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TOWARDS A UNIFIED THEORETICAL TREATMENT OF THE TRANSITION STATE IN THE REACTIONS OF UNSATURATED COMPOUNDS—II

THE REACTIVITY OF QUINOLINE

O. CHALVET, R. DAUDEL and T. F. W. MCKILLOP

Sorbonne and Centre de Mécanique Ondulatoire Appliquée, 23, rue du Maroc, Paris 19ème, France

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Abstract—The Delocalized Transition State Model is shown to encompass the results obtained from simple perturbation treatments and from the use of the Wheland model. The orientation of substitution reactions on quinoline can be explained by means of the delocalized model with the possible exception of homolytic reactions. In particular, the calculations emphasise the importance of the nature of the reagent and correctly predict the changes in orientation with different reagents.

INTRODUCTION

THE orientation of substitution in many heterocyclic ring systems appears to vary widely with the nature of the reagent employed in the reaction. Since the delocalized transition state model described in part I allows some account to be taken of the characteristics of the attacking species, application of the model to substitution reactions of heterocyclic, aromatic compounds should be an interesting test of its utility.

The reactivity of quinoline in nucleophilic, electrophilic and radical substitution has been the subject of considerable interest over a number of years and certain changes in orientation with reagent have been noted. Two of the most interesting observations are:

1. nucleophilic substitution on 1-alkyl quinolinium salts employing strong nucleophiles such as OH^- leads to substitution in the 2-position while attack by the weaker CN^- affords only the 4-substituted quinoline, and
2. electrophilic attack in a strongly acidic environment yields principally the 8- and 5-substituted products but in weaker acid the order of substitution is 3 > 6, 8.[2]

In an extensive attempt to correlate the chemistry of quinoline with the results of Hückel calculations, Brown and Harcourt[3] have suggested the use of different reactivity indices for weak and strong nucleophiles, but such a procedure is clearly limiting as it does not permit any graduation in the strength of the nucleophile. The calculations by Brown and Harcourt also employed wide variations in the auxiliary inductive parameters which perhaps made them less attractive to the practising organic chemist. While the change in orientation during nucleophilic reactions could be accounted for in this way, no index of reactivity was capable of explaining the strange behaviour of quinoline towards electrophilic reagents, and consequently Brown and Harcourt proposed that an indirect substitution mechanism involving a 1,4-dihydro quinoline species was operating in weak acid. In an earlier study Dewar[2] had also concluded that an indirect mechanism must be involved although he had favoured a 1,2-dihydro quinoline as the probable intermediate. Zahradnik and Parkanyi[4] have calculated almost all the known reactivity indices for quinoline and related compounds and, while of considerable interest, their results do not suggest any improvement in the interpretation of the reactivity of the various positions in quinoline. More recently, Adam and Grimison[5] have utilized the Extended Hückel Method to determine the charge densities and the σ-complex energy for quinoline but no attempt was made to consider the effects of varying the nature of the attacking group.

In addition to determining the extent to which the delocalized transition state model can accommodate the experimental results for quinoline, this paper will attempt to relate the use of this model to other approaches such as perturbation methods and the localized Wheland model.

Selection of parameters

Under the conditions pertaining in many substitution reactions it is quite evident that the equilibrium between the free base and its protonated form will lie almost totally in favour of the latter, and hence calculations have been performed for both quinoline and quinolinium ion. The parameters employed for these species have been kept as simple as possible and correspond to those used by Zahradnik and Parkanyi;[4] i.e. all resonance integrals are taken as β° and the Coulomb integrals, expressed in the form $\alpha = \alpha^\circ + k\beta^\circ$, have for all carbon atoms $k(\mathrm{C}) = 0$, while $k(\mathrm{N}) = 0\cdot5$ and $k(\mathrm{N}^+) = 2\cdot0$.

As discussed in part I, the present study makes the approximation of representing the attacking group, X, by a single orbital whose energy is also given in the form $\alpha_\mathrm{X} = \alpha^\circ + k\beta^\circ$. In principle one should assign to each nucleophile, electrophile and radical suitable values of k and of β_{rx}, the resonance integral between the substituting group and the carbon atom undergoing substitution, but the emphasis at present will be on establishing the general trends as these two parameters are varied widely.

Comparison with perturbation theory

Consider a molecular orbital of the substrate, ψ_m, being perturbed by the approach to atom r of a single orbital, ψ_x, of the attacking group. It is easily shown that, within the framework of simple Hückel theory where all non-neighbouring interactions are neglected, the change in energy of ψ_m is given by:

$$E = \frac{c_r^2\beta_{rx}^2}{E_m - E_x} \tag{1}$$

in which c_r is the coefficient of orbital ψ_m at atom r, β_{rx} is the resonance integral between r and the attacking group, and E_m and E_x are respectively the energies of orbitals ψ_m and ψ_x.[6] Since Eq. (1) has been used to calculate the effect on the total energy of a system undergoing nucleophilic and electrophilic attack,[7] it is of interest to compare the results of such an approach with those obtained by calculating the energy levels of the whole complex as is done in the delocalized transition state model.

Fig. 1 shows the amount by which the energy of the lowest unoccupied level of the quinolinium ion ($E = \alpha^\circ - 0\cdot317\beta^\circ$) is lowered on approaching each of the seven possible C atoms of the quinolinium system with a single orbital having in turn the energy $\alpha^\circ - 0\cdot4\ \beta^\circ$, $\alpha^\circ - 0\cdot6\beta^\circ$ and $\alpha^\circ - 0\cdot8\beta^\circ$. The calculations were performed assuming a resonance integral $\beta_{rx} = 0{\cdot}5\beta^{\circ}$. The three straight lines represent the behaviour predicted by simple perturbation theory i.e. the use of Eq. (1), while the curved lines show the actual energy reductions as determined by simple Hückel calculations on the complex. As might be expected, when the extent of the perturbation becomes marked the use of Eq. (1) is insufficient and, although such a procedure will usually predict the general order of reactivity at the different carbon atoms, the numerical energy differences are vastly over exaggerated.

