The Linear Free-Energy Relationship between Partition Coefficients and the Aqueous Solubility of Organic Liquids[1]

CORWIN HANSCH,[2] JOHN E. QUINLAN, AND GARY L. LAWRENCE

Department of Chemistry, Pomona College, Claremont, California 91711

Received July 14, 1967

In this report it is shown that there is a linear relationship between the logarithms of the aqueous solubilities of organic liquids and their octanol–water partition coefficients. Since the logarithm of the partition coefficient is an additive–constitutive property of organic molecules, the water solubility of liquids whose partition coefficients have not been measured can be calculated. Or, one can simply construct a table of constants for the water solubility of organic liquids analogous to parachor values or molar refractivities. A problem of increasing importance in physical biochemistry and pharmacology is the selection of a suitable solvent pair (water and an apolar liquid) to serve as a model for the aqueous and lipid phases in biological systems. We have been using octanol–water partition coefficients for whole molecules or parts of molecules to estimate relative strengths of hydrophobic bonding in such systems. The present study would indicate that, with the exception of hydrocarbons, one could expect similar results from almost any monofunctional liquid, such as an alcohol, alkyl halide, ester, ketone, etc., representing the lipid phase.

Since the classic work of Meyer[3] and Overton,[4] scientists concerned with the correlation of chemical structure with biological activity have been seeking suitable solvents to approximate the aqueous and fatty phases of living tissue. We have been using 1-octanol and water to obtain partition coefficients which could serve as hydrophobic bonding constants. When combined with suitable electronic and steric constants, these would form the basis for a multiple-parameter approach to structure-activity relationships in biochemical systems.[5]

Following the lead of Hammett[6] and Taft,[6] we have formulated[7] a substituent constant defined as in eq 1,

$$\pi_X = \log P_X - \log P_H \qquad (1)$$

where P_X is the partition coefficient of a derivative and P_H that of the parent molecule. Thus π is proportional to the free energy of transfer of the function X from one phase to another. Our work, as well as that of others,[8] has shown π to be an additive–constitutive property of organic compounds. We have shown that it can be used to account for the hydrophobic forces involved in the binding of organic compounds by proteins[5c] and enzymes.[5b]

Because of the analogy between the dissolving of an organic liquid in water and its partitioning between two solvents, it occurred to us that log P and π might be of use in correlating chemical structure with aqueous solubility.

The equilibrium between an organic liquid and its saturated aqueous solution may be thought of as the partitioning of the organic compound between itself and water. We therefore sought a linear relationship between the free-energy changes for the two kinds of partitioning represented by S and P in eq 2, where S is

$$\log \frac{1}{S} = a \log P + b \qquad (2)$$

the molal solubility of the organic liquid in water and P is its partition coefficient between 1-octanol and water. Fitting the data in Table I to eq 2 by the method of least-squares yields the sets of slopes and intercepts in Table II. The correlation coefficient is represented by r and s is the standard deviation of the regression of log $1/S$ on log P. The numbers following the slopes and intercepts are the 90% confidence intervals on these quantities.

All of the correlations are quite good, especially when one considers that only a small fraction (22 out of 156) of the partition coefficients were actually measured and that the solubility data were taken from the work of many investigators whose results were obtained by different techniques on compounds of various degrees of purity over a temperature range of 15–25°. The slopes of sets 1–9 are remarkably similar; the 90% confidence intervals all overlap or come very close to the slope 1.21 of set 10.

Most interesting are sets 10 and 11. Set 10 correlates the solubility of 140 liquids (alkanes excluded) with about as much precision as one could expect, considering the nature of the data. The equation with these constants accounts for 91% ($r^2 = 0.91$) of the variance in the data, leaving only 9% to imperfections in the mathematical model and experimental error in measuring S and calculating log P. The hydrocarbons behave somewhat differently as indicated by the intercept in set 9. The correlations embodied in set 1–11 show that the solubility of organic liquids in water is susceptible to evaluation by a Hammett-type substituent constant, linear, free-energy relationship.

Experimental Section

Only for those compounds in Table I marked by asterisks were experimentally determined partition coefficients used. Partition coefficients for the other compounds were calculated taking advantage of the additive nature of π and log P. The π values for CH_3 and CH_2 were taken as 0.50; for a double bond 0.30 was subtracted from the value for the corresponding

---

[1] This work was supported by Research Grant GM-07492 from the National Institutes of Health.

