

The Mechanism and Synthetic Utility of the Oxidative Cleavage of Ethers by Aqueous Bromine

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Abstract: Aqueous Br_2 oxidizes a wide variety of aliphatic ethers at 25° . Primary alkyl groups are converted to carboxylic acids and secondary alkyl groups to ketones. Bromination products appear when the reaction is conducted under strongly acidic conditions. Their formation can be completely suppressed by conducting the reaction in acetate buffers at pH 5. The reaction is attractive for degradative purposes because of the quantitative yields and the mild conditions. The rates are first order in ether and Br_2 and can be depressed by addition of Br^- , which converts Br_2 to Br_3^- , or by raising the pH above 5, which converts Br_2 to HOBr . Competition experiments indicate that the reaction proceeds by a mechanism involving simultaneous loss of H^+ from an α -carbon and an electron pair from the ether oxygen. The mechanism is isoelectronic with the Westheimer mechanism for the oxidation of alcohols by chromic acid. The reaction proceeds in the dark and the selectivity differs from either the light-catalyzed $\text{H}\cdot$ abstractions by $\text{Br}\cdot$ or the H^- abstractions by $(\text{C}_6\text{H}_5)_3\text{C}^+$.

Aqueous bromine (Br_2) is an effective oxidizing agent for formates, oxalates, alcohols, aldehydes, and carbohydrates.¹ It does not seem to have been recognized that it is also an effective oxidizing agent for simple aliphatic ethers and generally for all ethers containing an α -hydrogen. Illustrative is the example of diethyl ether, which is quantitatively oxidized to acetic acid at 25° . This oxidation of ethers by Br_2 has synthetic and degradative utility because of (1) the mild conditions, pH 1–6 at 25° ; (2) the yields, which are generally over 80%; (3) the satisfactory rates, of the order of 10^{-3} l. mole⁻¹ sec⁻¹ at 25° ; and (4) the availability of Br_2 . For these reasons, the scope and mechanism of the reaction have been examined.

The results can be divided into six areas: (1) determination of products and yields for a selection of ethers; (2) determination of the rate law and pH–rate profile for diisopropyl ether; (3) comparison of the products from benzyl isopropyl ether with those from an equimolar mixture of dibenzyl and diisopropyl ethers; (4) demonstration that the products differ from those of free-radical attack by Br atoms or from those of hydride abstraction by $(\text{C}_6\text{H}_5)_3\text{C}^+$; (5) a σ - ρ study using a series of benzyl methyl ethers; and (6) a study of the products formed on oxidation of ethers by $(\text{C}_6\text{H}_5)_3\text{C}^+$.

Several studies have been conducted on the light-catalyzed halogenation of ethers. Tetrahydrofuran and Cl_2 form 2,3-dichlorotetrahydrofuran.² Several ethers form α -chloro ethers.^{3–5} Benzyl methyl ethers were converted to benzaldehydes.⁶ N-Bromosuccinimide converted a variety of benzyl ethers to the substituted benzaldehydes.⁷ All of these studies appear to proceed *via* free-radical halogenations and differ from the ionic dark reaction which is the subject of the present paper.

Experimental Section

Products and Yields in the Reaction of Br_2 with Ethers. These are summarized in Tables I and II. Several representative examples will illustrate the methods and conditions.

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- (3) L. Horner, B. Anders, and O. Basedow, *Ann.*, **635**, 46 (1960).
- (4) L. Summers, *Chem. Rev.*, **55**, 301 (1955).
- (5) H. Bohme and A. Dorries, *Ber.*, **89**, 723 (1956).
- (6) D. G. Markees, *J. Org. Chem.*, **23**, 1490 (1958).
- (7) R. L. Huang and K. H. Lee, *J. Chem. Soc.*, 5947, 5963 (1964).

Peroxide-free diethyl ether (1.87 g, 0.0253 mole) was added to 15 ml of water in a 50-ml flask which was wrapped in aluminum foil to exclude light. The contents were cooled to 0° and 17 g (0.106 mole) of Br_2 was added. The contents were continuously stirred at 25° and aliquots periodically removed and examined by proton magnetic resonance (pmr) spectroscopy. The bands due to the ether (triplet, $J = 13$ cps, at δ 1.19, and quartet, $J = 13$ cps, at δ 3.52) continuously disappeared and the bands of acetic acid (δ 2.1) and bromoacetic acid (δ 4.0) appeared. After 3 days only bands of acetic and bromoacetic acids were present, showing the sum of their yields was 100%. At no time during the course of the reaction did any other pmr bands appear, so that no intermediate such as acetaldehyde accumulates. The ratio of yields was computed from the band areas.

