

438. *Studies of the Localization Theory of Organic Reactions.*
Part I. The Effects of Annellation and of Introducing Hetero-atoms.

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Fundamental equations are derived for the change in localization energy of a given position in a given molecule owing to fusion of a benzene or other ring system to the molecule, or to replacement of one of the carbon atoms of the molecule by a hetero-atom. These equations apply alike to atom, bond, and para-localization energies. They are illustrated for some special cases. Some general predictions of reactivities of heterocyclic systems are made, and the need for fundamental experimentation to determine parameters for hetero-atoms is indicated.

THE localization theory of organic reactions represents an attempt to approximate to relative heats of activation for the reaction of various organic compounds with a particular reagent, such as nitronium ion, osmium tetroxide, or maleic anhydride. Its name is derived from the fact that in this approximation the formation of the activated complex is regarded as being accompanied by a partial localization of some or all of the π -electrons present in the organic molecule. The problem of substitution in substituted benzenes has been considered by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), Dewar (*J.*, 1949, 463), and Longuet-Higgins (*J. Chem. Physics*, 1950, **18**, 283), in the Diels-Alder reaction by Brown (*J.*, 1950, 691, 2730), and in reaction of hydrocarbons with osmium tetroxide by Brown (*ibid.*, p. 3249). However, the general problem of the change in reactivity of a given conjugated system when a hetero-atom is introduced, when a benzene or other ring system is annelated to it, or when one or more substituents are attached to it, has not yet been considered. It is proposed to consider this problem in the present paper. The results apply quite generally to all reactions which lend themselves to treatment by the localization approximation, also both to polycyclic conjugated systems and to polyenes and aryl-polyenes, but the latter are not so susceptible to theoretical treatment owing to uncertainty in their precise stereochemistry, which is not present in the case of the relatively rigid polycyclic systems.

Annellation.—A problem of interest, particularly in the case of polycyclic hydrocarbons, is to predict the change in reactivity of a hydrocarbon when a benzene or other cyclic system is fused

is independent of the nature of X. In the example considered above, the qualitative result that the 3 : 4-bond of benzantracene is more reactive than the 9 : 10-bond of phenanthrene could have been predicted from the fact that the 3 : 4-bond of diphenyl has a greater mobile order than the 2 : 3-bond of phenanthrene, X being assumed to be benzene. The same data, X now being assumed to be naphthalene, lead to the result that the most reactive bonds in 1 : 2-5 : 6-dibenzanthracene, 1 : 2-7 : 8-dibenzanthracene, and 1 : 2-benzonaphthacene are more reactive than the 9 : 10-phenanthrene bond. Similarly, we expect the 1 : 2-bond of chrysene to be less reactive than this phenanthrene bond because the mobile order of the 1 : 2-bond of phenanthrene (0.705) is greater than that of the 3 : 4-bond of diphenyl. In view of the rather extensive mobile-order data available in the literature, together with some simple methods for judging qualitatively the relative mobile orders of bonds, this principle should prove very useful for qualitative predictions, particularly for the Diels-Alder and osmium tetroxide reactions.

The relation analogous to (7) for $L' - L'_0$, *i.e.*, with the inclusion of the overlap integral, can be written down from the relationships corresponding to (5) and (6) for K' (Brown, *Trans. Faraday Soc.*, *loc. cit.*). It differs from (7) in that the numerical constant 1.077 is now replaced by 1.034 and that the energy unit β is replaced by γ . The equation may be employed to estimate the relative rate constants for reaction of the two compounds

$$k/k_0 = \exp[(L'_0 - L')/RT]$$

It is again convenient to use the osmium tetroxide reaction as an example because experimental relative-rate data are available for this reaction (Badger and Reed, *Nature*, 1948, **161**, 237; Badger, *J.*, 1949, 456). For 20° and $-\gamma = 34$ kcal. we have

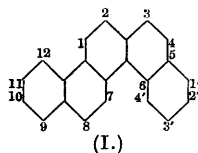
$$k/k_0 = \exp\{60.3(p_{ab}^r - p_{ab})[1 - (\delta_{ab} + \delta_{ab}^r)/4]\}. \quad \dots \quad (8)$$

expressing the reaction-rate-constant contribution from a particular bond in the YX compound relative to that of the corresponding bond in Y in the particular case of the osmium tetroxide reaction.

