

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Directive Effects in Electrophilic Aromatic Substitution¹

K. LEROI NELSON²

Received August 24, 1955

Recent developments in the study of directive effects in electrophilic aromatic substitution clearly indicate that there are four essential factors which control the orientation of an entering group relative to a substituent already present. Of these, only the polar effect of the substituent has been amply treated in the literature.³⁻⁵ The polar effect of the reagent has been almost completely neglected while the steric effects of both the substituent and reagent have usually been relegated to secondary importance. In this connection, it is interesting to note that the majority of good data on electrophilic substitution comes from nitration studies. The nature of the reagent has received so little serious attention because it is virtually a constant factor in most considerations.

Although many chemists have contributed to our present understanding of orientation effects, we are singularly indebted to Holleman⁶⁻⁷ for providing the majority of the data upon which the general theories have been based. Ingold³ and his associates have also made major contributions.

In the following sections an attempt is made to

bring the consideration of steric effects into proper perspective and to emphasize the balance of importance between the nature of the substituent already present and the nature of the substituting reagent. Since both steric and polar effects will be operative simultaneously, it will not be possible to observe one effect in the absence of the other. However, it is considered that sufficient data now exist to permit valid conclusions about each effect.

In the absence of any steric or polar influences, the position taken by an entering group should be purely random, *i.e.*, 40% *ortho*, 40% *meta*, and 20% *para*. This statistical distribution provides a convenient basis for considering the steric and polar effects of the substituent and the reagent.

POLAR EFFECT OF THE SUBSTITUENT

The broad variation in the directing influences of a variety of substituents is indicated by the data cited in Table I. Clearly, the popular division of substituents into two broad classes according as to whether they favor *ortho* and *para* substitution or *meta* substitution is more arbitrary than real. It seems certain that if a sufficient number and variety of substituents were compared, we would find a complete and regular gradation between both extremes.

A number of homomorphic²⁰ pairs have been included in Table I to allow correction for differences in the steric factors so that the polar factors can be compared. Because only one reaction (nitration) is involved, the effect of the reagent is essentially constant.

A similar broad variation in the effect of substituents on the reactivity of the benzene ring is indicated by the data cited in Table II.

(1) Presented as part of the Symposium on the Mechanisms of Homogeneous and Heterogeneous Reactions of Hydrocarbons under the joint sponsorship of the Petroleum Division and the Physical and Inorganic Division at the Kansas City Meeting of the American Chemical Society, March, 1954.

(2) Present address: Department of Chemistry, Brigham Young University, Provo, Utah.

(3) Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953. This and the following two references contain citations of earlier reviews of the subject.

(4) Ferguson, *Chem. Revs.*, **50**, 47 (1952).

(5) Ferguson, *J. Chem. Educ.*, **32**, 42 (1955).

(6) Holleman, *Die direkt Einführung von Substituenten in der Benzolkern*, Veit, Leipzig, 1910.

(7) Holleman, *Chem. Revs.*, **1**, 187 (1924).

TABLE I
ISOMER DISTRIBUTIONS IN THE MONONITRATION OF
MONOSUBSTITUTED BENZENES

Substituent	Distribution of Mononitro Derivatives			Refs.
	<i>ortho</i>	<i>meta</i>	<i>para</i>	
—H	(40)	(40)	(20)	—
—OH	40	(—)	60	7
—F	12.4	(—)	87.6	7
—Cl	29.6	0.9	69.5	8
—Br	36.5	1.2	62.3	8
—I	37.9	2.1	60.0	8
—CH ₃	58.5	4.4	37.1	9
—CH ₂ F	28	18	54	10
—CH ₂ CH ₃	43.0	6.5	48.5	11
—CH ₂ Cl	32.0	15.5	52.5	12
—CH(CH ₃) ₂	30.0	7.7	62.3	11
—CHCl ₂	23.3	33.8	42.9	7
—C(CH ₃) ₃	15.8	11.5	72.7	13
—CCl ₃	6.8	64.5	28.7	7
—Si(CH ₃) ₃	26.6	41.7	31.6	14
—CH ₂ CO ₂ Et	42.0	10.6	47.4	12
—CO ₂ Et	24.0	72.0	4.0	15
—CO ₂ H	18.5	80.2	1.3	7
—CN	17	81	(2)	16
—NO ₂	6.4	93.3	0.3	7
—CH ₂ N(CH ₃) ₃ ⁺	2	88	10	17
—N(CH ₃) ₃ ⁺	(—)	(100)	(—)	18
—CF ₃	(—)	(99)	(—)	19

TABLE II
RELATIVE RATES OF MONONITRATION OF BENZENE
DERIVATIVES

Substituent	Relative Rate	Ref.
—H	1	—
—CH ₃	22	21
—C(CH ₃) ₃	15.7	22
—CH ₂ CO ₂ Et	3.66	12
—Si(CH ₃) ₃	1.47	14
—CH ₂ Cl	0.302	12
—F	0.15	23
—Cl	0.033	23
—Br	0.030	23
—I	0.22	8
—CO ₂ Et	0.00367	15

(8) Roberts, Sanford, Sixma, Cerfontain, and Zagt, *J. Am. Chem. Soc.*, **76**, 4525 (1954).

(9) Jones and Russell, *J. Chem. Soc.*, 921 (1947).

(10) Ingold and Ingold, *J. Chem. Soc.*, 2249 (1928).

(11) Brown and Bonner, *J. Am. Chem. Soc.*, **76**, 605 (1954).

(12) Ingold and Shaw, *J. Chem. Soc.*, 575 (1949).

(13) Nelson and Brown, *J. Am. Chem. Soc.*, **73**, 5605 (1951).

(14) Speier, *J. Am. Chem. Soc.*, **75**, 2930 (1953).

(15) Ingold and Smith, *J. Chem. Soc.*, 905 (1938).

(16) Baker and Ingold, *J. Chem. Soc.*, 436 (1928).

(17) Goss, Hanhart, and Ingold, *J. Chem. Soc.*, 259 (1927).

(18) Vorlander and Siebert, *Ber.*, **52**, 283 (1919).

(19) Swarts, *Bull. acad. roy. Belg.*, 389 (1920).

(20) Brown, Barbarous, Berneis, Bonner, Johannesen, Grayson, and Nelson, *J. Am. Chem. Soc.*, **75**, 1 (1953).

(21) Ingold, Lapworth, Rothstein, and Ward, *J. Chem. Soc.*, 1959 (1931).

