

105. *A Theoretical Discussion of o : p Ratios and Orientation in Benzene Substitution.*

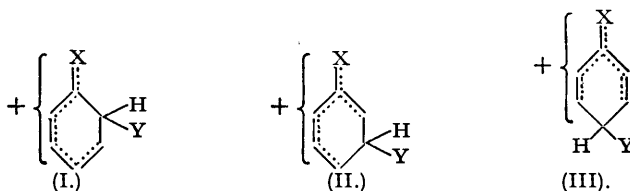
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Wheland's method (*J. Amer. Chem. Soc.*, 1942, **64**, 900) has been used to investigate the relation between directive power and electron affinity of substituents in cationoid benzene substitution, and in particular the relation to *o* : *p* ratios in substitution. The general problem of orientation is then considered and the various factors discussed. The electrostatic treatment of reaction rates is criticised.

It has long been known that substituents in benzene can be divided into two main classes, meta-directing and ortho-para-directing in cationoid substitution. An electronic interpretation of this distinction was given some time ago by Robinson [cf. "Outline of an Electro-chemical (Electronic) Theory of the Course of Organic Reactions", Institute of Chemistry, 1932; *J. Soc. Dyers Col.*, Jubilee Issue, 1934, 65] and by Ingold (cf. *Chem. Reviews*, 1934, **15**, 225), and a quantum-mechanical justification for the earlier theory has been devised by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900). Two points still remain unclear however; the large variation in *o* : *p* ratios in benzene substitution, and the precise factor which determines the relative orienting power of substituents of the same type.

Wheland's method (*loc. cit.*) has now been extended in the hope of finding qualitative solutions to those two problems; and the whole problem of orientation is then discussed in a general way.

Method.—Following Wheland, we assume that the transition state for *o*-, *m*-, and *p*-cationoid substitution of a benzene derivative PhX by Y^+ have the mesomeric structures (I), (II), and (III) respectively; that the group CHY is similar in all three transition states; and that CHY does not conjugate with the rest of the ring. The activation energies for *o*-, *m*-, and *p*-substitution will then run parallel to the differences in total π -electron energy between PhX, and (I), (II), and (III) respectively. These assumptions seem reasonable first approximations, although CHY will probably hyperconjugate markedly with the ring—*i.e.*, the transition states will only approximate to these extreme quinonoid forms.



In calculating the π -electron energies by the simple molecular-orbital method, several new parameters are involved besides the usual C-C exchange integral β . These are (1) the C-X exchange integral γ ; (2) the electron affinity of X relative to carbon δ ; (3) the change in electron affinity of the annular carbons due to the inductive effect of X. To make the calculations manageable, some simplifying assumptions must be introduced.

First, it is likely, from considerations of π -bond energies, that for the usual substituents $\gamma \simeq \beta$, and moreover calculation shows that moderate variations in γ do not qualitatively alter the relative stabilities of (I), (II), and (III). Therefore the calculations have been carried out only for $\beta = 1$ (electromeric substituent) and $\beta = 0$ (inductive substituent). Secondly, if the polarisability of a bond is independent of field strength—a reasonable first approximation—the change in electron-affinity due to induction should die away along a carbon chain by a constant factor for each bond. We may therefore assume that the electron affinity of C_1 in PhX (the carbon linked to X) is $\epsilon\delta$, of the *o*-carbons $\epsilon^2\delta$, etc. This assumption is justified by some work by Branch and Calvin (*cf.* "The Theory of Organic Chemistry", New York, 1941) who find that this relation holds in a number of cases with $\epsilon \simeq \frac{1}{3}$. Since calculation shows that the conclusions reached here are not qualitatively affected by changes in ϵ , it has been assumed throughout that $\epsilon = \frac{1}{3}$; so that the change in electron affinity of C_1 is $\delta/3$, of C_2 or C_6 $\delta/9$ etc.

Wheland calculated the subsidiary electron-affinity changes by a variation method, minimising the total π -electron energy. This procedure is both complicated and incorrect; for the changes in electron affinity are largely due to induction of σ -electrons, and Wheland neglects the corresponding changes in σ -electron energy. The present treatment seems at least equally valid.

