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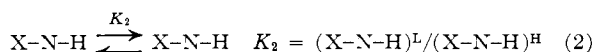
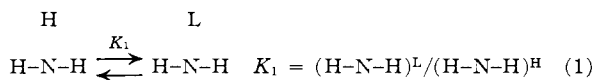
A New Substituent Constant, π , Derived from Partition CoefficientsBY TOSHIO FUJITA,^{1a} JUNKICHI IWASA,^{1b} AND CORWIN HANSCH

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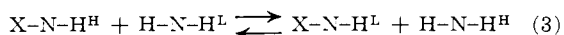
The partition coefficients between 1-octanol and water have been determined for 203 mono- and disubstituted benzenes. From these values a substituent constant, π , has been calculated for 67 functional groups. The constant π is defined as: $\pi = \log P_X - \log P_H$ where P_X is the partition coefficient of a derivative and P_H is that of the parent compound. π has been derived for many of the functions from eight different systems: benzene, nitrobenzene, aniline, phenol, benzyl alcohol, benzoic acid, phenylacetic acid, and phenoxyacetic acid. It is found that, although π varies continuously for a given function depending on its electronic environment, the range over which it varies is not great. In certain of the systems, π -values are related by a simple linear expression.

In recent work we have found² that a substituent constant, π , derived from partition coefficients, is very useful when used with the Hammett σ function in correlating biological activity with chemical constitution. π is defined as: $\pi = \log P_X - \log P_H$ where P_H is the partition coefficient of a parent molecule between two solvents (we have used 1-octanol-water as the reference system) and P_X is that for a derivative. Since π is derived from equilibria it, like σ ,³ is a free energy related constant. The purpose of the work described in this paper was to evaluate π in a variety of different systems (e.g., $X-C_6H_5-NH_2$, $X-C_6H_5-NO_2$, $X-C_6H_5CH_2OH$, where both strong and weak electronic interactions of the substituent X with other substituents are possible) in order to understand its limitations as a substituent constant. Our results also provide a variety of π -values for further work in structure-activity studies.

The implications of the above definition of π can be more clearly seen in the following way. If we use the symbol H-N-H to represent benzene and X-N-H to represent a simple derivative such as chlorobenzene, π results from a comparison of two equilibria



The superscripts H and L denote the hydrophilic (H_2O) and lipophilic (octanol) phases and refer to the phase in which the molecule is located; $\pi = \log K_2/K_1$. The ratio of the equilibrium constants is equivalent to the equilibrium constant for the reaction



The free-energy change resulting from the introduction of X on equilibrium 1 for a given set of conditions would then be

$$\log (K_2/K_1) \sim F_{X-N-H}^L + F_{H-N-H}^H - F_{X-N-H}^H - F_{H-N-H}^L \quad (4)$$

The free energy of an individual molecule in eq. 4 can be represented as the sum of its parts and their interaction⁴ in a simplified fashion as

(1) (a) On leave from Kyoto University, Kyoto, Japan. (b) On leave from Okayama University, Okayama, Japan.

(2) (a) C. Hansch, P. P. Maloney, T. Fujita, and R. M. Muir, *Nature*, **194**, 178 (1962); (b) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, C. F. Geiger, and M. J. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963); (c) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964).

(3) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(4) (a) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill

$$F_{X-N-H}^L = F_X^L + F_N^L + F_H^L + F_{XN}^L + F_{HN}^L + F_{XH}^L \quad (5)$$

In eq. 5 the terms on the right side represent the free energies of the substituents and their interactions with the basic aromatic structure (F_{XN}^L) or each other (F_{XH}^L). The other molecules in eq. 4 can be formulated as in eq. 5. Substitution of the four forms of eq. 5 into eq. 4 gives

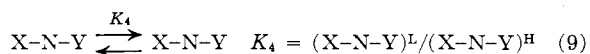
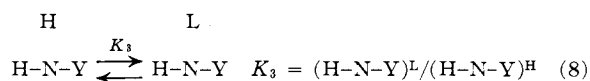
$$\log (K_2/K_1) \sim F_X^L + F_{XN}^L + F_{XH}^L + F_H^H + F_{HN}^H + F_{HH}^H - F_X^H - F_{XN}^H - F_{XH}^H - F_H^L - F_{HN}^L - F_{HH}^L \quad (6)$$

Using eq. 6, π_n (π_n represents the case where a mono-substituted benzene derivative is compared to benzene using octanol and water) can be defined as

$$\pi_n \sim \Delta F_X + \Delta F_{XN} + \Delta F_{XH} - \Delta F_H - \Delta F_{HN} - \Delta F_{HH} \quad (7)$$

where $F_X^L - F_X^H = \Delta F_X$, $F_H^H - F_H^L = -\Delta F_H$, etc.

When two functional groups are placed on the ring the situation is, of course, more complicated. The problem for two functional groups can be formulated as above for π_n .



