The Use of a Hydrophobic Bonding Constant for Structure-Activity Correlations

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SUMMARY

Evidence is presented to show that, assuming other factors constant, the variation in biological response in a set of congeneric drugs can be represented as a function of the partition coefficient. The form of this function is the same as the form of the normal distribution. Building upon this foundation, one can use substituent constants to quantitatively separate the hydrophobic bonding and the electronic and steric effects of substituents.

INTRODUCTION

The classic studies of Meyer and Overton (1, 2) on the linear relationship between the narcotic action of organic compounds and their partition coefficients between oil and water marked the first success of attempts to quantitatively correlate biological activity with chemical structure. Although this approach has received extensive study (3–6) by many other investigators, the results outside the rather confined area of nonspecific toxicity and narcotic action have been disappointing.

Recently (7–12), we have developed a substituent constant, π, which is defined as $\pi = \log(P_X/P_H)$ where P_H is the partition coefficient of a parent compound and P_X that of a derivative. π is a measure of the hydrophobic bonding power of a substituent and can be used to estimate the change in distribution of a drug between the various aqueous and lipophilic phases, including the final binding to the site of action.

It is our hypothesis (7) that for the general case the biological activity of a series of drugs, assuming that electronic and steric effects are constant, would depend on π or $\log P$ as follows:

$$\log \mathrm{BR} \equiv \log \frac{1}{C} = -k\pi^2 + k'\pi + k'' \quad (1)$$

In Eq. 1, BR is the biological response,[1] C is the molar concentration of drug produc-

[1] The symbol BR is used to represent biological response. In the sense in which we employ it, it is a rate term. For example, it represents the number of organisms killed, the increase in blood pressure, millimeters of growth, etc., per unit of time. In general, there are two ways in which activities are compared. In one, a molar concentration of drug is found which produces a standard biological response. For this condition we prefer to use $1/C$ to represent relative biological activity; that is, when a large amount of drug is needed to cause a standard effect, the organism shows a weak response to the drug.

In the second situation (Eqs. 11–18, Table 1) where a fixed amount of compound is applied and variable responses per unit of time are observed, we use the symbol BR in equations for the sake of simplicity. When equivalent biological response is represented by $1/C$, we are assuming that in comparing activities of a congeneric series of compounds we are comparing activities on the same areas of the dose-response curve. This will not be true for the second situation. Here we must make the assumption that we are making comparisons on the linear portions of the dose-response curves.

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TABLE 1
Comparison of linear with parabolic relation of biological response with lipophilic character