(22) Cohn, Hughes, Jones, and Peeling, *Nature*, **169**, 291 (1952).

(23) Bird and Ingold, *J. Chem. Soc.*, 918 (1938).

The relative rates for the halogens made it necessary to revise Holleman's⁶⁻⁷ observation that substituents which direct entering groups to *ortho* and *para* positions enhance the reactivity of the benzene ring while substituents which direct entering groups to the *meta* position deactivate the ring. The exception in the case of the halogens has long been rationalized on the basis that the polarizability is sufficient to counteract enough of the inductive effect to control orientation but not sufficient to completely overcome the deactivating effect of induction.

If corrections are made for differences in steric effects, the results shown in Tables I and II can be explained on the basis of the induction and resonance effects to be expected for each substituent. The unusually high proportion of *ortho* substitution in the case of several preponderantly *meta*-directing substituents has been variously explained on the basis of chelation or selective *para* deactivation but the detailed discussion may be more conveniently considered in the theoretical section.

STERIC EFFECT OF THE SUBSTITUENT

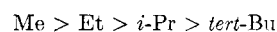
Steric interactions in electrophilic aromatic substitutions are predominantly of the F-Strain²⁴ type. With the possible exception of very large substituents and reagents, steric repulsion between substituent and reagent will only result in a lower proportion of *ortho* substitution with equivalent increases in the proportions of *meta* and *para* substitution. Where two or more adjacent substituents are already present, the B-Strain²⁴ type of interaction may operate to suppress the polarizability effect of the directing substituent. Wherever bulk interactions occur, the concept of homomorphism²⁰ provides a convenient basis for correlating the relative sizes of various substituents and reagents.

The isomer distributions observed in the mononitration of a series of monoalkylbenzenes under similar conditions are given in Table III.

TABLE III
DISTRIBUTION OF ISOMERS IN THE MONONITRATION OF THE
MONOALKYLBENZENES

Compound	Distribution of Isomers			Ref.
	<i>ortho</i>	<i>meta</i>	<i>para</i>	
Toluene	58.45	4.40	37.15	9
Ethylbenzene	45.0	6.5	48.5	11
Isopropylbenzene	30.0	7.7	62.3	11
<i>tert</i> -Butylbenzene	15.8	11.5	72.7	13

The proportion of *ortho* substitution clearly decreases in the order



as the substituent is changed but because hyperconjugation should decrease in the same order we must look further before deciding the actual cause

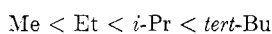
(24) Brown, Bartholomay, Jr., and Taylor, *J. Am. Chem. Soc.*, **66**, 435 (1944).

of this sequence. The ratios of isomers formed in the mononitration of the monoalkylbenzenes are given in Table IV. The fact that the ratio of *para* to *meta* substitution does not differ greatly in this

TABLE IV
ISOMER RATIOS FOR THE MONONITRATION OF THE MONOALKYLBENZENES

Compound	Isomer Ratios			Ref.
	<i>ortho</i> / <i>para</i>	<i>ortho</i> / <i>meta</i>	<i>para</i> / <i>meta</i>	
Toluene	1.57	13.3	8.5	9
Ethylbenzene	0.93	6.9	7.5	11
Isopropylbenzene	0.48	3.9	8.1	11
<i>tert</i> -Butylbenzene	0.22	1.4	6.3	13

series permits us to conclude¹³ that there are no pronounced differences in the electrical effects of the four alkyl substituents. This conclusion is further substantiated by the observation²² for different reaction conditions that the nitration of *tert*-butylbenzene actually is somewhat faster than toluene when the partial rate factors²⁵ for substitution in the *meta* and *para* positions are compared. Therefore, the marked decrease in substitution at the *ortho* position can be clearly attributed to the steric requirements of the alkyl substituents in the increasing order



The partial rate factors observed in the isopropylations of the monoalkylbenzenes (Table V) further illustrate the effect of the size of the substituent. Here also the rates of substitution in the *meta* and *para* positions, respectively, are not greatly different for the three monoalkylbenzenes while the rates of substitution in the *ortho* positions are markedly decreased as the size of the substituent increases.

TABLE V
PARTIAL RATE FACTORS FOR THE ISOPROPYLATION OF MONOALKYLBENZENES

Compound	Partial Rate Factors			Ratio (<i>p</i> / <i>m</i>) _f	Ref.
	<i>o</i> _f	<i>m</i> _f	<i>p</i> _f		
Toluene	2.4	1.8	4.3	2.4	27, 28
Isopropylbenzene	0.37	2.2	5.1	2.3	27, 29
<i>tert</i> -Butylbenzene	(0)	2.0	4.0	2.0	27, 30

On the basis of the data just cited together with many qualitative observations of similar nature it

(25) Rate of substitution at the single position relative to the rate of substitution at one position in benzene.²⁵

(26) Ingold and Shaw, *J. Chem. Soc.*, 2918 (1927).

(27) Condon, *J. Am. Chem. Soc.*, **70**, 2265 (1948).

(28) Condon, *J. Am. Chem. Soc.*, **71**, 3544 (1949).

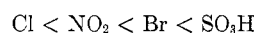
(29) Melpolder, Woodbridge, and Headington, *J. Am. Chem. Soc.*, **70**, 935 (1948).

(30) Hennion, Driesch, and Dee, *J. Org. Chem.*, **17**, 1102 (1952).

must be concluded that the steric effect of the substituent is frequently of primary importance and cannot be neglected. Of course, it must also be appreciated that the magnitude of the steric effect of the substituent will differ as the steric requirements of the reagent are significantly altered.

STERIC EFFECT OF THE REAGENT

A semi-quantitative insight into the steric effect of the reagent was given by Holleman.⁷ Thus, chlorination of chlorobenzene gives 39 per cent of the *ortho* isomer while bromination gives only 11 per cent of this isomer. From a number of results of this kind, he proposed the series



as the order for increasing steric hindrance due to the entering group. The most conclusive evidence now available for the steric effect of the reagent comes from recent alkylation studies (Table VI).

TABLE VI
ISOMER DISTRIBUTIONS FOR THE MONOALKYLATION OF TOLUENE

Entering Group	Isomer Distribution			Ref.
	<i>ortho</i>	<i>meta</i>	<i>para</i>	
Me	53.8	17.3	28.8	31
Et	45	30	25	32
<i>i</i> -Pr	37.5	29.8	32.7	28
<i>tert</i> -Bu	0	7	93	32

The results can only be interpreted on the basis of a pronounced steric effect which markedly decreases the proportion of *ortho* substitution as the size of the entering group is increased.