Peroxide-free diisopropyl ether was added to water followed by Br_2 in a manner and in molar proportions similar to those used with diethyl ether. After the reaction was complete, as evidenced by the pmr spectra (or the disappearance of the Br_2 color when the ether was in excess), an aliquot of the reaction mixture was poured into excess 2,4-dinitrophenylhydrazine dissolved in 2 M aqueous HCl. The precipitated dinitrophenylhydrazones were filtered, dried, and weighed. The relative amounts of acetone and bromoacetone were determined from the pmr spectrum of a solution of the dinitrophenylhydrazones in dichloromethane. The pmr band positions were δ 4.27 (BrCH_2) and 2.25 (CH_3) for the bromoacetone derivative and 2.10 and 2.18 for the acetone dinitrophenylhydrazone.

Purified tetrahydrofuran (1.0 g, 0.014 mole) was treated with 12.0 g (0.0705 mole) of Br_2 in 15 ml of water. The reaction mixture was stirred at 0° and the contents were monitored by pmr spectroscopy. At the end of 2 days the bands of tetrahydrofuran (complex multiplets centering at δ 1.91 and 3.78) had completely disappeared and only the bands of γ -butyrolactone (complex multiplet centering at δ 2.48, and triplet, $J = 6.5$ cps, at δ 4.47) were present.

Definitive identification was accomplished by adding authentic γ -butyrolactone directly to the reaction mixture and observing that the bands of the product were simply augmented.

Rates of Oxidation of Diisopropyl Ether by Br_2 . Rates of this reaction were studied to establish the rate law and to determine the variation of rate with pH, with and without added Br^- . The reaction flasks were wrapped in aluminum foil to exclude light since exploratory experiments had shown the presence of an independent light-catalyzed reaction.

Diisopropyl ether readily forms peroxides, so that the ether was passed through a basic alumina column (1 g of alumina/g of ether) immediately before use. Ether, purified in this manner, did not give a peroxide test with aqueous HI and starch.

The runs were conducted by combining 45 ml of approximately 10^{-3} M ether with 5 ml of approximately 0.1% aqueous Br_2 . The solutions were thermostated at $25.0 \pm 0.1^\circ$ before mixing, and no temperature change occurred during mixing. The Br_2 was determined iodometrically by quenching aliquots in acidified 4% aqueous KI and titrating with 0.002 N aqueous $\text{Na}_2\text{S}_2\text{O}_3$ to a starch end point. The $\text{Na}_2\text{S}_2\text{O}_3$ solution was stabilized with CHCl_3 and standardized periodically against standard aqueous KIO_3 . The initial

Table I. Products and Yields in the Oxidative Cleavage of Ethers by Aqueous Br₂ at 25° and pH 5 (Acetate Buffer)

Ether	Ratio, ether: Br ₂	Reactant in excess	Product ^a	% yield ^b
Diethyl	1:1	Ether	Acetic acid	100
	1:4	Equiv	Acetic acid	100
Dipropyl	1:1	Ether	Propionic acid	100
	1:4	Equiv	Propionic acid α-Bromopropionic acid	95 5
Diisopropyl	1:1	Ether	Acetone	90
	1:2	Equiv	Acetone	80
	1:4	Br ₂	Acetone Bromoacetone	<i>c,d</i> <i>c,d</i>
Dibenzyl	1:1	Ether	Benzaldehyde	80
	1:6	Br ₂	Benzoic acid 4-Bromobenzoic acid	55 ^d 45 ^d
Tetrahydrofuran	5:1	Ether	4-Hydroxybutyraldehyde	20
	1:4	Br ₂	γ-Butyrolactone	100
Isopropyl methyl	4:1	Ether	Acetone	70
	1:1	Ether	Acetone	40
Isopropyl ethyl	3:1	Ether	Acetone	70
	1:3	Equiv	Acetone	60
Cyclohexyl methyl	1:1	Ether	Cyclohexanone	50
Benzyl methyl	4:1	Ether	Benzaldehyde	80
	1:1	Ether	Benzaldehyde	30
Benzyl isopropyl	5:1	Ether	Benzaldehyde	95
	1:2	Equiv	Benzaldehyde Acetone	55 45

