

Aromatic Substitution. XXXV.¹ Boron Trifluoride Catalyzed Nitration of Benzene, Alkylbenzenes, and Halobenzenes with Methyl Nitrate in Nitromethane Solution

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Abstract: The competitive rates and isomer distributions of the BF_3 catalyzed nitration of benzene, alkyl-, halo-, and substituted polymethylbenzenes with methyl nitrate in nitromethane solution were determined. Relative nitration rates of alkylbenzenes were shown to correlate more closely with the stability of the corresponding π complexes, than those of the σ complexes. This trend is greatly enhanced with increasing alkyl substitution. Relative rates of nitration of substituted benzenes, 3-substituted toluenes, 2-substituted *p*-xylenes, and 3-substituted durenes were correlated with help of the Yukawa-Tsuno equation. The correlation of r values with the nature of the involved transition states is discussed.

Under usual conditions of electrophilic nitration (for example, in the classical studies of Ingold² and Hughes³) toluene reacts about 20 times more rapidly than benzene. In nitronium salt nitrations, however, toluene was found to react only slightly faster than benzene ($k_T:k_B \sim 1.6$),⁴ and *m*-xylene and mesitylene increase the relative rates only insignificantly. As pointed out by Schofield and Moodie,⁵ the reactions under these conditions seem to reach a limiting, encounter-controlled rate. In other words, the nitration of reactive alkylbenzenes can occur so fast that low substrate selectivities observed by competitive rate studies could have been caused by incomplete mixing of the reactants before the reaction. Studying the nitration of bibenzyl with nitronium salts, Ridd^{6,7} found a high proportion of dinitro products formed, indicating incomplete mixing before reaction. Experimental work, including flow techniques,⁸ were used in an attempt to overcome this difficulty. However, the rates of nitration of benzene and toluene are too fast to permit the measurement of noncompetitive rates even by this technique.⁹

Kinetic studies of nitration of pentamethylbenzene with nitronium salts in tetramethylene sulfone (sulfolane) solution were studied by Zollinger and Kreienbuhl.¹⁰ Surprisingly, they found a half-life for the nitration of $\tau_{1/2} > 20$ hr. In subsequent studies, however, they reported¹¹ that the nitration of pentamethylbenzene with nitronium salts is immeasurably fast. They further concluded that the rate of mixing of the reagents becomes so important that the pentamethyl-

nitrobenzene formed initially reacts with a second molecule of the nitrating agent.

The nitration of durene relative to mesitylene has also been studied by Zollinger's group.¹² Since there was always a substantial amount of dinitro products formed, besides other by-products, the relative reactivity could not be determined.

In order to avoid any difficulty of incomplete mixing before reaction, the present investigation has chosen another route to study nitration reactions.

A nitrating agent was sought which itself would not nitrate aromatics without the presence of a catalyst. Thus the nitrating agent could be mixed well with the aromatic substrate before any reaction takes place. A well-soluble catalyst is then added to initiate the nitration. Such nitrating agents are available,¹³ and among them alkyl nitrates were found to be the most convenient, for they are stable and well soluble in organic solvents.

Alkyl nitrates do not nitrate aromatic compounds in the absence of catalysts.¹⁴ However, good yields of nitrated products can be obtained if aromatic compounds and alkyl nitrates react in the presence of sulfuric acid,¹⁵⁻¹⁹ poly(phosphoric acid),²⁰ or Lewis acid halides.^{13,21,22} Recently, we have reported^{23a} that the $\text{CH}_3\text{ONO}_2\text{-BF}_3$ reagent is a suitable new nitrating agent. For example, the preparation of mononitropolymethyl-

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(23) (a) G. A. Olah and H. C. Lin, *Synthesis*, 488 (1973). (b) The competitive method of nitration for determining relative reactivities was originally developed by J. P. Wibaut (*Recl. Trav. Chem. Pays-Bas*, **34**, 291 (1915)) and used subsequently extensively by Ingold.²

benzenes, which are hardly accessible without dinitration products by other nitrating agents, was achieved in excellent yields. In present work, the BF_3 catalyzed nitration of benzene, alkylbenzenes, and halobenzenes with methyl nitrate in nitromethane solution was investigated to obtain a better insight into the mechanistic aspects of aromatic nitration.

Results and Discussion

Nitration of Benzene and Alkylbenzenes. Keeping the problem of possible incomplete mixing before reaction in mind, we have now carried out a detailed investigation of the relative rates of nitration of benzene and alkylbenzenes (polymethylbenzenes) with methyl nitrate- BF_3 in nitromethane solution.

Competitive nitrations^{23b} were carried out as follows. An equimolar quantity of benzene and the appropriate alkylbenzene in nitromethane were mixed with an amount of methyl nitrate sufficient to keep the mole ratio of the combined aromatic substrates-methyl nitrate constant at 20:1 (thus a practically constant excess of the aromatic was maintained). To the resulting solution, kept in a constant-temperature bath at 25°, a solution of BF_3 in nitromethane was added with stirring to initiate the nitration. Under the experimental conditions used, almost quantitative mononitration takes place. No traces of dinitro products or any other by-products were detected. The mixture was then analyzed by gas chromatography (see Experimental Section).

The relative reactivities of a number of alkylbenzenes and polymethylbenzenes relative to benzene, together with the isomer distributions of the mononitro products, are summarized in Table I.

