GEORGE A. OLAH

Mechanism of Electrophilic Aromatic Substitutions[1]

GEORGE A. OLAH

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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Electrophilic aromatic substitution is one of the most studied of organic reactions.[2] Excellent reviews are available, and it is not my purpose to give a general summary of the field. Instead I will attempt to concentrate on mechanistic aspects of current interest, emphasizing conclusions which can be reached from some of our recent work.

A single-step, direct substitution mechanism would be expected to involve a kinetic hydrogen isotope effect in deuterated (or tritiated) aromatics, but in many systems such an isotope effect is not observed. This observation, together with substantial evidence for the formation of ionic intermediates, leads to the generally accepted two-step mechanism. Attack of an electrophile on the aromatic compound forms an intermediate cyclohexadienyl cation (Pfeiffer–Wizinger complex,[3a] Wheland intermediate,[3b] Brown σ complex, or, as suggested by Doering,[4] benzenonium ion, although it should be now recognized that the systematic name for trivalent cyclohexadienyl cations is benzenium ion[5]).
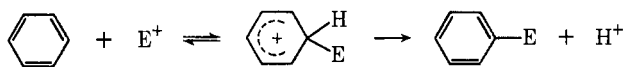
It is generally assumed, as stated, for example, by Ingold,[6] that cationic cyclohexadienyl intermediates represent satisfactory comparison models for the transition states of electrophilic aromatic substitutions.

Brown in his extensive studies[7] showed that there exists a simple linear relationship between relative rates of numerous electrophilic aromatic substitutions and the relative stabilities of the related σ complexes. He therefore concluded that the transition state for these reactions generally resembles a σ complex. Considerable direct experimental evidence has since been obtained to prove that σ complexes do exist as stable intermediates.[8] However, their existence does not necessarily prove that the transition states are always closely related to the σ complexes.

It was Dewar who originally proposed[9] that π complexes may play an important role in electrophilic aromatic substitutions. He suggested the mechanism
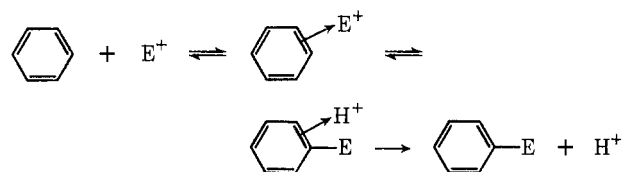
Consequently the rate of substitutions should parallel the stability of π complexes.

In previous studies[10] we reported a series of electrophilic aromatic substitutions involving strongly electrophilic reagents, which showed low substrate selectivity in the form of low $k_{toluene}/k_{benzene}$ rate ratios, but at the same time high positional selectivity (generally high ortho/para isomer ratios with only a small amount of the meta isomer formed). We expressed

(1) Aromatic Substitution. XXVIII. Part XXVII: G. A. Olah and S. Kobayashi, *J. Amer. Chem. Soc.*, **92**, 6369 (1970). (b) Based in part on a lecture presented in May 1970 at the joint meeting of the American Chemical Society and the Chemical Institute of Canada, Toronto, Ontario.

(2) (a) For recent reviews see: R. Breslow, "Organic Reaction Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1969; (b) L. Stock, "Aromatic Substitution Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1968; (c) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963); (d) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. I-IV, Wiley-Interscience, New York and London, 1963-1964; (e) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," American Elsevier Publishing Co., New York, N. Y., 1965; (f) P. B. D. De la Mare and J. Ridd, "Aromatic Substitutions—Nitration and Halogenation," Academic Press, New York, N. Y., 1959; (g) E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964); (h) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 264-417; (i) J. March, "Advanced Organic Chemistry, Reaction, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, pp 376-441.

(3) (a) P. Pfeiffer and R. Wizinger, *Justus Liebigs Ann. Chem.*, **461**, 132 (1928); (b) G. W. Wheland, *J. Amer. Chem. Soc.*, **64**, 900 (1942); "The Theory of Resonance," Wiley, New York, N. Y., (1944); (c) H. C. Brown and J. D. Brady, *J. Amer. Chem. Soc.*, **74**, 3570 (1952).

(4) W. v. E. Doering, M. Saunders, H. G. Boynton, H. W. Earhart, E. F. Wadley, W. R. Edwards, and G. Laber, *Tetrahedron*, **4**, 178 (1958).

(5) For a definition and naming of carbocations see G. A. Olah, *J. Amer. Chem. Soc.*, in press.

(6) C. K. Ingold, "The Transition State," *Spec. Publ. Chem. Soc.*, **No. 16**, 119 (1962).

(7) (a) For a summary see ref 2c; (b) H. C. Brown and K. L. Nelson in "Chemistry of Petroleum Hydrocarbons," B. T. Brooks, S. S. Kurtz, C. B. Board, and L. Schmerling, Ed., Vol. III, Reinhold, New York, N. Y., 1955, pp 465-578.

(8) (a) H. C. Brown and H. W. Pearsall, *J. Amer. Chem. Soc.*, **74**, 191 (1952); (b) H. C. Brown and W. J. Wallace, *ibid.*, **75**, 6267, 6268 (1953); (c) A. Klit and A. Langseth, *Z. Phys. Chem.*, **176**, 65 (1936); (d) D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.*, **73**, 2013 (1951); *Tetrahedron*, **5**, 186 (1959); (e) M. Kilpatrick and F. E. Luborsky, *J. Amer. Chem. Soc.*, **75**, 577 (1953); (f) G. A. Olah, S. J. Kuhn, and A. Pavlath, *ibid.*, **80**, 6535, 6541 (1958); *Nature (London)*, **178**, 693 (1956); (g) E. L. Mackor, A. Hofstra, and J. H. van der Waals, *Trans. Faraday Soc.*, **54**, 66, 187 (1958); (h) G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 1103 (1965); (i) V. Gold and F. L. Tye, *J. Chem. Soc.*, 2172 (1952); (j) C. Reid, *J. Amer. Chem. Soc.*, **76**, 3264 (1954); (k) G. Dallinga, E. L. Mackor, A. Hofstra, and A. A. Verrijn Stuart, *J. Mol. Phys.*, **1**, 123 (1958); (l) C. MacLean and E. L. Mackor, *J. Mol. Phys.*, **4**, 241 (1961); *Discuss. Faraday Soc.*, **34**, 165 (1962); (m) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **42**, 502 (1964); (n) H. H. Perkampus and E. Baumbgarten, *Angew. Chem.*, **76**, 965 (1964); H. H. Perkampus, *Advan. Phys. Org. Chem.*, **4**, 195 (1966); (o) ref 8; (p) D. M. Brouwer, E. L. Mackor, and C. L. MacLean in "Carbonium Ions," G. A. Olah and P. v. R. Schleyer, Ed., Vol. II, Wiley-Interscience, New York, N. Y., 1970, Chapter 20.

