in Figure X) is treated as an sp^3 carbon atom in the transition state, the nucleophilic oxygen atom (O2) is treated as an sp^3 atom, and the two remaining oxygen atoms are also treated as sp^3.

For acids **14** and **15**, the parameters defined by Beckaus[24] were employed for the aromatic rings. In addition, the parameters in Table VIII were defined in the transition state calculations.

For the calculation of the product derived from **14**, the parameters in Table IX were defined (C* = carbonyl CO).

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Electrophilic Nitration, Halogenation, Acylation, and Alkylation of α,α,α-Trifluoromethoxybenzene[1a]

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Abstract: Electrophilic nitration of α,α,α-trifluoromethoxybenzene gave 88–93% para and 12–7% ortho isomer with no meta isomer detected. The relative reactivity of α,α,α-trifluoromethoxybenzene compared to benzene (determined in competition experiments) was found to be comparable to that of fluorobenzene. A Hammett–Brown plot of log k_X/k_H vs. σ^+ for nitration with nitronium tetrafluoroborate in nitromethane solution gave excellent linear correlation (correlation factor $r = 0.999$). A σ^+ value of 0.067 was obtained for the OCF_3 group from this plot. $FeCl_3$- and I_2-catalyzed bromination also showed exclusive para/ortho orientation, whereas in the $FeCl_3$-catalyzed chlorination 6% meta isomer was also obtained. $FeCl_3$-catalyzed acetylation and benzoylation in nitromethane solution gave predominant (or exclusive) para substitution. The $AlCl_3$-catalyzed Friedel–Crafts alklation of α,α,α-trifluoromethoxybenzene with *tert*-butyl and benzyl chlorides gave nearly exclusive para or para/ortho substitution (99.4% para, 0.6% meta, and 85% para, 1% meta, 14% ortho, respectively). Isopropylation with isopropyl chloride (bromide) gave 29.5–28.5% ortho, 9.5–8.5% meta, and 61–63% para isomer. In attempted $AlCl_3$-catalyzed alkylation with methyl and ethyl chlorides chlorine exchange of the trifluoromethoxy group became predominant. BF_3-catalyzed alkylation with alkyl fluorides avoids such exchange. The amount of meta isomer in BF_3-catalyzed ethylation with ethyl fluoride increased to ~31% in contrast to related isopropylation, *tert*-butylation, and benzylation which showed no or very limited meta substitution. This is considered to be due to concurrent intramolecular ethyl and hydrogen shifts in the arenium ion type alkylation intermediates in the case of ethylation ($C_2H_5^+$ is a very poor leaving group), in contrast to *tert*-butylation and benzylation, where carbocationic alkyl shifts are intermolecular. Isopropylation is of intermediate nature, with both inter- and intramolecular alkyl shifts taking place. Attempts of methylation with CH_3F and BF_3 gave only marginal reaction. Alkylations (and to some degree chlorination) showing significantly increased meta substitution are considered to be affected by thermodynamically controlled intramolecular rearrangement processes taking place in the arenium ion intermediates of the substitution reactions but do not necessarily involve isomerization of the products themselves. Under predominantly kinetic conditions such as in nitration, bromination, and acylations or when alkyl (halogen) transfer is intermolecular, α,α,α-trifluoromethoxybenzene is predominantly para–ortho substituted. The $-I > +K$ effect of the CF_3O group, with the inductive effect diminishing with distance while the conjugative effect remains unaffected, results in predominant para substitution.

The study of the directing effect of substituent groups in benzene has provided over the years fundamental mechanistic understanding of electrophilic aromatic substitution reactions. In our continuing study of aromatic substitution, we extended our investigations to the directing effect of the trifluoromethoxy group in electrophilic nitration, halogenation, acylation, and alkylation of α,α,α-trifluoromethoxybenzene. Sheppard and co-workers[2a,b] have reported the preparation of α,α,α-trifluoromethoxybenzene by reacting phenol with carbonyl fluoride to form phenyl fluoroformate and its subsequent reaction with sulfur tetrafluoride. Feiring[2c] subsequently developed a much simplified synthesis by reacting phenols with carbon tetrachloride in HF. The reaction gave satisfactory yield with some substituted phenols but only low yield (ca. 10%) with phenol itself. As the reaction of 3-bromophenol with CCl_4 and HF gives *p*-bromo-α,α,α-trifluoromethoxybenzene in good yield (ca. 70%), its reduction with H_2 over Pd/C offers a convenient synthesis of α,α,α-trifluoromethoxybenzene. Early work on the electrophilic substitution of α,α,α-trifluoromethoxybenzene has been carried out by Yagupolsky et al.[3] as well as by Sheppard.[2] No systematic study has, however, been reported.

We undertook a detailed study of the directing effect of the trifluoromethoxy group in electrophilic nitration, halogenation, acylation, and alkylation of α,α,α-trifluoromethoxybenzene and report our findings herein.