^a In cases of mixed ethers where one alkyl group was primary and the other was secondary only the ketone product arising from the secondary alkyl group was determined. The difference in per cent yield between 100 and that listed is probably a good estimate of the yield of carboxylic acid arising from the primary alkyl group, either by direct attack or attack on the alcohol produced in cleavage. ^b The per cent yield was based on the reactant in deficiency. The reactions were generally run for about 1 day, and at that time reaction was complete. ^c The ultimate products were monobromo- and polybromoacetones. However, after 30 min at 25° when 65% of the ether had reacted, the ratio acetone:bromoacetone was 92:8, showing that the oxidation of ether is faster than bromination of the product, acetone. ^d These runs were conducted by Dr. Richard Fruit. The yields of benzoic acid and bromobenzoic acid were determined by filtering these products and direct weighing. The two acids could be separated by extracting the benzoic acid with hot water. A correction was made for the solubility of benzoic acid in water.

Table II. Products and Yields in the Oxidative Cleavage of Ethers by Br₂ in 60% Aqueous Acetic Acid at 25 or 55°^a

Ether	Ratio, ether:Br ₂	Product ^b	% yield ^c
Dibenzyl	5:1	Benzaldehyde	83
	1:1	Benzaldehyde	98
Benzyl methyl	3:1	Benzaldehyde	83
	1:1	Benzaldehyde	63
4-Methylbenzyl methyl	5:1	4-Methylbenzaldehyde	90
4-Chlorobenzyl methyl	1:1	4-Methylbenzaldehyde	74
4-Chlorobenzyl methyl	5:1	4-Chlorobenzaldehyde	66
	1:1 ^a	4-Chlorobenzaldehyde	53
3-Chlorobenzyl methyl	5:1 ^a	3-Chlorobenzaldehyde	71
	1:1	3-Chlorobenzaldehyde	50
4-Nitrobenzyl methyl	1:10	4-Nitrobenzoic acid	68

^a All runs were conducted at 25° except for the two noted. Reactions were generally complete within a day. ^b The substituted benzaldehydes were isolated as their 2,4-dinitrophenylhydrazones. The melting points agreed with literature values. ^c In all runs but the last, the ether was in excess. In such runs, the difference in yield between 100% and that listed is probably a measure of the consumption of Br₂ by oxidation of the methyl group, either directly or after its cleavage to methanol.

and final pH were measured on a Beckman Zeromatic pH meter and did not vary by 0.1 pH unit during the course of the reaction. Initial Br₂ concentrations were obtained by extrapolating the titration data back to zero time.

Second-order rate constants were obtained by plotting log[ether]·[Br₂]⁻¹ against time and multiplying the slope of the best linear fit by 2.30([ether]₀ - [Br₂]₀)⁻¹. Only data up to 15% completion were utilized in order to minimize the effect of the subsequent oxidation of 2-propanol by Br₂.

The rate law was shown to be

$$-d[\text{ether}]/dt = k_2[\text{ether}][\text{Br}_2]$$

as follows. Values of *k*₂ were calculated from runs at 25.0° and pH 4.6 (0.1 M acetate buffer) for ether:Br₂ ratios of 1:3, 1:2, 1:1, 2:1, and 3:1. The values of *k*₂ were invariant, being 3.85 × 10⁻³ l. mole⁻¹ sec⁻¹ ± 0.05. A small salt effect was found. When the buffer concentration was raised from 0.10 to 0.40 M, *k*₂ increased to 4.20 × 10⁻³.

Values of log *k*₂ as a function of pH and [Br₂] appear in Table III. Values of *k*₂ are an average of two to five runs which agreed to within 3%. The actual [Br₂]₀ varied from 1.3 × 10⁻³ to 3.1 × 10⁻³ in different runs, but the correction to 10⁻³ M was less than experimental precision.

Table III. Rate Constants for the Oxidation of Diisopropyl Ether by Br₂ at 25.0°

pH ^a	10 ³ <i>k</i> ₂ , l. mole ⁻¹ sec ⁻¹	pH ^a	10 ³ <i>k</i> ₂ , l. mole ⁻¹ sec ⁻¹
1.00	4.61	3.50 ^b	2.87
2.89	4.21	4.60 ^b	2.80
4.60	3.85	5.20 ^b	2.76
4.89	2.81	6.35 ^b	1.85
5.49	2.00	6.65 ^b	1.70

^a pH 1.00 was achieved by addition of H₂SO₄ to water. The other pH values were achieved by a 0.10 M acetate buffer. ^b These runs contained 0.10 M added NaBr.

