[CONTRIBUTION FROM THE UNIVERSITY OF NOTRE DAME]

A Molecular Orbital Theory of Organic Chemistry. VI.[1] Aromatic Substitution and Addition

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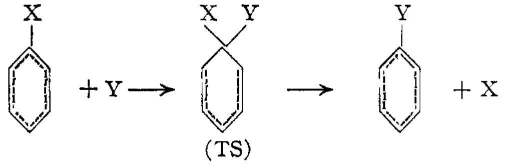
The results of Parts I–V are illustrated by their application to various reactions of aromatic compounds. It is shown that the predicted effects of annular heteroatoms and of substituents of all types on the rates of reaction and the orientation of the products agree qualitatively with the predictions of resonance theory. The present treatment leads also to semi-quantitative estimates of these effects, and of the relative rates of substitution at various positions in even AHs. (The validity of such calculations has been discussed in previous papers of this series.) The reactivities of even AHs in Diels–Alder reactions, and in reactions with osmium tetroxide, can also be estimated, the results agreeing reasonably with previous calculations,[5,6] and their significance in connection with carcinogenic activity is discussed. The problem of *o:p* ratios, etc., in substitution reactions is considered.

In Parts I–V[1] of this series, a general discussion of organic chemistry was given in terms of MO theory. Here the results will be illustrated by their application to some specific chemical problems, namely, the substitution and addition reactions of aromatic systems. It will be assumed that the transition state (TS) in a substitution reaction has the configuration postulated by Wheland,[3] in which the carbon atom undergoing attack has undergone a change in hybridization to sp^3 and is consequently removed from conjugation: *e.g.*



The activation energy ΔE may then be written in the form

$$\Delta E = C + \Delta E_\pi \qquad (1)$$

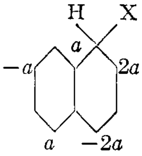
where C is a constant characteristic of the reagent and the replaced group and ΔE_π is the difference in π-electron binding energy between the initial and transition states. For a given type of substitution (X, Y constant), the activation energy ΔE, and so the rate of reaction, will be determined only by differences in ΔE_π. The transition state contains a mesomeric system similar to that in the initial state but lacking one carbon atom; in the case of electrophilic substitution it carries a formal positive charge relative to the initial state, in nucleophilic substitution a formal negative charge; in radical substitution there is no first order charge displacement.

(a) **Substitution in Alternant Hydrocarbons.**—In substitution of an even AH, the TS is an odd AH; for substitution by the three types of reagent the TS will be an odd AH cation, anion or radical. Since these differ only in the numbers of electrons present in the NBMO of the TS, which MO has zero energy, the term ΔE_π in (1) will be the same for substitution at a given position in a given even AH by reagents of all three types. The orientation of substitution, and the relative reactivity of different even AHs, should then be similar for all three types of reagent. This effect is known experimentally; thus naphthalene substitutes mainly α with electrophilic, radical and nucleophilic reagents.

In the case of an even AH, ΔE_π can be calculated at once from theorem 2 of Part II[1]

$$\Delta E_\pi = 2\beta(a_{or} + a_{os}) \qquad (2)$$

where a_{or}, a_{os} are the NBMO coefficients of the TS at the points of attachment to the center of attack. Thus for α-substitution in naphthalene the NBMO coefficients are as indicated in (I)



$$a = (11)^{-1/2}$$

I

hence $\Delta E_\pi = 2\beta(a + 2a) = 1.81\beta$. These energy differences ΔE_π may be called *localization energies* since they represent the energy required to localize reactive electronic groupings at specific atoms in even AHs. Values for substitution in different positions in a number of aromatic hydrocarbons are given in Table I, in units of β. The smaller the localization energy, the more readily should substitution occur.

The relative rates of substitution in different AH's have not been measured, but predictions made from Table I agree qualitatively with the information available. Thus reactivity rises in the series benzene < naphthalene < phenanthrene < anthracene < naphthacene < pentacene. The orientations predicted from Table I again agree in almost every case with those observed; *e.g.*, naphthalene (α), phenanthrene (9), anthracene (9), naphthacene (5), pyrene (3), chrysene (6), 1,2-benzanthracene (7), 3,4-benzpyrene (6).[4] Triphenylene is an exception, substituting 2 rather than 1; however, the predicted difference in reactivity between the two positions is small and the 1-position is sterically hindered. A second exception is the Friedel–Crafts acylation of 3,4-benzpyrene in the 1-position,[6] other substitution reactions giving 6-derivatives; it seems likely that in this case coördination with the electrophilic catalyst blocks the most reactive (6) position, leaving the next most reactive (1) position open to attack. Other cases are

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[1] For Parts I–V see THIS JOURNAL, **74**, 3341 ff. (1952).

