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NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

A MOLECULAR ORBITAL TREATMENT

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Abstract—One- and two-step mechanisms for nucleophilic aromatic substitution reactions are discussed by means of a molecular orbital treatment, in a modified Hückel approximation. A correlation between experimental and theoretical activation energies was found for reactions of fluoro-, chloro-, bromo-benzenes and -naphthalenes carrying one or two nitro groups as substituents, with amines and methoxide ion in ethanol.

THREE general types of mechanism have been recognized in nucleophilic aromatic substitution reactions—the benzyne, the S_N1 and the bimolecular mechanism. Except for a limited number of reactions, in which evidence for the formation of a benzyne intermediate has been obtained or the rate determining step is a unimolecular decomposition of the substrate, all other possible mechanisms have been grouped together in the broad bimolecular (S_NAr) classification. The common feature in these reactions is that they obey a kinetic law approximately of the first order in the substrate (AX) and in the nucleophile $Y^{\cdot\cdot}$, If the reaction

$$AX + Y^{\cdot\cdot} \rightarrow AY + X^{\cdot\cdot}$$

($Y^{\cdot\cdot}$ indicates a neutral or charged nucleophile) is strictly first order with respect to AX and $Y^{\cdot\cdot}$ at every stage of the reaction course and for all initial reagent concentrations, the mechanism is pure S_NAr free of complications. However, in many instances interaction of the nucleophile with the solvent, formation of a charge transfer complex or homogeneous catalysis occur as shown by detailed kinetic studies. A recent review of the complicating factors has been given by Ross.[1] Even the mechanism of the substitution free of complications has been the subject of extensive controversy.[2,3] Two possibilities[4] have been suggested; in the first it is assumed that substitution occurs by a one-step mechanism which has often been described as analogous to the substitution at saturated carbon atoms with synchronous bond formation and bond breaking. In the second a two-step mechanism is considered involving a stable intermediate complex for which the structure suggested by Wheland is assumed.[5] However evidence for a choice between the two mechanisms is not conclusive since the results of the experimental work by Bunnett[6a,b,c] are not applicable to all the situations and the arguments in accordance with quantum mechanics given

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[1] S. D. Ross, *Progr. Phys. Org. Chem.* **1**, 31 (1963).

[2] J. F. Bunnett, *Theoretical Organic Chemistry* p. 144. Butterworths, London (1959).

[3a] R. E. Parker and T. O. Read, *J. Chem. Soc.* 9 (1962); [b] D. H. Elias and R. E. Parker, *Ibid.* 2616 (1962); [c] R. E. Parker and T. O. Read, *Ibid.* 3149 (1962).

[4] J. F. Bunnett and R. E. Zahler, *Chem. Revs.* **49**, 273 (1951).

[5] G. W. Wheland, *J. Amer. Chem. Soc.* **64**, 900 (1942).

[6a] J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.* **80**, 6020 (1958); [b] J. F. Bunnett and R. H. Garst, *Ibid.* **87**, 3875 (1965); [c] **87**, 3879 (1965).

by Bunnett and Parker are strictly related to the particular model adopted for the transition state. It has been pointed out by Hammond[7] that the existence of unstable, non-isolable intermediates of high energy is not of vital importance to the interpretation of the kinetic results. In particular, Hammond has shown that Melander results[8] on the absence of isotope effect on the rate of electrophilic aromatic substitution does not unequivocally prove the existence of a two-step mechanism. Instead, it may be concluded that either there is a very stable intermediate or the intermediate does not exist. The same arguments can be applied to the interpretation of the small element effect found by Bunnett[9] in the nucleophilic aromatic substitution.