Results and Discussion

Nitration. α,α,α-Trifluoromethoxybenzene was nitrated under usual nitration conditions with a mixture of nitric and sulfuric acids in homogeneous glacial acetic acid solution, as well as under

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Table I. Nitration of Trifluoromethoxybenzene and Its Comparison with Halobenzenes

					% isomer distribution			
substrate (ArH)	reagent	solvent	temp, °C	k_{ArH}/k_B	ortho	meta	para	ref
trifluoromethoxybenzene	$NO_2^+BF_4^-$	CH_3NO_2	25	0.19	11.5	0	88.5	
	HNO_3-COOH	CH_3COOH	100		12.4	0	87.6	
	HNO_3-H_2SO_4		25		9.7	0	90.3	
	$AgNO_3$-BF_3	CH_3CN	25	0.01	7.0	0	93.0	
	CH_3ONO_2-BF_3	CH_3NO_2	25	0.01	9.8	0	90.2	
fluorobenzene	$NO_2^+BF_4^-$	sulfolane	25	0.45	8.5	0	91.5	24
	HNO_3-H_2SO_4	CH_3COOH		0.12	13	<1	86	24
	CH_3ONO_2-BF_3	CH_3NO_2		0.12	11.1	<1	88.6	24
	$AgNO_3$-BF_3	CH_3CN		0.06	27	1	72	24
chlorobenzene	$NO_2^+BF_4^-$	sulfolane	25	0.14	22.1	0.7	76.6	24
bromobenzene	$NO_2^+BF_4^-$	sulfolane	25	0.12	25.7	1.1	73.2	24

Table II. Halogenation of Trifluoromethoxybenzene and Its Comparison with Halobenzenes

							% isomer distribution			
substrate (ArH)	reagent	catalyst	solvent	temp, °C	time, h	k_{ArH}/k_B	ortho	meta	para	ref
trifluoromethoxybenzene	Br_2	$FeCl_3$	CH_3NO_2	25	1	0.09	12.5	0	87.5	
	Cl_2	$FeCl_3$	CH_3NO_2	25	1.5	0.05	22.9	6.0	71.1	
	Cl_2	I_2	CCl_4	25	1		3.8	0	96.2	
fluorobenzene	Br_2	$FeCl_3$	CH_3NO_2	25	1	0.48	11.9	<0.2	88.1	25
	Cl_2	$FeCl_3$	CH_3NO_2	25	1	0.29	25.5	2	72.5	26
chlorobenzene	Br_2	$FeCl_3$	CH_3NO_2	25	1	0.20	25.1	<0.2	74.9	25
	Cl_2	$FeCl_3$	CH_3NO_2	25	1	0.17	42.5	3.1	54.4	26
bromobenzene	Br_2	$FeCl_3$	CH_3NO_2	25	1	0.16	27.2	<0.2	72.8	25
	Cl_2	$FeCl_3$	CH_3NO_2	25	1	0.15	44.6	3.2	52.2	26

heterogeneous condition without the use of solvent (mixed acid and α,α,α-trifluoromethxybenzene are immiscible). We subsequently also carried out nitration using other nitrating reagents such as nitronium tetrafluoroborate, $AgNO_3/BF_3$, and CH_3ONO_2/BF_3. The data are summarized in Table I. Also included are the results of the competition studies of the nitration of benzene and α,α,α-trifluoromethoxybenzene. For comparison data of related nitrations of fluorobenzene as well as of chloro- and bromobenzene are also shown.

The nitration of α,α,α-trifluoromethoxybenzene under all the reaction conditions studied gave only para/ortho substitution, with *p*-nitro-α,α,α-trifluoromehoxybenzene as the major product (88–93%). In no case was meta isomer detected. This reflects the $-I > +K$ effect (we are using the symbol *K* for the conjugative effect[4]) of the CF_3O group. The inductive effect (*i*) diminishes with distance, whereas the resonance effect (*K*) is not affected. The nitration of α,α,α-trifluoromethoxybenzene is slower in comparison to benzene which is due to the overall deactivating effect of the trifluoromethoxy group on the benzene ring. The results of nitration of α,α,α-trifluoromethoxybenzene closely resemble those of fluorobenzene (see Table I).

The relative reactivity data of $k_{C_6H_5}/k_{C_6H_6}$ of the competitive nitration of benzene and substituted benzenes are best respresented as a Hammett–Brown plot of log k_H/k_H vs. σ^+, given in Figure 1. The negative slope is in accord with a strong electrophile (i.e., NO_2^+).

When log k_X/k_H for α,α,α-trifluoromethoxybenzene is plotted on this graph, it gives a σ^+ value for the OCF_3 group of +0.067. The positive value of σ^+ for the OCF_3 group clearly indicates the overall deactivating effect on the aromatic ring. The σ^+ value of the OCF_3 group closely resembles those for F ($\sigma^+ = -0.073$) and Cl ($\sigma^+ = +0.114$) and is in accord with the observed directing effect of the OCF_3 group indicating $-I > +K$ effect similar to those in halobenzenes.

Halogenation. Electrophilic bromination and chlorination of α,α,α-trifluoromethoxybenzene were studied in the presence of ferric chloride catalyst. Chlorination was also carried out with iodine catalyst. The data are summarized in Table II along with those of halobenzenes for comparison.

