ORIENTATION OF SUBSTITUTION IN THE BENZENE NUCLEUS

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I. PERCENTAGES OF ISOMERS IN AROMATIC SUBSTITUTION

It has been recognized for over three-quarters of a century that groups attached to the benzene nucleus influence the position taken by a second entering group, and during this period chemists have been drawing empirical correlations and postulating theories to explain this phenomenon. Although aromatic substitution is far from being understood completely, its qualitative features are generally recognized and are explicable in terms of present-day electron theories. Numerous studies have been reported in the post-war years to alter some of the earlier concepts on this topic; hence it is worth while to assemble for examination data on which the current viewpoints are based (71).

The earliest observations made concerning orientation were the preferential formation of ortho and para, or meta, isomers during the nitration, sulfonation, or halogenation of monosubstituted benzenes. Nitration has been studied the most extensively, and the proportions of isomers obtained in the mononitration of some substituted benzenes are listed in table 1. The substituent groups are listed in the order of decreasing percentage of meta isomer obtained.

Many empirical rules have been proposed for predicting the major orientation by a group in aromatic substitution. Some have been based on the electron or atomic structure of the substituents (2, 35, 38, 57, 77) such as that of Armstrong (2), which says in effect that groups attached by atoms forming only single bonds are ortho and para orienting and groups attached by atoms forming multiple bonds are meta orienting. Some empirical rules are based on the chemical properties of the corresponding monosubstituted benzenes (23, 41, 54, 61, 62) such as that of Olivier (62), which states that if the para isomer of

$XC_6H_4CH_2Cl$ is most easily hydrolyzed, X is an ortho- and para-directing group, while if the meta isomer is most readily hydrolyzed, X is a meta-orienting group. In addition, some rules are based on the physical properties of the respective monosubstituted benzenes (73, 74) such as that of Sverbely and Warner (74), which states that if the dipole moment of C_6H_5X is equal to, or greater than, 2.07 D, X is meta orienting, and if the moment is less than 2.07 D, X is ortho and para directing. Of course, there are exceptions[1] to each of these rules; however, they may serve as a guide for students in becoming familiar with the two groups of substituents.

TABLE 1

Percentages of isomers obtained in the nitration of monosubstituted benzenes (45, 46, 67)

SUBSTITUENT	ORTHO	PARA	META	SUBSTITUENT	ORTHO	PARA	META
	per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
OH	40	58	<2	CCl_3	7	29	64
F	12	87	<0.2	$COOC_2H_5$	24	4	72
Cl	31	69	<0.2	$COOCH_3$	21	6	73
Br	41	59	<0.2	CHO	21*		79
I	41	59	<0.2	COOH	18	2	80
CH_3	58	38	4	NO_2	5	2	93
$CH_2COOC_2H_5$	42	47.4	10.6	CF_3			99
CH_2Cl	32	52.5	15.5	$\overset{\oplus}{N}(CH_3)_3$			100
CH_2F	28	54	17				

* Ortho isomer plus para isomer.

II. ACTIVATION AND DEACTIVATION OF NUCLEAR CARBON ATOMS BY SUBSTITUENTS

The inception of the present-day theories of aromatic substitution is associated with the names of Lapworth, Robinson, and Ingold. It was Ingold and Shaw (44) who first pointed out that the preferential formation of ortho, meta, or para isomer may be due to the influence of a substituent upon the reactivity of nuclear carbon atoms through one of several combinations. For instance, an ortho–para-directing group may cause activation at the ortho and para positions and deactivation at the meta position; or it may cause activation at the ortho and para positions and not affect the meta position; or it may cause activation at all positions but to the greatest extent at the ortho and para positions. In any case, the net result would be a relative activation of the ortho and para carbon atoms. The actual case may be found through a study of the activation or deactivation by a substituent of each carbon atom in the ring relative to a carbon atom of unsubstituted benzene.

Thus, Ingold set out to determine by experimentation the influence that a substituent exerts on the reactivity of each nuclear carbon atom. He proposed that the effect of a substituent be expressed by a set of factors which indicate

[1] Of the empirical rules, there seem to be fewest exceptions to that of Hamick and Illingworth (35).

the probability of substitution at each position relative to a carbon atom of benzene, the probability of substitution at each carbon atom of benzene being set at unity. Ingold deduced that these factors, termed "partial rate factors," may be obtained by combining two types of experimental data: (*1*) the proportions of the three isomers produced upon the nitration, halogenation, etc., of monosubstituted benzenes and (*2*) the rates of reaction of monosubstituted benzenes relative to unsubstituted benzene. Then the partial rate factors, F, of the nuclear carbon atoms for a monosubstituted benzene would be

$$F_{\text{ortho}} = 3r\alpha,\ F_{\text{meta}} = 3r\beta,\ F_{\text{para}} = 6r\gamma$$

where r is the ratio of the rates of reaction of the substituted benzene and of benzene itself and α, β, and γ are the fractions of ortho, meta, and para substitution products, respectively. The integers are statistical corrections for the fact that there are two ortho atoms, two meta atoms, and one para atom in the substituted benzene, while there are six equivalent positions available for reaction in benzene.

TABLE 2

Partial rate factors for nitration of some monosubstituted benzenes (14, 45, 46)

SUBSTITUENT	ORTHO	META	PARA	SUBSTITUENT	ORTHO	META	PARA
H	1	1	1	Br	0.037	0.000	0.106
CH_3	43	3	55	$CH_2COOC_2H_5$	4.62	1.16	10.41
$COOC_2H_5$	0.0026	0.0079	0.0009	CH_2Cl	0.290	0.140	0.951
Cl	0.030	0.000	0.139				

From some careful studies of nitration in acetic anhydride at 18°C., Ingold and his collaborators (14, 45, 46) determined the partial rate factors for each nuclear carbon atom of some monosubstituted benzenes; their results are listed in table 2. The data give semiquantitative evidence for what was known qualitatively: that is, that a methyl group activates the benzene ring and is ortho and para directing, that halogens are also ortho and para directing but deactivate the benzene nucleus, while a carbethoxyl group is ring deactivating and meta orienting.

