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Electronic Representation of the Lipophilic Parameter π

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We have shown recently that the logarithm of partition coefficients can be related to molecular electronic indexes which can be calculated for various chemical agents. According to a theoretical interpretation of biological linear free energy relationships, the lipophilic parameter π should be related to similar electronic indexes calculated only for the substituents of a congeneric series of molecules. In this report it is shown that π values for benzoic acids can be correlated with appropriate electronic indexes calculated for the substituents of benzoic acid derivatives. These same electronic indexes are shown to also be suitable for correlating the π values derived for phenoxyacetic acids. Biological activities which are found to be linearly related to π can be related to the calculated electronic substituent indexes.

Considerable effort has been expended in attempting to describe biochemical and pharmacological processes on an electronic basis.[1-3] While notable insight into the electronic factors controlling the chemical behavior of important biomolecules has been gained, there are few instances where electronic indexes have been related directly to experimental measures of a biological response.[4] From the results of extrathermodynamic correlative studies[5-8] it is clear that attempts to gain insight into the electronic nature of biological processes will require the lipophilicity or hydrophobicity of the substrates or drugs to be taken into account. The interaction between a substrate and a biomacromolecule may be dominated by electronic factors, but the accessibility of the substrate to the region of the biomacromolecule where the interaction occurs is governed by lipophilic factors. Similar lipophilic factors also seem to contribute toward the "hydrophobic bonding" tendencies for a substrate.

Lipophilicity is a term commonly used to describe the tendency for a chemical agent to partition itself between aqueous and organic biophases. Partition coefficients provide a convenient measure of lipophilicity and are often used in establishing the relative rates with which chemical substances penetrate lipoidal membranes[9] or participate in the formation of a hydrophobic bond.[10] The most useful lipophilic indexes are the logarithm of the partition coefficient, log P, or in the case of congeneric series the substituent constant π which is defined by

$$\pi = \log P_X - \log P_H \quad (1)$$

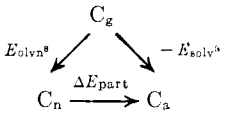
where P_X and P_H are, respectively, the partition coefficients for a substituted member and the parent member of a congeneric series.[11]

Experimental measures of lipophilicity have been used in combination with the results of simple Hückel calculations in correlating the analgesic activity of imidazolines[12] and the rates of acylation of substituted anilines by acetyltransferase.[13] Taking lipophilicity into account in this way, however, is quasi-empirical since theoretically justifiable relations prescribed by quantum perturbation theory[14] are blended with empirical indexes having no demonstrated basis in theory. In working toward a quantum chemical description of lipophilicity we have been investigating potential relationships between quantum chemical indexes and partition coefficients. Preliminary work has resulted in a

(1) B. Pullman and A. Pullman, "Quantum Biochemistry," Wiley-Interscience, New York, N. Y., 1963.
(2) B. Pullman, Ed., "Electronic Aspects of Biochemistry," Academic Press, New York, N. Y., 1964.
(3) B. Pullman and M. Weissbluth, Ed., "Molecular Biophysics," Academic Press, New York, N. Y., 1965.
(4) L. B. Kier, Ed., "Molecular Orbital Studies in Chemical Pharmacology," Springer-Verlag, New York, N. Y., 1970.
(5) C. Hansch, *Annu. Rep. Med. Chem.*, **1966**, 347 (1967).
(6) C. Hansch, "Physico-Chemical Aspects of Drug Action," E. J. Ariëns, Ed., Pergamon Press, New York, N. Y., 1968.
(7) C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).
(8) C. Hansch, *Farmaco Ed. Sci.*, **23**, 293 (1968).
(9) H. Davson and J. F. Danielli, "The Permeability of Natural Membranes," 2nd ed, Cambridge University Press, Cambridge, England, 1952.
(10) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides as Ions and Dipolar Ions," Reinhold, New York, N. Y., 1943.
(11) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).
(12) W. B. Neely, H. C. White, and A. Rudzik, *J. Pharm. Sci.*, **57**, 1176 (1968).
(13) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965).
(14) A. Cammarata, *J. Med. Chem.*, **11**, 1111 (1968).

correlation between log P and electronic indexes calculated for the π system[15] and the σ,π systems[16] of aromatic substances. We have extended these observations following an approach suggested by a recent analysis of biological linear free energy relationships[17] and we now present correlations between the lipophilic index π and electronic properties calculated solely for the substituents of aromatic compounds.