(9) M. J. S. Dewar, *J. Chem. Soc.*, 406, 777 (1946); *Nature (London)*, **176**, 784 (1954); M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949.

(10) (a) See Table I, footnote *g*; (b) G. A. Olah, S. J. Kuhn, S. Flood, and J. C. Evans, *J. Amer. Chem. Soc.*, **84**, 3687 (1962); (c) see Table I, footnote *i*.

the view that in these systems the transition state of highest energy (which determines substrate selectivity) is of a π-complex nature followed by σ-complex formation determining positional selectivity.

Our concepts attracted interest[2a] but were also criticized. In criticism[11] it was suggested that the above results could be a consequence of incomplete mixing before fast reaction with the very reactive electrophilic reagents. In my opinion our studies, including more recent work summarized in this Account, clearly indicate that we are not dealing with an experimental artifact but are encountering a new and important, quite general, type of electrophilic aromatic substitution displaying low substrate but at the same time high positional selectivity.

Correlation of Reaction Rates with Complex Stabilities

Brown and Stock found excellent correlation between relative rates of halogenation (and other electrophilic substitutions) and relative stabilities of σ complexes.[2c] It is difficult, however, to decide what are the proper values for the relative stabilities of the σ complexes, particularly for benzene and toluene, for which these values are not easily determined. For example, the current books of Breslow[2a] and March[2i] list the relative σ-complex stabilities of toluene and benzene as 7:1 (based on data of ref 8e), whereas the value according to Mackor[8g] is 790:1. The basicities of methylbenzenes were first measured by McCaulay and Lien[8d] by means of competitive extraction experiments in which mixtures of methylbenzenes competed for a limited amount of acid (HF–BF₃). Kilpatrick and Luborsky[8e] calculated absolute basicity constants from conductance experiments (in HF). Mackor, Hofstra, and van der Waals[8g] critically redetermined the basicity constants by the distribution technique, but under much more dilute conditions than used by McCaulay and Lien, allowing determination of activity coefficients for the solutions. The data of Mackor, et al.,[8g] must be considered the most reliable set of relative σ-basicity data for benzene and alkylbenzenes.

Table I summarizes the relative σ and π basicities of benzene and the methylbenzenes and the relative rates of some electrophilic aromatic substitution reactions. In Table I, the correlation between relative rates of certain halogenation and σ basicities is excellent. These data seem to strengthen the concept that for these reactions the transition state resembles the Wheland intermediate (σ complex). However, not all the rate data correlate with relative σ basicities.

Table I

Relative Rates of Aromatic Substitutions and Their Comparison with Relative σ and π Basicities

	Relative σ-complex stability $(HF–BF_3)$[8g]	Relative π-complex stability[a]	Relative bromination rate, Br_2 — 85% CH_3CO_2H	Relative bromination rate, Br_2 — CF_3CO_2H[b]	Relative chlorination rate, Cl_2 — CH_3CO_2H[c]	Relative chlorination rate, Cl_2 — CH_3CN[d]	Relative chlorination rate, Cl_2 — CF_3CO_2H[b]	Halogenation — Br_2–$FeCl_3$–CH_3NO_2[e]	Halogenation — Cl_2–$FeCl_3$–CH_3NO_2[f]	Nitration — $NO_2^+BF_4^-$ sulfolane[g]	Nitration — HNO_3 in sulfolane[k]	Acylation — $C_6H_5CH_2Cl$–$AlCl_3$–CH_3NO_2[i]	Acylation — i-C_3H_7Br–$AlCl_3$–CH_3NO_2[j]
Benzene	1	1.0	1	1	1	1	1	1.0	1.0	1.0	1	1.0	1.0
Methyl	790	1.5	605	2,580	340	1,530	2,445	3.6	13.5	1.6	20	3.2	2.0
1,2-Dimethyl	7,900	1.8	5,300	50,800	2,030			3.9	38.0	1.7	61	4.2	2.2
1,3-Dimethyl	1,000,000	2.0	514,000		180,000		247,000	5.6	110.0	1.6	100	4.6	2.8
1,4-Dimethyl	3,200	1.6	2,500	9,080	2,000		14,200	4.3	43.9	1.9	114	4.3	2.7
1,2,3-Trimethyl	2,000,000	2.4	1,670,000										
1,2,4-Trimethyl	2,000,000	2.2	1,520,000										
1,3,5-Trimethyl	630,000,000	2.6	189,000,000		30,000,000			15.9	632.0	2.7	400	5.2	0.3
1,2,3,4-Tetramethyl	20,000,000	2.6	11,000,000										
1,2,3,5-Tetramethyl	2,000,000,000	2.7	420,000,000										
1,2,4,5-Tetramethyl	10,000,000	2.8	2,830,000		1,580,000								
Pentamethyl	2,000,000,000		810,000,000		134,000,000								

[a] L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964. [b] G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, J. Amer. Chem. Soc., 86, 1039 (1964). [c] E. Baciocchi and G. Illuminati, Gazz. Chim. Ital., 92, 89 (1962). [d] L. J. Andrews and R. M. Keefer, J. Amer. Chem. Soc., 81, 1063 (1959). [e] G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, ibid., 86, 1044 (1964). [f] P. B. D. De la Mare, J. T. Harvey, M. Hasson, and S. Varma, J. Chem. Soc., 2756 (1958). [g] G. A. Olah, S. J. Kuhn, and S. Flood, J. Amer. Chem. Soc., 83, 4571 (1961). [k] J. G. Hoggett, R. B. Moodie, and K. Schofield, J. Chem. Soc. B, 1 (1969); Chem. Commun., 605 (1969). [i] G. A. Olah, S. J. Kuhn, and S. Flood, J. Amer. Chem. Soc., 84, 1688 (1962); G. A. Olah and N. Overchuk, ibid., 87, 5786 (1965). [j] G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuk, ibid., 86, 1046 (1964).

