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PARACHORS IN DRUG DESIGN

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Abstract—Parachor has been used extensively in physical organic chemistry for structure determination. It has rarely been used as a parameter for the correlation of structure and biological activity. We have reexamined the parachor concept for structure–activity correlations of some closely related analogs. Parachor is an additive and constitutive molecular parameter consisting of two physical properties, molar volume and surface tension, factors which appear to be important in the passage of a drug or hormone from the site of administration or synthesis to the site of action. Correlations between parachor values and biological activities for a number of drug classes have been examined. Good correlations were obtained for three classes: thyromimetic activity of 3'-substituted thyroxine analogs, blood clotting inhibitory activity of 5-substituted pentylamines, and local anesthetic activity of the paracaines. Correlations with parachor are comparable to those obtained with the Hansch hydrophobic constant π for six more drug classes: antibiotic activity of penicillins; fibrinolytic activity of 2,4-substituted benzoic acids; parasympatholytic activity of 2-alkyl-diphenhydramines; beta-receptor activity of sympathomimetics; fibrinolytic activity of 5-substituted salicylic acids; and isohemolytic concentrations for *n*-alcohols. The relative merits of parachor and partition coefficients in predicting biological activities are discussed. When data are available for both parameters, both correlations appear to be equally useful. Because the parachor is a truly additive and constitutive property and involves no new experimental measurements, its predictive usefulness in drug design deserves further evaluation.

Mathematical correlations between chemical structure and biological activity have been attempted by different workers in the search for analogs of drugs and bioactive compounds with higher and more selective activity by the use of different physico-chemical properties, e.g. solubility [1], partition coefficients [2, 3], polarizability [4], molar attraction constants [5], Hammett's electronic substituent constants [6, 7], Taft's steric substituent constants [8, 9], and molecular orbital charge density index [10]. Hansch [11–13] has made a major contribution to the field of drug design by using octanol–water partition coefficients in modified Hammett equations [14]. McGowan [15, 16] made the first attempt to correlate the parachor values of a large variety of organic compounds with their biological activity. For some antimicrobial compounds, he found a linear relationship between their narcotic potency and their parachor. Recently Leo *et al.*[17] have made a comparison of four parameters used in structure–activity studies. The activities of a variety of compounds of widely different chemical structure, as measured in different biological systems, were correlated with octanol–water partition coefficients, polarizabilities, molar attraction constants, parachors and molecular weights. In the systems analyzed by them, octanol–water partition coefficients correlated best with biological activities, and parachors gave the next best correlations. Potentially, the use of parachor has distinct practical advantages for the prediction of the biological activity of new and unsynthesized compounds, which has prompted us to investigate in detail its performance as a parameter for structure–activity correlations.

Parachor is defined in the equation 1 as the product of the molar volume and the fourth root of the surface tension [18]:

$$P = M.D^{-1}.Y^{1/4} = \Sigma P_a \qquad (1)$$

where P is parachor, M is molecular weight, D is density and Y is surface tension. Surface tension is a measure of the intermolecular attractive and repulsive forces. Parachor may be regarded as the molecular volume of a liquid of a surface tension equal to unity.

When the surface tensions of the compounds in an analogous series are numerically similar, the parachor values of the analogs are a good measure of their relative molecular sizes. The effect produced by a substituent group on the molecular size and the intermolecular interaction is reflected in the parachor value of the substituted analog. An important aspect of parachor for practical use is that it is a truly constitutive and additive property and may be expressed as the sum of the atomic parachors: P_a, corresponding to the individual atoms, with necessary corrections for the type of bondings. Extensive tabulations of these atomic parachors are available [19], and comparison of measured molecular parachors with those calculated from the atomic parachors indicates a close agreement of measured and calculated values, namely they differ by approximately 1 per cent. Further discussion of the atomic parachors used in the present study is given in Methods.

In biological systems the production of a pharmacological response depends upon the attainment of a certain concentration of the active molecule at the target site. The transport of a drug or active molecule from the point of administration or synthesis to the target tissue for the production of the selective biores-

ponse involves passage across multiple hydrophilic–lipophilic barriers, for which process molecular size and hydrophobic interactions should be important limiting factors. Hence the biological activity of a drug is likely to be related in part to its parachor value. Such considerations led us to examine the correlation between biological activity and the parachor value of a number of analogous series of drugs.