Theory.—Consider the partitioning of a compound between a polar and a nonpolar phase in terms of the cyclic process



in which C_g, C_a, and C_n are the compound as found in a gaseous, in an aqueous, and in an organic phase, respectively. In the first part of the cycle, the material is brought from a gaseous to a solvated state in a nonpolar solvent and the energy $E_{solv}{}^n$ associated with the process is a solvation energy. In the second part of the cycle, the nonpolar solvation shell is replaced by a polar solvation shell and for this process the energy change ΔE_{part} may be considered as the energy of partitioning. Finally the compound is stripped of its polar solvation shell and is returned to the gaseous state. The energy $-E_{solv}{}^a$ for this process is a desolvation energy.

The energy change for the entire cycle ΔE° is given by the relation

$$\Delta E^\circ = E_{solv}{}^n - E_{solv}{}^a + \Delta E_{part} \quad (2)$$

but since no net energy change takes place $\Delta E^\circ = 0$ and hence

$$\Delta E_{part} = E_{solv}{}^a - E_{solv}{}^n \quad (3)$$

From statistical mechanics, the energy of partitioning can be related to the partition coefficient P by the expression

$$\ln P = -\frac{1}{RT}\Delta E_{part} + f \quad (4)$$

where ln P is the natural logarithm of the partition coefficient, R is the gas constant in calories per mole-degrees Kelvin, T is the temperature in degrees Kelvin, and entropic factors, *i.e.*, the statistical mechanical partition functions, are collected into the intercept f and are assumed invariant for a given series of compounds.

From eq 3 and 4 it can be seen that an electronic description for partition coefficients requires a practical representation for the solvation energy. A simple and convenient model of the solvation process, which leads to an estimate of solvation energy, envisages a molecule to be taken from the gaseous state, placed within a cavity of solvent, and subsequently allowed to interact with the surrounding solvent. The energy for the process may be taken as the solvation energy appropriate to a molecule. This solvation energy can be represented to higher orders of approximation by the sum of energy components

$$E_{solv} = \Delta E_{el} + \Delta E_{pol} + \ldots \quad (5)$$

where ΔE_{el} and ΔE_{pol} are the electrostatic and polarization energy changes associated with the process. Higher order terms are neglected for the purposes of this study.

The electrostatic energy change may be given by the Born expression[18,19]

$$\Delta E_{el} = -\left(\sum_r \frac{Q_r^2}{2R_r} + \sum_r \sum_{\substack{s \\ r\neq s}} \frac{Q_r Q_s}{2 R_{rs}}\right)\left(1 - \frac{1}{D}\right) \quad (6)$$

where Q is the net charge on an atom r of the molecule, R_r is the effective radius of the atom, R_{rs} is the distance between atom r and an atom s of the molecule, and D is the dielectric constant for the medium about the molecule.

The polarization energy change may be taken to be similar in form to the relation deduced by Klopman[20,21] as representing an extreme for charge-controlled interactions

$$\Delta E_{pol} = \sum_w \sum_r \left[\left(\sum_{\substack{m \\ occ}} c_{mw}{}^2\right)\left(\sum_{\substack{n \\ unocc}} \frac{2c_{nr}{}^2}{\bar{E}_m - E_n}\beta^2\right) - \left(\sum_{\substack{u \\ unocc}} c_{uw}{}^2\right)\left(\sum_{\substack{v \\ occ}} \frac{2\,c_{vr}{}^2}{\bar{E}_u - E_v}\beta^2\right)\right] \quad (7)$$

The coefficients c_w and c_r are obtained from the ground state LCAO-MO's for the solute $\psi_j = \Sigma_r c_{jr}\phi_r$ and the surrounding solvation shell $\psi_k = \Sigma_w c_{kw}\phi_w$. $\bar{E}_m$ and $\bar{E}_u$ are the averages for the energies of the occupied and unoccupied LCAO-MO's, respectively, for the solvation sphere. Similarly E_n and E_v are the energies for the unoccupied and occupied LCAO-MO's, respectively, of the solute molecule. The quantity β is a parameterization for the interaction energy.