Recognition of the progressive deactivation of the ring toward electrophilic substitution as meta orientation increases is acknowledged by the common practice that weak reactions such as chloromethylation and the Friedel–Crafts reaction are not commonly performed (i.e., would give low yields) with substituted benzenes when the substituent is approximately one below the CH_2F group in table 1; stronger reactions, such as halogenation, are carried out when substituents are no more meta orienting than the carboxyl group, while only vigorous reactions, such as nitration and sulfonation, are successful when the strongly meta-orienting (ring-deactivating) groups below carboxyl are attached to the nucleus.

III. THEORY AND MECHANISM OF AROMATIC SUBSTITUTION

Nuclear substitutions may be divided into free-radical and ionic mechanisms as indicated below, and the latter may be further subdivided into electrophilic (cationoid) and nucleophilic (anionoid) reactions.

FREE-RADICAL MECHANISM	IONIC MECHANISM
Metalations*	I. Electrophilic
Wurtz–Fittig	A. Irreversible
Ullmann	Nitration
	Halogenation
	Acylation
	Chloromethylation
	B. Reversible
	Sulfonation
	Friedel–Crafts
	II. Nucleophilic
	Ammonolysis
	Hydrolysis
	Alcoholysis

* Mercuration in aqueous solution has been shown to be electrophilic (53).

Most attention has been focused upon the electrophilic irreversible reactions. The two most prominent mechanisms proposed for this type of substitution are the addition–elimination reaction suggested by Kekulé (51) in 1858 and the cationoid reaction proposed by Pfeiffer and Wizinger in 1928 (63) but almost conceived by Lapworth (56) in 1901. The latter mechanism makes the assumption that a reagent accepts a pair of electrons to form a covalent bond with a carbon atom of the ring, and the resulting transition intermediate then loses a proton to produce the final substituted derivative. If this mechanism is close to the actual mode of substitution into the aromatic nucleus, then it follows that an electrophilic reagent will react more readily with the carbon atom for which the least energy is required to form a covalent bond. This carbon atom will be the one at which electrons are the most accessible as the reagent approaches the aromatic molecule.

Only in recent years has conclusive evidence been obtained to show that the reactant in nitration is the nitronium ion, $\overset{\oplus}{N}O_2$. Oddly, the proof was gathered almost simultaneously by four independent groups (10, 20, 33, 79); it has been summarized by E. A. Braude (17).

Considering all data, nitration can be regarded as a two-stage process (17, 26)

$$ArH + \overset{\oplus}{N}O_2 \xrightarrow{\text{slow}} ArHNO_2^{\oplus};\quad ArHNO_2^{\oplus} + B \xrightarrow{\text{fast}} ArNO_2 + BH^{\oplus}$$

in which the intermediate, $ArHNO_2^{\oplus}$, is a π-complex and B is a proton acceptor, usually the solvent or an anion of sulfuric acid.

It has been assumed usually that halogenation also involves a cation, $X^{\oplus}$, produced through interaction of an acid catalyst with the halogen molecule

(12), i.e., $FeX_3 + X_2 \rightarrow FeX_4^{\ominus} + X^{\oplus}$. On the other hand, recent studies have revealed several significant facts to alter this viewpoint. (*1*) The most important fact is that it appears that ionization of the halogen–halogen bond occurs *during*, rather than *before*, association with the aromatic nucleus (69). (*2*) At low concentrations (*ca.* 0.001 *M*) halogenation is bimolecular, while at higher concentrations (0.02 *M*) bromination is trimolecular, being of second order with respect to bromine (69). (*3*) At low concentrations the rates are sensitive to the presence of water and hydrogen halide (69). (*4*) Aromatic compounds form reversibly 1:1 molecular addition compounds with bromine, iodine, or iodine chloride (9, 29, 37, 49). To account for these data, halogenation can be assumed to take place as follows:

$$ArH + X_2 \rightleftarrows ArHX_2$$

$$ArHX_2 + C \xrightarrow{\text{slow}} ArHX^{\oplus} + CX^{\ominus}$$

$$ArHX^{\oplus} + A \xrightarrow{\text{fast}} ArX + HA^{\oplus}$$

where X is a halogen atom, C is an acid catalyst (or, in high halogen concentration, a second halogen molecule), and A is a proton acceptor, either $CX^{\ominus}$, $X^{\ominus}$, or the solvent. At high dilution the second step may occur without the aid of the catalyst but with a higher heat of activation (70), and the solvent could serve as the proton acceptor; this would account for the second-order reaction at low concentrations. Water facilitates the reaction, probably owing to stabilization of the intermediate, $ArHX^{\oplus}$, by solvation; and HX retards reaction, owing to the formation of HX_3 (58, 70). It is noteworthy that if a benzene solution of iodine is treated with an anhydrous silver salt, reaction occurs to yield iodobenzene and silver iodide (13), the silver ion thereby serving in the capacity of C above.

It is quite possible, then, that electrophilic substitution of aromatic molecules proceeds through intermediate π-complexes, although the intermediate stages and reacting species may vary depending upon the experimental conditions. Several types of recent experimental data[2] have revealed the basic character of an aromatic nucleus, due to the availability of its π-electrons. The mobile (or π) electrons of benzene behave as "free electrons," but in substituted benzenes the π-electrons are undoubtedly localized as a result of polarization by the substituent. Thus, through such effects as resonance and field plus chain induction,

[2] Besides forming complexes of the type BX_2, where B is an aromatic molecule and X is a halogen atom, aromatic compounds have been found to react as a base in a number of systems. For example, Andrews and Keefer (1) have measured the solubilities of aromatic compounds in aqueous silver nitrate, and their data indicate that two water-soluble complexes, $ArAg^{\oplus}$ and $ArAg_2^{\oplus\oplus}$, are formed. Brown (19) has attributed the solubility of HCl–$AlCl_3$ in aromatic hydrocarbons to the formation of a complex with the aromatic molecules. Jura, Grotz, and Hildebrand (48) have found that aromatic substances and inorganic salts form colored complexes on the surface of silica gel, and McCaulay and Lien (60) have found methylbenzenes sufficiently basic to be extractible with HF–BF_3 in the vapor or liquid state. In all of these studies there is the same parallel trend of extent of reaction with respect to the donor character of the aromatic substances.