It has frequently been suggested that acylation of the benzene nucleus involves attack by an acylium ion, RCO⁺. However, the failure to obtain any *ortho* derivative in the acylation of toluene³³ is surprising in view of the small steric requirements that would be expected for the acylium ion. It is consequently anticipated that the actual intermediate has large steric requirements and is probably an addition compound of the acid chloride with the Friedel-Crafts catalyst. Evidence supporting this view has been obtained by Baddeley.³⁴ He found that naphthalene was acylated almost exclusively in the α -position in the absence of added reagents capable of combining with the acid chloride-aluminum chloride addition compound. The presence of molecular proportions of added nitrobenzene, nitromesitylene, or excess acid chloride led to considerable β -substitution as a consequence of the much greater steric requirements of the larger complexes.

Recognition that *ortho* substitution is strongly in-

(31) Brown and Jungk, unpublished results.

(32) Schlatter and Clark, *J. Am. Chem. Soc.*, **75**, 361 (1953).

(33) Pajeau, *Bull. soc. chim.*, [5], **13**, 544 (1946).

(34) Baddeley, *J. Chem. Soc.*, 99 (1949).

fluenced by the steric requirements of both the substituent already present and the substituting reagent should provide a valuable diagnostic tool in the study of reaction mechanisms.

POLAR EFFECT OF THE REAGENT

McCaulay and Lien³⁵ have verified that extensive isomerizations of dialkylbenzenes do occur under vigorous conditions with molar quantities of the catalyst leading to the exclusive formation of the *meta* isomer.^{35,36} On the other hand, Condon²⁸ has demonstrated that no *o*- or *m*-cymene is produced (either by isomerization or alkylation-dealkylation) when *p*-cymene is alkylated with propylene under mild conditions, yet under similar conditions all isomeric cymenes are obtained in the isopropylation of toluene (Table VII).

TABLE VII

ISOMER DISTRIBUTION IN THE ISOPROPYLATION OF TOLUENE (Both $\text{AlCl}_3\text{-MeNO}_2$ and $\text{BF}_3\text{-Et}_2\text{O}$ were used in each case)

Temperature, °C.	Isomer Distribution		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
5	37.5	29.8	32.7
65	37.6	27.3	34.9

These results clearly establish that for isopropylation there is very little difference in the rate of substitution between the *ortho*, *meta*, and *para* positions of toluene.

It has been suggested³⁷ that the high yield of the *meta* isomer obtained when toluene is isopropylated under mild conditions is a consequence of the high reactivity and corresponding low selectivity of the isopropyl carbonium ion. On this basis, the relatively high yield of the *meta* isomer (approaching random distribution) obtained in mild alkylations of alkylbenzenes should not be considered an anomalous property which is characteristic only of Friedel-Crafts substitutions. Thus, an examination of data on isomer distribution in the substitutions of toluene clearly demonstrated³⁷ that there was no sharp division between reactions which give a high proportion of *meta* substitution and those which give little or no *meta* substitution.

It was proposed³⁷ that the importance of *meta* substitution is related to the "activity" of the attacking species with the relative reactivity of toluene and benzene serving as a basis for measuring this activity.

The striking parallel between the amount of *meta* substitution and the relative reactivity of toluene and benzene suggested a definite correlation. A plot of the log of the relative toluene/benzene reactivities versus the log of the toluene *para/meta* ratios

indicated a simple linear relationship between these quantities.³⁷ In order to eliminate possible complications from steric factors, the partial rate factors for substitution were calculated (Table VIII) and the log of the partial rate factor for the *para* position of toluene was compared with the log of the ratio of the partial rate factors for the *para* and *meta* positions of toluene (Figure 1).

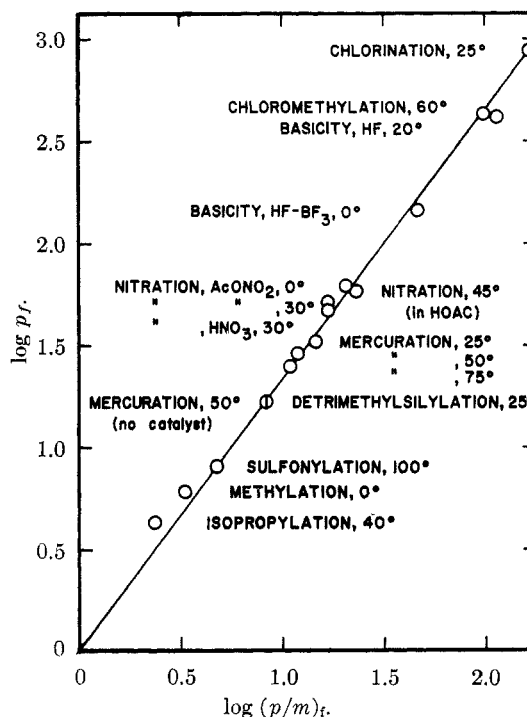


FIG. 1.—LINEAR RELATIONSHIP BETWEEN THE ELECTROPHILIC REAGENTS AND THE OBSERVED SELECTIVITY IN THEIR REACTIONS WITH TOLUENE.

The correlation of the activity of the reagent with the observed isomer distribution and molecular selectivity has a number of important implications. It has already been the basis for discovering inconsistencies in the literature data for chloromethylation and acylation. It then was found³⁷ that the existing data^{49,50} for the relative rates of chloromethylation were in error. The resolution of the inconsistency in the case of acylation has also been largely accomplished.⁵¹ The generalization should be very useful in guiding the choice of reaction conditions in order to give a maximum yield of a desired isomer.

The foregoing arguments have recently been utilized to demonstrate that a simple revision of the Hammett relationship is apparently applicable to electrophilic aromatic substitution reactions.⁵² The usual σ_m substituent constants are retained but new σ_p^+ substituent constants are required. There is good agreement with existing data. Unfortunately there are at present insufficient data with which to rigorously test this extended generalization. Qualitatively, it is expected that vari-

(35) McCaulay and Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952).

(36) Norris and Rubinstein, *J. Am. Chem. Soc.*, **61**, 1163 (1939).

(37) Brown and Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).

