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MOLECULAR ORBITAL CALCULATIONS FOR NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS IN AZA-COMPOUNDS

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Abstract Isolated Molecule, Localization and Delocalization approaches were applied, in the frame of HMO theory, to interpret the kinetics of nucleophilic aromatic substitution of halonitro-benzenes and naphthalenes, and of haloaza compounds. Amines and alkoxide ions in alcohols were considered as nucleophiles. Results were correlated with experimental activation energies and free energies. The best correlations were obtained by the delocalization approach, using Arrhenius activation energies.

The delocalization approach, successfully applied in the case of nucleophilic aromatic substitution of halonitro-benzenes and naphthalenes,[1,2] has now been used in MO calculations for the same kind of reactions in aza compounds. In the case of alternant hydrocarbons, mathematical relationships between the various reactivity indices have been found[3] and tested,[4] while for hetero-alternant molecules or substituted alternant hydrocarbons only qualitative interrelations have been found.[3] It was suggested that only comparisons with experimental data can decide which of the physical quantities related to each reactivity index is the most effective in determining the reaction mechanism and kinetics.

Therefore the isolated molecule (IM), localization (L) and delocalization (D) approaches[5,6] have been separately tested, choosing the following reactivity indices, respectively: π-electron density at the carbon atom site of attack ($q_{C'}^{0}$), Wheland's localization energy (W), and difference of π-electron energy in the transition (delocalized model) and initial states (ΔE_π).[1,2] Reactions considered were the piperidino dehalogenation in ethanol and the alkoxy dehalogenation in alcohols. In order to obtain directly comparable results, computations were performed both on halonitro-aromatics (halogen = Cl or Br) and on chloroaza-aromatics, for which experimental data are available. These molecules are represented and classified in Table 1.

Method of calculation

The standard HMO method has been used to evaluate the π-electron energy and densities in the initial molecules, and the π-energy in the Wheland model for the transition state. The described method of calculation[2] has been followed for the D approach: π-electron energy, charge densities and bond orders of the delocalized model for the transition state were obtained, both for piperidino and alkoxy dehalogenations. The necessary parameters were partly taken from previous work,[7] and partly chosen in such a way as to reproduce with reasonable agreement the dipole moments (μ) of a number of molecules. Theoretical values (μ_t) were obtained by vector addition of the calculated π-electron (μ_π) and σ-electron (μ_σ) contributions.

TABLE 1 MOLECULES CONSIDERED IN THE PRESENT WORK (X = Cl, Br)

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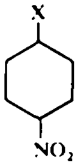

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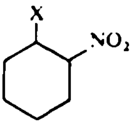

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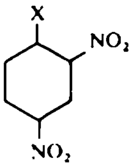

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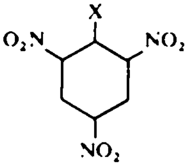

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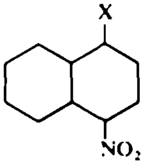

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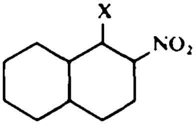

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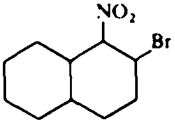

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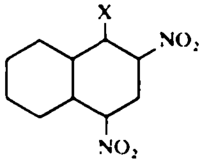

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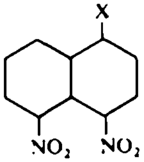

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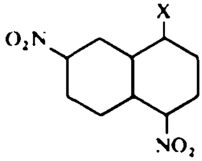

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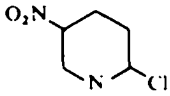

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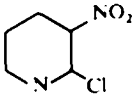

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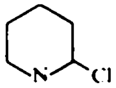

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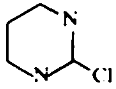

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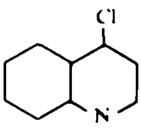

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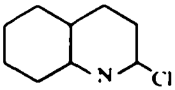

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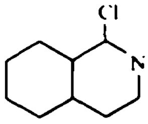

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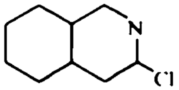

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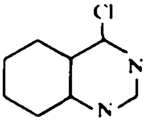

