DISPUTANDUM

Molar Attraction Constants Applied to Structure Activity Relationships

The correlation of biological activity with chemical structure has always been of great importance to the medicinal chemist as it often provides a fundamental basis for the rationalization of drug activity as well as a useful starting point for the design of potentially active compounds. In recent years there has been an upsurge of interest in this direction, particularly with the use of extra-thermodynamic substituent constants[1]. These have included values derived from partition experiments[2], steric and electronic parameters[3], and data from molecular orbital studies[4]. To date the author has been able to list over 40 different types, however, in many cases, little can be said about the physical significance of a particular constant other than that its use results in a mathematically significant improvement in the correlation of biological data.

For example, OSTRENGA[5] has recently suggested that molar attraction constants (F), (derived from the solubility parameter (δ)[6]) have great potential in correlation as they are readily available for most organic functional groupings, are additive on a constitutive basis and can be calculated without resort to experiment, such that[6,7]:

$$\delta = \Sigma F_i / \Sigma V_i \qquad (1)$$

where V_i is the molar volume of the functional group i. He further concluded that, although it was conceivable that F was related to the HANSCH π value[2] (derived from partition studies), there were instances where F gave good correlation of biological activity for a series of compounds whilst π did not.

The exact relationship between F and π can be deduced by considering HILDEBRAND and SCATCHARD'S[8] equations for the excess free energy of a regular solution:

$$\bar{F}^E = (x_1 V_1 + x_2 V_2)\,(\delta_1 - \delta_2)^2\,\phi_1\phi_2 \qquad (2)$$

where x is the mole fraction and ϕ the volume fraction. The molal free energy of the solute (2) in the solvent (1) can be written as:

$$\bar{F}_2^E - RT \ln \gamma_2 = V_2 \phi_1^2\,(\delta_1 - \delta_2)^2 \qquad (3)$$

where γ is the activity coefficient and R and T have their usual meaning. At infinite dilution of the solute as $\phi_1 \to 1.0$,

$$RT \ln \gamma_2^{\infty} = V_2(\delta_1 - \delta_2)^2. \qquad (4)$$

The partition coefficient (K) therefore can be expressed as:

$$RT \ln K = V_2[(\delta_a - \delta_2)^2 - (\delta_o - \delta_2)^2] \qquad (5)$$

where a and o refer to the aqueous phase and organic phase, respectively. HANSCH[2] has defined the term π as the difference in logarithms of the partition coefficients of a parent compound and its substituted derivative,

$$\pi_X = \log K_{(RX)} - \log K_{(RH)} \qquad (6)$$

Therefore:

$$\begin{aligned} 2.3\,RT\,\pi_X = {} & \delta_0^2\,(V_{(RH)} - V_{(RX)}) + \delta_a^2\,(V_{(RX)} - V_{(RH)}) \\ & + 2\delta_o(V_{(RX)}\,\delta_{(RX)} - V_{(RH)}\,\delta_{(RH)}) \\ & + 2\delta_a(V_{(RH)}\,\delta_{(RH)} - V_{(RX)}\,\delta_{(RX)}) \end{aligned} \qquad (7)$$

But $\delta = F/V$, therefore:

$$2.3\,RT\,\pi_X = V_X\,(\delta_a^2 - \delta_o^2) + 2F_X\,(\delta_o - \delta_a). \qquad (8)$$

π_X and F_X are thus connected by the molar volume of the functional group X. The reasonable correlation of biological data using F[5] can therefore be ascribed simply to this connection together with the unjustified assumption that, in a series of different functional groups, molar volumes are approximately constant.

Theoretically it is now possible to calculate π values using equation (8). Values of F_i and V_i have been reported in the literature[6,7,9,10] or can be calculated from tables of solubility parameters[11] and molecular weight and density values. In some cases the variation in published F values for a given functional group is considerable and the author has therefore restricted the calculation of π to aliphatic groupings for which detailed F and V values have recently been given[7,10]. δ_o values are well documented[11], but the choice of a value for δ_a is worthy of discussion. The usually quoted δ_a is in the region of 25 but it must be remembered that this value was obtained from data on the solubility of water in hydrocarbons[8]. KOSKAS and DURANDET[12] have shown that for aliphatic hydrocarbons in water δ_a is in the range 15.5–16.1. This is in agreement with the partition studies of WAKAHAYASHI et al.[13] who have indicated that $\delta_a = 16.3$. A water solubility parameter of 15.8 has therefore been taken as reasonable for the present purpose.