An operationally convenient form for the energy of solvation is, from eq 6 and 7,

$$E_{solv} = -a\sum_r Q_r{}^2 - p\sum_r \sum_{\substack{s \\ r\neq s}} \frac{Q_r Q_s}{R_{rs}} + b\sum_r S_r{}^E - q\sum_r S_r{}^N \quad (8)$$

where

$$a = \frac{1}{2\bar{R}_r}\left(1 - \frac{1}{D}\right),\ p = \frac{1}{2}\left(1 - \frac{1}{D}\right)$$

$$q = \sum_w \sum_{\substack{m \\ occ}} c_{mw}{}^2\beta^2,\ b = \sum_w \sum_{\substack{u \\ unocc}} c_{uw}{}^2\beta^2$$

and

$$S_r{}^E = \sum_{\substack{v \\ occ}} \frac{2\,c_{vr}{}^2}{E_v}\ S_r{}^N = \sum_{\substack{n \\ unocc}} \frac{2\,{}_{nr}c^2}{-E_n}$$

$\bar{R}_r$ is the average of the effective radii of the atoms in the molecule and Fukui's delocalizability indexes $S_r{}^E$, $S_r{}^N$[22-24] are used as estimates for the terms in eq 7

(15) K. S. Rogers and A. Cammarata, *J. Med. Chem.*, **12**, 692 (1969).
(16) K. S. Rogers and A. Cammarata, *Biochim. Biophys. Acta*, **193**, 22 (1969).
(17) A. Cammarata, *J. Med. Chem.*, **12**, 314 (1969).
(18) M. Born, *Z. Phys.*, **1**, 45 (1920).
(19) G. J. Hoijtink, E. de Boer, P. H. van der Meij, and W. P. Weijland, *Recl. Trav. Chim. Pays-Bas*, **75**, 487 (1956).
(20) G. Klopman and R. F. Hudson, *Theor. Chim. Acta*, **8**, 165 (1967).
(21) G. Klopman, *J. Amer. Chem. Soc.*, **90**, 223 (1968).
(22) K. Fukui, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jap.*, **27**, 423 (1954).
(23) K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **27**, 1247 (1957).
(24) K. Morokuma, H. Hato, and K. Fukui, *Bull. Chem. Soc. Jap.*, **36**, 541 (1963).

having a difference in energies in the denominator. The sums in eq 8 are taken over all atoms of a molecule.

No doubt eq 8 is a very crude operational representation for the energy of solvation. Its use is, however, justified by the agreement which is obtained with experiment.

Combining eq 8 with eq 3 and 4 leads to the relationship

$$\ln P = -(\Delta a') \sum_r Q_r^2 - (\Delta p') \sum_{\substack{r \\ r \neq s}} \sum_s \frac{Q_r Q_s}{R_{rs}} + (\Delta b') \sum_r S_r^E - (\Delta q') \sum_r S_r^N + f \quad (9)$$

in which each coefficient is divided by RT. The applicability of this relationship has been illustrated by a correlation of the partition coefficients for a series of molecules consisting of hydrocarbons, heteroatomic aromatics, substituted indoles, and substituted benzenes. The relation obtained[16] is given by the regression equation

$$\ln P = -2.705(\pm 0.23) \sum_r |Q_r^T| + 0.708(\pm 0.06) \sum_r S_r^E + 2.467$$

n	s	r	$F(1, 28)$
30	0.732	0.943	107.9

(10)

where $|Q_r^T|$ is the absolute value of the sum of the σ and π net charges on a given atom of solute as calculated using the Berthod and Pullman[25] modification of the Del Re method.[26] It may be inferred from eq 10 that $\Sigma_r Q_r^2$ and $\Sigma_r S_r^E$ are the dominant terms in eq 9.

