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Physicochemical–Activity Relations in Practice. 1. A Rational and Self-Consistent Data Bank

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A data bank of substituent constants for 26 ortho and 34 meta and para benzenoid substituents is presented for use in physicochemical–activity relations (PAR) studies. The distributive parameters π and π_-, a bulk parameter based on molar refraction, and positionally weighted electronic parameters F and R are listed for the three substituent positions. There are no gaps in the table caused by missing values and the interparameter correlations are low.

When a new, biologically active molecule is discovered, the common practice among medicinal chemists is to modify its structure in order to determine the effect of these changes on its potency. This often involves the introduction of different substituents into a molecule and Hansch has provided a method of correlating the differences in activity for the resulting series of compounds with the changes in their physicochemical properties which result from altering the substitution pattern.[1] The term "quantitative structure–activity relationships" (QSAR) has been used to describe the method[2] but this is a wide-ranging term which also embraces the Free and Wilson approach and the various quantum mechanical methods. It is therefore suggested that "physicochemical–activity relationships" (PAR) should be used to describe the original method of Hansch[1] and subsequent modifications by other workers.[3,4] The aim of PAR, then, is to explain the interactions between organic molecules and a biological system in terms of a few quantitative parameters which describe physicochemical properties of the organic molecules.

Since there is no rigorous way of selecting the most appropriate parameters to use and no unique analytical strategy, biased or equivocal conclusions may well be drawn unless these points are settled in advance.[4] Such an analytical strategy will be described in a forthcoming paper,[5] while the present paper gives the numerical values for a rationally selected and self-consistent set of physicochemical parameters, suitable for studying a wide range of benzenoid compounds.

In order that the problem shall be of manageable size, it is customary to study a congeneric series of compounds in which a parent molecule is modified by the presence of one or more substituents. Implicit in this approach is the assumption that all members of the series act on the biological system by the same mechanism and only their quantitative potency is modified by the substituents. The appearance over the last 10 years of a large number of successful PAR correlations in the literature supports this assumption.

As a further simplification, only cases in which the substitution occurs in a benzene ring will be considered at present. This covers a wide range of potential drug molecules. The data bank therefore comprises a set of "substituent constants" which define the relative magnitude of each property between compounds in the series, while the absolute value of the properties for any compound need not be known.

Selection of Substituents and Parameters. The data bank was restricted to stable, chemically accessible, and useful substituents having as wide a range of properties as possible. It was considered unsatisfactory to present a data bank having missing values where the parameters in question had not been measured and these considerations restricted the number of substituents to 34. Eight of these were not considered for the ortho position since they are bulky and it was expected that they would interact sterically with the side chain, thus rendering their parameter values invalid when applied to other systems. In compiling this data bank no attempt has been made to extend the list by including a large number of substituents of doubtful value.

The physicochemical parameters were required to satisfy the four following criteria. Firstly, each parameter must describe a likely interaction between a small molecule and its biological environment. Secondly, it must be possible to obtain parameters from the literature, measure them in a reproducible in vitro system using model compounds, or reliably deduce them from related values. Thirdly, since the ability to predict parameters and hence biological activities is central to the overall aim, a parameter, once measured in a model compound, must be applicable to the same substituent in another benzenoid compound. Finally, parameters must describe distinct physicochemical properties which are essentially uncorrelated with one another; the dangers in using highly correlated parameters together have been pointed out.[4,6]

In view of these criteria, the final selection comprised the distributive parameters π and π_-, the electronic parameters F and R, and the bulk parameter MR, as described below.