TABLE VIII
 PARTIAL RATE FACTORS FOR SUBSTITUTION IN TOLUENE

Reaction	Conditions	Partial Rate Factors			Ref.	
		o_f	m_f	p_f		
Chlorination	Cl ₂ in HOAc at 24°	611	5.3	887	38, 39	
Chloromethylation	CH ₂ O + HCl + ZnCl ₂ in HOAc at 60°	117	4.37	430	37	
Basicity	HF at 20°	145	3.6	414	40	
	BF ₃ -HF at 0°	103	3.1	145	41	
Nitration	AcONO ₂ in Ac ₂ O at 0°	47.1	3.00	61.8	21	
	at 30°	40.3	3.04	51.4	21	
	HNO ₃ in MeNO ₂ at 30°	36.8	2.77	46.7	21	
	HNO ₃ in 90% HOAc at 45°	42	2.5	58	22	
Mercuration	Hg(OAc) ₂ in HOAc with HClO ₄ at 25°	4.98	2.25	32.9	42	
	at 50°	4.20	2.41	28.8	42	
	at 75°	3.24	2.23	24.5	42	
	Hg(OAc) ₂ in HOAc only at 50°	4.63	1.99	17.0	43	
	at 70°	4.14	1.88	13.9	43	
	at 90°	3.52	1.74	11.4	43	
Detrimethylsilylation	ArSi(CH ₃) ₃ + H ₃ O ⁺ in HOAc at 25°	17.5	2.0	16.5	44, 45	
Sulfonylation	RSO ₂ Cl + AlCl ₃ at 100°	5.44	1.67	7.99	46, 47	
Methylation	MeBr + AlBr ₃ at 0°	5.66	1.82	6.05	31	
Isopropylation	C ₃ H ₈ + AlCl ₃ at 40°	2.37	1.80	4.27	27, 28	
For Comparison: Nitration	<i>tert</i> -Butylbenzene in 90% HOAc at 45° with HNO ₃	5.5	4.0	75	22	
	Ethyl phenylacetate in Ac ₂ O at 25° with HNO ₃	4.62	1.16	10.41	12	
	Trimethylsilylbenzene in Ac ₂ O at 0° with HNO ₃	1.17	1.84	8.82	14	
	Benzyl chloride in Ac ₂ O at 25° with HNO ₃	0.290	0.140	0.951	12	
	Iodobenzene in MeNO ₂ at 25° with AcONO ₂	.251	.0139	.792	8	
	Ethyl benzoate with AcONO ₂ at 18°	.0026	.0079	.0009	15	
	Bromination with Br ₂ and AlBr ₃ in CS ₂ at 55°	Fluorobenzene	.128	.0024	2.14	48
		Chlorobenzene	.0642	.00060	1.07	
Bromobenzene		.0402	.00030	0.519		

ous monosubstituted aromatics should give relationships such as are illustrated in Fig. 2. *meta*-Directing substituents should give lines having negative values for both $\log p_f$ and $\log (p/m)_f$. The data for bromination of the halobenzenes⁴⁸ appear to be in partial conflict with the indication of negative values of $\log p_f$ with positive values of $\log (p/m)_f$ for nitration.^{8, 23} If current investigation substantiates the bromination results, there will be good justification for questioning the conclusion⁵² that lines for all substituents should linearly radiate from the origin (statistical distribution). Alternatively, it may develop that substituents with counteracting inductive and conjugative effects cannot be correlated by this type of linear relationship.

THEORETICAL DISCUSSION

Up until the present time, theoretical attention has been focused almost exclusively upon the nature of the substituent. Since it has been established that the nature of the reagent is also of pri-

- (38) Condon, *J. Am. Chem. Soc.*, **70**, 1963 (1948).
 (39) de la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).
 (40) Kilpatrick and Luborsky, *J. Am. Chem. Soc.*, **75**, 577 (1953).
 (41) McCaulay and Lien, *J. Am. Chem. Soc.*, **73**, 2013 (1951).
 (42) Brown and McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2300 (1955).
 (43) Brown and McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2306 (1955).
 (44) Benkeser and Krysiak, *J. Am. Chem. Soc.*, **76**, 6353 (1954).
 (45) Benkeser and Thomas, unpublished results.
 (46) Truce and Vrieson, *J. Am. Chem. Soc.*, **75**, 5032 (1953).
 (47) Olivier, *Rec. trav. chim.*, **33**, 163 (1914).
 (48) Ferguson, Garner, and Mack, *J. Am. Chem. Soc.*, **76**, 1250 (1954).
 (49) Szmant and Dudek, *J. Am. Chem. Soc.*, **71**, 3763 (1949).
 (50) Vavon, Bolle and Calin, *Bull. soc. chim.*, [5], **6**, 1025 (1939).
 (51) Brown and Young, unpublished results.
 (52) McGary, Jr., Okamoto, and Brown, *J. Am. Chem. Soc.*, **77**, 3037 (1955).

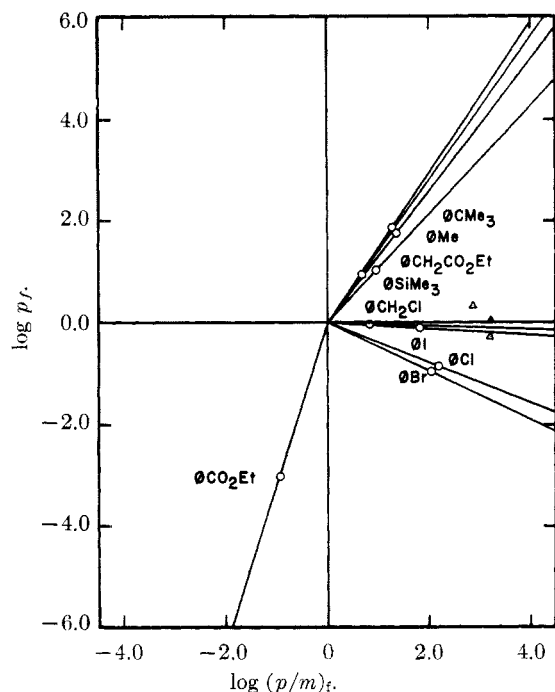


FIG. 2.—EXPECTED RELATIONSHIPS BETWEEN THE ACTIVITY OF THE ELECTROPHILIC REAGENTS AND THE SELECTIVITY OF THEIR REACTIONS WITH VARIOUS MONOSUBSTITUTED BENZENES. (Based upon the assumptions of statistical distribution for reagents of infinitely large activity and the validity of published nitration results.) The Δ 's indicate the apparent discrepancy for bromination of the halobenzenes.

mary importance, it is desirable to reinterpret the theoretical aspects of aromatic substitution with attention properly balanced between the steric and polar effects of both the substituent and the reagent.

