THE CLEAVAGE OF ETHERS[1]

ROBERT L. BURWELL, JR.

Department of Chemistry, Northwestern University, Evanston, Illinois

Received February 26, 1954

CONTENTS

---

[1] This paper was prepared in connection with a grant from the National Science Foundation for work in the field of ether cleavage.

I. INTRODUCTION

This review surveys the cleavage of ethers. While the author's interest is primarily in mechanism, he has attempted to cover all aspects of the subject.

To keep the subject within reasonable bounds, it was necessary to limit the field rather strictly and, to some extent, arbitrarily. Thus, the review deals primarily with cleavage of simple ethers containing no other functional groups, particularly groups which might "participate" in cleavage reactions. In the case of alkyl ethers, this policy is adhered to rather closely. It is not very practical, however, in the consideration of aryl ethers. Some of the most interesting examples of ether cleavage contain groups substituted on the ring. Furthermore, much of mechanistic interest can be learned by considering such substituted ethers. The influence of such substituents is largely electrostatic, and consideration of the substituted aromatic ethers does not materially alter the general plan of the review.

Ring-opening reactions of ethylene oxide and propylene oxide are not treated. Although these compounds have some of the properties of ethers, they possess others which are not characteristic of ethers and, in particular, an exalted activity. *i*-Cholesteryl ethers are similarly excluded.

Vinyl ethers, which may be considered as ethers of the enol forms of aldehydes or ketones, have also been excluded from consideration. The cleavage of such compounds may frequently involve initial addition to the double bond rather than initial cleavage of an oxygen–carbon bond (255). However, the cleavage of phenyl, allyl, benzyl, etc. ethers has been covered.

One might confine the meaning of cleavage of ethers to those cases in which the two alkyl groups end up attached to functional groups. Such a definition would exclude the following:

$$C_6H_5OCH_3 + CH_3MgBr \rightarrow C_6H_5OMgBr + CH_3CH_3$$

$$C_6H_5CH_2OR + H_2 \xrightarrow{Pd} C_6H_5CH_3 + HOR$$

$$R_2O + C_6H_6 \rightarrow RC_6H_5 + ROH$$

This review considers reactions in which one of the groups is converted into a hydrocarbon.

On the other hand, one might consider an elimination reaction, such as the following, as an ether cleavage reaction.

$$ROCH_2CH_3 \rightarrow ROH + CH_2{=}CH_2$$

This review, however, is primarily concerned with substitution reactions, and elimination reactions are considered only as they accompany other cleavage reactions.

Certain types of cleavage reactions involve preliminary oxidation of one of the groups at an α-position. Such reactions are not treated, but reference may be made to a recent review of reactions of this nature (124). The oxidative cleavage of hydroquinol ethers is also excluded (164).

Reactions of ethers with free radicals lie outside the scope of the present review.

When alone, simple alkyl ethers decompose only above 500°C. and then to hydrocarbon and ketone or aldehyde.

$$(RCH_2)_2O \rightarrow RCH_3 + RCHO$$

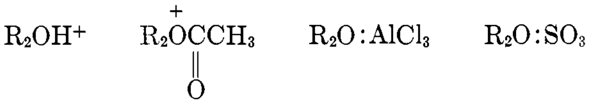
The reaction seems to proceed via free-radical intermediates (229).

Alkyl phenyl ethers decompose at about 400°C. to phenol and olefin (14).

Certain benzylic ethers decompose more readily, presumably consequent to the greater ease of formation of benzylic free radicals. Benzyl ether, itself, decomposes slowly at its boiling point (298°C.) to benzaldehyde and toluene (157, 163). Benzhydryl ether behaves similarly, although some tetraphenylmethane also appears (201). Ethers containing the triphenylmethyl group begin to decompose at 220–260°C. to triphenylmethane and an aldehyde or, if a secondary alkyl group is involved, to a ketone (205).

Cleavage reactions of ethers can be classified into the following groups:

1. Cleavage by acidic reagents which involve some sort of a generalized oxonium salt intermediate, as, for example:



$$R_2OH^+ \qquad R_2\overset{+}{O}\underset{\underset{O}{\|}}{C}CH_3 \qquad R_2O{:}AlCl_3 \qquad R_2O{:}SO_3$$

2. Cleavage by nucleophilic reagents in the absence of acids.
3. Cleavage by alkali metals.
4. Cleavage by reactions involving heterogeneous catalysts.