The important feature for the correlation of reaction rates is the adoption of a good model for the transition state. In the theoretical study of chemical reactivity three different approaches have been used for the study of S_NAr substitution:[10] the static, the localization and the delocalization approach. In the first,[11] similar properties, charge distributions and polarizabilities of the reactions, are used to correlate the activation energies; this model can be used only if the transition state is similar in structure to the reactants. In the second,[12] the Wheland model is used for the transition state: on the basis of the postulate and deductions given by Hammond,[7] the Wheland model is a good model for the (eventual) intermediate but not for the transition state. It can be used only if the transition state and the intermediate are similar in structure and energy. In the third approach[13] a model for the transition state is built with the assumption that the attacking and leaving group can form a pseudo atom connected through σ and π interaction to the aromatic substrate. This model owing to its flexibility is particularly useful since it can accomodate a wide range of different structures for the transition state. One of the major points is the fact that the total bond order between the pseudo atom and the bonded carbon can be larger than one with the consequence that the condition of synchronism of bond breaking and bond making is released. Therefore, the delocalization approach has been used to correlate theoretical and experimental activation energies for the substitution reactions of a number of halonitro-benzenes and naphthalenes by different nucleophiles.

CALCULATIONS

For a series of halonitro derivates of benzene and naphthalene, M.O. theory in the Huckel approximation has been used to calculate the π electron energy in reactants and transition states. For the reactants the π electrons in the aromatic system, in the nitro group and in the halogen atom were included. For the necessary parameters the following expressions were used:

$$\alpha_R = \alpha_C + k\,\beta_{CC}$$
$$\beta_{R-S} = h\,\beta_{CC}$$

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[7] G. S. Hammond, *J. Amer. Chem. Soc.* **77**, 334 (1955).

[8] L. Melander, *Ar. Riv. Kemi* **2**, 213 (1950).

[9] J. F. Bunnett, E. W. Garbish and K. M. Pruitt, *J. Amer. Chem. Soc.* **20**, 385 (1957).

[10a] R. D. Brown, *Molecular Orbitals in Chemistry, Physics and Biology* p. 485. Academic Press, New York (1964); [b] Kenichi Fukui *ibid.* p. 531. [c] M. J. S. Dewar, *Advances in Chemical Physics* Vol. 8; p. 65. Interscience, London (1965).

[11] G. W. Wheland and L. Pauling, *J. Chem. Soc.* **57**, 2086 (1935).

[12] M. Simonetta and G. Favini, *J. Chem. Phys.* **51**, 108 (1954).

[13a] M. Simonetta and S. Carrà, *Tetrahedron* **19**, Suppl. 2, 467 (1963); [b] M. Simonetta and S. Carrà, *Nitro Compounds* p. 383. Pergamon, Oxford (1964).

where

$$k_{Cl} = k_{Br} = 1{\cdot}0;\ k_F = 1{\cdot}5;^{14}\ k_N = 0{\cdot}5;$$
$$k_O = 1{\cdot}0;\ k_{C'} = 0{\cdot}167;^{15}\ h_{Cl-C} = h_{Br-C} =$$
$$= h_{F-C} = 0{\cdot}6;^{14}\ h_{NO} = 1{\cdot}0;\ h_{C'N} = 0{\cdot}5.^{15}$$

C′ is the carbon atom to which the nitro group is bonded. In the transition state leaving and attacking groups are considered as a whole, that is as one pseudo-atom P(X). The situation is depicted in Fig. 1, with the simplified assumption that the leaving and the attacking groups are equal. In the transition state the two orbitals b and b′ can be linearly combined to give a quasi-σ orbital:

$$\psi_\sigma = \frac{1}{\sqrt{2}}(b' + b)$$

and a quasi-π orbital:

