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Aromatic Substitution. XIV.[1] Ferric Chloride Catalyzed Bromination of Benzene and Alkylbenzenes with Bromine in Nitromethane Solution

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The ferric chloride catalyzed bromination of benzene and alkylbenzenes with bromine in nitromethane solution was investigated at 25°. Relative reactivities and isomer distributions were determined in competitive experiments by gas-liquid chromatography and infrared spectroscopy. The investigated Friedel-Crafts type brominations involving a strong electrophile (incipient bromonium ion) show low substrate but high positional selectivity. Relative rates show agreement with π- but not with σ-complex stabilities of the investigated alkylbenzenes, thus indicating that the reactions involve a π-complex type transition state in the substrate selectivity-determining step followed by σ-complex type transition states determining isomer distribution (positional selectivity).

Introduction

The bromination of aromatics by electrophilic brominating agents has been extensively reviewed by De la Mare and Ridd.[2]

The rates of bromination of alkylbenzenes and benzene with molecular bromine were investigated by Robertson and De la Mare[3] as well as by Brown and Stock.[4] These investigations using aqueous acetic acid solutions of bromine have shown that under the conditions used the bromination of aromatics shows high substrate and positional selectivity.

TABLE I

BROMINATION OF BENZENE AND ALKYLBENZENES WITH MOLECULAR BROMINE IN 85% ACETIC ACID SOLUTION AT 25°

Aromatic	$k_{Ar}:k_{benzene}$	Isomer bromoalkylbenzenes, % o-	m-	p-	Ref.
Benzene	1.0				
Toluene	340	31		69	3
	605	32.9	0.3	66.8	4a
Ethylbenzene	290				3
Isopropylbenzene	180				3
t-Butylbenzene	110	8		92	3
	138	1.20	1.47	97.3	4b
o-Xylene	5,320				4a
m-Xylene	51,400				4a
p-Xylene	2,520				4a
Mesitylene[a]	18,900,000				

[a] In acetic acid.

"Positive bromine" bromination of benzene and certain alkylbenzenes was investigated by De la Mare and co-workers with hypobromous acid in 50% aqueous dioxane solutions. These brominations, summarized in Table II, show considerable lower substrate selectivity and at the same time isomer distributions typical of electrophilic aromatic substitutions. Predominant *ortho-para* directing effects were observed with much higher *ortho*:*para* ratios than in molecular bromine brominations.

TABLE II

"POSITIVE BROMINE" BROMINATION OF BENZENE AND ALKYLBENZENES WITH HYPOBROMOUS ACID IN 50% AQUEOUS DIOXANE SOLUTION AT 25° (DE LA MARE)

Aromatic	$k_{Ar}:k_{benzene}$	Bromoalkylbenzenes, % o-	m-	p-	Ref.
Benzene	1.00				
Toluene	36.2	70.3	2.3	27.4	5
t-Butylbenzene	12.0	37.7	7.2	53.2	6

A comparison of aromatic bromination with molecular bromine with aromatic nitration[7] with NO_2^+ or alkylation[8] with incipient alkyl (aralkyl) carbonium ions (R^+) appears impossible upon the assumption that an incipient Br^+ ion is the active halogenating agent. "Positive bromine" formation in aqueous acetic acid or dioxane solutions is improbable, the positively polarized species in all probability being protonated hypobromous acid (H_2OBr^+) rather than free Br^+ ion.[9] Consequently, in its interaction with aromatic molecules it acts only as a moderate electrophile. Therefore, it was considered desirable to reinvestigate the bromination of benzene and alkylbenzenes in nonaqueous solutions, under reaction conditions somewhat similar to those of the previously investigated nitration and alkylation systems representing strongly electrophilic reagents.

Brown and McGary reported[10] that toluene reacted with bromine at 30° in the presence of an equimolar quantity of aluminum bromide to give an isomer distribution of 20% *o*-, 30% *m*-, and 50% *p*-bromotoluene. Although they have not investigated the possible effect of isomerization on the isomer distribution, they suggested that, with short reaction times, isomerization appears improbable. Consequently they concluded that the high *m*-isomer ratio observed is due to a high reactivity, but low selectivity substitution.[11]

Olah and Meyer[12] have investigated the aluminum halide catalyzed isomerization of bromotoluenes at 30°. They found that bromotoluenes isomerize rapidly, reaching an equilibrium composition of 38% *o*-, 44% *m*-, and 18% *p*-isomers in less than 15 min. This investigation indicated the difficulty of carrying out aluminum halide catalyzed bromination—in the absence of a basic solvent—under nonisomerizing conditions. It must be pointed out, however, that the activity of an incipient bromonium ion (or carbonium ion) should be much higher in a hydrocarbon medium than in a basic solvent (such as nitromethane). It is unfortunate that hydrocarbon media, providing considerably less "encumbrance" of the ionic reagent,

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(1) Part XIII: *J. Am. Chem. Soc.*, **84**, 3687 (1962).

(2) P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution, Nitration and Halogenation," Academic Press, Inc., New York, N. Y., 1959.