Table I. Competitive CH_3NO_2 - BF_3 Catalyzed Nitration of Benzene and Alkylbenzenes with Methyl Nitrate in Nitromethane Solution at 25°

ArH	$k_{\text{ArH}}/k_{\text{B}}$	Isomer distribution, %			
		Ortho	Meta	Para	Ortho/para
Benzene	1.0				
Toluene	25.5	63.9	3.4	32.7	1.95
Ethylbenzene	23.1	50.3	4.7	45.0	1.11
Isopropylbenzene	20.7	36.0	6.0	57.0	0.62
<i>tert</i> -Butylbenzene	19.4	10.9	11.7	77.4	0.14
1,2-Dimethylbenzene (<i>o</i> -xylene)	192.3	3-Nitro, 65.3; 4-nitro, 34.7			
1,3-Dimethylbenzene (<i>m</i> -xylene)	285.5	2-Nitro, 16.9; 4-nitro, 83.1			
1,4-Dimethylbenzene (<i>p</i> -xylene)	295.5				
1,2,3-Trimethylbenzene (hemimellitene)	914.6	4-Nitro, 88.6; 5-nitro, 11.4			
1,2,4-Trimethylbenzene (pseudocumene)	1076.2	3-Nitro, 8.7; 5-nitro, 45.5; 6-nitro, 45.8			
1,3,5-Trimethylbenzene (mesitylene)	956.8				
1,2,3,4-Tetramethylbenzene (prehnitene)	2154.5				
1,2,3,5-Tetramethylbenzene (isodurene)	1861.2				
1,2,4,5-Tetramethylbenzene (durene)	2188.3				
Pentamethylbenzene	2545.3				

In order to show whether incomplete mixing before reaction could have had any effect on the studied nitra-

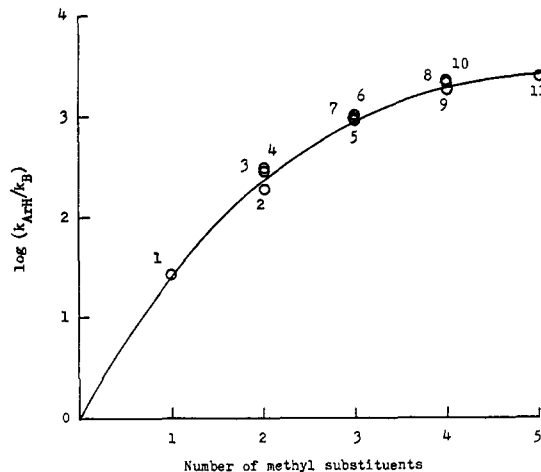


Figure 1. Relationship between relative nitration rates and the number of methyl substituents on the aromatic ring. The numbers 1-11 refer to the following aromatic substrates: 1, toluene; 2, *o*-xylene; 3, *m*-xylene; 4, *p*-xylene; 5, 1,2,3-trimethylbenzene; 6, 1,2,4-trimethylbenzene; 7, 1,3,5-trimethylbenzene; 8, 1,2,3,4-tetramethylbenzene; 9, 1,2,3,5-tetramethylbenzene; 10, 1,2,4,5-tetramethylbenzene; 11, pentamethylbenzene.

tions, we investigated (under identical conditions) the nitration of bibenzyl, a model compound suggested by Ridd^{6,7} to be exceptionally suitable for this purpose. Only 8.7% of dinitrobibenzyls were formed in the reaction, clearly indicating that mixing is not affecting the system. (Our more detailed studies relating to the question of the nitration of bibenzyl will be published in full separately.)

The relative reactivities of the monoalkylbenzenes shown in Table I are in the order $\text{CH}_3 > \text{Et} > i\text{-Pr} > t\text{-Bu}$. The regular and marked decrease in the ortho:para ratio from toluene to *tert*-butylbenzene can be ascribed primarily to the increasing importance of steric hindrance to ortho substitution, as the alkyl group becomes larger. These results are consistent with those²⁴ reported earlier.

In Figure 1 the logarithms of the rates of nitration of polymethylbenzenes relative to benzene at 25° are plotted against the number of methyl substituents on the aromatic nucleus. The relative rates were observed to increase with increasing methyl substitution of the ring. However, there is no linear correlation between the logarithms of the relative reactivities of polymethylbenzenes and the number of ring methyl substituents. This nonlinearity implies that the contribution of individual methyl groups to the total free energy of activation is not additive. Thus, in general, the further increase in reactivity caused by additional methyl groups decreases with increasing number of methyl groups already present on the aromatic ring.