Biological response	Equation	n[a]	r[b]	s[c]	Sig.[d] of π^2 term	Eq. no.
LD_{50} of RSCN against green chrysanthemum aphids (13)	$\log 1/C = 0.085\pi + 3.895$	6	0.708	0.176		9
	$\log 1/C = -0.057\pi^2 + 0.707\pi + 2.349$	6	0.989	0.043	<0.005	10
Relative activity of RSCN against black chrysanthemum aphids (13)	$\log BR = 0.162\pi + 3.432$	7	0.669	0.427		11
	$\log BR = -0.097\pi^2 + 1.129\pi + 1.401$	7	0.962	0.176	<0.01	12
Relative activity of RSCN against green peack aphids (13)	$\log BR = 0.240\pi + 2.323$	7	0.659	0.724		13
	$\log BR = -0.111\pi^2 + 1.455\pi - 0.427$	7	0.938	0.373	<0.025	14
Relative activity of RSCN against thrips (13)	$\log BR = 0.058\pi + 3.033$	7	0.132	1.029		15
	$\log BR = -0.237\pi^2 + 2.432\pi - 1.953$	7	0.947	0.372	<0.005	16
Relative activity of RSCN against red spider (13)	$\log BR = -0.153\pi + 4.459$	5	0.560	0.413		17
	$\log BR = -0.180\pi^2 + 2.004\pi - 1.653$	5	0.960	0.171	<0.10	18
Molar phenol coefficients for *Salmonella typhosa* (7)	$\log PC' = 0.454\pi + 0.477$	35	0.733	0.439		19
	$\log PC' = -0.288\pi^2 + 1.312\pi + 0.139$	35	0.919	0.259	<0.005	20
Toxicity of ROH to blowfly larvae (15)	$\log 1/C = 0.375\pi + 0.030$	8	0.816	0.352		21
	$\log 1/C = -0.230\pi^2 + 1.412\pi - 0.834$	8	0.957	0.193	<0.025	22
Toxicity of ROH to *Phormia terraenovae* (15)	$\log 1/C = 0.019\pi + 0.141$	8	0.124	0.205		23
	$\log 1/C = -0.122\pi^2 + 0.568\pi - 0.316$	8	0.789	0.139	<0.05	24
Narcotic action of ROH on frog ventricle (14)	$\log 1/C = 0.824\pi - 0.284$	10	0.937	0.711		25
	$\log 1/C = -0.135\pi^2 + 1.818\pi - 1.513$	10	0.978	0.458	<0.01	26
Narcotic action of *p*-amino benzoates on goldfish (16)	$\log 1/C = 0.538\pi + 3.999$	9	0.945	0.116		27
	$\log 1/C = -0.202\pi^2 + 1.134\pi + 3.623$	9	0.976	0.084	<0.05	28
Narcotic action of ROH on tadpoles (3)	$\log 1/C = 1.039\pi - 0.442$	10	0.987	0.311		29
	$\log 1/C = -0.097\pi^2 + 1.714\pi - 1.352$	10	0.995	0.215	<0.025	30
Germicidal titer of $RCOO^-$ on *Streptococcus haemolyticus* (25)	$\log 1/C = 0.361\pi - 0.144$	5	0.787	0.516		31
	$\log 1/C = -0.216\pi^2 + 2.948\pi - 7.472$	5	0.964	0.274	<0.10	32
Germicidal titer of $RCOO^-$ on *Bacillus diphtheriae* (25)	$\log 1/C = -0.211\pi + 3.559$	5	0.568	0.558		33
	$\log 1/C = -0.237\pi^2 + 3.107\pi - 7.580$	5	0.944	0.274	<0.10	34
Germicidal titer of $RCHOHCOO^-$ on *Diplococcus pneumoniae* (26)	$\log 1/C = 0.485\pi - 0.098$	7	0.880	0.692		35
	$\log 1/C = -0.113\pi^2 + 2.170\pi - 5.809$	7	0.987	0.259	<0.005	36
Germicidal titer of $RCHBrCOO^-$ on *S. haemolyticus* (26)	$\log 1/C = 0.082\pi + 2.677$	8	0.171	1.258		37
	$\log 1/C = -0.206\pi^2 + 3.171\pi - 7.825$	8	0.871	0.687	<0.025	38

[a] Number of points used in the regression.
[b] r is the multiple correlation coefficient.
[c] s is the standard deviation.
[d] Significance of the π^2 term as established by the F test.

ing an equivalent biological response, and k, k', and k'' are constants for a given series of congeneric drugs.

The basis for Eq. 1 can be simply pictured as follows: assume the partition coefficient (fat:water) of the lowest member of a congeneric series of drugs is zero. In this situation the drug will not be able to move through a lipid barrier and will be restricted to the aqueous phase. Assume the partition coefficient is gradually increased with each successive member to infinity. This last member will be localized in the first lipophilic area with which it comes in contact. Neither of these derivatives at the extremes will be able to find the sites of action which are dispersed throughout a multicompartment cell or organism, and hence will have no biological activity.

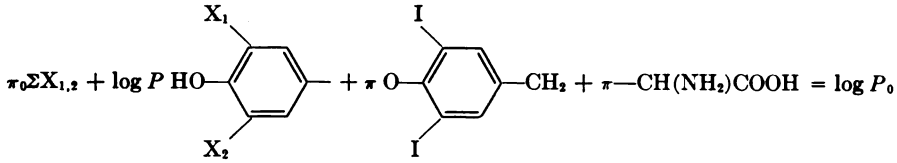
Some derivative between the first and last member will have an ideal partition coefficient, P_0, such that this member can achieve the maximum concentration at the sites of action with a minimum change in free energy. This drug will produce the maximum response.

The purpose of this paper is to summarize the experimental evidence already available in the literature supporting our hypothesis. If it can be clearly shown that Eq. 1 holds, then one can proceed with some confidence in stepwise fashion to evaluate the electronic and steric effects of substituents in other systems by the addition of other terms.

METHOD

Many investigators have shown for simple aliphatic systems that as each CH_2 group is added to RY (where Y is a functional group producing a quantitatively characterizable biological response) a constant ΔBR is, up to a point, observed. In all the examples in Table 1, except in Eqs. 19 and 20, activity of the basic function is modified only by addition of CH_3 or CH_2 groups. Electronic effects of such additions to the functional group are so small that they can be ignored. In the case of the system described by Eqs. 19 and 20, the electronic effects of the substituent on the phenolic OH are included in the π values since phenol was used as the parent compound from which π values were obtained (12). We are assuming that steric effects of the groups are of minor importance. The observed variations in biological activity will thus be due to variation in distribution and adsorption at the active sites caused by changes in π: these are the best possible systems with which to validate our hypothesis.