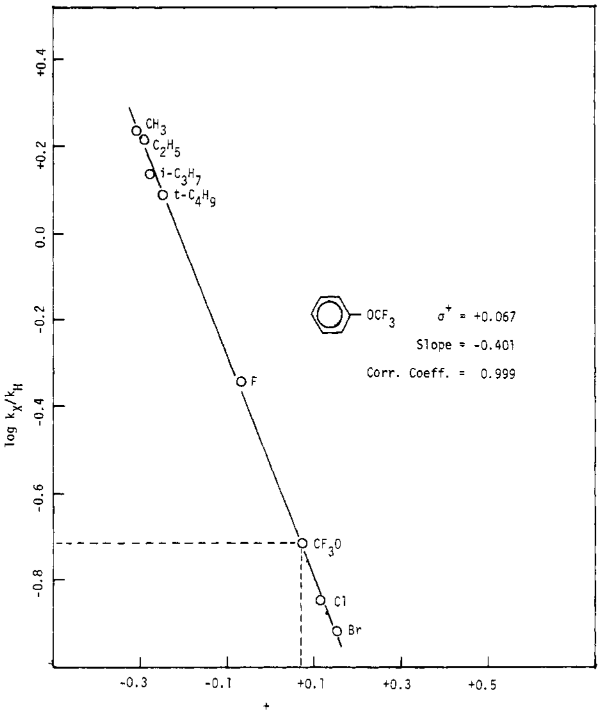

Figure 1. Relative rate vs. σ^+ for nitration of C_6H_5X/C_6H_6 with $NO_2^+BF_4^-$.

In the halogenation reactions the trifluoromethxy group again exhibits predominant para/ortho directing effect. In bromination and I_2 catalyzed chlorination no meta isomer was observed. The absence of meta isomer in the $FeCl_3$-catalyzed bromination of α,α,α-trifluoromethoxybenzene and the observed isomer distribution of 88% para and 12% ortho are similar to that observed in nitration. In the related $FeCl_2$-catalyzed chlorination, however, ortho substitution increased to 23%, which is in accord with the diminished steric requirement of chlorination compared to bromination. At the same time 6% meta isomer is also observed. This in part can be explained by consideration of the exclusive intermolecular nature of any halogen shifts of the bromoarenium ion

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[4] Ingold, C. K. *Structure and Mechanism*, 2nd ed.; Cornell University Press: Ithaca, 1969, p 74) recommended to replace his previous T notation (for tautomeric effect) with Olah's K notation (for conjugative effect): Olah, G. A. *Einführung in die Theoretische Organische Chemie*; Akademie-Verlag: Berlin, 1960; pp 180–181.

Table III. Ferric Chloride Catalyzed Acylation of α,α,α-Trifluoromethoxybenzene with Acyl Halides in Nitromethane Solution and Comparison with Fluorobenzene

substrate (ArH)	acyl halide	k_{ArH}/k_B	% isomer distribution ortho	meta	para
trifluoromethoxybenzene	CH_3COCl	0.03	0	0	100
	PhCOCl	0.03	2.6	0.5	96.8
fluorobenzene	CH_3COCl	0.51	0	0	100
	PhCOCl	0.40	1.3	0	98.7

intermediates, whereas the analogous chloro system can at least partially undergo intramolecular migration resulting in increased meta substitution. These effects are becoming very significant in intermolecular alkyl migration of *tert*-butyl, isopropyl, and benzyl groups (see subsequent discussion of alkylation). As previously stated, the overall deactivating effect of the trifluoromethoxy group on the benzene ring is evident from the relative rate data with respect to benzene.

Acylation. $FeCl_3$-catalyzed acetylation and benzoylation of α,α,α-trifluoromethoxybenzene in nitromethane solution was found to give predominant (or exclusive) para substitution. The results summarized in Table III are similar to those obtained in the acylation of fluorobenzene. Competitive acylation experiments with benzene showed, however, higher substrate selectivity ($k_{\phi OCF_3}/k_{\phi H}$ = 0.03 compared to $k_{\phi F}/k_{\phi H}$ = 0.4–0.5) indicative of the weaker conjugative effect of CF_3O compared with F.

Alkylation. Regioselectivity in Friedel–Crafts alkylation has frequently been considered to be anomalous,[5–7] and it has been difficult to explain directive effects in alkylation of alkyl (and halo) benzenes. Temperature, solvent, nature, and amount of catalyst seem to have a large effect on the isomeric composition of the products formed. In contrast, isomer distributions in substitutions such as nitration are little effected by conditions.

To explain the high proportion of meta isomer in Friedel–Crafts alkylation of toluene and other alkylbenzenes under conditions where alkylation products themselves are not isomerized, Brown suggested this to be a consequence of high reactivity and resulting low selectivity of the alkylating systems (according to his Selectivity Principle).[6]

We have previously pointed out that the isomer distribution in alkylation of aromatics, such as toluene, can be affected by thermodynamically controlled alkyl shifts in the arenium ion intermediates of the alkylation reactions.[8] Intramolecular shifts within the arenium ion intermediates, i.e., prior to their deprotonation to alkylated products, can readily occur as shown in studies of stable alkylarenium ions.[9] At the same time, the alkylation conditions do not necessarily lead to isomerization of formed alkylaromatic products. Consequently recovery of authentic samples of isomers from alkylation mixtures cannot prove "nonisomerizing" conditions.

Alkylation of toluene, under conditions where product isomerization was decreased or eliminated but intramolecular shifts in the alkylation intermediates are still possible, gave the following amounts of meta isomers: methylation 12–18%,[10] ethylation 14–24%,[10] isopropylation 14–17%,[10–12] *tert*-butylation 5–7%,[12,13] and benzylation 4–6%.[14–16] On the other hand, anisole tends to give ortho–para alkylation products and the amount of meta isomer is low, since the barrier for the isomerization in the benzenium ion intermediates of the alkylation is higher in the case of CH_3O- than in CH_3-substituted systems.[17]

Any relationship between reactivity and selectivity in electrophilic aromatic substitutions should be equally applicable not only to toluene and anisole but also to substituted benzenes containing weaker electron donating or weakly electron withdrawing substituents, such as fluoro or the presently studied trifluoromethoxy. Thus, study of alkylation of α,α,α-trifluoromethoxybenzene is of substantial importance, and no systematic study of its alkylation has yet been reported. We now carried out a study of its aluminum chloride catalyzed alkylation with alkyl halidesin nitromethane solution and of the BF_3-catalyzed alkylation with alkyl fluorides in excess of α,α,α-trifluoromethoxybenzene. The results are summarized in Tables IV and V. For comparison data for similar alkylations of fluorobenzene and halobenzenes are also given.