Distributive Parameters. π has been firmly established as the parameter of choice for correlating both binding to biological macromolecules and transport through a biological system.[7-10] Ideally, its use is restricted to molecules where comparatively little perturbing effect is exerted on the electrons of the benzene ring. In the case of compounds having electron-donating side chains, the partition coefficient is better described using π_-, a similar parameter

Table I. Complete Data Bank of Substituent Constants for 34 Substituents

Substituent	Ortho				Meta				Para				MR[a]
	π	π_-	F	R	π	π_-	F	R	π	π_-	F	R	
H[b]	0	0	0	0	0	0	0	0	0	0	0	0	0
Me	0.84[d]	0.49[i]	−0.07[j]	−0.12[j]	0.52[d]	0.50[i]	−0.05[j]	−0.05[j]	0.60[d]	0.48[i]	−0.05[j]	−0.14[j]	4.7
Et	1.39[d]	0.99[e]	−0.08[j]	−0.10[j]	0.99[d]	0.94[i]	−0.06[j]	−0.04[j]	1.10[e]	0.98[e]	−0.07[j]	−0.11[j]	9.4
n-Pr	1.89[e]	1.49[e]	−0.04[k]	−0.10[k]	1.45[d]	1.44[e]	−0.03[k]	−0.04[k]	1.60[e]	1.48[e]	−0.03[k]	−0.11[k]	14.0
i-Pr	1.77[e]	1.37[e]	−0.09[k]	−0.10[k]	1.33[d]	1.32[e]	−0.07[k]	−0.04[k]	1.43[d]	1.36[e]	−0.07[k]	−0.11[k]	14.0
n-Bu	2.39[e]	1.99[e]	−0.07[k]	−0.11[k]	1.92[d]	1.94[e]	−0.06[k]	−0.05[k]	2.10[e]	1.98[e]	−0.06[k]	−0.13[k]	18.7
t-Bu	2.17[e]	1.77[e]	−0.13[j]	−0.12[j]	1.70[d]	1.72[e]	−0.10[j]	−0.05[j]	1.88[e]	1.76[e]	−0.10[j]	−0.14[j]	18.5
Ph					1.92[d]	1.77[g]	0.14[j]	−0.03[j]	1.74[l]	1.74[g]	0.14[j]	−0.09[j]	24.3
CF_3	1.04[f]	1.34[i]	0.79[j]	0.16[j]	1.10[d]	1.49[i]	0.62[j]	0.07[j]	1.04[g]	1.05[g]	0.63[j]	0.19[j]	4.0
OH[c]	−0.41[d]	−0.58[i]	0.61[j]	−0.56[j]	−0.50[d]	−0.66[i]	0.48[j]	−0.22[j]	−0.61[d]	−0.87[i]	0.49[j]	−0.64[j]	1.5
OMe	−0.33[d]	−0.13[g]	0.52[j]	−0.43[j]	0.12[d]	0.12[i]	0.41[j]	−0.17[j]	−0.03[d]	−0.12[i]	0.41[j]	−0.50[j]	6.5
OEt	0.17[e]	0.37[e]	0.45[j]	−0.38[j]	0.62[e]	0.62[e]	0.36[j]	−0.15[j]	0.47[e]	0.35[i]	0.36[j]	−0.44[j]	11.3
O-*n*-Pr	0.67[e]	0.87[e]	0.46[j]	−0.39[j]	1.12[e]	1.12[e]	0.36[j]	−0.16[j]	0.97[e]	0.85[e]	0.37[j]	−0.46[j]	15.9
O-*i*-Pr	0.55[e]	0.75[e]	0.61[j]	−0.63[j]	1.00[e]	1.00[e]	0.48[j]	−0.25[j]	0.85[e]	0.73[e]	0.49[j]	−0.72[j]	16.0