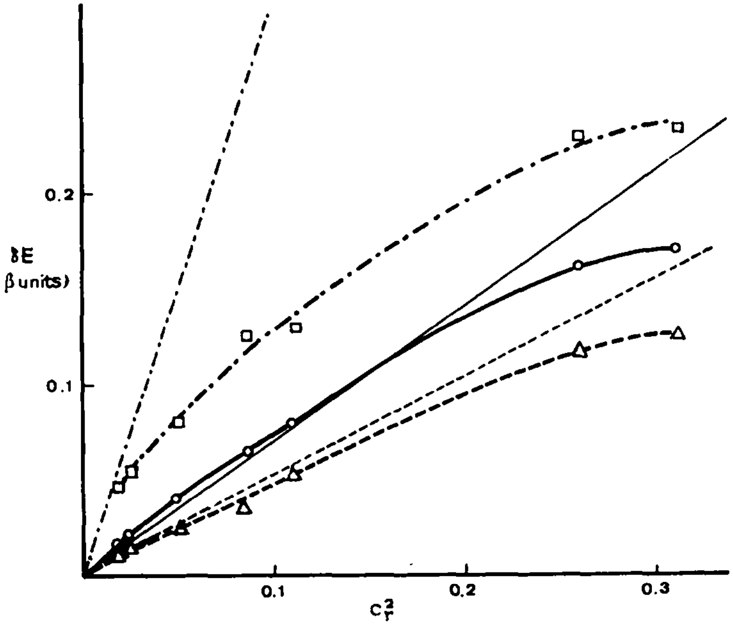
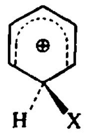


FIG. 1 Comparison of a simple perturbation approach with the delocalized model. SE is the amount by which the lowest unoccupied level of the quinolinium ion is lowered on approach to each of the seven possible carbon atoms of a reagent represented by a single orbital taking in turn the energies $\alpha^{\circ} - 0{\cdot}4\ \beta^{\circ}$, $\alpha^{\circ} - 0{\cdot}6\ \beta^{\circ}$ and $\alpha^{\circ} - 0{\cdot}8\ \beta^{\circ}$. Cr is the coefficient of each position in the lowest unoccupied level. The straight lines are the energies predicted by perturbation theory while the curved lines show the results obtained by the delocalized model.

Comparison with the Wheland model

The exact position of the transition state in a substitution reaction will depend on the reagent and, since the Wheland localized model represents one limiting possibility, it is important to demonstrate that the delocalized model can be made to resemble the Wheland model by correct choice of parameters. If one considers the Wheland model for electrophilic attack on a benzene ring (I) it is evident that one must select a large resonance integral between the incoming group and the C atom being attacked and very small resonance integrals for the bonds adjacent to the position undergoing substitution. Thus the following calculations used the resonance integrals shown in II.



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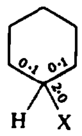


II

Since within each class of reagents (e.g. electrophiles) the Wheland model gives localization energies which are independent of the nature of the reagent, this must also be shown to be true of the representation employed here to simulate the Wheland model. Fig. 2 shows that the energy differences between complex formation at position 8 and the other possible atoms in the quinolinium ion are invariant over a wide range of α_x. Further, the order of these delocalized energies corresponds exactly to the order of localization energies calculated in the normal manner. In fact, there exists an excellent linear relation between the two sets as is shown in Fig. 3. Calculations for radical and nucleophilic attack yield similar results with equally good correlations between the two models indicating that the Wheland model can be well represented within the delocalization scheme.

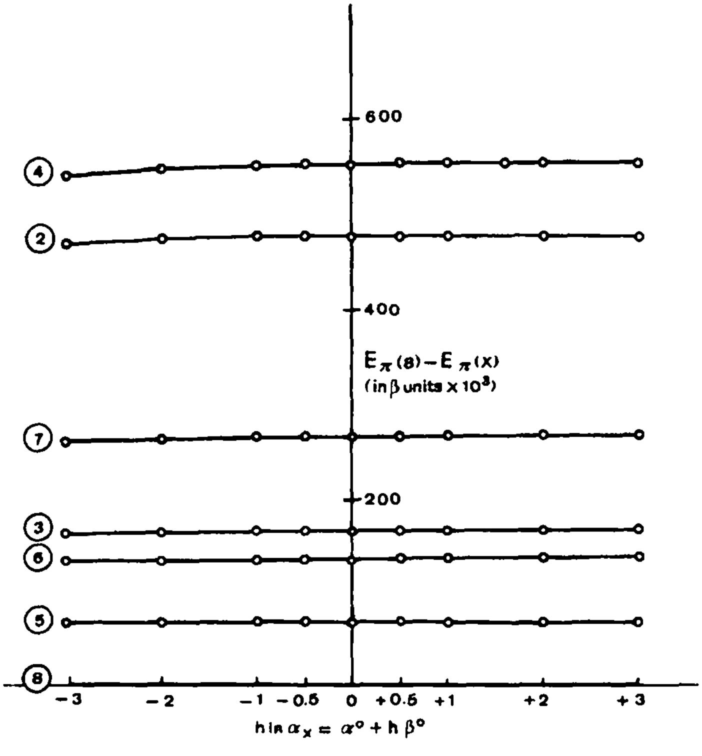


FIG. 2 The invariance to the nature of the reagent as represented by h in $\alpha_x = \alpha° + h\beta°$ of the relative energy differences for electrophilic complex formation at the possible position in the quinolinium ion when parameters are chosen to simulate the Wheland model.