[2] John Simon Guggenheim Fellow.

[3] H. Meyer, *Arch. Exptl. Pathol. Pharmakol.*, **42**, 109 (1899).

[4] E. Overton, *Vierteljahresschr. Naturforsch. Ges. Zuerich*, **44**, 88 (1899).

[5] (a) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964); (b) C. Hansch, E. W. Deutsch, and R. N. Smith, *ibid.*, **87**, 2738 (1965); (c) K. Kiehs, C. Hansch, and L. Moore, *Biochemistry*, **5**, 2602 (1966); (d) E. W. Deutsch and C. Hansch, *Nature*, **211**, 75 (1966); (e) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).

[6] J. F. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

[7] T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

[8] (a) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967); (c) D. J. Currie, C. E. Lough, R. F. Silver, and H. L. Holmes, *Can. J. Chem.*, **44**, 1035 (1966); (d) P. Bracha and R. D. O'Brien, *J. Econ. Entomol.*, **59**, 1255 (1966).

TABLE I

CORRELATION OF WATER SOLUBILITY WITH PARTITION COEFFICIENTS

Compound	Log P^{u}	Log $\frac{1}{S}$,^{a} obsd	Log $\frac{1}{S}$,^{b} calcd
1. Butanol	0.84	-0.026^{c}	0.169
2. 2-Methyl-1-propanol	0.61	-0.098^{d}	−0.110
3. 2-Butanol	0.61*	-0.285^{d}	−0.110
4. Pentanol	1.34	0.592^{c}	0.776
5. 3-Methyl-1-butanol	1.14	0.507^{e}	0.534
6. Methylbutanol	1.14	0.460^{e}	0.534
7. 2-Pentanol	1.14	0.276^{e}	0.534
8. 3-Pentanol	1.14	0.211^{e}	0.534
9. 3-Methyl-2-butanol	0.91	0.176^{e}	0.254
10. 2-Methyl-2-butanol	0.89*	-0.147^{e}	0.230
11. 2,2-Dimethylpropanol	1.36*	0.386^{e}	0.801
12. Hexanol	1.84	1.212^{c}	1.383
13. 2-Hexanol	1.61	0.867^{f}	1.104
14. 3-Hexanol	1.61	0.795^{f}	1.104
15. 3-Methyl-3-pentanol	1.39	0.361^{f}	0.837
16. 2-Methyl-2-pentanol	1.39	0.485^{f}	0.837
17. 2-Methyl-3-pentanol	1.41	0.697^{f}	0.861
18. 3-Methyl-2-pentanol	1.41	0.713^{f}	0.861
19. 4-Methyl-2-pentanol	1.41	0.787^{f}	0.861
20. 2,3-Dimethyl-2-butanol	1.17	0.370^{f}	0.570
21. 3,3-Dimethyl-1-butanol	1.86	1.125^{f}	1.408
22. 3,3-Dimethyl-2-butanol	1.19	0.613^{f}	0.594
23. Heptanol	2.34	1.809^{c}	1.990
24. 2-Methyl-2-hexanol	1.87	1.074^{g}	1.420
25. 3-Methyl-3-hexanol	1.87	0.984^{g}	1.420
26. 3-Ethyl-3-pentanol	1.87	0.832^{g}	1.420
27. 2,3-Dimethyl-2-pentanol	1.67	0.871^{g}	1.177
28. 2,3-Dimethyl-3-pentanol	1.67	0.843^{g}	1.177
29. 2,4-Dimethyl-2-pentanol	1.67	0.932^{g}	1.177
30. 2,4-Dimethyl-3-pentanol	1.71	1.217^{g}	1.226
31. 2,2-Dimethyl-3-pentanol	1.69	1.148^{g}	1.201
32. Octanol	2.84	2.346^{c}	2.597
33. 2,2,3-Trimethyl-3-pentanol	1.99	1.273^{h}	1.566
34. Cyclohexanol	1.23*	0.417^{i}	0.643
35. 4-Penten-1-ol	1.04	0.154^{j}	0.412
36. 3-Penten-2-ol	0.81	-0.055^{j}	0.133
37. 1-Penten-3-ol	0.81	-0.015^{j}	0.133
38. 1-Hexen-3-ol	1.31	0.588^{j}	0.740
39. 2-Hexen-4-ol	1.31	0.403^{j}	0.740
40. 2-Methyl-4-penten-3-ol	1.11	0.502^{j}	0.497
41. Benzyl alcohol	1.10*	0.454^{i}	0.485
42. 2-Butanone	0.29*	-0.678^{k}	−0.498
43. 2-Pentanone	0.79	0.169^{k}	0.109
44. 3-Pentanone	0.79	0.232^{k}	0.109
45. 3-Methyl-2-butanone	0.59	0.124^{k}	−0.134
46. 2-Hexanone	1.29	0.779^{k}	0.716
47. 3-Hexanone	1.29	0.827^{k}	0.716
48. 3-Methyl-2-pentanone	1.09	0.671^{k}	0.473
49. 4-Methyl-2-pentanone	1.09	0.711^{k}	0.473
50. 4-Methyl-3-pentanone	1.09	0.812^{k}	0.473
51. 2-Heptanone	1.79	1.422^{k}	1.323
52. 4-Heptanone	1.79	1.444^{d}	1.323
53. 2,4-Dimethyl-3-pentanone	1.39	1.299^{k}	0.837
