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PARAMETERS OF NITRO, CYANO AND IODO GROUPS FOR DEL RE CALCULATIONS

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The current interest in Del Ré type calculations in the medicinal chemical and biochemical field [1-6] encouraged us to assess parameter values for the three title groups. As is frequently encountered, the neglect of σ-electrons in biologically important compounds leads in many cases to ill-founded or questionable conclusions[7]. Although all valence electron methods such as EHT and CNDO/2, treating σ and π electrons simultaneously, are available, the medicinal chemist is frequently confronted with a large series of compounds having many atoms. This situation often rules out the use of these lengthy calculations and recourse has to be made to the less time consuming Del Ré method [8,9] for the evaluation of σ-charge densities.
The need for σ-charge densities has recently been demonstrated by Cammarata and Rogers [2] in their attempt to describe lipophilic character in terms of superdelocalisabilities and total charge densities. It appears that the necessary parameters for NO_2, CN and I are lacking although these groups are frequently used as substituents in pharmacologically interesting compounds.
In the Del Ré method, each bond AB is treated as a doubly occupied MO:

$$\Psi_{AB} = c_A\varphi_A + c_B\varphi_B$$

The secular determinant for each AB bond is

$$\begin{vmatrix} \alpha_A - E & \beta_{AB} \\ \beta_{AB} & \alpha_B - E \end{vmatrix} = 0$$

where $\alpha_A = \alpha_0 + \delta_A\beta_0$ and $\beta_{AB} = \varepsilon_{AB}\beta_0$. The bond parameter ε_{AB} is assumed to be dependent only upon the nature of A and B. The Coulomb parameter δ_A is determined according to

$$\delta_A = \delta_A^0 + \sum_{\text{A adj. to B}} \gamma_{A(B)}\delta_B$$

Table I. Parameter values for σ calculations on NO_2, CN and I groups

Bond	$C_{ar}-N$	N - O	$C_{ar}-C$	C - N	C - I
ε_{AB}	0.70	0.70	0.47	0.47	0.45
$\gamma_{A(B)}$	0.10	0.10	0.10	0.20	0.20
$\gamma_{B(A)}$	0.10	0.10	0.10	0.40	0.40
δ_A^0	0.12	0.38	0.12	0.20	0.12
δ_B^0	0.38	0.26	0.20	0.52	0.25

Table II. Hückel parameter values

Group	Atom	h	Bond	k
NO_2	N	0.6	N - O	1.0
	O	0.6	$C_{ar}-N$	0.6
NH_2	N	1.7	$C_{ar}-N$	0.7
$C_{ar}-CF_3$	C_{ar}	-0.1	$C_{ar}-C$	0.8
	F_3	0.5	$C-F_3$	2.0
C≡N	C	0.05	$C_{ar}-C$	0.7
	N	0.3	C - N	1.5
CHO	C	0.0	C=O	2.0
	O	1.0	$C_{ar}-C$	0.9

where δ_A^0 is estimated by considering the electronegativity of atom A. The inductive parameter $\gamma_{A(B)}$ accounts for the influence of atom B adjacent to A. Solution of the secular equation leads to the charge density Q_A

$$Q_A = \frac{\delta_B - \delta_A}{2\varepsilon_{AB}}\left[1 + ((\delta_B - \delta_A)/2\varepsilon_{AB})^2 \right]^{-\frac{1}{2}}$$

In summary, three parameters δ_A^0, $\gamma_{A(B)}$ and ε_{AB} are to be determined. Following the original procedure of Del Ré, the μ_σ dipole moments of a few reference compounds are calculated in the point-charge approximation. The initial estimate of the δ^0 values of I, C and N (of the CN group) is obtained from a plot (Fig.1) of known [8,9,10] δ^0 values against the orbital electronegativity of the groups [11]. The δ_N^0 of the NO_2 group is approximated as having a $tr^2 tr\, tr\, \pi$ hybridization. The δ_O^0 of the NO_2 group is more or less arbitrarily assigned a value of $\delta^\sigma = 0.26$.