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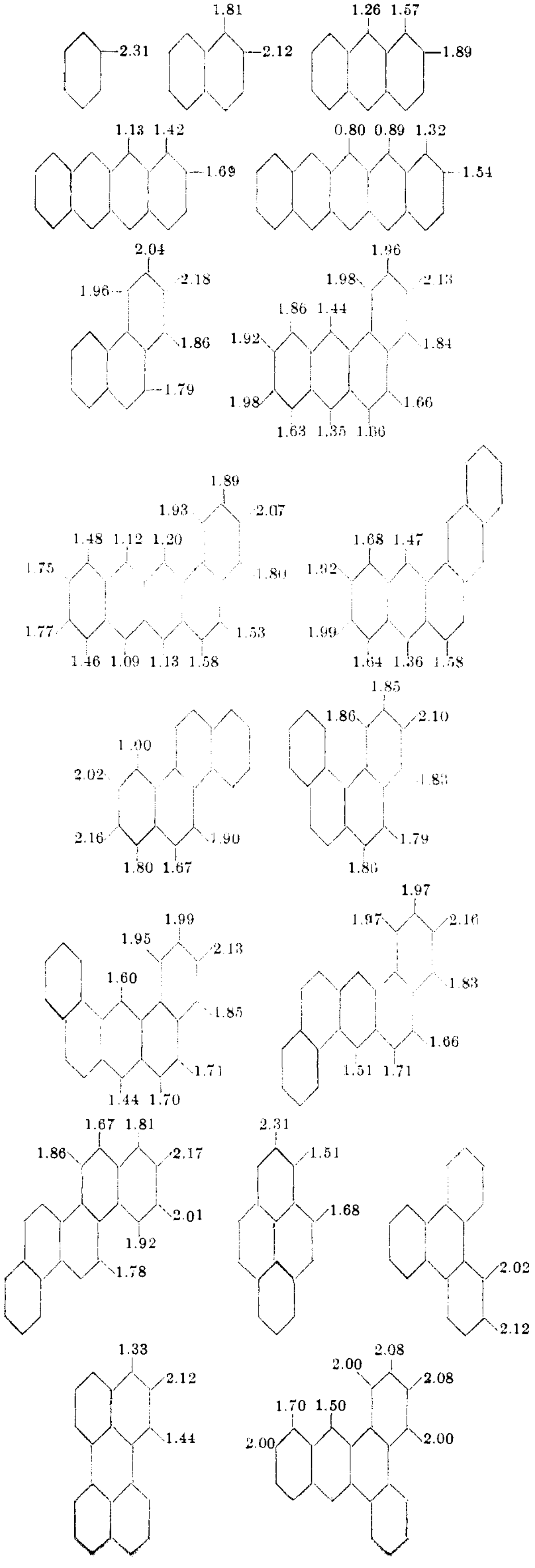
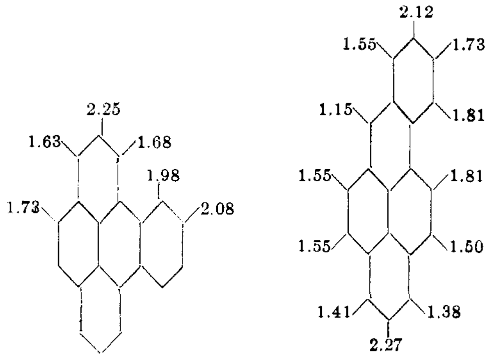
[3] G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

[4] For references see N. P. Buu-Hoi, P. and R. Daudel and C. Vroelant, *Bull. soc. chim.*, **16**, 211 (1949).

TABLE I

LOCALIZATION ENERGIES IN UNITS OF β

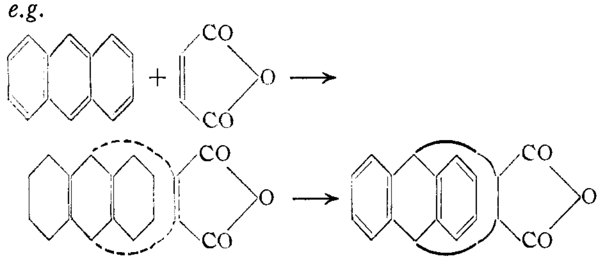




known where Friedel–Crafts reactions give unexpected products (*e.g.*, acenaphthene), probably for similar reasons.

Further work is desirable to check the predicted orientations in other ring systems, but it seems already likely that they will in general prove correct. Such calculations would then be of some practical value since the study of polynuclear hydrocarbons has been hampered by the difficulty of ascertaining the orientations of their derivatives.

(b) The Diels–Alder Reaction.—It is well known that many polynuclear aromatic hydrocarbons will undergo Diels–Alder reactions with active dienophiles such as quinone or maleic anhydride, and the evidence suggests that such reactions proceed by one-step processes through cyclic transition states; *e.g.*



Brown[5] pointed out that the energy difference between the initial and transition states should then