O-*n*-Bu	1.17[e]	1.37[e]	0.51[j]	−0.48[j]	1.62[e]	1.62[e]	0.40[j]	−0.19[j]	1.47[e]	1.35[e]	0.41[j]	−0.55[j]	20.7
O-*n*-Am	1.67[e]	1.87[e]	0.53[j]	−0.50[j]	2.12[e]	2.12[e]	0.42[j]	−0.20[j]	1.97[e]	1.85[e]	0.42[j]	−0.58[j]	25.3
OPh	0.97[g]	0.81[g]	0.93[j]	−0.64[j]	1.56[l]	1.56[g]	0.73[j]	−0.26[j]	1.34[g]	1.46[g]	0.75[j]	−0.74[j]	26.6
OAc	−0.58[g]	−1.02[g]	0.85[j]	−0.06[j]	−0.60[g]	−0.23[g]	0.67[j]	−0.03[j]	−0.58[g]	−1.06[g]	0.68[j]	−0.07[j]	11.6
NH_2[c]	−1.40[h]	−0.84[i]	0.05[j]	−0.59[j]	−1.29[h]	−1.29[i]	0.04[j]	−0.24[j]	−1.30[h]	−1.42[i]	0.04[j]	−0.68[j]	4.2
NMe_2[c]	0.16[g]	−0.48[g]	0.04[k]	−0.73[k]	0.11[g]	0.10[i]	0.03[k]	−0.29[k]	−0.08[g]	−0.69[g]	0.03[k]	−0.85[k]	14.4
NHAc	−0.14[g]	−0.74[g]	0.59[j]	−0.24[j]	−0.78[d]	−0.73[g]	0.46[j]	−0.10[j]	−0.56[g]	−1.21[g]	0.47[j]	−0.27[j]	14.6
NO_2					0.11[d]	0.54[i]	1.09[j]	0.05[j]	0.22[d]	0.45[i]	1.11[j]	0.16[j]	6.0
CHO	−0.43[g]	0.24[i]	0.84[k]	−0.13[k]	−0.47[f]	−0.08[g]	0.66[k]	−0.05[k]	−0.47[g]	−0.06[g]	0.67[k]	−0.15[k]	5.3
Ac					−0.28[d]	−0.07[i]	0.52[j]	0.07[j]	−0.39[d]	−0.11[i]	0.53[j]	0.20[j]	9.9
COOMe					−0.04[m]	0.43[i]	0.44[k]	0.07[k]	−0.04[p]	0.50[i]	0.45[k]	0.19[k]	11.4
COOEt					0.46[e]	0.93[e]	0.54[j]	0.05[j]	0.46[e]	1.00[e]	0.55[j]	0.14[j]	16.2
$CONH_2$					−1.51[n]	−0.57[o]	0.40[k]	0.05[k]	−1.51[n]	−0.88[o]	0.41[k]	0.14[k]	8.8
SMe	0.87[f]	0.30[g]	0.41[j]	−0.16[j]	0.64[d]	0.55[g]	0.33[j]	−0.07[j]	0.87[g]	0.32[g]	0.33[j]	−0.19[j]	13.0
SO_2Me					−1.25[d]	−1.02[f]	0.88[j]	0.08[j]	−1.20[g]	−1.02[g]	0.90[j]	0.22[j]	12.5
SO_2NH_2					−1.86[f]	−2.10[g]	0.67[j]	0.07[j]	−1.86[g]	−1.50[g]	0.68[j]	0.19[j]	11.3
CN	−0.33[f]	0.13[g]	1.06[j]	0.16[j]	−0.31[d]	0.24[i]	0.83[j]	0.06[j]	−0.33[d]	0.14[i]	0.85[j]	0.18[j]	5.2
F	0.00[d]	0.25[i]	0.88[j]	−0.29[j]	0.22[d]	0.47[i]	0.69[j]	−0.12[j]	0.15[d]	0.31[i]	0.71[j]	−0.34[j]	−0.4
Cl	0.76[d]	0.69[i]	0.86[j]	−0.14[j]	0.77[d]	1.04[i]	0.68[j]	−0.06[j]	0.73[d]	0.93[i]	0.69[j]	−0.16[j]	4.8
Br	0.84[d]	0.89[i]	0.91[j]	−0.15[j]	0.96[d]	1.17[i]	0.71[j]	−0.06[j]	1.19[d]	1.13[i]	0.73[j]	−0.18[j]	7.6
I	0.93[d]	1.19[i]	0.84[j]	−0.17[j]	1.18[d]	1.47[i]	0.66[j]	−0.07[j]	1.43[d]	1.45[i]	0.67[j]	−0.20[j]	12.8

