On the Additive–Constitutive Character of Partition Coefficients[1]

CORWIN HANSCH,* ALBERT LEO, AND DONALD NIKAITANI

Department of Chemistry, Pomona College, Claremont, California 91711

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The addition of a CH_2 or CH_3 group to a parent structure normally increases the logarithm of the octanol–water or ether–water partition coefficient (P) by about 0.5. This fact has proved to be widely useful in the calculation of partition coefficients when the value of a parent compound is known. However, it has now been discovered that, when such groups are attached to certain electron-withdrawing functions, little or no increase in log P is observed. This knowledge is important for the study of the additive–constitutive character of log P. It is also important in understanding the nature of the "hydrophobic forces" between water molecules and apolar portions of organic compounds.

In this report we continue our study[2] of the additive–constitutive nature of the partition coefficients of organic compounds between a water and an apolar phase. Additive–constitutive relationships break down sooner or later and further refinements must be introduced. It is now apparent that such a break often occurs between H–X and CH_3X when X is a very strong electron-withdrawing function. The main driving force for such study comes from the use of partition coefficients as systems for modeling "hydrophobic bonding" of organic compounds in biochemical systems.[3] We wish to consider hydrophobic character from the point of view of Frank and Evans.[4] Their view has been extended by Kauzmann,[5] especially in connection with biochemical systems. Hydrophobic forces are still poorly understood and the term hydrophobic bonding is a controversial one, the use of which has been criticized by Hildebrand.[6] His criticism has been answered by Némethy, *et al.*[7] Since a completely satisfactory term to describe the forces which tend to stabilize or destabilize nonpolar molecules in an aqueous environment has not been formulated, we shall refer to these collective properties as hydrophobic. In the present discussion we are interested in the forces which determine the equilibrium position of organic compounds when they are partitioned between an aqueous phase and an apolar solvent such as 1-octanol, ether, or benzene.

It has been pointed out that, when an apolar molecule is placed in water, the water tends to form a flickering cluster[7] or sweater[8] about the apolar molecule. When the apolar molecules leave the aqueous phase during partitioning, this flickering cluster of water is lost. The increase in entropy in the removal of the loosely held water molecules is one of the main forces causing the apolar molecules to leave an aqueous phase to partition into an apolar phase, such as an organic solvent, or macromolecular phase, such as a protein or membrane. Many linear relationships between the binding of organic compounds by apolar phases and the octanol–water partition coefficients are now known.[9] These same hydrophobic forces also play an important role in determining the solubility of organic compounds in water.[10] The partitioning might be partially illustrated as in Figure 1, where x represents a water molecule. These loosely structured water molecules are more or less lost, depending on the nature of the apolar phase when the compound is partitioned out of aqueous phase.

One of the interesting and important features of the partition coefficient is that it is an additive–constitutive property of organic compounds.[2] It is now possible to calculate the partition coefficients of complex compounds from suitable reference molecules with considerable confidence.[2] The ability to calculate partition coefficients is very important in drug design,[11] and it is for this reason among others that we have become very interested in the additive-constitutive character of the partition coefficient P. For convenience, the discussion will be cast in terms of log P and π, where π is defined as $\pi_X = \log P_X - \log P_H$. In this symbolism, P_X refers to the partition coefficient of a derivative and P_H refers to that of a parent compound. π_X is the logarithm of the partition coefficient of a molecular fragment such as CH_3, Cl, NO_2, etc. Our main concern in this paper is with electron-withdrawing effects of substituents on π for CH_2 and CH_3 functions.

The π values for CH_2 and CH_3 groups in a given solvent system such as octanol–water or ether–water are usually constant. This is apparent in Table I. Many such examples in homologous series are known.[2] The average π_{CH_3} for 15 different examples[2] where CH_2 is attached to a benzene ring is 0.50 ± 0.04.

We have now uncovered enough examples to make it quite apparent that π of about 0.5 per CH_2 or CH_3 does not hold when a strong electron-attracting group is adjacent to the alkyl moiety. This can be seen in Table I, where acetic and formic acid have almost the same value for log P in the ether–water system. Other cases support this example so that this constitutive property can be utilized in more refined calculations of log P. The examples of Table II illustrate the generality of this phenomenon.

In seven out of the ten examples of Table II, π is reduced from its usual value of about 0.5 to about 0.1. In three of the examples the value of π is about one-half the normal value.

A more extreme example is the following: for I, $CH_3(CH_2)_9N^+(CH_3)_3Br^-$, the log P of octanol–water is -0.16, and, for II, $CH_3(CH_2)_9N^+H_3Cl^-$, it is 0.85,

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[2] A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

[3] C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).

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

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

[6] J. H. Hildebrand, *J. Phys. Chem.*, **72**, 1841 (1968).

[7] G. Némethy, H. A. Scheraga, and W. Kauzmann, *ibid.*, **72**, 1842 (1968).