54. 5-Nonanone	2.79	2.575^{d}	2.537
55. Ethyl formate	0.23	-0.076^{i}	−0.571
56. Propyl formate	0.73	0.491^{i}	0.036
57. Methyl acetate	0.23	-0.517^{l}	−0.571
58. Ethyl acetate	0.73*	0.040^{m}	0.036
59. Propyl acetate	1.23	0.733^{l}	0.643
60. Isopropyl acetate	1.03	0.519^{l}	0.400
61. Butyl acetate	1.73	0.693^{i}	1.250
62. Isobutyl acetate	1.53	1.237^{l}	1.007
63. Methyl propionate	0.73	0.094^{i}	0.036
64. Methyl butyrate	1.23	0.779^{i}	0.643
65. Ethyl butyrate	1.73	1.275^{l}	1.250
66. Propyl butyrate	2.23	1.907^{n}	1.857
67. Ethyl valerate	2.23	1.767^{n}	1.857
68. Ethyl hexanoate	2.73	2.356^{n}	2.464
69. Ethyl heptanoate	3.23	2.737^{n}	3.071
70. Ethyl octanoate	3.73	3.387^{n}	3.678
71. Ethyl nonanoate	4.23	3.796^{n}	4.285
72. Ethyl decanoate	4.73	4.097^{n}	4.892
73. Diethyl ether	1.03	0.063^{o}	0.400
74. Methyl butyl ether	1.53	0.992^{o}	1.007
75. Methyl isobutyl ether	1.33	0.899^{o}	0.764
76. Methyl *sec*-butyl ether	1.33	0.734^{o}	0.764
77. Methyl *t*-butyl ether	1.06	0.210^{o}	0.437
78. Ethyl propyl ether	1.53	0.665^{o}	1.007
79. Ethyl isopropyl ether	1.33	0.554^{o}	0.764
80. Dipropyl ether	2.03	1.317^{o}	1.614
81. Propyl isopropyl ether	1.83	1.335^{o}	1.371
82. Methyl propyl ether	1.03	0.372^{o}	0.400
83. Methyl isopropyl ether	0.83	0.028^{o}	0.157
84. Cyclopropyl ethyl ether	1.24	0.638^{p}	0.655
85. Chloroethane	1.39	1.051^{l}	0.837
86. Chloropropane	1.89	1.527^{l}	1.444
87. 2-Chloropropane	1.69	1.358^{l}	1.201
88. Chlorobutane	2.39*	2.143^{l}	2.051
89. Isobutyl chloride	2.19	2.000^{l}	1.808
90. 1,3-Dichloropropane	2.28	1.614^{q}	1.918
91. Chloroform	1.97*	0.920^{i}	1.541
92. Bromoethane	1.60	1.055^{l}	1.092
93. Bromopropane	2.10*	1.733^{l}	1.699
94. 2-Bromopropane	1.90	1.631^{l}	1.456
95. Bromobutane	2.60	2.366^{l}	2.306
96. Isobutyl bromide	2.40	2.432^{l}	2.063
97. Isoamyl bromide	2.90	2.886^{l}	2.670
98. 1,3-Dibromopropane	2.70	2.081^{r}	2.428
99. Iodomethane	1.50	1.000^{i}	0.971
100. Iodoethane	2.00*	1.600^{i}	1.578
101. Iodopropane	2.50	2.290^{i}	2.185
102. Iodobutane	3.00	2.960^{i}	2.792
103. Diiodomethane	2.50	2.340^{i}	2.185
104. $(ClCH_2CH_2)_2S$	2.73	2.370^{i}	2.464
105. 1-Pentyne	1.98*	1.640^{s}	1.553
106. 1-Hexyne	2.48	2.360^{s}	2.160
107. 1-Heptyne	2.98	3.010^{s}	2.767
108. 1-Octyne	3.48	3.660^{s}	3.374
109. 1-Nonyne	3.98	4.240^{s}	3.981
110. 1,8-Nonadiyne	3.46	2.980^{s}	3.350
111. 1,6-Heptadiyne	2.46	1.750^{s}	2.136
112. 1-Pentene	2.20	2.670^{s}	1.820
113. 2-Pentene	2.20	2.540^{s}	1.820
114. 1-Hexene	2.70	3.230^{s}	2.428
115. 2-Heptene	3.20	3.820^{s}	3.035
116. 1-Octene	3.70	4.620^{s}	3.642
117. 4-Methyl-1-pentene	2.50	3.240^{s}	2.185
118. 1,6-Heptadiene	2.90	3.340^{s}	2.670
119. 1,5-Hexadiene	2.40	2.690^{s}	2.063
120. 1,4-Pentadiene	1.90	2.080^{s}	1.456
121. Cyclopentene	1.75	2.100^{s}	1.274
122. Cyclohexene	2.16	2.580^{s}	1.772
123. Cycloheptene	2.57	3.160^{s}	2.270
124. Benzene	2.13*	1.637^{i}	1.736
125. Toluene	2.69*	2.292^{l}	2.415
126. Ethylbenzene	3.15*	2.880^{l}	2.974
127. Propylbenzene	3.68*	3.302^{l}	3.617
128. Fluorobenzene	2.27*	1.796^{t}	1.905
129. Chlorobenzene	2.84*	2.363^{t}	2.597
130. Bromobenzene	2.99*	2.547^{t}	2.780
131. Nitrobenzene	1.85*	1.777^{t}	1.396
132. 1,2,4-Trimethylbenzene	3.65	3.320^{s}	3.581
133. *o*-Xylene	3.15	2.780^{s}	2.974
134. Isopropylbenzene	3.43	3.380^{s}	3.314

