

143. The Significance of the Transition State in Aromatic Substitution.

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Attention is directed to the view that the only correct way to predict the favourable positions of substitution of the more complex aromatic and heterocyclic ring-systems lies in evaluating the energy difference between the mesomeric ground state of the molecule and the transition state of a bimolecular reaction process. This transition state is essentially quinonoid, and has a considerable degree of bond-localisation. The oxidation-reduction potentials of the possible corresponding quinones, or of the formation of the corresponding dihydro-derivatives, can be used to give a first approximation to this energy difference, and the most probable transition states can consequently be deduced by the direct inspection of quinonoid structures.

Applications of this correlation between oxidation-reduction potentials and points of aromatic substitution lead directly to explanations of (i) the ortho-para ratio in benzene substitution, (ii) substitution in the naphthalene series and in particular of 2-substituted naphthalenes, (iii) side-chain reactivity of heterocyclic molecules, (iv) the Mills-Nixon effect, and (v) substitution of polycyclic aromatic hydrocarbons.

Homolytic (*i.e.*, free-radical) substitution is also reviewed, and in this connection semi-quinonoid structure is significant.

SEVERAL features of aromatic substitution, notably (i) variations in the ortho-para ratio, (ii) the complete inertness of the 3-position in substances such as β -naphthol and *isoquinoline*, and (iii) the differences between the mode of attack of heterolytic (*i.e.*, ionic or polarised) reagents, whether electrophilic or nucleophilic, and homolytic (free-radical) reagents, have not yet received a satisfactory interpretation in the light of modern electronic theories though it is now more than twenty years since the essential difference between the ortho-para and the meta types of benzene substitution was clearly explained by reference to the internal electron redistributions which could occur in all aromatic ring systems on the approach of a polar reagent.

Unfortunately, the development of the theory of resonance has tended to obscure the original conceptions of Robinson and Ingold (cf. Robinson's Institute of Chemistry Lectures, 1932), according to which the electromeric rearrangements which explained the directive effects of substituent groups occurred during the course of the substitution reaction, by establishing, from dipole moment and other types of physical measurement, that mesomerism in the normal states of aromatic molecules does lead, even before any chemical reaction has occurred, to an unequal distribution of electron-densities at the different carbon centres in any aromatic substance of general type C_6H_5R , where R is a polar group. Consequently the fallacy of assuming that the original British theory of aromatic substitution is but a pictorial representation of Pauling's applications of the resonance theory to evaluate the stable states of aromatic ring systems has had the unfortunate effect of retarding advances of the theory of aromatic substitution which could have been made some years ago in the light of more exact studies of the mechanism of substitution reactions in general.

In 1941 the author suggested (*Trans. Faraday Soc.*, 1941, **37**, 772) that the essential difference between homolytic (*i.e.*, free-radical) substitution (in which all centres and not merely the ortho and para positions are subject to attack) and heterolytic (*i.e.*, polar) substitution was to be traced to the fact that whereas an attacking ion (such as NO_2^+) or a polar reagent perturbs an aromatic molecule whilst still at a distance, thus converting it by a tautomeric ($T \curvearrowright$) change into a transition state which is quite different from the mesomeric stable state, a neutral free-radical reagent, having no such polarising influence, attacks the normal aromatic molecule. Nevertheless, substitution processes of both types are essentially bimolecular, and the correct method of assessing the reactivity at various carbon atoms for any substitution process is therefore to estimate the energy difference between the normal state and the transition state of the aromatic molecule, as has been attempted by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), and not merely to evaluate local electron densities for any one structure. Even elucidative attempts to consider this energy difference lead to conclusions which help to elucidate the unsolved problems enumerated at the beginning of this paper.