(3) P. W. Robertson, P. B. D. De la Mare, and B. E. Swedlund, *J. Chem. Soc.*, 782 (1953).

(4) (a) H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, **79**, 1421, 5175 (1957); (b) *ibid.*, **81**, 5615 (1959).

(5) P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 36 (1956).

(6) P. B. D. de la Mare and J. T. Harvey, *ibid.*, 131 (1957).

(7) G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **83**, 4571 (1961).

(8) G. A. Olah, S. J. Kuhn, and S. H. Flood, *ibid.*, **84**, 1688 (1962).

(9) J. Arotsky and M. C. R. Symons, *Quart. Rev.* (London), **16**, 282 (1962).

(10) H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2309 (1955).

(11) H. C. Brown and K. L. Nelson, *ibid.*, **75**, 6296 (1953).

(12) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962).

generally are also well suited for concurrent or consecutive isomerizations.

Results and Discussion

It is surprising that, although Friedel–Crafts bromination of aromatics using ferric halides as catalysts is used extensively as a preparative method, apparently no detailed mechanistic investigation of the reaction has been made.

Using the competitive rate determination method, the reactivity of benzene and alkylbenzenes was compared in anhydrous ferric chloride catalyzed brominations by adding neat bromine to a nitromethane solution of the substrates and catalyst at 25°.

In nitromethane solution ferric chloride displays a monomeric molecular weight and thus must be in the form of the 1:1 complex $CH_3NO_2:FeCl_3$, similar to the CH_3NO_2–$AlCl_3$ system investigated by Schmerling.[13]

Products were analyzed by gas–liquid chromatography and infrared spectroscopy (see Experimental part). Table III lists the observed relative rate data and isomer distributions. Competitive bromination of mesitylene and benzene could not be evaluated, because of peak interference in the gas–liquid chromatographic analysis. Competitive bromination of mesitylene with toluene could be studied, however. From these data and the toluene:benzene relative rate the reactivity of mesitylene with respect to that of benzene was established.

Table III

Ferric Chloride Catalyzed Competitive Bromination of Benzene and Alkylbenzenes in Nitromethane Solution at 25° (Neat Bromine Added)

Aromatic	$k_{Ar}:k_{benzene}$	Isomer bromoalkylbenzenes, % o-	 m-	 p-
Benzene	1.0			
Toluene	2.3	64.6	1.8	33.6
Ethylbenzene	2.4	55.8	1.6	42.6
o-Xylene	2.4	68.1% 3-Bromo-*o*-xylene		
		31.9% 4-Bromo-*o*-xylene		
m-Xylene	2.7	83.1% 4-Bromo-*m*-xylene		
		16.9% 2-Bromo-*m*-xylene		
p-Xylene	1.7	100% 2-Bromo-*p*-xylene		
Mesitylene	10.2	100% Bromomesitylene		

Using neat bromine the difficulty of obtaining a uniform distribution of reactants arises, since the reactions are so rapid that they take place at the point of entrance of the reagent, the bromine perhaps not being properly divided between the competitors.[14] Thus if toluene reacts faster than benzene, it would become impoverished in the layer adjacent to the bromine drop. The error thus introduced would usually make the competitors (toluene–benzene) seem too nearly equal in speed. However, if the reactivity difference is not too large, the error probably would be only slight for these well matched competitors.

In accordance with the increased possibility of diffusion phenomena playing an important role,[15] the addition of neat bromine into the reaction mixture always resulted in dibromination (see Experimental part) even when a substantial excess of aromatics was present. The amount of dibromination at maximum amounted to 30% of the monobromo products.

Dibromination, besides indicative of imperfect homogenization of the reaction system, can affect both the relative rates and isomer distributions under the competitive reaction conditions employed if one of the products is preferentially removed by a substantially faster reaction. The relative rate data may be affected through a difference between the relative reactivity of bromobenzene and alkylbromobenzenes involved in the dibrominations. Since bromotoluenes, for example, react under the experimental conditions twice as fast as bromobenzene (see Table IV), dibromination should lower the $k_T:k_B$ ratio. Since *m*-bromoalkylbenzenes, could be expected to react faster than either the *o*- or *p*-isomers, dibromination may explain the observed low *m*-bromotoluene isomer ratio. To check the above possibility, we measured the relative rates of bromination of benzene and bromotoluenes under competitive conditions. The results obtained are summarized in Table IV.

Table IV

Relative Rates of Ferric Chloride Catalyzed Bromination of Benzene, Bromotoluenes, and Bromobenzene at 25° in Nitromethane Solution (Neat Bromine Added)

	$k_{Ar}:k_H$
Benzene	1.0
o-Bromotoluene	0.51
m-Bromotoluene	.82
p-Bromotoluene	.56
Bromobenzene	.30

As may be seen from Table IV, although *m*-bromotoluene reacts faster than the *o*- and *p*-isomers, the differences are not sufficiently large to cause a substantial deviation in the observed values of isomer distribution in the bromination of toluene.