TABLE I (*Continued*)

Compound	Log P[u]	Log $\frac{1}{S}$,[a] obsd	Log $\frac{1}{S}$,[b] calcd
135. *m*-Nitrotoluene	2.42	2.439[r]	2.088
136. *o*-Dichlorobenzene	3.55	3.006[i]	3.459
137. *m*-Dichlorobenzene	3.55	3.077[i]	3.459
138. Ethyl benzoate	2.62	2.280[i]	2.330
139. Aniline	0.90*	0.410[i]	0.242
140. Propionitrile	0.16*	−0.280[i]	−0.656
141. Pentane	2.50*	3.270[s]	3.340
142. Isopentane	2.30	3.180[s]	3.092
143. 2-Methylpentane	2.80	3.790[s]	3.711
144. 3-Methylpentane	2.80	3.830[s]	3.711
145. Hexane	3.00	3.960[s]	3.958
146. Heptane	3.50	4.530[s]	4.577
147. 2,4-Dimethylpentane	3.10	4.390[s]	4.082
148. 2,2-Dimethylpentane	3.10	3.670[s]	4.082
149. Octane	4.00	5.240[s]	5.195
150. Cyclopentane	2.05	2.650[s]	2.783
151. Cyclohexane	2.46	3.180[s]	3.290
152. Methylcyclopentane	2.35	3.300[s]	3.154
153. Cycloheptane	2.87	3.510[s]	3.797
154. Methylcyclohexane	2.76	3.850[s]	3.661
155. Cyclooctane	3.28	4.150[s]	4.304
156. 1,2-Dimethylcyclohexane	3.06	4.270[s]	4.032