Consider now the potential significance of eq 9 in relation to the lipophilic parameter π defined by eq 1. Neglecting the term involving the cross-products $Q_r Q_s$, it may be noted from eq 9 that each atom of a molecule makes an independent contribution to the partition coefficient. In other words, according to the model used in estimating solvation energies, each atom of a molecule behaves as if it were surrounded by its own solvation sphere. Let the partition coefficient for a substituted member of a congeneric series be given by $\ln P_{RX} = L_{CX} + L_R' + f$, where L_{CX} is the collection of terms in eq 9 referring to a substituent and the atom of the nucleus to which it is attached and L_R' is the collection of terms for the rest of the nucleus. In like manner the unsubstituted or parent member of the series can have its partition coefficient given by $\ln P_{RH} = L_{CH} + L_R'' + f$. The substituent parameter π is then defined by the difference, $\pi = \ln P_{RX} - \ln P_{RH} = (L_{CX} - L_{CH}) + (L_R' - L_R'')$. It seems likely that since the greatest variation in the values for the electronic indexes Q^2, S^E, and S^N will occur for a substituent rather than for the atoms of a common drug nucleus, the difference $L_R' - L_R''$ might in general be expected to be small in comparison with the difference $L_{CX} - L_{CH}$. In other words, a reasonable representation for π in terms of electronic indexes would, in the present context, be given as

$$\pi = -(\Delta a') \sum_r' Q_r^2 + (\Delta b') \sum_r' S_r^E - (\Delta q') \sum_r' S_r^N \quad (11)$$

where the summation symbols are primed to designate that the summation is taken only over the atoms of a substituent and the atom of the nucleus to which it is attached. The applicability of eq 11 as a representation for π forms the basis for this study.

Results and Discussion

Calculations for a substituted series of 3-methyl- and 4-methylbenzoic acids were made following the Berthod and Pullman[25] modification of the Del Re[26] procedure which applies to the σ and π frameworks of conjugated substances. The heteroatom model was used in treat-

TABLE I

PARTITION COEFFICIENTS, π VALUES, AND MOLECULAR ORBITAL SUBSTITUENT INDEXES FOR SUBSTITUTED BENZOIC ACIDS

X	$\Sigma' S^{E a}$	$\Sigma' \lvert Q^T \rvert^a$	log P^b	π^c
4-Br	3.083	0.100		0.98
4-Cl	2.863	0.081	2.72	0.87
4-Me	1.945	0.228	2.27	0.42
4-F	1.532	0.405	1.66	0.19
4-MeO	3.148	0.566	1.93	0.08
H	0.857	0.121	1.85	0.00
4-HO	1.870	0.945		−0.30
4-CN	1.364	0.703	1.54	−0.31
4-MeCONH	4.453	2.037	1.06	−0.79

[a] Calcd for derivatives of 3-methylbenzoic acid. [b] Values for benzoic acids were reported by C. Hansch, E. J. Lien, and F. Helmer, *Arch. Biochem. Biophys.*, **128**, 319 (1968). [c] Values for the benzoic acid series were reported by T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).

TABLE II

MOLECULAR ORBITAL SUBSTITUENT INDEXES FOR BENZOIC ACIDS AND π VALUES FOR PHENOXYACETIC ACIDS

X	$\Sigma' S^{E a}$	$\Sigma' \lvert Q^T \rvert^a$	π^b
4-Br	3.083	0.100	1.02
3-Br	3.152	0.121	0.94
3-Cl	2.941	0.104	0.76
4-Cl	2.863	0.081	0.70
4-Me	1.945	0.228	0.52
3-Me	1.869	0.248	0.51
4-F	1.532	0.405	0.15
3-F	1.594	0.372	0.13
3-MeO	3.248	0.548	0.12
4-MeO	3.148	0.566	−0.04
4-H	0.857	0.121	0.00
3-H	0.905	0.122	0.00
4-Me_2N	5.304	0.660	−0.20
3-MeCO	3.240	1.394	−0.28
4-MeCO	3.193	1.415	−0.37
3-CN	1.438	1.002	−0.30
4-CN	1.364	0.703	−0.32
3-HO	1.955	0.782	−0.49
4-HO	1.870	0.945	−0.61
3-MeCONH	4.551	2.197	−0.79
3-NH_2	2.314	1.097	−1.29
4-NH_2	2.203	1.128	−1.63

[a] Calcd for derivatives of 3- or 4-methylbenzoic acid. [b] Values for the phenoxyacetic acid series were reported by T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).