To eliminate dibromination due to high local bromine concentrations and to imperfect mixing of reactants before reactions and to provide a better controlled and more dilute reaction system, competitive bromination of benzene and alkylbenzenes was carried out using the above-described conditions with the exception that bromine was introduced as its solution in nitromethane. Under these conditions no di- or higher brominated products were found in the reaction mixtures. Data obtained are summarized in Table V.

Table V

Ferric Chloride Catalyzed Competitive Bromination of Benzene and Alkylbenzenes in Nitromethane Solution at 25° (Nitromethane Solution of Bromine Added)

Aromatic	$k_{Ar}:k_{benzene}$	Isomer bromoalkylbenzenes, % o-	 m-	 p-
Benzene	1.0			
Toluene	7.1	71.1	1.6	27.3
o-Xylene	34.3	51.7% 4-Bromo-*o*-xylene		
		38.3% 3-Bromo-*o*-xylene		
m-Xylene	534	69.3% 4-Bromo-*m*-xylene		
		30.7% 2-Bromo-*m*-xylene		
p-Xylene	31.5			
Mesitylene	>1000			

In evaluating results of bromination obtained in nitromethane solutions, the effect of the solvent on the reaction must also be considered.

It was found by Illuminati and Marino[16] that molecular bromine in nitromethane solution is itself a brominating agent. Consequently, in addition to the Lewis acid-catalyzed bromination, a second concurrent bromination also can take place, in which the brominating agent is the complex $CH_3NO_2 \cdot Br_2$. In this complex the bromine molecule can be only moderately polarized, as compared with the polarizing effect of the strong

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(13) L. Schmerling, *Ind. Eng. Chem.*, **40**, 2072 (1948).

(14) A. W. Francis, *J. Am. Chem. Soc.*, **48**, 655 (1926).

(15) We are grateful to Professor H. C. Brown for pointing out these possible effects and for his useful criticism relating the possibility of diffusion control in low substrate selectivity substitutions.

(16) G. Illuminati and G. Marino, *Gazz. chim. ital.*, **84**, 1127 (1954).

Lewis acid, ferric chloride. Consequently, molecular bromine in nitromethane is only a weak electrophilic substituting agent and shows accordingly high positional selectivity in bromination of benzene and alkylbenzenes. That this is indeed the case was proved in competitive bromination in nitromethane solution with $CH_3NO_2 \cdot Br_2$ in that $k_{\text{toluene}}:k_{\text{benzene}}$ was found to be >200.

However, the nitromethane promoted bromination of aromatics is substantially slower than the $FeCl_3$-catalyzed bromination and thus its effect in all probability is not too substantial except with such reactive aromatics as *m*-xylene or mesitylene, where the noncatalytic bromination may more seriously affect the rates.

In attempting to minimize the effect of the solvent on the brominations, we used in subsequent experiments a solution of bromine and ferric chloride in nitromethane as brominating agent. In this system at least a part of the bromine must be already complexed by the catalyst.

Table VI summarizes data on competitive brominations of benzene and methylbenzenes with ferric chloride and bromine in nitromethane.

TABLE VI

FERRIC CHLORIDE CATALYZED COMPETITIVE BROMINATION OF BENZENE AND METHYLBENZENES IN NITROMETHANE SOLUTION AT 25° (NITROMETHANE SOLUTION OF BROMINE AND FERRIC CHLORIDE ADDED)

Aromatic	$k_{\text{Ar}}:k_{\text{benzene}}$	Isomer bromoalkylbenzene, % *o*-	*m*-	*p*-
Benzene	1.0			
Toluene	3.6	68.7	1.8	29.5
o-Xylene	3.9	67.1% 3-Bromo-*o*-xylene		
		32.9% 4-Bromo-*o*-xylene		
m-Xylene	5.6	79.8% 4-Bromo-*m*-xylene		
		21.2% 2-Bromo-*m*-xylene		
p-Xylene	4.3	100% 2-Bromo-*p*-xylene		
Mesitylene	15.9	100% Bromomesitylene		

No evidence of the formation of di- or higher brominated products within the limit of the analytical methods used was observed in brominations using nitromethane solution of bromine and ferric chloride. The reactions show low substrate, but high positional selectivity in close agreement with previously reported nitration[7] and benzylation.[8]

Owing to the basic nature of the solvent and its complexing ability with the catalyst even using a 2:1 $FeCl_3:Br_2$ mole ratio, part of the bromine must still be complexed to the nitromethane, and the bromine: ferric chloride complex (in limiting case $Br^+FeCl_3Br^-$) itself must be substantially solvated.

The effect of solvation on the reaction was observed, when competitive brominations of toluene and benzene were carried out with increasing dilution of the nitromethane solution of the brominating agent ($FeCl_3$ + Br_2). Table VII summarizes the data.