A further, and much more serious, criticism of Wheland's method applies also to the present work. The application of the molecular-orbital method to ions, using the parameters that hold for neutral molecules, is not strictly justifiable. (This point has been discussed in detail elsewhere by Coulson and Dewar, *Trans. Faraday Soc.*, in course of publication.) However there are good grounds for believing that any errors so introduced will apply alike to all the calculations reported here, so that the relative values of the *o*-, *m*-, and *p*-activation energies should be reliable.

Substituents can be divided into three electronic types; pure inductive substituents, and anionoid and cationoid electromeric substituents. Those of the first type will be represented by the present model with $\gamma = 0$. As a model of an anionoid electromeric ($-E$)^{*} substituent we may take X to be an atom with an unshared electron pair; thus there will be eight π -electrons to be fitted into the four lowest-energy orbitals of PhX, and six to fit into the three lowest-energy orbitals of (I), (II), and (III). As a model of a cationoid electromeric ($+E$) substituent, we take X to be an atom with a vacant orbital; so that PhX will contain six π -electrons, and each transition state four.

The calculations have been carried out for various values of δ ranging from -1 to 3 , and the results are shown graphically in Figs. 1—3; the quantity ΔE being the difference in π -electron energy between PhX and the corresponding transition state, in units of β (in this approximation

* The sign convention of Robinson (*loc. cit.*) has been used throughout since it seems more logical than that of Ingold (*loc. cit.*). The latter would describe $-NMe_3^+$ as a negative, $-O^-$ as a positive substituent.

$\beta \approx 18$ kcal./mol.). Calculation of dipole moments suggests that few, if any, substituents fall outside the range $-1 < \delta < 2$.

Conclusions.—The electronic theory of organic reactions assumes that differences in reaction rates are due only to activation energy differences, the steric factor (or the entropy of activation) being constant. With this assumption we can deduce from Figs. 1—3 the following rules for cationoid substitution of PhX, if in fact orienting power is determined mainly by the electron affinity of X.

(1) The overall rate of substitution should fall with increasing electron affinity of X for each class of substituent.

(2) For a $-I$ (anionoid inductive) substituent the order of rates should be $o > p > m$; for a $+I$ substituent, $m > p > o$. In both cases the spread of relative rates should increase with I -activity of X.

(3) For a $-E$ substituent, $(o, p) \gg m$; and with increasing δ , the ratio $o : p$ should fall. For $\delta = 0$, the ratio $o : p$ should be about unity.

(4) For a $+E$ substituent, $m \gg (o, p)$, and the directive power should increase with δ for normal values of δ ; but the $o : p$ ratio should increase with δ in the same range. The $o : p$ ratio should always be considerably greater than unity.

Comparison with Experiment.—(1) It is well known that the rate of substitution in a series of similarly substituted benzenes falls with increasing electron affinity of the substituent. The

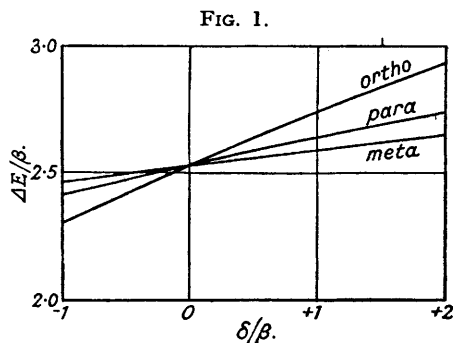
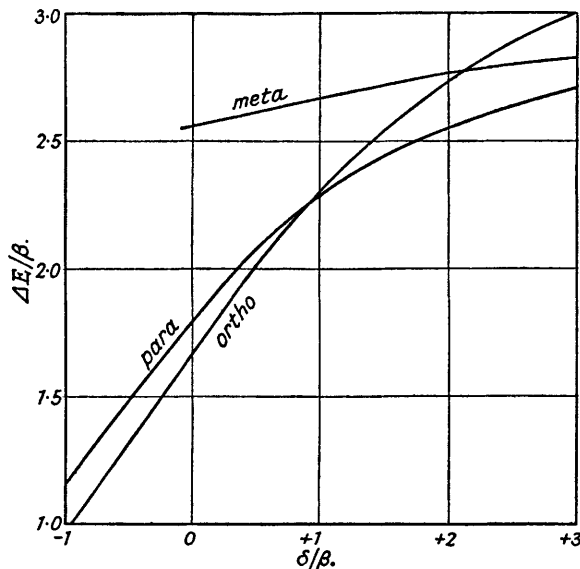