Competition Experiments. The runs in Table IV were designed to show (1) the effect of light on product distribution and (2) the difference between the internal competition of R₁ and R₂ for oxidation by Br₂ in R₁OR₂ and the external competition in equimolar R₁OR₁ plus R₂OR₂. The products were isolated as the 2,4-dinitrophenylhydrazones (DNP). The DNP of benzaldehyde was very insoluble in refluxing CH₂Cl₂ and was thus separated from the DNP's of acetone and bromoacetone. The relative amounts of the latter two were determined from the pmr spectra.

Table IV. Intramolecular and Intermolecular Competition of Alkyl Groups in Ethers for Br₂ in 60% Aqueous Acetic Acid at 25°

Ether(s) ^a	Reaction conditions	Products	% yields
Ethyl isopropyl	Dark	Acetone	27
		Bromoacetone	54
Diethyl and diisopropyl	Dark	Acetone	40
		Bromoacetone	50
Benzyl isopropyl	Dark	Acetone	1
		Bromoacetone	26
		Benzaldehyde	47
Benzyl isopropyl	Light ^b	Benzaldehyde	90
	Dark	Acetone	53
Dibenzyl and diisopropyl	Dark	Bromoacetone	27
		Benzaldehyde	6
Dibenzyl and diisopropyl	Light ^b	Benzaldehyde	90

^a The ratios of reactants were 1:1 for R₁OR₂ and Br₂ and 1:1:1 for R₁OR₁, R₂OR₂, and Br₂. ^b Irradiation was provided by a 240-w sunlamp. This caused the Br₂ to disappear within 1 hr at 25°, which was much faster than the dark reaction.

σ - ρ Study. The kinetics were studied for the oxidation of a series of substituted benzyl methyl ethers by Br_2 at 25.0° in 60% aqueous acetic acid. The reactions were conducted under pseudo-first-order conditions with the ether concentration about 10^{-2} M and the Br_2 concentration about 10^{-3} M . The ether concentration was at least 15-fold M excess in each run. The pseudo-first-order rate constants were divided by the molarity of ether to obtain the second-order rate constants, k_2 . The rate constants are presented in Table V.

Table V. Rate Constants for the Oxidation of Benzyl Methyl Ethers by Br_2 in 60% Aqueous Acetic Acid at 25°

Benzyl substituent	$k_2 \times 10^4$, l. mole ⁻¹ sec ⁻¹	σ	Deviation in log k_2 from a line of slope -1.75
4-Methyl	6.17	-0.170	+0.22
Unsubstituted	1.84	0.00	+0.03
4-Chloro	0.640	+0.227	-0.05
3-Chloro	0.418	+0.373	+0.03
4-Nitro	0.340	+0.778	+0.65

It was not possible to include the 4-methoxybenzyl and 3-methylbenzyl methyl ethers because of bromination of the aryl ring.

Oxidation of Ethers with $(\text{C}_6\text{H}_5)_3\text{C}^+\text{BF}_4^-$. It has long been known that triarylcation ions are reduced to triarylmethanes by aliphatic ethers.⁸ The data in Table VI summarize some results. The reactions were conducted by dissolving 1.0 g of $(\text{C}_6\text{H}_5)_3\text{C}^+\text{BF}_4^-$ in 30 ml of CH_3CN and adding the ether. After the reaction time listed in Table VI, 30 ml of water was added. The triphenylmethane was removed by filtration and recrystallized to constant melting point from 10% diethyl ether in alkanes. The filtrate was treated with excess 2,4-dinitrophenylhydrazine in 2 M aqueous HCl. The dinitrophenylhydrazones were crystallized to constant melting point from ethanol or xylenes.

Table VI. Products from $(\text{C}_6\text{H}_5)_3\text{C}^+\text{BF}_4^-$ plus Ethers and Esters

Reactant	Molar ratio, reactant: fluoro- borate	% yields		Reaction time, days
		$(\text{C}_6\text{H}_5)_3\text{C}^+$ CH	DNP of	
Diethyl ether	100	90	40 acetaldehyde	20
	1	95	0	12
Diisopropyl ether	6	70	50 acetone	1
	1	84	14 acetone	12
Benzyl isopropyl ether	2	80	50 benzaldehyde ^a	12
	1	95	30 benzaldehyde ^a	12
Dibenzyl ether	6	90	24 benzaldehyde	12
	1	80	12 benzaldehyde	12
Dibenzyl and di- isopropyl ethers ^b	1:1	80	20 benzaldehyde	12
Tetrahydrofuran	1	81	0	3
Anisole	1	0 ^c	0	1
4-Bromoanisole	1	0 ^d	0	5
Ethyl acetate	10	83	0	23
Benzyl acetate	1	0 ^e	25 benzaldehyde	12