In the $AlCl_3$-catalyzed *tert*-butylation and benzylation of α,α,α-trifluormethoxybenzene in nitromethane solution the amount of meta isomer formed is very low (<1%). In isopropylation with isopropyl chloride or bromide the amount of meta isomer is increased to 9.5% and 8.4%. Besides alkylated α,α,α-trifluoromethoxybenzenes, halogen exchange products of the trifluoromethoxy group such as chlorodifluoro and dichlorofluoromethoxybenzene were also observed. Indeed, when α,α,α-trifluoromethoxybenzene itself was reacted with $AlCl_3$, it gave α,α,α-chlorodifluoro- and α,α,α-dichlorofluoromethoxybenzene, respectively. In the case of attempted $AlCl_3$-catalyzed methylation and ethylation with methyl and ethyl chloride, the halogen exchange reactions became predominant compared to those of alkylation.

To avoid halogen exchange, consequently, we carried out BF_3-catalyzed alkylations of trifluoromethoxybenzene with alkyl fluorides. As shown in Table V, BF_3-catalyzed alkylations with alkyl fluorides were achieved. No meta isomer was observed in isopropylation, *tert*-butylation, and benzylation, but ethylation gave a significant increase of meta substitution (~31%). Attempted methylation gave only marginal yields, although meta-substitution again was high (~30%), but data are not sufficient at the time for quantitative evaluation.

The high amount of meta isomer in ethylation is indicative, as in the case of toluene, of the concurrent occurrence of alkyl (and hydrogen) shifts in the arenium ion intermediates of the alkylations. As ethyl migration leads to take place via an intramolecular process, this inevitably leads to an increase of the meta isomer in the ethylation reaction. In contrast, in isopropylation and even more so in *tert*-butylation and benzylation, the alkyl groups tend to migrate intermolecularly, thus causing less or no increase in meta substitution.

The observed regioselectivities (reflected by the p+o/m isomer ratios) showing the sequence *tert*-butylation, benzylation > isopropylation ≫ ethylation are thus considered to be affected by the increasing preference for intermolecular (as opposed to intramolecular) alkyl group migrations in the alkyltrifluoromethoxybenzenium ion intermediates (σ complexes). The corresponding BF_3-catalyzed alkylations of fluorobenzene with alkyl fluorides (Table V) gave strikingly similar results.

The relative reactivities compared with benzene were determined in competitive experiments. These results show that α,α,α-trifluoromethoxybenzene is overall deactivated when compared to benzene. The results (Tables VI–VIII) of competitive alkylation of trifluoromethoxybenzene, which are in accord with previously discussed nitration and halogenation, show that the trifluoromethoxy group closely resembles fluorine as a substituent group.

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Table IV. $AlCl_3$-Catalyzed Alkylation of Trifluoromethoxybenzene with Alkyl Halides and Comparison with Halobenzenes[a]

	trifluoromethoxybenzene			fluorobenzene[12,15]			chlorobenzene[12,15]			bromobenzene[12,15]		
alkyl halide	% ortho	% meta	% para	% ortho	% meta	% para	% ortho	% meta	% para	% ortho	% meta	% para
i-C_3H_7Cl	29.4	9.5	61.1									
i-C_3H_7Br	28.5	8.4	63.1	41.8	1.9	56.3	49.8	7.9	42.3	51.4	11.3	37.3
t-C_4H_9Cl	0	0.6	99.4									
t-C_4H_9Br	0	0.8	99.2	1.8	0.1	98.1		5.5	94.5			100
$C_6H_5CH_2F$	14.1	0.4	85.5									
$C_6H_5CH_2Cl$	14.2	1.1	84.7	14.7	0.2	85.1	33.0	0.6	66.4	32.5	0.7	66.3
$C_6H_5CH_2Br$	14.4	0.4	85.6									

[a] Reactions generally carried out in CH_3NO_2 solutions at 25 °C for 30 min.

Table V. BF_3-Catalyzed Alkylation of Trifluoromethoxybenzene with Alkyl Fluorides and Comparison with Fluorobenzene[a]

alkyl fluoride	trifluoromethoxybenzene			fluorobenzene		
	% ortho	% meta	% para	% ortho	% meta	% para
C_2H_5F	24.6	31.4	44.0	28.8	23.2	48.0
i-C_3H_7F	14.2	0	85.8	29.8	0	70.2
t-C_4H_9F	0	0	100.0	0	0	100.0
$C_6H_5CH_2F$	12.1	0	87.9	14.7	<0.2	85.1

[a] Reactions were carried out in excess of aromatics at −30 to +25 °C for 30 min.