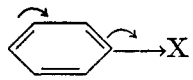
the substituent of a monosubstituted benzene builds up a permanent polarization around the nucleus and the electron density about the nuclear carbon atoms varies depending upon the nature of the substituent. In addition, an attacking cationic reagent may polarize the nuclear carbon atoms as it comes within bonding distance and reaction will tend to occur at the most polarizable carbon atom. If the preferential formation of ortho, meta, or para isomers is determined by the permanent polarization of the nucleus, plus any polarization that may occur by the attacking reagent, then it should be possible to interpret experimental data in terms of conceivable effects that can influence the electron distribution of the ring. The fundamental assumption is still made that reaction will occur to the greatest extent at the carbon atom from which an electron pair is the most accessible as the reagent approaches the aromatic molecule.

IV. DIRECTIVE EFFECTS IN AROMATIC SUBSTITUTION

There are several effects in operation that influence the orientation in aromatic substitution which are hardly separable for study of their individual roles. For instance, there will always be an inductive effect by the substituent, be it small or large. Nevertheless, there are experimental data which provide evidence for the occurrence of such influences as induction, resonance, polarization by the reagent, and a small steric hindrance.

A. The inductive effect

When a group is substituted for hydrogen in the benzene nucleus it destroys the symmetry of the electron distribution and, depending upon its relative electronegativity with respect to hydrogen, will increase or decrease the electron density at the C_1 carbon atom. If, for example, the group has a large electronegativity, it will attract the nuclear π-electrons, but the withdrawal will be greatest through electromeric shifts from the ortho and para carbon atoms.



This essentially induces a relative alternating charge distribution around the ring with an overall electron density less than that of benzene; consequently, the derivative reacts more slowly than benzene and chiefly at the meta position. For instance, in the two series (7, 67) given below there is an increased amount of meta isomer produced in nitration with increasing electronegativity of the groups in the α-position.

DERIVATIVE NITRATED	YIELD OF META ISOMER	DERIVATIVE NITRATED	YIELD OF META ISOMER
	per cent		*per cent*
$C_6H_5CH_3$	4	$C_6H_5C(CH_3)_3$	~5
$C_6H_5CH_2Cl$	15.5	$C_6H_5C(CH_3)_2NO_2$	29
$C_6H_5CHCl_2$	34	$C_6H_5CH_2NO_2$	50
$C_6H_5CCl_3$	64	$C_6H_5CBr_2NO_2$	84

Field polarization also occurs and probably is significant for highly polar groups. Thus, owing to the powerful attraction for the π-electrons exerted by the positively charged nitrogen atom of the $\overset{\oplus}{N}(CH_3)_3$ group, the nuclear electrons are considerably localized to make the group 100 per cent meta directing.[3] Latimer and Porter (57), and more recently Price (65), made calculations which can be taken as a measure of the field induction of the nuclear π-electrons by the substituent of a monosubstituted benzene. Probably because of a fortuitous correlation between the permanent polarity of the ring and field polarization, there is, as shown in table 3, a fair parallelism between the increasing orders of polarizing force and per cent of meta isomer produced in nitration.

TABLE 3

The electrostatic polarizing force of groups on an adjacent carbon–carbon double bond (65)

GROUP	POLARIZING FORCE	META ISOMER FORMED IN NITRATION	GROUP	POLARIZING FORCE	META ISOMER FORMED IN NITRATION
	dynes	*per cent*		*dynes*	*per cent*
F	−1.12	<0.2	$COCH_3$	0.89	55
Cl	−0.68	<0.2	CCl_3	0.93	64
Br	−0.55	<0.2	CHO	0.98	79
I	−0.39	<0.2	$COOCH_3$	1.23	73
CH_3	−0.39	4	COOH	1.25	82
CH_2Cl	0.36	16	CF_3	1.41	99
H	0.45	(40)*	CN	1.80	88
CH_2NO_2	0.68	50	NO_2	2.21	93
$CHCl_2$	0.75	34	$\overset{\oplus}{N}(CH_3)_3$	3.21	100

* Since there are two hydrogen atoms meta and three ortho–para to any particular reference position in the benzene ring, random unoriented replacements would go 40 per cent meta to the reference position.

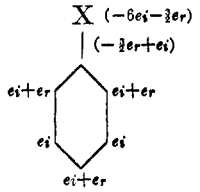
B. Combined inductive plus resonance effects

Superimposed upon the inductive effect to influence the permanent electron distribution of the ring is the effect of resonance. Depending upon the nature of the substituent, electrons are either withdrawn from or furnished to the ortho and para carbon atoms; this affects the relative abilities of the nuclear carbon atoms to donate an electron-pair for the formation of a covalent bond with the reagent, and thereby leads to preferential substitution at the ortho, meta, or

[3] Roberts, Clement, and Drysdale (68a) suggest that the meta-directing power of the $\overset{\oplus}{N}(CH_3)_3$ group is due to a greater stabilization of the transition state through resonance when reaction occurs at the meta position than when at the ortho or para position. They base their challenge on the fact that the $\sigma_p - \sigma_m$ (see page 62) values for the trimethylammonium group are too small and of the wrong sign to support the charge distribution proposed above; however, it is quite possible that solvation and direct field effects obscure the differences between the effects of the highly polar $\overset{\oplus}{N}(CH_3)_3$ group on *m*- and *p*-situated substituents.

para carbon atom. An important study for substantiation of the theoretical concepts of the role of chain induction and resonance in aromatic substitution, at least to a semiquantitative degree, has been provided by Ri and Eyring (50, 68). It is significant because from experimental data on substitution and certain reasonable assumptions, Ri and Eyring were able to calculate an independent physical property, the dipole moments, of monosubstituted benzenes in good agreement with observed values.