^a It is emphasized that no acetone DNP was present. ^b Dibenzyl ether:diisopropyl ether:fluoroborate was 1:1:1. ^c The product was 95% 4-methoxytetraphenylmethane. ^d The pmr spectrum indicated no decrease or change in the CH_3O band. ^e An unidentified solid, mp 213-214 $^\circ$, was obtained by recrystallization of this fraction from CCl_4 .

(8) P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Soc.*, **78**, 144 (1956).

(9) H. J. Dauben, L. R. Honnen, and K. H. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).

Preparation of Ethers. Many of the ethers were commercially available and were purified by distillation and/or chromatography on alumina. For the ethers synthesized, the following listing gives the method of preparation, the yield, the pmr spectrum in some cases, and the literature reference. No attempt was made to optimize yields.

Methyl 2-propyl ether was prepared in 45% yield from CH_3Br and $\text{NaOCH}(\text{CH}_3)_2$.¹⁰ Ethyl 2-propyl ether was prepared in 41% yield from $\text{CH}_3\text{CH}_2\text{Br}$ and $\text{NaOCH}(\text{CH}_3)_2$.¹⁰ The pmr spectrum consisted of a multiplet centered at δ 3.50 (CH), a triplet ($J = 7$ cps) at 3.35 (CH_2), a triplet ($J = 7$ cps) at 1.12 (CH_3 of ethyl), and a doublet ($J = 6$ cps) at 1.10 (CH_3 of 2-propyl).

Benzyl methyl ether was prepared in 57% yield from $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ and NaOCH_3 .¹¹ The pmr spectrum consisted of a multiplet at δ 7.23 (aryl H) and singlets at 4.30 (CH_2) and 3.20 (CH_3).

Benzyl 2-propyl ether was prepared in 53% yield from $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ and $\text{NaOCH}(\text{CH}_3)_2$.¹¹ The pmr spectrum consisted of a multiplet centered at δ 7.28 (aryl H), a singlet at 4.39 (CH_2), a heptet ($J = 6$ cps) at 3.53, and a doublet ($J = 6$ cps) at 1.10 (CH_3).

3-Chlorobenzyl methyl ether was prepared in 72% yield from 3- $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$ and NaOCH_3 .⁷ The pmr spectrum consisted of two bands at δ 7.43 and 7.17 (aryl H) and singlets at 4.33 (CH_2) and 3.33 (CH_3).

4-Chlorobenzyl methyl ether was prepared in 57% yield from 4- $\text{ClC}_6\text{H}_4\text{Cl}$ and NaOCH_3 .¹² The pmr spectrum consisted of two bands at δ 7.18 and 7.16 (aryl H) and singlets at 4.25 (CH_2) and 3.25 (CH_3).

3-Methylbenzyl methyl ether was prepared in 72% yield from 3- $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$ and NaOCH_3 .¹² The pmr spectrum consisted of a multiplet centered at δ 7.12 (aryl H) and singlets at 4.32 (CH_2), 3.23 (OCH_3), and 2.21 (aryl CH_3).

4-Methylbenzyl methyl ether was prepared in 72% yield from 4- $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$ and NaOCH_3 .⁶ The pmr spectrum consisted of a multiplet centered at δ 7.09 (aryl H) and singlets at 4.26 (CH_2), 3.18 (OCH_3), and 2.20 (aryl CH_3).

4-Methoxybenzyl methyl ether was prepared in 56% yield from 4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{Cl}$ and NaOCH_3 .⁸ The pmr spectrum consisted of doublets ($J = 9$ cps) at δ 7.22 (o -H) and 6.82 (m -H's) and singlets at 4.28 (CH_2), 3.58 (aryl OCH_3), and 3.23 (OCH_3).