BENZENE STRUCTURE

The elucidation of the structure of the benzene ring has attracted the serious attention of chemists for more than a century. In many respects, however, Thiele's⁵³ proposal of mutually neutralized partial valences comes very near to the picture given by modern theory.³ In the present concept,



each carbon atom of the benzene ring is regarded as being bound by σ -bonds to a hydrogen atom and two adjacent carbon atoms with the surplus electron occupying an atomic p -orbital. Just as in ethylene, where 2 p -orbitals laterally overlap to form a relatively strong π -bond in addition to the σ -bond, in benzene the 6 p -orbitals laterally overlap to form a closed group of relatively strong π -bonds. The lobes of the p -orbitals are directed perpendicularly to the plane of the ring and through interaction (hybridization) give a result which can be described as a hexagonal ring of CH groups with an annular π -electron cloud above and below the

(53) Thiele, *Ann.*, 306, 125 (1898).

ring. Resonance hybridization of the two Kekulé⁵⁴ structures accomplishes essentially the same end and is usually preferred in treatments of the chemistry of aromatic substances. The usual Kekulé formula has been used throughout this paper with the implicit assumption of hybridization to an actual system which would be better represented physically by a formula such as a modern interpretation of Thiele's.⁵³

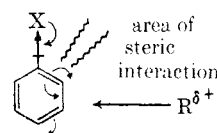
SUBSTITUTION MODEL

Almost as soon as chemists were able to distinguish the positions of substitution, generalizations have been put forth to explain and correlate observed facts. Many empirical rules have been proposed to aid in the prediction of the primary orientation of substituents as based upon various properties of the substituent groups and their constituent atoms. Although each has some merit, none is completely satisfactory.

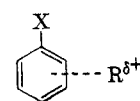
The general picture of electrophilic aromatic substitution may be conveniently described in terms of a model such as the following in which an electron-deficient reagent,



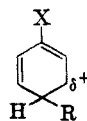
approaches and reacts with the benzene nucleus.



Any steric interaction between the substituent and the reagent will decrease the proportion of *ortho* substitution and correspondingly increase the proportions of *meta* and *para* substitution. Due to the differences in polar character between H and X, the distribution of the π -electrons will not be uniform around the ring even in the undisturbed molecule. The proximity of the reagent may further distort the distribution of the π -electrons as reaction occurs. Finally, the reactivity of the reagent will determine to what extent it can take advantage of or be affected by the steric and polar effects of the substituent. Dewar⁵⁵ considers that the rate-determining step will be governed by the formation and stability of the π -complex, but it has been shown⁵⁶ that the rate is instead largely determined by the stability of the σ -complex.



π - Complex



σ - Complex

(54) Kekulé, *Bull. soc. chim.*, 3, 98 (1865).

(55) Dewar, *Electronic Theory of Organic Chemistry*, Oxford University Press, New York, New York, 1949.

(56) Brown and Brady, *J. Am. Chem. Soc.*, 74, 3570 (1952).

NATURE OF STERIC EFFECTS

As the history of organic chemistry has unfolded, various types of steric hindrance have been proposed to explain apparent anomalies. Frequently, such proposals were resorted to merely because no other explanation could be given. When careful studies uncovered many cases of misapplication, the concept of steric hindrance somewhat fell into disrepute. However, the areas of correct application are now rather well established. Because the term steric hindrance implies direction of operation of the effect, it should be reserved for cases of retarded reaction with the term steric assistance applying in the other direction.

The existence of restricted rotation in ethane and its homologs^{57,58} cannot (in the strict sense) be due to "bulk" interactions between non-bonded atoms. Taft⁵⁹ has proposed that such non-bulk interactions are the result of steric hindrance to motion. This steric hindrance to motion is really a manifestation of non-compressional repulsion of closely situated electronic clouds. For this reason, polar hindrance to motion would seem to be a more appropriate term. These secondary effects are relatively unimportant for this discussion since they are only involved in entropy considerations whereas the primary (bulk) steric effects are directly involved in energy considerations. The bulk steric effects are manifestations of compressional repulsion of electronic clouds in contact. This paper will consider only the bulk type of steric interaction.

Although F-Strain²⁴ is the type of bulk interaction which is usually involved in electrophilic aromatic substitution, two or more adjacent substituents may operate to suppress the resonance effect of the directing substituent by means of the B-Strain²⁴ type of bulk interaction. The concept of homomorphism²⁰ provides a valuable tool for correlating the relative sizes of various substituents.

NATURE OF POLAR EFFECTS

Electronegativity is defined⁶⁰ as the power of an atom in a molecule to attract electrons to itself. The electrostatic attraction between the positively charged nucleus and the surrounding orbital electrons will depend upon the magnitude of the nuclear charge, the number of electrons, and their distance from the nucleus. In principle, electronegativity may be regarded as the net electrostatic attraction between the nucleus and the valence electrons as a result of the screening effect of the electrons of the inner orbitals. The well known decrease of atomic and ionic radii as one arranges the elements within any given period in the order

of increasing atomic number is illustrative of the effectiveness of this attraction. When dissimilar atoms are bonded together, the valence electrons will not be equally shared but will be shifted toward the more electronegative atom proportional to the difference in electronegativity of the two atoms. In polyatomic molecules the situation is complex but, nevertheless, the distribution of valence electrons will involve a balance between the attraction of all the constituent atoms.