Considering first *heterolytic substitution*, Hughes and Ingold and their colleagues have several times pointed out (cf. *J.*, 1937, 1257; 1941, 608) that in bimolecular aromatic substitution the incoming reagent must attack the aromatic ring at an angle from above the plane of the ring, displacing the ejected hydrogen atom downwards, as shown in (I). Consequently, the carbon atom at the point of attack becomes more nearly aliphatic in type, with a hybridised sp^3 -electron structure approaching that of methane, and the consequent electron redistribution within the aromatic ring [conventionally represented by Robinson's curved arrow (\curvearrowright)

symbolism] produces a transition state (II) of quasi-quinonoid character, in which the electron



orbits are much more closely defined than in a normal aromatic molecule. Though it is the substituent group, R, which, by its electron-donating or accepting capabilities determines essentially, in the benzene series, whether the transition state shall resemble (II), corresponding to para- (or similarly ortho-) substitution, or not (when the group R is electromerically inoperative the transition state involves a polarised C-H bond, as in meta-substitution), the actual energy-level of the quinonoid structure (II) with its comparatively localised double bonds very largely determines the rate of chemical change. Hence comparisons of the relative energy levels of the quinonoid transition complexes will help us in considering relative rates of substitution at different points in aromatic molecules. Without venturing into theoretical computations for these structures [which approximate to Wheland's "Type II" structures (*loc. cit.*)] we can deduce clear reasons for many features of aromatic substitution by comparison with oxidation-reduction potential data for corresponding quinones, following lines already suggested, in one restricted field, by Hammick and Mason (*J.*, 1946, 640). Some examples of this approach are given below.

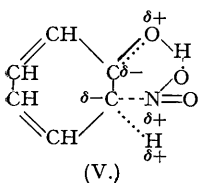
1. *The Ortho-Para Ratio.*—It is a significant feature of benzene substitution that para-substitution occurs much more easily than it should on a statistical basis, for this should give an ortho-para ratio of 2 : 1 except in cases of obvious steric hindrance.

Now the transition state for para-substitution is similar to that of a 1 : 4-benzoquinone (III), whilst that for ortho-substitution is similar to that of a 1 : 2-quinone (IV), and there



is an oxidation-reduction potential difference of about 0.1 volt between the 1 : 4- and the 1 : 2-benzoquinones, which is invariably of such sign that the 1 : 4- (or para-) quinonoid state has the lower energy content. This potential difference corresponds to an energy difference of *ca.* 4.5 kilocal. in the benzene series, and can clearly be associated with the structural fact that the 1 : 2-quinones have a large resultant dipole moment, and thus require extra electrostatic energy for their formation (*cf.* Waters, *J.*, 1933, 1551).

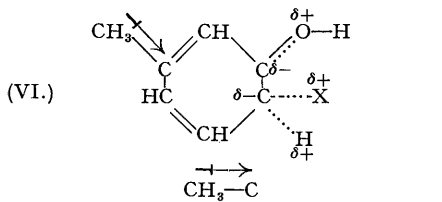
The inference to be drawn therefore is that the activation energy needed for the formation of the transition complex for para-substitution is significantly less than that required for ortho-substitution. Hence preferential para-substitution is to be expected in



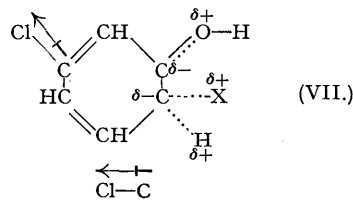
most cases. However variations in the ortho-para ratio can often be associated with the natures of the attacking reagent and the solvent used.

This is particularly true for nitration and sulphonation reactions of phenols, amines, and their derivatives. It seems therefore that chelation of the attacking group must be taken into account even in the transition state. Thus the ortho-nitration of phenol may well be favoured comparatively by the formation of a chelated transition complex such as (V) which can be compared with the transition complex which must be formed in the intramolecular Kolbe and Claisen rearrangements of phenol derivatives.

Again, polar groups in both the ortho- and the meta-positions to the "directing substituent" would undoubtedly affect the energy levels of the quasi-quinonoid complexes, possibly as follows :



reduces net dipole field and slightly favours ortho-substitution with respect to -OH



increases net dipole field and further diminishes ortho-substitution with respect to -OH

Though the available experimental evidence is most scanty (cf. Hollemann, "Die Direkte Einführung von Substituenten in den Benzolkern," 1910), it tends to support this view.