FIG. 2.
Anionoid electromeric ($-E$) substituent.



effect is shown clearly by the relative rates (benzene = 1) of nitration of the halogeno-benzenes under standard conditions, determined by Ingold and Shaw (*J.*, 1927, 2918), *viz.*, PhI > 1 , PhBr 0.36, PhCl 0.027, PhF 0.0107.

(2) The effect of increasing δ in an inductive substituent is shown well by the orientation of nitration in the ω -chlorotoluenes (Table I) [the data throughout this paper are taken from Holleman ("Die direkte Einföhrung von Substituenten in den Benzolkern", 1910, and *Chem. Reviews*, 1925, 1, 187) and Beilstein except where specifically stated]. Chlorine substituents, which increase the electron affinity of methyl, lower the $o : p$ ratio and increase the $m : (o, p)$ ratio (the ratios given are corrected for the statistical factor, and give the relative rates of substitution in single positions of each type). The $o : p$ ratios are smaller than the present discussion would

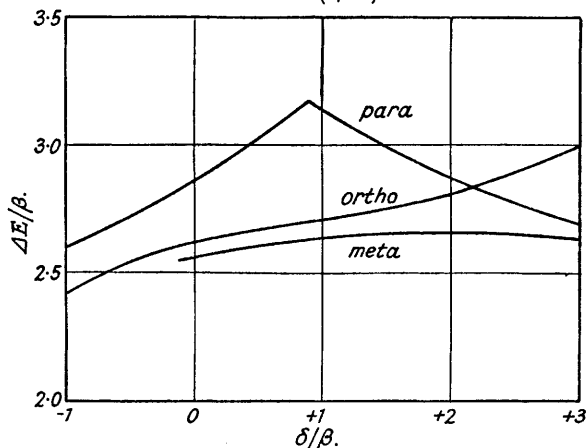
TABLE I

Compound.	<i>o</i> , %.	<i>m</i> , %.	<i>p</i> , %.	$\frac{1}{2}o : p$.	$\frac{1}{2}m : (\frac{1}{2}o + p)$.
Ph·CH ₃	58.8	4.4	36.8	0.80	0.03
Ph·CH ₂ Cl	40.9	4.2	54.9	0.37	0.02
Ph·CHCl ₂	23.3	33.8	42.9	0.27	0.31
Ph·CCl ₃	6.8	64.5	28.7	0.12	1.09

lead one to expect; but this difference can probably be ascribed to slight steric hindrance, the frequency factor for *o*-substitution being smaller than for *p*- (see below).

Other compounds Ph·CH₂Z, when Z has a high electron affinity (*e.g.*, Ph·CH₂⁺NMe₃), also substitute in the order *m* > *p* > *o*. Possibly Ph·SO₃H is another example; the -SO₃H group seems to be a +*I* rather than a +*E* substituent, judging by its inefficiency in activating an adjacent methylene group. Substitution of Ph·SO₃H gives appreciable quantities of *p*-derivatives as by-products, but no detectable amount of *o*-. Diphenyliodonium nitrate, Ph₂I⁺NO₃⁻, also gives some (14%) *p*-, but no *o*-derivative on nitration (Sandin, McClure, and Irwin, *J. Amer. Chem. Soc.*, 1939, **61**, 3061).

FIG. 3.

Cationoid electromeric (+*E*) substituent.

(3) The effect of increasing electron affinity in a -*E* substituent is shown clearly by the data in Table II for nitration of the halogeno-benzenes. Electron affinity rises in the series I < Br < Cl < F, and the *o* : *p* ratio falls in the same order. The effect is also shown by the *o* : *p* ratios in the series Ph·Ph, Ph·NHAc, Ph·OMe, PhF (Table II); electron affinity rises along the series Ph < NHAc < OMe < F, and the *o* : *p* ratio falls.