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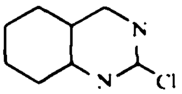

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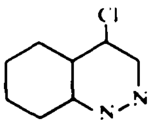

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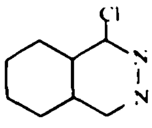

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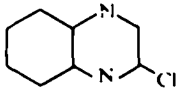


(F9)

TABLE 2. PARAMETERS USED FOR COULOMB (α_R) AND EXCHANGE (α_{RS}) INTEGRALS IN HÜCKEL MO CALCULATIONS

$$\alpha_R = \alpha_C + h_R \cdot \beta_{CC} \qquad \beta_{RS} = k_{RS} \cdot \beta_{CC}$$

Atom R	h_R	Bond R– S	k_{RS}
N (nitrogroup)	1·1^{a}	CN (nitrogroup)	0·5^{a,b}
O	0·7^{a}	NO	1·0^{a}
N (aza-group)	0·45	CN (aza-group)	0·8
Cl, Br	1·0	NN	0·6
C (adjacent to N)	0·08	CCl, CBr	0·45
C (adjacent to two N)	0·16		
P(Cl, N), P(Br, N)^{c}	–0·4	C P(Cl, N), C- P(Br, N)	1·0
P(Cl, O), P(Br, O)	–0·6	C—P(Cl, O), C –P(Br, O)	1·0

[a] From Ref. 7.

[b] For compounds B5, $\beta_{CN} = 0{\cdot}5 \cos 40^\circ \cdot \beta_{CC}$ (see text).

[c] P = pseudoatom in transition state (D approach).

The finally adopted values for the Hückel parameters are gathered in Table 2. In the case of 4,5-dinitronaphthalene derivatives, the *peri* effect has been taken care of, assuming that the planes of the two nitro groups are rotated by 40° with respect to the plane of the naphthalene ring; the β_{CN}-value has been consequently corrected. Deviations from planarity are expected in several other molecules listed in Table 1, due to *ortho* and *peri* effects. Assuming that these effects are of lesser entity, their consequences on the parameter values have been overlooked. Table 3 shows μ_π-values computed by the parameters of Table 2, together with μ_σ-values obtained by vector addition of σ-bond and lone-pair moments. The following values were used: μ (C—N) = 0·45 D;[8] μ (N O) = 0·50 D;[9] μ (lone pair) = 0·50 D;[10] μ (C_{arom}– H) = 0;[11] μ (C -Cl) = 2·34 D; μ (C—Br) = 2·19 D. The last two values were calculated from the measured moments of CH_3Cl and CH_3Br,[12] assuming μ (C^+_{aliph} $-H^-$) = 0·40 D.[11,13] The molecules were assumed planar, with bond angles and bond distances deduced from published data.[14]

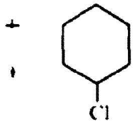
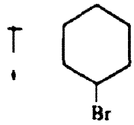
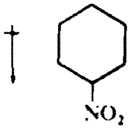
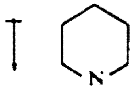
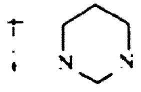
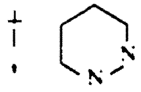
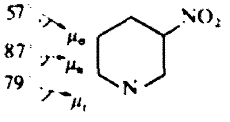
It is a feature of the D approach that, in the transition state, leaving (X) and attacking (Y) groups are considered together as a pseudoatom P(X, Y), that contributes a quasi-π orbital and two electrons to the π-electron system. The Coulomb integral for the pseudoatoms and the exchange integral for the carbon-pseudoatom π-bonds were determined in such a way as to obtain a reasonable average value of β_{CC} (of the order of −60 kcal/mole[15]) (see later). Also these parameters are included in Table 2.

Calculations were performed on an IBM 1620- 20K computer.