[a] Calculated from [R]D data given in ref 20 and 21. [b] All parameters = 0 for the hydrogen substituent, by definition (values of MR are adjusted accordingly). [c] Ionizable substituents. $\Sigma\sigma$ for all other groups in the ring must lie within the stated limits, see text. [d] Calculated from values given in ref 25, phenoxyacetic acid series. [e] Extrapolated from other homologs according to the rules: $-CH_2-$ = 0.50; single branch in carbon chain = −0.12; double branch in carbon chain = −0.22. [f] Para value used. [g] Measured by the authors, see Experimental Section. [h] As for d, toluene series. [i] As for *d*, phenol series. [j] The product of $\mathcal{F}$ and $\mathcal{R}$ from ref 13 and appropriate positional weighting factors (see text). [k] As for *j*, but $\mathcal{F}$ and $\mathcal{R}$ calculated from σ_m and σ_p from ref 24. [l] π_- value used. [m] As for *d*, benzoic acid series. [n] Calculated from C. Hansch and A. Leo, computer listing of substituent parameters (1973), toluene series. [o] As for *n*, aniline series. [p] Meta value used.

where the model compounds are aniline or phenol.[7] The parameters π and π_- are thus alternative measurements of the same property and must not be used together. (A further parameter π_+ used for electron-withdrawing side chains has been devised[7] but occasions for its use in modern drug design are so rare that it was not considered worthwhile to include it in this data bank.)

The above is naturally something of a simplification since the values for π for a given substituent form a continuous spectrum, varying according to the nature of the model compound in which they are measured. Nevertheless, the compromise of selecting the appropriate π-type term works well in practice. As one would expect, π values for strongly interacting substituents such as NH_2 and NO_2 vary over a wide range and the user might bear this in mind when applying the given values to his own series of compounds.

Electronic Parameters. Hammett's[11] parameter σ has long been recognized by organic chemists to comprise two qualitatively distinct components, viz. the inductive effect propagated through the σ bonds and the resonance or mesomeric effect caused by conjugation between a lone pair of electrons or a π-bond system in the substituent with the π electrons in the benzene ring. These two components contribute differently to the influence of substituents on different reactions and thus σ is not a universally applicable parameter.[12]

In recent years this fact has led a number of workers to devise a wide range of different σ-type parameters relating to various reaction series. Swain and Lupton[13] showed that many of these can be expressed as a linear combination of two principal components which they termed $\mathcal{F}$ and $\mathcal{R}$ (for "field" and "resonance", respectively). The ratio of the contributions of $\mathcal{F}$ and $\mathcal{R}$ for any reaction series is, in general, unique to that reaction. In particular, reactions of meta- and para-substituted benzenoid compounds were found to differ and thus $\mathcal{F}$ and $\mathcal{R}$ cannot be used directly in comparing the reactivities of a series of substituted benzenes in which

Table II. Hammett σ Values for Phenols and Anilines

Substituent	σ_{ortho}[a]	σ_{ortho}[b]	σ_{meta}[c]	σ_{para}[c]
H	0	0	0	0
Me	−0.13	0.10	−0.07	−0.17
Et		0.05	−0.07	−0.15
n-Pr			−0.05	−0.13
i-Pr	−0.23	0.03	−0.07	−0.15
n-Bu			−0.07	−0.16
l-Bu	−0.52		−0.10	−0.20
Ph	0.00		0.06	−0.01
CF_3			0.43	0.54, 0.74[b]
OH		−0.09	0.12	−0.37
OMe	0.00	0.00	0.12	−0.11,[a] −0.27
OEt		0.02	0.10	−0.24
O-*n*-Pr			0.10	−0.25
O-*i*-Pr			0.10	−0.45
O-*n*-Bu			0.10	−0.32
O-*n*-Am			0.10	−0.34
OPh			0.25	−0.32
OAc			0.39	0.31
NH_2		0.00	−0.16	−0.15,[a] −0.66
NMe_2			−0.21	−0.12,[a] −0.83
NHAc			0.21	0.00
NO_2	1.24	1.72	0.71	1.24,[a] 1.26[b]
CHO	0.75		0.36	1.03,[a] 0.99[b]
Ac			0.38	0.84,[a] 0.81[b]
COOMe			0.32	0.44, 0.75[b]
COOEt			0.37	0.45, 0.72[b]
$CONH_2$	0.72		0.28	0.36
SMe			0.15	0.21,[a] 0.00
SO_2Me			0.60	0.92,[a] 1.14[b]
SO_2NH_2			0.46	0.57, 0.80[b]
CN			0.56	0.88,[a] 1.00[b]
F	0.54	0.47	0.34	0.06
Cl	0.68	0.67	0.37	0.23
Br	0.70	0.71	0.39	0.23
I	0.63	0.70	0.35	0.18

[a] Values specifically applicable to phenols from ref 23. [b] Values specifically applicable to anilines from ref 24. [c] Values from benzoic acid series, ref 24, unless otherwise noted.