As the first example, we may take phenanthrene and benzantracene, already considered above. From (8) we derive $k/k_0 = 8$ for the reaction-rate constant of the 3 : 4-bond of benzantracene relative to the 9 : 10-bond of phenanthrene. These bonds are far more reactive than any others in their respective molecules so this figure will also represent the relative reaction-rate constants for the two molecular species. The value found experimentally by Badger and Reed (*loc. cit.*) is 10. It will be noticed that k/k_0 is an exponential function of the quantity $p^r - p$, so that agreement even in order of magnitude is to be regarded as satisfactory.

Another important example is provided by the pair benzantracene and 1 : 2-5 : 6-dibenzanthracene. It is found on inserting the appropriate values into (8), and assuming that p_{ab}^r , the mobile order of the 5 : 6-bond in 2-phenylnaphthalene, is the same as in unsubstituted naphthalene, that k/k_0 for the 3 : 4-bonds of these two hydrocarbons comes to 0.63. However, the annelation of a benzene ring to the 5 : 6-bond of benzantracene produces another bond equivalent to the 3 : 4-bond of dibenzanthracene. These two bonds are far more reactive than all others in dibenzanthracene, so the relative molecular rate constants for benzantracene and dibenzanthracene will be $0.63 \times 2 = 1.3$. This is in excellent agreement with the experimental value of 1.3 (Badger, *loc. cit.*). Here we have the interesting case of the 3 : 4-bond of benzantracene being deactivated by annelation, and in spite of this the resultant molecule is more reactive than benzantracene owing to the formation of another equivalent reactive bond.

It is apparent that a complication arises when the annelation gives rise to other bonds of reactivity comparable with the one under consideration, especially when they are not equivalent to it by symmetry, as they happen to be in the case just considered. However, even in these cases it is usually possible to determine k/k_0 for all reactive bonds in the molecule such that k_0 represents the bond rate constant of either the phenanthrene 9 : 10-bond or the benzantracene 3 : 4-bond. The procedure again is best illustrated by an example. We



shall calculate the molecular rate constant for 5 : 6-benzochrysene (I) relative to phenanthrene. It is apparent from general considerations (Brown, *J.*, 1950, 3249) that the only bonds sufficiently reactive to be considered are 1 : 2, 3 : 4, and 7 : 8. To consider, first, the reactivity of the 3 : 4-bond relative to phenanthrene, we regard benzochrysene as formed by annelation of the 1 : 2-bond of naphthalene to the 3 : 4-bond of phenanthrene. Substitution of the appropriate values in (8) yields $k/k_p = 0.21$, where we have written k_p to indicate that the 9 : 10-phenanthrene bond is being used as reference point. Similarly, the reactivity of the 7 : 8-bond is treated by regarding benzochrysene as formed by

fusion of the 1:2-bond of naphthalene to the 1:2-bond of phenanthrene. This time we find $k/k_p = 0.06$. The reactivity of the 1:2-bond can be found first by finding the reactivity of the 1:2-bond of chrysene relative to phenanthrene and then the change in its reactivity due to annelation of a benzene ring to the 5:6-chrysene bond. However, little error is introduced in treating benzochrysene as 1:2-5:6-dibenzophenanthrene and assuming that the effect of the two annelations upon the 9:10-phenanthrene bond is additive. This is easily seen to be equivalent to assuming that the relative rate constant for the 1:2-bond of 5:6-benzochrysene is the product of relative rate constants for the 1:2-bond of chrysene and the 1:2-bond of 3:4-benzophenanthrene. In the latter way we obtain $k/k_p = 0.016$, but in view of the approximations invoked this cannot be taken to indicate more than order of magnitude. To obtain the molecular relative rate constant we sum over all bonds of the molecule. As mentioned above, the only significant contributions come from the three bonds just considered, and we conclude that the relative rate constant for benzochrysene is 0.3. Unfortunately, the value has not yet been determined experimentally.