Table VI. Competitive $AlCl_3$–CH_3NO_2-Catalyzed Isopropylation of Trifluoromethoxybenzene and Benzene with Isopropyl Bromide at 25 °C and Comparison with Related Alkylation of Halobenzenes[12]

substrate (ArH)	k_{ArH}/k_B	% isomer distribution		
		ortho	meta	para
benzene	1.0			
trifluoromethoxybenzene	0.03	28.5	8.4	63.1
fluorobenzene	0.23	41.8	1.9	56.3
chlorobenzene	0.10	49.8	7.9	42.3
bromobenzene	0.08	51.4	11.3	37.3

Table VII. Competitive $AlCl_3$–CH_3NO_2-Catalyzed *tert*-Butylation of Trifluoromethoxybenzene and Benzene with *tert*-Butyl Bromide at 25 °C and Comparison with Related Alkylation of Halobenzenes[12]

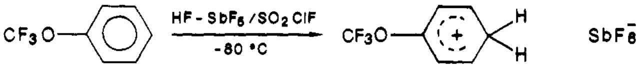
substrate (ArH)	k_{ArH}/k_B	% isomer distribution		
		ortho	meta	para
benzene	1.0			
trifluoromethoxybenzene	0.08	0	0.8	99.2
fluorobenzene	0.16	3.6	0.1	96.3
chlorobenzene	0.03	0	5.5	94.5
bromobenzene	0.02	0	3.0	97.0

Table VIII. Competitive $AlCl_3$–CH_3NO_2-Catalyzed Benzylation of Trifluoromethoxybenzene and Benzene with Benzyl Chloride at 25 °C and Comparison with Related Halobenzenes[15]

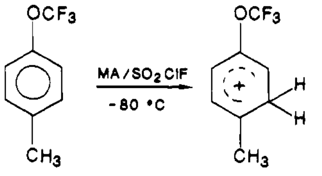
substrate (ArH)	k_{ArH}/k_B	% isomer distribution		
		ortho	meta	para
benzene	1.0			
trifluoromethoxybenzene	0.10	14.2	1.1	84.7
fluorobenzene	0.46	14.7	0.2	85.1
chlorobenzene	0.24	33.0	0.6	66.4
bromobenzene	0.18	32.5	0.7	66.8
iodobenzene	0.28	30.6	0.7	68.7

To further study the suggested intramolecular migration of substituents in the arenium ion like intermediates of the substitution reactions of α,α,α-trifluoromethoxybenzene we also attempted to prepare long-lived trifluoromethoxyarenium ions. No such ions were previously known or studied.

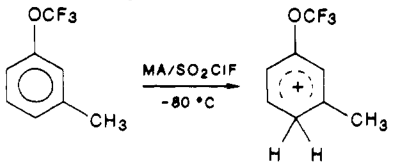
The protonation of α,α,α-trifluoromethoxybenzene and methyl-substituted α,α,α-trifluoromethoxybenzenes was investigated with superacids (FSO_3H/SbF_5 or HF/Sb_5) in a low nucleophilicity solvent (SO_2ClF) under so-called stable ion conditions. α,α,α-Trifluoromethoxybenzene was not protonated when treated with 1:1 magic acid (FSO_3H/SbF_5) at −80 °C in SO_2ClF. It was, however, successfully protonated by the even stronger HF/SbF_5 (1:1) in SO_2ClF at −80 °C. The ^{13}C NMR spectrum of protonated α,α,α-trifluoromethoxybenzene consists of five peaks at δ 45.8 (t), 119.4 (q), 125.0 (d), 182.9 (d), and 183.3 (s), indicating protonation at the para position forming the 4-α,α,α-trifluoromethoxybenzenium ion.



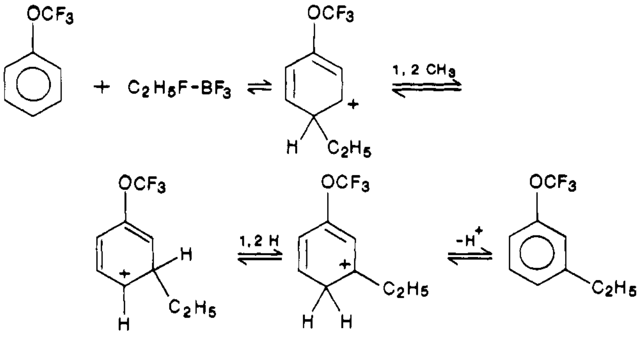
More nucleophilic *p*-methyl-α,α,α-trifluoromethoxybenzene was protonated with magic acid at −80 °C in SO_2ClF. The ^{13}C NMR spectrum of the protonated species consists of eight peaks at δ 45.5 (q), 71.7 (t), 145.7 (d), 146.7 (q), 169.4 (s), 193.5 (d), 211.0 (d), and 218.6 (s). When the formed 2-methyl-5-α,α,α-trifluoromethoxybenzenium ion was quenched with ice water *p*-methyl-α,α,α-trifluoromethoxybenzene was recovered unchanged. These data are in accord with ring protonation without methyl group migration.



The protonation of *m*-methyl-α,α,α-trifluoromethoxybenzene was also carried out and similar results were obtained. The structure of the protonated species is assigned to the 2,4-substituted ion, based on its ^{13}C NMR spectrum.



No methyl or hydrogen migration was observed in the methyltrifluoromethoxybenzenium ions at low temperature. When the temperature was raised to −50 °C they decompose before there is any indication of isomerization. Whereas consequently no isomerization process could be studied, this only proves that isomeric methyl-α,α,α-trifluoromethoxybenzenes (i.e., the products of methylation of α,α,α-trifluoromethoxybenzene) do not rearrange at low temperature under superacidic stable ion conditions. The situation is different in alkylations, such as ethylation reaction of α,α,α-trifluoromethoxybenzene, where during the reaction ipso protonated ions must be formed, which as shown in our previous studies[8] are capable of underging intramolecular rearrangement to more stable 2,4-substituted ions prior to deprotonation, thus accounting for observed high (31%) meta substutition.