They made the following assumptions: (*1*) As a first approximation, the inductive effect of a substituent X causes equal charges, e_i, to be induced on each carbon atom of the ring. (*2*) The total induced charge, $6e_i$, is balanced by an equivalent charge, $-6e_i$, on the substituent X. (*3*) The resonance effect produces a charge e_r on each of the two ortho carbon atoms and the para carbon atom but does not affect the meta position. (*4*) The total resonance charge of $3e_r$ is balanced by $-\frac{3}{2}e_r$ on the group X and $-\frac{3}{2}e_r$ on the carbon atom to which X is attached. The charge distribution will therefore be



According to the theory of absolute reaction rates, the specific rates of reaction at a carbon atom y in a monosubstituted benzene and with any carbon atom of benzene itself can be given by equations 1 and 2, respectively.

$$k_y = K\frac{kT}{h}e^{-(\Delta F+e_ye_n/rD)/kT} \tag{1}$$

$$k_H = K\frac{kT}{h}e^{-\Delta F/kT} \tag{2}$$

In these equations K is the transmission coefficient, taken as unity by Ri and Eyring; k and h are Boltzmann's and Planck's constants; T is the absolute temperature; ΔF is the free energy of activation for a benzene carbon atom; e_y is the difference between the charge on carbon atom y in the presence and absence of the group X; e_n is the charge on the reactant ($\overset{\oplus}{N}O_2$), taken as 4.8×10^{-10} E.S.U.; r is the distance of separation of the charges e_y and e_n when reaction occurs, which was taken to be 10 per cent greater than the normal C—X covalent bond distance; and D is the dielectric of the medium, which was chosen as unity. The activating or deactivating effect of a group X at a carbon atom Y is taken to be e_ye_n/rD.

Division of equation 1 by equation 2 gives the ratio of specific rates for any carbon atom with respect to benzene to be

$$k_y/k_H = e^{-e_ye_n/rDkt} \tag{3}$$

As Ingold and Shaw (44) deduced earlier, the values of the ratio k_y/k_H can be obtained by multiplying the overall relative rates of reaction of the substituted benzene with respect to benzene by the percentages obtained in nitration. Hence, by combining the results from competitive nitrations with benzene and orientation percentages, Ri and Eyring were able to calculate the charges e_y on the nuclear carbon atoms of several monosubstituted benzenes. With the knowledge of these charges and the geometry of the model, they then calculated the dipole moments of several benzene derivatives (table 4).

TABLE 4

Calculated dipole moments of benzene derivatives from nitration studies (68)

SUBSTITUENT	CALCULATED MOMENT	OBSERVED MOMENT	SUBSTITUENT	CALCULATED MOMENT	OBSERVED MOMENT
	debyes	*debyes*		*debyes*	*debyes*
CH_3	0.48	0.44	Br	−1.68	−1.53
F	−1.20	−1.45	I	−1.27	−1.30
Cl	−1.54	−1.55	$COOC_2H_5$	−1.30	−1.91

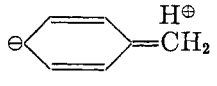
TABLE 5

Relative rates of bromination of monoalkylbenzenes (11)

SERIES	I	II	III	IV	V
R	C_6H_5R	$C_6H_5CH_2R$	$C_6H_5(CH_2)_2R$	$C_6H_5(CH_2)_3R$	$C_6H_5(CH_2)_4R$
CH_3	100	100	100	100	100
CH_3CH_2	70	80	106	89	93
$(CH_3)_2CH$	40	53	101	84	
$(CH_3)_3C$	18	30	112	81	

C. Hyperconjugation

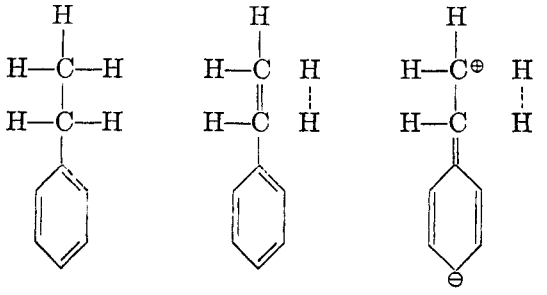
Ingold (44) formerly attributed the activating effect of the methyl group to induction, but more recent experimental data have shown that the relative rates of bromination of alkylbenzenes are not consistent with the relative electronegativities of the respective alkyl groups. Instead, the directive influences of alkyl groups (11, 58) can be explained in terms of hyperconjugation,



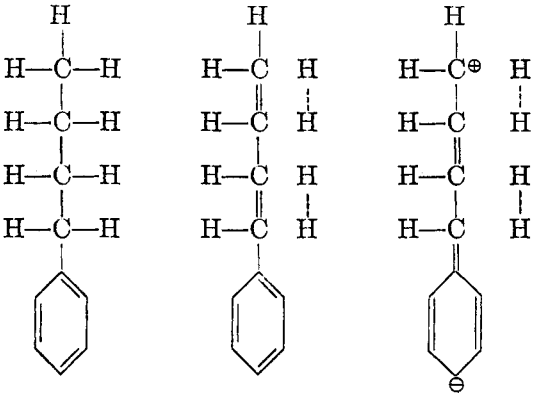
wherein the overall electron density of the ring is increased above that of benzene, particularly at the ortho and para carbon atoms.