2. *Naphthalene Substitution.*—The oxidation–reduction potential difference of 0.085 volt between 1 : 2- and 1 : 4-naphthaquinones accords with the preferential substitution of naphthalene in the α -position. The quinonoid transition complex conception has more striking results when we come to consider the substitution of β -naphthol.

The transition state (VIII) corresponds to the structure of 1 : 2-naphthaquinone, whereas the state (IX) would have as its equivalent 2 : 3-naphthaquinone, which has never been prepared. We are justified therefore in saying that the transition state (IX) would require an exceedingly high energy of activation, essentially because it disturbs the benzenoid resonance-stability of two aromatic rings at the same time, and to this we can ascribe the exclusive monosubstitution of β -naphthol, and its many analogues, in the adjacent 1-position.

Naturally, substitution in the 5–8 positions in the other ring can occur in naphthalene, and also in quinoline and *isoquinoline* derivatives (to instance but a few) without the formation of a 2 : 3-quinonoid complex. In structure (VIII) we may presume that the unsubstituted

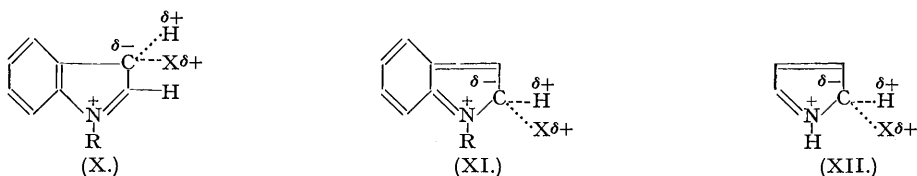


ring can still retain very closely the low energy level of normal benzene. If, however, we consider possible modifications of both rings, then the *amphi*-quinonoid structure also represents a transition state of lower energy than (IX), and indeed the disubstitution of β -naphthol occurs in the 6-position. Again, 2-methylnaphthalene sulphonates in the 6-position. To quote Fieser and Fieser ("Organic Chemistry," 1944, p. 773): "the *amphi* position exerts a definite control over the course of the heteronuclear substitution."

3. *Reactivity in the Quinoline, isoQuinoline, and Thiazine Series.*—In many papers Mills and his colleagues have related the activity of substituent methyl groups in quinoline, *isoquinoline*, and thiazole to the ease of formation of methylene bases from the corresponding quaternary salts (cf. Mills and Raper, *J.*, 1925, **127**, 2466). These methylene bases have, of course, quinonoid structures, but, even if we presume that this side-chain reactivity requires only the production of a transition state, the many striking differences between the reactive and the non-reactive positions in substituted heterocyclic bases (cf. Mills and Smith, *J.*, 1922, **121**, 2724) become obvious.

Bond fixation, or variations in local electron-density in the *normal* structures of heterocyclic systems (cf. Dewar, *Trans. Faraday Soc.*, 1946, **42**, 764, 767; Longuet-Higgins and Coulson, *ibid.*, 1947, **43**, 87) are of significance only in so far as they give a clue to the ease of the *initial* polarisation of such molecules on the approach of an electric charge. This necessarily occurs before the quasi-bonded transition state (which involves sp^3 -hybridisation) is formed, and, since an easily polarised state usually indicates an ensuing transition state of relatively low energy level, these calculations, when they can be made, which is unfortunately but seldom, are of great value.

Direct visualisation of the transition state is not only pictorially more explicative to the organic chemist but is a process which is capable of direct experimental application, for we can easily measure both the oxidation–reduction potentials of the relevant quinolines and those of the equilibria between the heterocyclic bases and their dihydro-derivatives, and thereby obtain cogent figures for comparing with the *relative* reactivities of different classes of heterocyclic bases towards polar substituting agents. Without proceeding thus far, we can already note as the inactive positions in heterocyclic systems those which would involve transition states analogous to that of the unknown 2 : 3-naphthaquinone.