RESULTS AND DISCUSSION

The results of HMO calculations are collected in Table 4. The ability of the different theoretical approaches to interpret the kinetics of aromatic nucleophilic substitution has been tested by correlating the calculated values of the different reactivity indices with experimental data on reactivity. For the latter, both free energies of activation ($\Delta G^{\ddagger}$) and Arrhenius activation energies ($\Delta E^{\ddagger}$) were taken into consideration. The necessary data were found in the literature cited in a previous paper,[1] in a paper on 4,7-dinitronaphthalene derivatives,[16] and in reviews.[17] $\Delta G^{\ddagger}$'s were evaluated at 60°. For piperidino dechlorination of 2-chloropyrimidine (E2) a new Arrhenius plot has been drawn using data from two different sources,[17] obtaining $\Delta E^{\ddagger} = 12{\cdot}2$, and $\Delta G^{\ddagger}$ (60°) = 23·2 kcal/mole. Kinetic data for the reaction of picryl halides (A4) with piperidine or alkoxide ions were not found in the literature; we used the data for the reaction with aniline in ethanol,[18] assuming this to be a good model for reaction with piperidine.[*] In the case of A3 molecules, experimental data

Table 3. Dipole moments of reference molecules (debye)

Molecule	μ_π	μ_σ	μ_t (calcd.)	μ (exptl.)[a]
	−0·67	2·34	1·67	1·58[b]
	−0·70	2·19	1·49	1·54[b]
	3·07	0·95	4·02	3·96[b]
	1·48	0·97	2·45	2·23[b]
	1·34	1·07	2·41	2·44[c]
	2·23	1·65	3·88	3·97[c]
	2·56	0·97	3·43	3·31[b]

[a] Ref. 12.
[b] Benzene, 25°.
[c] Dioxane, 35°.

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[*] From published values of log A, the following activation entropies were obtained: picryl chloride, $\Delta S^{\ddagger}$ (60°) = −34·2 e.u.; picryl bromide, $\Delta S^{\ddagger}$ (60°) = −30·1 e.u. Values given by Parker and Read[18] seem to be incorrect.

TABLE 4. HMO VALUES OF $q_{C'}$, W, ΔE_{π}, q_P, $q_{C'}$ AND $p_{C'-P}$

	IM	L	D			
Molecule	$10^2 q^{0}_{C'}$	W ($\|\beta_{CC}\|$ units)	ΔE_{π} ($\|\beta_{CC}\|$ units)	q_P [a]	$q_{C'}$ [b]	$p_{C'-P}$ [c]
			Reaction with piperidine in EtOH			
A1	3·11	4·528	1·875	1·205	1·077	0·742
A2	3·53	4·513	1·876	1·225	1·076	0·746
A3	5·00	4·438	1·812	1·142	1·080	0·755
A4	6·91	4·361	1·763	1·110	1·082	0·767
B1	4·33	4·294	1·716	1·044	1·097	0·774
B2	4·97	4·277	1·718	1·070	1·096	0·781
B3	4·52	4·423	1·791	1·096	1·083	0·752
B4	7·07	4·203	1·650	1·006	1·099	0·785
B5	4·17	4·308	1·727	1·053	1·096	0·772
B6	4·83	4·274	1·697	1·023	1·098	0·774
C1	7·92	4·232	1·711	1·130	1·104	0·801
C2	8·63	4·217	1·717	1·161	1·102	0·809
E1	6·65	4·285	1·763	1·200	1·100	0·800
E2	11·70	4·029	1·619	1·136	1·129	0·851
F2	9·56	4·155	1·636	1·049	1·111	0·804
F3	9·98	4·045	1·586	1·042	1·122	0·827
F5	16·25	3·886	1·445	0·950	1·131	0·836
F6	12·05	3·996	1·573	1·064	1·132	0·842
F8	11·64	4·035	1·575	1·039	1·120	0·828
F9	9·42	4·141	1·559	0·889	1·108	0·767
			Reaction with alkoxide ions in alcohols[d]			
A1			2·095	0·990	1·128	0·750
A2			2·101	1·019	1·128	0·758
A3			2·020	0·937	1·133	0·757
B1			1·906	0·857	1·154	0·769
B2			1·914	0·891	1·155	0·782
B3			1·989	0·882	1·135	0·748
B4			1·834	0·830	1·158	0·777
B5			1·919	0·863	1·152	0·768
B6			1·883	0·836	1·154	0·767
E1			1·988	1·054	1·165	0·821
E2			1·833	1·007	1·204	0·868
F1	10·05	4·130	1·783	0·840	1·167	0·794
F2			1·829	0·882	1·173	0·802
F3			1·780	0·893	1·190	0·829
F4	3·78	4·363	2·056	1·112	1·161	0·816
F6			1·771	0·913	1·201	0·843
F7	10·49	4·093	1·671	0·706	1·159	0·750
F8			1·768	0·892	1·189	0·830
F9			1·717	0·699	1·156	0·735

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[a] π-electron density at the pseudoatom.

