NMR Spectroscopic Studies. All ^1H and ^{13}C NMR spectra were obtained on Varian A-56-60, HA-100, and XL-100 instruments equipped with a variable temperature unit. All chemical shifts are reported from external Me_4Si.

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Oxyfunctionalization of Hydrocarbons. 8.[1] Electrophilic Hydroxylation of Benzene, Alkylbenzenes, and Halobenzenes with Hydrogen Peroxide in Superacids

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The hydroxylation of benzene, alkylbenzenes, and halobenzenes with hydrogen peroxide was carried out in high yields in superacidic media at low temperature. Phenols formed are protonated by the superacid and thus are deactivated against further electrophilic attack or secondary oxidation.

Introduction

Although there have been reports of the direct, one-step hydroxylation of aromatic compounds with peracids in the presence of acid catalysts, monohydroxylated products, i.e., phenols, have generally been obtained in only low yield.[2] While moderate to good yields of phenols, based on the amount of hydrogen peroxide used, were reported for the $AlCl_3$-catalyzed reaction of simple aromatics with hydrogen peroxide, a tenfold excess of the aromatics was used over hydrogen peroxide.[2k] The conversion of the aromatics thus was low, probably due to the fact that introduction of an OH group into the aromatic ring markedly increases its reactivity and thus tends to promote further reactions.[3]

It is well recognized that phenols are completely protonated in superacidic solutions.[4] This raised the possibility that protonation of phenols, once formed in these media, might cause their deactivation to further electrophilic attack. We wish to report the results of the electrophilic hydroxylation of aromatics with hydrogen peroxide in superacidic media, which allow the clean, high-yield preparation of monohydroxylated products.

Results and Discussion

Solutions of aromatics were reacted with 98% hydrogen peroxide in FSO_3H–SO_2ClF and FSO_3H–SbF_5 (1:1)–SO_2ClF solution at −78 °C, respectively. Formed protonated phenols were analyzed by ^1H NMR spectroscopy.[4] Results are summarized in Table I.

Data indicate that protonation of the starting aromatics, which are benzene, ethylbenzene, toluene, *p*-xylene, in increasing order, themselves decrease the yields of hydroxylation in magic acid (FSO_3H–SbF_5 (1:1)–SO_2ClF) solution. In the weaker acid system, FSO_3H–SO_2ClF, the protonation of aromatic hydrocarbons is reversible; thus, no such deactivation is apparent. No hydroxylation of phenol and anisole was observed with hydrogen peroxide in superacids, as was also the case with nitrobenzene and benzonitrile. The formally strongly electron-donating –OH and OCH_3 groups protonate in the reaction medium, preventing further reaction. Yields (based on the aromatics used) are high, because the phenols produced are protonated and thus deactivated toward further electrophilic attack.

A more comprehensive study of the hydroxylation of halo- and alkylbenzenes is summarized in Table II, showing isomer distributions and yields obtained. Data, in this case, were obtained by quenching the solutions and analyzing acidic products by gas–liquid chromatography. All aromatics, including polymethylbenzenes, show predominant ortho–para orientation. Hydroxylation of *m*-xylene, for example, did not yield 3,5-dimethylphenol. It should be noticed, however, that in several cases the position of the methyl group of phenols produced differs from that of the starting hydrocarbons. This is the case for 2,6-dimethylphenol obtained from *o*-xylene, 2,4-dimethylphenol from *p*-xylene, 2,3,6-trimethylphenol from 1,2,3-trimethylbenzene, and 2,4,6-trimethylphenol from 1,2,4-trimethylbenzene. The amount of these products cannot

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Table I. Hydroxylation of Aromatics with Hydrogen Peroxide in Superacids at −78 °C

Acid	Substituted arene	% yield[a] of phenols H	CH_3	C_2H_5	p-$(CH_3)_2$	$(CH_2)_3CO_2H$	F	Cl	Br
FSO_3H–SO_2ClF		60	>90	>90	80	>90			Polymer
FSO_3H–SbF_5 (1:1)–SO_2ClF		80	30	60	No		>90	>90	>90

[a] Based on direct ^1H NMR analysis of the reaction mixtures.