Carbon and hydrogen are dissimilar atoms, but there is a symmetrical arrangement of these atoms in benzene so that the distribution of valence electrons in benzene will be symmetrical as far as the whole molecule is concerned. When, however, one of the hydrogen atoms is replaced by a substituent, X, this symmetry is destroyed. The electronic distribution in the C—X bond will be different from the C—H bond which it replaces and this difference will be partially transmitted⁶¹ to the rest of the molecule so that electronic distributions in the other C—C and C—H bonds will be somewhat different than in the unsubstituted benzene. The π -electrons of the benzene nucleus are mobile and not restricted to any particular ring position so that the distribution of the π -electrons is more susceptible to the difference in electronegativity between H and X than are the electrons of the σ -bonds. The transmission of this effect beyond the region of the C—X bond is commonly referred to as the inductive effect.³

In spite of the many treatments devoted to the subject, the exact nature of the inductive effect is not fully established. Differences of opinion are concerned primarily with the mode of transmission of the inductive effect from the substituent to the various positions of the benzene ring and to the entering group. Principles of electrostatics provide that the effect of a localized charge will be inversely proportional to the distance from that charge. This is the underlying assumption in considerations of the direct field effect.⁶²⁻⁶⁴ Adherents of the direct field effect consider that the electrostatic influence of the substituent is transmitted partly through the solvent and partly through the "solvent cavity" (body of the molecule and the space between solvent and molecule). The results of Roberts⁶⁴ demonstrate that much refinement is necessary before this theory could be satisfactory (if it is valid).

It is considered by others that the inductive effect is transmitted only through the chain of atoms by means of an induced but diminishing distortion

(57) Kistiakowsky, Lacher, and Stitt, *J. Chem. Phys.*, **7**, 289 (1939).

(58) Pitzer, *J. Chem. Phys.*, **8**, 711 (1940).

(59) Taft, *J. Am. Chem. Soc.*, **75**, 4231, 4534, 4538 (1953).

(60) Pauling, *The Nature of the Chemical Bond*, 2nd Ed., Cornell University Press, Ithaca, New York, 1940.

(61) Lewis, *Valence and the Structure of Atoms and Molecules*, the Chemical Catalog Company, New York, New York, 1923.

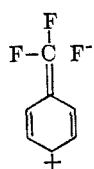
(62) Bjerrum, *J. physik. Chem.*, **106**, 219 (1923).

(63) Kirkwood and Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).

(64) Roberts and Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953).

of the electron distribution from one bond to the next. The result is essentially the same as that given by the direct field theory. The English School³ on the other hand maintains that the inductive effect is coulombic in origin but that it is also transmitted by means of conjugation so that the effect decreases in the order $o > p > m$.

The arguments center around two substituents; namely, CF_3 and NMe_3^+ which both give essentially exclusive *meta* orientation. The preferential relay of the inductive effect to the *ortho* and *para* positions of the benzene ring was proposed by Ingold³ and others of the English School to explain the practically exclusive formation of *meta* derivatives with these substituents. Roberts⁶⁵ has shown that a small conjugative effect of the type illustrated can provide a qualitative explanation of the effect of CF_3 . It is doubtful, however, that this factor alone is



(9 forms)

sufficient to explain the exclusive formation of the *meta* isomer in electrophilic substitution. Roberts⁶⁶ has further shown that the effects of $m\text{-NR}_3^+$ on reactions of NR_2 and CO_2H are not very different from $p\text{-NR}_3^+$ and that the effect of the $m\text{-NR}_3^+$ is a little stronger than for the $p\text{-NR}_3^+$. This is interpreted on the basis that no conjugative effect is involved and that the inductive effect is essentially coulombic and has the order $o > m > p$. Roberts proposes to explain the strong *meta*-directing influence of NR_3^+ on the basis of some empirical calculations which show that an intermediate (σ -complex) with the entering group at the *m*-position will be approximately 10 kcal./mole more stable than for the corresponding intermediate having the entering group at the *p*-position. The *meta* intermediate does not require positive charges to appear on adjacent atoms while the *para* intermediate does. The CF_3 group could involve the same general pattern with the effect being due to



the strong C—F dipole. In this case, however, the conjugative effect, which might be regarded as being analogous to hyperconjugation, could also contribute.

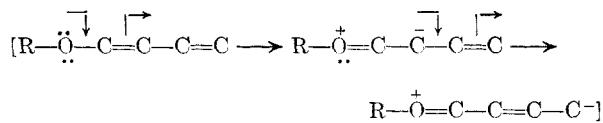
(65) Roberts, Webb, and McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).

(66) Roberts, Clements, and Drysdale, *J. Am. Chem. Soc.*, **73**, 2181 (1951).

The present facts do not allow us to make a final decision as to the mode of transmission of the inductive effect. It is hoped that the necessary data will soon become available so that the dilemma may be settled without prejudice. It may be correct to assume that there is a fundamental coulombic induction with $o > m > p$ upon which in some instances a conjugative relay might be superimposed to a sufficient extent to give a new overall order of $o > p > m$. Resonance stabilization of the intermediate could be something rather distinct from the underlying inductive effect and in certain cases, such as with NR_3^+ , may be the predominant effect.

Resonance^{3,60,67-71} is a concept that is easier to apply than to define or describe. If the formula giving the correct arrangement of constituent atoms for a compound or radical can be written with more than one valid distribution of the valence electrons, the actual electronic structure cannot be represented correctly by any of the individual structures but must be something intermediate. The correct structure will be the weighted mean of all the valid contributing structures. The concept of resonance does not in any way connote the actual shift or oscillation of electrons.

For molecules which contain double bonds it is often expedient to focus attention upon the structures contributing to the resonance hybrid which involve partial ionization of π -bonds. This partial ionization becomes more important when the atoms involved in the double bond are electrically dissimilar whether they have different substituents or are themselves different. In molecules which contain alternate double and single bonds, the π -bonds seem to be coupled and act as a unit. They are said to be conjugated. In contrast with the inductive effect which rapidly diminishes in magnitude as it is transmitted along a chain of atoms, electronic displacements of the conjugative type may be transmitted undiminished along a conjugated system. The conjugative effect, however, can only influence alternate positions. Thus, in aromatic molecules the *meta* position is unaffected by the conjugative effect of the substituent.



(67) Pauling, In Gilman's *Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York, New York, 1943, Vol. II, Chapt. 26.

(68) Remick, *Electronic Interpretation of Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York, New York, 1949.

(69) Wheland, *The Theory of Resonance*, John Wiley and Sons, Inc., New York, New York, 1944.

(70) Wheland, *Advanced Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York, New York, 1949.

(71) Baker, *Hyperconjugation*, Oxford University Press, New York, New York, 1952.