One possible limitation to the use of equations (7) and (8) must be mentioned. The annelation relationships (5) and (6) have only been investigated for alternant hydrocarbons, *i.e.*, hydrocarbons containing only even-membered rings; it has not yet been determined if they are still valid for hetero-molecules or for radical systems. Consequently, at present we can apply (7) and (8) with confidence only to reactions for which both the original molecule and the residual molecules are hydrocarbon systems. Reactions for which this is true are the Diels-Alder reaction and the reaction with osmium tetroxide.

Hetero-atoms.—Another problem of importance is to predict the change in reactivity of a conjugated system, Y, when one of its carbon atoms is replaced by a hetero-atom such as nitrogen. Suppose it is the i th atom that is replaced by a hetero-atom. We may write the π -electron energy of the resultant molecule as

$$E = E_0 + W_i \dots \dots \dots (9)$$

where E_0 is the π -energy of Y, and we may take (9) as defining W_i , which will be termed the perturbation energy, and for a given hetero-atom will in general depend upon which atom, i , is replaced.

A similar expression may be written for E' , so that we can immediately derive

$$L - L_0 = W'_i - W_i \dots \dots \dots (10)$$

If we now consider the L.C.A.O. molecular-orbital approximations to the various quantities appearing in (10), it is possible to put the right-hand side into a more convenient form. The major effect of the replacement of the i th carbon atom by a hetero-atom is to alter its coulomb term, α_i . We can then expand E and E' as a Taylor series in $\delta\alpha_i$ and thus obtain

$$W_i = \delta\alpha_i [dE/d\alpha_i + (d^2E/d\alpha_i^2)(\delta\alpha_i)/2 + \dots] \dots \dots (11)$$

with an analogous expression for W'_i . It is convenient to write $h_i\beta$ for $\delta\alpha_i$, β being the resonance integral, and to make the usual assumption that h_i depends upon the nature of the hetero-atom only and not upon i . The differential coefficients in (11) are just the charge, q_i , and self-polarisability, $\pi_{i,i}$, of position i (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, 191, 39). These may be inserted into (11) and the corresponding expression for W'_i , and the results incorporated into (10) to give

$$L - L_0 = h\beta[(q'_i - q_i) + (\lambda'_i - \lambda_i)h/2 + \dots] \dots \dots (12)$$

where λ_i , a pure number, has been written for $\beta\pi_{i,i}$.

Equation (12) is simplified further if the original or residual molecule or both are alternant hydrocarbons, since for these latter all the q_i are unity (Coulson and Rushbrooke, *Proc. Camb. Phil. Soc.*, 1940, 36, 193).

Longuet-Higgins (*J. Chem. Physics*, 1950, 18, 283) has discussed some aspects of substitution reactions of aromatic and heterocyclic systems, using the equivalent of equation (12) but retaining only the first term, $q' - q$. However, another interesting application of (12) is to reactions such as the Diels-Alder reaction and osmium tetroxide reaction where, if the original molecule is an alternant hydrocarbon, then so also is the residual molecule. If we retain only the first non-vanishing term in (12), we have for these reactions

$$L - L_0 = (-\beta)(\lambda_i - \lambda'_i)h^2/2 \dots \dots \dots (13)$$

To illustrate the order of magnitude of the changes in reactivity predicted by (13) some values are given in Table I. The self-polarisabilities have been taken from the literature (Coulson

TABLE I.

Reactivities of aza-hydrocarbons relative to parent hydrocarbons.

(a) Osmium tetroxide reaction at the 9 : 10-bond.

	Position.	$L - L_0$ *		Position.	$L - L_0$ *
1-Azaphenanthrene		-0.022 β	3-Azaphenanthrene		-0.005
2-Azaphenanthrene		+0.004	4-Azaphenanthrene		-0.003

(b) The Diels-Alder reaction.

Quinoline	1 : 4	-0.023 β	3'-Aza-1 : 2-benzanthracene	9 : 10	+0.001
<i>iso</i> Quinoline	1 : 4	+0.048	4'-	9 : 10	+0.002
	5 : 8	-0.004	3-	9 : 10	-0.002
1-Aza-anthracene	9 : 10	-0.028	4-	9 : 10	-0.021
2-	9 : 10	-0.006	6-	9 : 10	-0.027
1'-Aza-1 : 2-benzanthracene	9 : 10	+0.002	7-	9 : 10	-0.005
2'-	9 : 10	-0.003	8-	9 : 10	-0.025

* It is assumed for convenience that $h = 1$.

and Longuet-Higgins, *Proc. Roy. Soc.*, 1948, *A*, **195**, 188; Brown, *Experientia*, 1950, **6**, 376; Greenwood, unpublished results).