Table II. Yields and Isomer Distributions of the Hydroxylation of Aromatics[a]

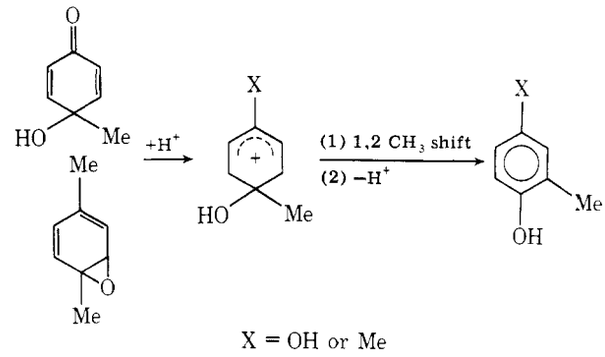
Starting aromatic	Registry no.	% isomer distribution[b]			% yield[c]
Benzene	71-43-2				67
Fluorobenzene	462-06-6	24 (2)	3 (3)	73 (4)	82
Chlorobenzene	108-90-7	28 (2)	7 (3)	65 (4)	53
Toluene	108-88-3	71 (2)	6 (3)	23 (4)	67
Ethylbenzene	100-41-4	68 (2)	6 (3)	26 (4)	70
sec-Butylbenzene	135-98-8	49 (2)	11 (3)	40 (4)	55
Isobutylbenzene	538-68-2	65 (2)	7 (3)	28 (4)	83
n-Amylbenzene	538-68-1	64 (2)	7 (3)	29 (4)	67
o-Xylene	95-47-6	12 (2,6)	59 (2,3)	29 (3,4)	63
m-Xylene	108-38-3	16 (2,6)	2 (2,5)	82 (2,4) 1 (2,3)	73
p-Xylene	106-42-3	64 (2,5)	36 (2,4)		65
1,2,3-Trimethylbenzene	526-73-8	3 (2,3,6)	91 (2,3,4)	6 (3,4,5)	43
1,2,4-Trimethylbenzene	95-63-6	9 (2,4,6)	30 (2,3,6)	61 (2,3,5 + 3,4,6)	57
1,3,5-Trimethylbenzene	108-67-8	100 (2,4,6)			57

[a] In FSO_3H–SO_2ClF solution at dry-ice temperature. [b] Based on chromatographic analysis of quenched phenolic products. Parentheses show position of substituent(s). [c] Based on aromatics used.

Table III. Hydroxylation of Ethylbenzene in Various Acidic Media

Acid system	Reaction temp, °C	% yield[a]	% isomer distribution ortho	meta	para
FSO_3H–SO_2ClF	−78	70	68	7	26
HF–BF_3	−78	79	69	9	21
CF_3SO_3H–SO_2ClF	~−50	80	65	9	26
HF	~20	41	55	13	32
CF_3CO_2H	~20	17			
CH_3CO_2H	~20	1			

[a] See Table II, footnote *c*.



X = OH or Me

be accounted for by possible impurities in the starting hydrocarbons. Further, in a control experiment, starting hydrocarbons at the low reaction temperature did not tend to isomerize. *p*-Xylene did not show isomerization under the reaction condition employed. Thus, it is reasonable to suggest that in the hydroxyarenium ion intermediates of the reactions 1,2-methyl shifts can take place prior to deprotonation.

Kaubisch et al.[5] have reported that *p*-xylene 1,2-oxide is converted to 2,4-dimethylphenol in 87% yield under neutral conditions and *o*-xylene 1,6-oxide produced 2,6-dimethylphenol in 37% yield in the presence of CF_3CO_2H. It also has been reported that 4-hydroxy-4-methylcyclohexadienone yielded 2-methylhydroquinone under acid conditions.[6] These examples tie in well with the suggested mechanism for our present observations.

To gain further information on the hydroxylation reaction of aromatics, ethylbenzene was hydroxylated in various acidic media (Table III).

In HF–BF_3 solution, the yield of ethylphenols was similarly high as in FSO_3H–SO_2ClF and CF_3SO_3H–SO_2ClF solutions and the isomer distributions in these solvents, and even in the weaker HF system, were almost identical. This indicates that the active hydroxylating species is not a persulfuric acid but protonated hydrogen peroxide.

In preparative experiments hydroxyaromatic products were separated from quenched reaction mixtures by distillation. Results are shown in Table IV. Phenolic products were obtained in good yields except in the case of the benzene–FSO_3H system which solidified at the reaction temperature, did not dissolve, was difficult to mix with hydrogen peroxide, and

Table IV. Preparative Hydroxylation of Aromatics[a]

Starting aromatics (g, mol)	H_2O_2, mol	Acid (4–2 mL of SO_2ClF)	Phenolic products g (mol)	Isolated yield, %
Benzene (1, 0.013)	0.015	FSO_3H	0.19 (0.0020)	16
Benzene (1, 0.013)	0.015	FSO_3H–SbF_5 (1:1)	0.66 (0.0070)	54
Isobutylbenzene (1.11, 0.0083)	0.010	FSO_3H	0.63 (0.0042)	50
1,3,5-Trimethylbenzene (0.99, 0.0082)	0.010	FSO_3H	0.54 (0.0040)	48

[a] All experiments were carried out at −78 °C.

tended to heat up suddenly by heat of reaction. On the other hand, in FSO_3H–SbF_5 (1:1)–SO_2ClF solution benzene dissolved readily, was easily mixed with hydrogen peroxide, and gave phenol in 54% isolated yield.