According to Condon,²⁵ the way to determine whether σ - or π -complex formation is rate determining in a given reaction is to compare the relative rates of substitution with the relative stabilities of the corresponding complexes. On this basis, there should be a linear relationship between the logarithms of the rate of aromatic substitution and the logarithms of either the π or the σ basicity of the hydrocarbon in question. When this is done, it is found in many substitution re-

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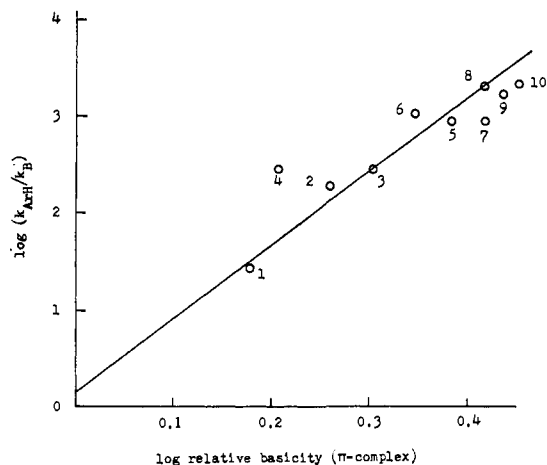


Figure 2. Free-energy relationship between relative nitration rates and π basicity. The numbers 1-10 refer to the same aromatic substrates as mentioned in Figure 1. Correlation coefficient, 0.9635.

actions²⁵⁻³¹ that the relative rates show similarities to σ -complex and not to π -complex stabilities. The reverse seems, however, more likely to be the case in nitration. The relative nitration rates and the corresponding π and σ basicities³² of benzene and methylbenzenes are tabulated in Table II. In Figures 2 and 3,

Table II. Relative Rates of Nitration of Benzene and Methylbenzenes and Their Comparison with π and σ Basicities

ArH	Relative nitration rates	Relative π -complex ^a stability with HCl	Relative σ -complex ^b stability with HF-BF ₃
Benzene	1.0	1.0	1
Toluene	25.5	1.5	790
1,2-Dimethylbenzene	192.3	1.8	7,900
1,3-Dimethylbenzene	285.5	2.0	1,000,000
1,4-Dimethylbenzene	295.5	1.6	3,200
1,2,3-Trimethylbenzene	914.6	2.4	2,000,000
1,2,4-Trimethylbenzene	1076.2	2.2	2,000,000
1,3,5-Trimethylbenzene	956.8	2.6	630,000,000
1,2,3,4-Tetramethylbenzene	2154.5	2.6	20,000,000
1,2,3,5-Tetramethylbenzene	1861.2	2.7	2,000,000,000
1,2,4,5-Tetramethylbenzene	2188.3	2.8	10,000,000
Pentamethylbenzene	2545.3		2,000,000,000

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the logarithms of the relative nitration rates are plotted against the logarithms of the corresponding π and σ basicities, respectively. For comparison, the correlation coefficients obtained from a regression analysis³³ are also shown in these figures. Comparing these

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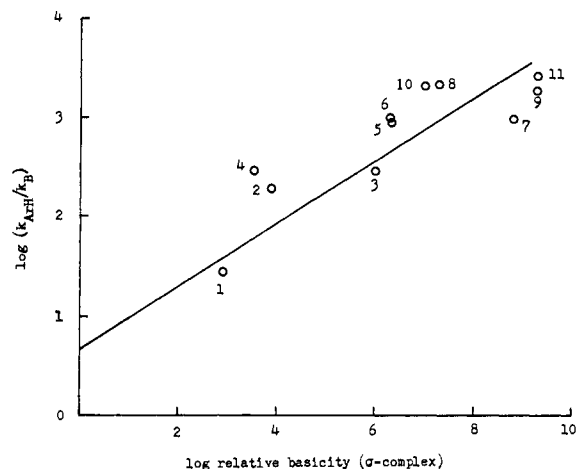


Figure 3. Free-energy relationship between relative nitration rates and σ basicity. The numbers 1-11 refer to the same aromatic substrates as mentioned in Figure 1. Correlation coefficient, 0.8996.

two figures, and the correlation coefficients, it can be seen that there is a better linear correlation in Figure 2 than in Figure 3. It is obvious from data of Table II that relative rates of nitration indicate that the transition states of highest energy are of considerably more π - than σ -complex nature, *i.e.*, they lie early on the reaction coordinate and thus are affected relatively little by increasing methyl substitution of the aromatic substrates.

Another fact which confirms this analysis is that the relative reactivities of mesitylene, durene, and pentamethylbenzene in selective halogenations by molecular bromine and molecular chlorine³⁴ are pentamethylbenzene > mesitylene > durene, whereas nitration under present conditions give the order of reactivity: pentamethylbenzene > durene > mesitylene. The order in the latter case would be inexplicable if σ -type transition states of highest energy were involved.

Nitration of Substituted Benzenes and Methylbenzenes.

The nature of the transition states in electrophilic aromatic substitution was discussed in some detail in our previous studies.^{1,32} The most important factors which influence both substrate and positional selectivities are the nature of the electrophile and the nature of the substrate. These factors also determine the position of the transition state on the reaction coordinate. Whereas in many aromatic substitutions³² the nature of the electrophiles can be easily changed by substituents in the electrophilic reagent, in nitration such changes till now could only be affected by changing substantially the nucleophilicity of the aromatic substrates.¹ With substantially nucleophilic aromatic substrates, such as methylbenzenes, further alkyl substitution has only limited effect on the nature of the transition states, which lie already "early" on the reaction coordinate. This may be the reason why there is no linear relationship observed in Figure 1. In order to confirm this point the CH₃NO₂-BF₃ catalyzed nitration of monosubstituted benzenes, such as 3-substituted toluenes, 2-substituted *p*-xylenes, and 3-substituted durenes, with methyl nitrate were carried out. The results are summarized in Table III.