[a] S is the molal concentration. [b] Calculated values for compounds 1–140 were made using constants in set 10. Values for compounds 141–156 were found using constants in set 9. [c] J. A. V. Butler, D. W. Thompson, and W. H. Maclennan, *J. Chem. Soc.*, 674 (1933). [d] S. R. Palit, *J. Phys. Chem.*, **51**, 837 (1947). [e] P. M. Ginnings and R. Baum, *J. Am. Chem. Soc.*, **59**, 1111 (1937). [f] P. M. Ginnings and R. Webb, *ibid.*, **60**, 1388 (1938). [g] P. M. Ginnings and M. Hauser, *ibid.*, **60**, 2581 (1938). [h] P. M. Ginnings and D. Coltrane, *ibid.*, **61**, 525 (1939). [i] A. Seidell, "Solubilities of Organic Compounds," Vol. 2, 3rd ed, D. Van Nostrand Co., New York, N. Y., 1941. [j] P. M. Ginnings, E. Herring, and D. Coltrane, *J. Am. Chem. Soc.*, **61**, 807 (1939). [k] P. M. Ginnings, D. Plonk, and E. Carter, *ibid.*, **62**, 1923 (1940). [l] H. Führer, *Ber.*, **57**, 510 (1924). [m] A. P. Altshuller and H. E. Everson, *J. Am. Chem. Soc.*, **75**, 1727 (1953). [n] H. Sobotka and J. Kahn, *ibid.*, **53**, 2935 (1931). [o] G. M. Bennett and W. G. Phillip, *J. Chem. Soc.*, 1930 (1928). [p] I. Fischer and L. Ehrenberg, *Acta Chem. Scand.*, **2**, 669 (1948). [q] P. Gross, *J. Am. Chem. Soc.*, **51**, 2362 (1929). [r] P. M. Gross, J. H. Saylor, and A. Gorman, *ibid.*, **55**, 650 (1933). [s] C. McAuliffe, *J. Phys. Chem.*, **70**, 1267 (1966). [t] P. M. Gross and J. H. Saylor, *J. Am. Chem. Soc.*, **53**, 1744 (1931). [u] Experimentally determined partition coefficients were used for compounds marked by asterisks (see Experimental Section).

alkane[7] and for a branch in the chain (*e.g.*, isopropyl *vs.* *n*-propyl) 0.20 was subtracted from the value for the straight-chain compound. The value for cyclohexane was estimated in two ways. Subtracting log P for phenoxyacetic acid from 4-cyclohexylphenoxyacetic acid[6] gives log P for cyclohexane as 2.51 (hydrogen is taken as zero). The π value for OH is −1.16 (log P *n*-propyl alcohol −1.50); subtracting this from log P for cyclohexanol yields 2.39. We have chosen the value of 2.46 for cyclohexane and hence the value of 0.41 for each cyclic CH_2 group. Other cycloparaffins were calculated by adding or subtracting 0.41 for each CH_2 to cyclohexane. Log P for $(ClCH_2CH_2)_2S$, mustard gas, was calculated by adding 2(0.39), π for 2 Cl, to log P of 1.95 for diethyl sulfide. π for Cl is found by subtracting 2.00 (log P $CH_3CH_2CH_2CH_2$–) from log P of 2.39 for 1-chlorobutane. The values for the alcohols were based on 1-propanol (log P 0.34) and *t*-butyl alcohol (log P 0.37) in addition to the values marked in Table I. The values for the ethers were based on log P 2.03 for ethyl butyl ether. The example of compound 40, Table I, serves to illustrate the method of calculation. To the value of 0.61 for 2-butanol was added 1.00 for the two additional carbon atoms. From 1.61 was subtracted 0.20 for a branch in the chain and 0.30 for the double bond to obtain the figure of 1.11. Cyclopropyl ethyl ether was calculated as follows. Subtraction of 2.00 from 2.03 for butyl ethyl ether yields the value of 0.03 for the –OEt fragment. Subtracting 0.29 for 2-butanone from the value[7] of 1.50 for CH_3COCH_2CH-*c*-C_3H_5 yields a value of 1.21 for the cyclopropyl group. Thus 0.03 + 1.21 = 1.24 for compound 84, Table I.