It seems likely that for nitrogen h is not greater than unity, and that higher terms in the expansion (12) are less important than the first two, so the values given in Table I for $L - L_0$ are likely to be at least qualitatively correct. The values, which are listed assuming $h = 1$, are all very small, the greatest change in reactivity being for 1 : 4 Diels-Alder addition to *iso*quinoline compared with naphthalene. This figure probably corresponds to relative rate constants of 10 : 1 for the 1 : 4-positions in the respective molecules, and since naphthalene has two equivalent pairs of positions and the 5 : 8-positions of *iso*quinoline are similar in reactivity to the 1 : 4-naphthalene positions, the tabulated value would indicate that *iso*quinoline should react about six times as rapidly as naphthalene with, say, maleic anhydride.

The results presented in Table I, and similar results for other systems, have more important uses than this, however. If a position in a hydrocarbon could be found for which $\lambda_i - \lambda_j^\ddagger$ is unusually large, then the relative rates of reaction of the hydrocarbon and the corresponding aza-hydrocarbon found experimentally could be employed to determine $h^2\beta$ for nitrogen. The resonance integral β likewise could be determined from experimental relative rate constants for pairs of hydrocarbons, pairs for which (7) is applicable being particularly appropriate. This affords an experimental means for determining the parameter h . There may, however, be complicating factors, one of which must now be considered in connection with another use for the data of Table I.

It is sometimes suggested (Badger, *J.*, 1950, 1809) that the reactivity of a bond towards osmium tetroxide is partly determined by the charges at either end of the bond. At present there is no satisfactory experimental evidence to support this suggestion and some theoretical evidence (Brown, *J.*, 1951, 1950) against it. However, a hetero-molecule will have in general a relatively large dipole moment compared with its parent hydrocarbon, so there will be a stabilization of the activated complex of the former relative to that of the latter owing to induction forces involving the dipole moment of the heterocyclic system and the polarisable electrons of the osmium tetroxide, similar to the forces responsible for the difference in stability of the *endo*- and *exo*-forms of Diels-Alder adducts (cf. *idem, ibid.*, p. 1612). Qualitatively, such effects would be expected to increase the reactivity of hetero-molecules compared with their parent hydrocarbons by a greater amount than that predicted by (13). Consequently, experimental investigation of reactivities of hetero-molecules should serve to throw more light both upon the theoretical treatment of such systems and upon the mechanism of bond reactions. Badger and Lynn's measurement of the rate of reaction of methyl-dibenzacridine with osmium tetroxide (*J.*, 1950, 1726) indicates little difference in reactivity from the corresponding methyl-benzanthracene. Since we should expect theoretically that this latter compound would have very similar reactivity to the methyl-dibenzanthracene, this measurement points to an insignificant influence of the hetero-atom on the reactivity, as would be expected from the results of Table I. This suggests in turn that the polarity of the hetero-molecule plays little part in its reactivity, but clearly a more thorough experimental investigation is still needed.

Similar remarks apply to the Diels-Alder properties of hetero-molecules. In this case there is the possibility of quantitative studies of equilibria to determine the parameter h . Perhaps the most interesting result in Table I is the increased Diels-Alder reactivity of the 1 : 4-positions in *iso*quinoline compared with naphthalene, in view of the recently reported formation of an

adduct of the latter with maleic anhydride (Kloetzel and Herzog, *J. Amer. Chem. Soc.*, 1950, **72**, 1991). The other conclusion to be drawn generally from (13) is that from the standpoint of preparative organic chemistry if a certain hydrocarbon adds maleic anhydride then so will all its aza-derivatives (excepting cases where the nitrogen atom occupies one of the positions which would normally undergo addition). Some isolated examples appear in the literature; *e.g.*, Huisgen (*Annalen*, 1949, **564**, 16) has reported Diels–Alder reactivity of a substituted 1-aza-anthracene. Since substituents have a relatively small effect upon bond or Diels–Alder reactivity unless they are at one of the reactive positions (to be discussed in Part II) the present theory predicts reactivity for a large number of reported heterocyclic derivatives. As a representative example may be quoted the derivatives of 2 : 3-benzacridine reported by Cairns and Kermack (*J.*, 1950, 1322).