$$\psi_\pi = \frac{1}{\sqrt{2}}(b' - b)$$

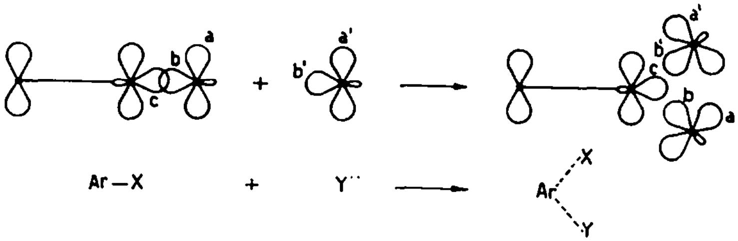

FIG. 1. Orbitals for the reactans and transition state

The first one is used with orbital c to form a σ bond between the pseudo atom and the aromatic ring. Orbitals a and a′ accomodate two pairs of electrons. These electrons are not included in the calculations since we are comparing series of similar reactions and the contribution of these electron interactions to the energy of the transition state is here assumed to be approximately the same in the series. The two electrons in the ψ_π orbital (contributed by the b′ orbital of the attacking species) enter in conjugation with the aromatic π-electron system giving a total number of π-electrons equal to the number in the initial molecule. When X and Y are different the coefficient of b and b′ in ψ_σ and ψ_π may be widely different and structures similar to those recently proposed for the Janovsky complexes may occur.[16] The parameters for the pseudo atom P(X) when the nucleophile is piperidine in ethanol were evaluated by trial to obtain a reasonable β value and satisfactory values were found to be:

$$k_{P(F)} = k_{P(Cl)} = k_{P(Br)} = -1$$
$$h_{P(F)-C} = 1;\qquad h_{P(Cl)-C} = h_{P(Br)-C} = 0{\cdot}7$$

The fact that ψ_π orbital is less stable than the carbon $2_{p\pi}$ orbital is related to its antibonding character.

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[14] A. Streitweiser, *Molecular Orbital Theory for Organic Chemists* pp. 117–128. Wiley, New York (1961).

[15] M. Simonetta and A. Vaciago, *Nuovo Cimento* **11**, 596 (1954).

[16] R. J. Pollit and B. C. Saunders, *J. Chem. Soc.* 4615 (1965).

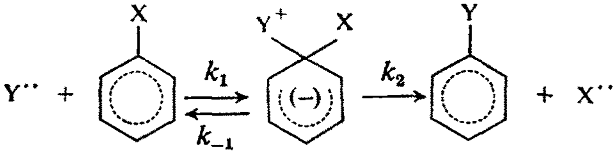
The π contribution to activation energies was obtained as the difference between π electron energies in initial compounds and transition states; charge distribution q and bond orders p for transition states were also calculated by standard techniques. The relevant results for the compounds under consideration are collected in Tables 1, 2 and 3. Calculations for fluoronaphthalene and iodo compounds were not performed owing to the lack of available experimental documentation.

DISCUSSION

The activation energy $\Delta E^{\neq}$ for the reactions discussed in the present work can be written as:

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

where ΔE_{π} is the difference in energy of π electrons in the transition and initial states; ΔE_{solv} is the corresponding variation of solvation energy; ΔE_{Σ} includes the difference in the σ electron, nuclear repulsion, zero point and thermal effects energies. The crude assumption has been made that, for a given halogen reactant and solvent, $(\Delta E_{\Sigma} + \Delta E_{solv})$ is a constant for all the considered reactions in the benzene and naphthalene series respectively. The possibility of a correlation of calculated ΔE_{π} and experimental ΔE_{exp} as obtained by Arrhenius plot of measured second order rate constants has been sought. The existence of such correlation would suggest the assumption that ΔE_{solv} is a constant within each series.[10c] If the reaction follows a one-step mechanism activation energies correspond to the height of the one potential energy barrier in the reaction path. For the two-step mechanism the following scheme can be formulated:



(I) (II) (III)

where the Wheland model is assumed for the intermediate (II). In the scope of the steady-state hypothesis the rate of the reaction is given by:

$$-\frac{d[I]}{dt} = \frac{k_1 k_2 [Y^-][I]}{k_{-1} + k_2} \tag{1}$$

In the two limit situations $k_2 \gg k_{-1}$ and $k_{-1} \gg k_2$ the right hand side of Eq. (1) reduces to:

$$k_1 [Y^-][I] \qquad \text{or} \qquad k_2 K [Y^-][I]$$

respectively (K is the equilibrium constant k_1/k_{-1}). In both cases ΔE_{exp} is a good approximation to the height of the highest potential energy barrier. The same is approximately true if k_2 and k_{-1} are of the same order of magnitude and their ratio is nearly independent of the temperature within the rather narrow temperature range experimentally investigated. If $k_{-1} = \alpha k_2$, we obtain from (1) $-d[I]/dt = k_1[Y^-][I]/(1 + \alpha)$. It follows that the correlation between experimental ΔE_{exp} and calculated