The partition coefficients were determined as previously described.[8a] Where possible, analysis of the phases was done using a Cary Model 14 spectrophotometer. For those molecules not adsorbing strongly in the ultraviolet region, vapor phase chromatography was used for analysis. Complete details of this latter method will be published elsewhere.

The values for log 1/S in Table I were selected, where possible, for solubility at 20–25°. In some instances several values were given for a particular compound at different temperatures and in these cases we interpolated to 25°.

Discussion

In considering the correlations obtained with sets 1–11, one must face the result that, except for the alkanes and possibly the alkenes, each of the liquids appears to partition between itself and water in much the same way as it partitions between octanol and water. That equations with constants of sets 10 and 11 should hold can be rationalized from the thermodynamic point of view as follows. Consider the ith solute of a group whose solubilities and partition coefficients are being compared. For pure solute in equilibrium with a saturated aqueous solution we can equate the chemical potentials of the solute in the two phases. In eq 3,

$$\mu_i(l) = \mu_i^\circ(H_2O) + RT \ln S \tag{3}$$

μ_i(l) and $\mu_i^\circ(H_2O)$ are the chemical potentials of the pure liquid solute and of the solute in a 1 M ideal aqueous solution, the hypothetical standard state for the solute. S is the molar concentration of solute in the saturated aqueous solution. This expression ignores any nonideality of the solution and the thermodynamic activity of the solute has been replaced by its molar concentration.

Similarly for the partitioning of the same solute between water and octanol, we have at equilibrium

$$\mu_i^\circ(H_2O) + RT \ln C_i(H_2O) = \mu_i^\circ(\text{oct}) + RT \ln C_i(\text{oct}) \tag{4}$$

where μ_i° has the same significance as in eq 3, in one case referring to the aqueous solution and in the other to the octanol solution. C_i refers to the molar concentration of the solute in each of the phases. Substituting P, the partition coefficient for the ratio $C_i(\text{oct})/C_i(H_2O)$, eq 3 and 4 yield

$$\mu_i^\circ(H_2O) = \mu_i(l) - RT \ln S = \mu_i^\circ(\text{oct}) + RT \ln P \tag{5}$$

from which we obtain

$$\log \frac{1}{S} = \log P + \frac{\mu_i^\circ(\text{oct}) - \mu_i(l)}{2.303RT} \tag{6}$$

which is of the same form as eq 2. The last term in eq 6 is related to the free-energy change in dissolving 1 mole of pure solute in octanol to give a 1 M ideal solution. For the ideal solution the only contribution to this term is the entropy of mixing. The value of the intercept calculated on this basis is −1.28.

The octanol–water partition coefficients were all determined at low concentrations, 10^{-2} to 10^{-3} M in

TABLE II

Type of compd	No. of compd[a]	Slope[b]	Intercept[c]	r	s
1. Alcohols	1–41	1.113 ± 0.08	−0.926 ± 0.12	0.967	0.136
2. Ketones	42–54	1.229 ± 0.13	−0.720 ± 0.19	0.980	0.164
3. Esters	55–72	1.013 ± 0.06	−0.520 ± 0.15	0.990	0.201
4. Ethers	73–84	1.182 ± 0.25	−0.935 ± 0.35	0.938	0.160
5. Alkyl halides	85–104	1.221 ± 0.20	−0.832 ± 0.45	0.928	0.235
6. Alkynes	105–111	1.294 ± 0.37	−1.043 ± 1.13	0.953	0.319
7. Alkenes	112–123	1.294 ± 0.13	−0.248 ± 0.33	0.985	0.131
8. Aromatics	124–139	0.996 ± 0.11	−0.339 ± 0.31	0.975	0.179
9. Alkanes	141–156	1.237 ± 0.18	0.248 ± 0.54	0.953	0.199
10. All compounds less alkanes	1–140	1.214 ± 0.05	−0.850 ± 0.11	0.955	0.344
11. All compounds	1–156	1.339 ± 0.07	−0.978 ± 0.15	0.935	0.472

[a] Number of compound in Table II. [b] a in eq 3. [c] b in eq 2.

octanol and 10^{-3} to 10^{-4} M in water. The assumption of ideality in eq 4 is therefore reasonable. However, almost half of the compounds in Table I have solubilities exceeding 0.1 M and ten have solubilities greater than 1.0 M. The effect of considering nonideality would be to add a term, $RT \ln \gamma_i$, to eq 3 and 6 where γ_i is the activity coefficient of the ith solute in its saturated aqueous solution. Inasmuch as most of these aqueous solutions would be expected to show positive deviations from Raoult's law, most values of γ_i would be greater than one. The correction term $RT \ln \gamma$ would therefore account for at least part of the difference between the contribution of the intercept of -1.28 due to entropy of mixing and the observed value of -0.85 in set 10.