Berliner and coworkers (11) have determined the relative rates of bromination of a large number of alkylbenzenes in acetic acid in the dark; their results are summarized in table 5. The decreasing order of reaction rates in series I is due to fewer and fewer α-hydrogen atoms in going from methyl to *tert*-butyl, which decreases the first-order hyperconjugation as pictured above. Berliner attributes

the order in series II to a decrease in the second-order hyperconjugation of the type:



The fewer the number of β-hydrogen atoms, the fewer such structures are possible and therefore the smaller is the rate of bromination. A similar type of hyperconjugation can account for series IV, for which the smaller the number

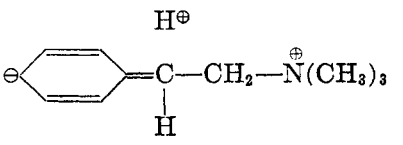


of δ-hydrogen atoms, the smaller the number of such structures that are possible. The relative importance of the number of hydrogen atoms available for hyperconjugation decreases in the order $\alpha > \beta > \gamma$, as shown by the progressively smaller spacing of the series I to V. Although there is a certain novelty to some of the structures proposed by Berliner, they do present a structural approximation scheme to account for his experimental results.

With the concepts of hyperconjugation and induction, it is possible to account for the decreasing amount of meta isomer produced in nitrating the following compounds (43).

SUBSTANCE	YIELD OF META ISOMER	SUBSTANCE	YIELD OF META ISOMER
	per cent		*per cent*
1. $C_6H_5\overset{\oplus}{N}(CH_3)_3$	100	1. $C_6H_5NO_2$	93
2. $C_6H_5CH_2\overset{\oplus}{N}(CH_3)_3$	88	2. $C_6H_5CH_2NO_2$	67
3. $C_6H_5(CH_2)_2\overset{\oplus}{N}(CH_3)_3$	19	3. $C_6H_5CH_2CH_2NO_2$	13
4. $C_6H_5(CH_2)_3\overset{\oplus}{N}(CH_3)_3$	5		

The more remote the positive charge from the ring, the smaller is the electron-withdrawing inductive effect. In the first series, the big drop in per cent of meta isomer comes between compounds 2 and 3, because in compound 3 hyperconjugation of the α-methylene group



favors ortho and para substitution, but this hyperconjugation is dampened in compound 2, owing to the proximity of the positive charge on the nitrogen. Similarly, the inductive effect of the nitro group in the second series decreases progressively. In $C_6H_5NO_2$ meta orientation is attributable to the combined inductive and resonance effects; in $C_6H_5CH_2NO_2$ the inductive effect outweighs the effect of hyperconjugation, while in $C_6H_5CH_2CH_2NO_2$ the decreased inductive effect is outweighed by the ortho–para-directing hyperconjugation of the α-methylene group.

D. Steric effects

The steric effect is the most difficult of all to single out from other factors for study of its influence upon orientation. There is one study to indicate that its magnitude is small; for, from a kinetic investigation of the nitration of toluene, Jones and Russell (47) found a difference in activation energies between the ortho and para carbon atoms of 200 cal. At least a small steric barrier should be expected for ortho substitution, owing to van der Waals repulsions between the substituent and the attacking reagent, and this expectation is substantiated by the fact that there is a 15° angle between the plane of the ring and the carbon–halogen bonds in *o*-dichloro- and *o*-dibromobenzenes, while *p*-dibromobenzene is coplanar (8).

From relative rates of propylation of alkylbenzenes compared to benzene and from the ratios of isomers produced in propylation, Condon (21) calculated the partial rate factors for toluene and isopropylbenzene listed in table 6. (Recall that the partial rate factors are integers to express the probability of reaction at a given nuclear carbon atom compared to a carbon atom of benzene.) It is observed in table 6 that the partial rate factors for the meta and para positions of toluene and cumene are of the same magnitudes, so that the several-fold decrease for that of the ortho position of cumene can be attributed to a steric effect.

Caution must be used in attributing certain experimental data to steric effects. For instance, it might be expected that steric hindrance would increase the para:ortho ratio and indeed, it is found that the ratio increases for nitration from 1.3 to 7.7 in going from toluene to *tert*-butylbenzene (58). On the other hand, the para:ortho ratio decreases for the halobenzenes from fluorobenzene to iodobenzene. Obviously other factors are involved, and the latter sequence is explicable in terms of induction and resonance. Dipole moments of the halobenzenes (3, 34) indicate that the decreasing order of electron withdrawal from

the ring is F > Cl > Br > I; from classical theory it is expected that this inductive effect will deactivate the ortho positions more than the para. In addition, it has been found (3, 34) that the order of decreasing electron-releasing resonance effect also is F > Cl > Br > I. Thus among the halogens, through induction, fluorine deactivates the ortho position the most, and through resonance, activates the para position the most (owing to the symmetry stabilization of the *p*-quinoid form). Consequently, the difference between the reactivities of the para and ortho atoms should be greatest for fluorine and least for iodine. This

TABLE 6

Relative rates of propylation of alkylbenzenes (21)

COMPOUND	RELATIVE RATE OF PROPYLATION	PARTIAL RATE FACTORS		
		Ortho	Meta	Para
C_6H_6	1			
$C_6H_5CH_3$	2.1	1.95	1.6	5.5
$C_6H_5CH_2CH_3$	1.91			
$C_6H_5CH(CH_3)_2$	1.69	0.35	2.2	5.1
$C_6H_5C(CH_3)_3$	1.4			

TABLE 7

Partial rate factors in nitration of halobenzenes (46)

	F*	Cl	Br	I*
Rate C_6H_5X/rate C_6H_6	0.16	0.003	0.030	0.15
Per cent ortho isomer	12	31	41	41
Per cent para isomer	87	69	59	59
Partial rate factor F_o	0.058	0.031	0.037	0.185
Partial rate factor F_p	0.836	0.137	0.106	0.531
Ratio F_p/F_o	14.6	4.42	2.88	2.87

*The figures for fluorine and iodine are only approximate, for they are taken from measurements of Bird and Ingold (14), who estimate a possible error of the order of 10 per cent.

expectation is verified by experimental evidence which appears in the last row of table 7, where there are given the ratios of the partial rate factors at the para and ortho positions of the halobenzenes.