In comparing N, H, etc., in eq. 8 and 9 with the corresponding entities in eq. 1 and 2, we are assuming that perturbations affecting solubility attributed to the introduction of Y can be ignored where they are not accounted for in the terms used in eq. 1. Proceeding then as for π_n , we obtain

$$\pi_1 = \log (K_4/K_3) \sim F_{X-N-Y}^L + F_{H-N-Y}^H - F_{X-N-Y}^H - F_{H-N-Y}^L \quad (10)$$

$$\begin{aligned} &= \log (K_4/K_3) \sim F_X^L + F_{XN}^L + F_{XY}^L + F_H^H + F_{HN}^H + F_{HY}^H - F_X^H - F_{XN}^H - F_{XY}^H - F_H^L - F_{HN}^L - F_{HY}^L \quad (11) \end{aligned}$$

$$\pi_1 \sim \Delta F_X + \Delta F_{XN} + \Delta F_{XY} - \Delta F_{HY} - \Delta F_H - \Delta F_{HN} \quad (12)$$

Subtracting eq. 7 from 12 yields

$$\pi_1 - \pi_n = \Delta\Pi \sim \Delta F_{XY} + \Delta F_{HH} - \Delta F_{HY} - \Delta F_{XH} \quad (13)$$

Thus $\Delta\Pi$ is the change in the partition coefficient of a particular function when it is placed in a new aromatic system in comparison to its partition coefficient when attached to benzene. Or, conversely, it is the change in the partition coefficient of a group attached to benzene when another function is attached to the ring.

For analytical purposes, each of the terms in eq. 13, such as ΔF_{XY} , should be replaced by two terms, such as $\Delta F_{X\leftarrow Y}$ and $\Delta F_{X\rightarrow Y}$, where the arrows indicate the solubility-modifying action of one substituent upon the other.

$$\Delta\Pi_{1-n} \sim \Delta F_{X\rightarrow Y} + \Delta F_{X\leftarrow Y} + 2\Delta F_{H\rightarrow H} - \Delta F_{H\rightarrow Y} - \Delta F_{H\leftarrow Y} - \Delta F_{X\rightarrow H} - \Delta F_{X\leftarrow H} \quad (14)$$

From a consideration of eq. 14 one would not expect π -values derived from different systems for a given function to be constant or necessarily to be related in any simple way. Fortunately, in practice the situation appears simpler than eq. 14 would lead one to expect. When one compares the π_n values with those derived from the other seven systems (Table I), it is apparent that π , like σ ,⁵ varies continuously for a given function, depending on its environment, but that in general the range over which it varies is not great. The greatest variance from the normal occurs when two strongly interacting groups such as nitro and amino are placed on the ring together. For inert groups such as alkyl (compare CH_3), the values are essentially constant from system to system as well as in the *meta* and *para* positions. The fact that one set of constants would suffice for either the derivatives of phenol or aniline again calls to mind the similarity between π and σ .

The relatively small variance in π derived from different systems is most fortunate. This implies that a few sets of values (possibly three: π_n , π^- , π^+) should do for most ρ - σ - π analyses^{2c} one would normally wish to carry out in correlations of biological activity with chemical structure. The π -values would be those from phenols needed when strong electron-releasing groups such as $-\text{OH}$, $-\text{NH}_2$, $-\text{NHR}$, or $-\text{NR}_2$ are attached to a conjugated system. The π^+ constants would be necessary when strong electron-attracting groups such as cyano or nitro are conjugated with the variable function. As discussed below, the situation with π^+ is, in practice, more complex than with π^- .

Although the parameter $\Delta\Pi$ is a complex one as indicated above, in some circumstances it appears to depend simply on σ_X ; that is

$$\Delta\Pi_{1-n} = k\sigma_X \quad (15)$$

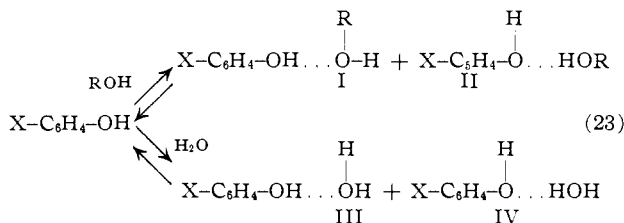
This can be seen from least-squares fits of $\Delta\Pi$ obtained from Table I to eq. 15 which yields eq. 16-22.