In the above discussion of heterocyclic systems it has been supposed that the predominant effect of the hetero-atom is to perturb the Coulomb term of the carbon atom it replaces. However, it seems likely that the resonance integrals of all bonds ending at the hetero-atom will also be perturbed. The effect of these perturbations is to add to the right-hand side of (11) the additional Taylor series

$$\delta\beta\{\sum_j\partial E/\partial\beta_{ij} + \frac{1}{2}\sum_j\sum_k(\partial^2 E/\partial\beta_{ij}\partial\beta_{ik})\delta\beta + \dots\} \dots \dots \dots (14)$$

where the summations are over all atoms adjacent to the hetero-atom at *i*. If we write for convenience the perturbation $\delta\beta$ as $h\beta$ and use the identities of the differential coefficients with mobile bond orders and self-bond polarisabilities (Coulson and Longuet-Higgins, *loc. cit.*) (14) becomes

$$h\beta(\sum_j 2p_{ij} + \sum_j\sum_k\pi_{ij,ik} h\beta + \dots) \dots \dots \dots (15)$$

p_{ij} being the mobile order of the *i* : *j* bond and $\pi_{ij,ik}$ being the mutual polarisability between bonds *i* : *j* and *i* : *k*. Strictly we should also add to (11) a series of cross terms, the first of which is $\sum_j \pi_{i,j} h\beta^2$, but for alternant hydrocarbons the atom-bond polarisabilities, $\pi_{i,j}$, are identically zero, and since *h* is small (see below) the term will be unimportant in other cases.

The expression for the change in localization energy then becomes

$$L - L_0 = h\beta[(q_i^* - q_i) + (\lambda_i^* - \lambda_i)h/2 + \dots] \\ + h\beta[2(F_i - F_i^*) - (Y_i^* - Y_i^*)h + \dots] \dots \dots \dots (16)$$

where F_i is the free valency of position *i* and Y_i is a dimensionless function of the mutual bond polarisabilities. For the usual case when the hetero-atom replaces a carbon atom, *i*, with two neighbours, *a* and *b*, it is

$$Y_i = (\pi_{ai,ai} + 2\pi_{ai,bi} + \pi_{bi,bi})\beta$$

In particular, when the hetero-atom is nitrogen, *h* is probably very small (cf. Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87) and may be considerably less than 0.1. Furthermore, for most positions in alternant hydrocarbons Y_i is of the order 0.1, so the second term in

TABLE II.

The effect of perturbation of the resonance integral.

Osmium tetroxide reaction at 9 : 10-bond.		Diels–Alder reaction.	
	$F_i - F_i^*$		$F_i - F_i^*$
1-Aza-phenanthrene	0.057	Quinoline	5 : 8 0.053
2- "	0.008	isoQuinoline	1 : 4 0.328
3- "	0.012		5 : 8 0.005
4- "	0.003	1-Aza-anthracene	9 : 10 0.060
		2-Aza- "	9 : 10 0.009
		3-Aza-1 : 2-benzanthracene	9 : 10 0.004
		4-Aza- "	9 : 10 0.051

the second series in (16) will usually be quite negligible. To illustrate the importance of the first term of the second series, values of $F_i - F_i^*$ are given in Table II for some of the compounds considered in Table I. It is clear that, apart from the exceptional case of 1 : 4-addition to isoquinoline, where in any case the assumption of constancy in σ -bond energy changes is likely to break down, the effect of the first term of the second series will be negligible compared with that of the second term of the first series owing to the small value of *h*.

Equation (12) or the more general equation (16) should apply for all reactions which can be treated by the localization theory, not only the Diels–Alder and osmium tetroxide reactions. Unfortunately, the familiar substitution reactions of conjugated systems involve radical residual molecules for which self- and mutual-atom- and bond-polarisabilities are not available

in the literature, so one has to be content at present with the elegant qualitative treatment by Longuet-Higgins (*J. Chem. Physics*, 1950, **18**, 283) using only the first term in (16), *i.e.*, $q_i^2 - q_i$.

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