(11) (a) C. D. Ritchie and H. Win, J. Org. Chem., 29, 3093 (1964); (b) W. S. Tolgyesi, Can. J. Chem., 43, 343 (1965) (for a rebuttal, see G. A. Olah and N. Overchuk, ibid., 43, 3279 (1969); (c) J. D. Ridd, "Studies on Chemical Structure and Reactivity," Methuen, London, p 152; (d) H. C. Brown and R. Wirkkala, J. Amer. Chem. Soc., 88, 145 (1966); (e) H. Cerfontain and A. Telder, Recl. Trav. Chim. Pays-Bas, 86, 377 (1967); (f) S. W. Caille and J. P. Corriu, Chem. Commun., 1251 (1967); Tetrahedron, 25, 2005 (1969); and most notably (g) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 290.

In the early sixties we suggested that the rates of a number of observed electrophilic aromatic substitutions are related to π basicities and not σ basicities of the substrates.

Substitutions which showed relative rates related to the π basicities of the aromatic substrates included nitronium salt nitrations, Friedel–Crafts-type alkylations, bromination, and chlorination using strongly electrophilic halogenating agents ($FeCl_3$ or $AlCl_3$ catalysts). Many additional electrophilic aromatic substitutions reported in the literature (such as the classical Ingold nitrations,[12] Brown's alkylation,[13] many halogenations,[2f] sulfonations,[14] and other reactions) cannot be considered to follow closely σ basicities but show intermediate character or much closer relationship to the π basicities.

In view of the discussed relationship of substitution rates and complex stabilities (which are significantly different for σ and π complexes, as shown in Table I), the wide acceptance of the view that transition states of electrophilic aromatic substitutions generally resemble σ complexes is surprising. The observed low substrate but high positional selectivity reactions in our work made it necessary to suggest that substrate selectivity is determined in an early π complex, followed by formation of σ complexes (for the ortho, meta and para isomers) determining positional selectivity.[10] It was concerning this suggestion that a controversy arose relating to the mechanism of electrophilic aromatic substitution.[11]

Substituent Effects in Electrophilic Reagent Influencing Selectivity

Our recent work[15,16] has specifically proved that the transition states of electrophilic aromatic substitutions are not rigidly fixed, resembling always the Wheland intermediates, but frequently represent a much earlier state on the reaction coordinate resembling starting aromatics. The nature of the transition state will be discussed in more detail later.

Friedel–Crafts Benzylation. We recently found that it is possible to vary in a systematic way the electrophilicity of reagents, such as alkylating agents, by introducing suitable substituents. Thus a regular change of the transition state of highest energy can be observed from σ complex to π complex. The first
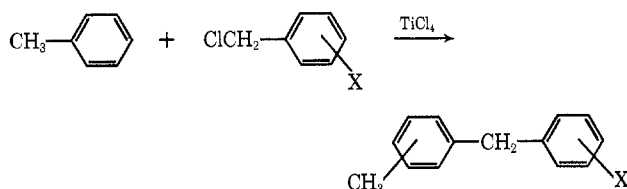
(12) C. K. Ingold, et al., Nature (London), **158**, 448 (1946); J. Chem. Soc., 2400 (1950), and subsequent papers.
(13) H. C. Brown and M. Grayson, J. Amer. Chem. Soc., **75**, 6285 (1953); H. C. Brown and B. A. Bolto, ibid., **81**, 3320 (1959); H. C. Brown and G. Marino, ibid., **81**, 3308 (1959); for a review see ref 2c.
(14) For a summary see H. Cerfontain, "Mechanistic Aspects in Aromatic Sulfonation," Wiley-Interscience, New York, N. Y., 1968.
(15) G. A. Olah, M. Tashiro, and S. Kobayashi, J. Amer. Chem. Soc., **92**, 6369 (1970).
(16) G. A. Olah and S. Kobayashi, ibid., in press.

Table II

TiCl₄-Catalyzed Benzylation of Benzene and Toluene with XC₆H₄CH₂Cl at 30°

XC₆H₄CH₂Cl	$k_{toluene}/k_{benzene}$	% methyldiphenylmethane isomer			1/2 ortho:para
		Ortho	Meta	Para	
p-NO₂	2.5	59.6	6.2	34.2	0.87
o-F	4.8	39.3	7.8	52.9	0.37
m-F	4.6	37.7	7.8	54.5	0.35
p-F	8.7	43.0	6.5	50.5	0.43
o-Cl	4.6	38.8	7.2	54.0	0.36
m-Cl	6.4	43.1	6.5	50.4	0.43
p-Cl	6.2	40.1	5.0	54.9	0.37
H	6.3	40.5	4.3	55.2	0.37
o-CH₃	19.1	24.6	3.4	72.0	0.17
m-CH₃	7.8	41.3	2.5	56.2	0.37
p-CH₃	29.0	31.4	2.1	66.5	0.24
2,4,6-(CH₃)₃	39.1	15.9	3.0	81.1	0.10
o-CH₃O	60.3	23.2	1.3	75.5	0.15
m-CH₃O	13.2	47.5	2.3	50.2	0.47
p-CH₃O	97.0	28.6	1.5	69.9	0.20
2,4,6-(CH₃O)₃-3,5-(CH₃)₂-	136.0	18.3	1.1	80.6	0.11

system we studied was the titanium tetrachloride catalyzed benzylation of toluene and benzene with substituted benzyl chlorides.[15]

Data of Table II show the effect of substituents both on substrate selectivity (as reflected in the $k_{toluene}/k_{benzene}$ rate ratios) and on positional selectivity (as shown with isomer distributions, primarily in the ortho/para ratios). Electron-donating substituents ortho and para to the benzylic center increase the k_t/k_b ratio and at the same time decrease the ortho/para isomer ratio in the methyldiphenylmethanes formed, i.e., para substitution is becoming predominant. In contrast electron-withdrawing substituents decrease k_t/k_b and increase the ortho/para isomer ratio.

Friedel–Crafts Acylation. We were able to show the effect of substituents on the electrophilicity of the reagent, causing a change of the transition state of highest energy from σ- to π-complex nature, also in other typical electrophilic aromatic substitutions, such as Friedel–Crafts acylations.[16]

Friedel–Crafts acylation of aromatic hydrocarbons, like toluene and benzene, are characterized by generally high selectivity of the reactions reflected by high substrate rate ratios (generally $k_{toluene}/k_{benzene} > 100$) and related predominant para substitution. The latter was always considered as a consequence of the steric requirements of the acylating agents, causing large steric ortho hindrance.[2,7]

When acetylation and benzoylation of toluene and benzene with acyl and substituted acyl halides were studied, the results clearly proved the importance of substituents in the electrophilic substituting agent influencing both substrate and positional selectivity. Tables III and IV summarize data.