ΔE_π can be found independently of the detailed reaction mechanism as in our model of the transition state the degree of bond making and breaking is not specified *a priori*. The results of a number of nitro-chloro and nitro-bromobenzene and naphthalene derivatives for the reaction with piperidine in ethanol are shown in Fig. 2, from which it appears that the correlation is good. When the activation energy for reaction with piperidine was not available the activation energy for reaction with aniline in ethanol was used since the data are very close in all known cases. This supports the choice of the model for the transition state and the previously made assumptions about ΔE_{sol} and ΔE_Σ. The sum $(\Delta E_{sol} + \Delta E_\Sigma)$ is equal for chloro and bromo compounds. It has also been found that the choice of particular values for the parameters in the initial molecules is not crucial since a good correlation was also shown in a previous work[13b] where a different choice was made. The two parallel straight lines for chloro and bromo derivatives in Fig. 2 have been drawn by the least square method with the condition that $\beta_{CC} = -60$ kcal/mole, the value previously used by Mulliken *et al.*[17] for the benzenium ion. Dewar[10c] using the Wheland model for various substitution reactions found different and always very low values for β. This was explained as a defect of the model. The fact that $(\Delta E_\Sigma + \Delta E_{Solv})$ is constant within each series confirms that each term ΔE_Σ and ΔE_{Solv} is a constant as accidental compensation seems very improbable. Since it is reasonable to assume that ΔE_Σ is roughly the same in the benzene and naphthalene series the lower values of ΔE_{exp}

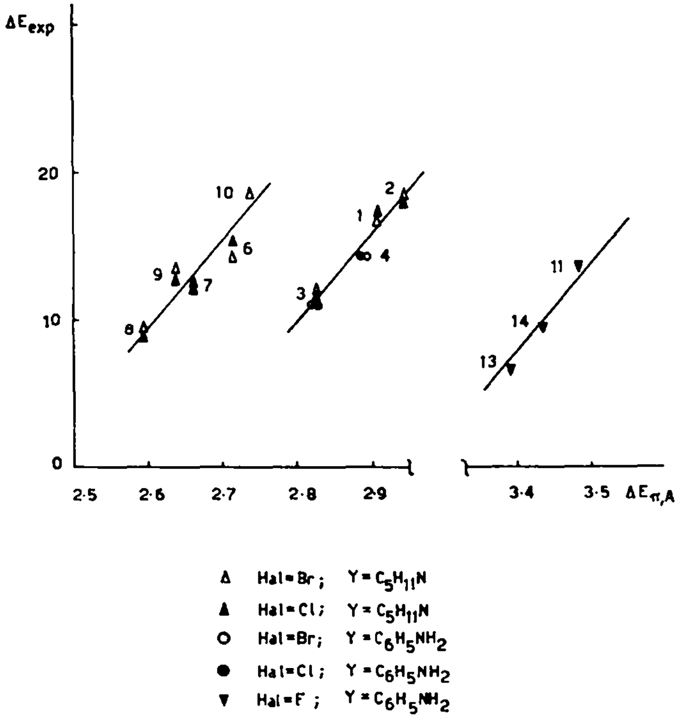


FIG. 2. Plot of ΔE_{exp} *vs* ΔE of$_\pi$ R-Hal with nucleophile Y.