TABLE II

PARALOCALIZATION ENERGIES IN UNITS OF β, FOR THE MOST REACTIVE PARA POSITIONS IN SOME ALTERNANT HYDROCARBONS

Compound	Predictions by Brown[4] Points of attack	Predictions by Brown[4] E/β	This paper Points of attack	This paper E/β	Experiment[a] Points of attack (if any)
Benzene	1:4	4.00	1:4	4.62	....
Phenanthrene	1:4	3.77	1:4	3.82	....
Naphthalene	1:4	3.68	1:4	3.62	1:4 (?)
1,2-5,6-Dibenzanthracene	5:10	3.51	5:10	3.04	5:10
1,2-7,8-Dibenzanthracene	5:10	3.51	5:10	3.02	5:10
1,2-3,4-Dibenzanthracene	5:10	3.48	5:10	3.00	5:10
Pentaphene	5:14	3.45	5:14	2.83	5:14 + 8:13[b]
1,2-Benzanthracene	5:10	3.41	5:10	2.79	5:10
Anthracene	9:10	3.31	9:10	2.52	9:10
1,2-Benznaphthacene	5:12 6:11	3.36 3.28	5:12 6:11	2.33 2.21	6:11
Naphthacene	5:12	3.25	5:12	2.25	5:12
Pentacene	6:13	3.18	6:13	1.60	6:13

[a] The compounds are arranged in order of increasing reactivity to maleic anhydride, insofar as this is known. [b] As Brown[5] has pointed out, the monoadduct is a simple anthracene derivative, and should react more readily than pentaphene itself with maleic anhydride. In fact, only the double adduct can be isolated from the reaction.

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(5) R. D. Brown, *J. Chem. Soc.*, 691, 2730 (1950).

be related to the difference in π-electron energy between the parent AH and the AH, or pair of AH's, obtained by removing the two carbon atoms at which addition takes place. Brown estimated these *paralocalization energies* by an ingenious semi-empirical method for a number of hydrocarbons and showed that in fact Diels–Alder reactions are observed only when the corresponding paralocalization energy is small. These paralocalization energies can also be estimated approximately by the NBMO method, since to a first approximation the paralocalization energy should be equal to the sum of the individual localization energies at the two carbon atoms. Values so calculated are compared with the more accurate results of Brown in Table II, and it will be noticed that they show an excellent correlation with the accurate values and with the experimental evidence.

(c) **Oxidation with Osmium Tetroxide.**—The oxidation of AH's to dihydrodiols with osmium tetroxide is probably a reaction similar to the Diels–Alder reaction in that attack takes place simultaneously at two atoms in the hydrocarbon, but in this case the steric requirement is that the atoms should be directly linked to one another, *i.e.*, ortho and not para. The case of reaction should then run parallel to the π-electron energy difference between the parent AH and the AH obtained by removing those two atoms—*i.e.*, the *ortholocalization energy*. Brown[6] has shown such a parallel to exist. Here again, the ortholocalization energies can be estimated by the NBMO method, though a little more complexity is involved. Suppose the atoms removed are s and t, and let atom s be also linked to atom r, atom t to atom u in the parent AH. Let the NBMO coefficients of atoms r, t in the odd AH obtained by removing atom s be a_r, a_t, respectively; and the coefficients of atoms s, u in the odd AH obtained by removing atom t be b_s, b_u, respectively. Then it has been shown[1] that, to a first approximation, the orders of the various bonds are

$$\begin{aligned} p_{rs} &= a_r \qquad & p_{st} &= b_s \\ p_{st} &= a_t \qquad & p_{tu} &= b_u \end{aligned} \tag{3}$$

The two values for p_{st} will not in general agree, since they are approximate only; we may take their mean

$$p_{st} = \frac{1}{2}(a_t + b_s) \tag{4}$$

The ortholocalization energy is then given[1] approximately by

$$\begin{aligned} E_0 &= 2\beta(p_{rs} + p_{st} + p_{tu}) \\ &= \beta(2a_r + a_t + b_s + 2b_u) \end{aligned} \tag{5}$$

Values so calculated are compared in Table III with the accurate values obtained by Brown and with the results of experiment; the agreement is qualitatively excellent.[7]

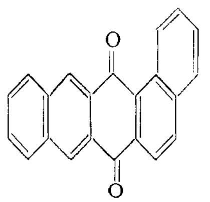
TABLE III

ORTHOLOCALIZATION ENERGIES OF SOME HYDROCARBONS

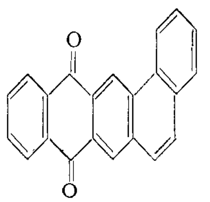
Hydrocarbon	Most reactive bond[a]	Ortholocalization energy[b] Calcd. Brown[8]	This paper
Benzene	1:2	3.53	3.46
Triphenylene	1:2	3.38	2.99
Naphthalene	1:2	3.26	2.68
1,2-3,4-Dibenzanthracene	5:6	3.24	2.70
Anthracene	1:2	3.20	2.16
Chrysene	1:2	3.12	2.08
3,4-Benzphenanthrene	1:2	3.10	2.23
1,2-Benzpyrene	6:7	3.08	2.02
Phenanthrene	9:10	3.07	2.15
Pyrene	1:2	3.06	2.35
1,2-5,6-Dibenzanthracene	3:4	3.05	1.94
1,2-7,8-Dibenzanthracene	3:4	3.04	1.99
1,2-Benzanthracene	3:4	3.03	1.90
1,2-Benznaphthacene	3:4	3.01	1.84
Pentaphene	6:7	3.01	1.74

[a] Both theoretical methods predict similar orientations for attack, and these agree with experiment in all cases that have been studied. [b] The definition of ortholocalization energy used here differs slightly from Brown's, the values here being uniformly greater by 2 β.