TABLE VII

EFFECT OF SOLVATION OF THE BROMINATING AGENT IN THE FERRIC CHLORIDE CATALYZED BROMINATION OF BENZENE AND TOLUENE IN NITROMETHANE SOLUTION AT 25°

Concn. of brominating agent (mole/l. CH_3NO_2) $FeCl_3$	Br_2	$k_{\text{toluene}}:k_{\text{benzene}}$	Isomer bromotoluene, % *o*-	*m*-	*p*-
3.0	1.5	3.6	68.7	1.8	29.5
1.0	1.0	5.3	69.5	1.5	29
1.0	0.5	5.4	68.5	1.5	30
0.5	.25	6.5	66.5	1.3	32.2
.2	.1	25	60.8	~1	38.2
.1	.05	32	58.4	~1	40.6

With increasing solvation the brominating agent becomes increasingly more selective, giving higher toluene:benzene rates. The amount of the *m*-isomer simultaneously decreases, although in view of the small amount of this isomer present this observation is difficult to follow quantitatively. It is, however, significant that the *ortho:para* isomer ratio also changes depending on the degree of dilution (solvation) of the brominating agent. On dilution, the *ortho:para* isomer ratio decreases with simultaneous significant increase of the toluene:benzene reactivity ratio This observation indicates that the nature of the brominating agent is changing from a predominant incipient bromonium ion to a bulkier and weaker electrophile, which in the limiting case may reach the character of a polarized covalent complex. The bromination reaction accordingly also changes from a bromonium type low substrate selectivity reaction to a more selective bromination involving increasingly higher substrate reactivity values. However, the positional selectivity of the brominations, besides the steric effect influencing *o*-substitution, remains unchanged, all brominations being of high positional selectivity with only minor amounts of the *m*-isomer formed.

The experimental data indicate that the activity of the brominating agent is dependent on its concentration and thus the degree of solvation in the solvent used (nitromethane). That the effect of dilution of the brominating agent is predominantly that of solvation and not of simple physical dilution, making higher substrate selectivity possible in a slower reaction system, was demonstrated by the finding that the isomer distributions are also dependent on the change of concentration of the solution. Simple dilution without affecting the reactivity of the reagent should have no effect on the isomer distributions.

If the concentration of the solutions used is considered (see Experimental part) there is little difference in results by adding a nitromethane solution of bromine to a solution of catalyst and substrates in the same solvent or premixing catalyst and bromine in the solvent and using this brominating solution.

The competitive method of rate determination, suited otherwise to follow fast reactions (such as the present bromination), can be applied only if the reactivities are dependent on the aromatic substrates. One of the criticisms raised concerning low substrate selectivity aromatic substitutions has been whether they are indeed kinetically controlled processes, or whether the fast reactions involving strong electrophiles are diffusion controlled, the entering substituent reacting rapidly and practically without discrimination between substrate molecules with which it collides; *i.e.*, the reactions are statistically controlled by the relative concentrations of aromatics. In this case only mixing or diffusion speeds should affect the reaction rates, and it may be meaningless to discuss relative reactivities of different substrates. Should this be the case, it would be expected that not only would the activation energy differences between different substrate molecules become less and less important, but the same should also apply for activation energy differences of individual positions in substituted benzenes. Accordingly, in the bromination of toluene, for example, an isomer composition approximating the statistical distribution (40% *ortho*, 40% *meta*, and 20% *para*) would be expected, which is contrary to the observed high positional selectivity.

In order to establish whether the present brominations indeed involve competition, a fairly wide range concentration variation of toluene and benzene in competitive bromination experiments was investigated at 25°. If the reactions involve competition between substrate molecules, then the relative rates should change according to concentration ratios (taking for granted that the reactions are first order in aromatics); however, if the fast reactions are statistically regulated, then the relative rates should be directly proportional to the concentrations. Table VIII shows the data obtained from the concentration variation of toluene and benzene, the ratio varying from 9:1 to 1:4, a range more than sufficient to evaluate the system.

TABLE VIII

FIRST-ORDER DEPENDENCE OF THE FERRIC CHLORIDE CATALYZED BROMINATION OF TOLUENE AND BENZENE IN AROMATICS

Ratio of toluene:benzene	Obsd. relative rate	$k_T:k_B$
9:1	36	4.0
4:1	15.2	3.8
2:1	7.0	3.5
1:1	3.6	3.6
1:2	1.8	3.6
1:4	0.85	3.4
	Average	3.7

From data of Table VIII, the conclusion must be drawn that the brominations are indeed dependent (in the first order) on the aromatic substrates. Thus the competitive rate determination can be used to establish the relative reactivities of benzene and alkylbenzenes for the present halogenation reaction. It is hoped that the demonstration of the first-order dependence of this bromination reaction on concentration is sufficient to discount the possibility of a diffusion controlled process.[17]

The observed spread of the relative reactivity values (4–3.4) is partly a consequence of the limitation of the analytical method (caused by substantial differences, under the used concentration variations, of the relative amounts of bromotoluenes and bromobenzene). But it also could indicate further imperfections in the system, predominantly lack of complete mixing of the reagents before reaction.