4-Nitrobenzyl methyl ether has been prepared but the results have not yet been published.¹³ Our product agreed in boiling point (120-122 $^\circ$ (2 mm)), and the pmr spectrum identified the structure and demonstrated that the purity was >95%. The pmr spectrum consisted of doublets ($J = 8.5$ cps) at δ 8.10 (m -H) and 7.43 (o -H) and singlets at 4.40 (CH_2) and 3.43 (CH_3). The relative areas were within experimental error of the required 2:2:2:3. It was found that in the preparation of the ether it was necessary to avoid the reducing action of NaOCH_3 , which accounts for the slightly aqueous conditions employed. After several unsuccessful attempts, the following procedure gave a satisfactory yield. A mixture of 30 g (0.18 mole) of 4- $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$ and 100 ml of methanol was heated to 60 $^\circ$. A solution of 11.2 g (0.20 mole) of KOH in 40 ml of methanol was added with stirring at 60-65 $^\circ$. The mixture was stirred an additional 2 hr, cooled, and filtered. The precipitate was washed with the minimum amount of benzene and dried. The precipitate was crude 4,4'-dinitrostilbene, 11.0 g (45% yield). The filtrate was treated with 200 ml of water and 100 ml of alkanes and the organic layer was dried over Drierite. Distillation gave 12.4 g (41%) of the desired ether.

Cyclohexyl methyl ether was prepared in 28% yield from CH_3I and $\text{KOC}_6\text{H}_{11}$.¹⁴ The pmr spectrum consisted of a broad unresolved multiplet at δ 1-2 and a singlet at 3.10 (CH_3).

Discussion

Products. The oxidative cleavage of ethers by aqueous Br_2 is a most general reaction. Primary alkyl groups are converted to carboxylic acids and secondary alkyl groups are converted to ketones. The yields shown in Table I and II are illustrative of what can be achieved. Noteworthy are the high yields, the absence

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(12) G. A. Russell and R. C. Williams, *ibid.*, **86**, 2357 (1964).

(13) Dr. Dexter B. Sharp, Monsanto Chemical Co., Creve Coeur, Mo.

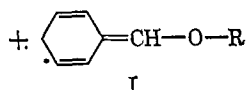
(14) A. I. Vogel, *J. Chem. Soc.*, 1809 (1948).

of bromination products, and the quantitative conversion of tetrahydrofuran to γ -butyrolactone.

If the reactions are conducted under more acidic conditions, α -bromo acids appear, undoubtedly by bromination of the intermediate aldehydes. For example, in 10–25% aqueous HBr, the yields of propionic acid and α -bromopropionic acid (from dipropyl ether) are comparable for either a deficiency or an excess of Br_2 . Also in the more acidic conditions, bromination of ketones becomes competitive with the initial oxidative cleavage so that bromo ketones appear, even with limited amounts of Br_2 . Data in Table IV illustrate this effect.

The products ultimately isolated arise both from initial oxidation of one of the two alkyl groups of the ether and by oxidation of the mole of alcohol formed in the initial cleavage. Despite this complexity, the data in Table I can still be used to detect the alkyl group that was initially attacked. For example, with isopropyl methyl ether, 70% of the Br_2 goes to produce acetone when the ether: Br_2 ratio is 4:1, whereas only 40% acetone is produced when ether: Br_2 is 1:1. The greater the excess of ether, the more the products will be dictated by initial attack on the ether. Thus the data show that the initial attack is on the isopropyl group and the oxidation of the methyl is largely, if not completely, due to subsequent oxidation of the methanol formed on cleavage. By analogous reasoning, the rates of attack on alkyl groups in ethers are in the order benzyl > isopropyl > ethyl > methyl.

Benzyl ethers produce benzaldehydes and, with an equivalent amount of Br_2 , yields of 90% of benzaldehyde can be achieved. Excess Br_2 continues the oxidation to benzoic acid, and in such a run a 5% yield of 4-bromobenzoic acid was isolated from benzyl methyl ether. A possibility was envisioned that the ring substitution could have arisen by addition of Br^- to I. This exotic possibility seems to have been dispelled by a



run that was saturated with NaCl. No 4-chlorobenzoic acid could be detected, nor could any 4-hydroxybenzoic acid be detected under any conditions. Even addition of NaBr failed to increase the yield of 4-bromobenzoic acid. Apparently the benzyl group undergoes simple electrophilic aromatic substitution by Br_2 to a small degree in dilute aqueous solution (a surprise to us). More reactive aromatic rings such as 4-methoxy and 3-methylbenzyl are completely brominated before ether cleavage, and this is a major limitation to the utility of the reaction.