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[17] N. Muller, L. W. Pickett and R. S. Mulliken, *J. Amer. Chem. Soc.* **76**, 4770 (1954).

for naphthalene derivatives should depend on a difference in ΔE_{Solv}. The horizontal distance between the two lines is $0{\cdot}19\,|\beta| \simeq 10$ kcal/mole that is of the expected order of magnitude for the difference in ΔE_{Solv} owing to the different size of transition states. For fluorobenzenes experimental data are available for the reaction with aniline in alcohol of: 1-F-4-NO_2-benzene:[18] $\Delta E_{exp} = 13{\cdot}5$ kcal/mole; 1F-2,4 dinitrobenzene[3a] $\Delta E_{exp} = 6{\cdot}4$ kcal/mole; 2F-1,3 dinitrobenzene[3c] $\Delta E_{exp} = 9{\cdot}4$ kcal/mole. These values and the corresponding theoretical values for ΔE_π give three points practically lying on a straight line in the diagram of Fig. 2 parallel to the line for bromo and chloro-benzene derivatives. It can be seen from the graph that $(\Delta E_\Sigma + \Delta E_{Solv})$ has a negative sign in all cases. The fact that the line for fluoro compounds is displaced to the right of the line for chloro and bromo benzenes means that a larger absolute value of $(\Delta E_\Sigma + \Delta E_{Solv})$ is pertinent to fluoro derivatives. This suggests that in the transition state the C—F bond stretching is smaller than for C—Br or C—Cl bonds; in accord to the fluorine:chorine ratio values found and discussed by Parker and Read.[3a] Besides ΔE_{Solv} may be expected to have a larger negative value for the transition states of the above mentioned reactions of fluoro derivatives owing to the greater aptitude to solvation of the fluoride ion. Picryl halides don't fit in the previously discussed correlation; a possible explanation is that owing to the excessive electron attractive power of three nitro groups attached to the same benzene ring the simple treatment for the initial and transition states is no longer valid. Adapted values for the parameters of the nitro group should be used. A linear dependence between experimental activation energies for the reaction with methoxide ion in methanol and amines in ethanol has also been found as shown in Fig. 3. This means that if for methoxy dehalogenation a similar correlation exists between experimental activation energy $(\Delta E_{exp,M})$ and the calculated difference in π electron energy $(\Delta E_{\pi,M})$ as for reactions with amines, then a linear relation must exist between ΔE_π and $\Delta E_{\pi,M}$. We use the first order perturbation theory to calculate $\Delta E_{\pi,M}$ from ΔE_π, assuming that the only significant difference between the π-systems in the two transition states is due to the difference of coulomb integrals for the pseudo atom, we get:

$$\Delta E_{\pi,M} = \Delta E_\pi + q_{P(X)} \cdot \delta k_{P(X)} \tag{2}$$

where $\delta k_{P(X)}$ *is the difference of the coulomb integrals of the pseudo atom in the* two cases. The consistency of Fig. 3 and Eq. (2) would exist if $q_{P(X)}$ is constant. From Tables 1 and 2 it is seen that the variation of $q_{P(X)}$ around its average value is within 10%. Owing to the greater electronegativity of O^- over N, $\delta k_{P(X)}$ must be positive and a value of 0·2 can be estimated. Applying Eq. (2) the values of $\Delta E_{\pi,M}$ were calculated and the correlation with $\Delta E_{exp,M}$ values are shown in Fig. 4a, and 4b for benzene and naphthalene derivatives respectively.

On the same Fig. the points and the lines for reactions with amines are also shown. It can be seen that the lines for methoxidehalogenation practically coincide with the previous ones. This means that $(\Delta E_\Sigma + \Delta E_{Solv})$ are almost the same for the two different reactants even if ΔE_Σ and ΔE_{Solv} should conceivably be different. It should be remembered that the oversimplified model can not be used in the present form to discuss some of the interesting features recently studied in nucleophilic aromatic substitution such as the influence on reactivity of dispersion forces between

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[18] C. W. Bevan and J. Hirst, *J. Chem. Soc.* 254 (1956).