π values have been calculated for a range of aliphatic functional groupings for partition between water and 1-octanol and water and cyclohexane (Table). The agreement between the calculated and experimental values of π is good in some cases. In particular the result for the inert $-CH_2$ group in the inert solvent cyclohexane lends much support to the choice of $\delta_a = 15.8$ (if $\delta_a = 25$ is taken instead, π_{CH_2} has a value close to 8.5). There are, though, some notable discrepancies and in general the values for cyclohexane are in closer agreement than those for 1-octanol, with strongly polar groups giving poorer agreement than others. Possible reasons for these differences are the variation in published F values and the accuracy of the experimental studies. One must also bear in mind that molar attraction constants were first proposed for the evaluation of δ values of polymers where uncertainties in the F value of a given functional group would in most cases lead to very little error in the δ value for the whole molecule[6].

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A more important and fundamental limitation of equation (8) is the range of applicability of solubility parameters and hence molar attraction constants. HILDEBRAND and SCOTT[16] have warned against the use of the solubility parameter concept for polar compounds unless the dipole is well buried within the molecule and specific directional forces are unimportant. In order to overcome this problem various attempts have been made lately to extend HILDEBRAND and SCATCHARD's equation to polar compounds such as acids, alcohols and ketones by the use of polar[17] and even 'three-dimensional' solubility parameters[18], but the success has been very limited. There is no reason why the above analysis of the inter-relationship between π and F could not be re-examined in such a manner but it is doubtful whether there would be any significant improvement in the π values calculated for partition between water and 1-octanol and for polar groupings in general. It is therefore concluded that F values are only a rather inaccurate measure of relative partition coefficient that ignore differences in molar volumes of functional groups. In view of the uncertainties associated with F values[9] and the problems of applying regular solution theory to polar systems, it seems highly advisable to use experimentally measured parameters such as π for structure activity correlation.

Calculated and experimental π values

Functional group	Cyclohexane		1-Octanol	
	Calculated π	Experimental π[a]	Calculated π	Experimental π[b]
$-CH_2-$	0.65	0.65	0.60	0.50
-OH	—3.75	—3.50	—1.78	—1.2
NH_2-	—1.22	—2.3	—0.74	—1.3
-Cl	0.55	0.7	0.62	0.47
-CHO	—0.47	—1.2		
-COOH	—3.14	—2.5	—2.3	—0.47
CH_3CO-	0		—0.51	—0.7
$-CH=CH_2$	2.6			
CH_3COO-	0.07	—0.2	1.0	—0.3
-CO	—0.65	—0.5		
-CN	—1.8	—1.25	—1.1	—0.84
Phenyl	1.85	2.75	2.1	1.9[c]
Cyclohexyl	3.85	4.2[d]	3.65	2.51[c]
Sum of squares of differences between calculated π and experimental π	3.8		6.3	

[a] Reference [14]. [b] Reference [15]. [c] Reference [2]. [d] Estimated from solubility data.

Zusammenfassung. Molare Anziehungskonstanten wurden herangezogen, um Beziehungen zwischen chemischer Struktur und biologischer Wirkung zu verstehen.

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PRO NATURA INTEGRA

Editor's note. Under the title of 'Pro Natura Integra', papers on fundamental research in the field of bio-protection will appear. Over-population, under-nutrition and changes in environment have led to ecological disturbances in the balance of Nature which threaten the existence of mankind. Man is faced with uncertainty through the changes in his environment. This most critical crisis can only be over-come by a society which has the will to carry out a biophylaxis which is scientifically founded, ecologico-economically co-ordinated and biopolitically responsible. H. M.

The Environmental Crisis. Commentary on the 1970 European Conservation Year

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This is an attempt to give a survey of recent studies of the environmental crisis in the United States and some activities to control it. The dimensions of this problem are much too large to be dealt with in some depth within the scope of this paper. Emphasis has therefore been given to developments which have led to issues in the scientific and public debate.

Conditions in the United States have caused a more precipitous development of the environment crisis than in in Europe. The interaction of various factors involving the response of the public to the environmental crisis, new scientific findings on the effects of pollutants (DDT) and the coinciding popularization of ecological concepts lead to a consensus of opinion on bio-political measures such as the 'Environment Policy Act' passed in December, 1969.

A review of these developments in the United States was written at the suggestion of Professor H. MISLIN, who is concerned with the formulation of a biopolitic for Europe, based on Ecology[1].