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Table III. $\text{CH}_3\text{NO}_2\text{-BF}_3$ Catalyzed Nitration of Monosubstituted Benzenes, 3-Substituted Toluenes, 2-Substituted *p*-Xylenes, and 3-Substituted Durenes with Methyl Nitrate at 25°

Aromatic compd	Rel reactivity	Isomer distribution, %			
Benzene and Substituted Benzenes					
Benzene	1.0	Ortho	Meta	Para	
Toluene	25.5	63.9	3.4	32.7	
Anisole	186.8	27.9	1.2	70.9	
Fluorobenzene	0.12	11.1	0.3	88.6	
Chlorobenzene	0.03	31.4	1.0	67.6	
Bromobenzene	0.03	33.3	1.3	65.4	
Iodobenzene	0.10	41.8	1.6	56.6	
Toluene and Substituted Toluenes					
Toluene	1.0	2-Nitro	4-Nitro	6-Nitro	
3-Methyltoluene (<i>m</i> -xylene)	11.2	16.9	83.1		
3-Methoxytoluene	20.4	21.5	40.3	38.2	
3-Fluorotoluene	0.07	5.0	10.7	84.3	
3-Chlorotoluene	0.03	6.4	25.7	67.9	
3-Bromotoluene	0.03	9.3	26.7	64.0	
3-Iodotoluene	0.06	9.9	33.4	56.7	
<i>p</i> -Xylene and Substituted <i>p</i> -Xylenes					
<i>p</i> -Xylene	1.0	3-Nitro	5-Nitro	6-Nitro	
2-Methyl- <i>p</i> -xylene (pseudocumene)	2.50	8.6	46.0	45.4	
2-Methoxy- <i>p</i> -xylene	2.60	20.7	69.7	9.6	
2-Fluoro- <i>p</i> -xylene	0.06	3.0	76.9	20.1	
2-Chloro- <i>p</i> -xylene	0.03	6.1	61.7	32.2	
2-Bromo- <i>p</i> -xylene	0.03	10.5	59.6	29.9	
2-Iodo- <i>p</i> -xylene	0.04	8.3	64.2	27.5	
Durene and Substituted Durenes					
Durene	1.0				
3-Methyldurene (pentamethylbenzene)	1.16				
3-Methoxydurene	0.80				
3-Fluorodurene	0.23				
3-Chlorodurene	0.13				
3-Bromodurene	0.10				
3-Iododurene	0.16				

Comparison of the relative reactivities given in Table III reveals substantial differences in substituent effects. The most striking difference is in the overall spread in rates. Thus methoxy and methyl groups in mono-substituted benzenes activate about 200 and 25 times, respectively, compared to the parent aromatic, benzene. The trend of activation decreases as the number of methyl group in the aromatic increases. In the case of substituted durenes, pentamethylbenzene reacts about the same rate as durene, and 3-methoxydurene reacts even slower than durene itself. (Although BF_3 is known to complex with ethers, under the experimental conditions there is always a substantial excess of uncomplexed anisole present, thus data are not affected by the deactivity effect of complexing.)

For an attempt of more quantitative treatment of the results, a Hammett-type linear relationship was employed. The inadequacy of the Hammett equation in the form, $\log(k/k_0) = \rho\sigma^+$ or $\log(k/k_0) = \rho\sigma$, using a single set of substituent (and reaction) constants for correlating the rates of aromatic substitutions has recently been pointed out.^{35,36} An improved free-energy relation was empirically derived by Yukawa and Tsuno,³⁵ taking into consideration both conjuga-

tive and inductive effect of substituents. They showed that for a large number of electrophilic reactions, the relation $\log(k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)]$ is more satisfactory than the Hammett-Brown equation. Consequently, we have applied the Yukawa-Tsuno equation to our results. For simplicity and to avoid difficulties in the ortho substituents, only the case of para nitration was considered. From the relative reactivities, after statistical correction, of Table III and several known substituent constants,^{34,35,37} five sets of ρ and r values were obtained by means of regression analysis.³⁸ These values are shown in Table IV.

Table IV. Yukawa-Tsuno ρ and r Values in Para Nitration

Substituent constants used ^a		3-Substituted durenes	2-Substituted <i>p</i> -xylenes	3-Substituted toluenes	Monosubstituted benzenes
A	r	-0.38	-0.15	-0.08	0.39
	ρ	-2.6	-4.8	-5.9	-5.8
B	r	-0.02	0.18	0.27	0.72
	ρ	-2.2	-4.2	-5.0	-5.0
C	r	-0.04	0.12	0.19	0.57
	ρ	-2.2	-4.4	-5.4	-5.5
D	r	-0.01	0.14	0.21	0.56
	ρ	-2.2	-4.4	-5.5	-5.8
E	r	0.01			
	ρ	-2.2			

^a A, Hammett σ and Brown σ^+ (L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963)); B, Bekkum σ^n (H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959)) and Brown σ^+ ; C, Taft σ^0 (R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960)) and Brown σ^+ ; D, Yukawa-Tsuno σ^0 (ref 37) and Brown σ^+ ; E, Bekkum σ^n and Illuminati $\bar{\sigma}$ (ref 34).