Experiments designed to show the effect of mixing on the reactions using various type of mechanical, magnetic, and vibrational stirrers, as well as rapid flow systems (with reaction times as short as 0.001 sec., mixing the solutions of the reagents fed from synchronously driven high speed burets in a capillary mixing tube) showed only slight increase of the toluene:benzene relative rates. However, it must be considered that in none of these experiments was it possible to obtain direct evidence of complete mixing before reaction. Any change of the relative rates indicates that mixing has some effect on the reaction. It is thought, however, that this effect, which certainly must be considered in the case of any fast reaction, is not decisive under the competitive reaction conditions, adding the brominating agent to a large excess of the substrates, as the difference in reactivity of benzene and toluene is not large. The availability of better mixing methods in fast reactions would allow a more detailed investigation of this factor. It was found in these experiments that mixing had a larger effect only in cases where the concentration of the solutions was also changed simultaneously. Thus, although in more dilute solutions it should be expected that a better mixing of the reagents before reaction is possible, this effect could not be unambiguously proved, as the effect of dilution (solvation) of the brominating agent was found itself to influence the reactions (see previous discussion).

Mechanism.—A comparison of the relative reactivities for Friedel–Crafts bromination of benzene and alkylbenzenes with the relative stabilities of known π-complexes of the same substrates (and with previously investigated $NO_2^+BF_4^-$ and $C_6H_5CH_2Cl \cdot AlCl_3 \cdot CH_3NO_2$ substitution rates) shows good agreement as summarized in Table IX. On the other hand, no correlation seems to exist with HF + BF_3 complex stabilities (σ-complexes). Consequently, it is suggested that this bromination system, involving a strong electrophile (incipient if not necessarily free bromonium ion) in an organic solvent (nitromethane), shows substrate reactivities of benzene and alkylbenzenes corresponding to π- and *not* σ-complex stabilities. Friedel–Crafts bromination therefore shows significant differences from previously investigated molecular or "positive bromine" brominations, carried out in aqueous acetic acid or dioxane solutions. In these solutions either a considerably more solvated, and therefore less electrophilic and more selective halogenating agent, is present, producing brominations through a σ-complex type activated state or, even more plausibly, the bromonium species as such is not present except in the form of a weakly electrophilic precursor, which then interacts with the aromatic in a highly selective reaction.

The observed isomer distributions very much represent the nonisomerized distributions obtained in kinetically controlled substitutions. The low *meta* and high *ortho* content substantiates this view, in comparison with our previous investigations[18] of the Friedel–Crafts isomerization of halotoluenes. The presence of the basic solvent prevents ring protonation by the acids and eliminates isomerizing conditions.

Kinetic Isotope Effect.—Deuterium isotope effects of the order of four have been found previously in aromatic iodinations.[19] They were, however, either absent[20a] or considerably smaller in aromatic brominations.[20b] Berliner and Schueller[21] for example recently found an isotope effect of $k_H:k_D = 1.15$ in the bromination of 4,4′-dideuteribiphenyl. All of these investigations were, however, carried out in aqueous solutions (*e.g.*, 50% acetic acid) where obviously highly selective bromination takes place.

In order to determine whether electrophilic aromatic bromination in the present nonaqueous system shows a kinetic isotope effect, the previously described competitive method was used. Competitive bromination of benzene and benzene-d_6 with Br_2 + $FeCl_3$ in nitromethane could not be used, since mass-spectroscopic investigations showed extensive hydrogen–deuterium exchange. Anhydrous $AgClO_4$ + Br_2 in nitromethane provided, however, a bromination system which caused only slight hydrogen exchange and could therefore be used. At 25° a very small secondary isotope effect, $k_H:k_D = 1.08 \pm 0.03$, was observed which was only slightly larger than the error of determination. The reasons for small secondary isotope effects in elec-

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(17) Preliminary kinetic measurements in flow systems indicate the reaction velocity of the bromination of benzene and toluene have a half-time in the order of 10^{-3} sec. Thus even if the reactions are fast, they are many orders of magnitude apart from the velocity of a diffusion controlled reaction.

(18) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962).

(19) E. Grovenstein, Jr., and D. C. Kilby, *J. Am. Chem. Soc.*, **79**, 2972 (1957); A. Grimison and J. H. Ridd, *Proc. Chem. Soc.*, 256 (1958); *J. Chem. Soc.*, 3019 (1959); E. Shilov and F. Weinstein, *Nature*, **182**, 1300 (1958); E. Berliner, *Chem. Ind.* (London), 177 (1960).

(20) (a) L. Melander, *Arkiv Kemi*, **2**, 213 (1950); P. B. D. De la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957); (b) H. Zollinger, *Experientia*, **12**, 165 (1956); P. G. Farrell and S. F. Mason, *Nature*, **183**, 250 (1959); E. Berliner, ref. 11.

(21) E. Berliner and K. E. Schueller, *Chem. Ind.* (London), 1444 (1960).