Equations 16-22 are arranged in order of decreasing susceptibility of the constant function ($Y = \text{OH}$, NH_2 , etc.) to the variable function (X) as indicated by the constant associated with σ . The coefficient of correlation is indicated under r , and s is the standard deviation. The term $s_{\Delta\Pi}^2$ is the variance in $\Delta\Pi$ to be ac-

		No. of points	r	s	$s_{\Delta\Pi}^2$	
$\Delta\Pi_{\pi_{\text{aniline}}} - \pi_n$	$= 0.905\sigma + 0.016$	11	0.974	0.079	0.109	(16)
$\Delta\Pi_{\pi_{\text{phenol}}} - \pi_n$	$= .823\sigma + .061$	24	.954	.097	.101	(17)
$\Delta\Pi_{\pi_{\text{benz.alc.}}} - \pi_n$	$= .469\sigma + .041$	11	.937	.086	.040	(18)
$\Delta\Pi_{\pi_{\text{POA}}} - \pi_n$	$= .362\sigma + .037$	22	.754	.100	.022	(19)
$\Delta\Pi_{\pi_{\text{PAA}}} - \pi_n$	$= .307\sigma - .004$	16	.787	.080	.016	(20)
$\Delta\Pi_{\pi_{\text{BA}}} - \pi_n$	$= .111\sigma + .104$	19	.291	.125	.016	(21)
$\Delta\Pi_{\pi_{\text{nitroB}}} - \pi_n$	$= -0.509\sigma + .282$	20	.676	.250	.109	(22)

counted for by the regression analysis. The correlation for the first three examples (aniline, phenol, benzyl alcohol) is surprisingly high for such a simple treatment and would indicate that eq. 15 is a good approximation and that all of the terms in eq. 14 except the first apparently play small roles, at least in these instances. Results from eq. 15 indicate that with derivatives of aniline, phenol, and benzyl alcohol, the three functional groups ($-\text{NH}_2$, $-\text{OH}$, and $-\text{CH}_2\text{OH}$) play the primary role in determining the relative solubility of the molecules, and, hence, their distribution coefficients. This role is modified in direct proportion to electron release or withdrawal by the variable function X .

In attempting to rationalize the correlation obtained with eq. 15, the factors governing the relative solubility of the various compounds which can be considered are the hydrogen bonding power, degree of polarization, and van der Waals forces. The sign of $\Delta\Pi$ for the phenol series shows that electron withdrawal by substituent X increases the solubility of the phenol in the octanol phase relative to water. This is particularly striking in the case of nitrophenols. For the nitro group itself, π_n is close to zero or slightly negative indicating that this group has little preference for the octanol phase or the water phase. Knowing this, it is at first surprising that the partition coefficient of 31.5 for phenol is increased to 100 in the case of 3-nitrophenol. Since the electron withdrawal will have negligible effect on solubility owing to van der Waals forces, and increased polarization would result in increased water solubility, $\Delta\Pi$ for the phenol series must be related to changes in hydrogen bonding. The nature of these interactions can be illustrated as



Electron withdrawal by X would inhibit bonding of the type shown in II and IV, but promote bonding of the type shown in I and III. Octanol, being more nucleophilic than water, would compete more effectively in bonding of the type in I and III. Thus, pure electron withdrawal could by this means raise the partition coefficient (octanol/water) of a phenol. Working in the same direction would be electron decrease on the phenolic oxygen which would inhibit water-solubilizing forces indicated by IV. Which of these two actions promoting solubility in octanol makes the greatest contribution is, at present, uncertain.

The great importance of the oxygen lone pair electrons for lowering the partition constant stands out

(5) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959).