[8] E. Grunwald, R. L. Lipnick, and E. K. Ralph, *J. Amer. Chem. Soc.*, **91**, 4333 (1969).

[9] C. Hansch and W. J. Dunn, III, *J. Pharm. Sci.*, **61**, 1 (1972).

[10] C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).

[11] C. Hansch, in "Drug Design," E. J. Ariens, Ed., Academic Press, New York, N. Y., 1971, p 271.

TABLE I

ADDITIVITY OF LOG *P*

Octanol–water system				
Compound	Registry no.	Log *P*	π	π/CH$_2$
CH$_3$OH	67-56-1	−0.66		
			1.00	0.50
C$_3$H$_7$OH	71-23-8	0.34		
			0.54	0.54
C$_4$H$_9$OH	71-36-3	0.88		
			0.52	0.52
C$_5$H$_{11}$OH	71-41-0	1.40		
			0.63	0.63
C$_6$H$_{13}$OH	111-27-3	2.03		
			3.10	0.51
C$_{12}$H$_{25}$OH	112-53-8	5.13		
Benzene	71-43-2	2.13		
			0.56	0.56
Toluene	108-88-3	2.69		
			0.46	0.46
Ethylbenzene	100-41-4	3.15		
			0.53	0.53
Propylbenzene	103-65-1	3.68		

Ether–water system			
Compd	Registry no.	Log *P*	π/CH$_2$
HCOOH	64-18-6	−0.44	
			0.10
CH$_3$COOH	64-19-7	−0.34	
			0.56
C$_2$H$_5$COOH	79-09-4	0.22	
			0.48
C$_3$H$_7$COOH	107-92-6	0.70	
			0.56
C$_4$H$_9$COOH	109-52-4	1.26	
			0.67
C$_5$H$_{11}$COOH	142-62-1	1.93	

TABLE II

COMPARATIVE PARTITION COEFFICIENTS

Solvent system	Compound	Registry no.	Log *P*[a]	Δ log *P*
Ether–water	HCONH$_2$	75-12-7	−2.85	0.25
	CH$_3$CONH$_2$	60-35-5	−2.60	
Ether–water	CH$_3$CHO	75-07-0	−0.48	0.27
	CH$_3$COCH$_3$	67-64-1	−0.21	
Ether–water	C$_6$H$_5$CHO	100-52-7	1.74	0.01
	C$_6$H$_5$COCH$_3$	98-86-2	1.75	
Benzene–water	C$_6$H$_5$CHO		2.10	0.10
	C$_6$H$_5$COCH$_3$		2.20	
Octanol–water	C$_6$H$_5$CHO		1.48	0.10
	C$_6$H$_5$COCH$_3$		1.58	
Octanol–water	C$_6$H$_5$NHCHO	103-70-8	1.15	0.01
	C$_6$H$_5$NHCOCH$_3$	103-84-4	1.16	
Octanol–water	CH$_3$CONH$_2$		−1.21[b]	0.16
	CH$_3$CONHCH$_3$	79-16-3	−1.05	
Octanol–water	HCOOH		−0.54	0.23
	CH$_3$COOH		−0.31	
Ether–water	HCOOH		−0.44	0.10
	CH$_3$COOH		−0.34	
Ether–water	(COOH)$_2$	144-62-7	−0.90	−0.07
	CH$_2$(COOH)$_2$	141-82-2	−0.97	
Octanol–water	HCON(CH$_3$)$_2$		−1.01	0.24
	CH$_3$CON(CH$_3$)$_2$		−0.77	
Octanol–water	HCONH$_2$		−1.46	0.25
	CH$_3$CONH$_2$		−1.21[b]	

[a] The log *P* values are from ref 2 or were experimentally determined. [b] Calculated from butyramide.

calculated from the dodecyl derivative. Despite the fact that compound I contains three more CH$_3$ groups, it is more hydrophilic than compound II. In view of the preceding and following discussion, it is not surprising that the three methyl groups attached to the nitrogen atom are not "seen" in hydrophobic terms. Recent calculations by Pullman, *et al.*,[12] make this understandable. They have shown that the positive charge "on nitrogen" in acetylcholine CH$_3$COOCH$_2$-CH$_2$N$^+$(CH$_3$)$_3$ is almost entirely dispersed onto the 11 hydrogen atoms on the adjacent four carbon atoms.

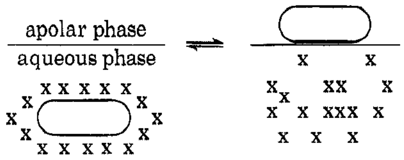


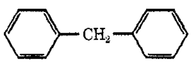
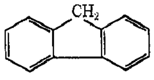
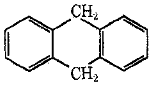
Figure 1.

The charge calculated for N is only +0.06, while most of the hydrogens carry charges of +0.07.