TABLE IX

COMPARISON OF RELATIVE STABILITIES OF COMPLEXES OF ALKYLBENZENES (*p*-XYLENE = 1) WITH BROMINATION RATES

Benzene ring substituents	Ag^+	HCl	Br_2	I_2	Picric acid	$C_2(CN)_4$	$Br_2 + FeCl_3$ in CH_3NO_2	$HF + BF_3$
H	0.98	0.61	0.46	0.48	0.70	0.26	0.23	
CH_3	1.04	0.92	0.64	0.52	.84	0.49	0.83	0.01
C_2H_5	0.86	1.06			.74			
o-$(CH_3)_2$	1.26	1.13	1.01	0.87	1.03	0.91	0.91	2.0
m-$(CH_3)_2$	1.19	1.26	0.96	1.00	0.98	0.79	1.30	20.0
p-$(CH_3)_2$	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1,3,5-$(CH_3)_3$	0.70	1.59		2.65	1.12	2.22	3.70	2800.0

trophilic aromatic substitutions have been discussed previously.[7,8]

Conclusions

The electrophilic aromatic brominations described using anhydrous conditions and a strong electrophile (such as the system $Br_2 + FeCl_3$) have shown low substrate but high positional selectivity substitution. The isomer distributions seem to be characteristic for electrophilic aromatic substitution involving only small steric effects (incipient Br^+ as compared with Br_2 which displays a substantial steric effect).

There seems to be no direct correlation between substrate and positional selectivity from the obtained data. Calculation of partial rate factors and selectivity factors cannot be applied. (Values for m_f may be considerably smaller than 1.)

It is suggested that this bromination system represents a further example of electrophilic aromatic substitution of alkylbenzenes with strong electrophiles, similar to the previously discussed nitration and alkylation systems, where low substrate, but high positional selectivity, is observed in accordance with a mechanism involving a π-complex type transition state in the low substrate selectivity rate-determining step, followed by lower energy level transition states of σ-complex nature, determining positional selectivity.

Experimental

The purity of the alkylbenzenes employed was similar to that of those used in previous investigations. Anhydrous ferric chloride (purified, sublimed Fisher reagent) and pure bromine (99.9%, The Dow Chemical Co.) were used without further purification.

Nitromethane was purified according to Winstein and Smith.[22] Nitromethane (Eastman Kodak spectroscopic grade) was washed three times with a solution containing 25 g. of $NaHCO_3$ and 25 g. of $NaHSO_3$ per liter of water, then with water, 5% sulfuric acid, water, and aqueous $NaHCO_3$, dried overnight over Drierite with shaking, and then passed through a 2-ft. column of $^1/_{16}$ in. Type 4A Linde Molecular Sieves. It was then fractionated at 160 mm. and 58° from a small amount of molecular sieve powder to yield solvent neutral to bromphenol blue in ethanol and dry to Karl Fischer reagent; $n^{25}D$ 1.3790. Benzene-d_6 was obtained from Ciba A.g. Basel, Switzerland.

Competitive Bromination of Benzene and Alkylbenzenes. (a) **Neat Bromine Added.**—Benzene (0.25 mole), 0.25 mole of alkylbenzene, and 20 g. (0.13 mole) of $FeCl_3$ were dissolved in 50 g. of nitromethane. The filtered solution was placed in a reaction flask in a constant temperature bath and 2.4 g. (0.015 mole) of bromine was added to the vigorously stirred mixture (generally in the course of 10 min.). The temperature of the mixture was kept at 25 ± 0.5° during the reaction.

After the addition of the bromine the reaction mixture was stirred for an additional 5 min., then washed with 200 ml. of 5% HCl–water solution, subsequently with 100 ml. of water, dried over $CaCl_2$, and analyzed by gas–liquid chromatography.

A typical preparative material balance of a competitive bromination mixture of toluene and benzene (based on separation of components by preparative gas–liquid chromatography) gave the following distribution of products (mole %): bromobenzene, 26.3%; dibromobenzene, 3.8%; bromotoluene, 54%; dibromotoluenes, 15%. No higher brominated products could be identified and the residue contained only the excess of the starting aromatic hydrocarbons.

(b) **Nitromethane Solution of Bromine Added.**—Benzene (0.25 mole), 0.25 mole of alkylbenzene, and 5 g. (0.03 mole) of $FeCl_3$ were dissolved in 50 g. of nitromethane. The filtered solution was placed in a reaction flask in a constant temperature bath at 25 ± 0.5° and 0.05 mole of Br_2 dissolved in 30 g. of nitromethane was added to the rapidly stirred solution over a 10-min. period. The reaction temperature was kept at 25°. After addition of the bromine solution, the mixture was stirred for an additional 5 min., then quenched with 200 ml. of ice–water. The organic layer was separated, washed with 150 ml. of water, dried over $CaCl_2$, and analyzed by gas–liquid chromatography.