(25) H. Berthod and A. Pullman, *J. Chim. Phys. Physiochim. Biol.*, 942, (1965).

(26) G. Del Re, *J. Chem. Soc.*, 4031 (1958).

ing the contribution of a Me group to a π system. Substituents such as NO_2, SCF_3, SF_5, N=NR, and SO_2R were not considered because of uncertainties regarding proper parameter choice for the σ and/or the π system calculation. Large aliphatic substituents such as *n*-Pr, *tert*-Bu, *i*-Pr also were not considered since S^E, S^N values for these substituents should be calculated following alternative methods. The substituents considered and the electronic indexes related to these substituents are found in Tables I and II. A wide range in electron-donating and -withdrawing properties is represented by the substituents selected so that a good test of eq 11 is indeed being made, within the limitations of the computational technique employed.

I is shown in eq 12. Replacing log P by the corresponding π values, the derived relationship becomes that shown in eq 13. The fits illustrated by eq 12 and 13 are both highly significant at greater than the 99.99% confidence level and tend to confirm at least the general outlines of the partition theory which has been discussed. Including the π values for the 4-Br and 4-OH substituents slightly increases the range and the number of data points for which the approach holds in the benzoic acid system as shown in eq 14.

One of the characteristic properties of substituent constants which makes them so generally useful is that substituent constants determined for one congeneric series may also be used in connection with a second con-

	n	s	r	$F(2,4)$	
$\log P = -1.059(\pm0.155)\sum_r'\lvert Q_r^T\rvert + 0.322(\pm0.084)\sum_r' S_r^E + 1.744$	7	0.178	0.961	24.65	(12)
$\pi = -1.026(\pm0.154)\sum_r'\lvert Q_r^T\rvert + 0.277(\pm0.084)\sum_r' S_r^E + 0.032$	7	0.178	0.961	24.22	(13)
				$F(2,6)$	
$\pi = -1.061(+0.113)\sum_r'\lvert Q_r^T\rvert + 0.297(\pm0.062)\sum_r' S_r^E + 0.041$	9	0.165	0.963	44.37	(14)
				$F(2,19)$	
$\pi = -1.057(\pm0.175)\sum_r'\lvert Q_r^T\rvert + 0.209(\pm0.087)\sum_r' S_r^E + 0.103$	22	0.414	0.810	18.14	(15)
				$F(2,16)$	
$\pi = -0.973(\pm0.095)\sum_r'\lvert Q_r^T\rvert + 0.294(\pm0.055)\sum_r' S_r^E - 0.020$	19	0.205	0.931	52.13	(16)
				$F(1,9)$	
$\log(1/C) = 0.605(\pm0.078)\pi + 3.490$	11	0.138	0.932	59.86	(17a)
$\log(1/C) = -1.089(\pm0.182)\sum_r'\lvert Q_r^T\rvert + 4.151$	11	0.171	0.894	35.80	(17b)
				$F(1,5)$	
$\log[(B)/(F)] = 0.519(\pm0.091)\pi - 0.276$	7	0.155	0.930	32.38	(18a)
$\log[(B)/(F)] = -0.923(\pm0.199)\sum_r'\lvert Q_r^T\rvert + 0.180$	7	0.184	0.900	21.45	(18b)
				$F(1,4)$	
$\log(1/C) = 1.777(\pm0.367)\pi + 3.569$	6	0.339	0.924	23.38	(19a)
$\log(1/C) = -3.720(\pm0.358)\sum_r'\lvert Q_r^T\rvert + 5.508$	6	0.167	0.982	108.1	(19b)
$\log(1/C) = 0.994(\pm0.121)\pi + 2.711$	6	0.157	0.971	67.61	(20a)
				$F(2,3)$	
$\log(1/C) = -1.176(\pm0.119)\sum_r'\lvert Q_r^T\rvert + 0.315(\pm0.067)\sum_r' S_r^E + 2.754$	6	0.132	0.985	49.56	(20b)
				$F(1,5)$	
$\log(1/C) = 0.550(\pm0.098)\pi + 1.543$	7	0.115	0.928	31.38	(21a)
$\log(1/C) = -0.820(\pm0.148)\sum_r'\lvert Q_r^T\rvert + 2.069$	7	0.116	0.927	30.60	(21b)
$\log(1/C) = 0.853(\pm0.060)\pi + 0.067$	7	0.075	0.987	199.1	(22a)
				$F(2,4)$	
$\log(1/C) = -1.539(\pm0.142)\sum_r'\lvert Q_r^T\rvert + 0.154(\pm0.060)\sum_r' S_r^E + 0.515$	7	0.093	0.984	63.65	(22b)