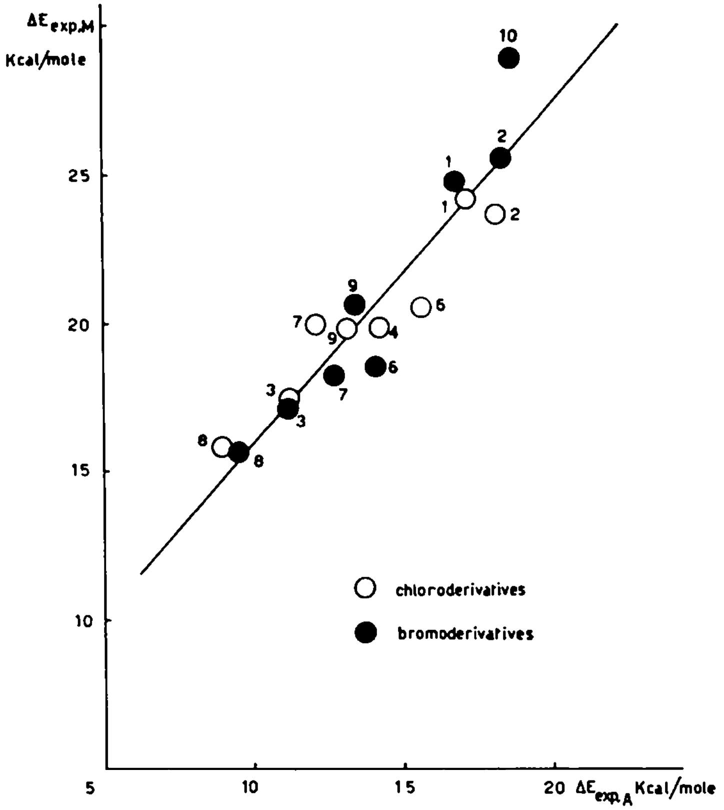

FIG. 3. ΔE_{exp} for reactions with methoxide ions *vs* ΔE_{exp} for reactions with amines (benzene and naphthalene derivatives)

substrate and nucleophile,[19] the catalysis by amines or other compounds[1] and the influence of the solvent on this phenomenon.[20] The experimental results were used for the reaction of piperidine and aniline in hydroxylic solvents to calibrate the Hückel parameters on the assumption that in these solvents the amine catalysis effect is very small, so that activation energies calculated from the measured total rate constants are practically the same as those from the non catalytic rate constants. For instance the reaction of 1-F-2,4-dinitrobenzene with N-methyl-aniline[6a] it is:

$$\Delta E_{exp,tot} = 11{\cdot}04 \text{ kcal/mole} \qquad \text{at [Amine]} = 0{\cdot}19;$$
$$\Delta E_{exp,non\ cat} = 10{\cdot}84 \text{ kcal/mole}$$

The molecular orbital calculation can not be used to support a choice between the one-step and the two-step mechanisms. However, when using the model some of the previous conclusions on S_NAr reactions based on quantum mechanics arguments are no longer applicable. There is no violation of the Pauli exclusion principle in the transition state although the total bond order $(1 + p_{C-P})$ between ring carbon and pseudo atom is bigger than one,[4] and so there is no need to invoke the use of 3d orbitials by the attacked carbon atom.[8a] On the same grounds there is no justification

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[19] J. F. Bunnett, *J. Amer. Chem. Soc.* 79, 5969 (1957).

[20a] H. Suhr, *Ber. Bunsenges. Phys. Chem.* 67, 893 (1963); [b] H. Suhr, *Chem. Ber.* 97, 3277 (1964).