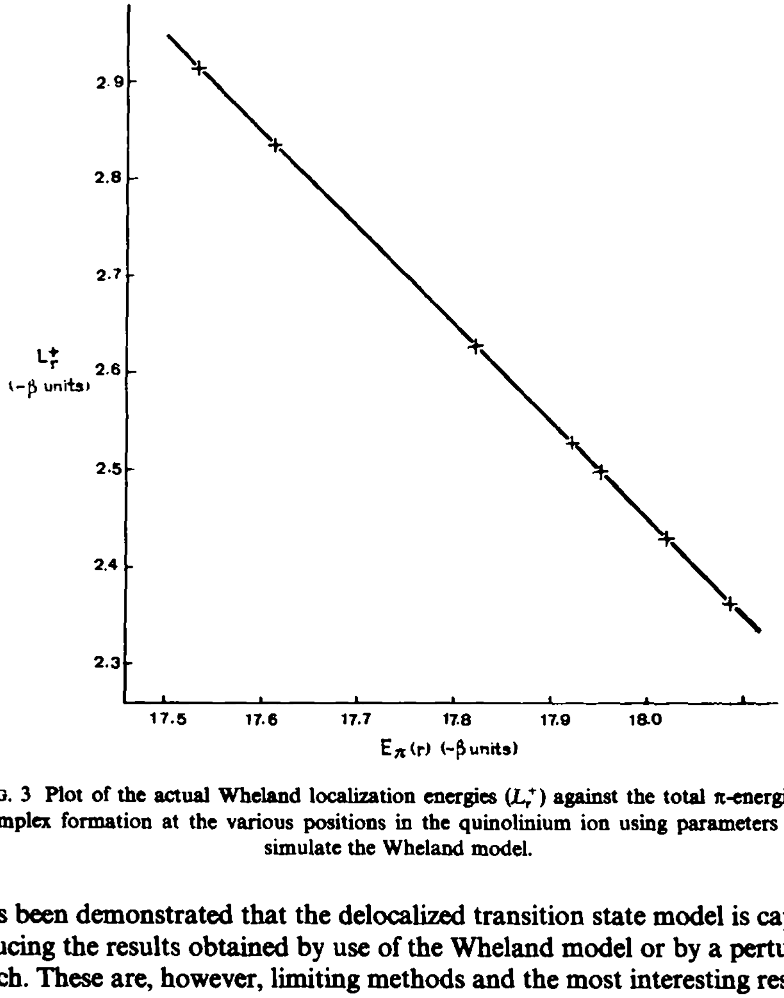


FIG. 3 Plot of the actual Wheland localization energies (L_r^+) against the total π-energies complex formation at the various positions in the quinolinium ion using parameters to simulate the Wheland model.

It has been demonstrated that the delocalized transition state model is capable of reproducing the results obtained by use of the Wheland model or by a perturbation approach. These are, however, limiting methods and the most interesting results are likely to arise in the intermediate region which is inaccessible to most other reactivity indices. The remainder of this paper will examine the effect of varying α_x for the reagent and β_{rx} between the reagent and substrate with a view to interpreting so far as possible the known chemical reactivity of quinoline.

Variation of β_{rx}. The second order perturbation energy given by Eq. (1) i.e.

$$\delta E = \frac{c_r^2 \beta_{rx}^2}{E_m - E_x}$$

indicates that δE should increase in a parabolic manner with β_{rx}. Figure 4 shows the total π-energy of the complex for nucleophilic substitution at positions 4 and 6 of the quinolinium ion plotted against β_{rx} taking the orbital ψ_x as having an energy $\alpha^\circ - 3\beta^\circ$. The expected behaviour is confirmed. In Fig. 5 the difference in energy between the complex at atom 4 and for the other positions is shown as a function of β_{rx}. From these curves it can be seen that the parabolic form predicted by perturbation theory breaks down as the magnitude of the perturbation increases. There are, however, no significant "crossings" of the energies for the range of β considered in this instance and hence increasing β is seen merely to accentuate the differences in energy between attack at various positions. A more subtle result of the choice of β will become evident later.

Variation of α_x. While chemical intuition suggests "reasonable" values for the energy of a single orbital representing an incoming nucleophile, electrophile or radical, the present study covers a wide range of values which at times may seem unreasonable. Since both quinoline and the quinolinium ion have all their molecular orbitals lying within the range $\alpha^\circ + 3\beta^\circ$ to $\alpha^\circ - 3\beta^\circ$, these values have been taken as the limits irrespective of the nature of the incoming group in case any unforeseen misbehaviour occurred, Nucleophilic, electrophilic and radical attack on the neutral molecule and the quinolinium ion will now be considered in turn.