Chemistry.—To test whether the calculated MO substituent indexes are sufficient to describe the partitioning characteristics for a congeneric series, a regression analysis based on eq 11 was done using log P values reported[27] for para-substituted benzoic acids. The regression equation derived for the data of Table

(27) C. Hansch, E. J. Lien, and F. Helmer, *Arch. Biochem. Biophys.*, **128**, 319 (1968).

generic series. The MO properties calculated for the substituents on 3- and 4-methylbenzoic acids are found to have this property since they can be used to describe the partitioning characteristics of substituted phenoxyacetic acids. Using the data of Table II, it is thus found that the π values for phenoxyacetic acids are fit by the regression equation 15. The most poorly fit points are for 4-NMe_2, 3-NH_2, and 4-NH_2. Upon

deleting these points a substantial improvement in fit is obtained (note eq 16).

The inability of a relation such as eq 16 to take into account amino substituents may indicate a need for including higher order terms, *e.g.*, Q_rQ_s, in defining the lipophilicity for these substituents. Alternatively, a process other than simple solvation may be occurring with these substituents, *e.g.*, quaternary ion formation. A distinction between the various possibilities is a subject for future investigations.

Biology.—The measured biological activities for a variety of compounds have been found to be linearly related to π. According to the electronic representation of π developed in this work, biological activities which correlate with π may also correlate with $\Sigma_r'Q_r^2$, $\Sigma_r'S_r^E$, or a linear combination of these indexes depending upon whether, for the substituents considered, electrostatic, polarization, or the sum of electrostatic and polarization energies dominate in the solvation process. In the comparisons, which follow, biological systems which have been reported as having their activities related to π are now investigated using the electronic substituent indexes found in Table II as lipophilic parameters.

a. Protein Binding.—Table III gives the concentrations of differing phenols which are necessary to produce a 1:1 phenol–bovine serum albumin complex. These are taken from a study made by Hansch, *et al.*,[28] covering a wide variety of substituted phenols. The data of Table III lead to the regression equations 17a and 17b.

TABLE III

CONCENTRATION OF PHENOL TO PRODUCE A 1:1 PHENOL–PROTEIN COMPLEX

Substituent	log (1/C)[a]	π[a]	$\Sigma_r'S_r^E$	$\Sigma_r'\|Q_r^T\|$
3-F	3.60	0.47	1.594	0.372
3-Cl	4.26	1.04	2.941	0.104
3-Me	3.65	0.56	1.869	0.248
3-CN	3.25	−0.24	1.438	1.002
3-OH	3.23	−0.66	1.955	0.782
3-OMe	3.43	0.12	3.248	0.548
4-F	3.70	0.31	1.532	0.405
4-Cl	4.07	0.93	2.863	0.081
4-Br	4.29	1.13	3.083	0.100
4-Me	3.76	0.48	1.945	0.228
4-OMe	3.59	−0.12	3.148	0.566

[a] Data from C. Hansch, K. Kiehs, and G. L. Lawrence, *J. Amer. Chem. Soc.*, **87**, 5770 (1965).