[b] π-electron density in the transition state at the carbon atom site of attack.

[c] π-bond order between pseudoatom and adjacent carbon.

[d] results for most molecules in IM and L approaches are reported above.

for reaction with piperidine in methanol were used, since activation energies in ethanol were not available; on the other hand, the difference in these two solvents is hardly significant in such reaction.

Experimental data are obviously affected by such effects as built-in solvation,[19] α-aza effect,[20] and base catalysis.[21] Since at the present time quantum-mechanical models are unable to take care of these and similar effects, we chose reactions in alcohols, that is in solvents where these effects are minimized and the general trend of reactivity in a series of compounds should mainly depend on the electronic structure of initial molecules and transition states.

The activation energy of a reaction in solution can conveniently be described as the sum of a π-electron and a solvation contribution, plus a residual term including σ-electron, nuclear repulsion, zero-point and thermal energy differences. Whenever a linear correlation can be established between the calculated π-electron contribution and the experimental $\Delta E^{\ddagger}$ for a series of compounds, this means that the sum of all other contributions to $\Delta E^{\ddagger}$ is approximately constant within the series[2] (condition 1). If $\Delta G^{\ddagger}$ instead of $\Delta E^{\ddagger}$ is correlable, this means that $(\Delta H^{\ddagger}_{solv} + \Delta H^{\ddagger}_{res} - T\Delta S^{\ddagger})$ remains constant within the series[22] (condition 2). $\Delta H^{\ddagger}_{solv}$ and ΔH_{res} are enthalpy terms corresponding to the previously defined energy terms.

Both procedures were tried, using the standard least-squares linear correlation. Different correlations have been sought for benzenic (A), naphthalenic (B) and aza-aromatic derivatives. The last compounds have been further classified as monocyclic (E) and bicyclic (F). When $\Delta E^{\ddagger}$ was correlated, the poorest results were given by the IM method, while the D approach proved the best: all the correlation coefficients (r) in the last approach were greater than 0·9, and in all but one case they were higher for the D approach than for the other ones. When $\Delta G^{\ddagger}$ was correlated, again the D approach gave the best fit: the average value of the r-coefficients was 0·93, while the corresponding figure, when $\Delta E^{\ddagger}$ values were used, was 0·95. However, this small difference does not necessarily imply that condition 1 is better satisfied than condition 2, since the choice of parameters is not rigid. Because of the qualitative agreement between the two treatments, and the slightly better correlation with $\Delta E^{\ddagger}$ values, only the results of this kind of correlation are presented in Table 5. It can be noted that in the IM and L approaches molecules from classes E and F lie on the same regression lines. In the D approach, molecules from classes E and F lie on different lines. The slopes of the lines for molecules E1 and E2 are 53·5 kcal/mole (reaction with piperidine) and 63·8 kcal/mole (reaction with ethoxide ion). Molecules C1 and C2 give points too close for a significant determination of the slope. Correlations for the D approach are also shown in Fig. 1 (carbocyclic compounds) and Fig. 2 (N-heterocycles).