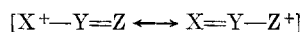
Since the *meta* position is not affected by conjugative factors, it should serve as an excellent basis for correlations of isomer distribution.¹² The *ortho/meta* ratio exhibits the combined effects of both steric and polar factors while the *para/meta* ratio is affected only by polar influences. The *ortho/para* ratio is ambiguous and, therefore, is generally unsatisfactory for correlating the effects of various substituents. In the event that there were no conjugative relay of the inductive effect, we could perhaps regard the partial rate factor for substitution in the *meta* position (m_i) as a measure of the importance of the inductive effect. In a similar way, we could regard the ratio of the partial rate factors for substitution in the *para* and *meta* positions (p/m)_{*i*} as a measure of the importance of the conjugative effect. This line of reasoning would then logically lead us to the conclusion (in the absence of steric factors) that the orienting influence of the substituent is predominantly determined by the conjugative effect. Such a conclusion seems to be quite generally valid.

We should recognize three aspects of the operation of polar factors. The presence of the substituent, X, attached to the ring will set up a certain distribution of the π -electrons in the undisturbed molecule through the superimposed operations of induction and resonance. The difference between the ground state electron distributions of unsubstituted benzene and benzene containing the substituent is termed *polarization*.³

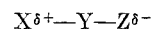
As reaction proceeds the attacking reagent will tend to approach more or less preferentially to the positions of highest electron density. In this stage the substituent and the reagent will likely exert direct electrostatic influence upon each other through the solvent. Now as the reagent comes closer to bonding distance, the substituent and reagent will exert most of their influence upon each other through the aromatic nucleus. The entering group will exert an electrostatic attraction upon the substituent and the valence electrons of the aromatic molecule through the superimposed operations of induction and resonance. The ability of the substituent (and the aromatic nucleus) to respond to this attraction is called polarizability. *Polarizability* is the difference between the electron distributions in the ground state and the transition state and is developed predominantly through the conjugative effect.³

Most authors have paid relatively little attention to the nature of the reagent. The fallacy in so doing should be obvious when it is realized that the reagent plays such an integral part in polarizability. In the sense that the reagent is the direct cause of the observed polarizability, it is convenient to refer to the reagent as the *polarizer*. This term was chosen to emphasize the polar character of the reagent as opposed to its energy character. It seems likely that two factors can describe the

nature of various polarizers; namely, magnitude and geometry of electrical charge. Thus, a small ion of unit charge, X⁺, could effect stronger polarizability than a hybrid ion where the charge is not localized such as



which in turn could effect a stronger polarizability than a dipole such as



We should also expect to find a secondary polarizability effect in the polarizer but this will not significantly alter our qualitative description of the polarizer.

The *meta*-directing substituents apparently can be subdivided into two classes depending upon whether or not the atom attached to the benzene ring is involved in multiple bond formation. Those preponderantly *meta*-directing substituents which have multiple bonds in a position *alpha* to the ring lead to an unusually high preponderance of *ortho* over *para* substitution. Of the suggestions that have been offered to explain this behavior, two are particularly attractive. Waters⁷² has discussed this on the basis of chelate formation. These substituents concerned are just those that form internal chelates with *ortho* groups such as OH. It is a plausible assumption to consider that the electrophilic reagent (which has the necessary charge type) is preferentially attracted (direct field effect) to the substituent. We might consider that subsequent reaction has the substituent as the point of origin instead of the bulk of the solution. Regardless of the point of origin, energy considerations still greatly favor the *meta* position. The point of origin (close to the *ortho* positions and distant from the *para* position) should largely favor the *ortho* position at the expense of the *para* position since the energy considerations should be closely similar. Ingold favors another explanation.³ He suggests that the resonance form which preferentially removes electrons from the *ortho* position requires the delocalization of only one π -bond while the corresponding form which would preferentially remove electrons from the *para* position requires the delocalization of two π -bonds. Since greatest stability and lowest energy are associated with species having the greatest electron delocalization (uncertainty of electronic position), the uncertainty principle then leads to the prediction that the greater positive charge would be at the *para* position thus preferentially deactivating the *para* position toward substitution. Ingold³ has carried out some empirical calculations from which he concludes that this explanation is correct while the explanation based on chelation is in error. Without additional experimental evidence, it is impossible to make any sound conclusions. It is possible that

(72) Waters, *J. Chem. Soc.*, 727 (1948).

each may be involved and it is almost certain that chelation will be required to explain results such as the high proportion of *ortho* isomer produced in the mercuration of nitrobenzene⁷³ and benzoic acid.⁷⁴

NATURE OF THE TRANSITION STATE

Melander⁷⁵ has demonstrated for nitration and bromination that there is no isotope effect in the loss of the substituted proton. This was taken to mean that there is no significant loosening of the proton in the transition state. Hammond⁷⁶ has considered the possibility that Melander's results cast doubt on the existence of a metastable intermediate in nitration and bromination. Without conclusion, he also considered the alternate possibility that Melander's results could be interpreted on the basis that the transition states are considerably displaced from the configuration of the intermediate. The correlation of the rates of halogenation of the methyl benzenes with their relative basicities toward $\text{HF}-\text{BF}_3$ ^{38,56} provides supporting evidence for the conclusion that metastable intermediates are involved in electrophilic aromatic substitution. The lack of correlation between the rates of halogenation of the methylbenzenes with their relative basicities toward HCl leads to the conclusion that the important intermediates are σ -complexes and not π -complexes.⁵⁶ It is further considered that these σ -complexes are intermediates and not transition states.⁵⁶ However, the correlation between halogenation rates and σ -complex stability^{38,56} demonstrates that the transition states (for halogenation) are qualitatively similar to the σ -complex intermediates.

For certain reactions, the nature of the π -complex may have significant influence on the nature of the transition state. The presumed energy characteristics of various reaction paths are illustrated in Fig. 3.

The large differences in relative rates and isomer distributions in substitution when the substituent is kept constant (Table VIII and Fig. 1) can only be reconciled on the basis that the nature of the reagent is of primary importance in determining the nature of the transition state.