Changing not only the electrophilicity of the reagent but also the nucleophilicity of the aromatic substrate can cause the same effect. This is reflected by the extensive literature of Friedel–Crafts acylations,[2d]

Table III

Relative Rates and Isomer Distributions in the Boron Trifluoride and Aluminum Chloride Catalyzed Acetylation of Toluene and Benzene in Carbon Disulfide Solution at 25° [16]

Acyl halide	Catalyst	k_t/k_b	% ortho	% meta	% para
HCOF	BF_3 [a]	34.6	43.3	3.5	53.2
CH_3COF	BF_3 [a]	130.0	1.2	1.1	97.7
CH_3COCl	$AlCl_3$	141.0	2.5	2.0	95.5
CH_3CH_2COCl	$AlCl_3$	89.2	2.6	3.1	94.3
$(CH_3)_2CHCOCl$	$AlCl_3$	84.4	3.2	2.4	94.4
$CH_2ClCOCl$	$AlCl_3$	78.2	11.1	2.3	86.6
$CHCl_2COCl$	$AlCl_3$	51.4	17.3	3.2	79.5

[a] Reaction carried out without solvent.

Table IV

Relative Rates and Isomer Distributions in the Aluminum Chloride Catalyzed Benzoylation of Toluene and Benzene with Substituted Benzoyl Chlorides in Nitromethane Solution at 25° [16]

Benzoyl chloride	k_t/k_b	% ortho	% meta	% para
C_6F_5COCl	16.1	35.4	7.8	56.8
$2,4-(NO_2)_2C_6H_3COCl$	29.0	42.4	3.0	54.6
$3,5-(NO_2)_2C_6H_3COCl$	38.9	9.4	6.8	83.8
$p-NO_2C_6H_4COCl$	52	9.5	1.2	89.3
$2,5-F_2C_6H_3COCl$	96.2	12.3	1.6	86.1
C_6H_5COCl	153.5	8.1	1.2	90.7
$p-CH_3C_6H_4COCl$	164.4	7.8	1.1	91.1
$p-FC_6H_4COCl$	170	8.0	1.1	90.9
$2,4,6-(CH_3)_3C_6H_2COCl$	196	2.3	0.6	97.1
$p-CH_3OC_6H_4COCl$	233	14.9	1.5	83.6

showing that the high selectivity observed in the reactions of toluene compared to benzene does not increase rapidly with further methyl substitutions of the aromatic ring, as would be expected on the basis of known σ basicities. [8] Thus with increasingly more basic aromatics even a relatively weak electrophile will result in the highest energy transition states becoming "early" on the reaction coordinate, resembling more starting aromatics than intermediates.

Steric effects, as suggested, can play an important role in effecting the isomer distributions in Friedel–Crafts acylations (particularly ortho substitution), but they cannot be considered as the only major reason for the observed isomer distributions.

Sulfonylation. I wish to suggest that many additional examples similar to the above can be found. A systematic study of aromatic substitutions to prove this point is in progress in our laboratories. Some illustrative examples of sulfonylation [16] are summarized in Table V.

Sulfonation. Cerfontain's [14] sulfonation data (Table VI) show increasing electrophilicity of the reagent with increasing acid strength. It is again reflected in regular change of both substrate and positional selectivity, attributed by Cerfontain to two different sulfonating agents ($H_3SO_4^+$ at low and $H_2S_2O_7$ at high sulfuric acid concentrations).

Halogenation. Electrophilic halogenation of toluene and benzene particularly emphasizes the great variation which can be observed depending on the nature of

Table V

AlCl₃-Catalyzed Methyl- and Phenylsulfonylation of Toluene and Benzene [16]

	k_t/k_b	% ortho	% meta	% para
CH_3SO_2Cl	3.9	54.5	7.9	37.4
$p-NO_2C_6H_4SO_2Cl$	2.8	51.0	(~8)	41
$p-ClC_6H_4SO_2Cl$	7.5	37.0	(~8)	55
$C_6H_5SO_2Cl$	9.0	28.4	8.7	62.9 [a]
$p-CH_3C_6H_4SO_2Cl$	17.0	14.5	<1.0	85.5
$p-CH_3OC_6H_4SO_2Cl$	83.0	5.6	<1.0	94.4

[a] F. R. Jensen and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4046 (1958).

Table VI

Sulfonation of Benzene and Toluene with Sulfuric Acid of Various Strengths [14]

% H_2SO_4	k_t/k_b	% ortho	% meta	% para
77.8	106	21.2	2.1	76.7
81.5	57			
84.3	47	38.8	2.6	58.6
89.1	25			
99–100 in $C_6H_5NO_2$	5.1	50.2	4.9	44.9 [a]

[a] F. J. Stubbes, C. D. Williams, and C. N. Hinshelwood, *J. Chem. Soc.*, 1065 (1948).

the halogenating agent. The data of Table VII indicate the great diversity of substrate and positional selectivity which can be obtained in various systems. No single set of numerical data can thus be considered as "characteristic" for electrophilic halogenations, [11f] which cover numerous reactions of differing nature.

Nitration. Electrophilic aromatic nitration of reactive aromatics, such as toluene and benzene, must be considered as a substitution reaction with the transition state of highest energy resembling more starting hydrocarbons than intermediates. This is in accordance with Ingold's fundamental work [2h,12] proving that the nitrating agent in usual electrophilic nitrations is the highly reactive ion (NO_2^+).

Ingold, Hughes, [12] and their coworkers, generally using reaction media composed of 40% nitric acid and 60% acetic anhydride or nitromethane, found in nitrations of toluene–benzene a rate ratio (k_t/k_b) of 27. The isomer distribution in the nitration of toluene was found to be 67% ortho, 4% meta, and 40% para.

As nitrations of benzene and toluene were too fast to measure their rates by absolute rate studies, Ingold developed the competitive method of rate determination to determine their relative rates, k_t/k_b.

Kuhn and I have subsequently developed a new efficient nitration method by using stable nitronium salts (like tetrafluoroborate) as nitrating agents. [17] Nitronium salt nitrations are also too fast to measure their absolute rates, but the use of the competition method showed in our work low substrate selectivity, e.g., k_t/k_b of 1–2. On the basis of the Brown selectivity rules, if these fast reactions followed σ-complex routes

(17) G. A. Olah and S. J. Kuhn, *Chem. Ind. (London)*, 98 (1956); *J. Chem. Soc.*, 4257 (1956); *J. Amer. Chem. Soc.*, **83**, 5464 (1961).