It was evident from qualitative observations that irradiation, even by simple sunlamps, greatly increased the rate of disappearance of Br_2 . Where the irradiated reaction gives the same products as the dark reaction, it would presumably be preferable from a synthetic viewpoint. However, in the one case investigated with care, benzyl isopropyl ether (Table IV), the irradiated reaction gave different products. In retrospect we regret that we did not examine the light-catalyzed reaction more extensively.

Rate Law. The rates of oxidation of diisopropyl ether were studied at 25° in an acetate buffer at pH 4.6.

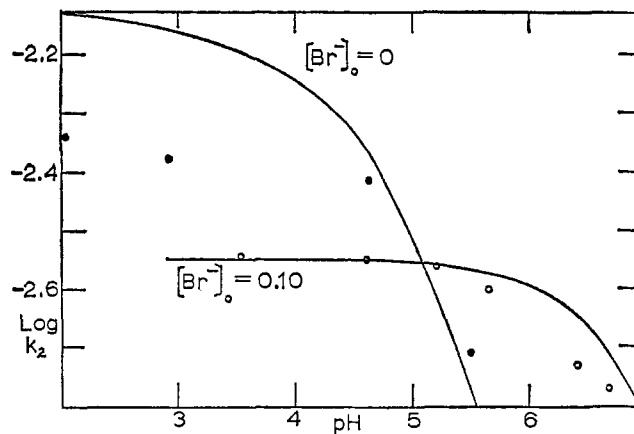


Figure 1. $\text{Log } k_2$ for the oxidation of diisopropyl ether by Br_2 at 25.0° for $[\text{Br}^-]_0 = 0$, closed circles, and $[\text{Br}^-] = 0.10$, open circles.

Rate constants were constant when calculated on the basis of the rate law

$$-d[\text{ether}]/dt = k_2[\text{ether}][\text{Br}_2] \quad (1)$$

as described in the Experimental Section.

The observed values of k_2 could still be in error by a factor of 2 if the oxidation of 2-propanol was very much faster than oxidation of the ether. This possibility was eliminated by directly measuring the rate of oxidation of 2-propanol by Br_2 under identical conditions. The rate law has already been shown to be

$$-d[\text{ROH}]/dt = k_2[\text{ROH}][\text{Br}_2] \quad (2)$$

for ethanol¹⁵ and 2-propanol.¹⁶ The value of k_2 for 2-propanol at 25° at pH 4.6 was $2.90 \times 10^{-3} \text{ l. mole}^{-1} \text{ sec}^{-1}$ using 0.1 M acetate buffer and 0.1 M NaBr. Under identical conditions, k_2 for the oxidation of diisopropyl ether was $2.80 \times 10^{-3} \text{ l. mole}^{-1} \text{ sec}^{-1}$ and, interestingly, the two rate constants are virtually identical.

pH-Rate Profile. Figure 1 shows two calculated profiles. These are calculated for 25° on the basis that the rate law is eq 1 with $\text{log } k_2 = 3.88$, that the initial stoichiometric Br_2 concentration was 10^{-3} M , and that $[\text{Br}_2]$ is reduced by the equilibria

$$17 = \frac{[\text{Br}_2^-]}{[\text{Br}_2][\text{Br}^-]} \quad (3)^{17}$$

and

$$9 \times 10^{-9} = \frac{[\text{HOBr}][\text{Br}^-][\text{H}^+]}{[\text{Br}_2]} \quad (4)^{18}$$

One curve is for $[\text{Br}^-]_0 = 0$, no added Br^- , and the other is for $[\text{Br}^-] = 0.10$, 0.10 M added NaBr. The added Br^- depressed the rate at low pH, but delays the sharp decline at higher pH values.

The experimental $\text{log } k_2$ values also appear in Figure 1. For the runs with 0.1 M added NaBr the fit is

(15) S. Bugarszky, *Z. Physik. Chem.*, **38**, 561 (1910); L. Farkas, B. Perlmutter, and O. Schachter, *J. Am. Chem. Soc.*, **71**, 2829 (1949); B. Perlmutter-Hayman and V. Weissman, *ibid.*, **84**, 2323 (1962).

(16) C. G. Swain, R. A. Wiles, and R. F. W. Bader, *ibid.*, **83**, 1945 (1961).

(17) R. O. Griffith, A. McKeown, and A. G. Winn, *Trans. Faraday Soc.*, **28**, 101 (1932).