In the case when Hammett σ and Brown σ^+ constants were used (row A), three of the four r values obtained were negative. The negative values of r were unusual, but not unreasonable. Since Hammett σ constants were obtained from the ionization constants of benzoic acids, resonance interactions between para substituents and the carboxyl group were included, *i.e.*, $\sigma = \sigma_I + \sigma_R$. The negative r values imply that the resonance contribution of substituents in the nitration of durenes, *p*-xylenes, and toluenes is less than in the ionization of benzoic acids. The negative r values obtained for substituted durenes in rows B, C, and D should be considered as the results of the steric inhibition of resonance (SIR).³⁴ After applying Illuminati's $\bar{\sigma}$, derived from his polymethylbenzene (PMB) approach, instead of Brown's σ^+ , an r value of 0.01 was obtained as shown in row E.

Table IV shows that the obtained values of r increase with decreasing nucleophilicity of the aromatic substrates. In other words, the different values of r reflect the different position, thus nature, of the transition state. This is quite consistent with the proposal by Yukawa and Tsuno that r would be a parameter characteristic of the structure of the possible transition state, as well as a parameter for measuring the availability of resonance in the transition state.

Our data indicate that not only different types of reactions can have different values of r , as reported previously,³⁵ but also in the same type of reactions we can

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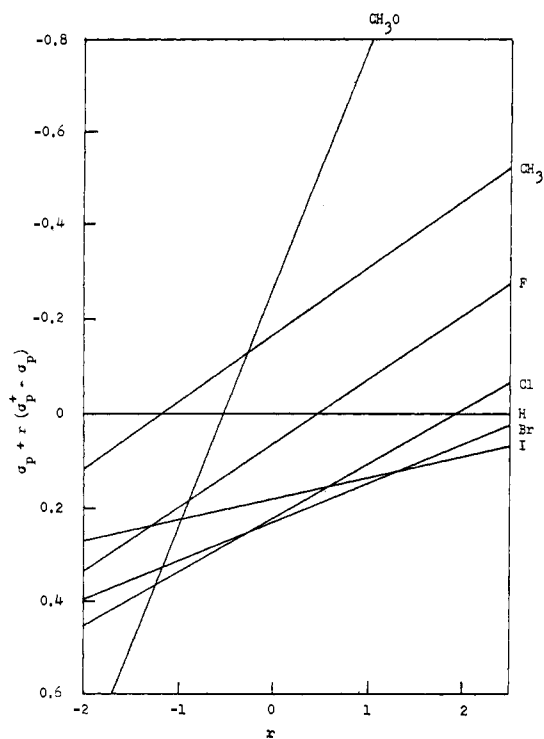


Figure 4. Variation of the Yukawa-Tsuno substituent constants, $\sigma_p + r(\sigma_p^+ - \sigma_p)$, with r values.

have different values of r , depending, for example, on substituents present or changes in the reagent systems. Different values of r reflect different sets of substituent constants caused by various degrees of resonance stabilization of the transition state by different substituents.

Recently, Johnson and Schofield³⁹ argued against the use of the Hammett equation in structure-reactivity correlations. In electrophilic substitution in benzenoid systems, they used the benzylation and benzylation data reported by Olah and coworkers^{32,40,41} as example and calculated the ρ values of both reactions using Brown's σ^+ constants for each substituent. From their calculation, they concluded that for certain substituents the reaction with the less reactive electrophile would become faster than the reaction with the more reactive one. The flow of their conclusion, in our view, lies in the fact that they used the same values of σ^+ for both reactions involving early and late transition states, but still tried to utilize the observed ρ values in denoting the nature of the transition states. Indeed, the results calculated by Johnson and Schofield strongly indicate the inapplicability of a single set of substituent constants for reactions involving widely varying transition states. This indication was also confirmed by our present experimental results, in agreement with the excellent recent review of substituent effects by Ehrenson, Brownlee, and Taft.⁴²

A plot of the Yukawa-Tsuno substituent constants, $\sigma_p + r(\sigma_p^+ - \sigma_p)$, of some substituents against r is shown in Figure 4. From this figure, the variation of

the substituent constants with r values can clearly be seen. The most striking change is found with the methoxy substituent. The relative order of the halogen substituents in influencing the reactivity can also be seen in Figure 4. It has been reported previously by de la Mare⁴³ that the combination of $-I$ and $+K$ effects can cause any order of reactivity among the halogen substituents. Different slopes of the lines in Figure 4 can be used to explain these changes. Since lines of different slopes cross, different values of r may give a different order of reactivity of a given substrate with halogen substituents.

Schofield, Moodie, and coworkers⁴⁴ have reported kinetic studies of nitration of halobenzenes. They found in the case of 1,2,4,5-tetrachlorobenzene and pentachlorobenzene that the chlorine atom is activating compared to hydrogen. Although they attempted to account for these results on the basis of steric and electronic factors, we feel that differences in the nature of the transition states provide a better explanation. From Figure 4, an r value near 2 predicts the relative order of activation $\text{Cl} > \text{H}$. Another example of the relative order of activation $\text{Cl} > \text{H}$ is shown as the fact that *o*-chloronitrobenzene is more reactive than nitrobenzene.^{45,46} This may also be explained by assuming a later transition state for the reaction, with $r \sim 2$.

Studies are in progress on the nitration of substituted benzenes containing two or more electron-withdrawing substituents, and full results will be reported in a forthcoming paper.