For nine different classes of drugs we found a comparable or better correlation between biological activity and parachor when compared with those obtained with octanol–water partition coefficients; in all nine cases parachor gave good predictively useful correlations.

METHODS

Computation of parachors. The parachor values of organic compounds can be obtained in two ways: (1) from standard tables by additive summation of the parachors of all the atoms and other structural features occurring in the compound; and (2) by experimental determination of surface tension and density, and then calculation from the formula. Sugden [18] prepared the original table of atomic and structural parachors. It was assumed initially that the parachor was a strictly additive property; but subsequently, the constitutive nature of parachor became evident in certain classes of compounds, e.g. different values of oxygen in esters, ethers, alcohols and acids. A number of modified tables of parachors of atoms and structural elements were prepared later by Mumford and Phillips [20] and Vogel [21]; an exhaustive list of parachors of many different classes of organic compounds has been compiled by Quayle [19]. The latter author reviewed the tables of all previous workers and summarized the results into a table of "recommended parachors." We have used Quayle's table of recommended parachors for the calculation of all parachors reported in this paper. With the help of the parachor tables, it is possible to calculate the molecular parachor value of any compound if the chemical structure of the compound is known.

Statistical methods. Statistical correlations were carried out by stepwise multiple regression analysis using a computer program of the Institute of Computer Science, Univeristy of Guelph. Equations 2–5 were used for the regression analysis of nine different drug classes:

$$\log A = k_1 P + C_1 \quad (2)$$

$$\log A = -k_2 P^2 + k_3 P + C_2 \quad (3)$$

$$\log A = k_4 \pi + C_3 \quad (4)$$

$$\log A = -k_5 \pi^2 + k_6 \pi + C_4 \quad (5)$$

where A = calculated biological activity, P = parachor value, π = Hansch's hydrophobic constant [11, 12]; all k's are coefficients and all C's are constants.

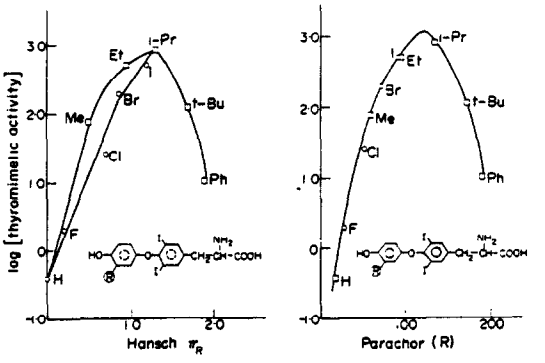


Fig. 1. Thyromimetic activity of 3′-substituted thyroxine analogs [22, 23] plotted as a function of: (a) the Hansch π_R of the 3′-substituent [11, 12], and (b) the parachor of the 3′-substituent.

Equations 2 and 4 represent the effect of parachor and π, respectively, on the biological activity of the different bioactive compounds. Equations 3 and 5 relate the effect of the simple and square terms of P and π to the biological activity.

RESULTS AND DISCUSSION

3′-Substituted thyroid hormone analogs. In Fig. 1, the thyromimetic activity of ten 3′-substituted analogs of thyroid hormone was plotted against both parachor and Hansch π value of the substituent. Parachor gave a better correlation than the π value. In the plot for π, the halogens and the alkyl substituents fall on different curves. The method of regression analysis was applied to the data for equations 6–11. Here the number of cases (n) = 10.

	r	s	F	
$\log A = 0{\cdot}009\,(\pm 0{\cdot}014)\,P + 0{\cdot}933$	0·45	1·06	2	(6)
$\log A = -0{\cdot}0003\,(\pm 0{\cdot}0001)\,P^2 + 0{\cdot}078\,(\pm 0{\cdot}007)\,P - 1{\cdot}571$	0·99	0·14	277	(7)
$\log A = 1{\cdot}01\,(\pm 1{\cdot}24)\,\pi + 0{\cdot}777$	0·55	0·99	3	(8)
$\log A = -2{\cdot}51\,(\pm 0{\cdot}69)\,\pi^2 + 5{\cdot}78\,(\pm 1{\cdot}38)\,\pi - 0{\cdot}65$	0·96	0·33	49	(9)
$\log A = -0{\cdot}0003\,(\pm 0{\cdot}0001)\,P^2 + 0{\cdot}078\,(\pm 0{\cdot}004)\,P - 0{\cdot}30\,(\pm 0{\cdot}003)\,\sigma - 1{\cdot}55$	0·99	0·14	191	(10)
$\log A = -2{\cdot}64\,(\pm 0{\cdot}56)\,\pi^2 + 5{\cdot}95\,(\pm 1{\cdot}11)\,\pi - 1{\cdot}13\,(\pm 1{\cdot}11)\,\sigma - 0{\cdot}65$	0·98	0·26	54	(11)