According to the previous partition of activation energy, it is:

$$\Delta E^{\ddagger} = \Delta E_{\pi} + \Delta E_{solv} + \Delta E_{\Sigma}$$

Therefore the slope of the linear correlation between $\Delta E^{\ddagger}$ (in kcal/mole) and ΔE_{π} (in $|\beta_{CC}|$ units) gives the value of $|\beta_{CC}|$ in kcal/mole. (The same meaning can be attributed to the slope of the regression straight lines in the L approach). It appears from the Figs and Table 5 that $|\beta_{CC}|$-values ranging from 45 to 93 kcal/mole were obtained in the D approach, with large values of 95% confidence limits. These reasonable slopes (weighed average 67·5 kcal/mole) were obtained with the acceptable

TABLE 5. CORRELATION COEFFICIENTS (r) AND SLOPES[a] $\left(\frac{\text{Kcal mole}}{|\beta_{CC}|\text{ unit}}\right)$ FOR THE LINEAR CORRELATIONS OF EXPTL. $\Delta E^{\ddagger}$'s AGAINST CALCD. VALUES OF q_C°, W AND ΔE_a IN THE IM, L AND D APPROACHES, RESPECTIVELY

Reaction	Molecules	IM	L		D	
		r	r	slope	r	slope
Piper. in EtOH	A1, 2, 3[b], 4[c] (X = Cl, Br)	0·961	0·973	58·4 ± 13·8	0·990	83·8 ± 12·2
Piper in EtOH	B1, 2, 4, 5, 6 (X = Cl, Br) B3	0·649	0·891	40·3 ± 15·4	0·930	63·7 ± 19·0
Piper in EtOH	E1, 2 F2, 3, 5, 6, 8, 9	0·913	0·896	28·3 ± 14·0		·
Piper. in EtOH	F2, 3, 5, 6, 8, 9				0·945	45·0 ± 21·5
MeO⁻ in MeOH	A1, 2, 3 (X = Cl, Br)	0·959	0·972	85·0 ± 28·6	0·984	92·6 ± 23·0
MeO in MeOH	B1, 2, 4, 5, 6 (X = Cl, Br) B3	0·571[d]	0·953	56·5 ± 13·6	0·904	72·9 ± 26·0
EtO⁻ in EtOH	E1, 2 F1, 2, 3, 4, 6, 7, 8, 9	0·898	0·844	40·1 ± 20·8	–	
EtO⁻ in EtOH	F1, 2, 3, 4, 6, 7, 8, 9		–	–	0·943	47·1 ± 16·6

[a] each slope is given with the relevant 95% confidence limits (Ref. 23).

[b] in methanol.

[c] Reaction with aniline in ethanol.

[d] Non-significant correlation according to t-test (Ref. 23).

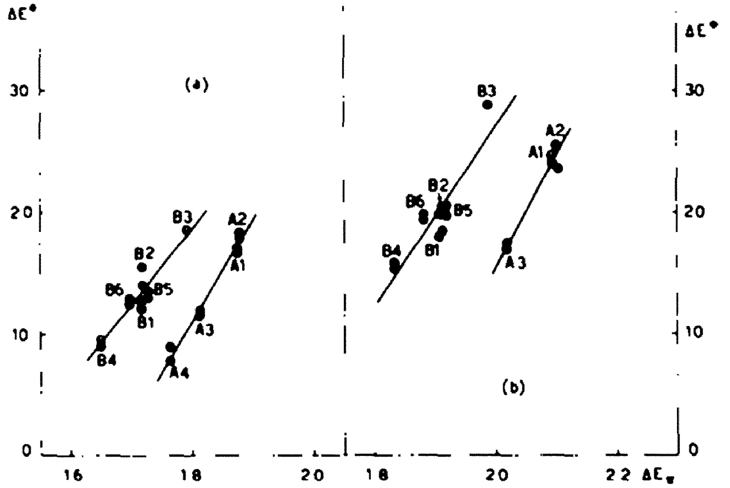

FIG. 1 Reactions of nitroactivated halogeno-aromatic compounds with piperidine in EtOH (a) and with MeO⁻ in MeOH (b). Plot of activation energies ($\Delta E^{\ddagger}$; kcal/mole) against ΔE_a-values ($|\beta_{CC}|$ units). Halogen = Cl(●) or Br(⊖). For $\Delta E^{\ddagger}$-values of A3 and A4 in case (a), see text.