E. Polarization by the attacking reagent

The polarization factor is a composite of the polarizability of the nuclear carbon atoms and the polarizing power of the reagent (66). Because there is a parallelism between polarity and polarizability (27), the effect upon orientation of polarization at the point of attack by the reagent is obscured,[4] although there

[4] In this connection, Waters (78) has expressed the belief that the resonance theory has retarded advancement of an understanding of aromatic substitution by obscuring the conceptions of Robinson and of Ingold that electromeric rearrangements rather than permanent polarizations explain directive effects.

are a few experimental observations which indicate that the polarizability factor is real. For instance, it may account for the difference in the rates of nitration and halogenation (25) of the halobenzenes, which increase in the order F < Cl < Br < I. From the studies of Andrews and Keefer (1) on the argentation of aromatic compounds and of Kharasch (52) on the hydrolysis of mercurials, aside from theoretical reasons, it can be deduced that the polarizabilities of halophenyl groups decrease in the order bromophenyl > chlorophenyl > fluorophenyl. Hence, if nitration proceeds by the cation $\overset{\oplus}{NO_2}$, while halogenation involves only the neutral molecule, then the nitronium ion evokes a more

TABLE 8

Orientation of various types of electrophilic substitutions (21, 39, 53)

GROUP	ISOMERS			REACTION
	Ortho	Meta	Para	
	per cent	*per cent*	*per cent*	
OH	13		87	Bromination
	53		47	Chlorination
	40	<3	58	Nitration
CH_3 ($AlCl_3$)	40		60	Bromination
	31	25	44	Propylation
	58	4	38	Nitration
	19	7	74	Mercuration
Br ($FeCl_3$)	13	2	85	Bromination
($AlCl_3$)	8	30	62	Bromination
($FeCl_3$)	42	7	51	Chlorination
($AlCl_3$)	30	5	65	Chlorination
	41	<0.2	59	Nitration
Cl ($AlBr_3$)	15	9	76	Bromination
($FeBr_3$)	11	2	87	Bromination
No catalyst	18	1	81	Bromination
($AlCl_3$)	30	4	66	Chlorination
($FeCl_3$)	39	5	56	Chlorination
	31	<0.2	69	Nitration

powerful polarization on the aromatic molecule and the difference in polarization activation will be greatest for iodobenzene and least for fluorobenzene.

It is conceivable that differences in the polarizing power of the reagent cause the differences in orientation in various types of electrophilic substitutions. Usually the ratios of isomers produced in different types of substitution are in the same ranges, but in a few instances there are marked changes. For example, chlorination of phenol gives close to a 50:50 ratio of ortho and para isomers but bromination gives a 10:90 ratio. Again, fluorobenzene is chlorinated more rapidly than is benzene, while fluorobenzene is nitrated much more slowly than is benzene. The percentages of isomers produced in the nuclear substitution of several benzene derivatives are listed in table 8.

V. CORRELATION OF PHYSICAL AND CHEMICAL PROPERTIES WITH ORIENTATION

The semiquantitative success in explaining orientation in aromatic substitution in terms of the permanent polarity of substituted benzenes, arising through such effects as induction and resonance, is due, as has been said before, to

TABLE 9

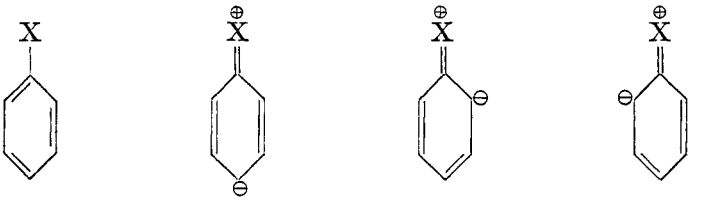
Comparison of physical and chemical properties of monosubstituted benzenes with orientation

I (45, 46, 67)		II (3, 76)		III (28)	
Group	Meta isomer formed in nitration	Group	Dipole moment	Group	$\Delta\lambda$
	per cent		*debyes*		*mμ*
OH	<2	OH	1.61	NH_2	26.5
F	<0.2	NH_2	1.53	OCH_3	13.5
Cl	<0.2	OCH_3	1.16	OH	7
Br	<0.2	CH_3	0.4	Br	6.5
I	<0.2	F	−1.44	Cl	6.0
CH_3	4	Cl	−1.64	CH_3	3
CH_2Cl	16	Br	−1.68	CN	20.5
$CHCl_2$	34	I	−1.69	COOH	26
$COCH_3$	55	CH_2Cl	−1.85	$COCH_3$	42
CCl_3	65	$COOC_2H_5$	−1.95	CHO	46
$COOC_2H_5$	72	$CHCl_2$	−2.04	NO_2	64
CHO	79	CCl_3	−2.1		
COOH	80	CHO	−2.75		
CN	81	$COCH_3$	−2.9		
NO_2	93	CN	−3.91		
		NO_2	−3.95		