In these regression equations, r is the correlation coefficient, s is the standard deviation and F is the variance ratio of Snedecor. The figures in parentheses are the 95 per cent confidence intervals. The quality of the fit as indicated by the F-test shows what is apparent in Fig. 1, that the parachor gives a statistically better fit than the Hansch π; viz. for equations 7 and 9, F has a value of 277 for parachor and 49 for π. In both cases, the correlations are nonlinear, as indicated by the lack of fit to equations 6 and 8. The introduction of more parameters, in this case P^2 or π^2, into the linear equations is likely to result in a better fit, since the basic correlations are nonlinear. It would be unwise, however, to draw any mechanistic conclusions based on the nature of the new parameters.

In addition to the equations shown above, correlations involving the Hammett electronic constant, σ, of the substituent and a coefficient, ρ, for the reaction system were investigated, for the thyromimetic analogs only, using equations 12 and 13.

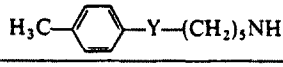
$$\log A = k_7P^2 + k_8P + \rho\sigma + C_5 \quad (12)$$

$$\log A = k_9\pi^2 + k_{10}\pi + \rho\sigma + C_6 \quad (13)$$

From these data it appears that for optimum thyromimetic activity the parachor value for the 3'-substituent of the outer ring of thyroxine analogs should be between 110 and 130 with a mean value of approximately 120. Hence, it may be predicted that 3'-substitution with groups like —$COCH_3$ (P = 107), —NCS or —SCN (P = 115) and —CH_2CH_2Cl (P = 134 should give highly potent thyromimetic or antithyroxine compounds. Parachor is an approximate measure of the size or volume of a species.

The parachor values of thiocyanate and iodide are very close. From Jorgensen's thyroid hormone receptor model [24], a "groove" (equivalent to the parachor value of about 120) on the functional receptor may be involved. If the stereospecific binding of the 3'-iodine atom of thyroxine into this groove is an essential part of thyromimetic action, then the inhibitory action of thiocyanate may be explained by its occupancy of this groove on the functional receptor.

Table 1. Relative blood clotting inhibitory activity of 5-substituted pentylamines*



Substituent Y	Parachor	Hansch π†	Relative activity‡	Log activity
$-SO_2NH-$	156·3	−1·82	24	1·3802
$-SO_2N(CH_3)-$	192·6	−1·26	29	1·4624
$-NHSO_2-$	156·3	−1·05	20	1·3010
-CONH-	79·1	−1·49	6	0·7782
-NHCO-	79·1	−0·97	2	0·3010
-NHCONH-	112·1	−1·30	5	0·6990
-COO-	63·8	−4·36	8	0·9031
-OOC-	63·8	−4·36	2	0·3010
-NH-	33·0	−1·23	2	0·3010
$-NHCH_2-$	73·0	−0·47	2	0·3010
$-CH_2-$	40·0	+0·56	1	0·0000

* The number of cases n = 11; the regression equations are:

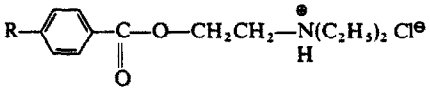
	r	s	F
$\log A = 0{\cdot}0087\,(\pm 0{\cdot}0032)\,P - 0{\cdot}1274$	0·89	0·24	35·28
$\log A = 0{\cdot}00001\,(\pm 0{\cdot}0088)\,P^2 + 0{\cdot}0085\,(\pm 0{\cdot}018)\,P - 0{\cdot}117$	0·89	0·26	15·68
$\log A = -0{\cdot}062\,(\pm 0{\cdot}245)\,\pi + 0{\cdot}603$	0·18	0·53	0·31
$\log A = -0{\cdot}128\,(\pm 0{\cdot}132)\,\pi^2 - 0{\cdot}644\,(\pm 0{\cdot}638)\,\pi + 0{\cdot}258$	0·62	0·45	2·50

For these analogs with polar substituents, parachor gives a better fit than the Hansch π, as shown by the values of the statistical terms.