Using the data from Table 2 we have derived the equations in Table 1 by the method of least squares. In Tables 1 and 2, $\Sigma\pi$ and $\log P_0$ have been calculated by taking advantage of the additive character of $\log P$ and π (11, 12). For example, log P_0 for the thyroxine analogs was estimated as follows:



In Eq. 2, $\pi_0\ \Sigma X_{1,2}$ represents the ideal lipophilic character for substituents X_1 and X_2. In this study only substituents in 3′ and 5′ positions of the outer thyroxine ring were varied. Log P for the iodine-containing moiety in Eq. 2 was calculated by adding 2.38 ($2\pi_I$) obtained from the phenol system (12) to 2.11 [log P for anisol (12)]. The approximation of considering the iodine-containing fragment as a derivative of anisol instead of p-methyl phenyl ether is not a serious one. Experience indicates the error would be of the order of 0.1 to 0.2 unit.

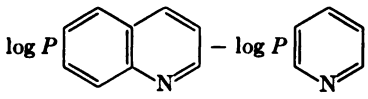
Log P_0 for the p-aminobenzoate series was obtained as follows:

$$\pi_0\,R + \log P\,H_2N\text{–}C_6H_5 + \pi_{COOCH_3} - \pi_{CH_3} = \log P_0 \quad (3)$$

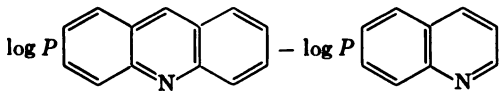
$$2.81 + 0.90 - 0.01 - 0.50 = 3.20$$

In Eq. 3, π_{COOCH_3} is for the aromatic function (11). π_H is taken as zero.

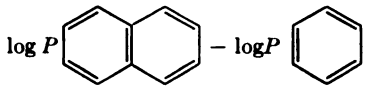
While the above method of calculating $\log P$ values is not a complete substitute for their experimental determination, it does give surprisingly good values when special interactions such as hydrogen bonding do not occur (11). The following example using aromatic compounds illustrates the kind of precision one can expect under favorable conditions using this technique.



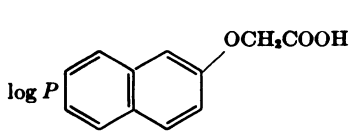
$$= 2.03 - 0.65 = 1.38 \quad (4)$$



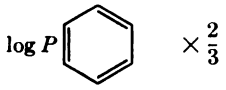
$$= 3.40 - 2.03 = 1.37 \quad (5)$$



$$= 3.37 - 2.13 = 1.24 \quad (6)$$



$$= 2.54 - 1.27 = 1.27 \quad (7)$$



$$= 2.13 \times \frac{2}{3} = 1.42 \quad (8)$$

Average: $\pi = 1.33$

The above example plus those for simpler systems (11) support the calculations we have used in Tables 2 and 3. The value for π_{SCN} was determined from $CH_3(CH_2)_3SCN$. Log P for butyl thiocyanate was found to be 2.03. Subtracting from this the value 2.00 for the butyl group gives 0.03 for π_{SCN}. π for the aliphatic OH was taken as −1.80. Log P for *p*-dimethylaminoazobenzene is 4.60. All log P and π values refer to the octanol:water system.

DISCUSSION

The results in Table 1 demonstrate the usefulness of the additive nature of π. More important, the parabolic dependence of log BR on π or log P clearly stands out. If one hopes to make a quantitative separation of the different effects of a substituent, then Eq. 1 appears to be a far better general assumption from which to start than the linear relationship ($\log BR = k\pi + c$ of Meyer and Overton which has received such wide acceptance. The good linear correlations which have been found are special forms of the general case. These are found whenever the range of π for the congeneric series investigated is so small that one is, in effect, working on the "linear" portion of the parabolic relationship. A linear dependence of log BR on π should also be expected when a one-step partitioning is involved. Such cases arise when the drug action occurs on the outside of a cell membrane or in enzymic studies (9).

The high correlations obtained with the equations in Table 1 containing the π^2 term indicate that the activity curve is symmetric. As long as molecules are sufficiently soluble to test, the fall off in activity is not precipitous as one might expect from the "cut-off" hypothesis (6).