It is possible to correlate most of the reactions ascribed to the first three types in terms of existing theories of the mechanism of organic reactions, and primarily in terms of bimolecular nucleophilic displacement reactions (S_N2) and carbonium-ion reactions (S_N1). Presumably all such reactions involve the solvent to some extent. However, there are rarely data which make it worthwhile to discuss this point in the present review and the "concertedness" of ether cleavage reactions is only occasionally considered.

It will be seen that the cleavage of a carbon–oxygen bond in ethers has many points of similarity to the cleavage of the same bond in alcohols. One thinks of alcohols as being more reactive than ethers, but this is true only in terms of the ready cleavage of the oxygen–hydrogen bond of alcohols. Reactions involving the cleavage of carbon–oxygen bonds occur at least as readily in ethers as in alcohols and in some cases more easily. For example, cleavage of this bond in ethers by nucleophilic reagents alone requires displacing species of very high nucleophilic potential. Since such species are commonly very strong bases, they would remove a proton from an alcohol. The resulting alkoxide ion would be much less reactive in these reactions than would an ether, owing to the negative charge on the alkoxide ion.

The cleavage of alkyl aryl ethers was reviewed in 1938 (164).

II. OXONIUM SALTS

Many of the cleavage reactions of ethers have been assumed to proceed through oxonium salts of such structures as

$$R_2OH^+ \text{ and } R_2\overset{+}{O}COCH_3$$

The origin of the assumption of the high reactivity of such species may be traced to the original proposal of the oxonium theory by Collie and Tickle (57) and Baeyer and Villiger (9).

In an ether,

$$-\overset{|}{\underset{|}{C}}-OR$$

a process which transfers net positive charge to the oxygen atom will increase any tendency for the departure of the group to the left as a carbonium ion. It may also be presumed usually to increase the rate of attack of nucleophilic species.

A. Trialkyloxonium salts

The oxonium salts, R_3O^+, constitute a group of compounds closely related to the conjugate acids of ethers, R_2OH^+. Examination of the cleavage of an alkyl group from an oxonium salt is of interest as a model for the probable behavior of the conjugate acids of ethers.

Oxonium salts were first prepared and studied by Meerwein (183, 184). In the oxonium salts which have been prepared, R is methyl, ethyl, or propyl or else two of the R groups are part of a ring, as in tetrahydrofuran. The salts melt at about 100°C. They are soluble in several polar organic solvents and in water but not in hydrocarbons.

The oxonium salts are among the strongest alkylating agents known. Nucleophilic attack by A^- on one of the carbon atoms attached to oxygen results in formation of RA and expulsion of an ether:

$$A^- + R_3O^+ \rightarrow RA + R_2O$$

The anion in an oxonium salt must be one of low nucleophilic potential, such as BF_4^-, $SbCl_6^-$, or picrate. Attempts to prepare the iodide lead to $RI + R_2O$.

At much above 100°C. even the more stable salts decompose. Thus, the tetrafluoborate yields an ether and an alkyl fluoride. Decomposition of ethyldimethyloxonium fluoborate gives less ethyl fluoride than the purely statistical, indicating that the decomposition is probably a nucleophilic displacement.

The displacing anion (or molecule), A^-, may be an alkoxide or phenoxide ion, in which case two molecules of ether result. Alcohols and phenols react similarly, though more slowly. Organic acids or aqueous solutions of their salts give esters. The conjugate bases of malonic ester or acetoacetic ester lead to alkylated malonic or acetoacetic esters. Ammonia, pyridine, dialkyl sulfides, and certain ketones are alkylated.

The half-life of trimethyloxonium hydroxide in aqueous solution (to form an alcohol and an ether) is a few minutes. Triethyloxonium hydroxide reacts about 0.1 as rapidly, tripropyl about 0.07 as rapidly, and the ethyloxonium salt derived from pentamethylene oxide about 0.04 as rapidly. This is what would be expected if the reaction was a nucleophilic attack by hydroxide ion. The general thermal stability of these salts may be correlated similarly.