Table III. Correlation Coefficients between Parameters in the Data Bank

π	π_-	F	R	MR
0.95[a]				
−0.34	−0.22			
−0.11	0.01	0.12		
0.54	0.49	−0.15	−0.25	

[a] The expected high correlation between π and π_- is of no significance since these parameters are never used together.

there is both meta and para substitution. Thus, a new limitation was perforce introduced from which the original Hammett equation did not suffer. Furthermore, in common with Hammett, Swain and Lupton made no attempt to include ortho substitution in their general approach. All these difficulties could be overcome if the $\mathcal{F}$ values for any substituent in the ortho, meta, and para positions were found to bear a constant ratio to one another and $\mathcal{R}$ behaved similarly. With this thought in mind Williams and Norrington[14] undertook a systematic study of data from the literature which led to positional weighting factors f and r for the three positions.[15] The products $f\mathcal{F}$ and $r\mathcal{R}$ (now termed F and R) thus allow substituents in all these positions to be mixed freely and carry the additional advantage that, for the first time, σ-type parameters can be satisfactorily applied to ortho substituents.

Bulk Parameters. Experience has shown[16] that a parameter representing the volume of the substituents on each compound, relative to other members of the same series, may often be linearly correlated with the biological measurement. A refinement may be introduced by employing two such parameters, one representing intermolecular interactions and obtained by summing over the meta and para substituents and the other covering intramolecular interactions and referring to ortho substituents only.

Of the various parameters proposed,[2,16-19] the present choice falls on one based on the refractive index of model compounds. The molar refraction at the wavelength of the sodium D line, MR, has been extensively tabulated[20,21] and these values are not dependent on the position of the substituent in the benzene ring. In order that they may be expressed on a scale where the value for the hydrogen substituent is zero, MR for H has been subtracted from all values.

Parameter Values. The complete data bank is given in Table I. Many of the parameter values were available from the literature although, in the opinion of the present authors, these have never been collected in a form convenient for the practicing drug design scientist. Of the remainder, some were determined by direct measurement and the rest were found by inter- and extrapolation from known values. The values given therein may be freely used in PAR studies subject to two qualifications.

Firstly, where two or more substituents are present in the same molecule (attached to the same or an exactly equivalent benzene ring) the parameters for the molecule as a whole are obtained by summing the parameter values for the individual substituents. Care must be exercised, however, if two substituents are in adjacent positions and might be expected to perturb each other sterically.[22,23] Such deviation will probably only be serious where substituents having π orbitals, or lone pair electrons overlapping the π orbitals of the aromatic ring, are twisted out of position by neighboring groups.

Secondly, special consideration must be given to the substituents OH, NH_2, and NMe_2 which are capable of becoming ionized in the biophase. The actual degree of ionization will be determined by the electronic nature of the rest of the molecule and since the parameter values given refer only to the nonionized form, such substituents should only be used when this form comprises more than 99% of the total. This will occur when $\Sigma\sigma$ for all groups in the ring relative to the substituent (including the side-chain) lies in the appropriate range, calculated from the Hammett equations for the respective substituted benzenes.[23,24] These ranges, which assume a pH in the biophase of 7.4, are: for OH, $\Sigma\sigma < 1.1$; for NH_2, $\Sigma\sigma > -2.3$; and for NMe_2, $\Sigma\sigma > -0.9$. To assist these calculations, Table II lists the appropriate σ constants for all groups in the data bank for which they are available. Since Table II is specifically applicable to the substituents OH, NH_2, and NMe_2, the figures applying to aniline or phenols are used whenever possible. Thus, it differs in some respects from the commonly published tables of data based entirely on the ionization of benzoic acids.