TABLE I
 VALUES FOR π DERIVED FROM EIGHT DIFFERENT SYSTEMS^a

Function H ^b	Phenoxyacetic acids 0	Phenylacetic acids 0	Benzoic acids 0	Benzyl alcohols 0	Phenols 0	Anilines 0	Nitrobenzenes 0	Benzenes 0
2-F	0.01 ± 0.01	0.04 ± 0.02 ^c			0.25 ± 0.01			} 0.14 ± 0.02
3-F	.13 ± .03	.19 ± .02 ^c	0.28 ± 0.01		.47 ± .01	0.40 ± 0.02		
4-F	.15 ± .01	.14 ± .01	.19 ± .01		.31 ± .01	.25 ± .02		} .71 ± .03
2-Cl	.59 ± .03 ^c				.69 ± .01			
3-Cl	.76 ± .02	.68 ± .03	.83 ± .02	0.84 ± 0.03	1.04 ± .01	.98 ± .02	0.61 ± 0.03	} .86 ± .02
4-Cl	.70 ± .03	.70 ± .04	.87 ± .01	.86 ± .02	0.93 ± .01		.54 ± .03	
2-Br	.75 ± .06 ^c				.89 ± .01			} .86 ± .02
3-Br	.94 ± .01	.91 ± .03 ^c	.99 ± .01		1.17 ± .01		.79 ± .02	
4-Br	1.02 ± .05 ^c	.90 ± .01	.98 ± .01		1.13 ± .01			} .86 ± .02
2-I	0.92 ± .01				1.19 ± .01			
3-I	1.15 ± .01	1.22 ± .02	1.28 ± .01		1.47 ± .01			} .86 ± .02
4-I	1.26 ± .03 ^c	1.23 ± .03	1.14 ± .01		1.45 ± .01			
2-CH ₃	0.68 ± .05 ^c							} .56 ± .02
3-CH ₃	.51 ± .01	0.49 ± .03 ^c	0.52 ± .02	.50 ± .02	0.56 ± .01	.50 ± .02	.57 ± .03	
4-CH ₃	.52 ± .05 ^c	.45 ± .03	.42 ± .03	.48 ± .03	.48 ± .01	.49 ± .02	.52 ± .02	} .56 ± .02
2-Et	1.22 ± .03 ^c							
3-Et	0.97 ± .01				.94 ± .01			} .56 ± .02
3- <i>n</i> -Pr	1.43 ± .02							
3- <i>i</i> -Pr	1.30 ± .03							} .56 ± .02
4- <i>i</i> -Pr	1.40 ± .01							
3- <i>n</i> -Bu	1.90 ± .01							} .56 ± .02
4- <i>sec</i> -Bu	1.82 ± .02							
3- <i>t</i> -Bu	1.68 ± .01							} .56 ± .02
4-Cyclopentyl	2.14 ± .03							
4-Cyclohexyl	2.51 ± .03							} .56 ± .02
3-C ₆ H ₅	1.89 ± .01							
3,4(CH ₂) ₃	1.04 ± .01							} .56 ± .02
3,4(CH ₂) ₄	1.39 ± .01							
3,4(CH) ₄	1.24 ± .01							} .56 ± .02
3-CF ₃	1.07 ± .02	1.16 ± .03 ^c	1.07 ± .01		1.49 ± .01			
3-CH ₂ OH					-1.02 ± .03	- .95 ± .02	- .65 ± .02	} -1.03 ± .02
4-CH ₂ OH					-1.26 ± .05		- .60 ± .02	
3-CH ₂ COOH					-0.61 ± .02		- .40 ± .02	} -0.72 ± .03
4-CH ₂ COOH							- .47 ± .03	
3-COOH	-0.15 ± .01	-0.32 ± .02 ^c	-0.19 ± .01		.04 ± .01		- .02 ± .02	} - .28 ± .02
4-COOH					.12 ± .01		.03 ± .03	
CONH ₂								} -1.49 ± .02
3-COOCH ₃			-.05 ± .03					
2-COCH ₃	.01 ± .01							} -0.01 ± .03
3-COCH ₃	-.28 ± .01							
4-COCH ₃	-.37 ± .02							} - .55 ± .02
3-CN	-.30 ± .01	-.28 ± .06 ^c	-.37 ± .01		-.24 ± .01		-.68 ± .02	
4-CN	-.32 ± .01		-.31 ± .02		.14 ± .03		-.66 ± .02	} - .57 ± .02
2-OH		-.54 ± .02						
3-OH	-.49 ± .01	-.52 ± .02	-.38 ± .01	-.61 ± .02	-.66 ± .01	-.73 ± .04	.15 ± .03	} - .67 ± .01
4-OH	-.61 ± .01		-.30 ± .01	-.85 ± .04	-.87 ± .03	-1.07 ± .02	.11 ± .02	
2-OCH ₃	-.33 ± .01							} - .02 ± .02
3-OCH ₃	.12 ± .01	.04 ± .02 ^c	.14 ± .01		.12 ± .01	.03 ± .02	.31 ± .02	
4-OCH ₃	-.04 ± .01	.01 ± .02	.08 ± .01	.00 ± .02	-.12 ± .01		.18 ± .02	} - .02 ± .02
3-OCF ₃	1.21 ± .01							
3-OCH ₂ COOH			-.69 ± .01		-.70 ± .02		-.48 ± .02	} - .86 ± .02
4-OCH ₂ COOH					-.81 ± .02		-.52 ± .02	
-OCOCH ₃								} - .64 ± .01
3-NH ₂								
4-NH ₂				-1.15 ± .02	-1.29 ± .03		-.48 ± .02	} -1.23 ± .02
3-N(CH ₃) ₂					-1.63 ± .02		-.46 ± .02	
2-NO ₂	-0.23 ± .05 ^e				0.10 ± .01			} .18 ± .02
3-NO ₂	.11 ± .01	-.01 ± .02 ^c	-.05 ± .01	0.11 ± .02	.33 ± .01			
4-NO ₂	.24 ± .03	-.04 ± .02	.02 ± .01	.16 ± .02	.54 ± .02	.47 ± .02	-.36 ± .02	} - .28 ± .02
3-NHCOCH ₃	-.79 ± .01				.50 ± .01	.49 ± .02	-.39 ± .02	
3-NHCOC ₆ H ₅	.72 ± .01							} - .97 ± .02
4-N=NC ₆ H ₅	1.71 ± .04							
3-NHCONH ₂	-1.01 ± .03							} 1.69 ± .04
3-SCH ₃	0.62 ± .01							
3-SCF ₃	1.58 ± .01							} 1.69 ± .04
3-SO ₂ CH ₃	-1.26 ± .05	-1.25 ± .01						
3-SO ₂ CF ₃	0.93 ± .01							} -1.82 ± .02
3-SF ₃	1.50 ± .01							
SO ₂ NH ₂								