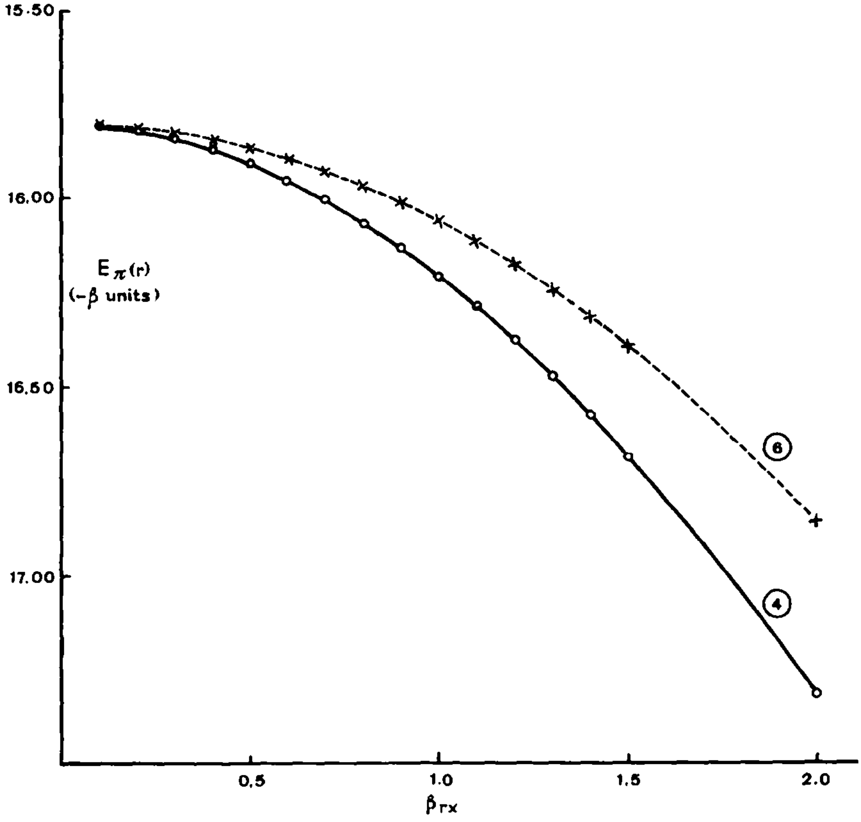


Fig. 4 The variation of the total π-energy for complex formation at positions 4 and 6 in the quinolinium ion as β_{rx}, the resonance integral between the reagent and substrate, is varied.

Nucleophilic attack

The π-energy of the complex at position 4 is taken as the base in Figs 6, 7 and 8 and $E_\pi(4) - E_\pi(r)$ is plotted for a series of values representing the Coulomb integral of the attacking group. Apart from Fig. 7, all subsequent results have been determined

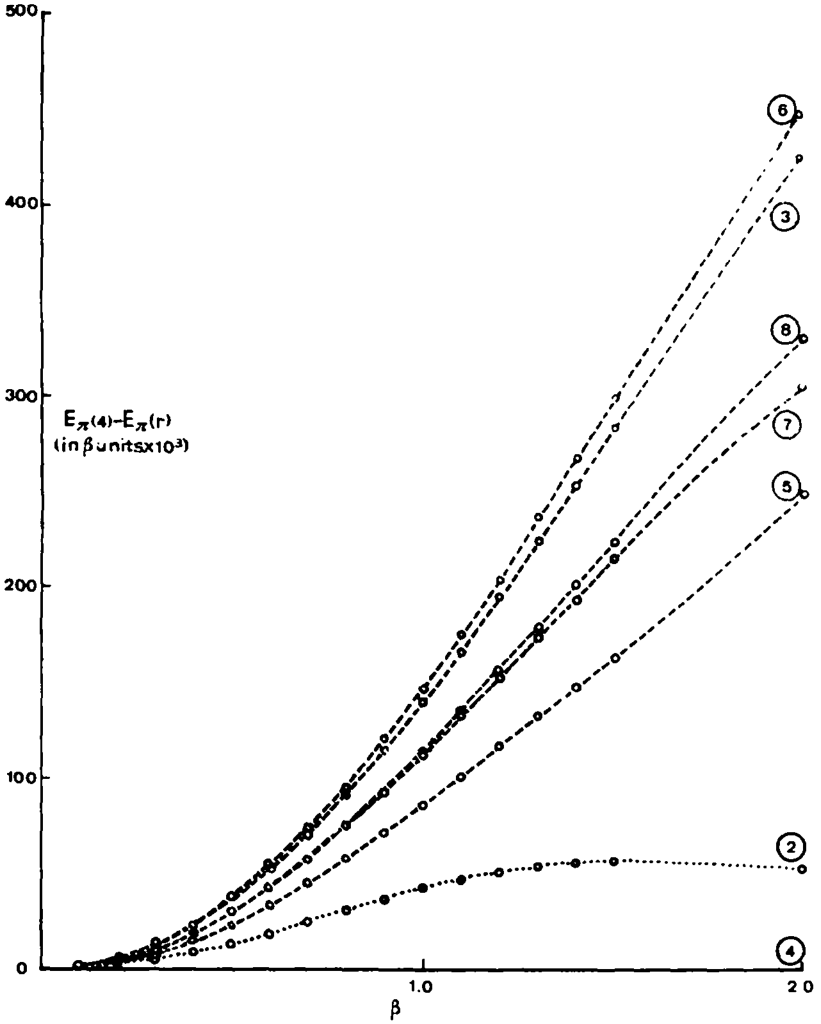


FIG. 5 Plot of the differences between the π-energy for complex formation at position 4 and the other possible positions of the quinolinium ion as β_{rx} the resonance integral between reagent and substrate is varied.

for the resonance integral $\beta_{rx} = 0{\cdot}5\beta^{\circ}$. Fig. 6 shows the energy differences for attack on the quinolinium ion when $\beta_{rx} = 0{\cdot}5\beta^{\circ}$, while Fig. 7 is the corresponding graph with $\beta_{rx} = 0{\cdot}1\beta^{\circ}$. It can be seen that for nucleophilic attack on the quinolinium ion there is a marked "crossing" in the energies for the 2 and 4 positions. Hence for a nucleophile with $\alpha_x = \alpha^{\circ} + h\beta^{\circ}$ and $h < -0{\cdot}1$ the 4 position is preferentially substituted where as for $h > -0{\cdot}1$ the 2 position becomes the more favoured position. Such a phenomenon is in accord with the experimental observations on 1-alkyl quinolinium salts, which undergo 4-substitution with the weak CN^- nucleophile but yield only 2-substituted product when a stronger nucleophile such as OH^- is employed.[1] Thus the delocalized state model presents a most attractive explanation