† References 11 and 13.

‡ References 25 and 26.

Table 2. Relative local anesthetic activity of the paracaines (4-substituted dialkylaminoalkylbenzoic esters)*



Para-substituent	Parachor	Hansch π†	Relative anesthetic activity‡	Log activity
$-NH_2$	45·5	−1·23	1·0	0·0000
$-NHC_2H_5$	128·5	+0·08	10·0	1·0000
-OH	29·8	−0·67	0·5	−0·3010
$-OC_2H_5$	115·3	+0·38	1·4	0·1461
$-CH_3$	55·3	+0·56	0·8	−0·0969
-H	15·5	0·00	0·85	−0·0806
-F	26·1	+0·14	0·25	−0·6021
-Cl	55·2	+0·71	0·33	−0·4815
-Br	68·0	+0·86	0·50	−0·3010
$-NO_2$	75·7	−0·28	0·1	−1·0000

* The number of cases = 10; the regression equations are:

	r	s	F
$\log A = 0{\cdot}0079\,(\pm 0{\cdot}0094)\,P - 0{\cdot}655$	0·55	0·47	3·47
$\log A = 0{\cdot}00024\,(\pm 0{\cdot}00022)\,P^2 - 0{\cdot}027\,(\pm 0{\cdot}031)\,P + 0{\cdot}287$	0·79	0·37	5·71
$\log A = -0{\cdot}0074\,\pi - 0{\cdot}1713$	0·01	0·56	
$\log A = -0{\cdot}034\,(\pm 1{\cdot}032)\,\pi^2 - 0{\cdot}018\,(\pm 0{\cdot}755)\,\pi - 0{\cdot}158$	0·03	0·60	0·003

These compounds containing polar and halogen substituents show a fair correlation with parachor. There is no correlation with Hansch π. This verifies the findings of Büchi and Perlia [27] regarding the lack of correlation of activity with the distribution coefficient.

† Reference 13.

‡ Reference 27.

It is also possible that such a groove occurs in the halogenating enzyme peroxidase, which iodinates the thyronine nucleus to synthesize thyroxine *in vivo*. The occupancy of the proposed groove in the halogenating enzyme peroxidase by thiocyanate may result in decreased iodination and consequently decreased levels of thyroxine. The natural goitrogen in Brassica plants, allylisothiocyanate, has two portions in the molecule, allyl and isothiocyanate, both of which have parachor values nearly equal to that of the iodine atom.

Other drug classes. In Tables 1–7 and Fig. 2, the biological activities of analogous series of eight drug classes have been correlated against both the parachor and the Hansch π values of the substituents. In some drug classes, e.g. 5-substituted pentylamines (Table 1), paracaines (Table 2), halogen-substituted penicillins (Table 3), fibrinolytic benzoic acids (Table 4), parasympatholytic 2-alkyl-diphenhydramines (Table 5), sympathomimetic *N*-alkyl-epinephrines (Table 6), fibrinolytic 5-substituted salicylic acids (Table 7) and isohemolytic *n*-alcohols (Fig. 2), both the parachor and the Hansch π gave an approximately equal or comparable fit for the linear relationship. The addition of the squared-term of π improves the correlation significantly in certain cases (Tables

Table 3. Antibiotic activity of penicillin analogs containing substituents on the phenoxy group*

Substituents at 2	3	4	5	6	Σ Parachors of substituents	Hansch Σ π†	Log activity‡
H	H	H	H	H	77·5	0·00	5·86
H	H	Cl	H	H	117·2	0·74	5·79
H	H	OCH_3	H	H	137·3	−0·04	5·69
H	H	NO_2	H	H	137·7	0·06	5·53
Cl	H	H	H	H	117·2	0·59	5·40
H	CF_3	H	H	H	149·3	1·09	5·38
Cl	H	H	Cl	H	156·9	1·35	5·24
H	CH_3	H	CH_3	H	157·5	1·02	5·03
H	CF_3	NO_2	H	H	209·5	1·15	5·03
Cl	H	Cl	H	H	156·9	1·33	4·97
Br	H	Br	H	H	182·5	1·77	4·87
Cl	Cl	H	H	Cl	186·6	1·94	4·72
H	H	c-Hx§	H	H	225·0	2·52	4·70
H	H	t-Bu	H	H	230·2	1·71	4·67
H	CH_3	CH_3	CH_3	H	187·5	1·54	4·65
Cl	Cl	Cl	Cl	Cl	276·0	3·44	4·25
Cl	H	Ph	H	H	291·7	2·50	4·10