^a The values reported in this table supersede those previously reported.² The small changes are the result of a more refined technique evolved in the determination of partition coefficients. ^b The following values for log *P* enable one to calculate *P* for any of the 203 compounds listed in Table I: benzyl alcohol, 1.10 ± 0.01; phenol, 1.46 ± 0.01; aniline, 0.90 ± 0.01; nitrobenzene, 1.85 ± 0.01; benzene, 2.13 ± 0.01. See Experimental section for values for phenoxyacetic, phenylacetic, and benzoic acids. Of course, taking advantage of the additive character of π allows one to estimate *P* for a variety of compounds. The error values refer to the standard deviation. ^c These values were obtained by coulometric determination; see Experimental section.

when one compares in, for example, the phenoxyacetic acid series the functions -OCH₃ (π = 0.12) and -OCF₃ (π = 1.21), or -SO₂CH₃ (π = -1.26) and SO₂CF₃ (π = 0.93). A single fluorine group has a very low π -value (~0.14). The great difference in each of these two

pairs is to be attributed to the inductive effect of the fluorine atoms on the oxygen lone pair electrons. A secondary effect in the same direction will be the inductive effect of the fluorines on the oxyacetic acid side chain.

The fact that the carboxyl group does not have nearly so low a π -value as either the phenolic -OH or the -CH₂OH function would indicate that hydrogen bonding of type I and III might be less important (ignoring van der Waals forces) for a low partition coefficient than types II and IV.

The behavior of $\Delta\Pi$ for the aniline and benzyl alcohol series would appear to be the same as that of the phenols. In each of these series very good correlation between $\Delta\Pi$ and σ_X occurs and the increase in solubility in octanol relative to water upon the introduction of the electron-withdrawing substituents is again to be attributed to modification in hydrogen bonding ability of the -NH₂ and -CH₂OH functions. In these three instances, then, $\Delta\Pi$ is primarily a measure of the interaction $X \rightarrow Y$.

For the OCH₂COOH and CH₂COOH functions, $\Delta\Pi$ appears to have much the same characteristics as those considered above. Although the correlation between $\Delta\Pi$ and σ is not nearly so good (as indicated by r), this is attributed in part to the relatively large standard deviation compared to the small variance to be explained ($s_{\Delta\Pi^2}$).

The problem with the benzoic acids and nitrobenzenes where we are dealing with strong electron-attracting functions is different. In each of these cases a low correlation is observed and the curve is shifted so that it does not pass through the origin. The very poor correlation with the benzoic acids is in part attributed to the relatively large error in $\Delta\Pi$ compared to its absolute value. The nitrobenzenes present a clearer case for analysis. Here the susceptibility constant of 0.509 reflects the relatively large values for $\Delta\Pi$.

In attempting to find a more suitable expression for $\Delta\Pi$ for the nitrobenzene than eq. 15, we have assumed that the success of the latter is attributed to the fact that in the simplest situation of one very dominant functional group $\Delta\Pi \sim \Delta F_{X \rightarrow Y}$, and that the influence of X on Y is proportional to σ_X . Modifying eq. 14 analogously, we obtain eq. 24.

$$\Delta\Pi_{1-n} = k_Y\sigma_X + k_X\sigma_Y + 2k_H\sigma_H - k_H\sigma_Y - k_Y\sigma_H - k_H\sigma_X - k_X\sigma_H \quad (24)$$

Since σ_H is by definition zero, eq. 24 becomes

$$\Delta\Pi_{1-n} = (k_X - k_H)\sigma_Y + (k_Y - k_H)\sigma_X \quad (25)$$

Using k_H as a zero point of reference, we can say

$$\Delta\Pi_{1-n} = k_X\sigma_Y + k_Y\sigma_X \quad (26)$$

A least-squares fit of the data on nitrobenzenes to eq. 26 yields eq. 27.

$$\Delta\Pi_{\pi_{\text{nitro}} - \pi_n} = -0.605\sigma_X - 1.662\sigma_Y + 1.538 \quad \begin{matrix} r & s \\ 0.702 & 0.248 \end{matrix} \quad (27)$$

This result is only slightly better than that obtained with eq. 22. Probably the main reason for the failure of eq. 26 is the over-simplified assumption that the solubility-modifying effect of one substituent on another is proportional to α .

The $\Delta\Pi$ values derived from the nitrobenzene system cluster into three groups

1. 3-OH, 4-OH, 3-NH₂, 4-NH₂ $\Delta\Pi = 0.74$ to 0.77
2. 3-OCH₃, 4-OCH₃, 3-COOH, 4-COOH, 3-COCH₃, 4-COCH₃ $\Delta\Pi = 0.19$ to 0.33
3. 3-CH₃, 4-CH₃, -H, 3-Cl, 4-Cl, 3-Br, 3-NO₂, 4-NO₂, 3-CN, 4-CN $\Delta\Pi = -0.17$ to 0.06

Thus the usual effect of the nitro group is to raise π . This is quite evident in groups 1 and 2 above and would appear to occur because of the constraint on hydrogen bonding attributed to the electron attraction of the nitro group on the lone pair electrons of oxygen and nitrogen.