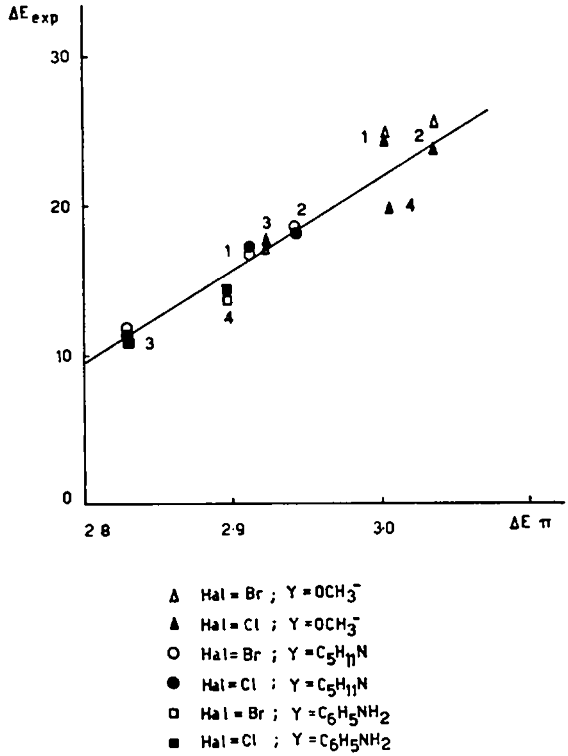


FIG. 4a Plot of ΔE_{exp} *vs* ΔE_{π} of benzene derivatives R-Hal for reaction with nucleophile Y.

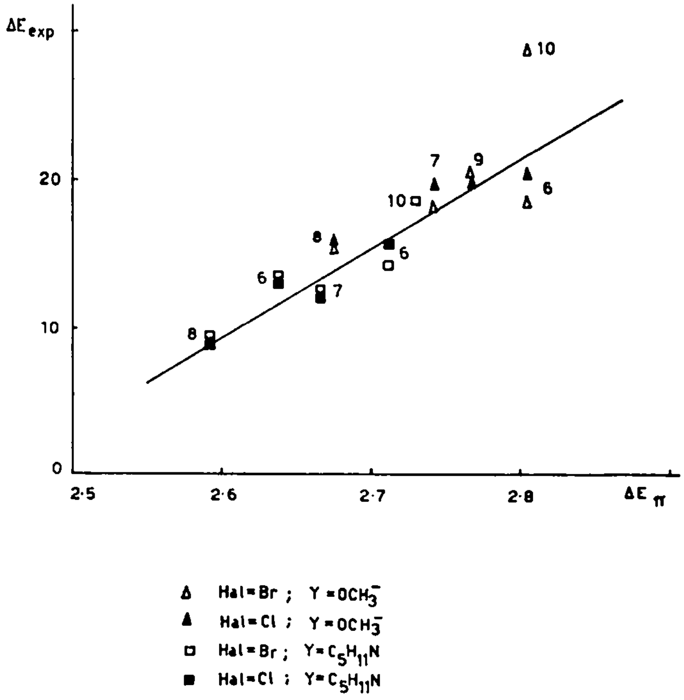
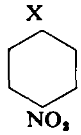
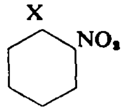
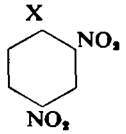
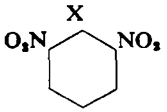
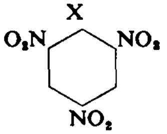


FIG. 4b Plot of ΔE_{exp} *vs* ΔE_{π} of naphthalene derivatives R-Hal for reactions with nucleophile Y.

for a distinction of mechanisms between the benzene and the naphthalene series.[3b] From Tables 1 and 2 it is seen that p_{C-P} does not show a sensible variation in going from the benzene to the naphthalene series. The contribution of the leaving and attacking groups to the total bond order $(1 + p_{C-P})$ may be different for different nucleophiles and different halogens; so that there is no reason why the one-step mechanism can not accommodate the lower energies of activation and the lower fluorine:chlorine ratio for the naphthalene reactions than for the benzene reactions. Finally, an alternative explanation may be given of the fact that no base catalysis is found in several cases, for instance in the reaction of 1-Cl- and, 1-Br-2,4-dinitrobenzenes

TABLE 1. ENERGIES (β UNITS) CHARGES AND BOND ORDERS IN INITIAL MOLECULES (IC) AND TRANSITION STATES (TS)

Compound X = Cl, Br	$E_{\pi}(IC)$	$E_{\pi}(TS)$	ΔE_{π}	q_X	q_P	$q_{C'}$ IC	$q_{C'}$ TS	$p_{C'-P}$
(1) 	−16·819	−13·907	2·912	1·922	0·477	0·949	1·229	0·587
(2) 	−16·821	−13·878	2·944	1·921	0·489	0·937	1·215	0·586
(3) 	−23·481	−20·651	2·830	1·914	0·481	0·913	1·248	0·610
(4) 	−23·483	−20·586	2·897	1·913	0·574	0·902	1·266	0·663
(5) 	−30·738	−28·182	2·557		0·388		1·484	0·610