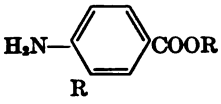
When dealing with very lipophilic mole-

TABLE 2

Data[a] used in derivation of equations in Table 1

Compound	$\Sigma\pi$	Eqs. 9 & 10 $\log \frac{1}{C}$ obs.	Eqs. 11 & 12 log BR obs.	Eqs. 13 & 14 log BR obs.	Eqs. 15 & 16 log BR obs.	Eqs. 17 & 18 log BR obs.
n-C_4H_9SCN	2.0	—	3.10	1.64	1.76	—
n-$C_6H_{13}SCN$	3.0	3.93	4.16	3.39	3.67	—
n-$C_8H_{17}SCN$	4.0	4.33	4.45	3.87	3.88	3.49
n-$C_{10}H_{21}SCN$	5.0	4.45	4.53	4.01	3.96	3.82
n-$C_{12}H_{25}SCN$	6.0	4.52	4.58	4.10	4.01	4.06
n-$C_{14}H_{29}SCN$	7.0	4.54	4.54	4.08	3.83	3.41
n-$C_{16}H_{33}SCN$	8.0	4.39	4.32	3.81	2.15	2.93

		Eqs. 21 & 22 log BR obs.	Eqs. 23 & 24 log BR obs.	Eqs. 25 & 26 $\log \frac{1}{C}$ obs.	Eqs. 29 & 30 $\log \frac{1}{C}$ obs.
CH_3OH	0.5	—	—	−0.204	—
C_2H_5OH	1.0	0.127	0.072	0.187	0.481
n-C_3H_7OH	1.5	0.554	0.149	0.770	0.959
n-C_4H_9OH	2.0	1.253	0.349	1.301	1.523
n-$C_5H_{11}OH$	2.5	1.398	0.580	1.700	2.152
n-$C_6H_{13}OH$	3.0	1.318	0.182	—	—
n-$C_7H_{15}OH$	3.5	1.223	0.100	3.155	3.420
n-$C_8H_{17}OH$	4.0	1.121	0.049	3.699	3.886
n-$C_9H_{19}OH$	4.5	—	—	—	4.602
n-$C_{10}H_{21}OH$	5.0	—	—	4.523	5.000
n-$C_{11}H_{23}OH$	5.5	—	—	—	5.301
n-$C_{12}H_{25}OH$	6.0	—	—	5.222	5.124
n-$C_{14}H_{29}OH$	7.0	—	—	4.000	—

	$\Sigma\pi$	Eqs. 27 & 28 $\log \frac{1}{C}$ obs.	$RCOO^-$ R	$\Sigma\pi$	Eqs. 31 & 32 $\log \frac{1}{C}$ obs.	Eqs. 33 & 34 $\log \frac{1}{C}$ obs.
CH_3	0.50	4.131	n-C_7H_{15}	4.0	1.000	—
C_2H_5	1.00	4.538	n-C_9H_{19}	5.0	1.602	1.903
i-C_3H_7	1.32	4.833	n-$C_{11}H_{23}$	6.0	2.505	2.806
n-C_3H_7	1.50	4.943	n-$C_{13}H_{27}$	7.0	2.806	2.505
t-C_4H_9	1.71	4.860	n-$C_{15}H_{31}$	8.0	2.204	1.903
s-C_4H_9	1.82	4.907	n-$C_{17}H_{35}$	9.0	—	1.301
i-C_4H_9	1.82	5.041	—	—	—	—
n-C_4H_9	2.00	5.167	—	—	—	—
n-C_5H_{11}	2.50	5.200	—	—	—	—

$RCHOHCOO^-$ R	$\Sigma\pi$	Eqs. 35 & 36 $\log \frac{1}{C}$ obs.	Eqs. 37 & 38 $\log \frac{1}{C}$ obs. $RCHBrCOO^-$
n-C_7H_{15}	4.00	1.301	1.903
n-C_9H_{19}	5.0	1.903	2.806
n-$C_{11}H_{23}$	6.0	3.107	3.107
n-$C_{13}H_{27}$	7.0	3.709	4.010
n-$C_{15}H_{31}$	8.0	4.612	4.913
n-$C_{17}H_{35}$	9.0	4.612	4.913
n-$C_{19}H_{39}$	10.0	—	2.505
n-$C_{21}H_{43}$	11.0	4.311	2.204

[a] C is the molar concentration of compound used to cause an equivalent biological response. BR is the relative biological response produced by a fixed amount of drug.

cules such as those higher members of the groups in Table 2, one cannot be sure that true solutions are attained in either the *in vitro* or *in vivo* tests. In the *in vitro* tests micelle formation may occur. In the *in vivo* tests where only a few milligrams of drug per kilogram of tissue is being considered, a large fraction of the drug will be adsorbed by proteins or fats. It is well known from the work of Klotz (19) and others that proteins as well as lipids (20) have great binding power for all kinds of organic compounds.