The effect of σ of one substituent upon the solubility characteristics of another substituent is obviously very complex; however, two limiting situations stand out. The two extremes are represented by the functions in the above groups, 1 and 3. Those in group 1 are strong hydrogen bonders with lone pair electrons. Those in group 3 are weak hydrogen bonders, in some instances having no lone pair electrons. While NO₂ and CN have hydrogen-bonding power, their strong electron-attracting character appears to make them relatively immune to the electron-attracting effect of other groups such as COOH and NO₂.

The solubility-modifying effect of a series of substituents (X) on a given function (Y) if Y is the dominant group in determining the relative solubility of the molecule (as in the case of the phenols, anilines, and benzyl alcohols) is given by the simple relation expressed in eq. 15, and the first term in eq. 26 is not important for practical purposes. However, when the situation is reversed and the variable function X becomes dominant, as in the example of the nitrobenzenes with group 1 substituents, then the first term in eq. 26 becomes important. The solubility-modifying effect of Y on X is then not linearly related to σ_Y but depends on the complex way in which the solubilizing forces in X are modified by Y. That good correlation can be obtained if one focuses attention on the dominant group can be nicely illustrated with the benzoic acids. If, in deriving the coefficients for eq. 21 we omit the 3-OH, 4-OH, 3-OCH₃, and 4-OCH₃ groups where the effect $Y \rightarrow X$ is greater than $X \rightarrow Y$, we obtain eq. 28.

$$\Delta\Pi_{\pi_{\text{BA}} - \pi_n} = 0.360\sigma_X - 0.014 \quad \begin{matrix} r & s & s_{\Delta\Pi^2} \\ 0.886 & 0.057 & 0.014 \end{matrix} \quad (28)$$

Two facets of interest are evident from eq. 28; the correlation is much better than that obtained with eq. 21, as indicated by r , and the curve goes much closer to the origin as it theoretically should.

With the nitrobenzenes the results are not as satisfactory. In this series it is more often the variable function X which would play the dominant role as far as relative solubility goes. Using the ten substituents in group 3, we obtain eq. 29.

$$\Delta\Pi_{\pi_{\text{nitroB}} - \pi_n} = -0.123\sigma_X - 0.026 \quad \begin{matrix} r & s & s_{\Delta\Pi^2} \\ 0.648 & 0.953 & 0.0053 \end{matrix} \quad (29)$$

Although the correlation obtained using eq. 29 is no better than that obtained with eq. 22, with the former equation the curve does go close to the origin as it should.

In summary, one can say that although π varies for a given substituent from system to system, the variance for similar systems is not great. For the purpose of correlation of chemical structure with biological activity,² a rather good approximation can, in general, be obtained with two sets of values. The values from the phenoxyacetics appear to be a good compromise when strongly interacting groups are not involved. The values obtained with phenol should be used when phenols or aromatic amines are encountered.

Experimental

Partition Coefficients.—Except for the indicated compounds in Table I, the analyses of the concentrations of the partitioned substances were made using a Cary Model 14 spectrophotometer. Those compounds in Table I indicated by ref. *c* were determined coulometrically.^{2b} The 1-octanol was purified by washing with dilute sulfuric acid and then sodium hydroxide followed by distillation. For the partitioning, octanol saturated with distilled water and distilled water saturated with octanol were used. Usually, 50–150-ml. portions of octanol were used with 50–400-ml. portions of water. The volume ratio of the two phases and the amount of sample were chosen so that, in most cases, the absorbance of a sample from the water layer after partitioning had a value between 0.2 and 0.9 using a 1-cm. cell. Only the concentration of the sample in the water layer was determined, and that in the octanol was obtained by difference. The very small amount of octanol dissolved in the water was found to have no effect on the absorption curve at wave lengths higher than 220 $m\mu$. Generally, the absorption peak of the K-band (260–350 $m\mu$) was used except for the halobenzenes, toluene, and benzene where the B-band was used. For the phenylacetic and benzoic acids and benzyl alcohols, the absorbance at a certain wave length (230–250 $m\mu$) of the E-band was used.⁶