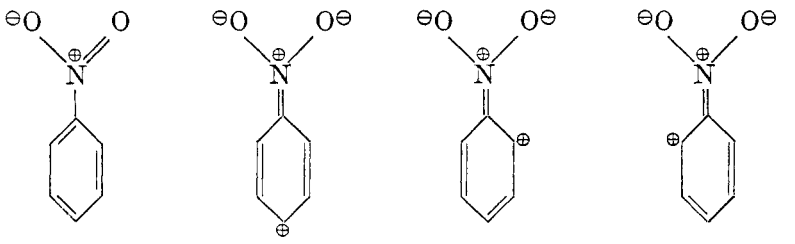
IV (64)		V (30)		VI (36)	
Substituent	Spectroscopic moment	Substituent	ΔE_0	Substituent	$\sigma_p - \sigma_m$
	$(cm.\ mole/l.)^{\frac{1}{2}}$		*mμ*		
OH	34	OH	−217	F	−0.275
OCH_3	31	NH_2	−210	Br	−0.159
F	21	OCH_3	−131	Cl	−0.146
I	21	CH_3	−76	CH_3	−0.101
CH_3	7	Cl	24	I	−0.076
Cl	6	Br	(+28)	CN	0.322
Br	4	COOH	(+49)	COOH	0.373
CH_2Cl	−3	$COOCH_3$	(+58)	NO_2	0.56
$CHCl_2$	−11	CN	(+76)	$COCH_3$	0.568
CCl_3	−17	NO_2	(+91)	CHO	0.745
CN	−19				
COOH	−28				

polarity outweighing the importance of other factors such as polarization by the reagent and steric hindrance. There are several physical and chemical properties which also depend upon the polarity of the ring, brought about chiefly through induction and resonance, and it would therefore be reasonable

to expect a correlation between these properties and orientation. In table 9 are listed certain physical and chemical properties of monosubstituted benzenes along with the per cent of meta isomer produced in nitration. Dipole moments are listed in column II. It has been well established that the observed moments of aromatic molecules are largely the composites of the moments arising from induction and resonance. Beginning with the groups which are strongly ortho and para directing, the resonance and induction moments are both directed towards the ring, which indicates that there is a larger nuclear electron density over that in benzene, particularly at the ortho and para carbon atoms. Passing down through the halogens, the larger induction moment is directed away from the ring. This results from an overall nuclear electronic charge below that in benzene, but owing to resonance among such forms as



the electron density is lowest at the meta carbon atoms, so that the compounds are still substituted chiefly in the ortho and para positions. Finally, the moments from induction and resonance are both directed away from the ring. Hence, the much reduced nuclear electron density causes ring-deactivation and, because resonance among such forms as



reduces the electron density at the ortho and para positions relative to the meta positions, the substituents are meta directing.

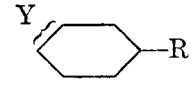
In column III of table 9 are listed the bathochromic shifts, $\Delta\lambda$, of the primary absorption band (203 mμ) of benzene for monosubstituted benzenes. As a first approximation, ultraviolet absorption ranges depend upon the energy differences between excited and ground states and $\Delta\lambda$ is largely dependent upon the electronic interaction through resonance between the nucleus and the substituent, irrespective of whether the resonance causes a decrease or an increase in the nuclear electron density. Consequently, when descending column III, along with the decrease in ortho- and para-directing power there is a decrease in the resonance interaction between ring and substituent and in $\Delta\lambda$. This trend passes through a minimum when the groups change from chiefly ortho and para

directing to meta directing, at which time all three quantities begin and continue to increase.

In column IV are listed what Platt (64) has termed "spectroscopic moments." Substituents perturb the symmetry of the oscillating charges of the benzene nucleus and, according to the Sklar–Förster (31, 42) theory, will affect the intensity of light absorption by monosubstituted benzenes in the 255-mμ region. Assuming that the perturbation, or "spectroscopic moment," is proportional to the square root of the intensity increment upon monosubstitution of benzene, Platt calculated the moments for a number of benzene derivatives that absorb close enough to 255 mμ, and with intensities sufficiently small, to be related certainly to this "forbidden" transition of benzene. Thus, without attributing the effect separately to resonance or induction, there is found in table 9 a correlation between spectroscopic moment and orientation in substitution.

In column V appear the changes in oxidation potentials of 1,4-naphthoquinone and phenanthrenequinone (in parentheses) by the substituents listed. From theory (16) it has been shown that substituents which increase the nuclear electron density through resonance or induction should lower the oxidation potential of a parent quinone and that groups which lower the nuclear electron density should have the opposite effect. Since the overall nuclear electron density parallels the nuclear reactivity and varies inversely with the per cent of meta isomer produced in substitution, the general trend in column IV qualitatively substantiates the theory.

Hammett (36) has been able to correlate the effects of substituents, Y, in the meta and para positions upon equilibria or reaction rates at the side chain R



by means of the equation $\log k_Y - \log k_H = \sigma\rho$, where the k's are the rate or equilibrium constants for the substituted and unsubstituted reactants, ρ is a reaction constant dependent upon the nature of R with respect to the conditions of reaction, and σ is a substituent constant dependent upon the nature and position of the group Y. Hammett has made the interpretation that the σ-value is a measure of the change in electron density at R produced by Y, and ρ is a measure of the susceptibility of the particular reaction at R to a change in electrical charge there. In column VI of table 9 are listed the differences between the σ-values of several groups when para and meta to R. Qualitatively, generalizations such as the following can be made from Hammett's summarizations: The greater a group Y orients to the meta position in nitration, (*1*) the more Y increases the acid strength of *p*-phenols and decreases the base strength of *p*-anilines, (*2*) the more it facilitates replacement of a para halogen atom (16), and (*3*) the more difficult it makes replacement of the halogen atom X of a *p*-CH_2X group.

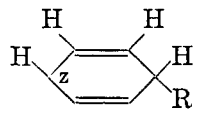
Although the sequences of the six columns in table 9 are not identical, there

is a definite parallel trend of the properties listed[5] with the per cent of meta isomer found in nitration and nuclear reactivity. A perfect correlation should not be expected, because the properties in columns I and II primarily affect the ground states of the molecules, while the properties in columns III to VI involve the ground and excited states.