Table VII

Electrophilic Halogenation of Toluene and Benzene with Reagents of Various Nature

Halogenating agent	Catalyst	Solvent	k_t/k_b	% ortho	% meta	% para	Ref
Cl_2	$FeCl_3$	CH_3NO_2	13.5	67.8	2.3	29.9	a
HOCl	H^+	H_2O	60.0	74.6	2.2	23.2	b
Cl_2		CH_3COOH	344.0	59.8	0.5	39.7	c
		CH_3CN	1650	37.6	0.5	62.4	d
Cl_2		CH_3NO_2	2445.0	33.6	0.15	66.4	e
Br_2	$FeCl_3$	CH_3NO_2	7.1	71.8	1.6	27.3	f
HOBr		H_2O–dioxane	36.2	70.3	2.3	27.4	g
Br_2	$ZnCl_2$	CH_3CO_2H	148.0				h
Br_2		CH_3COOH	605.0	32.9	0.3	66.8	i
		CF_3CO_2H	2580	17.6	0.2	82.4	i
I^+	(electrochemical)	CH_3CN	2.0	47.0	6.0	47.0	j
ICl	$ZnCl_2$	CH_3CO_2H	140.0				h

[a] G. A. Olah, S. J. Kuhn, and B. A. Hardie, *J. Amer. Chem. Soc.*, **86**, 1055 (1964). [b] See Table I, footnote *f*. [c] L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **81**, 5615 (1959). [d] See Table I, footnote *d*. [e] L. M. Stock and A. Himoe, *J. Amer. Chem. Soc.*, **83**, 1937, 4605 (1961). [f] See Table I, footnote *b*. [g] P. D. B. De la Mare and J. T. Harvey, *J. Chem. Soc.*, 36 (1956). [h] R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, **78**, 5623 (1956). [i] H. C. Brown and L. M. Stock, *ibid.*, **79**, 1421, 5175 (1957); H. C. Brown and R. A. Wirkkala, *ibid.*, **88**, 1447 (1966). [j] L. Miller, E. P. Kayawa, and C. B. Campbell, *ibid.*, **92**, 2821 (1970).

they would also have a predictably low positional selectivity (with high meta isomer content). However, the observed low substrate selectivities were all accompanied by high discrimination between available positions (typical isomer distributions of nitrotoluenes were (%) ortho:meta:para = 66:3:31). Consequently, a meta position would seem to be sevenfold deactivated compared to a benzene position, giving a partial rate factor of $m_f = 0.14$. These observations are inconsistent with any mechanism in which the individual nuclear positions compete for the reagent (in the σ-complex step).

In explanation, we suggested the formation of a π complex in the first step of the reactions followed by conversion into σ complexes (which are of course separate for the individual ortho, para, and meta positions), allowing discrimination in orientation of products. The use of the competitive method of rate determination was criticized,[11b] primarily based on the assumption that the nitronium salt reagents used were too reactive to allow real differentiation under competitive reaction conditions and low substrate selectivity was the consequence of the fast reactions before uniform mixing of the reagents could be achieved. It was claimed that if very low concentrations of nitronium salts and very efficient mixing were used, reactions gave results comparable to "normal" σ-route nitrations.[11b] We have, however, shown that, under conditions leading to higher substrate selectivity in nitronium salt nitrations, the highly diluted solutions did not contain any more nitronium salts, because the impurity levels of the solutions exceeded the concentration of the reactive nitronium salts.[11b] Furthermore, competitive experiments in highly efficient high-speed flow systems, including stopped-flow techniques, with reaction times as short as 0.002 sec and varying the toluene/benzene mole ratio in the experiments from 1:10 to 10:1 led to no significant change in either positional or substrate selectivities.[11b,18]

Nitronium tetrafluoroborate nitrations with four competing aromatics (toluene, benzene, fluorobenzene, and chlorobenzene) gave also only very slightly changed k_T/k_B ratios.[11a]

The remaining major argument against our results was based on the observation that in nitronium salt nitrations, even when using large excess of the aromatic hydrocarbons, dinitrations were observed to take place (generally less than 5% in the case of toluene and benzene,[11b] but much higher—as observed by Ridd—[19] in the case of bibenzyl). These observations do not necessarily, in my view, represent proof for the diffusion-controlled nature of nitronium ion salt nitrations, as suggested. The nitro group of monosubstituted aromatic nitro compounds, being a polar n-donor group, can readily interact with excess NO_2^+ competing with or even in preference to the π system, and cause subsequently increased dinitration by transferring the nitro group to a favored ortho position or to a suitable positioned (folded) adjacent ring (as in the case of bibenzyl). Experimental evidence shows increased ortho dinitration (compared to para) in the case of nitrobenzene (the main isomer being, of course, *m*-dinitrobenzene) and similarly changed ratios of 2- and 4-nitro isomers in the dinitration of bibenzyl.[18,19]

It should be mentioned that substantial dinitration of bibenzyl is observed, even when it is in large excess over the nitrating agent, not only in nitronium salt nitrations (as with $NO_2^+BF_4^-$ in sulfolane) but also in the more classical Ingold-type nitrations with HNO_3.[18] Consequently, I feel that however interesting is Ridd's work on the nitration of bibenzyl[19] (discussed in the accompanying Account) it does not affect the general concepts of electrophilic aromatic substitution discussed in this Account.

Whereas electrophilic nitrations of toluene and benzene show less variation in both substrate and particularly positional selectivity than previously dis-

(18) G. A. Olah and H. C. Lin, manuscript in preparation.

(19) P. F. Christy, J. H. Ridd, and N. D. Stears, *J. Chem. Soc. B*, 797 (1970).

Table VIII

Nitration of Toluene and Benzene

Nitrating agent	Solvent	k_t/k_b	% ortho	% meta	% para	Ref
$NO_2^+PF_6^-$	CH_3NO_2	1.6	68.2	2.0	29.8	10
$NO_2^+BF_4^-$	Sulfolane	1.7	65.4	2.8	31.8	10
$NO_2^+BF_4^-$	CH_3CN	2.3	69	2	29	10
HNO_3	80% H_2SO_4	4.8				20
	77% H_2SO_4	5.0				20
	75.3% H_2SO_4	7.2				20
	68.3% H_2SO_4	17.2	60	3	37	20
HNO_3	CH_3NO_2	21	58.5	4.4	37.1	2h, 12
	$(CH_3CO)_2O$	23	58.4	4.4	37.2	
CH_3COONO_2	CH_3CN	44	63	2	35	18
HNO_3	Sulfolane, H_2SO_4	37	61.6	2.9	35.5	11b

cussed alkylations and acylations, by no means can selectivity be considered constant. Table VIII summarizes some representative values of nitration of toluene and benzene. Thus I must conclude that if a single nitrating agent (*i.e.*, the nitronium ion) is the effective reagent in all nitrations, as argued by Ingold,[12] its activity must be dependent on the medium. Substrate selectivity changes reflect the differing reactivity of the nitronium ion in different media. In the strongly exothermic nitrations the early π-type transition state is of highest energy. With varying reactivity of the nitrating agent the energy maxima leading to the π complexes can change relative to those leading to the subsequent σ complexes. The reversibility of π-complex formation therefore can increase when the π- and σ-complex-type transition states are becoming closer in energy, while the further will still predominate. This can result in increased substrate selectivity (k_t/k_b increasing from 1–2 to 20–40), but the positional selectivity (determined in the σ step) is little changed.