(c) **Nitromethane Solution of Bromine and Ferric Chloride Added.**—Benzene (0.25 mole) and 0.25 mole of alkylbenzene was dissolved in 50 g. of nitromethane. The reaction flask was placed in a constant temperature bath at 25°. A filtered solution of 0.1 mole of ferric chloride and 0.05 mole of bromine in 30 g. of nitromethane was then added to the vigorously stirred aromatic solution in the course of 15 min. The reaction temperature was kept at 25°. The reaction mixture was then quenched with 200 ml. of ice–water. The organic layer was separated, washed twice with 150 ml. of water, dried over $CaCl_2$, and analyzed by g.l.c.

Quantitative analyses of the reaction mixtures (by gas–liquid chromatography and by mass spectroscopy) revealed no dibrominated or other higher molecular weight products. It was possible to account for more than 98% of the material as unchanged aromatics and the corresponding monobrominated products.

Competitive Bromination with Varying Concentrations of the Brominating Agent.—Benzene (0.1 mole) and 0.1 mole of toluene were dissolved in 100 ml. of nitromethane. The reaction flask was placed in a constant temperature bath at 25°. A filtered solution of bromine and ferric chloride in 50 ml. of nitromethane, according to concentrations shown in Table VII, was added to the vigorously stirred solution of the aromatics in the course of 15 min. The reaction mixture was then quenched with 200 ml. of water. The organic layer was separated, washed with dilute caustic solution, and water. After drying over calcium chloride it was analyzed by gas–liquid chromatography. The data obtained are summarized in Table VII.

Determination of Kinetic Isotope Effect.—Benzene (0.1 mole) and 0.1 mole of benzene-d_6 and 0.02 mole of $AgClO_4$ were dissolved in 10 g. of nitromethane. Bromine (0.02 mole) dissolved in 10 g. of nitromethane was added dropwise to the vigorously stirred solution. After the bromine addition was complete, the mixture was stirred for another 5 min.; AgBr was then filtered off, the organic layer washed twice with 50 ml. of water, dried over $CaCl_2$, and analyzed by mass spectroscopy.

Analysis of Reaction Mixtures.—Relative rates and isomer distributions were determined by gas–liquid chromatography, carried out on Perkin–Elmer Model 154-C and Model 154-D vapor fractometers using thermistor and hydrogen flame ionization detectors, respectively. Peak areas were established with the use of Perkin–Elmer Model 194 and Infotronics Model CRS-1 integrators. A 4-m. by 0.25 in. stainless steel packed column with polypropylene glycol (UCON LB 550-X) supported on diatomaceous earth, and polypropylene glycol coated 150 ft. by 0.01 in. Golay capillary columns were used. The column temperature on the packed column was 150°. Approximately 50 ml. of hydrogen per minute was used as carrier gas. Sample sizes injected were between 50 and 100 μl. The column temperature of the capillary Golay column was 100°. Helium was used as the carrier gas at a pressure of 10 p.s.i. Samples of 10 μl. were generally injected.

Relative response data were determined by running known solutions of the various alkylbromobenzenes with bromobenzene in excess benzene, in approximately those proportions occurring in the reaction mixtures.

The isomers of bromo-*o*- and -*m*-xylenes did not separate on the packed column and were analyzed on the Golay capillary column.

The isomeric bromotoluenes and bromoethylbenzenes were not separated sufficiently well with the above-described capillary

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[22] Method used in Department of Chemistry, University of California, Los Angeles, Calif. Above method is an improvement of that of B. B. Smith and J. E. Leffler, *J. Am. Chem. Soc.*, **77**, 1700 (1955), and of C. J. Thompson, M. J. Coleman, and R. V. Helm, *ibid.*, **76**, 3445 (1954).

TABLE X

RETENTION TIMES OF MONOBROMOALKYLBENZENES ON PACKED COLUMN (COLUMN TEMPERATURE 150°)

Compound	Retention time, min
Bromobenzene	6
Bromotoluenes	10
o-Bromoethylbenzene	12
p-Bromoethylbenzene	14
Bromo-*o*-xylenes	18
Bromo-*m*-xylenes	17
Bromo-*p*-xylene	16
Bromomesitylene	26

RETENTION TIMES OF MONOBROMOALKYLBENZENES ON GOLAY CAPILLARY COLUMN (100°)

Compound	Retention time, min.
Bromobenzene	18
o-Bromotoluene	26
p-Bromotoluene	27
3-Bromo-*o*-xylene	51
4-Bromo-*o*-xylene	53
2-Bromo-*m*-xylene	42
4-Bromo-*m*-xylene	43
Bromo-*p*-xylene	42
Bromomesitylene	75

column although it was possible to separate the *ortho* from the combined *meta* and *para* isomers.

In order to separate the isomeric bromotoluenes, use was made of a high sensitivity Perkin–Elmer Model 226 vapor fractometer using a hydrogen flame ionization detector and a 150 ft. × 0.01 in. bifilar spiral Golay capillary column. The liquid phase was made up of 80% *m*-bis-(*m*-phenoxyphenoxy)-benzene and 20% Apiezon L. The column temperature was 60°. Helium was used as the carrier gas at a pressure of 20 p.s.i.; 2-μl. samples were injected. The isomeric bromotoluenes were separated with the following retention times: *o*-bromotoluene, 45 min.; *p*-bromotoluene, 48 min.; and *m*-bromotoluene, 48.5 min.