TABLE II.

X in PhX.	<i>o</i> , %.	<i>m</i> , %.	<i>p</i> , %.	$\frac{1}{2}o : p$.	X in PhX.	<i>o</i> , %.	<i>m</i> , %.	<i>p</i> , %.	$\frac{1}{2}o : p$.
I	41.1	—	58.7	0.35	Ph	53	—	47	0.56
Br	37.6	—	62.4	0.30	NHAc (a)	40.7	—	59.3	0.34
Cl	30.1	—	69.9	0.22	OMe	20	—	80	0.10
F	12.4	—	87.6	0.07					

(a) In 80% HNO₃.

Further evidence is provided by the nitration of acetanilide in strongly acid media. Under these conditions acetanilide forms a salt, Ph·NH⁺CMe₂OH, and the group NH⁺CMe₂OH must have a much higher electron affinity than -NHAc. Therefore increase in acidity of the solvent should lower the *o* : *p* ratio, an effect shown by the data in Table III (nitration at -20°). It will be noticed that salt-formation does not alter the *o* : *p* orienting effect of -NHAc. It is of course well known that salt-formation in aniline leads to *m*-direction, the group -NH₃⁺

TABLE III.

Nitrating agent.	<i>o</i> , %.	<i>p</i> , %.	Nitrating agent.	<i>o</i> , %.	<i>p</i> , %.
80% HNO ₃	40.7	59.3	HNO ₃ -90% H ₂ SO ₄	4.5	95.5
90% HNO ₃	24.5	75.5	HNO ₃ -100% H ₂ SO ₄	—	100

having no electrons free for conjugation; this result confirms that the proton in $(\text{Ph}\cdot\text{NHAcH})^+$ is attached to oxygen and not to nitrogen.

(4) Substitution of $+E$ -substituted benzenes gives appreciable quantities of o -, but hardly any p -derivative, together with the dominant m -derivative. Some examples are given in Table IV; the $o:p$ ratio rises with increasing $+E$ activity, *i.e.*, in the series $\text{CO}_2\text{Et} < \text{CO}_2\text{H} < \text{NO}_2$, which is probably the order of increasing δ . (The data are for nitration at 0° .)

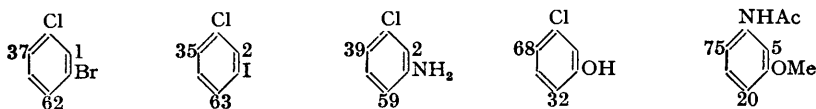
TABLE IV.

X in PhX.	o , %.	m , %.	p , %.	$\frac{1}{2}o:p$.	$\frac{1}{2}m:(\frac{1}{2}o+p)$.
CO_2Et	28.3	68.4	3.3	4.3	2.0
CO_2H	18.5	80.2	1.3	7.1	3.8
NO_2	6.4	93.2	0.25	12.8	13.5

No attempt has been made to calculate from the observed $o:m:p$ ratios the corresponding activation energy differences, and to compare these with values calculated from Figs. 1—3. Although the calculated values are of the right order of magnitude, lying in the range 0—5 kcal. for the values of δ to be expected from calculations of dipole moments, the whole method is too approximate to justify any such quantitative correlation.

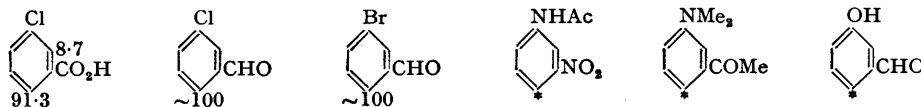
Orientation in Polysubstituted Benzenes.—The present method could be extended to polysubstituted benzenes without difficulty, but the calculations would be tedious. Since, however, the effect of a substituent in benzene is only to perturb a mesomeric system already covering six nuclei, one might expect that to a first approximation the perturbations due to several different substituents in the same ring should be additive and so also their directive effect. This additivity was in fact established experimentally some time ago by Holleman (*loc. cit.*), and so the principles already laid down give a simple interpretation of substitution in the more complex cases. A few examples of orientation in two types of m -disubstituted benzenes will suffice; the data are for nitration, and the figures represent proportions of mononitro-derivative, while asterisks indicate the main points of attack when the proportions of isomers have not been determined.