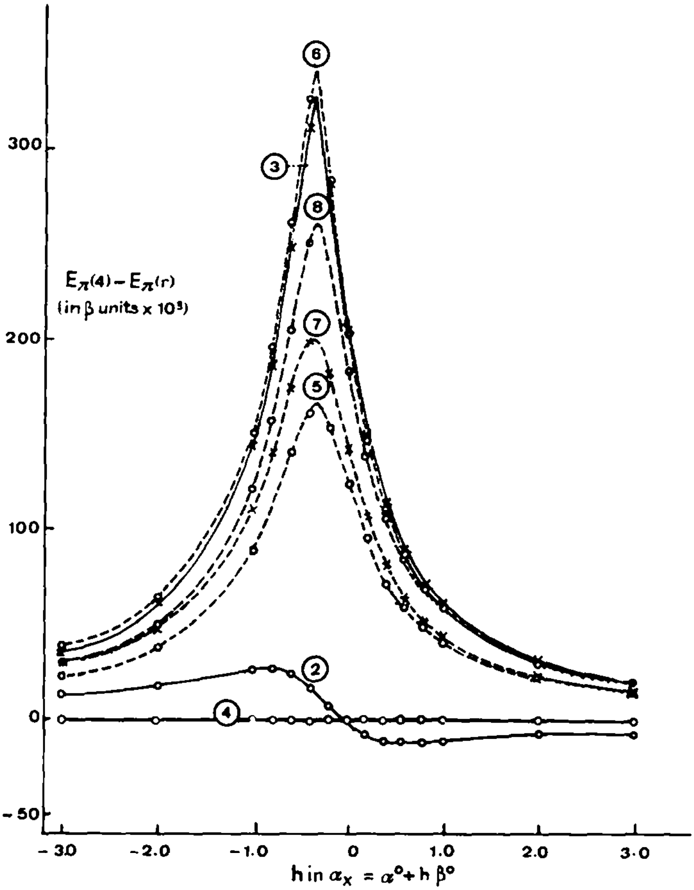


FIG. 6 The variation of the relative energy differences for nucleophilic attack on the quinolinium ion with the nature of the reagent as represented by h in $\alpha_x = \alpha^\circ + h\beta^\circ$. The resonance integral between substrate and the reagent β_{rx} is taken as 0·5.

for the observed change in orientation of substitution. Comparison of Figs 6 and 7 indicates that the value of β_{rx} selected makes very little difference to the general trends but one effect, which will require further examination when numerical values are assigned to each particular reagent, is that change of β_{rx} causes the point of crossing to vary slightly. Fig. 8 is the graph obtained for nucleophilic attack on the neutral quinoline molecule. There is a small crossing between the energies for attack at position 2 and 4 but it does not occur until $\alpha_x = \alpha^\circ + \beta^\circ$ which seems to represent an unacceptably low-lying orbital for a nucleophile. Experimentally, it is observed that the Chichibabin reaction, i.e. attack by the amide anion, yields principally 2-substituted quinoline[8] but there is still considerable doubt as to the mechanism of such a reaction, suggestions having been made that the intermediate is an aryne.[9] or, alternatively, that initial addition of an electrophile e.g. Li^+ to the nitrogen lone pair occurs and that attack is effectively on the quinolinium system.[3]

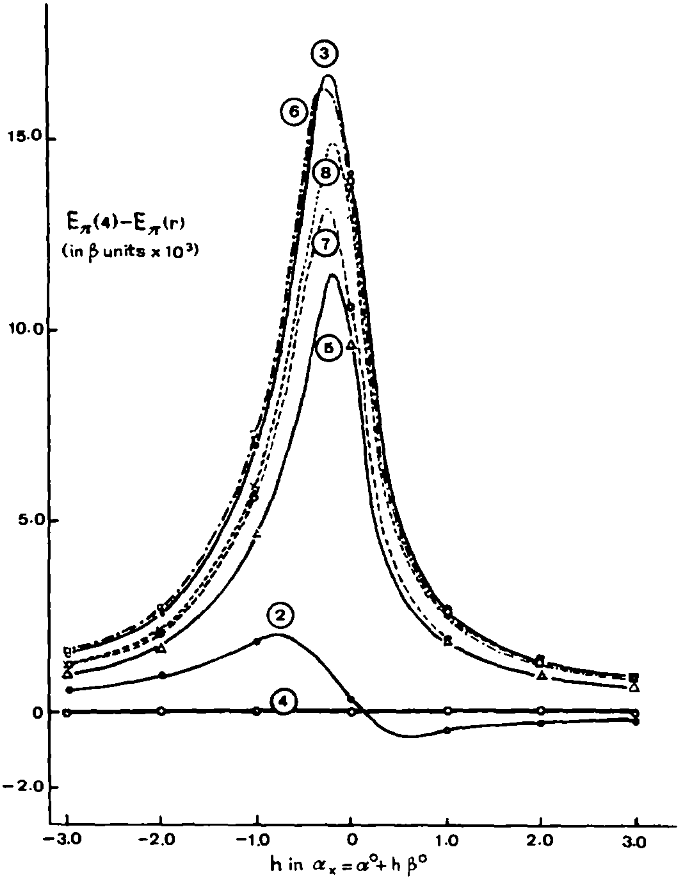


FIG. 7 The variation of the relative energy differences for nucleophilic attack on the quinolinium ion with the nature of the reagent as represented by h in $\alpha_x = \alpha^\circ + h\beta^\circ$. The resonance integral between substrate and the reagent β_{rx} is taken as 0·1.