Bird and Marshall[29] have reported a study of the serum binding characteristics for 72 penicillins differing mainly in the nature of the side chain. The largest single congeneric series represented had substituted benzylamino moieties as the side chain. Serum binding values for these compounds, given by the ratio of the fraction bound (B) to the fraction free (F), are shown in Table IV. These data are correlated by equations 18a and 18b.

b. Inhibition of Hill Reaction.—Hansch and Deutsch[30] have correlated the activities for a number of inhibitors of the Hill reaction, which is the photochemically activated, O_2-evolving reaction in plants mediated by chloroplasts, using lipophilic indexes. Table V gives select anilides of isobutyric acid which function as inhibitors. These data are correlated by regression equation 19a,b. In this instance, the fact that a 4-NMe_2 substituent is included in arriving at eq 19b does not diminish the significance of the fit; rather eq 19b seems to provide a more satisfactory fit than does eq 19a.

TABLE IV

BINDING OF PENICILLINS TO SERUM (SUBSTITUTED BENZYLAMINO SIDE CHAIN)

Substituent	log [(B)/(F)]	π[a]	$\Sigma_r'S_r^E$	$\Sigma_r'\|Q_r^T\|$
4-Me	0.176	0.52	1.945	0.228
4-Cl	0.086	0.70	2.863	0.081
3-F	−0.455	0.13	1.594	0.372
3-NH_2	−0.867	−1.29	2.314	1.097
3-OH	−0.645	−0.49	1.955	0.782
4-OH	−0.575	−0.61	1.870	0.945
4-OMe	−0.213	−0.04	3.148	0.566

[a] From Table II.

TABLE V

INHIBITORS OF THE HILL REACTION

Substituent	log (1/C)	π	$\Sigma_r'S_r^E$	$\Sigma_r'\|Q_r^T\|$
Anilides of Isobutyric Acid				
4-Cl	5.2	0.70	2.863	0.081
3-Cl	4.8	0.76	1.945	0.228
4-Br	5.0	1.02	3.083	0.100
3-Me	4.8	0.51	1.869	0.248
4-Me	4.5	0.52	1.945	0.228
4-NMe_2	3.0	−0.20	5.304	0.660
***N*-Phenylcarbamates**				
4-COMe	2.2	−0.28	3.245	1.394
4-Me	3.2	0.51	1.869	0.248
4-OH	2.3	−0.49	1.955	0.782
4-Cl	3.5	0.76	2.941	0.104
4-Br	3.6	0.94	3.152	0.121
4-H	2.9	0.0	0.905	0.122

A second series of inhibitors represented by 3-substituted *N*-phenylcarbamates are found in Table V. These data are adequately summarized by the regression equations 20a and 20b. A polarization component seems to be necessary in accounting for the lipophilicities of these compounds, as indicated by the appearance of the term involving S^E in eq 20b. The differing forms for eq 19b and 20b do not indicate a difference in the mode of action for the two series of inhibitors, but rather serve to point out that the partitioning characteristics for the substituents considered are controlled by differing electronic properties.

c. Toxicity.—The toxicity of certain substances seems to be controlled by the ability of these substances to penetrate lipophilic barriers which separate components vital to cell life from external agents. Hansch and Fujita[31] have investigated factors controlling the toxicity of substituted benzoic acids to mosquito larvae, and Table VI presents some of the activities which were considered. These data are fit by the relations 21a and 21b.

The same authors also studied factors influencing the toxicity of phenols to Gram-positive and Gram-negative bacteria. Table VII presents data selected from this study. No appreciable difference between the minimum toxic concentrations for the phenols found in

(28) C. Hansch, K. Kiehs, and G. L. Lawrence, *J. Amer. Chem. Soc.*, **87**, 5770 (1965).

(29) A. E. Bird and A. C. Marshall, *Biochem. Pharmacol.*, **16**, 227 (1967).

(30) C. Hansch and E. Deutsch, *Biochim. Biophys. Acta*, **112**, 381 (1966).