So far we have not discussed the other reaction parameter, ρ . By definition,³⁵ ρ is a measure of the general demand for electrons at the reaction site. The variation ρ does not appear to be dependent upon the change in r value.³² Nevertheless, Norman and Radda³⁶ have recently reported that the parameter r increases regularly with ρ in a series of reactions examined. Results in Table IV also show that the r values most likely increase with increasing negative values of ρ .

In conclusion, r values have been found to be a good measure of the position and thus the nature of the transition state. The lower the r value, the earlier the transition state lying on the reaction coordinate. The higher the r value, the later the transition state lying on the reaction coordinate.

The Nature of the Nitrating Agent and Its Effect on Selectivity. Finally the question can be raised, what is the nature of the nitrating agent in the methyl nitrate-boron trifluoride nitrating system? Is this system simply forming the nitronium ion (NO_2^+) in the first step of the reaction (similarly as in the generally accepted Ingold's scheme of protic acid catalyzed nitration) or does it only form a polarized coordination complex ($\text{CH}_3\text{ONO}_2 \cdot \text{BF}_3$), which is then displaced by the aromatic in a more selective reaction?

Spectroscopic (ir and Raman) study of dilute methyl nitrate-boron trifluoride systems in nitromethane solution did not show the presence of detectable con-

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Table V. Gas-Liquid Chromatographic Analysis Data

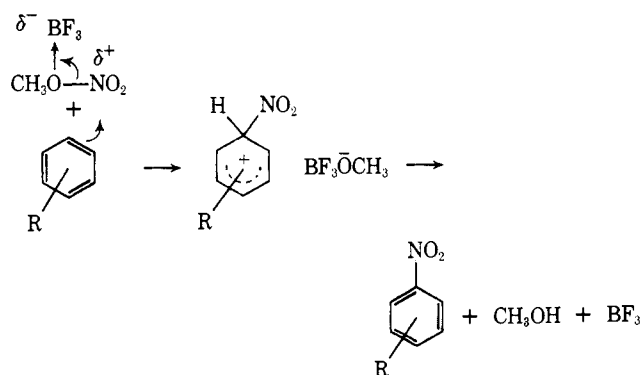
Nitro compd	Column ^a	Condi- tions ^b of column	Retention time, sec	Nitro compd	Column ^a	Condi- tions ^b of column	Retention time, sec
Nitrobenzene	C	V	597	<i>p</i> -Nitroiodobenzene	C	I	1240
<i>o</i> -Nitrotoluene	C	V	684	<i>o</i> -Nitroanisole	D	VIII	336
<i>m</i> -Nitrotoluene	C	V	805	<i>m</i> -Nitroanisole	D	VIII	270
<i>p</i> -Nitrotoluene	C	V	897	<i>p</i> -Nitroanisole	D	VIII	293
<i>o</i> -Nitroethylbenzene	C	V	757	3-Fluoro-2-nitrotoluene	A	VI	691
<i>m</i> -Nitroethylbenzene	C	V	1003	3-Fluoro-4-nitrotoluene	A	VI	1343
<i>p</i> -Nitroethylbenzene	C	V	1173	3-Fluoro-5-nitrotoluene	A	VI	863
<i>o</i> -Nitroisopropylbenzene	C	V	776	5-Fluoro-2-nitrotoluene	A	VI	716
<i>m</i> -Nitroisopropylbenzene	C	V	1090	3-Chloro-2-nitrotoluene	C	IV	778
<i>p</i> -Nitroisopropylbenzene	C	V	1343	3-Chloro-4-nitrotoluene	C	IV	1397
<i>o</i> -Nitro- <i>tert</i> -butylbenzene	C	V	936	3-Chloro-5-nitrotoluene	C	IV	965
<i>m</i> -Nitro- <i>tert</i> -butylbenzene	C	V	1243	5-Chloro-2-nitrotoluene	C	IV	908
<i>p</i> -Nitro- <i>tert</i> -butylbenzene	C	V	1703	3-Bromo-2-nitrotoluene	C	IV	1276
3-Nitro- <i>o</i> -xylene	C	V	1089	3-Bromo-4-nitrotoluene	C	IV	2309
4-Nitro- <i>o</i> -xylene	C	V	1551	3-Bromo-5-nitrotoluene	C	IV	1634
2-Nitro- <i>m</i> -xylene	C	V	838	5-Bromo-2-nitrotoluene	C	IV	1495
4-Nitro- <i>m</i> -xylene	C	V	1564	3-Iodo-2-nitrotoluene	D	III	299
2-Nitro- <i>p</i> -xylene	C	V	927	3-Iodo-4-nitrotoluene	D	III	456
Nitromesitylene	C	V	916	5-Iodo-2-nitrotoluene	D	III	325
4-Nitro-1,2,3-trimethylbenzene	C	IV	1369	3-Methoxy-2-nitrotoluene	D	VII	267
5-Nitro-1,2,3-trimethylbenzene	C	IV	1841	3-Methoxy-4-nitrotoluene	D	VII	488
3-Nitro-1,2,4-trimethylbenzene	C	IV	640	5-Methoxy-2-nitrotoluene	D	VII	393
5-Nitro-1,2,4-trimethylbenzene	C	IV	1168	2-Fluoro-3-nitro- <i>p</i> -xylene	A	VI	592
6-Nitro-1,2,4-trimethylbenzene	C	IV	997	2-Fluoro-5-nitro- <i>p</i> -xylene	A	VI	688
5-Nitro-1,2,3,4-tetramethyl- benzene	C	IV	2765	2-Fluoro-6-nitro- <i>p</i> -xylene	A	VI	646
4-Nitro-1,2,3,5-tetramethyl- benzene	C	IV	1258	2-Chloro-3-nitro- <i>p</i> -xylene	A	VI	1115
3-Nitrodurene	C	IV	1130	2-Chloro-5-nitro- <i>p</i> -xylene	A	VI	1229
Nitropentamethylbenzene	C	IV	2845	2-Chloro-6-nitro- <i>p</i> -xylene	A	VI	1169
<i>o</i> -Nitrofluorobenzene	C	V	696	2-Bromo-3-nitro- <i>p</i> -xylene	A	VI	1774
<i>m</i> -Nitrofluorobenzene	C	V	482	2-Bromo-5-nitro- <i>p</i> -xylene	A	VI	1960
<i>p</i> -Nitrofluorobenzene	C	V	549	2-Bromo-6-nitro- <i>p</i> -xylene	A	VI	1885
<i>o</i> -Nitrochlorobenzene	C	I	513	2-Iodo-3-nitro- <i>p</i> -xylene	D	III	467
<i>m</i> -Nitrochlorobenzene	C	I	418	2-Iodo-5-nitro- <i>p</i> -xylene	D	III	522
<i>p</i> -Nitrochlorobenzene	C	I	458	2-Iodo-6-nitro- <i>p</i> -xylene	D	III	490
<i>o</i> -Nitrobromobenzene	C	I	763	2-Methoxy-3-nitro- <i>p</i> -xylene	D	III	183
<i>m</i> -Nitrobromobenzene	C	I	611	2-Methoxy-5-nitro- <i>p</i> -xylene	D	III	413
<i>p</i> -Nitrobromobenzene	C	I	677	2-Methoxy-6-nitro- <i>p</i> -xylene	D	III	204
<i>o</i> -Nitroiodobenzene	C	I	1412	3-Methoxy-6-nitrodurene	B	II	727
<i>m</i> -Nitroiodobenzene	C	I	1125	3-Fluoro-6-nitrodurene	C	IV	947
				3-Chloro-6-nitrodurene	C	I	1177
				3-Bromo-6-nitrodurene	C	I	1985
				3-Iodo-6-nitrodurene	C	I	3935