(d) **Oxidation to Quinones.**—The mechanism of oxidation of hydrocarbons to quinones is not known, but it can be deduced from the preceding results. If the oxidation involves a simultaneous attack at two carbon atoms, it should take place at the two atoms with the minimum combined localization energy; in 1,2-benzanthracene, these are the 5,6-positions, the ortholocalization energy for these being less than the 7,12-paralocalization energy. Since oxidation gives the 7,12-quinone, one may deduce that the first step is rather a one-center attack by some electron-deficient cation which takes place at the point with the smallest localization energy. The secondary attack should then take place in such a way as to give the most stable possible product; that is, at the position of opposite parity to the first with the largest combined localization energy provided the product is a Kekulé AH (in the case of *ortho* positions, this will be the ortholocalization energy calculated from (8); in other cases it will be the sum of the simple localization energies). These considerations lead correctly to the prediction that 1,2-benzanthracene should give the 7,12-quinone. Some further examples are given in Table IV; the case of 1,2-benznaphthacene is particularly interesting since it is not at all easy to predict on the basis of current theory whether the 7,14- (VII) or the 8,13-quinone (VIII) should be formed



VII



VIII

(e) **Biochemical Oxidation of Aromatic Hydrocarbons.**—An analogous argument suggests that the biochemical oxidation of hydrocarbons to dihydro-*o*-diols is a reaction akin to the osmium tetroxide oxidation, since it involves attack at double bonds and not at reactive meso positions; these reactions cannot therefore involve one-center attacks by radicals as some authors have suggested. However,

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(6) R. D. Brown, *J. Chem. Soc.*, 3249 (1950).

(7) The use of the NBMO method to calculate ortholocalization and paralocalization energies involves a cruder approximation than its use to calculate simple localization energies so a quantitative correspondence would not be expected in the former cases.

TABLE IV

PREDICTED ORIENTATION AND RELATIVE EASE OF ATTACK IN CrO_3 OXIDATION OF AROMATIC HYDROCARBONS TO QUINONES

Hydrocarbon	Predicted quinone	$\Delta E/\beta$ for primary attack	Quinone formed
Benzene	1,4	2.31	..
Naphthalene	1,4	1.81	1,4
Phenanthrene	9,10	1.79	9,10
Chrysene	1,2	1.67	1,2
Pyrene	3,8 + 3,10	1.51	3,8 + 3,10
1,2-Benzanthracene	7,12	1.35	7,12
Anthracene	9,10	2.16	9,10
Naphthacene	5,12	1.13	5,12
1,2-Benzonaphthacene	8,13	1.09	8,13
Pentacene	6,13	0.80	6,13

the reactions cannot be strictly analogous to the osmium tetroxide oxidations since the products are invariably *trans*-diols.[8] It seems more likely that in this case the first step is an addition of some biochemical acceptor to a double bond to form a π-complex, and that the latter then reacts with some nucleophilic reagent such as HO^- or H_2O to give a *trans*-diol derivative; the reaction would then be analogous to the usual electrophilic additions to olefins, which will be discussed in more detail in a later paper of this series.

(f) **Carcinogenic Activity.**—A. and B. Pullman noticed[9] that carcinogenic activity is shown only by hydrocarbons having a phenanthrene structure with a bare 9,10-bond which they called the *K-region* of the molecule. They found a semi-quantitative correspondence to hold between carcinogenic activity and a theoretical quantity which they termed the *total charge density of the K-region*, this being defined as the sum of the bond order of the K-region bond and the indices of free valency of the terminal atoms. It can be shown that the corresponding quantity in MO theory is linearly related to the ortholocalization energy of the K-region, being greater the less the ortholocalization energy. Accepting the empirical correspondence[10] between bond orders and free valencies determined by the MO and VB methods, this result implies that the first step in carcinogenic action is an attachment of the hydrocarbon to some acceptor grouping in the cell by one-step addition to the K-region bond. Undoubtedly this in itself cannot be the basis of carcinogenicity, since many hydrocarbons with low minimum ortholocalization energies are non-carcinogenic; but it does seem to eliminate from consideration free radical mechanisms for carcinogenesis. (It is still entirely possible that the preliminary association with cell constituents involves formation of π-complexes rather than simple adducts, the more so in view of the arguments from biochemical oxidation which were considered above.)

(g) **Addition vs. Substitution.**—Many reactive hydrocarbons, particularly the higher acenes, tend to undergo addition rather than substitution with the usual electrophilic reagents. Both reactions will of course proceed through similar intermediate cations, formed by addition of the reagent; addition should be favored by an increase in stability of this intermediate, prolonging its life, and by an increase in relative stability of the product. Addition should therefore be favored by a low localization energy at the point of primary attack, and a low combined localization energy (ortho- or para-) with some other position. These conditions are fulfilled especially well in the higher polyacenes, and also by the reactive K-regions of many phenanthrene derivatives; it is just these types of compound that tend to undergo addition instead of substitution.