values of the pseudoatom parameters given in Table 2. The h_P values correspond to an orbital considerably less stable than a carbon $2p_\pi$ orbital, as can be expected for an antibonding MO; the choice of β_{C-P} as equal to β_{CC} amounts to assume that the overlap between the carbon $2p_\pi$ and the pseudoatom antibonding orbitals is similar to the π-overlap in benzene. When the condition $|\beta_{CC}| = 60$ kcal/mole[15] is imposed to all regression lines in the D approach, fairly good correlations are still obtained: r-values range from 0·89 to 0·95, and their average is 0·91. The horizontal distance between any two parallel straight lines of the last kind gives the difference of $(\Delta E_{solv} + \Delta E_\Sigma)$ (in $|\beta_{CC}|$ units) for two series of molecules and/or for two different reactions. Within the same reaction of either carbocyclic compounds (Fig. 1) or N-heterocycles (Fig. 2), such distance is probably mainly due to a difference in ΔE_{solv}, and the relative position of the lines for 1-ring and 2-ring compounds, respectively, has been already justified on this ground.[2] Comparisons when the nucleophile or the activating centre (NO_2, $-N{=}$) is different are not possible owing to the many variable factors contributing to the activation energy.

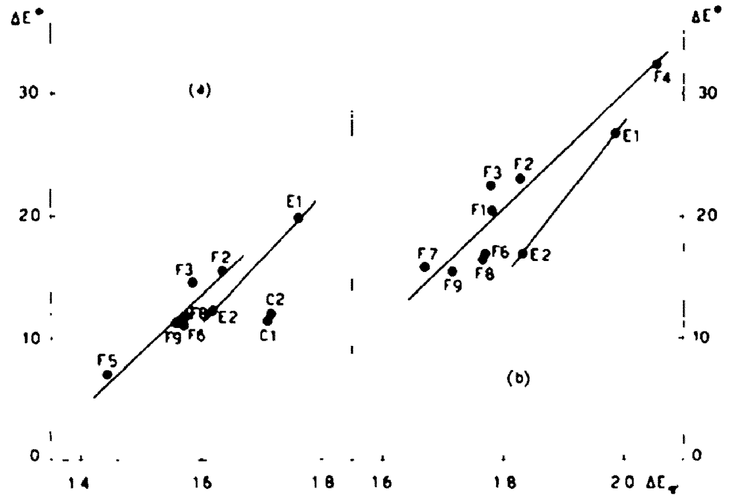

Fig. 2 Reactions of chloro-azaaromatic compounds with piperidine in EtOH (a) and with EtO⁻ in EtOH (b). Plot of activation energies ($\Delta E^{\ddagger}$; kcal/mole) against ΔE_π-values ($|\beta_{CC}|$ units).

We also carried out a simple calculation for the localized quasi-σ bond between pseudoatom and adjacent carbon in the transition state of piperidino dehalogenations. It has been assumed direct proportionality between Coulomb integral and ionization potential for the carbon orbitals; the Coulomb integral for the pseudoatom bonding orbital has been obtained from the h-values of Cl (Table 2) and amine N (taken as 0·9), and taking into account the fact that h_P for the antibonding orbital is $-0{\cdot}4$ (Table 2), arriving at a value of $(\alpha_P)_{bonding} = \alpha_C + 2{\cdot}3\ \beta_{CC}$. The exchange integral has been assumed equal to β_{CC}. From this calculation we obtained a rough estimate of the σ-electron density at the pseudoatom. From this value and the q_P-values (Table 4) the total electron charge at the pseudoatom was obtained.

Numerical values are in the range 3·06 (A2)–2·73 (F9), that is the pseudoatom is never far from neutral. If the total charge on the pseudoatom and adjacent carbon (= $q_{C'} + q_P + 2$) is considered, the results are in the range 4·30 (A2)–4·00 (F9). This means that the rest of the molecule assumes a negative charge usually lesser than unity. This is at variance with the L approach, where this charge is bound to be unity.

In conclusion it can be said that the delocalization approach is able to interpret the kinetic behaviour of N-heterocyclic halogeno-derivatives in nucleophilic aromatic substitutions, as well as that of the similar nitro-activated carbocyclic compounds. Its application has been attempted also in the case of nucleophilic substitution at the vinylic carbon of 1,1-diaryl-2-halogenoethylenes,[22] but, owing to the meagreness of experimental results, it is not yet possible to decide whether the mechanism of that reaction is suitable to such model.

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