After discounting the methyl groups of compound I, it is seen that compound II is still more lipophilic than I in the octanol–water system. This may be related to the fact that the more concentrated positive charge on the nitrogen in II is able to interact with oxygen in octanol more effectively. Octanol is more basic than water.

A similar effect appears when a methylene group is placed between two benzene rings (Table III). It would appear in the three examples from Table III that the normal flickering cluster of water molecules does not form around the methylene groups; that is, log *P* for the whole molecule is simply that for the sum of two benzene rings.

TABLE III

		Log *P*		
	Registry no.	Obsd	Two benzene rings	Calcd
	101-81-5	4.14	4.26	4.76
	86-73-7	4.18	4.26	4.76
	613-31-0	4.25	4.26	5.26

Another set of examples in which π_{CH_2} is much less than 0.5 is that of the following benzyl derivatives (Table IV). In the set from Table IV, the calculated

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(12) B. Pullman, P. H. Courrière, and J. L. Coubeils, *Mol. Pharmacol.*, **7**, 397 (1971).

TABLE IV

Compound	Registry no.	Log P Obsd	Log P Calcd	Δ log P
$C_6H_5CH_2CN$	140-29-4	1.56	1.79	−0.23
$C_6H_5CH_2OH$	100-51-6	1.10	1.47	−0.36
$C_6H_5CH_2CONH_2$	103-81-1	0.45	0.92	−0.47
$C_6H_5CH_2NH_2$	100-46-9	1.09	1.51	−0.42
$C_6H_5CH_2COCH_3$	103-79-7	1.44	1.84	−0.40
$C_6H_5CH_2COOCH_3$	101-41-7	1.83	2.46	−0.63

values are the sum of log P_{benzene} + log P_{CH_3X}. For example, log $P_{C_6H_5CH_2OH}$ = log P_{benzene} + log P_{CH_3OH} = 2.13 + (−0.66) = 1.47. In every one of the above instances, log P falls short of the calculated value and, except for the CN function, it is about one CH_2 short of the expected value.

A single function operating only through the inductive effect does not appear to have as profound an effect on log P. For example, log $P_{I_2} = 2.49$ ∴ log $P_{EtI} = \pi_{Et} + {}^1/_2 \log P_{I_2} = 1.00 + 1.24 = 2.24$. The experimental value for EtI is 2.00. Again the observed value is lower than the calculated value. The agreement is closer in iodobenzene where the electronic effect of the benzene ring is present: log $P_{C_6H_5I}$ = log $P_{C_6H_6}$ + ${}^1/_2$ log P_{I_2} = 3.37. The observed log $P_{C_6H_5I}$ = 3.25. Of course, the validity of taking ${}^1/_2$ log P_{I_2} for the value of a covalently bound I is open to question and needs further study.

There is no reason to predict *a priori* that the effect upon the partition coefficient of replacing H by CH_3 would reside primarily in the structure of the solvent around those two groups. One must also consider the possibility that those two groups will affect the solvation of the polar group, and that the polar solvation effect can explain the lack of a normal increase in hydrophobicity produced when CH_3 replaces H. However, it will be seen that such a postulate leads to a predicted effect exactly the reverse of that observed.

First of all, the methyl group releases electrons more readily than does a hydrogen. Since it more effectively satisfies the demands of the electron-seeking substituent, it reduces its total polarity and thus decreases its affinity for the highly polar aqueous phase. Furthermore, the methyl group is bulkier and might be expected to shield some of the polar group's charge from the polar surroundings. Both these effects would tend to make the log P increment for the first methyl group greater than for subsequent ones, rather than smaller as is observed, and thus one concludes that they are of minor importance compared to that of the reduction in electron density in the methyl group. The greater positive charge on the methyl group's hydrogen atoms may reduce the electron correlation with the atoms of the water molecules and in turn reduce the structured nature of the aqueous envelope surrounding this first methyl group.

Electron withdrawal makes the alkyl group more positive. One could argue that this positive character provides the hydrogen atoms with some hydrogen-bonding character so that they have more affinity for the aqueous phase. This effect could simply offset the normal hydrophobic character of the CH_3 or CH_2 function.

Another and more interesting possibility is that, when a CH_3 or CH_2 group attains a certain degree of positive character, water molecules do not form as stable a flickering cluster around the group. Consequently, there is less or no desolvation when such a group moves from the aqueous to the apolar phase. If this is true, one must ask what are the predominant forces holding the envelope of water molecules about a hydrocarbon moiety. Since carbon atoms in alkyl groups are covered by hydrogens, it seems likely that it is the interaction of these hydrogens with the water molecules which produces the loose envelope of water. Assuming that the lack of hydrophobic character means the envelope of water does not form, this could be attributed to lack of electron correlation between the alkyl hydrogens and the atoms of the water molecule.

The above observations, when taken with other information,[2] indicate that the partition coefficient can be a useful tool to the physical–organic chemist for the study of electronic influence on the interaction of solutes with solvents.

Registry No.—I, 2082-84-0; II, 143-09-9.