(h) **Substitution in Alternant Heterocyclic Systems.**—The properties of alternant heterocyclic systems can be related to those of isoconjugate AHs, as Longuet-Higgins[11] has shown. The activation energy (ΔE of equation (1)) is given, for any heterocyclic compound, by

$$\Delta E = \Delta E_0 - \sum_r \alpha_r(q_r - q_r') \qquad (6)$$

where ΔE_0 is the corresponding activation energy for the isoconjugate AH; q_r, q_r' are the charge densities at atom r in the initial and transition states, respectively; and α_r is the coulomb term of atom r. If the heterocyclic compound is alternant, this becomes

$$\Delta E = \Delta E_0 - A \sum_r \alpha_r a_{or}^2 \qquad (7)$$

where a_{or} is the NBMO coefficient of atom r in the TS, and $A = +1, -1, 0$ for electrophilic, nucleophilic and radical substitution, respectively.

To a first approximation, $\alpha = 0$ for all atoms except the heteroatoms; equation (7) then implies, as Longuet-Higgins[11] pointed out, that a heteroatom should activate all positions of opposite parity to itself toward nucleophilic substitution and deactivate them toward electrophilic substitution; while the reactivities of positions of like parity to the heteroatom should remain unchanged. The magnitude of the effects can be estimated from equation (7): thus the NBMO coefficients of the TS (I) show that replacement of the 2- or 4-carbon atoms in naphthalene by nitrogen should activate the 1-position strongly to nucleophilic substitution and deactivate it strongly to electrophilic substitution, nitrogen atoms in the other ring having much smaller effects. 4-Chloroquinoline and 1-chloroisoquinoline do in fact undergo nucleophilic replacement of chlorine much more readily than does α-chloronaphthalene.

This treatment as it stands is inadequate since it predicts that positions of like parity to the heteroatom (*e.g.*, the β-positions in pyridine) should remain unaffected, and also that the heteroatom should have no effect on radical substitution.

Now in addition to its effects on the π-electrons a heteroatom will induce positive charges on adjacent carbon atoms, and so increase their effective electron affinities, by polarizing the intervening σ-

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[8] *Cf.* Biochemical Society Symposia No. 5; Biological Oxidation of Aromatic Rings, Cambridge, 1950.

[9] A. Pullman and B. Pullman, *Acta de l'Union Inter. c/le Cancer*, **6**, 57 (1948); *Bull. soc. chim. Biol.*, **31**, 343 (1949); *J. chim. phys.*, **46**, 212 (1949).

[10] C. A. Coulson, P. Daudel and R. Daudel, *Rev. Scientifique*, **85**, 29 (1947); *Bull. soc. chim.*, **15**, 1181 (1948).

[11] H. C. Longuet-Higgins, *J. Chem. Phys.*, **18**, 265, 275, 283 (1950).

bonds. Quantitative studies[12] of the inductive effect suggest that if the coulomb term of the heteroatom is α, that of an adjacent carbon atom will be changed to $\epsilon\alpha$, of a next-adjacent carbon to $\epsilon^2\alpha$ etc.; with $\epsilon \sim 0.3$. These carbon atoms will then affect substitution in accordance with equation (7). The most important effect is that of atoms adjacent, and therefore of opposite parity, to the heteroatom, since these will affect substitution at positions of opposite parity to themselves—*i.e.*, of like parity to the heteroatom. Consequently by this indirect action a heteroatom should also deactivate to electrophilic, and activate to nucleophilic, substitution positions of like parity to itself; although of course the direct effect on positions of opposite parity should be greater. It is well known that heterocyclic compounds undergo electrophilic substitution much less readily than do isoconjugate hydrocarbons, and that the deactivation is usually greater at positions of opposite parity to the heteroatoms (*e.g.*, the α,γ-positions in pyridine).

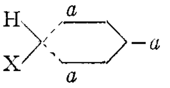
Free radical substitution should be facilitated by heteroatoms without any marked orientation, since according to theorem 60 of Part IV[1] heteroatoms at any position stabilize odd alternant radicals more than they stabilize even alternant systems. There should be a slightly greater activation of positions of opposite parity to the heteroatom but the difference should be small. The experimental evidence suggests that pyridine is substituted more readily by radicals than is benzene, and all three positions show similar reactivity.[13,14]

The idea that heteroatoms in unstarred positions should stabilize odd AH anions is supported[15] by the observation that β-picoline is much more acidic than toluene, the methyl group being alkylated readily by sodamide and methyl iodide.

Equation (7) cannot be tested experimentally at present for lack of experimental data.

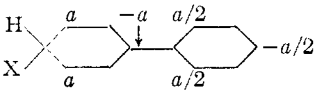
(i) **Effect of ±E Substituents.**—An AH bearing a $\pm E$ substituent is itself an AH, and substitution in it may be studied by the methods used in (a) above. It is interesting, however, to compare the substituted AH with the unsubstituted AH—*i.e.*, to determine the effect, if any, of the substituent. The analysis need be carried out only for hydrocarbons since in the present approximation the effects of different structural changes will be additive. (Additivity has also been established experimentally for the combined effect of two or more substituents on substitution.[16])

If the substituent is attached at an inactive position in the TS, it will not affect the NBMO of the latter since the substituted TS will be cross-conjugated. Hence a $\pm E$ substituent has no first-order effect on the rate of any mode of substitution involving a TS in which the substituent is attached at an inactive atom. It is also easily seen that a $\pm E$ substituent at an active position will not alter the relative magnitudes of the NBMO coefficients of the TS, but it will reduce their absolute magnitudes since the NBMO now spills over into the substituent. This will be clear from a comparison of the TS's (IX) and (X) for substitution in benzene and diphenyl. It follows that a $\pm E$ substituent should facilitate substitution of all types at positions of unlike parity to its point of attachment, which conclusion agrees qualitatively with that of current theory.