There exists the possibility that certain nitronium ion precursors (like protonated acetyl nitrate or nitryl halide–Lewis acid–halides complexes) can also be nitrating agents in their own right, without first forming the nitronium ion.

Coombes, Moodie, and Schofield[20] recently found from kinetic nitration studies in 68.3% H_2SO_4 $k_{toluene}/k_{benzene}$ to be 17.2. By increasing the acid strength, the rate ratio decreased in 75.3% H_2SO_4 to 7.2 and in 77.7% to H_2SO_4 to 5.0. The authors concluded that in acid more concentrated than 68.3% reactions proceed by what was termed "encounter rate." Such limiting encounter rates were reached with more reactive aromatics (starting with xylenes) even in weaker acid media. Similar disappearance of aromatic substrate reactivity differences is indeed observed in the nitronium nitration of methylbenzenes.[10] Thus I feel that there is no discrepancy between the results and conclusions of Moodie and Schofield and ours. Aromatic substitutions on encounter may be considered as exothermic reactions involving early, π-complex type

transition states of highest energy. Differences in substrate selectivity of related aromatics (like toluene and benzene) are becoming insignificant, whereas positional selectivities (determined in subsequent σ-type transition states) are remaining high.

Electrophilic nitrations of toluene and benzene show little change in positional selectivity (isomer distribution), although somewhat more differentiation in substrate selectivity (as shown in Table VIII). As discussed, the relatively low k_t/k_b values and high ortho/para isomer ratios indicate early transition states of highest energy.

Not only the electrophilicity of the reagent but also the nucleophilicity of the aromatic substrate can affect the relative position and heights of the involved transition states. Whereas nitrations cannot be widely varied by changing the reactivity of the nitrating agent, selectivity of the reactions can be substantially changed by suitable deactivating substituents in the aromatics, which cause the relative height of the barrier to σ-complex formation to increase significantly and thus cause the σ-type transition states to become of highest energy. This is well demonstrated in comparing nitration of nitrobenzene and nitrotoluenes.[18,21] High substrate and positional selectivity (with preference for para nitration relative to the methyl group) indicate the σ pattern of the reactions. There is also an interesting difference in selectivities when carrying out the nitronium salt nitrations using aprotic (nitromethane) or protic (96% H_2SO_4) solvent media (as shown in Table IX). In the latter system the nitroaromatic substrates must be at least partially protonated, thus decreasing the n-donor interaction with the reagent NO_2^+ and its subsequent direction to ortho positions. In superacid media (like FSO_3H–SbF_5, "magic acid") this effect is even better shown. Nitration of nitrobenzene gives 4.4% o-, 90% m-, and 5.6% p-dinitrobenzene.

Electrophilic nitrations resemble in all aspects other aromatic substitutions. Because it is more difficult to vary the reactivity of the nitrating agents, the

(20) (a) R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1969); (b) see also Table I, footnote *h*.

(21) Rate studies of nitration of nitrotoluenes were reported by F. H. Westheimer and M. S. Kharasch, *J. Amer. Chem. Soc.*, **68**, 178 (1946); J. C. D. Brand and R. P. Paton, *J. Chem. Soc.*, 281 (1952); J. G. Tillett, *ibid.*, 5142 (1962).

Table IX

Competitive Nitration of Nitrobenzene and Nitrotoluenes with $NO_2{}^+PF_6{}^-$ [18]

	Relative rate CH$_3$NO$_2$	96% H$_2$SO$_4$	% dinitrotoluene 2,3-	2,4-	2,5-	2,6-	3,4-	3,5-
Nitrobenzene	1	1	o:m:p in CH$_3$NO$_2$ = 10:88.5:1.5; in 96% H$_2$SO$_4$ = 7.1:91.5:7.4					
o-Nitrotoluene	384	545	57.4 71.2		1.7	40.9 28.8		
m-Nitrotoluene	91	138	42 28.4		18.6 9.9		35.8 60.1	3.6 1.6
p-Nitrotoluene	147	217		99.8 99.8			0.2 0.2	

change in selectivities is best achieved by varying the nucleophilicity of the aromatics.

The Role of Intermediate Complexes

The question must be raised to what degree are the well-investigated σ complexes involved in the pathway of electrophilic aromatic substitutions. In 1956 we reported the preparation of a series of σ complexes formed by the reaction of HF–BF$_3$, DF–BF$_3$, alkyl fluoride–BF$_3$ and acyl fluoride–BF$_3$ systems, as well as NO$_2$F + BF$_3$, with aromatics.[8f] One such example was the formation of the C$_2$H$_5$F–BF$_3$ complex from mesitylene.
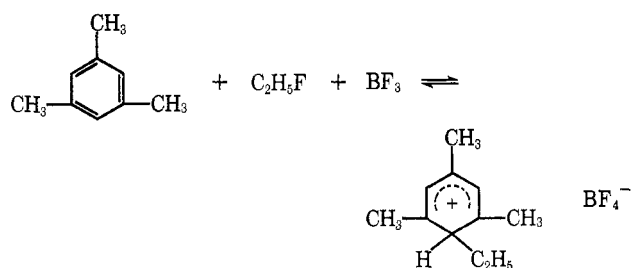
Nakane[22] recently, in a detailed low-temperature ir, uv, and nmr spectroscopic and boron-isotope exchange study, reinvestigated the toluene–ethyl fluoride–boron trifluoride complex. He concluded that the primary complex formed at −80° is not a σ complex, but a termolecular oriented π complex (with the C–F bond in ethyl fluoride not being broken). Only when the temperature is raised does the ionization and σ-complex formation take place. Zollinger[23] was indeed first able to show the existence of an oriented π complex (as a separate entity from a σ complex) in the iodination of the sterically hindered 2-naphthol-6,8-disulfonic acid and a σ complex in the bromination of the same substrate. Zollinger's and Nakane's findings obviously do not exclude σ complexes as intermediates in electrophilic aromatic substitutions. In fact, a series of σ-complex intermediates were isolated and studied by spectroscopic methods.