(1) Both substituents $-E$. Substitution should occur almost exclusively in the 2:4:6-positions. Moreover, since most $-E$ substituents have $\delta > 0$, substitution should occur mainly para to the one with the higher electron affinity. From the following results:



it may be deduced that para-directive power rises in the series $\text{I} < \text{Br} < \text{N} < \text{Cl} < \text{O}$, which is probably also the series of increasing electron affinity.

(2) One substituent $+E$, one $-E$. Examination of Figs. 2 and 3 shows that for average values of δ , the $(o,p):m$ ratio for a $-E$ substituent should be greater than the $m:(o,p)$ ratio for a $+E$ one. Therefore in the present case substitution should occur *op* to the $-E$ substituent. Moreover since the $o:p$ ratio is usually small for $-E$ substituents, large for $+E$ ones, substitution should occur mainly para to the $-E$ substituent, the main by-product being the 1:2:3-derivative. The following examples illustrate these points:



Steric Hindrance.—Although the simple electronic treatment is thus generally satisfactory, its implied neglect of steric hindrance cannot be correct. Examination of models shows that in most o -disubstituted benzene derivatives, the substituents are closer than the sum of their van der Waals radii; the formation of such compounds must therefore be hindered, and the proportion of o -isomer should be less than that calculated from purely energetic considerations.

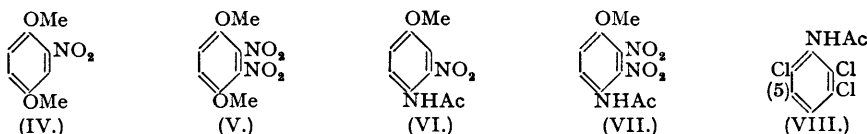
This effect appears to be small in most cases since the electronic theory is so successful and since, as Scheffer (*Proc. K. Akad. Wetensch. Amsterdam*, 1913, 15, 1109, 1118) and Bradfield and Jones (*J.*, 1928, 1006) have shown, the frequency factors for o - and p -substitution are similar in many cases. However there is clear evidence that in substitution of PhX by Y^+ , steric hindrance to o -substitution can be important if X or Y^+ is large.

Thus the ratio of frequency factors for *o*- to *p*-nitration of toluene is close to unity (0.75), but that for sulphonation is only 0.0053 (the ratios are calculated from the data of Holleman, *loc. cit.*). Nitration is little hindered, the active agent being the small NO_2^+ cation; but in sulphonation, where the active agent is probably the large ion H_3SO_4^+ , *o*-substitution is greatly hindered.

The effect of enlarging X is shown very clearly in the series PhMe, PhEt, PhPr, PhBu^t, along which the *o* : *p* ratio falls. Quantitative data are lacking, but the effect is very marked, toluene giving more *o*-nitro-derivative than *p*-, while with PhBu^t only the *p*-nitro-derivative can be isolated. It seems impossible to explain these differences in electronic terms.

Special Effects.—(1) Chlorination or nitration of phenol gives *o*- and *p*-derivatives in comparable amounts, although phenol esters and ethers give much more *p*-isomer as the present arguments require. This difference might be due to a preliminary ionisation of the phenol, the agent substituted being $\text{Ph}\cdot\text{O}^-$ and not $\text{Ph}\cdot\text{OH}$; O^- must have a relatively low electron affinity and should therefore give a relatively large *o* : *p* ratio. But bromination of phenol gives about 90% of *p*-bromophenol; and this difference cannot be due to steric hindrance since the ratio of *o*- to *p*-frequency factor is the same (~ 0.5) for both chlorination and bromination. It therefore seems quite likely that hydrogen-bonding in the transition state is responsible for the large *o* : *p* ratios in nitration and chlorination; hydrogen bonding is known to be important in *o*-nitrophenol and *o*-chlorophenol, but not in *o*-bromophenol.