$a = (3)^{-1/2}$

IX



$a = (3.75)^{-1/2}$

X

A semi-quantitative estimate of $\pm E$ activity of a $\pm E$ substituent S may be given by extending this argument. Suppose S is attached to an odd AH R at an active position r. Let the NBMO coefficient of r in RS be a_r, and let the NBMO coefficients of active atoms in S in RS be b_s. Then an estimate of the $\pm E$ activity of R is given by the quantity $A^{\pm}$, defined by

$$A^{\pm} = a_r^{-2} \sum_s b_s^2 \qquad (8)$$

since $A^{\pm}$ is a measure of the extent to which the zero MO of R spills over into S, and it is easily seen that $A^{\pm}$ is characteristic of S and independent of the substrate R. Some such values are given in Table V.

TABLE V

Substituent	$A^{\pm}$
$-CH{=}CH_2$	1
$-CH{=}CH-CH{=}CH_2$	2
—Ph	0.75
$-CH{=}CHPh$	1.75
α-Naphthyl	1.49
β-Naphthyl	1.37
9-Anthryl	1.87
$-CH{=}CPh_2$	2.5

Again, few experimental results are available to check these values but they seem qualitatively reasonable. For instance, the basic strengths of aromatic amines are less than those of aliphatic amines since the conjugation between nitrogen and the ring in the former is broken in the salt; the decrease in basic strength is then a measure of the conjugating power of the $\pm E$ substituent attached to nitrogen. Hence the decrease in basic strength in the series aniline > β-naphthylamine > α-naphthylamine implies increasing $\pm E$ activity in the series Ph < β-naphthyl < α-naphthyl as predicted from Table V.[17]

The effect of $\pm E$ substituent on the ease of a reaction such as substitution can be expressed in terms of its $A^{\pm}$. Let the NBMO coefficient of the un-

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(12) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," New York, N. Y., 1946; J. C. McGowan, *Chemistry and Industry*, 632 (1948); *cf.* M. J. S. Dewar, *J. Chem. Soc.*, 463 (1949).

(13) *Cf.* D. H. Hey and E. W. Walker, *ibid.*, 2213 (1948). The *o*-isomer predominates, presumably through selective activation of positions adjacent to nitrogen, as discussed in section (n) below.

(14) Notice that Wheland[8] had predicted significantly greater reactivity in the α,γ-positions. Here the present treatment seems more satisfactory than the MO method, to which it is only a first approximation. The same curious situation has arisen much more forcibly in a study of light absorption and a possible explanation will be given in papers dealing with that problem. Such discrepancies cannot reasonably be held against the present treatment so long as they continue to operate in its favor.

(15) H. C. Brown and W. A. Murphey, Abstracts of 119th Meeting of the American Chemical Society, 1951.

(16) A. F. Holleman, "Die Direkte Einfuhrung von Substituenten in den Benzolkern," 1910; *Chem. Revs.*, **1**, 187 (1925).

(17) It is easily shown that the effect of the $\pm E$ group in this connection should run parallel to its $\pm E$ activity.

substituted TS at the point of attachment of the substituent be a_r, and the energy difference between the unsubstituted initial and transition states be ΔE_0. Then the corresponding energy difference ΔE_s for the substituted TS is given approximately by

$$\Delta E_s = \Delta E_0(1 + a_r^2 A^{\pm})^{-1/2} \tag{12}$$

Note that if the substituent is attached to an inactive atom, $a_r = 0$ and $\Delta E_s = \Delta E_0$, as stated earlier. Note also that a_r will be greatest for substitution in the ring bearing the substituent, so that the effect of the latter tends to be localized (*cf.* the effect of heteroatoms in heterocyclic systems).

(j) **+E Substituents.**—The effects of $+E$ substituents can be derived from those of equivalent $\pm E$ substituents in the same way that the properties of heterocyclic compounds were derived from those of equivalent AH's. The effect will fall into two parts; the first identical with that for the equivalent $\pm E$ substituent, the second a measure of energy changes due to changes in charge density at the heteroatoms. Since these will vanish (approximately) if the substituent is attached to a neutral AH, the effect of the $+E$ substituent R^+ will then be approximately the same as that of the equivalent $\pm E$ substituent R. Differences arise when the $\pm E$ substituent is attached to an active atom in an odd AH ion. In the notation of the previous section, it is easily shown that the stabilizing effect on the odd AH ion S is given by

$$\Delta E^{+} = \Delta E^{\pm} \pm a_r^2 d^2 \alpha_s (1 + a_r^2 A^{\pm})^{-1} \tag{13}$$

where

$$d_s = b_s/a_r \tag{14}$$

d_s being defined to be a characteristic of R, and α_s being the coulomb term of atom S in R. The sign is negative for odd AH anions, positive for odd AH cations. This result implies that a $+E$ substituent at an active atom stabilizes an odd AH anion more efficiently, an odd AH cation less efficiently, and an odd AH radical about as efficiently as does the equivalent $\pm E$ substituent.