Our own nuclear magnetic resonance spectroscopic studies of σ complexes[8h] and their formation, for example, from methylbenzenes with ethyl fluoride–antimony pen-

tafluoride showed[24] that the long-lived arenium ion complexes observed are those in which the ethyl group or methine hydrogen is generally shifted from the geminal to a more stabilized position, i.e.
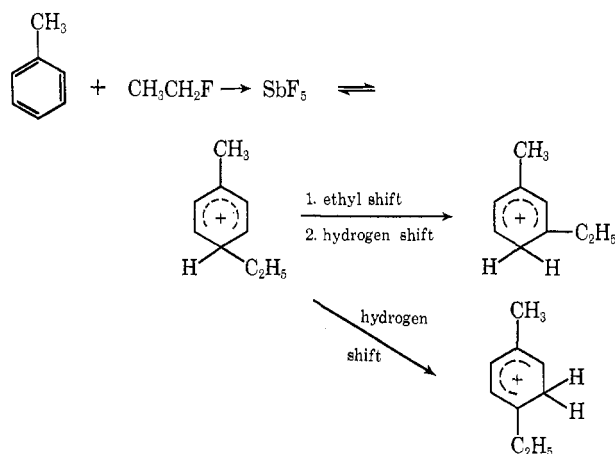
The formation of the m-dialkylbenzenium ion thus can take place intramolecularly prior to deprotonation and explains the ease of isomerization within the σ complexes (a fact of substantial importance when considering isomer distributions as reflecting positional selectivity in Friedel–Crafts alkylations).

The Nature of the Transition States

In order to explain the low substrate but high positional selectivities observed in highly exothermic electrophilic aromatic substitutions, it is necessary to suggest that in these reactions the transition state of highest energy leads to formation of a (oriented) π complex (in the substrate selectivity determining step), followed by formation of complexes for the ortho, para, and meta positions, which differ substantially in energy. Figure 1a depicts the potential energy curve for such a reaction (for simplicity only the left side of the curve is shown).

In contrast Figure 1b depicts the energy diagram in the case where formation of the σ complexes is the significant step of the reaction. (The possible importance of proton elimination (the right side of the energy curves) is for the time being not taken into consideration; see, however, the subsequent discussion of the role of kinetic hydrogen isotope effects.)

It should be emphasized that not only the absolute heights of the π- and σ-type transition states should be considered but also their relative heights to each

(22) R. Nakane, A. Natsubori, and O. Kurihara, J. Amer. Chem. Soc., 87, 3597 (1965); 88, 3011 (1966); R. Nakane, T. Oyama, and A. Natsubori, J. Org. Chem., 33, 275 (1968); 34, 949 (1969); R. Nakane and T. Oyama, J. Phys. Chem., 70, 1146 (1966).

(23) M. Christen, W. Koch, W. Simon, and H. Zollinger, Helv. Chim. Acta, 45, 2077 (1962).
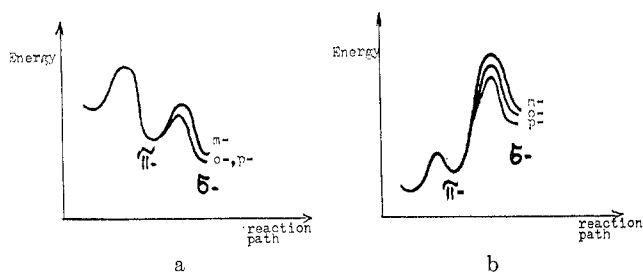
(24) G. A. Olah, unpublished.

Figure 1. (a) Potential energy curve (left side) of reaction with highest energy transition state resembling starting aromatics (π complex); (b) potential energy curve (left side) of reaction with highest energy transition states resembling σ complexes.

other. When the energy maxima are becoming close in heights, the reactions can increasingly reverse through the π state and therefore intermediate selectivities can be observed.

In the interaction of an electrophile with an aromatic substrate a weak reagent–substrate complex (outer complex[25]) is formed first. The formation of such complexes is reversible and does not lead to substituted products. Aromaticity is not lost in such complexes, as indicated by spectroscopic studies (as in the quoted work of Zollinger and Nakane) showing only slight changes in the aromatic substrates.

As the reagent moves closer to bonding distance, the highest lying occupied aromatic π orbital containing an electron pair overlaps with the empty orbital of the electrophile, forming a two-electron three-center bond (π complex). The formed complex is indeed a bridged tetracoordinated carbonium ion (benzonium ion).[26] Opening of the three-center bond of the benzonium ion leads to the trivalent benzenium ion (σ complex) which frequently can be directly observed.

"outer" complex π-complex σ-complex
               benzonium ion   benzenium ion
               (tetracoordinated)   (trivalent)
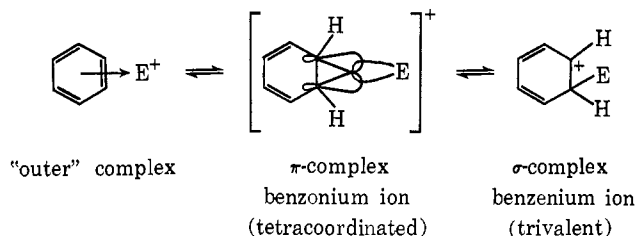
In highly exothermic substitutions the aromatic substrate is generally little deformed at the early transition state of highest energy. In the extreme case there is no resonance interaction in the transition state which is also not present in the isolated reactants. With decreasing reactivity of the electrophile (or with weaker aromatic nucleophiles) a greater degree of charge transfer is necessary to reach the transition state. Therefore the extent of formation of the new σ bond at the transition state is dependent on the nature of the reagent, increasing with decreasing reagent reactivity, until it reaches the Wheland intermediate in limiting case.

According to the "Hammond postulate"[27] the transition state of a single-stage reaction is generally more similar to either the reactant or the product, whichever is at highest energy level. If the postulate is applied to electrophilic aromatic substitution, the transition state of highest energy should be more similar to the intermediate the higher the potential energy of the latter, and to the starting aromatics as the more exothermic the reaction involving a strong electrophile with high potential energy.