(18) The value 9×10^{-9} for 25° was estimated from the value of 6.7×10^{-9} at 20° (M. Eigen and K. Kustin, *J. Am. Chem. Soc.*, **84**, 1335 (1962)) and the temperature coefficient (H. A. Liebhafsky, *ibid.*, **61**, 3513 (1939)).

satisfactory with the calculated curve in view of perturbations by activity coefficient effects, largely unknown, and the possibility of minor equilibria such as that involving BrO_3^- . For runs with no added Br^- the fit at the two higher pH values is good, but a severe discrepancy develops for the two lower pH runs. However, it is these latter two runs that are most susceptible to errors due to adventitious Br^- and to Br^- produced as the reaction progresses. Over-all, it is concluded that the picture generated by eq 1, 3, and 4 is largely correct.

Competition Experiments. Of the experiments reported in Table IV the most revealing is that Br_2 selectively attacks dibenzyl ether relative to diisopropyl ether in the light but just the reverse in the dark. This unequivocally demonstrates the difference in mechanism between the dark reaction and the light-catalyzed reaction. Also informative is the fact shown in Table VI that $(\text{C}_6\text{H}_5)_3\text{C}^+$ selectively attacks dibenzyl ether relative to diisopropyl ether.

A difference in selectivity is also shown between the light and the dark reaction in the Br_2 oxidation of benzyl isopropyl ether, benzyl being exclusively oxidized in the light-catalyzed reaction and both benzyl and isopropyl being oxidized in the dark reaction. The benzyl group is also exclusively attacked in the abstraction of hydride by $(\text{C}_6\text{H}_5)_3\text{C}^+$ (Table VI).

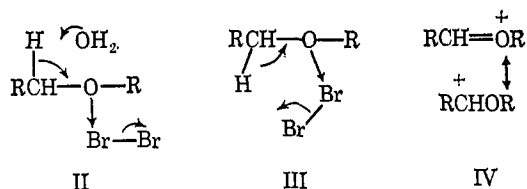
The above differences between the light and the dark reaction suggest a nonradical path for the dark reaction since all precedent indicates a free-radical chain mechanism for the light-catalyzed reaction. Similarly, the difference selectivity between the dark reaction and the hydride abstraction by $(\text{C}_6\text{H}_5)_3\text{C}^+$ indicates that the dark reaction is not a simple hydride abstraction.

It is proposed that the mechanism of the dark reaction closely parallels the synchronous electron pair loss and H^+ loss which was proposed by Westheimer for the oxidation of *alcohols* by chromic acid.¹⁹⁻²¹ Applied to the Br_2 oxidation of ethers, the transition state would be structure II or III and the initial product structure IV. Structure III is preferred over III because H_2O is more basic than Br^- .

(19) F. Westheimer, *Chem. Rev.*, **45**, 419 (1949).

(20) F. Westheimer, *et al.*, *J. Am. Chem. Soc.*, **71**, 25 (1949); **73**, 65 (1951); **74**, 4383, 4387 (1952); **80**, 3030 (1958); **82**, 406 (1960); *J. Chem. Phys.*, **11**, 506 (1943); **17**, 61 (1949).

(21) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 81-90.



Although it is not really germane to the argument, there is precedent for Br_2 -ether complexes containing a Br - O bond, and $(\text{C}_2\text{H}_5)_2\text{OBr}_2$ and $(\text{C}_2\text{H}_5)_2\text{OBr}_3$ have been isolated.²²⁻²⁴ The addition products of halogens and dioxane are also known.²⁵

σ - ρ Studies. The data in Table V generate a σ - ρ plot with marked curvature. The slope, ρ , varies from -3 to near 0 over $\sigma = -0.17$ to $+0.78$. This suggests a change in the rate-limiting step in a complex sequence. This is regarded as mildly favoring the Westheimer mechanism, in contrast to a direct hydride-transfer mechanism.

It is of interest that a σ - ρ study on the chromic acid oxidation of alcohols showed a negative ρ for the initial chromate ester formation and a positive ρ for the ester decomposition.²⁶

Oxidations by $(\text{C}_6\text{H}_5)_3\text{C}^+$. These oxidations (Table VI) exhibit one predominant feature. The yield of $(\text{C}_6\text{H}_5)_3\text{CH}$ was generally $>90\%$, showing that reaction was complete, but the yields of aldehyde are low. It is concluded that oxidation of the aldehyde competed with oxidation of the ether.

Oxidations by Cl_2 and I_2 . At a pH of 5, diethyl ether was quantitatively oxidized to acetic acid by Cl_2 . I_2 was inert under the same conditions toward diethyl, diisopropyl, and dibenzyl ethers.

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