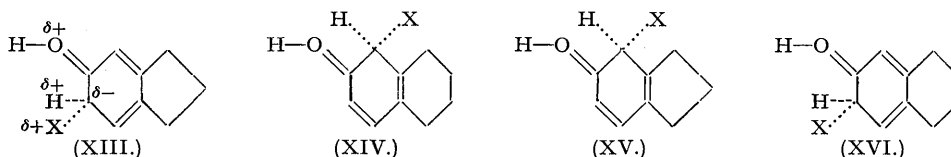


A comparison between pyrrole and indole is cogent in this connection. Pyrrole substitutes preferentially in the α -position, which, as Robinson (*loc. cit.*) has pointed out, is reached by

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an electron redistribution analogous to that which occurs on para-substitution (XII). Indole, in contrast, substitutes preferentially in the β -position, by attack of the same reagents which substitute pyrrole in the α -position. As (X) and (XI) indicate, the β -substitution of indole does not involve electron-redistribution in the benzene ring, though this is necessary for α -substitution.

4. *The Mills-Nixon Effect* (cf. *J.*, 1930, 2510).—The differences between the positions of bromination, and of coupling with diazo-compounds, of 5-hydroxyindane and *ar*-tetrahydro- β -naphthol are essentially differences of chemical reactivity, and not of chemical structure, though the dipole moment difference between dibromoindane and dibromotetralin is structural (Sidgwick and Springall, *J.*, 1936, 1532). As Longuet-Higgins and Coulson have pointed out (*Trans. Faraday Soc.*, 1946, **42**, 756) we can only find evidence for the reactivity difference (which is indeed most pronounced) by considering that the transition complexes (XIII) and (XIV) have lower energy contents than (XV) or (XVI). This becomes equivalent to Mills's



original viewpoint of bond-fixation, but it is bond fixation of the quinonoid state and not of the benzenoid state. In this connection we do know from *X*-ray data that the valency angles of the quinones are not identical with those of benzene, and that quinonoid molecules have a considerable degree of rigidity. Even a slight bond-deformation is bound to have a considerable effect on the oxidation-reduction potential of a quinone.

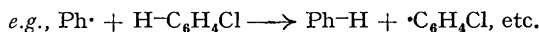
5. *Substitution of Higher Hydrocarbons*.—The prediction of the points of substitution of the polycyclic aromatic hydrocarbons from consideration of the "partial double-bond character" of the hydrocarbon itself is almost impossible, but it may be noted that in complex molecules, such as phenanthrene, chrysene, pyrene, and perylene, the usual polar substituting agents always attack the molecules at the same points as those which are converted into carbonyl groups in the most stable quinones which can be derived from these hydrocarbons by oxidation. These same points are also attacked first by reducing agents, so that in the hydrocarbons themselves bond-fixation of the same type occurs in the transition states developed by both cationoid and anionoid attack. Fries's rule (*Annalen*, 1927, **454**, 121) relating the stability of the quinonoid states of these higher aromatic hydrocarbons to the maximum number of Kekulé benzenoid rings which can be developed, does in fact involve the assumption of bond fixation in quinones. It may therefore be used as a guide to the position of substitution of polycyclic aromatic hydrocarbons.

Homolytic reactions, involving substitution by free neutral radicals, require somewhat different treatment. Since Wheland (*loc. cit.*) and others have attempted calculations on the totally unjustified assumption that free-radical substitution is always ortho-para, it is important first to recapitulate the facts. First, in no case is the reaction simple, so much so that the total isolated yield of primary substitution products from a free-radical substitution has seldom, if ever, been recorded as being over 40%. On account of the experimental difficulty of handling such reaction products, it has regularly happened that the less soluble, and much more crystallisable, para-substitution products have been isolated with comparative ease, whereas the other isomers, though probably present, have not been identified. The only available figures given for reaction yields (chiefly for reactions with pyridine, cf. Hey *et al.*, *J.*, 1940, 349) are too variable to warrant more than the conclusion that all possible isomers may be formed in comparable amounts (cf. Hey, *Ann. Reports*, 1940, **37**, 282).