As far as is discernible, Eq. 1 appears to hold equally well for both situations. The results obtained with Eqs. 22 and 24 where the insects were immersed in the pure alcohols are comparable to those in which aqueous solutions were used.

In looking at the activity (chemical potential) of a series of molecules, as for example the alcohols, it seems plausible to assume that the activity of the lowest member, e.g., CH_3OH, would be primarily determined by the water with which it will be so strongly bound. The activity of a high member of the series will be little affected by water, but quite strongly determined by lipophilic cell constituents. Thus the chemical potential of a congeneric series will have a point of inflection.

That part of a substituent(s) effect represented by $\Sigma\pi$ or $\log P$ is, of course, exceedingly complex. Consider a single molecule of a drug injected into the molecular maelstrom of, for example, the blood stream of a test animal. In moving only millimeters through the swarms of proteins, lipids, and lipoproteins, many partitionings involving hydrophobic bonding will occur even without crossing a cellular membrane. These will be so numerous and diverse in nature that the overall lipophilic character represented by $\Sigma\pi$ or $\log P$ can be expected to give a reasonable approximation of a substituent(s) average effect on the making and breaking of hydrophobic bonds in the drug's random walk to the site of action. However, when that site is reached the last partitioning may involve stereospecific hydrophobic bonding to an enzyme. Here, a substituent's position may be all important. We have shown (9) in studies where purified enzymes were used that a substituent in a *para* position on a benzene ring could aid in the hydrophobic bonding of the substrate to the enzyme, but that a substituent in the *meta* position could not.

There appear then to be three roles for hydrophobic bonding by substituents: first, that in the random walk of the drug to the site of action; second, that of orienting the drug on an enzyme or protein; third, that of causing allosteric effects (21, 22) in the protein or enzyme which may or may not occur in the binding process. Good judgment and ingenuity will be necessary to separate these effects by means of substituent constants and regression analysis. So far our studies indicate that at least for many systems the most important role for the lipophilic character of a substituent appears to be that played in the movement of the drug to the site of action. Good correlations of structure and activity can be obtained by neglecting steric effects of the substituents.

In Table 3 we have summarized the calculated ideal values for lipohydrophilic character ($\log P_o$) of the various series of congeneric drugs so far determined. As these values begin to accumulate for various series of organic compounds in different test organisms, they will aid in the design of new drugs. What little experience we have accumulated (10) supports the expectation that different drugs producing equivalent biological responses in a given system must be (neglecting steric factors) isolipotropic as well as isoelectronic. This is simply another way of stating the long known principle of bioisosterism. An example of this can be seen in systems 12 and 13 of Table 3. In this case, the activities of two different series of plant growth-regulators acting on *Avena* coeloptiles to produce cell elongation show very similar dependence on lipophilic character. Different lipophilic character is necessary when different reaction sites are involved. In example 18, the azobenzenes producing cancer of the liver in mice have a much lower $\log P_o$ value than the hydrocarbons and benzacridines (7) causing skin cancer in

TABLE 3
Ideal lipophilic:hydrophilic character for various drug series

System	log P_0	Ref.
1. Toxicity RSCN to green peach aphids	6.58	Eq. 14
2. Toxicity RSCN to green chrysanthemum aphids	6.23	Eq. 10
3. Toxicity RSCN to black chrysanthemum aphids	5.85	Eq. 12
4. Toxicity RSCN to red spider	5.60	Eq. 18
5. Toxicity RSCN to thrips	5.16	Eq. 16
6. Narcotic action ROH on tadpoles	7.04	Eq. 30
7. Narcotic action ROH on frog ventricle	4.93	Eq. 26
8. Toxicity ROH to blowfly larvae	1.27	Eq. 22
9. Toxicity ROH to *Phormia terraenovae*	.53	Eq. 24
10. Narcotic action of aminobenzoates on goldfish	3.20	Eq. 28
11. Phenol coefficient for *Salmonella typhosa*	3.73	Eq. 20
12. Cell elongation by phenylacetic acids	2.35	(17)
13. Cell elongation by phenoxyacetic acids	2.03	(18)
14. ED_{50} of barbiturates	2.40	(10)
15. Penetration of brain by benzeneboronic acids	2.30	(10)
16. Penetration of tumor by benzeneboronic acids	1.58	(10)
17. Carcinogenicity of hydrocarbons	6.07	(7)
18. Carcinogenicity of azobenzenes	4.83	(7)
19. Thyromimetic action of thyroxine derivatives	5.19	(7)

mice. The role of hydrophobic bonding in the movement of the azobenzenes from the digestive system to the liver is quite different from that in movement through skin. Different electronic and steric effects might also be involved.