Although apparently complex, the general pattern of the curves can be readily understood in the light of perturbation concepts as has already been pointed out by other workers.[7] If the orbital representing the nucleophile is higher in energy than the lowest unoccupied orbital of the substrate (III) the electrons from the nucleophile may be viewed as undergoing transfer to this previously unoccupied orbital. In the complex, however, the energy of the unoccupied levels is perturbed by the nucleophile according to Eq. (1) and hence the larger the coefficient of the unoccupied orbital the greater is the lowering of the π-energy of the complex. Thus, in that region where the nucleophile orbital is higher than the lowest unoccupied level of the substrate, the reactivity will be governed by the frontier orbital density. As the orbital of the nucleophile is lowered towards the unoccupied level, the extent of perturbation increases and the differences in energy on attack at the various positions will become maxima at approximately the level of the first unoccupied orbital of the substrate. Since only interactions between occupied and unoccupied levels produce a net change in total energy, further lowering of the nucleophile orbital energy diminishes

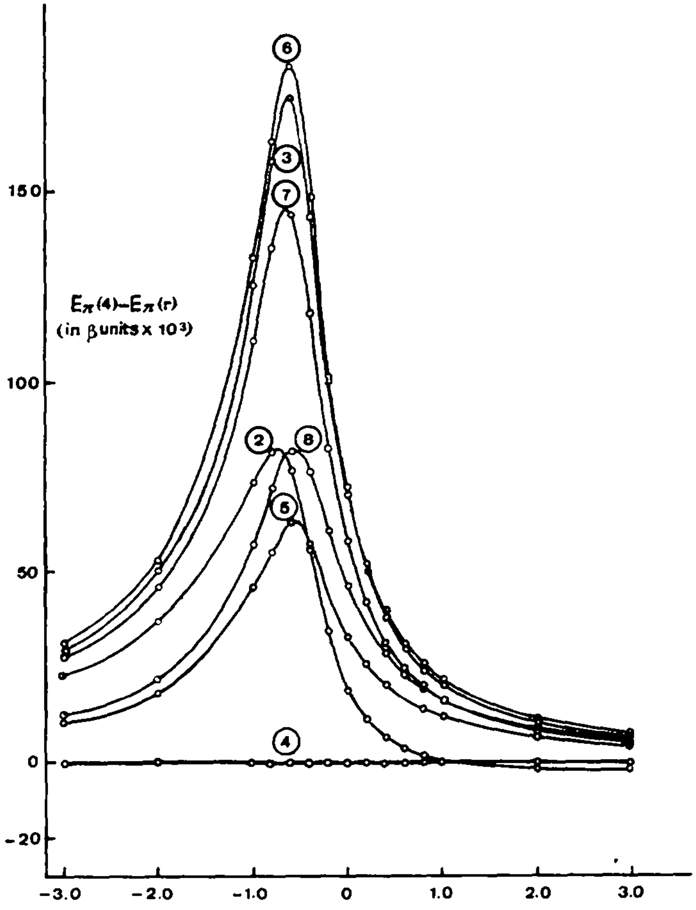
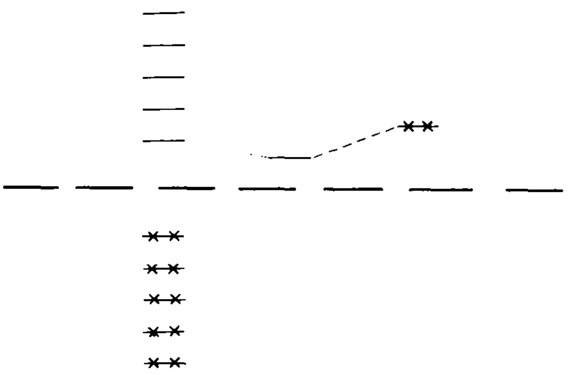


FIG. 8 The variation of the relative energies for nucleophilic attack on neutral quinoline.

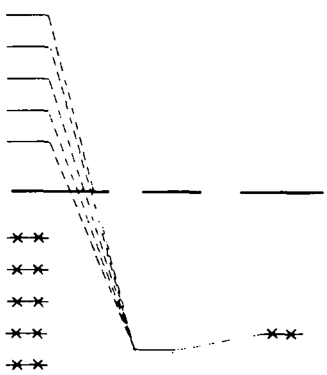
the perturbations. Eq. (1) indicates that the perturbation is proportional to c_r^2 but inversely proportional to the single power of the difference in energy between the perturbing levels. Consequently, on further lowering of the nucleophile orbital the perturbation energy begins to follow more closely the sum of the squares of the coefficients for *all* unoccupied levels rather than merely the first unoccupied level. In effect, this means that the energies of the complex follow the net charges of the atoms undergoing substitution and IV may be described as the region of charge control. It is possible to include in these calculations a purely coulombic term which in combination with the charge effect noted above will assist in producing more pronounced separations of the energies for attack at different positions. Such a procedure has not been adopted in the present study.

Electrophilic attack

In the delocalized transition state model the electrophile is represented by a single vacant orbital and perturbations in this case are going to be with the occupied levels

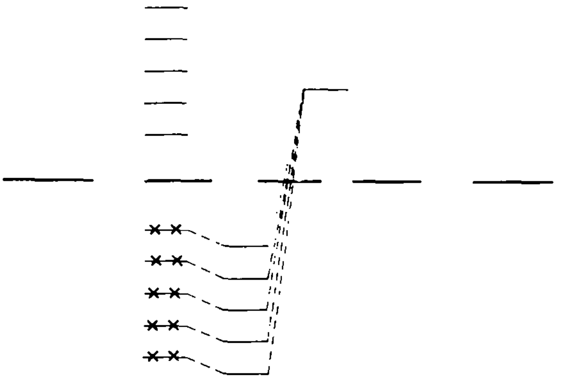


III. Frontier control

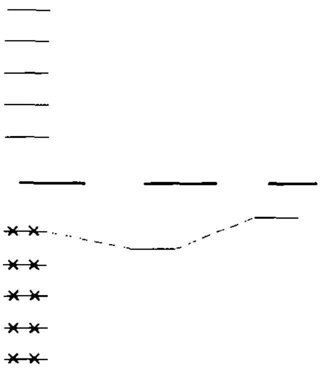


IV. Charge control

of the substrate. By analogues reasoning to the nucleophilic case it can be seen that if the electrophile orbital energy is high as in V the reactivity will follow the total charges, but as the level is lowered the interaction with the highest filled orbital will become dominant and a region of frontier density control is reached as in VI. If the electrophile orbital energy is made lower than the highest filled level then electron transfer will occur in the complex, but the reactivity will still be frontier controlled under the electrophilic level is made extremely low.