The Role of Proton Elimination as Reflected by Kinetic Hydrogen Isotope Effects

The question of kinetic hydrogen isotope effects in electrophilic aromatic substitutions is well reviewed,[28] and therefore I will comment on only one specific aspect. In substitutions where the transition state of highest energy is of a π-complex nature no primary kinetic hydrogen isotope effects are expected; experimental evidence so far bears this out.[28f] As replacement of hydrogen by deuterium in aromatics enhances the π basicity it is of interest to note that nitration (also some other substitutions) of perdeuteriobenzene gave a small but significant inverse secondary isotope effect ($k_H/k_D = 0.89 \pm 0.03$), the heavy compound reacting faster.[10] As pointed out by Halevi[29] this observation strongly strengthens the suggested π-complex type transition-state concept of the reaction.

Conclusions

In electrophilic aromatic substitutions the transition state of highest energy can resemble either the Wheland intermediate (σ complex) or starting aromatics (π complex).

It is evident that the nature of the transition states in aromatic substitutions has a profound effect on both substrate and positional selectivity. In exothermic reactions of low substrate selectivity the transition state of highest energy is of a π-complex nature. In this case, a highly reactive electrophile interacts with the aromatic substrate (like toluene) with relatively little deformation of the latter in the transition state. The generally very fast reactions take place with little substrate discrimination (as π bases) and can be considered as, or close to, encounter controlled. Subsequent σ-complex formation leads to positional selectivity. In these reactions, the σ complexes themselves also lie relatively early on the reaction path, and therefore ortho substitution is favored over para and,

(25) Using Mulliken's definition: R. S. Mulliken, *J. Amer. Chem. Soc.*, **72**, 600 (1950); **74**, 811 (1952); *J. Phys. Chem.*, **56**, 801 (1952).

(26) For a definition of carbocations, including differentiation of tetra- and pentacoordinated carbonium ions from trivalent carbenium ions, see G. A. Olah, *J. Amer. Chem. Soc.*, in press.

(27) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(28) (a) L. C. S. Melander, "The Use of Nuclide in the Determination of Organic Reaction Mechanism," Reilly Lectures, Vol. XI, University of Notre Dame Press, Notre Dame, Ind., 1955; (b) L. C. S. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960; (c) H. Zollinger, *Experientia*, **12**, 165 (1956); *Annu. Rev. Phys. Chem.*, **13**, 400 (1962); (d) H. Zollinger, *Advan. Phys. Org. Chem.*, **2**, 163 (1964); (e) E. Berliner, *Progr. Phys. Chem.*, **2**, 253 (1964); (f) H. Cerfontain, H. J. Hofman, and A. Telder, *Recl. Trav. Chim. Pays-Bas*, **83**, 493 (1964); G. A. Olah, *J. Tenn. Acad. Sci.*, **40**, 77 (1965).

(29) E. A. Halevi and B. Ravid, *Pure Appl. Chem.*, **8**, 339 (1964).

of course, meta. For the most frequently studied reactions of toluene with strongly electrophilic reagents the ortho/para isomer ratio is generally close to or greater than 2:1, in spite of possible steric ortho hindrance. On the other hand, in selective reactions with increasingly weaker electrophiles (or with aromatics of lesser nucleophilicity) which show higher substrate selectivity, the σ transition states are of "late" nature resembling the intermediates and the ortho/para ratio decreases, para substitution becoming predominant. Early transition-state reactions will reflect charge distribution of the aromatics. In alkylbenzenes, such as toluene, charge density is highest around the ortho and para positions (as shown in the case of toluene, based on Pople CNDO/2 calculations). Further as there are two ortho but only one para position, the ortho/para ratio will be high (>2).

In reactions indicating late transition states of highest energy, e.g., resembling the Wheland intermediates, the isomer distributions obtained relate to charge density in the cyclohexadienyl cations (Wheland intermediates, σ complexes). Nmr studies of σ complexes[3p] including the recent study of the $C_6H_7^+$ ion itself[30] and semiempirical self-consistent-field calculations, indicate a charge distribution in benzenium ions with 5-10% of the charge present at each meta carbon atom, about 26% at each ortho carbon, and about 30% at the para carbon (relative to the methylene group). It

charge in toluene   percent charge in benzenium ion
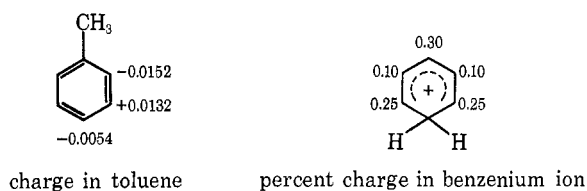
follows that a substituent will exert a more powerful effect on the benzenium ion (σ complex) when it is para to the entering reagent than when it is ortho, and even more so than when it is meta. With an electron-donating substituent like the methyl group

in toluene, the stability of intermediate ions will decrease in the order para > ortho > meta, resulting in a low ortho/para isomer ratio, as indeed is found experimentally in high-selectivity reactions.

Consideration of the nature of the transition states enables an understanding of substrate selectivities separate from that of positional selectivities. It also brings to light the importance of ortho/para isomer ratios in the context of positional selectivities and further allows their correlation with substrate selectivities. This realization supplements the well-demonstrated importance of meta/para isomeric substitution ratios, on which the Brown-selectivity treatment is based.

It should be pointed out that Norman and Taylor[31] must be credited with first emphasizing the importance of the ortho/para ratio, discussing contributions from (a) steric hindrance, (b) steric acceleration, (c) interaction between the substituent and the reagent, (d) electronic effects, and (e) solvent effects. They considered that, due to the complexity of factors involved, it is difficult to evaluate individual effects separately. Our work provided, however, clear indication for the dependence of the ortho/para isomer ratios on the nature of the transition states, effected through electrophilicity of the reagents or nucleophilicity of the aromatics.

Some years ago it seemed that electrophilic aromatic substitution was a closed field in which most of the significant work was already done. It is rewarding to see that recent work opened up new aspects and interest, which is expected to continue.

(30) G. A. Olah, R. H. Schlosberg, D. P. Kelly, and Gh. D. Mateescu, *J. Amer. Chem. Soc.*, **92**, 2546 (1970).

(31) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965, pp 301-310; G. Klopman, *J. Amer. Chem. Soc.*, **90**, 223 (1968); G. Klopman, personal communication.

Mechanism of Aromatic Nitration

JOHN H. RIDD

William Ramsay and Ralph Forster Laboratories, University College, London WC1 0AJ, England

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Up to 1960, the nitration of aromatic compounds by solutions of nitric acid in sulfuric acid or organic solvents was confidently discussed in terms of the attack by the nitronium ion. In the following 5 years, the

contributions of several groups of workers combined to raise doubts over the importance of this mechanism of nitration and to raise new problems concerning the form of the transition state. Recent work has gone some