All the signs in Eqn 1 are physically meaningful and are as expected.

Residual analysis for Eqn 1 found that the imidazoles and compounds with an aliphatic amine side chain systematically deviated from the general model with imidazoles diffusing through the barrier more slowly than expected and aliphatic amines diffusing more rapidly. Imidazole compounds are electronically complicated and the simple charge model apparently does not adequately estimate their electronic nature. Aliphatic amines are polar compounds and are relatively strong bases compared to the other classes of compounds. The basicity of the aliphatic amines may be a factor that affects their flux, but this is not yet clear. Indicator variables for these two types of compounds were included and the fit was significantly improved. The final model generated by PLS is:

$$\log J_{ss} = 0.256 - 4.176\Sigma e_H - 1.388\Sigma e_P + 3.807(\Sigma e_H \times \Sigma e_P) + 0.634 \log MF - 0.008\ MW - 0.753\ Imidazole + 0.626\ Amine \quad (2)$$

$s = 0.217$; $r^2 = 0.972$; $n = 103$; $F = 468.34$

The standard error of estimation is reduced by about 40% compared with Eqn 1. Calculated results using Eqn 2 are listed in Table 1.

TABLE 2

Contribution analysis for predictors in Eqn 2

Predictor	Fraction
Σe_H	0.253
Σe_P	0.118
$\Sigma e_H \times \Sigma e_P$	0.134
log MF	0.261
MW	0.102
Imidazole	0.068
Amine	0.064

Contribution analysis (Table 2) shows the total contribution of the various atomic charges to the final model is 50.5%, indicating the importance of the charge terms.

The applicability of the model was demonstrated by crossvalidation (Cramer et al., 1988). The entire data set was randomly divided into halves. Each half was used to generate a model to predict the other half. The two models used for prediction are given by Eqns 3 and 4:

$$\log J_{ss} = 0.248 - 3.984\Sigma e_H - 1.526\Sigma e_P + 4.163(\Sigma e_H \times \Sigma e_P) + 0.646 \log MF - 0.008\ MW - 0.681\ Imidazole + 0.609\ Amine \quad (3)$$

$$\log J_{ss} = 0.285 - 4.335\Sigma e_H - 1.214\Sigma e_P + 2.970(\Sigma e_H \times \Sigma e_P) + 0.591 \log MF - 0.008\ MW - 0.815\ Imidazole + 0.688\ Amine \quad (4)$$

Prediction quality: $s_p = 0.238$; $r^2_p = 0.966$;

$n = 103$; $F_p = 378.12$

where the subscript p represents prediction.

By comparing Eqns 2–4, it can be seen that the coefficients are stable, although, as expected, they do not remain the same. It is more difficult to predict target values which are not included in the derived model than to fit the same values.

Thus, it is also expected the uncertainty in predictive models will be larger than in the fitted model. Nevertheless, results show that the quality of prediction is almost as good as that of fitting. The uncertainty for prediction, using Eqns 3 and 4, is only about 8% higher than that for fitting and the difference in r^2 for both cases is less than 1%. This strongly indicates that Eqn 2 is robust and highly applicable. Predicted results using Eqns 3 and 4 are listed in Table 1.

It has been found that uneven charge distribution in molecules is an important factor affecting flux. Charge values of hydrogen atoms and of atoms having unconjugated electron pair(s) are significantly related to flux. The effects of atomic charge on flux are additive and comparable for different functional groups and different classes of compounds. Thus, atomic charges are universal descriptors for flux and the maximum flux of many classes of compounds through PDMS membrane can be predicted with a simple model combining atomic charge with simple physico-chemical properties. Steady state flux decreases with increasing atomic charge and molecular weight, but increases with solubility in the chosen solvent. Results of crossvalidation indicate that flux data from fifty diverse compounds is sufficient to generate a general model for prediction.

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