In none of the studied α,α,α-trifluoromethoxybenzenes was O-protonation of the OCF_3 group observed, which is in accord with the strong electron-withdrawing effect of the CF_3 group, rendering the oxygen a much weaker donor.

Conclusions

The study of α,α,α-trifluoromethoxybenzene allowed us to extend our knowledge of electrophilic aromatic substitution of benzenoid systems to the novel CF_3O substituent. Electrophilic nitration, halogenation, and acylation of α,α,α-trifluoromethoxybenzene show para/ortho directing effect with no or only very low amounts of meta isomer formed, in accordance with the negative inductive and positive conjugative effect of the OCF_3 group. $AlCl_3$- and BF_3-catalyzed alkylation with alkyl chlorides and fluorides, respectively, gave similar para/ortho direction for *tert*-butylation, isopropylation, and benzylation, but in the case of ethylation substantially increased (~31%) meta substitution was observed. As migration of the ethyl group is intramolecular, whereas *tert*-butyl, isopropyl, and benzyl groups, due to the much higher stability of their cations, can readily migrate intermolecularly, the results provide further significant insight into aromatic alkylations. A strikingly similar behavior is observed in the related alkylations of fluorobenzene. α,α,α-Trifluoromethoxybenzene-like fluorobenzene is para/ortho directing. There seems to be no theoretical reason or experimental observation (under kinetic conditions) that would indicate significant change in substitution to greatly enhanced formation of the meta isomer, except suggested intramolecular rearrangement of the alkylarenium ion intermediates of the ethylation reaction prior to their deprotonation.

Experimental Section

Alkyl halides, benzene, and halophenols were commercially available reagents. Anhydrous hydrogen fluoride (Air Products) was used as received. Anhydrous aluminum trichloride, ferric chloride, and boron trifluoride were of commercially available highest purity. Nitromethane was purified as reported previously[18a] based on a procedure of Winstein and Smith. Nitronium tetrafluoroborate was prepared as described.[18b] Drybox techniques were used in handling reagents and preparing solutions. All reactions were carried out with the usual protection from moisture and with well-dried apparatus.

α,α,α-Trifluoromethoxybenzene[2a,3a,19] was prepared by an improvement of the Pd/C-catalyzed hydrogenolysis of *p*-bromo-α,α,α-trifluoromethoxybenzene, obtained by the reaction of 3-bromophenol with carbon tetrachloride in HF.[2c] *p*-Methyl-α,α,α-trifluoromethoxybenzene (bp 50–51 °C (38 mmHg) [lit.[2a] bp 131 °C], $C_8H_7F_3O$, M^+: 176) and *m*-methyl-α,α,α-trifluoromethoxybenzene (bp 49–50 °C (36 mmHg) [lit.[2a] bp 134–135 °C], $C_8H_7F_3O$, M^+: 176) were prepared from the corresponding bromo-α,α,α-trifluoromethoxybenzenes by Grignard reaction with *N*-formylpiperidine[20] and ionic hydrogenation with trifluoroacetic acid/triethylsilane.[21] The isomeric *p*-ethyl- (bp 64–65 °C (25 mmHg), $C_6H_9F_3O$, M^+: 190), *m*-ethyl- (bp 63–64 °C (25 mmHg), $C_9H_9F_3O$, M^+: 190), *o*-ethyl- (bp 62–65 °C (25 mmHg), $C_9H_9F_3O$, M^+: 190), *p*-isopropyl- (bp 67–69 °C (25 mmHg), $C_{10}H_{11}F_3O$, M^+: 204), *m*-isopropyl- (bp 65–67 °C (25 mmHg), $C_{10}H_{11}F_3O$, M^+: 204), *o*-isopropyl- (bp 65–68 °C (21 mmHg), $C_{10}H_{11}F_3O$, M^+: 204), *p*-benzyl- (bp 83–85 °C (3 mmHg), $C_{10}H_{11}F_3O$, M^+: 252), *m*-benzyl- (bp 79–81 °C (3 mmHg), $C_{14}H_{11}F_3O$, M^+: 252), and *o*-benzyl- (bp 76–79 °C (o mmHg), $C_{14}H_{11}F_3O$, M^+: 252) α,α,α-trifluoromethoxybenzenes were also prepared from the corresponding bromo-α,α,α-trifluoromethoxybenzenes by the corresponding Grignard reactions and subsequent ionic hydrogenation. Preparation of *p-tert*-α,α,α-trifluoromethoxybenzene (bp 69–71 °C (25 mmHg), $C_{11}H_{13}F_3O$, M^+: 218, calcd 60.55% C, 5.96% H, 26.15% F; found 60.31% C, 5.83% H, 26.30% F) was carried out by $AlCl_3$-catalyzed *trans-tert*-butylation of α,α,α-trifluoromethoxybenzene with 2,6-di-*tert-p*-cresol with use of Tashiro's method.[22] *m-tert*-Butyl-α,α,α-trifluoromethoxybenzene was prepared from *m*-bromo-α,α,α-trifluoromethoxybenzene according to the literature procedure.[23] Isomeric nitro-, chloro-, and bromo-α,α,α-trifluoromethoxybenzenes were known compounds prepared from the corresponding nitro-, chloro-, and bromophenols.[3] Acetyl and benzoyl-α,α,α-trifluoromethoxybenzenes were prepared from the corresponding bromo derivatives via their Grignard reagents and reaction with aryl halides: *p*-acetyl (bp 49 °C (15 mmHg), $C_9H_7F_0O_2$, M^+: 204), *m*-acetyl (bp 51 °C (13 mmHg), $C_9H_7F_3O_2$, M^+: 204), *p*-benzoyl (mp 43 °C, $C_{14}H_9F_3O_2$, M^+: 266). All compounds showed expected characteristic IR and NMR spectroscopic data.