^a A, a stainless steel open tubular column, 150 ft × 0.01 in. wall coated with poly(propylene glycol); B, a stainless steel open tubular column, 100 ft × 0.02 in. wall coated with butanediol succinate; C, a stainless steel open tubular column, 150 ft × 0.01 in. wall coated with butanediol succinate; D, a stainless steel packed column, 12 ft × 1/8 in., with solid support 80-100 mesh Chromosorb W and liquid phase 1.75% butanediol succinate. ^b Column conditions [column temperature, °C (carrier gas, helium, pressure (psi) or flow rate (ml/min)): I, 180 (30 psi); II, 180 (20 psi); III, 180 (40 ml/min); IV, 160 (30 psi); V, 160 (20 psi); VI, 140 (30 psi); VII, 170 (40 ml/min); VIII, 160 (40 ml/min).

centration of the NO₂⁺ ion. This, however, does not necessarily exclude a lower concentration of the ion present, not detectable with these methods (<1-2%). This, of course, would be more than sufficient for kinetic nitration of aromatics. Also methyl nitrate is known to readily form NO₂⁺BF₄⁻ with BF₃ containing HF (which can be present, due to inevitable impurities, in the nitrating system).

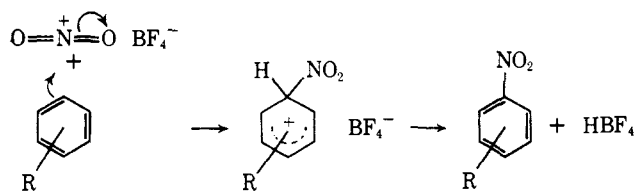
The observed higher substrate selectivity data of nitration of aromatics with CH₃ONO₂-BF₃, as compared to NO₂⁺BF₄⁻ nitration, however, seem to indicate a more selective nitrating system. It is therefore likely that indeed it is not the free nitronium ion, but the polarized boron trifluoride complex which is the nitrating agent, being displaced by the aromatic substrate.

For comparison it must be also pointed out that the linear nitronium ion, O=N⁺=O, has no vacant bonding orbital, thus its interactions with aromatics is



also a displacement type reaction, with the significant difference that the displacement involves the internal displacement of a π -electron pair to the oxygen atom.

This process obviously is of lower energy than the intermolecular displacement involving breaking of a



σ bond. Thus the higher reactivity and lower selectivity of the nitronium ion nitration can be explained.