We are concerned here with the common solubility-limiting characteristics of a large group of compounds. The dissolution of such compounds in water is a complex process and a variety of forces such as hydrogen bonding, dipole interactions, and dispersion forces have been recognized as factors which must be considered.[9] The concept of the hydrophobic "bond" which has been developing from the studies of Frank and Evans[10] seems to us to be useful in understanding the results.

The hydrophobic "bond" is complex, involving polar and apolar interactions. While the concept has been particularly fruitful in rationalizing biochemical phenomena,[5,11–13] Scheraga[14] and his coworkers have applied it to association of organic molecules in aqueous solution.

It has been shown that the transfer of a hydrocarbon from a nonpolar environment to an aqueous one is exothermic for aliphatic hydrocarbons and approximately athermal for aromatics. The low solubility of these and other organic compounds in water is associated with a large negative entropy of solution[15] which is due to the formation of a loosely held but highly structured envelope of water molecules around the apolar portions of the organic molecules as they enter the solution. It is predominantly the molecular size and shape which determines how many water molecules enter into the structured sheath around the apolar portions of the organic solute molecule and therefore determines the magnitude of the negative entropy of solution.

The linear free-energy relationships embodied in sets 1–11 as well as the constitutive and additive nature of π indicate that the major factor determining the partitioning of organic molecules between aqueous and organic phases is the extent to which they form hydrophobic bonds. *The effects of hydrophobic bonding so outweigh the various interactions of solute molecules with the organic member of the solvent system* that the excellent correlations of sets 10 and 11 result. Thus using these equations and π values derived from measurements of octanol–water partition coefficients for a limited number of organic compounds, it is possible to predict aqueous solubility of large numbers of organic liquids with quite satisfactory precision.

One of the important problems of structure–activity studies in biochemical systems is the selection of a suitable apolar liquid to model the lipid phases in biological systems. A suitable solvent pair such as water and 1-octanol could then be used as a reference system in the study of apolar interactions. Many different studies have been made attempting to correlate various kinds of biological responses with the way in which enzyme substrates or drugs distribute themselves between two phases. While many different solvents or combinations of solvents have been used, no extensive comparative studies of the relative value of different solvents have been made. The results in sets 1–11 would indicate that most monofunctional aliphatic liquids (except the alkanes) might give similar results.

In conclusion, one can say that the correlation obtained with the constants of set 10 justifies the assumptions made in deriving eq 6. As has been repeatedly pointed out,[11,13] one of the justifications for studies of apolar interactions of small molecules with themselves is that it enables us to understand better their interactions with proteins and the internal bonding of proteins. In addition to showing that the water solubility of organic liquids is an additive–constitutive property, the present results help to clarify our understanding of the Meyer–Overton model using organic solvents to approximate biolipophilic phases.

Acknowledgment.—We are indebted to Susan M. Anderson, Smith Kline and French research associate, for the determination of a number of the partition coefficients used in this work.

---

[9] J. H. Hildebrand, "Solubility of Non-Electrolytes," Reinhold Publishing Co., New York, N. Y., 2nd ed, 1936.

[10] H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).

[11] G. Némethy and H. A. Scheraga, *J. Phys. Chem.*, **66**, 1773 (1962).

[12] C. Tanford, *J. Am. Chem. Soc.*, **84**, 4240 (1962).

[13] I. M. Klotz, *Brookhaven Symp. Biol.*, **13**, 25 (1960).

[14] A. Y. Moon, D. C. Poland, and H. A. Scheraga, *J. Phys. Chem.*, **69**, 2960 (1965).

[15] W. Kauzmann, *Advan. Protein Chem.*, **14**, 37 (1959).