Preparation of α,α,α-Trifluoromethoxybenzene.[2c] 4-Chlorophenol (25 g, 0.194 mol), carbon tetrachloride (55 mL), and anhydrous hydrogen fluoride (100 mL) were charged into a 500 mL stainless steel pressure reaction vessel at −78 °C. The autoclave was closed and heated to 150 °C overnight. The reaction vessel was then cooled to room temperature and excess hydrogen fluoride was removed under reduced pressure. The reaction mixture was subsequently poured into ice in a plastic beaker. The reaction mixture was extracted with 200 mL of ether which was added to the aqueous mixture and stirred for 30 min. The reaction mixture was extracted with 200 mL of ether which was added to the aqueous mixture and stirred for 30 min. The organic layer was separated in a plastic separatory funnel. The ether solution was washed with cold KOH solution (3 × 50 mL, 5% aqueous) and dried over $MgSO_4$. Distillation gave 4-chloro-α,α,α-trifluoromethoxybenzene (23.1 g, 60.7%), bp 141–143 °C (lig.[2c] bp 142–145 °C). *p*-Chloro-α,α,α-trifluoromethoxybenzene (20.0 g, 0.10 mol), a solution of sodium hydroxide (8.0 g, 0.2 mol) in ethanol (200 mL), and 10% Pd on C (1.0 g) were charged into a Parr hydrogenation bottle (500 mL). The mixture was hydrogenated at 40 psi for 5 h. The ethanol solution was then filtered into a separatory funnel containing 300 mL of water and 25 mL of Freon 113 (1,1,2-trifluorotrichloroethane). The organic layer was separated and washed with water and dried over $CaCl_2$. Distillation gave α,α,α-trifluoromethoxybenzene (12.1 g, 74.4%), bp 104–105 °C, $C_7H_5F_3O$, M^+: 162, calcd 51.9% C, 3.08% H, 35.18% F; found 52.0% C, 3.01% H, 35.62% F.

Nitration of α,α,α-Trifluoromethoxybenzene with Nitronium Tetrafluoroborate. α,α,α-Trifluoromethoxybenzene (1.62 g, 10 mmol) was dissolved in 5 mL of nitromethane and kept at 25 °C with vigorous stirring. Nitronium tetrafluoroborate (266 mg, 0.2 equiv) was added to the solution and the solution was stirred for 2 h. The reaction mixture was then quenched with ice water and extracted with ether (10 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, and analyzed by GC–MS.

Competitive nitrations were carried out similarly with 10 mmol each of benzene and the corresponding substituted benzenes shown in Figure 1.

Ferric Chloride Catalyzed Halogenation of α,α,α-Trifluoromethoxybenzene. α,α,α-Trifluoromethoxybenzene (1.62 g, 10 mmol) and anhydrous ferric chloride (325 mg, 2 mmol) were dissolved in nitromethane (5 mL). While the solution was kept at 25 °C with vigorous stirring, 2 mmol of halogen (Br_2 or Cl_2) in nitromethane was added. The reaction mixture was reacted at the indicated temperature and time. It was thereafter quenched with ice water, and the organic layer was separated, extracted with ether, washed with water, dried over $CaCl_2$, and analyzed by GC–MS.

Ferric Chloride Catalyzed Acylation of Trifluoromethoxybenzene. Trifluoromethoxybenzene (1.62 g, 10 mmol) and anhydrous ferric chloride (487 mg, 3 mmol) were dissolved in nitromethane (5 mL). Acyl halide (benzoyl chloride or acetyl chloride, 3 mmol) was added through a syringe and the mixture was stirred for 1 h at room temperature, poured into ice water, and extracted with ether. The extract was washed with water and aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and analyzed by GC–MS.

Aluminum Trichloride Catalyzed Alkylation of α,α,α-Trifluoromethoxybenzene with Alkyl Halides. α,α,α-Trifluoromethoxybenzene (1.62 g, 10 mmol) and $AlCl_3$ (270 mg) were dissolved in 5 mL of nitromethane. While the solution was kept at 25 °C with vigorous stirring, 2 mmol of alkyl halide dissolved in 1 mL of nitromethane was added. The reaction mixture was reacted at the indicated time and temperature. It was thereafter quenched with ice water and analyzed by GC–MS.

Boron Trifluoride Catalyzed Alkylation of α,α,α-Trifluoromethoxybenzene with Alkyl Fluorides. α,α,α-Trifluoromethoxybenzene (2.43 g,

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15 mmol) was cooled to −30 °C and the corresponding alkyl fluoride (3 mmol) was then added. While the solution was stirred, a slow stream of boron trifluoride was introduced for 30 s. It was then allowed to warm up to 25 °C and further reacted for 30 min. The reaction mixture was subsequently quenched with ice water and extracted with ether (10 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, and analyzed by GC–MS.