The partition coefficient was calculated as $P = C_{\text{octanol}}/C_{\text{H}_2\text{O}}(1 - \alpha)$, where α , the degree of dissociation, is zero except for the three acid series. As we pointed out earlier,^{2a} ignoring association of the acids in the octanol phase does not, for our purposes, introduce a serious error in the partition coefficient. With phenoxyacetic acid, $\log P$ varied from 1.28, when the concentration in the octanol phase was $10^{-2} M$, to 1.21, when the concentration in the octanol phase was $10^{-4} M$; $\log P$ for phenylacetic acid ranged from 1.41, when the concentration in octanol was $2 \times 10^{-2} M$, to 1.30, when octanol concentration was $2 \times 10^{-4} M$. Benzoic acid varied from 1.88 to 1.81 when the octanol concentration varied from 10^{-2} to $10^{-4} M$. Since our primary concern is with π and $\Delta\Pi$, we have minimized errors in these constants by subtracting the value of $\log P_H$ from $\log P_X$ determined under conditions such that the concentrations of the acids in the octanol layers were equivalent. The necessary range of values for $\log P_H$ was found by plotting P vs. $\log C_{\text{octanol}}$. Carbon dioxide-free conditions must be maintained with the acidic and basic compounds.

Each determination was done in at least duplicate at two different volume ratios and the average value for π has been reported. In certain instances, ionization constants for acids for the calculation of α were not available. These were calculated from the Hammett relationship.

p-Aminophenol presented a special problem because of its high susceptibility to oxidation. To minimize this, partitioning was done in a 1% sodium thiosulfate solution. Previous work had shown low concentrations of salts to have no effect on P .

The volatile compounds benzene, toluene, and the halobenzenes also presented special difficulties. For these substances it was necessary in making up solutions to consider partitioning between the air in the volumetric flask and water. The following procedure was found to give consistent results. A small amount of the liquid was placed in a small vial, capped with a cover glass, and weighed. The vial was then dropped into a volumetric flask filled to the mark with water. The flask was immediately stop-

pered with a well ground stopper saturated with water, and shaken until solution was complete. If the ground stopper was not thoroughly saturated with water, significant losses of the organic compound occurred. The amount of compound used was so small that the increase in total volume of the solution could be neglected. The amount of compound in the water phase ($a - x$) was calculated as

$$\frac{a - x}{\text{vol. of H}_2\text{O}} / \frac{x}{\text{vol. of air}} = P \quad (30)$$

In eq. 30, a is the amount of sample used; $P(\text{H}_2\text{O}/\text{air})$ for benzene is 1.64 as determined by Milligan.⁷

To calculate the partition coefficients of the other volatile compounds between air and water, the following equation was used

$$P = 1.64 \times \frac{\text{solubility of compd. in H}_2\text{O}}{\text{solubility of benzene in H}_2\text{O}} \times \frac{\text{vapor press. of benzene}}{\text{vapor press. of compd.}} \quad (31)$$

The solubilities and vapor pressures were taken from the literature.⁸ The following values for $P(\text{H}_2\text{O}/\text{air})$ were thus estimated: toluene, 1.74; fluorobenzene, 1.25; chlorobenzene, 2.45; bromobenzene, 4.92. In general, when a small amount of air is involved, this correction is so small compared to the experimental error that it can be neglected.

The compounds were weighed and introduced into the partitioning system in a fashion similar to that used for the standard solution. For bromobenzene it was necessary to use a 10-cm. cell because of its low water solubility and low absorbance.

After some initial experience, constant temperature was not maintained during the partitioning. Experimental variations attributed to temperature proved to be less than those inherent in the analytical method. It is known that, when dilute solutions are used and the solvents are quite insoluble in each other, that the partition coefficient is not very sensitive to variations in temperature.⁹ The partition coefficient for phenoxyacetic acid was determined at 0°. The result was not significantly different from values obtained at room temperature. The temperature during this work was about $25 \pm 5^\circ$.

The measurement of partition coefficients of extremely insoluble aromatic compounds¹⁰ such as naphthalene, anthracene, and phenanthrene^{2c} also presents special problems. Fortunately, the absorbance of these compounds is often so high that very small amounts can be determined spectrophotometrically.

In the particularly bad case of anthracene, for example, 0.50 ~ 0.1 mg. was weighed using a Cahn electromicrobalance. This was dissolved in 25 ml. of methanol and diluted to 1 l. with water to make the standard solutions (methanol was not used for the partitioning). The absorbance of the methanol at the wave lengths chosen for analysis was so small that it can be safely ignored. To determine the concentration after partitioning it was necessary to use a 10-cm. cell.

In partitioning these polycyclic aromatic compounds, more gentle shaking for shorter periods of time (30–45 min. instead of 90) was advantageous in avoiding emulsification. Nevertheless, some persistent cloudiness inevitably remained even after prolonged centrifuging and standing. Although small corrections were made for this, the accuracy of these partition coefficients is lower than that of most of the compounds in Table I.

In using the 10 cm. or longer cells, one must be extra careful of the purity of the octanol. Commercially available octanol contains small amounts of impurity which absorbs at higher wave lengths than pure octanol.

Preparation of Compounds.—A few of the compounds used in this work had not previously been reported. **3-Isopropylphenoxyacetic acid** was made from 3-isopropylphenol by the usual pro-

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cedure.¹¹ After recrystallization from hexane, it melted at 63.5–64.5°.