(2) Another special effect is observed in 1 : 2 : 4-trisubstituted benzenes, where a $-E$ and a $+E$ substituent are ortho to one another. If the third substituent is $-E$, the main monosubstitution product is the 1 : 2 : 3 : 4-one. Thus (IV) gives mainly (V) on nitration, and (VI) gives (VII). This result is unexpected, since a simple application of the principles already



discussed would suggest that a *m*-dinitro-compound should be formed in each case. The explanation is probably this; conjugation of the adjacent $-E$ and $+E$ groups tends to increase the bond-order of the annular bond between them, and so to cause an alternation of bond-order round the ring. The two groups (*e.g.*, NHAc, NO_2 in VI) are thus insulated from the rest of the ring by bonds of low order; substitution is therefore directed by the third group, and into the ortho position to which it is attached by the bond of higher order. This explanation could be checked by the methods used in the first part of this paper.

(3) Several authors have drawn attention to the effect on orientation of the steric inhibition of mesomerism between substituents and the ring (cf. Wheland, "The Theory of Resonance", John Wiley, 1944). A good example is the nitration of 2 : 3 : 6-trichloroacetanilide (VIII) in the 5-position, a reaction quoted as anomalous by Holleman. Presumably the $-E$ effect of NHAc is sterically inhibited by the *o*-chlorine atoms; nitration occurs in the 5-positions, *op* to two chlorine atoms, the 4-position being only *o* to one.

Relation to Electrostatic Theories of Substitution.—A number of authors have tried to calculate activation energies on the assumption that they are due only to electrostatic interactions between the reagents (cf. Moelwyn-Hughes, "Reactions in Solution", Oxford, 1947); and this concept has been applied to benzene substitution by Ri and Eyring (*J. Chem. Physics*, 1940, **8**, 433) and by Kenner (*Proc. Roy. Soc.*, 1946, *A*, **185**, 119). These calculations implicitly assume that reagents can approach to within bonding distance without appreciable distortion of their electron orbitals, and that they then react without activation. This is of course very far from being the case, reactions in general occurring by continuous adiabatic processes where the electron orbitals and charge distribution change continuously throughout. The electrostatic calculations are therefore quite worthless from an *a priori* point of view.

That they are moderately successful in practice would seem to be due to a general correlation between polarity and polarisability in most molecules. Consequently the energy of the transition state for attachment of a cation to some atom in a molecule runs inversely to the static negative charge on that atom in the unperturbed reactant. Therefore, although the electrostatic calculation gives a rough idea of the real activation energy in most cases, it does so only through a fortuitous correlation of two distinct effects.

Relation to the π -Complex Theory.—It has been suggested (Dewar, *J.*, 1946, 707) that the rate-determining step in substitution is the formation of a π -complex between the reagent and

reactant. This idea is not at variance with the main argument of the present paper, which discusses the orientation rather than the rate of substitution; and, as was emphasised earlier, the orientation will follow the same principles if transition states of the type considered in this paper are concerned, no matter whether or not their precursors are intermediate π -complexes.

One additional piece of evidence for the π -complex theory may be mentioned; Bennett, Brand, James, Saunders, and Williams (*J.*, 1947, 474) have found that the rate of nitration of dinitrotoluene (DNT) in sulphuric acid to trinitrotoluene (TNT) is given by

$$\frac{-d[\text{DNT}]}{dt} = k_1[\text{DNT}][\text{NO}_2^+]\{[\text{HSO}_4^-] + k_2[\text{H}_2\text{S}_2\text{O}_7^-] + k_3[\text{H}_2\text{SO}_4]\}$$

They concluded that a termolecular reaction was involved. Since true termolecular reactions are virtually unknown in organic chemistry, it seems much more likely that an intermediate compound is formed reversibly from two of the reactants, this intermediate then reacting with the third reactant to give TNT. Such an intermediate would most reasonably be formulated as a π -complex, derived from $\text{DNT} + \text{NO}_2^+$. Since DNT must be a very poor electron donor, the π -complex should be unusually unstable; and its reversible formation, and failure to give TNT in absence of a base, would be easy to understand.

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