Maxwell's well known energy distribution law provides a suitable basis for rationalizing the observed directing effects toward various reagents. It is first assumed that the free energies of activation for substitution at the *ortho*, *meta*, and *para* positions are not the same but yet not greatly different. Now let us compare two reactions in which the magnitudes of the free energies of activation are greatly different. When the free energy of activation is relatively low, a rather high proportion of the

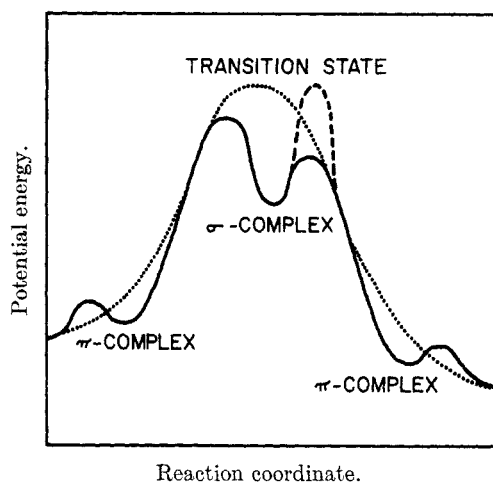
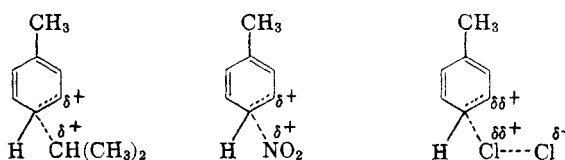


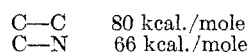
FIG. 3.—SCHEMATIC REPRESENTATION OF THE POSSIBLE ROLES OF METASTABLE COMPLEXES AND TRANSITION STATES IN ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS. Simple transition state for reaction not involving complexes. ——— Expected course of reaction for nitration and bromination where the loss of the proton is not kinetically significant. - - - - Expected course of reaction for sulfonation where the loss of the proton is kinetically significant.

attacking species will have sufficient energy to form the transition states for reaction at any of the positions. In such a case we should expect very little difference in the rates of substitution. When the free energy of activation is relatively high, a very low proportion of the attacking species will have sufficient energy for reaction at *any* of the positions but a significantly greater proportion will have sufficient energy to react at *that* position requiring least energy. In this case we should expect a rather large difference in the rates of substitution at the three positions.

It is instructive to consider the nature of the transition states for alkylation, nitration, and chlorination. For the present argument, the isopropyl carbonium



ion, $\text{CH}(\text{CH}_3)_2^+$, and the nitronium ion, NO_2^+ , are considered to be essentially discrete species with rather fully developed charges while chlorine is at best dipolar. The energy⁷⁷ to be gained by formation of the new bonds



suggest that alkylation may involve transition states with significantly lower free energies of activation. Thus, alkylation gives almost random distribution while nitration is fairly selective. In the

(73) Jackson, Jr., and Frant, *J. Am. Chem. Soc.*, **77**, 5625 (1955).

(74) Dimroth, *Ann.*, **446**, 148 (1925).

(75) Melander, *Arkiv. Kemi*, **2**, 213 (1950).

(76) Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(77) Pitzer, *J. Am. Chem. Soc.*, **70**, 2140 (1948).

case of chlorination, a considerable proportion of the energy to be gained by formation of the new C—Cl bond may be required

C—Cl	78 kcal./mole
Cl—Cl	57.1 kcal./mole

to supply the energy needed to break the old Cl—Cl bond. We might then expect a high free energy of activation and a very low proportion of the attacking species having sufficient energy to react with all positions but (relatively speaking) a much larger proportion having sufficient energy to react with the position requiring the least energy. Bromination without catalysts (or with mild catalysts such as iodine) is comparable to chlorination. However, for bromination with more electrophilic catalysts such as FeBr₃ and AlBr₃, the reagent would be considerably more polar (Br—Br bond already largely broken), the free energies of activation should be considerably lower and the selectivity should be much less. Price⁷⁸ has found this to be the case. If the bromonium ion, Br⁺, could be formed as a discrete species, it should be relatively nonselective and give a nearly random distribution. This may have been accomplished by de la Mare, Ketley, and Vernon.⁷⁹

Inherent in the transition state theory is the consideration that the degree of new bond formation is proportional to the free energy of activation. In the transition states for electrophilic aromatic substitution, the new bonds will be largely ionic with varying covalent contributions depending in large measure upon the nature of the reagent (polarizer). The correlation demonstrated in Table VIII and Fig. 1 can be readily interpreted on the basis that the relative reactivity and isomer distribution is directly related to the degree of covalency of the partially formed new bond in the transition state. On this basis, a species with a fully developed charge will give a transition state in which the new bond is almost completely ionic and distribution will be non-selective. A species that is essentially covalent will be extremely selective. In these

(78) Price and Kane, private communication.

(79) de la Mare, Ketley, and Vernon, *Research*, **6**, 125 (1953).

terms, a transition state having the greatest degree of covalency in the partially formed new bond will most closely resemble the σ -complex intermediate. This concept should find considerable utility in studying the nature of the attacking species.

Thus, we can conclude that chloromethylation in acetic acid solution⁸⁷ and benzylation in nitrobenzene⁸¹ are both reactions which involve attack on the benzene ring by dipolar rather than fully ionic species.

There have been a number of attempts to account for the isomer distributions observed in electrophilic aromatic substitution by estimating the relative electron density at individual positions of the aromatic ring⁸⁰⁻⁸² or the index of free valency,⁸³ or the relative stability of an idealized transition state or carbonium ion intermediate.⁸⁴⁻⁸⁹ The latter treatments most closely approach the interpretations expressed here. However, these treatments are based largely on data from nitration studies. Since they do not take the nature of the reagent into significant account, they can only be regarded as first approximations. The importance and nature of the reagent must be included before any theoretical treatment can be considered satisfactory.

Acknowledgment. This paper was written and presented with the helpful suggestions and encouragement of Professor Herbert C. Brown to whom thanks are due for his contributions in the development of a better understanding of aromatic substitution.

LAFAYETTE, INDIANA

- (80) Ri and Eyring, *J. Chem. Phys.*, **8**, 433 (1940).
 (81) Price, *Chem. Revs.*, **29**, 37 (1941).
 (82) Sanderson, *Science*, **122**, 598 (1955) (Reference added in revision—author).
 (83) Daudel and Pullman, *J. Chim. Phys.*, **43**, 77 (1946).
 (84) Wheland, *J. Am. Chem. Soc.*, **64**, 900 (1942).
 (85) Price, *J. Am. Chem. Soc.*, **73**, 5833 (1951).
 (86) Dewar, *J. Am. Chem. Soc.*, **74**, 3357 (1952).
 (87) Roberts and Streitwieser, Jr., *J. Am. Chem. Soc.*, **74**, 4723 (1952).
 (88) Hey and Williams, *Disc. Faraday Soc.*, **14**, 216 (1953).
 (89) Sixma, *Rec. trav. chim.*, **72**, 543 (1953).