IC = initial compound
TS = transition state
q_P = π electron charge density at pseudo atom
$q_{C'}$ = π electron charge density at carbon atom site of reaction
$p_{C'-P}$ = π bond order between pseudo atom and C′

TABLE 2. ENERGIES (β UNITS) CHARGES AND BOND ORDERS IN INITIAL MOLECULES (IC) AND TRANSITION STATES (TS)

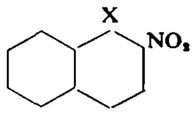
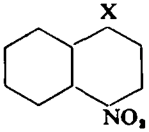
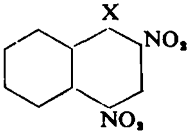
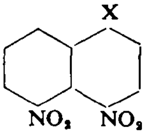
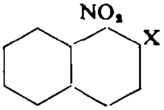
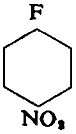
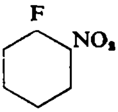
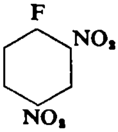
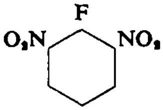
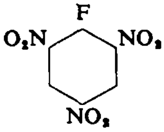
Compound X = Cl, Br	$E_{\pi}(IC)$	$E_{\pi}(TS)$	ΔE_{π}	q_X	q_P	$q_{C'}$ IC	$q_{C'}$ TS	$p_{C'-P}$
(6) 	−22·521	−19·809	2·712	1·906	0·467	0·915	1·297	0·638

TABLE 2. (*Continued*)

(7) 	−22·523	−19·863	2·660	1·908	0·410	0·928	1·282	0·599
(8) 	−29·192	−26·599	2·592	1·896	0·419	0·882	1·296	0·619
(9)  *	−29·108	−26·469	2·639	1·896	0·420	0·822	0·930	0·615
(10) 	−22·519	−19·790	2·729	1·914	0·374	0·922	1·218	0·546

* Molecular models have shown that owing to the peri effect the planes of the two nitro groups are rotated by about 40° with respect to the naphthalene ring. In the calculations a value of $\beta_{CN'} = \beta_{CN} \cos 40°$ was used.

TABLE 3. ENERGIES (β UNITS) CHARGES AND BOND ORDERS IN INITIAL MOLECULES (IC) AND TRANSITION STATES (TS)

Compound	$E_{\pi(IC)}$	$E_{\pi(TS)}$	ΔE_π	q_F	q_P	$q_{C'}$ IC	$q_{C'}$ TS	$p_{C'-P}$
(11) 	−17·787	−14·306	3·481	1·949	0·677	0·946	1·234	0·667
(12) 	−17·789	−14·283	3·506	1·948	0·713	0·936	1·233	0·809
(13) 	−24·446	−21·060	3·386	1·944	0·659	0·910	1·241	0·695
(14) 	−24·448	−21·020	3·428	1·943	0·726	0·899	1·250	0·698
(15) 	−31·050	−27·714	3·336					

with N-methyl-aniline.[6a] This may be explained by the assumption of a two-step mechanism with $k_2 \gg k_{-1}$ but also with the assumption of one-step mechanism. A similar suggestion has been made by Barlin and Chapman,[21] for nucleophilic aromatic substitutions in Cl-methyl purines.

When mild or strong acceleration is present,[6b,6c] the observed rate constants assume the mathematical form:

$$k_{\text{tot}} = k_{\text{non cat}} + k_{\text{cat}}\,[\text{B}]$$

B being the catalyst. $k_{\text{non cat}}$ may be the sum of two terms, k' and k''; the first one related to the one-step and the second to the two-step mechanism. Either k' or k'' might be exceedingly small.

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[21] G. B. Barlin and N. B. Chapman, *J. Chem. Soc.* 3017 (1965).