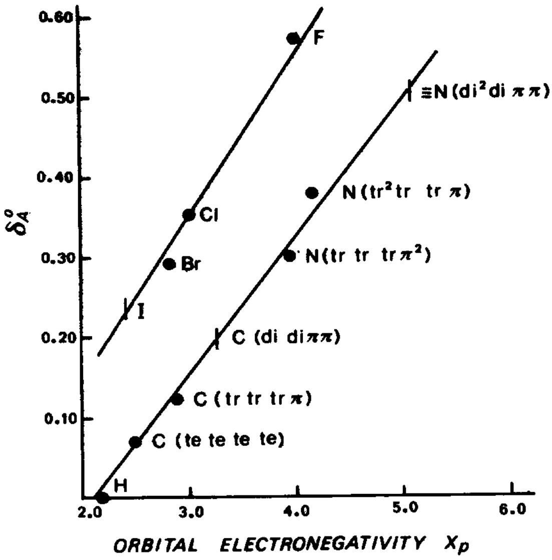

FIG.1—The δ_A^0 parameter as a function of the orbital electronegativity (Pauling scale).

The initial ε_{CI} value is obtained from an approximately linear relationship between published ε_{CX} (X = H,F,Cl,Br) values and experimental bond distances. The other ε_{AB} as well as all $Y_{A(B)}$ values are found by a systematic variation of these values within a reasonable range. The final parameter values are listed in Table I.

The μ_π dipole moments are calculated from the charge densities obtained from the simple Hückel theory. The Hückel parameters used are mainly those recommended by Streitwieser [12] except those listed in Table II which differ only slightly from those of ref.12. In order to check the internal consistency of the various h and k parameters, the $10^4\Sigma\Delta q(\pi)$ values of fourteen C_6H_5X compounds (X = H, the substituents of Table II, the halogens, OH, NMe_2, Me and OMe) are calculated and plotted against the resonance delocalization parameter σ_R^0 of Taft [13]. The following regression equation is found:

	n	r	S	F
$10^4\Sigma\Delta q(\pi) = 1158.81(\pm 50.53)\,\sigma_R^0 + 40.17$	14	0.989	47.38	525.90

This excellent fit gives us more confidence in the calculated μ_π values. Vectorial addition of the μ_σ and μ_π moments results in μ_{calc} values which are compared with the experimental dipole moments [14]. The excellent agreement between experimental and calculated dipole moments

Table III. Calculated and experimental dipole moments (D)

Compound	μ_σ	μ_π	μ_{calc}	μ_{exp}[b]	Compound	μ_σ	μ_π	μ_{calc}	μ_{exp}[b]
$C_6H_5NO_2$	1.01	3.31	4.32	3.98	4-Cl-C_6H_4CN	1.40	1.02	2.42	2.50
CH_3CN	3.05	1.16	4.21	3.97	4-Br-$C_6H_4NO_2$	0.85	3.56	2.71	2.69
C_6H_5CN	3.19	0.70	3.89	3.93	4-Br-C_6H_4I	0.18	0.02	0.20	0.49
CH_3I	1.70		1.70	1.64	3,5-$(NO_2)_2$-C_6H_3Br	0.85	3.52	2.67	2.3
C_2H_5I	1.83		1.83	1.89	3,5-Cl_2-$C_6H_3NO_2$	0.76	3.59	2.83	2.68
C_6H_5I	1.69	0.17	1.52	1.70	2,4-$(NO_2)_2$-C_6H_3I	1.45	3.48	3.83	3.4
t-1-I-2-Br ethylene	0.17	0.13	0.16	0.39	4-Cl-$C_6H_4NO_2$	0.75	3.63	2.88	2.81
1,2-I_2ethane[a]	0.38		0.38	0.55	4-I-C_6H_4CN	1.53	0.98	2.48	2.84
CI_3H	1.02		1.02	0.96	4-NO_2-C_6H_4CN	2.30	3.12	0.82	0.66
$C_6H_5CF_3$	1.55	1.41	2.96	2.86	4-NO_2-$C_6H_4NH_2$	1.92	4.85	6.77	6.29

[a]Dihedral angle of 80° and 90% trans conformer. [b]Ref.14.

(Table III) can be judged from the regression equation:

$$\mu_{exp} = 0.90(\pm 0.02)\mu_{calc} + 0.18$$

n	r	S	F
20	0.994	0.17	1503.4

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