Secondly, the rate of reaction is very fast with all the aromatic and heterocyclic substances that have yet been tested. The observed rates of reaction, for reactions involving diaroyl peroxides or aromatic diazo-compounds, are in fact the rates of free radical formation and not of radical substitution. However, the experiments of Fieser and his colleagues (*J. Amer. Chem. Soc.*, 1942, **64**, 2053, 2060) with free alkyl radicals indicate that quinones and aromatic nitro-compounds are substituted more easily than is benzene itself. Though these compounds can be attacked quite easily by anions (*e.g.*, OH^- , NH_2^-), free-radical substitution and substitution by anionoid reagents are not comparable, because free radicals are electrophilic and not nucleophilic reagents. There is, for instance, quite a difference between the free radical

substitution of pyridine in all three positions and the reaction of pyridine with sodamide which yields only the α -substituted product.

It is already evident that two types of homolytic substitution of aromatic systems must be considered: (a) attack on hydrogen:



which may, or may not, lead to the formation of biaryls characteristic of the initial radical, and (b) attack on nuclear carbon, as in the formation of a phenylpyridine from phenyl radicals and pyridine.

In type (a) reactions the transition state is a linear one with respect to the C—H bond of the aromatic molecule, and may never perturb seriously the benzenoid resonance-structure of the aromatic ring. Thus substituent groups in the attacked aromatic molecule ($\text{C}_6\text{H}_5\text{Cl}$ in the example quoted) would not be expected to influence very much the ease of radical attack on any individual C—H bond. Type (a) reactions should therefore proceed at approximately the same rate not only in all (ortho, meta, and para) orientation positions in any one aromatic or heterocyclic compound, but also at the various C—H bonds in different aromatic molecules.

Type (b) reactions do, however, perturb the electron-distributions within aromatic and heterocyclic rings much more seriously. The spatial arrangement of the radical-molecule complex is probably close to that of (I), and there will be some degree of bond localisation—rather like that of (II) but without the fractional polar charges—since the transition state is now a semi-quinone. Wheland has indicated that the redistribution of but one electron should lead predominantly to ortho-para reactivity even in nitrobenzene and pyridine. It will undoubtedly be difficult to check this calculation, though already preparative experiments indicate a predominance of para-product in the radical substitution of nitrobenzene and of ortho-substitution in the case of pyridine. However, it is already evident that the consideration of semi-quinonoid structures is important. Semi-quinones usually have such high energy levels that two-electron changes occur preferentially (as in most examples of the polarographic reduction of organic compounds), but nevertheless the reductions of many quinones and heterocyclic bases have been shown to be two-stage processes, involving semi-quinonoid radicals. These substances are certainly those which are attacked most easily by alkyl radicals derived from diacyl peroxides. Again, the action of nitrobenzene and nitrothiophen (Price, *J. Amer. Chem. Soc.*, 1943, 65, 757, 2380) in retarding radical-chain polymerisation has been ascribed to the facility of producing a radical-molecule adduct of comparatively low energy-level. When it becomes possible to investigate the substitution reactions of free radicals which have less intrinsic energy than free phenyl or free methyl, but more available energy than triphenylmethyl, we may well find that the points of chemical reactivity are those which will lead to the production of the most stable semi-quinones. Though it is pure speculation, it would be interesting to know whether the unusual metabolic hydroxylations of 1:2:5:6-dibenzanthracene and of 3:4-benzopyrene could in this way be classified as homolytic processes, for it does not by any means follow that the most stable semi-quinonoid structure derivable from a polycyclic hydrocarbon corresponds to the most stable quinonoid structure.

I have to thank several of my Oxford colleagues for their helpful comments on the applicability of these views.

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