If triethyloxonium tetrafluoborate is allowed to react in a 2 molar aqueous solution of NaA, both ethyl ether and ethyl A result. The per cent of ethyl A with various anions, A^-, is: fluoride, trace; chloride, 12 per cent; bromide, 23 per cent; iodide, 53 per cent; thiocyanate, 64 per cent. This order is that of increasing nucleophilic reactivity of the anions.

Similar direct attack by anions of the type mentioned above on simple alkyl ethers is unknown. For example, (+)-*sec*-butyl methyl ether is unaffected by the methoxide ion at 200°C. (45).

It seems reasonable to expect that the conjugate acid of ethyl ether, $(C_2H_5)_2OH^+$, would resemble $(C_2H_5)_3O^+$ in cleavage of the carbon–oxygen bond. It is thus of interest to examine cleavage reactions of ethers in the presence of strong acids to see whether the expected parallelism exists (to anticipate a little, it does). However, cleavage of ethers by nucleophilic displacement is less flexible than the corresponding cleavage of oxonium salts. Media of high acidity are required to convert an ether to its conjugate acid. Since anions of high nucleophilic potential are often also strong bases, there will be limitations upon having such anions and conjugate acids of ethers present in the same medium. One could, for example, hardly expect to have the conjugate acid of ethyl ether present in solution with the hydroxide ion or with the conjugate base of malonic ester.

An ether interchange reaction might proceed via an oxonium salt intermediate when an ether is treated with an alkylating agent.

$$R_2O + R'X \rightarrow R_2R'O^+ + X^- \rightarrow RR'O + RX$$

The literature reports two types of reactions which may be of this nature. If anisole is heated with dimethyl sulfate at 155°C., dimethyl ether is formed along with sulfonated anisole. Isoamyl ether forms methyl isoamyl ether along with sulfur dioxide, amylene, and higher-boiling products. Methyl benzyl ether behaves similarly (18), as do ethyl sulfate and isoamyl ether (17).

Ethyl benzyl ether when heated at 185°C. with 1-benzylpyridinium chloride for 6 hr. gives an 18 per cent yield of benzyl ether (151). Anisole and phenetole behave similarly.

B. Conjugate acids of ethers

Solutions of small amounts of ethyl ether in solvent sulfuric acid exhibit freezing-point lowerings corresponding to the presence of two particles per molecule of ether. There seems little doubt that one is dealing with a solution of $(C_2H_5)_2OH^+$ and HSO_4^- (104, page 47). If one names $H_3O^+HSO_4^-$ hydronium bisulfate, this compound may be called diethylhydronium bisulfate.

If ethyl ether and sulfuric acid are mixed mole for mole, slightly more heat is evolved than when water and sulfuric acid are similarly mixed. Upon cooling this solution, the solid complex $(C_2H_5)_2O \cdot H_2SO_4$, m.p. −65°C., is formed (53). By analogy with hydronium perchlorate and hydronium bisulfate, it seems likely that this solid is best represented as diethylhydronium bisulfate, although no rigorous proof of this exists.

Dilution of mixtures of simple normal alkyl ethers and sulfuric acid within a few hours of their preparation regenerates the ether. Six hundred volumes of methyl ether (as a gas) are soluble in one volume of sulfuric acid; this is about a 1:1 mole ratio. This mixture can be stored for months. Dilution and warming release the ether. Such a procedure was employed for handling methyl ether commercially before the development of modern techniques for handling compressed gases (67).

In weak acids, on the other hand, ether is insufficiently basic to be converted to the diethylhydronium ion. In glacial acetic acid, for example, ether is not converted to the conjugate acid (156). Even so, there may be interaction of the nature of hydrogen bonding between acid and ether which serves to transfer some positive charge to the oxygen atom of the ether.

Study of the partial pressures of ethyl ether from solutions shows slight positive deviation from Raoult's Law with acetic acid and a larger positive deviation with acetic anhydride. Increasingly negative deviations are exhibited by solutions in chloroacetic acid, dichloroacetic acid, trichloroacetic acid, and nitric acid. The vapor pressure of ether is substantially zero when the mole fraction of nitric acid exceeds 0.5 (287).