* The data, when subjected to regression analysis, indicate that parachor gives a better fit than Hansch π in terms of the values of the correlation coefficient r and the F term. The number of cases is 17.

	r	s	F
$\log A = -0{\cdot}00845(\pm 0{\cdot}00179)P + 6{\cdot}541$	0·93	0·19	99·9
$\log A = 0{\cdot}00001(\pm 0{\cdot}00002)P^2 - 0{\cdot}01172(\pm 0{\cdot}01044)P + 6{\cdot}823$	0·94	0·20	48·4
$\log A = -0{\cdot}49192(\pm 0{\cdot}12495)\pi + 5{\cdot}708$	0·91	0·23	68·4
$\log A = 0{\cdot}0455(\pm 0{\cdot}1079)\pi^2 - 0{\cdot}630(\pm 0{\cdot}350)\pi + 5{\cdot}774$	0·91	0·23	34·1

† Reference 28.
‡ Log $(1/C)$, where, C represents CD_{50} (clinical dose for 50 per cent activity in mice) [28, 29].
§ Cyclohexyl.

Table 4. Fibrinolytic activity of 2,4-substituted benzoic acids*

2,4-Substituents	Parachor	Hansch π†	Log % activity†
2-H, 4-NO_2	90·9	0·02	1·845
2-H, 4-Et	111·0	0·97	2·000
2-H, 4-Cl	70·0	0·87	2·021
2-H, 4-i-Pr	147·0	1·40	2·086
2-H, 4-I	105·8	1·14	2·114
2-H, 4-n-Pr	149·5	1·43	2·146
2-H, 4-t-Bu	183·5	1·68	2·182
2,4-di-Cl	110·4	1·57	1·903

* The regression equations are as follows (n = 8):

	r	s	F
$\log A = 0{\cdot}57(\pm 0{\cdot}48)P + 43{\cdot}43$	0·73	20·84	7·0
$\log A = 0{\cdot}005(\pm 0{\cdot}014)P^2 - 0{\cdot}64(\pm 3{\cdot}85)P + 114{\cdot}76$	0·77	21·65	3·5
$\log A = 35{\cdot}49(\pm 38{\cdot}47)\pi + 72{\cdot}35$	0·66	22·96	4·7
$\log A = -9{\cdot}16(\pm 78{\cdot}66)\pi^2 + 51{\cdot}11(\pm 139{\cdot}24)\pi + 68{\cdot}69$	0·67	24·96	2·0

From a comparison of the correlation coefficient r and the significance of the regression equation F, it may be seen that the parachor gives a slightly better fit than the Hansch π.

† Reference 30.

Table 5. Parasympatholytic activity of 2-alkyl-diphenhydramines*

Substituent	Parachor	Hansch π†	Log % activity‡
H	15·5	0·00	2·00
CH_3	55·5	0·51	2·32
C_2H_5	95·5	0·97	2·62
n-C_3H_7	134·1	1·43	2·69
i-C_3H_7	131·8	1·30	2·81
n-C_4H_9	173·1	1·90	2·74
i-C_4H_9	171·9	1·82	3·20

* The number of cases = 8; the regression equations are:

	r	s	F
$\log A = 0{\cdot}007(\pm 0{\cdot}004)P + 1{\cdot}90$	0·87	0·25	19·5
$\log A = 0{\cdot}00001(\pm 0{\cdot}00001)P^2\ 0{\cdot}007(\pm 0{\cdot}019)P + 1{\cdot}92$	0·87	0·27	8·1
$\log A = 0{\cdot}593(\pm 0{\cdot}378)\pi + 2{\cdot}02$	0·84	0·28	14·3
$\log A = -0{\cdot}107(\pm 0{\cdot}732)\pi^2 + 0{\cdot}803(\pm 1{\cdot}510)\pi + 1{\cdot}97$	0·84	0·30	6·2

Regression analysis shows a slightly better fit for the parachor than for the Hansch π value.

† References 11 and 12.

‡ References 31 and 32.