Experimental Section

Materials. Nitromethane, boron trifluoride, methyl nitrate, benzene, alkylbenzenes, and their nitro derivatives are, except stated below, commercial materials. They were, whenever necessary, purified before use. Nitromethane was purified as described previously.⁴⁷ 2-Iodo-*p*-xylene and 2-fluoro-*p*-xylene were prepared by Sandmeyer and Schiemann reactions, respectively, from 2,5-dimethylaniline. Nitro-2-methoxy- and nitro-2-halo-*p*-xylenes were prepared from the corresponding nitro-2-amino-*p*-xylenes.⁴⁸ Nitro-1,2,3-trimethylbenzenes,⁴⁹ nitro-1,2,4-trimethylbenzenes,⁴⁹ nitrotetramethylbenzenes,^{23a} and nitropentamethylbenzene^{23a} were prepared according to the procedures reported. Chloro-, bromo-,

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and iododurenes were prepared by the method of Tohl.⁵⁰ Methoxydurene and fluorodurene were prepared from aminodurene, which was obtained by reduction of nitrodurene. 6-Nitro 3-substituted durenes were prepared by the nitration of the corresponding substituted durenes with the nitrating agent described by Olah and Lin.^{23a}

Procedure for Competitive Nitration. In a typical experiment, 10 mmol of benzene, 10 mmol of toluene, and 1 mmol of methyl nitrate were mixed with 45 ml of nitromethane. Into this solution, 1.5 mmol of boron trifluoride in a 5-ml nitromethane solution was added. The reaction mixture was vigorously stirred and the temperature was kept constant at 25° during the reaction. The reaction time was generally 50 min. After that, the reaction solution was quenched with ice-water, extracted with ether, washed with 5% sodium bicarbonate solution, dried over magnesium sulfate, concentrated, and analyzed by gas-liquid chromatography.

Analytical Procedure. The analyses of all products were carried out by gas-liquid chromatography, using a Perkin-Elmer Model 900 gas chromatograph equipped with a hydrogen flame ionization detector and either open tubular capillary columns or packed column. Peak areas were obtained with an Infotronics Model CRS-100 electronic printing integrator. Relative response data were determined as described previously.

Characteristic retention times of the nitro compounds along with type of columns conditions are listed in Table V.

Acknowledgment. Support of our work by a grant of the U. S. Army Office of Research, Durham, N. C., is gratefully acknowledged.

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Synthesis of *trans*-3,4-Dihydroxy-3,4-dihydrobenzoic Acid¹

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received October 30, 1973

Abstract: The synthesis of racemic *trans*-3,4-dihydroxy-3,4-dihydrobenzoic acid (**2**) is described. Reaction of *trans*-1,2-dihydrophthalic acid (**3**) with excess peracid afforded **4** that was converted to the mono methyl ester **6** via anhydride **5**. Decarboxylation of **6** gave iodide **7**. Reaction of **7** with zinc dust afforded **8** as an unstable complex that, on treatment with triethylamine, was converted to **9**. Hydrolysis of **9** with aqueous potassium hydroxide and acidification gave racemic **2**. Monoepoxidation of **3** afforded **14** that reacted with hot methanol to give **16**.

Chorismic acid (**1**) is the branch point intermediate in the biosynthesis of aromatic amino acids and growth factors in bacteria.²⁻⁴ The importance of **1** in the biosynthesis of aromatic substances in other microorganisms and plants has become apparent.²⁻⁵ One of the enzymic transformations of **1** is the cleavage of the enolpyruvyl group giving *trans*-3,4-dihydroxy-3,4-dihydrobenzoic acid (**2**).^{4,6,7} The acid-catalyzed conversion of **1** to **2** has also been observed.⁴

The metabolic function of **2** is not clearly understood. It may play a part, directly or indirectly, in metal

(1) Financial support from the National Institutes of Health, Grant No. 1R01-GM19103, and from Hoffmann-LaRoche, Inc., Nutley, N. J., is gratefully acknowledged.

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(3) F. Lingens, *Angew. Chem.*, **80**, 384 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 350 (1968).

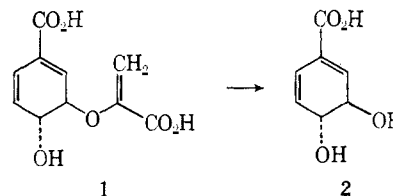
(4) I. G. Young, F. Gibson, and C. G. MacDonald, *Biochim. Biophys. Acta*, **192**, 62 (1969).

(5) R. G. H. Cotton and F. Gibson, *Biochim. Biophys. Acta*, **156**, 187 (1968).

(6) Reaction catalyzed by extracts from *Aerobacter aerogenes*. The absolute configuration of **1** and **2** is that shown in Scheme I.

(7) I. G. Young and F. Gibson, *Biochim. Biophys. Acta*, **177**, 182 (1969).

Scheme I



metabolism.⁴ Attempts to demonstrate that **2** is a precursor of 3,4-dihydroxybenzoic acid in *Aerobacter aerogenes* have not been successful.⁸

Because of our interest in the intermediates in the biosynthesis of aromatic amino acids and growth factors in microorganisms and plants, a synthesis of racemic **2** has been accomplished.⁹ The synthetic sequence is outlined in Scheme II.

(8) 3,4-Dihydroxybenzoic acid is formed from dehydroshikimic acid rather than via the shikimic acid → **1** pathway: see ref 4 and references cited therein.

(9) The synthesis of racemic *trans*-2,3-dihydroxy-2,3-dihydrobenzoic acid has also been completed: R. M. DeMarinis, C. N. Filer, S. M. Waraszkievicz, and G. A. Berchtold, *J. Amer. Chem. Soc.*, **96**, 1193 (1974).