If one can build with confidence on Eq. 1, assuming that it is a good model for the variation in BR with the hydrophobic effects of substituents, then regression analysis employing additional extrathermodynamically derived substituent constants can be used for other systems to delineate the various effects of a given substituent. For example, we have shown (7) how a parameter for electronic effects can be linearly combined with Eq. 1 to yield Eq. 39.

$$\log \frac{1}{C} = -k\pi^2 + k'\pi + \rho\sigma + k'' \quad (39)$$

In Eq. 39, ρ and σ are the familiar Hammett constants (10) and k, k', and k'' are constants for a given congeneric series of drugs in a particular biological system. We have also shown (9) how steric effects can be treated using E_s and π. Eventually, more complex situations than that indicated by Eq. 39 might be explored. For example, one might factor the electronic term in Eq. 39 for a series of benzene derivatives as follows:

$$\log \frac{1}{C} = -k\pi^2 + k'\pi + k_1\sigma_1 + k_2\sigma_2 + k_3\sigma_3 + k_4\sigma_4 + k_5\sigma_5 + k_6\sigma_6 + k'' \quad (40)$$

In Eq. 40, σ_1–σ_6 represent the electron densities at the various positions on the ring. It might well be that more than one position plays a significant role in a given drug action. By regression analysis and suitable variation of substituents, one could establish the relative importance of the electron densities in the various positions. With the great amount of experience (23) in quantum mechanical calculations of relative electron densities and the ready availability of large computers, such analyses are within reach. The fact that π and log P have already given as good correlations with calculated electron densities (7, 9) as with the experimentally determined σ constants bodes well for such an approach.

Through the factoring of substituent effects, the success or failure of the concept of bioisosterism (ref. 6, p. 72) becomes

more understandable. For example, a comparison of σ_m values of the halogens (F = 0.34, Cl = 0.37, Br = 0.39, I = 0.35) shows that if the primary function of the halogen in producing a given ΔBR is through electron withdrawal from the *meta* position of a benzene ring and steric effects and lipophilic character are not important, then these functions would be bioisosteric. Under these conditions one could also expect very similar results with the following: CF_3 = 0.43, $COCH_3$ = 0.31 and SCF_3 = 0.40. An example of this type of activation comes from the study of the action of ethyl phenyl phosphates on houseflies (7). Biological response in this case depends almost entirely on σ so that functions seemingly as diverse as SO_2CH_3 (σ^- = 1.05) and CN (σ^- = 1.00) confer approximately the same activity.

However, if π also plays a role, quite different results would be expected for the above functions (π for these functions: F = 0.13, Cl = 0.76, Br = 0.94, I = 1.15, CF_3 = 1.07, $COCH_3$ = −0.28 and SCF_3 = 1.58). Now only I, Br, and CF_3 are bioisosteric with respect to both σ and π. An example of this type of activation comes from the study of plant growth-regulator activity of the phenoxyacetic acids (18). Here the 3-I, 3-Br, and 3-CF_3 derivatives have essentially the same activity.

In a situation where only lipophilic character is important, one finds strange equivalents. For instance, in a series of penicillin derivatives tested on *Staphylococcus aureus* in mice (24), it is found that the derivative with the 3-CF_3 and 4-NO_2 groups ($\Sigma\pi$ = 1.15) has the same minimum inhibitory concentration as the derivative containing a $-CH_2CH_2-$ unit (π = 1.0). Many more examples can be found in this and another penicillin series (8), the activities of which appear to depend almost solely on π. However, the strangeness disappears when one assumes that in these examples isolipotropic molecules give equivalent responses.

The work in this paper, when taken with that previously reported and that in progress, makes us optimistic about the possibilities for the quantitative use of substituent constants in pharmacological problems. One surprising aspect of the analyses up to this point is the number of cases in which it has not been necessary to invoke steric effects to obtain good correlations. While these can be of the utmost importance, the "lock and key" theory does not seem to be so demanding that it precludes many good correlations with a simple two-parameter equation.

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