(31) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

TABLE VI

TOXICITY OF BENZOIC ACIDS TO MOSQUITO LARVAE

Substituent	log (1/C)	π	$\Sigma_r' S_r^E$	$\Sigma_r' \lvert Q_r^T \rvert$
4-Cl	2.060	0.87	2.863	0.081
4-Br	2.030	0.98	3.083	0.100
3-Cl	2.000	0.83	2.941	0.104
4-F	1.850	0.19	1.532	0.405
4-Me	1.660	0.42	1.945	0.228
4-OMe	1.600	0.08	3.148	0.566
4-OH	1.290	−0.30	1.870	0.945

TABLE VII

TOXICITY OF PHENOLS TO BACTERIA

Substituent	log (1/C)[a]	log (1/C)[b]	π	$\Sigma_r' S_r^E$	$\Sigma_r' \lvert Q_r^T \rvert$
3-OH	−0.33	−0.33	−0.49	1.955	0.782
3-OMe	0.20	0.23	0.12	3.248	0.548
3-Me	0.42	0.42	0.51	1.869	0.248
4-OMe	0.03	0.12	−0.04	3.148	0.566
4-Me	0.42	0.42	0.52	1.945	0.228
4-Cl	0.77	0.77	0.70	2.863	0.081
4-Br	0.96	1.04	1.02	3.083	0.100

[a] *Vs. M. pyogenes* var. *aureus*. [b] *Vs. S. typhosa*.

Table VII are noted with *Mycobacterium pyogenes* var. *aureus* and *Salmonella typhosa* as the test organisms. For the former Gram-positive test system, the toxicities are correlated by the expressions 22a and 22b. Here also the differing forms for eq 21b and 22b indicate that the substituents considered in each case have their lipophilicities controlled by differing electronic properties. No difference in the toxicological mechanism of action for the two series should be inferred from these relations.

Conclusions

The problem of obtaining a practical electronic description of lipophilicity is essentially the problem of obtaining an accurate electronic representation for solvation energy. A naive model for obtaining an expression for solvation energy was used in this study and an operationally limited MO method was used in estimating the required electronic indexes. Within these bounds, excellent agreement between calculated electronic indexes and π values derived from partition coefficients is gained. More sophisticated methods for determining solvation energies as well as for calculating the required electronic indexes will certainly have to be employed in gaining a generally satisfactory electronic representation of lipophilicity. In particular, higher order terms in the expression giving the energy of solvation (eq 5) will most probably have to be taken into account in order to describe correctly the partitioning behavior of conformationally distinct molecules.

The success of the present approach in correlating the lipophilic parameter π with electronic indexes derived for substituents which are conjugated with an aromatic nucleus most probably is, in part, a consequence of an effective cancellation of a number of terms in the expression giving the energy of solvation (eq 5). A difference of solvation energies is required in evaluating the energy of partitioning and a second difference is made in defining π in terms of the energy of partitioning.

In this study, the lipophilic parameter π, for substituents which conjugate with an aromatic nucleus, is found to be represented by electronic terms identified directly with a substituent rather than with remote atoms of the aromatic nucleus. It may thus be said that the change in the nature of the solvation shell about a substituent upon transferring a molecule from an aqueous or polar to a nonaqueous or nonpolar phase is a dominant factor governing the relative order observed for the partition coefficients of a congeneric series. Changes in the nature of the solvation shell about the aromatic nucleus upon making a similar transfer between phases consequently distinguish one congeneric series from another.

From a practical perspective, the correlations found between biological activity and π, or its electronic representation, indicate the substituents on the molecules are passing from an aqueous to a lipophilic phase. Passage of molecules through lipophilic membranes would certainly be reflected by a correlation involving π as would a binding process between a macromolecule and a drug molecule which leads to an envelopment of the substituent by hydrophobic regions of the macromolecule. A binding process which does not directly involve the substituents is, therefore, expected to bear no relation to π even though the nature of the binding may be traced to hydrophobic factors. Hansch and coworkers[32] have presented similar interpretations regarding the significance of π in correlating biological activities.

Although an electronic description of lipophilicity is still in a crude stage of development, it can be said that at least the lipophilic characteristics of aromatic substances can be represented in electronic terms. The Berthod–Pullman modification of the Del Re approach has been found to be computationally convenient for determining the electronic indexes used in estimating lipophilic order. Because of the simplicity of the calculations involved, it now seems possible to provide estimates of the relative partitioning characteristics for many compounds without recourse to tables of log P, which may be incomplete for certain molecular features, or without having to prepare model systems for experimental determinations of partition coefficients. Electronic approaches to the study of structure–activity relationships show promise of having considerable flexibility and once the limitations of these approaches are better defined significant progress in our understanding of biological processes may be expected.

(32) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).