V. Charge control



VI. Frontier orbital control

These phenomenon are shown in Fig. 9 for the quinolinium ion and Fig. 10 for the neutral species. It has been demonstrated experimentally that nitration in strong acid occurs via the quinolinium ion[10] and from Fig. 9 it is evident that for a strong electrophile like NO_2^+ where $h > 0$ that substitution should occur in the 8- and the 5-positions preferentially. This is in accord with experiment. For nitration in weaker acids such as acetic acid, however, the order of reactivity is $3 > 6, 8$ and it is impossible to account for such an observation by means of the delocalized transition state model. It is almost certain that substitution in weaker acids occurs by means of an indirect-addition-elimination reaction.[11]

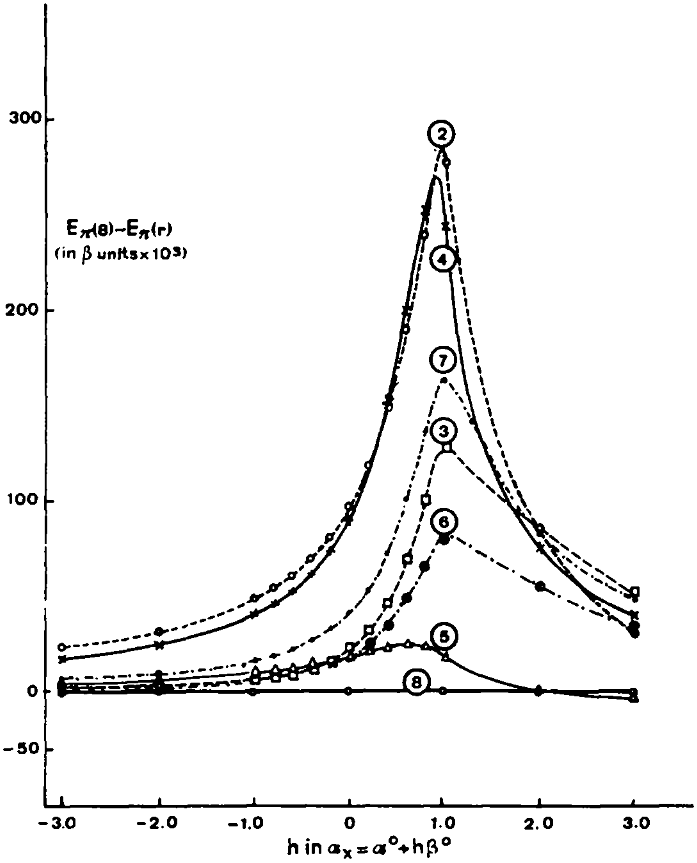


Fig. 9 The variation of the relative energies for electrophilic attack on the quinolinium ion.

Radical attack

As indicated in part I the simplified delocalized transition state model employed here is most likely to break down for the case of radical attack, but the results are recorded to show the general behaviour predicted. Since the radical is represented as an orbital containing one electron, perturbation will occur with both the occupied and the unoccupied orbitals of the substrate. As a result lowering of the radical orbital energy level from a highly antibonding state to a deep-bonding state will produce two distinct maxima in the energy separations. The first will be the maximum perturbation with the lowest unoccupied level and will be identical in order to that for nucleophilic substitution, whereas the second will be similar to the order for electrophilic substitution and results from the dominance of the perturbation with the highest filled level of the substrate. Figs 11 and 12 demonstrate this very clearly for the case of the quinolinium ion and the neutral quinoline respectively. The many crossings in the energies for the complex mean that several positions can become very important in radical reactions and it is hardly surprising that the favoured position changes dramatically with the nature of the radical and the conditions under which it is generated. Brown and Harcourt[3] have discussed some of the experimental results obtained for radical reactions on quinoline but the experimental results and the above calculations cannot be described as in good agreement. Almost certainly more precise knowledge of the mechanistic course of radical reactions on aromatic systems and a more comprehensive treatment of all the orbitals of the attacking group will be necessary before theory and experiment are in accord.

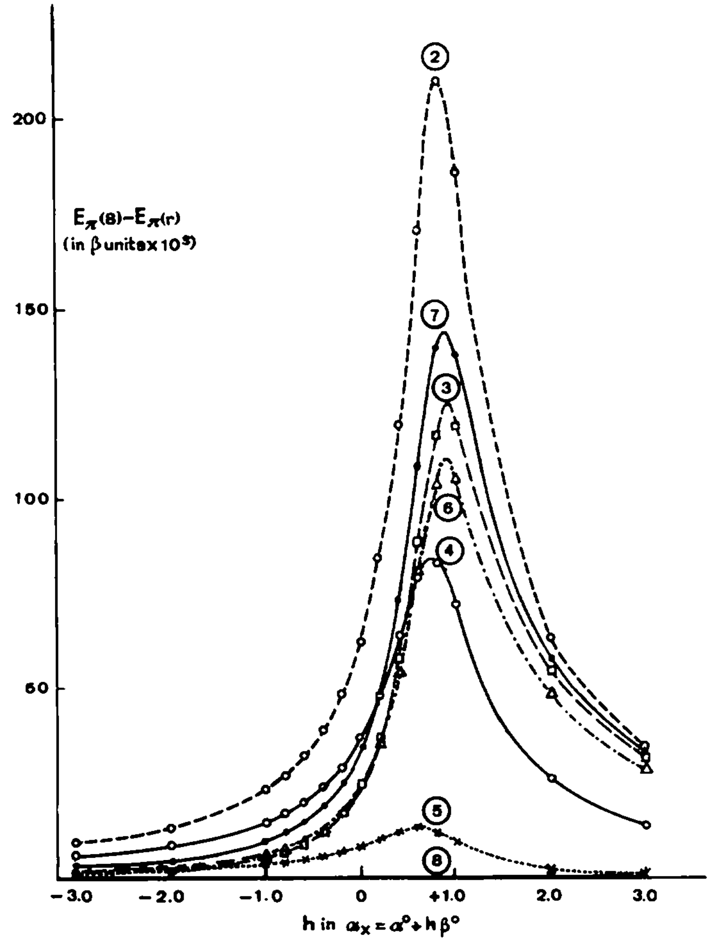


FIG. 10 The variation of the relative energies for electrophilic attack on neutral quinoline.