Competitive Alkylation of α,α,α-Trifluoromethoxybenzene and Benzene with Alkyl Halides. To an equimolar mixture of benzene (5 mmol) and α,α,α-trifluoromethoxybenzene (5 mmol) was added $AlCl_3$ (2 mmol) in 2 mL of nitromethane. While the solution was kept at 25 °C with vigorous stirring, alkyl halide (2 mmol) dissolved in 1 mL of nitromethane was added. The reaction mixture was reacted at 25 °C for 30 min. It was thereafter quenched with ice water, extracted with ether, dried over $MgSO_4$, and analyzed by GC–MS.

Analyses. GLC analyses were carried out on a Varian Associates Model 3300 gas–liquid chromatograph, using a 50-m glass column coated with OV 1018 oven temperature from 90 to 190 °C, He pressure 30 psi, and FID detector. Peak areas were determined by the use of a Varian 4270 integrator system.

Separation of isomeric methyl- and ethylfluorobenzenes was carried out on a 50-m carbovax fused silica column at 45 °C, 30 psi He pressure, using a FID detector.

Mass spectrometric analyses were carried out with a Hewlett-Packard Model 5985A GC-MS spectrometer and a Finnigan MAT Ion Trap Detector.

^1H NMR spectra were obtained on a 60-MHz Varian EM-360 spectrometer. ^{13}C NMR spectra were obtained on Varian Model FT-80 and XL-200 NMR spectrometers equipped with variable temperature broad-band and $^1H/^{19}F$ probes.

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Determination of Thermodynamic Parameters in Lariat Ether Complexes Using Ion-Selective Electrodes

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Abstract: Ion-selective electrodes were used to determine Na^+ and K^+ equilibrium stability (binding) constants (expressed within as log K_S) for a series of carbon-pivot lariat ethers in anhydrous methanol over the temperature range 15–41 °C. A plot of ln K_S vs. $1/T$ gives a slope of $-\Delta H/R$ and the intercept is $\Delta S/R$. This method for determining ΔH and ΔS for complexation reactions requires less than 0.5 g of sample, can be conducted in 8 h, utilizes inexpensive equipment, and affords acceptable precision for the compounds examined. The binding phenomenon has been assessed from the thermodynamic perspective by using the following 2-substituted derivatives of 15-crown-5: **1**, $CH_2OC_6H_4$-2-OCH_3; **2**, $CH_2OC_6H_4$-4-OCH_3; **3**, $CH_2OCH_2CH{=}CH_2$; **4**, CH_2OH; **5**, CH_2O-*t*-Bu; **6**, $CH_2OCH_2CHOHCH_3$; **7**, $CH_2OCH_2C_6H_4$-2-OCH_3; **8**, $CH_2OCH_2C_6H_5$. The differences in enthalpic and entropic contributions reveal surprising differences in the cooperativity between macroring and sidearm when cations are bound.

The importance of thermodynamic measurements in understanding cation complexation by macrocycles is obvious from the huge number of reports which have addressed this subject during the past two decades. These data were catalogued in a massive review published in 1985 by Izatt, Christensen, and their coworkers.[1] We have recognized in our own work with lariat ethers that a better understanding of the complexation process would result from thermodynamic data combined with the equilibrium cation binding data (log K_S values) which we have previously obtained.[2] Unfortunately, thermodynamic parameters determined by calorimetric measurements require special, sophisticated, and often expensive equipment, a considerable amount of sample, complicated computer fitting programs, and a good deal of effort even by the most skilled workers. We present here a method for obtaining both ΔH and $T\Delta S$ for the complexation process which (1) requires less than half a gram of sample, (2) can be completed in a single day, (3) utilizes inexpensive equipment, and (4) affords acceptable precision for a variety of macrocyclic compounds when binding either Na^+ or K^+. We present here the results of a systematic study of carefully selected carbon-pivot lariat ethers based on the 2-substituted 15-crown-5 framework which demonstrate the value of this approach.

Table I. Thermodynamic Parameters for the Reactions of Na^+ and K^+ with 15-Crown-5 and 18-Crown-6 in Methanol

study	ΔH	$T\Delta S$	log K_S
15-Crown-5 with Sodium Cation			
this study	−4.19 ± 0.05	0.30 ± 0.03	3.29
Michaux and Reisse[a]	−5.50 ± 0.20	−1.23 ± 0.24	3.14
Izatt et al.[b]	−4.99 ± 0.03	−0.24	3.48
Izatt et al.[c]	−5.40 ± 0.05	−0.90	3.30
Okahara[d]			3.27
18-Crown-6 with Sodium Cation			
this study	−7.40 ± 0.11	−1.50 ± 0.09	4.34
Michaux and Reisse[a]	−7.50 ± 0.07	−1.55 ± 0.11	4.37
Izatt et al.[b]	−8.40 ± 0.30	−2.4	4.36
18-Crown-6 with Potassium Cation			
this study	−11.3 ± 0.02	−3.03 ± 0.04	6.09
Michaux and Reisse[a]	−12.70 ± 0.10	−4.30 ± 0.15	6.16
Izatt et al.[b]	−13.41 ± 0.06	−5.14	6.06
Frensdorff[e]			6.08

[a] See ref 5. [b] See ref 4. [c] See ref 6. [d] See ref 7. [e] See ref 3.

Results and Discussion

Our method is based on the well-known temperature dependence of the equilibrium constant. Within a relatively narrow temperature range (15–41 °C over which ΔH is assumed to be constant), log K_S values for complexation between either Na^+ or K^+

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