Experimental Section

Hydroxylation of Aromatic Compounds. To a vigorously stirred solution of the corresponding aromatics in the appropriate superacidic solvent (FSO_3H–SO_2ClF, FSO_3H–SbF_5–SO_2ClF, CF_3SO_3H–SO_2ClF, HF–BF_3, or HF), a solution of 98% hydrogen peroxide (FMC Corp.) in the same solvent was added dropwise at the specified temperature (generally −78 °C), kept constant by external cooling. Some of the aromatics did not completely dissolve into acidic solvents and these reactions were carried out in the well-stirred heterogeneous systems. As the reactions proceeded, however, the media became homogeneous because formed product phenols are soluble in the acidic solvents. An aliquot of the resulting solution was analyzed by ^1H NMR at the same low temperature. After 30-min reaction time, the solution was quenched by dropwise addition to ice-cold aqueous sodium chloride solution. The mixture was extracted with ether. The ether extracts washed with 10% sodium bicarbonate solution to remove acid and phenols were then extracted by 10% sodium hydroxide or Claisen's alkali solution. The dried ether layer was rotary evaporated to remove the solvent, and residual products were analyzed by IR, GLC, and NMR, usually showing only unreacted aromatics. After acidification of the phenol extracts and ether extraction, the solvent was distilled and the products were analyzed either by GLC, after methylation by dimethyl sulfate in aqueous alkali solution, or after trimethyl silylation in the case of cresols [using a Perkin-Elmer Model 900 gas chromatograph equipped with 0.010 in. i.d. × 150 ft. stainless-steel capillary column, coated with MBMA (*m*-bis(*m*-phenoxy)benzene + apiezon L) and operated at a column temperature of 140 or 160 °C with 20 psi of He pressure]. Alternatively, products were isolated by vacuum distillation. The generally used quantities in analytical runs were 0.0027 mol of aromatics, 0.0030 mol of hydrogen peroxide, 2 mL of acid, and 1 mL of solvent. In preparative runs, 0.013 mol of aromatics was reacted with 0.015 mol of hydrogen peroxide. Acidic solvents used were FSO_3H–SO_2ClF or SO_2 at −78 °C, FSO_3H–SbF_5 (1:1)–SO_2ClF at −78 °C, HF–BF_3 at −78 °C, CF_3SO_3H–SO_2ClF at ca. −50 °C (its melting point), HF at −78 °C, CF_3CO_2H and CH_3CO_2H at room temperature.

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Stereochemistry of the Reductive Debromination of (*R*)-*meso*- and (*S*)-*meso*-3-Methyl-2,4-dibromopentane

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The reductive 1,3-dehalogenations of the stereoisomeric 3-methyl-2,4-dibromopentanes with zinc, chromous sulfate, or sodium have been shown to proceed by an inversion process at one carbon atom and by a nonstereospecific process at the other. (*R*)-*meso*-3-Methyl-2,4-dibromopentane gave only the trans isomer of 1,2,3-trimethylcyclopropane, while the (*S*)-*meso*-dibromide gave mixtures of the *cis*- and *trans*-cyclopropanes.

The reductive 1,3-dehalogenation synthesis of cyclopropanes was first reported by Gustavson[1,2] and Freund.[3] The method has been extensively used preparatively,[4] but mechanistic studies have been few. The present study provides a partial remedy for that deficiency by an investigation of the stereochemistry of the process with three different reducing agents.

Some stereochemical information was in the literature prior to the publication of the present work.[5-9] Most notable is the report of Fry and Britton[5] on reductions of stereoisomeric 2,4-dibromopentanes. They found that the meso and *dl* forms gave roughly the same mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes upon electrochemical reduction in Me_2SO and that the 2*S*,4*S* isomer of the dibromide gave a mixture of the *cis*-cyclopropane and the (1*R*,2*R*)-cyclopropane with high optical purity. The results require a stepwise mechanism with loss of stereochemistry at one carbon and essentially complete inversion at the other. A similar result was obtained with sodium naphthalenide as reducing agent, but larger experimental errors made the conclusions less definitive.

A contrasting result was obtained by Trost[7] on the reactions of *meso*- and *dl*-2,4-dibromopentane with *n*-butyllithium in THF at low temperatures. The reactions were stereoselective, with the meso compound forming primarily *cis*-1,2-dimethylcyclopropane and the *dl* compound forming primarily the *trans*-cyclopropane. Since the experiment was not done with an optically active 2,4-dibromopentane, it cannot be determined if one of the carbons undergoes stereospecific inversion or retention in this experiment, nor can it be determined whether the predominant overall stereochemistry is double inversion or double retention. Several mechanistic possibilities must therefore be considered.

An interesting stereoselectivity has been observed in the reductive debromination of *meso*- and *dl*-bis(α-bromobenzyl)

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