Anal. Calcd. for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found: C, 67.84; H, 6.99.

4-Isopropoxyphenylacetic acid was made in the same way as the 3-isomer and melted at 83.5–84.5°.

Anal. Calcd. for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found: C, 67.93; H, 7.34.

3-Methylthioacetophenone.—In 50 ml. of methanol was dissolved 10 g. of 3-acetylthiophenol.¹² To this solution was added 9 g. of potassium hydroxide dissolved in the minimum amount of water. Dimethyl sulfate (23 g.) was then added slowly to the stirred mixture. At this point 10 ml. of 50% potassium hydroxide and 10 g. of dimethyl sulfate were added. After a few minutes stirring, the methanol was removed *in vacuo* and the residual oil extracted with ether. Distillation yielded 7.5 g. of product, b.p. 107–108° (1 mm.).

Anal. Calcd. for C₉H₁₀OS: C, 65.00; H, 6.06. Found: C, 65.33; H, 6.24.

3-Methylsulfonylaceto-phenone.—The above methylthioacetophenone (5 g.) was dissolved in 12.5 ml. of glacial acetic acid and heated to 40°. To this warm solution was added dropwise 6.5 g. of potassium permanganate in 250 ml. of water. After the addition was complete, a small amount of sodium bisulfite was added to decompose the excess permanganate and the temperature was

raised until all of the crystals which had separated during the oxidation dissolved. The hot solution was filtered to remove the manganese dioxide. Upon cooling, 6 g. of colorless crystals separated. After recrystallization from water the melting point of the product was 105–106°.

Anal. Calcd. for C₉H₁₀O₄S: C, 54.50; H, 5.08. Found: C, 54.68; H, 4.93.

3-Methylsulfonylphenylacetic Acid.—The methylsulfonylaceto-phenone (4 g.) was added to 2 g. of morpholine and 0.6 g. of sulfur and the mixture heated on an oil bath at 130–140 for 5 hr. The thick oil so obtained was leached with ethyl acetate and the 5 g. of morpholine crystals which were left were hydrolyzed with 100 ml. of 2 N potassium hydroxide for 18 hr. Upon acidification, 1 g. of the phenylacetic acid separated. After recrystallization from ethyl acetate–hexane, the product melted at 101–102°.

Anal. Calcd. for C₉H₁₀O₄S: C, 50.40; H, 4.70. Found: C, 50.48; H, 4.64.

3-Ureidophenoxyacetic acid.—Potassium cyanate (0.5 g.) was added to a solution of 1 g. of 3-aminophenoxyacetic acid in 7 ml. of 1 N hydrochloric acid at room temperature. After a few minutes, 1.2 g. of product separated. It was purified by recrystallization from ethanol, m.p. 198° dec.

Anal. Calcd. for C₉H₁₀N₂O₄: C, 51.42; H, 4.77. Found: C, 51.44; H, 5.05.

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A Correlation of Chemical Shifts with Inductive Effect Parameters

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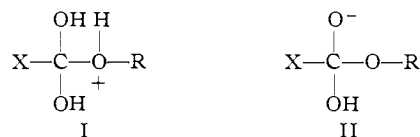
An attempt has been made to correlate the chemical shifts of the acetic acid and succinic acid protons of acetates and succinates with the polar substituent constant σ^* of the alcohol group of the esters. Factors responsible for deviations from linearity are discussed. σ^* -Values are proposed for the allyl and *n*-amyl groups.

Introduction

Considerable effort has been made in recent years to relate proton and F¹⁹ chemical shifts with the electronic properties of substituents.^{1–7} Taft⁸ has been particularly successful in correlating contributions through resonance and induction of substituents in the *para* and *meta* positions of fluorobenzenes with F¹⁹ chemical shift values.

The inductive effect of a substituent X can be expressed in terms of a polar substituent constant σ^* ,⁹ the value of which is obtained from the acidic and alkaline hydrolysis rates of esters of the type X–COOR, relative to the standard acetates. Underlying this method is the assumption that steric and resonance effects are the same in the acidic and alkaline hydrolyses, and thus do not enter into an expression featuring the ratio of the rate constants.

The transition states for such hydrolyses (I and II) clearly indicate not only a dependence on the electron-donating properties of X but also of R, a fact borne



out in those cases studied where R has been varied.¹⁰ It is reasonable to conclude that the acyl and alkyl components are mutually dependent, and that the electronic properties of one will influence the electron density at the other. Such mutual dependence can be extended to the neutral ester molecule III, especially when one considers the existence of resonance structures such as IV, and a relation should exist between the



inductive effect parameter of the alkyl component and a physical property measuring the electron density at the acyl portion, such as the chemical shift of protons attached to it, which is a reliable measure *provided no other factors are operating*. For this reason we have examined the change in the proton chemical shifts of the acetic acid and succinic acid protons of various acetates and succinates, relative to methyl acetate and dimethyl succinate, respectively, against a change in

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