It must be emphasized that the figures in this data bank are by no means final. Indeed, they can never be, since the concept of substituent parameters remaining constant between one system and another is only an approximation.

Nevertheless, the authors believe that this is the first data bank published which covers a reasonable spread of different substituent groups whose parameters are reasonably uncorrelated with each other (Table III) and, furthermore, which has no missing values. The user is not, therefore, forced to choose between omitting either a compound or a parameter when a value is missing, or alternatively of devising a crude and possibly incorrect substitute value.

Experimental Section

Measurement of Partition Coefficients. Partition coefficients were determined between 1-octanol and water and, in the case of ionizable compounds, the aqueous phase was brought to a pH at which the ionization was suppressed to <1%. The 1-octanol (Koch Light, pure) and aqueous phase were mutually saturated before use.

The test compounds were dissolved in the aqueous phase to yield a solution which could be estimated spectrophotometrically, using a Unicam SP800 spectrophotometer. A uv peak having an absorption of 0.5–1.0 was commonly used.

Every partition coefficient was measured using two volume ratios and two concentrations. Each was done in triplicate, giving a total of 12 determinations per compound. The solutions were gently shaken at room temperature at ≃60 strokes per minute. Two of each set of three were shaken for 2 days while the third was left for an extra day to test if equilibrium had been attained. At the end of this time a sample of the aqueous phase was removed, centrifuged for 1 hr at 1000 g, and again estimated spectrophotometrically.

In each case π was calculated as $\pi = \log P_x - \log P_H$ where P_x is the partition coefficient of the test compound and P_H is the partition coefficient of the corresponding unsubstituted compound.[25]

The model compounds used in measuring π values were as follows: *p*-CHO, phenoxyacetic acid; *p*-CF_3, phenylacetic acid; *o*-OPh, NHAc, *p*-OPh, NHAc, SMe, SO_2Me, benzoic acid; *o*-OAc, NMe_2, CHO, *m*-OAc, NMe_2, *p*-OAc, NMe_2, SO_2NH_2, toluene. The model compounds used in measuring π_- values were: *o*-OMe, NHAc, CN, *m*-Ph, OAc, NHAc, CHO, *p*-Ph, NHAc, CHO, SMe, phenol; *o*-OPh, OAc, NMe_2, *p*-NMe_2, anisole; *o*-SMe, *m*-OPh, SMe, SO_2NH_2, *p*-CF_3, OPh, OAc, SO_2Me, SO_2NH_2, aniline.

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Physicochemical-Activity Relationships in Practice. 2. Rational Selection of Benzenoid Substituents

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A rational method is presented for the selection of substituents to be introduced into a benzenoid ring system of a biologically active compound in order to explore a defined physicochemical parameter space. The method, which may be readily programmed for use on a computer, relies on maintaining a minimum distance between compounds in the multidimensional physicochemical parameter space. The series of compounds produced will then have a well-spread set of minimally correlated physicochemical parameter values and could thus be used for the reliable correlation of the variation in the biological activities of the members of the series with changes in these physicochemical parameters. Some examples of the use of the present method under various conditions are given, and it is compared with alternatives in the literature.

Many papers involving the use of the method of physicochemical-activity relationships (the PAR method) have been published,[1,2] and it is now well established as an aid to the design of biologically active molecules.[3,4] Unfortunately, the method has often been applied to series of compounds which are far from ideal for the purpose. This is usually because the method was applied as an afterthought, and the compounds in the series were not chosen at the onset with the aim of testing rigorously the hypotheses implicit in the method. In these cases the range of values for some of the physicochemical parameters may be small, and the chance of finding a real relationship between activity and these parameters will therefore be correspondingly small. Also, correlations may exist between the physicochemical parameters under test, leading to problems in distinguishing which parameters are truly correlated with activity.[5] These factors often give rise to regression equations which are inadequate for the prime objective of predicting which new members of the series will have higher biological activities. Before the PAR method is applied predictively it