As the separation of isomeric bromotoluenes (and bromoethylbenzenes) represented difficulties even with the use of highly efficient capillary columns, they were also analyzed by infrared spectroscopy, reference being made to the characteristic out-of-plane hydrogen deformation absorption bands in the 12–14 μ region. Samples were weighed into carbon disulfide at two concentrations (10% and 2% wt./vol.) so that both weak and strong absorption bands could be measured accurately. The solutions were scanned on a double beam infrared spectrometer with sodium chloride optics. Analyses were carried out by the standard base line technique with suitable corrections made for the interference of any isomer on the others by use of an electronic computer. The following analytical wave lengths (μ) were used for the analyses: *o*-bromotoluene, 13.42; *m*-bromotoluene, 13.0; *p*-bromotoluene, 12.48; *o*-bromoethylbenzene, 13.4; *m*-bromoethylbenzene, 12.96; *p*-bromoethylbenzene, 12.22.

It was found advantageous for the infrared analyses to separate the combined bromotoluene or bromoethylbenzene fractions by preparative scale vapor phase chromatography, thus eliminating solvent and other aromatic interferences. Accuracy of the isomer ratios is within ±3 relative %, as checked with mixtures of known composition.

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Aromatic Substitution. XV.[1] Ferric Chloride Catalyzed Bromination of Halobenzenes in Nitromethane Solution

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The ferric chloride catalyzed bromination of benzene and halobenzenes with bromine in nitromethane solution was investigated at 25°. Relative reactivities and isomer distributions were determined in competitive experiments by gas–liquid chromatography.

Introduction

The electrophilic bromination of halobenzenes has been investigated in detail by Hollemann,[2] De la Mare,[3] Ferguson,[4] and one of us[5] in previous work. De la Mare and Ridd[6] have recently reviewed the field.

Results

Our investigations on the bromination of benzene and alkylbenzenes[1] have now been extended to the competitive bromination of benzene and halobenzenes. Brominations were carried out using anhydrous ferric chloride as catalyst in nitromethane solution, under conditions identical with those reported previously for the bromination of alkylbenzenes.[1]

Table I and II summarize data for the competitive bromination of benzene and halobenzenes, together with the corresponding isomer distributions, using neat bromine as brominating agent. (Analyses were carried out with gas–liquid chromatography, as described in the Experimental part.)

As in the related bromination of alkylbenzenes,[1] use of neat bromine presents difficulties in that local excesses of bromine promote dibromination to a certain degree, and it is consequently advisable to use nitromethane solutions of bromine instead of neat bromine. The data obtained are summarized in Table II.

TABLE I

FERRIC CHLORIDE CATALYZED COMPETITIVE BROMINATION OF BENZENE AND HALOBENZENES IN NITROMETHANE SOLUTION AT 25° (NEAT BROMINE ADDED)

Aromatic, benzene	$k_{\text{halobenzene}}:k_{\text{benzene}}$	Isomer bromohalobenzene, %		
		o-	*m*-	*p*-
Benzene	1.0	10.5		
Fluoro-	0.69	10.5	<0.2	89.5
Chloro-	.35	20.3	< .2	79.7
Bromo-	.30	23.6	< .2	76.4

TABLE II

FERRIC CHLORIDE CATALYZED COMPETITIVE BROMINATION OF BENZENE AND HALOBENZENES IN NITROMETHANE SOLUTION AT 25° (CH_3NO_2 SOLUTION OF Br_2 ADDED)

Aromatic, benzene	$k_{\text{halobenzene}}:k_{\text{benzene}}$	Isomer bromohalobenzene, %		
		o-	*m*-	*p*-
Benzene	1.0			
Fluoro-	0.27	10.5	<0.2	89.5
Chloro-	.12	22.1	< .2	77.9
Bromo-	.10	26.0	< .2	74.0

As nitromethane itself is capable of promoting high selectivity brominations, the bromination of benzene and halobenzenes was carried out using a nitromethane solution of bromine and excess ferric chloride in order to minimize the effect of solvent. Table III summarizes data from competitive brominations with this system.

The competitive method of relative rate determination could be used conveniently in these investigations, since the concentration variation of benzene and halobenzenes, as investigated in the case of chloro-

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(2) A. F. Hollemann, *Chem. Rev.*, **1**, 187 (1925).

(3) P. B. D. De la Mare, *J. Chem. Soc.*, 4450 (1954).

(4) L. N. Ferguson, A. Y. Garner, and J. S. Mack, *J. Am. Chem. Soc.*, **76**, 1250 (1954).

(5) G. Olah, A. Pavlath, and G. Varsanyi, *J. Chem. Soc.*, 1823 (1957).

(6) P. B. D. De la Mare and J. H. Ridd, "Aromatic Substitution, Nitration and Halogenation," Academic Press, Inc., New York, N. Y., 1959.