CONCLUSION

The delocalized transition state model has been applied to the case of reactions on quinoline and the quinolinium ion and the general trends emerging from its use have been examined. It has been shown that this model can be adapted to reproduce the results from the use of perturbation theory and the Wheland model. For nucleophilic and electrophilic substitution the method is believed to yield a reliable guide to the reactivity of aromatic molecules, but there is still considerable doubt as to its utility for radical reactions.

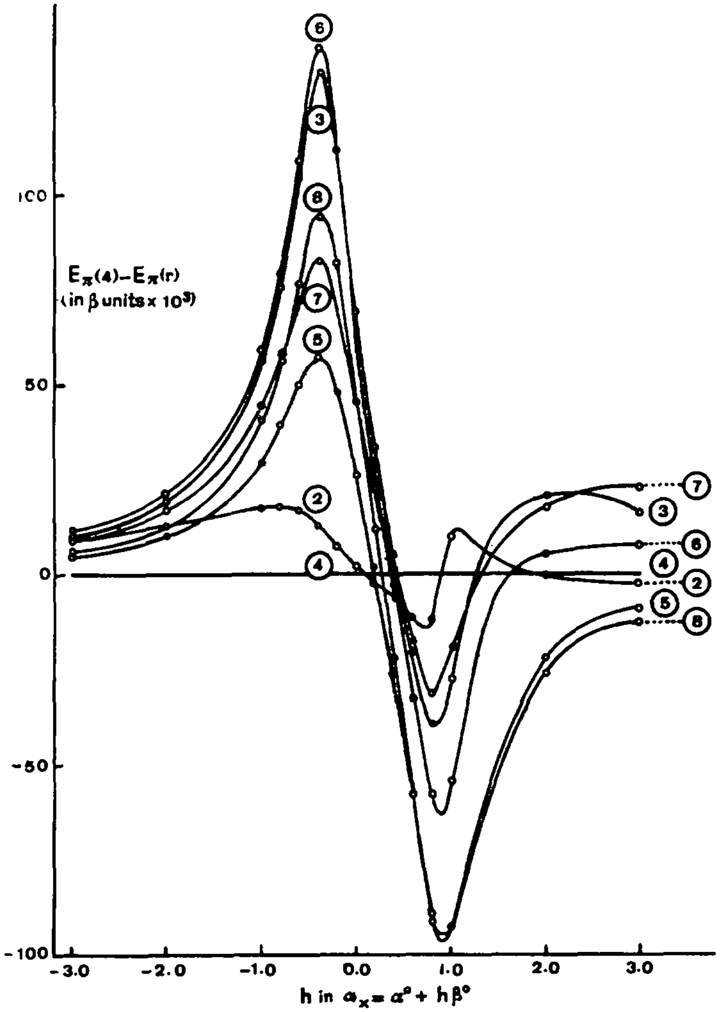


FIG. 11 The variation of the relative energies for radical attack on the quinolinium ion.

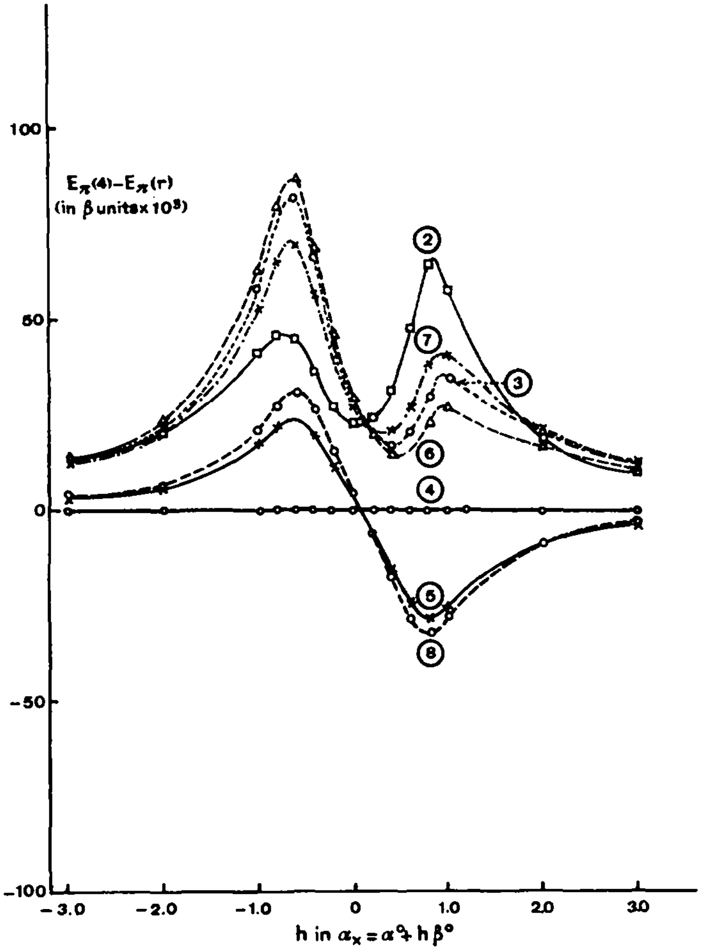


FIG. 12 The variation of the relative energies for radical attack on neutral quinoline.

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