Table 6. Sympathomimetic activity of *N*-alkyl-epinephrines*

Substituent	Parachor	Hansch π†	Log % β-receptor activity‡
H	15·5	0·00	2·000
CH_3	55·5	0·51	2·065
i-C_3H_7	131·8	1·30	2·111
t-C_4H_9	168·1	1·68	2·117
$-C(CH_3)_2-CH_2-Ph$	332·6	3·57	2·146

* Regression analysis was carried out on the data in the table; the number of cases is 5. The values of the correlation coefficient *r* and the *F* term show that the parachor gives a fit almost as good as that of Hansch π. The regression equations are as follows:

	r	s	F
$\log A = 0{\cdot}0004(\pm 0{\cdot}0004)P + 2{\cdot}03$	0·88	0·03	10·6
$\log A = -0{\cdot}0001(\pm 0{\cdot}0001)P^2 + 0{\cdot}0012(\pm 0{\cdot}0006)P + 1{\cdot}99$	0·98	0·01	35·1
$\log A = 0{\cdot}036(\pm 0{\cdot}031)\pi + 2{\cdot}04$	0·88	0·03	10·4
$\log A = -0{\cdot}017(\pm 0{\cdot}010)\pi^2 + 0{\cdot}099(\pm 0{\cdot}036)\pi + 2{\cdot}01$	0·99	0·01	56·9

† References 11 and 12.

‡ References 31 and 33.

Table 7. Fibrinolytic activity of 5-substituted salicylic acids*

5-Substituent	Parachor	Hansch π†	Log activity‡
H	15·5	0·00	0·82
Cl	55·2	0·69	1·52
Br	68·0	0·85	1·40
I	90·3	1·19	1·70
CH_3	55·5	0·48	1·16
C_2H_5	95·5	0·94	1·30
s-C_4H_9	171·9	1·82	2·16
t-C_4H_9	168·2	1·68	2·00
Ph	190·0	1·89	2·22
Cyclohexyl	225·0	2·51	2·52
Ph-CH_2-	230·0	2·39	2·40
NO_2	75·7	0·11	1·16

* The regression equations are as follows (n = 12):

	r	s	F
$\log A = 0{\cdot}007(\pm 0{\cdot}002)P + 0{\cdot}82$	0·96	0·17	112·2
$\log A = -0{\cdot}00001(\pm 0{\cdot}00002)P^2 + 0{\cdot}008(\pm 0{\cdot}008)P + 0{\cdot}77$	0·96	0·17	51·2
$\log A = 0{\cdot}643(\pm 0{\cdot}092)\pi + 0{\cdot}92$	0·98	0·12	234·2
$\log A = 0{\cdot}006(\pm 0{\cdot}135)\pi^2 + 0{\cdot}63(\pm 0{\cdot}35)\pi + 0{\cdot}92$	0·98	0·12	105·5

For the fibrinolytic activity (hanging clot test) of the 5-substituted salicylic acid analogs, the Hansch π gives a better fit than the parachor, as indicated by the statistical terms.

† References 11 and 13.

‡ Reference 30.

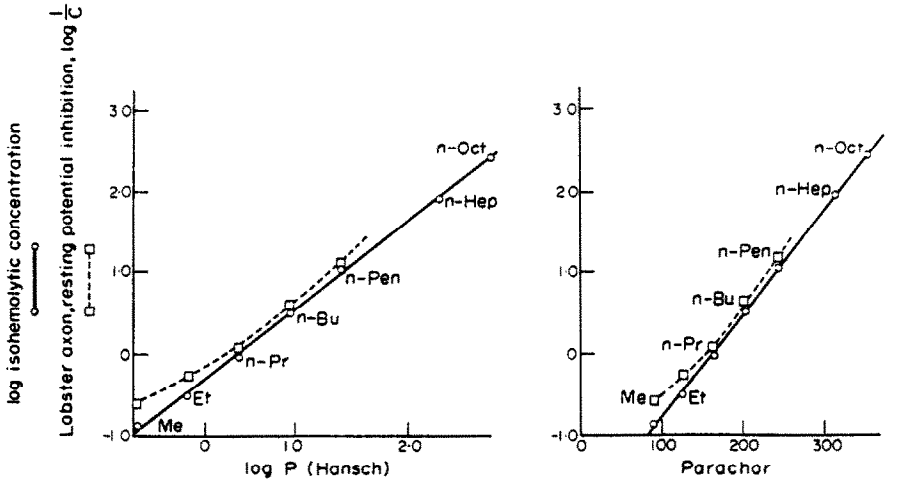


Fig. 2. Isohemolytic activity and inhibition of lobster axon resting potential by *n*-alcohols [34, 35] plotted against (a) the Hansch π values, and (b) the parachors of the alcohols.