Attempts to apply (13) quantitatively must again be deferred for lack of data, but one point may be emphasized. In the case of nucleophilic substitution, both terms in (13) have like signs and so one can predict unambiguously that a $+E$ substituent will direct such substitution into positions of unlike parity to its point of attachment. In the case of electrophilic substitution, however, the terms have opposite signs; if $\Delta E^{\pm}$ predominates, the substituent will be "*o,p*-directing," if the sum, then it will be "*m*-directing." The greater the $A^{\pm}$ of the equivalent $\pm E$ substituent the greater $\Delta E^{\pm}$; and the smaller the proportion of heteroatoms in the substituent, the less the sum. In this way the apparent anomaly of the —CH=CH—COR group (which is *o,p*-directing) can be very satisfactorily explained; in it the *o,p*-directing term $\Delta E^{\pm}$ outweighs the *o,p*-unidirecting sum.

(k) **Effect of ±E Substituents on Radicals and Ions.**—At this point it will be convenient to consider the effect of a $\pm E$ substituent R on the stability of a simple methyl ion or radical. At first sight it might appear that there would be no first-order difference in π-electron energy between R and RCH_2, since the first-order perturbation energy vanishes, just as the total π-electron energy of RS, S being an even AH, is to this approximation the same as the sum of the π-electron energies of R and S. However, in forming RCH_2, the zero energy AO of CH_3 remains unchanged, while all the bonding MO's of R are depressed; whereas in RS, some of the bonding MO's are depressed, others raised. The net effect is therefore much greater in the former case, and it can be estimated approximately as follows. Let the π-electron energy of R be ΔE_0, and its $\pm E$ activity be $A^{\pm}$. Then the π-electron energy of $RCH{=}CH_2$, ΔE_1, is given approximately by

$$\Delta E_1 = \Delta E_0 - 2\beta \tag{15}$$

Let the π-electron energy of RCH_2 be ΔE_2. The NBMO coefficient of the methylene is given by $(1 + A^{\pm})^{-1/2}$. Hence

$$\Delta E_1 \simeq \Delta E_2 - 2\beta(1 + A^{\pm})^{-1/2} \tag{16}$$

Combining (15) and (16), the stabilizing effect of R on CH_3 is given approximately by

$$\begin{aligned}\Delta E &= \Delta E_0 - \Delta E_2 \\ &= 2\beta(1 - (1 + A^{\pm})^{-1/2})\end{aligned} \tag{17}$$

which is very approximately $A^{\pm}\beta$. Hence $A^{\pm}$ should be a measure of the stabilizing effect of the substituent. It is easily seen that the same should apply for ions. Although the chemical evidence is obscured by steric effects, it does suggest that the stabilizing effect on both ions and radicals rises in the series Ph < β-naphthyl < α-naphthyl < 9-anthryl as Table V requires.

(l) **−E Substituents.**—The effects of $-E$ substituents can again be derived from those of hydrocarbon equivalents; here odd AH anions. Only the simplest case need be considered, that of monatomic $-E$ substituents (MeO, Me_2N, etc.), equivalent to the group $-CH_2^-$. One complication arises; if X is a heteroatom, the CX and CC resonance integrals are not in general the same, and allowance must be made for this in calculating the NBMO coefficients (*cf.* Theorem 7 of Part I[1]). For the present this complication will be neglected.

The approximate stabilizing effect ΔE^- of a $-E$ substituent R on an even AH S can be written down from the results of section (i)

$$\Delta E^- = 2\beta(1 - (1 + A^{\pm})^{-1/2}) + \alpha(1 - (1 + A^{\pm})^{-1}) \tag{18}$$

where $A^{\pm}$ is the $\pm E$ activity of S, regarded as a $\pm E$ substituent. It follows that the effect of R should be greater, the greater α and certainly mesomeric stabilization falls in the series $PhCH_2^-$ > $PhNH_2$ > PhOH > PhF, the series of increasing electron affinity of the $-E$ groups. (Of course changes in β must also be taken into account, but in this series they are probably small.)

The stabilizing effects on odd alternant systems can also be written down; if R is attached at a point with NBMO coefficient a_s, then

$$\Delta\epsilon = n\beta a_s + n\alpha/2 \tag{19}$$

where n = 0, 1 and 2 for odd AH anions, radicals and cations, respectively. Hence to a first approximation, a $-E$ substituent at an active position stabilizes an odd AH cation strongly, an odd AH radical less strongly, and an odd AH anion not at all. At an inactive position such a substituent should have no first-order effect.