VI. THEORETICAL TREATMENTS

In 1935 Wheland and Pauling (81) made a quantum-mechanical study of the charge distribution of monosubstituted benzenes and correlated these charges with the orienting influence of the substituents. They attributed the effect that the substituent has upon the nuclear electron distribution to resonance, induction, and polarization at the point of attack by the reagent. The latter factor was found to be minor except in cases such as the halobenzenes, where, according to their calculations, the permanent polarization leaves all atoms in the ring with very nearly the same charge and, as a result, any small difference in polarizability is made more prominent. Because of the presence of several adjustable parameters, Wheland and Pauling felt that their treatment could not be considered as a pure quantum-mechanical theory of directed substitution in aromatic nuclei but that the three effects considered are certainly real and are in the directions calculated.

Wheland (80) later gave a quantum-mechanical discussion of orientation and centered attention not upon the charge distribution in the isolated molecules, but upon the energies of these structures contributing to the activated complex in which a covalent bond is formed between the aromatic ring and the reagent. Earlier work has pointed out the importance of the structure

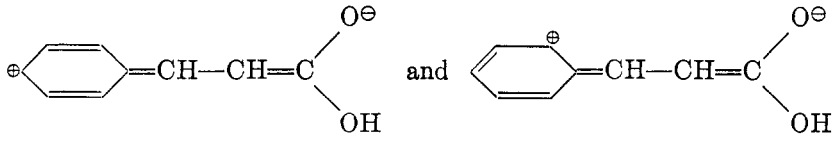


for that of the activated complex where R is an electrophilic reagent and z is a positive charge. In order to form the covalent bond with the cation $R^{\oplus}$, there must be a pair of unshared electrons available at the point of attack. The problem then is to determine the amount of energy which must be supplied in order to provide at the point of attack an unshared pair of electrons. This is equivalent to the problem of determining the difference in energies, α, between the normal benzene molecule and a "polarized" benzene molecule in which two electrons are held fixed on the carbon atom attacked and the remaining four π-electrons are distributed among the remaining five carbon atoms. α is not the activation energy but a part of it, and the smaller the value of α for reaction at a given

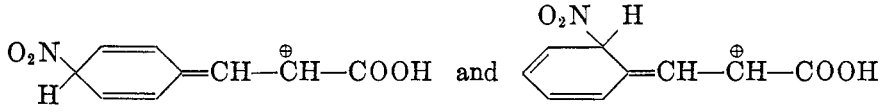
[5] Frances (32) and Holler (40) have pointed out trends in the orienting influence of groups with the melting point, boiling point, and the entropy of melting of benzene derivatives but no theoretical connection has been drawn between these physical properties and orientation. Dennis, Powell, and Astle (25) have found that the relative ease of reduction of the nitro group of substituted nitrobenzenes at a dropping mercury electrode is explicable in terms of induction and resonance.

nuclear carbon atom, the more rapid will be reaction at that carbon atom. The qualitative agreement of Wheland's results with rates of substitution illustrates that at least his assumptions are in the correct direction.

Semitheoretical treatments of aromatic substitutions have been given also by Daudel and A. Pullman (24), B. Pullman (66), and C. A. Coulson and H. C. Longuet-Higgins (22). These approximation methods suggest that the nature of the transition state of the reacting aromatic molecule has more than a minor importance and some isolated experimental data point to this same deduction. For instance, styrene derivatives such as $C_6H_5CH{=}CHNO_2$, $C_6H_5CH{=}CHSO_2Cl$, $C_6H_5CH{=}CHCHO$, and $C_6H_5CH{=}CHCOOH$ are less reactive than benzene (i.e., $k_{C_6H_5CH=CHCOOH}/k_{C_6H_6} = 0.111$) but give less than 2 per cent meta orientation. The inductive effect of the beta group, assumed to be transmitted about 90 per cent across the vinyl group, decreases the electron density of the ring, particularly at the ortho and para carbon atoms, and should therefore produce meta orientation. The resonance effect, due to such forms as



should also lead to meta orientation. A possible explanation of the anomalous ortho- and para-orienting property of styrene and azobenzene derivatives, as well as the larger order of rate of reaction of benzene derivatives containing strongly ortho–para-directing groups, is to assume that the transition state for reaction at the ortho or para carbon atoms is much more stable than when reaction occurs at the meta carbon atoms (16, 42). Thus, Bordwell and Rohde (15) propose that forms such as



account for the stabilization of the transition states for reaction at the ortho and para positions. Perhaps the lack of equivalent forms (when meta-directing groups are attached directly to the ring) causes the difference in orienting properties between the β-substituted styrenes and the correspondingly substituted benzenes.

W. A. Waters (78) apparently independently suggested, as did Wheland, that the method of assessing the activation at various carbon atoms is to estimate the energy difference between the normal molecule and the transition state. Since the transition state involves a quinoid structure, Waters used the oxidation potentials of quinones to explain ortho:para ratios and the Mills–Nixon effect.

VII. SUMMARY

Mechanisms have been proposed for the electrophilic substitution of monosubstituted benzenes on the basis of kinetic and other data. It has been shown

that experimental observations concerning the relative reactivity of monosubstituted benzenes and their orientation characteristics can be attributed to the permanent polarization of the aromatic nuclei induced by the substituents, while steric repulsion and polarization by the attacking reagent have second-order effects. There is found a strong correlation between orientation in the substitution of monosubstituted benzenes and certain of their physical properties which also depend primarily on their electron distributions in their ground or excited states. Although the qualitative features of aromatic substitution are fairly well understood, there are a number of points that still require clarification. For instance, a more conclusive picture of the mechanism of aromatic substitution and the role of catalysts in halogenation is desirable. Also, there are uncertainties about the magnitude of the steric effect, about the nature and importance of the "transition state" in aromatic substitution, and whether the inductive effect is transmitted to the ring in the order ortho > meta > para, according to Coulomb's law, or in the order ortho > para > meta, owing to electromeric shifts.

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