1 and 6), whereas the addition of P^2 causes a relatively small change in the correlation.

n-Alcohols. In Fig. 2, the isohemolytic concentrations of *n*-alcohols [35] and inhibition of the lobster axon resting potential by *n*-alcohols were plotted as a function of (a) the Hansch π [13] values and (b) the parachors of the *n*-alcohols. The partition coefficient gave a slightly better correlation than the parachor for the linear-term equation. But for the squared-term equation, both parameters gave an equal correlation. The method of regression analysis was applied to the data for equations 14–17. The number of cases (n) is 7.

The plot includes the data for another assay namely the inhibition of resting potential in lobster axons from the study of Hansch and Glave [34], whose regression analysis has not been shown here. The plots are indicative of good correlations in the second case also.

	r	s	F	
$\log A = 0{\cdot}013\,(\pm 0{\cdot}001)P - 2{\cdot}04$	0·999	0·05	3817·1	(14)
$\log A = 0{\cdot}00001\,(\pm 0{\cdot}00001)P^2 + 0{\cdot}012\,(\pm 0{\cdot}003)P + 1{\cdot}98$	0·999	0·05	1856·2	(15)
$\log A = 1{\cdot}019\,(\pm 2{\cdot}036)\pi - 1{\cdot}43$	0·999	0·04	4578·9	(16)
$\log A = 0{\cdot}004\,(\pm 0{\cdot}043)\pi^2 + 1{\cdot}002\,(\pm 1{\cdot}897)\pi - 1{\cdot}42$	0·999	0·05	1852·8	(17)

Structure–activity correlations have been reviewed in this paper for nine classes of drugs. The correlations of biological activities with parachor are comparable to those obtained with the Hansch hydrophobic constant π. It appears that parachor and π measure the same fundamental property, that of the ability of the molecule to cross hydrophobic regions of membranes and to undergo hydrophobic bonding to receptor proteins. The parachor is perhaps a more consistent measure of this property for a series of drugs in which both alkyl and halogen derivatives are present (Fig. 1).

The choice between parachor and the Hansch constant for making structure–activity correlations will be influenced by the availability of appropriate parachor and π values. Because parachor is an additive and constitutive property, the molecular parachor of any compound can be calculated from the chemical structure using the extensive compilations that exist for atomic and group parachor values [19]. Leo *et al.* [17] have argued that the parachor may have limited usefulness because of the experimental difficulties in obtaining accurate surface tension measurements for organic compounds. In practice, however, there is little necessity for such measurements, since the parachor tables for a large number of compounds are already available.

The parachor and the octanol–water partition coefficients (π) are closely related properties; therefore the π values should also be additive and constitutive. However, extensive compilations of individual atomic and group contributions to the π value are not available. It is not yet possible to predict the π values, and hence the biological activities, in some cases, of large complex molecules such as steroids and alkaloids. Parachor values can be readily calculated for such molecules and biological activity correlations can then be made using these parachors. For complex molecules such as steroids, correlations between biological activity and physical properties have not been extensively employed because the physical measurements are not readily available [36]. The parachors of these molecules, obtained by calculation, have shown interesting correlations with steroid biological activities [37].*

Many drug responses do not correlate well with either the Hansch hydrophobic constant (π) or with parachor. Presumably in these cases, the passage of the compound across membranes or binding to

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hydrophobic regions of proteins is not a limiting factor in the biological action. Hansch has refined his correlations with octanol–water partition coefficients by including terms for electronic effects and steric effects in Hammett equations containing more than one physical parameter [13]. Apparently, similar corrections will frequently improve the statistical correlation of biological activities and modified parachor values. We believe that the major advantages of the use of parachor in correlations with biological activities of drugs and hormones are its ease of calculation, its application to large complex molecules and its predictive features. For the prediction of biological activity by the parachor method, it is only necessary to know the activity of existing analogs. It is not necessary to synthesize or to make any physical measurements on the proposed compound in order to predict its biological activity. Except for a few studies [15–17], no systematic analysis of the use of parachor in quantitative structure–activity correlation studies has been reported. It appears to us that the parachor, based on calculation, is potentially more advantageous than other structure–activity parameters based on measured physical properties of new analogs.

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