Consider now the differences in total π-electron energy between the initial and transition states for substitution of an even AH R, and of RCH_2^-. Let CH_2^- be attached to atom s in the TS from R, the NBMO coefficient there being b_s, and let the energy difference be ΔE_0, ΔE_s for R, RCH_2^-, respectively. Then from (18) and (19)

$$\Delta E_s = \Delta E_0 - nb_s\beta + 2\beta(1 - (1 + A^{\pm})^{-1/2}) \quad (20)$$

where $n = 2$ for electrophilic, 1 for radical, and 0 for nucleophilic substitution. For substitution at various positions in the AH, the final term in (20) will remain approximately constant; also when $b_s = 0$, $\Delta E_s > \Delta E_0$. Hence the substituent (CH_2^-) should deactivate R to nucleophilic substitution at all positions, and to radical or electrophilic substitution at points of like parity to the point of attachment of the substituent, and it should accelerate radical or electrophilic substitution at other positions. These conclusions agree in general with current theory and experiment although detailed quantitative information is still lacking. The effect of replacing CH_2^- by a heteroatomic $-E$ substituent can be discussed only for electrophilic substitution which is fortunately the most important case; we then have

$$\Delta E_s = \Delta E_0 - 2b_s\beta + 2\beta(1 - (1 + A^{\pm})^{-1/2}) - \alpha(1 + A^{\pm})^{-1} \quad (21)$$

The change has the effect of deactivating the whole of R to substitution, since the last term in (21) will be roughly independent of the point of attack. The predicted orientation of substitution remains unaffected. This conclusion again resembles that from current theory.

(m) **Activities of $+E$ and $-E$ Substituents.**—It is less easy to find concise definitions of $+E$ or of $-E$ activity analogous to that of $\pm E$ activity. The best measure seems to be the difference (A^+) in π-electron energy between RH and RCH_2^- for a $+E$ substituent R, and the difference (A^-) between SH and SCH_2 for a $-E$ substituent S. In the notation of the previous sections

$$A^+ = 2\beta(1 - (1 + A^{\pm})^{-1/2}) - \sum_s d_s^2\dot{\alpha}_s(1 + A^{\pm})^{-1}$$
$$A^- = 2\beta b_s + \sum_s b_s^2\alpha_s \quad (22)$$

the sums in each case being over the heteroatoms in the substituents, and also over any carbon atoms whose electron affinities are appreciably altered by inductive effects. A quantitative test of (22) must be deferred for lack of adequate data.

(n) **Ortho–para Ratios, etc.**—The first-order treatment given above often predicts identical reactivities for positions in molecules which in fact are known to differ chemically; the ortho and para positions in monosubstituted benzenes are good examples. This problem has been discussed elsewhere[18] and it was shown that the discrepancies could be ascribed to the changes in electron affinity of carbon atoms adjacent to heteroatoms, brought about by the inductive ($+I$) effects of the latter. Here similar conclusions will be reached by a simpler and more general argument, using the results obtained in section (h) above.

Consider the TS for a substitution reaction; the carbon atom r at which attack takes place is linked by four σ-bonds, and since its environment will have relatively little selective influence on these, the charge density q_r at that atom will be approximately the same for various substitution reactions with a given reagent. Suppose the coulomb term of the atom to be α_r, and the charge density in the initial state to be q_r'. Then the π-electron energy difference ΔE_r between the initial and transition states is given to a second approximation by

$$\Delta E_r = \Delta E_r' + \alpha_r(q_r - q_r') \quad (23)$$

where $\Delta E_r'$ is the first approximation obtained previously. Evidently this second-order effect leads to a selective activation of positions adjacent to heteroatoms or heteroatomic substituents (with $+I$ activity) if those positions were electron-deficient (low q') in the initial state; and to a selective deactivation if those positions were electron-rich. Since σ-bonds have low polarizabilities, we may take $q_r = 1$ in (23) as a first approximation; and the charge distributions brought about by various substituents have been deduced in earlier papers of this series.[1] From these considerations it follows that positions adjacent to cyclic heteroatoms or $+E$ substituents should be selectively activated, and positions adjacent to $-E$ substituents selectively deactivated, to substitution. These conclusions agree with those reached previously[16] and with experiment; thus the $o:2p$[19] ratio is less than unity for substitution of $-E$-substituted benzenes, and greater than unity for substitution of $+E$-substituted benzenes, and the effect increases with the $+I$ activity of the substituent.[18]

It should be emphasized that this electronic influence on $o:p$-ratios etc., may be outweighed by steric effects or hydrogen bonding; such extraneous factors have been discussed elsewhere.[18] It should also be noted that similar factors may arise in ring systems other than benzene, and may even be transmitted to neighboring rings; thus nitration of quinoline gives comparable amounts of 5- and 8-nitroquinoline, although the analysis given previously would suggest that the 5-position should be selectively deactivated; however, the 8-position is only two bonds removed from the nitrogen, which under the conditions of the reaction will be present as the highly positive ion $\geqslant\overset{+}{N}H$; selective inductive deactivation of the 8-position might therefore be expected. In the case of α-nitronaphthalene, where the nearest heteroatom is now three bonds away from the 8-position, nitration gives predominantly 1,8-dinitronaphthalene, in spite of the fact that formation of this isomer must involve considerable steric hindrance.

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[18] M. J. S. Dewar, *J. Chem. Soc.*, 463 (1949).

[19] The factor 2 is a statistical factor allowing for the fact that there are 2 ortho positions, but only one para.