The only ether complexes with acids which have been extensively studied are those with the hydrogen halides. There might, *a priori*, be some doubt as to whether true oxonium salts would be formed in such cases or whether the interaction would more appropriately be considered as hydrogen bonding.

Ethyl ether dissolves in a large excess of liquid hydrogen bromide at the boiling point of the latter with the liberation of 22 kcal. per mole of ether. The heat of solution of $(C_2H_5)_2O \cdot HBr(s)$ in liquid hydrogen bromide can amount to no more than 10 per cent of this. The corresponding heat of solution of methanol is 13 kcal. (177).

The solid compound $(CH_3)_2O \cdot HBr$ melts at −13°C. (172) and boils at 3–5°C. (89). $(CH_3)_2O \cdot HCl$ melts at −96°C. (122) and boils at about −12°C. (175). The boiling point of methyl ether is −24°C.

The conductivity of hydrogen chloride–methyl ether mixtures has been measured at −89°C. (173). Maximum conductivity is found at 17 per cent methyl ether. This conductivity is large and when corrected with a typical temperature coefficient would correspond about to that of 10 per cent sulfuric acid at 18°C. At −89°C. this conductivity is 0.047 mho. For $(CH_3)_2O \cdot HCl$ containing 44.3 per cent hydrogen chloride the conductivity is about one-tenth of that. The conductivity rapidly declines as the mole fraction of methyl ether becomes more than 0.5 but is still measurable even in low concentrations of acid. Where the mole fraction of the acid is greater than 0.5, the conductivities of solutions of methanol are severalfold less than those of methyl ether. Ethyl ether resembles methyl ether, but at similar mole fractions the conductivities are about one-fourth those of methyl ether.

All in all, the data probably indicate that the solid complexes with hydrogen halides are substantially hydronium salts, that is, that solid dialkylhydronium halides are analogous to dialkylammonium halides. When the mole fraction of the hydrogen halide is 0.5 or greater, the ether–hydrogen halide complexes are extensively ionized, at least the complexes of the simpler alkyl ethers are. With excess ether it is questionable whether one deals primarily with ion pairs or with hydrogen-bonded complexes, but even in such cases there is measurable electrolytic dissociation.

In the vicinity of 0–30°C., methyl ether and hydrogen halides are apparently associated in the vapor phase. The degree of association has been determined by measurement of the change in pressure on mixing the pure vapors. Adsorption on the walls of the container interferes with accuracy. For the association of methyl ether and hydrogen chloride, the most recently reported values of K_p are 0.473 at 1°C. and 0.131 at 30°C. (89); values given by other workers (175) are 0.28 at 0°C. and 0.10 at 29.2°C. From the first set of data, $\Delta H = -7$ kcal. Methyl ether–hydrogen bromide behaves similarly, but the relative degrees of association are reported to be somewhat less (174). The enthalpy change in the reaction is computed to be -5 kcal.

It seems most likely that the complexes formed in the vapor phase are hydrogen-bonded. The heats of reaction are of the right order of magnitude for this. Formation of ion pairs seems unlikely.

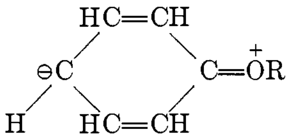
It appears that solutions of ethers in strong acids will consist to a considerable degree of the conjugate acids of ethers in the form of oxonium salts. Therefore, one would wish to know the dependence of the basicity of an ether upon its structure, since the rate of reaction of an ether via reaction of its conjugate acid either in a nucleophilic displacement or in a carbonium-ion reaction will in part depend upon the actual rate of reaction of the conjugate acid but also in part upon the equilibrium concentration of the conjugate acid (i.e., the basicity of the ether). Unfortunately, very little can be said about this, in particular in regard to variation of basicity in the sequence methyl ether, ethyl ether, isopropyl ether, and *tert*-butyl ether. One might consider the corresponding sequence, methylamine, etc., in which case the variation of basicity in aqueous solution is small and without definite trend. However, the fact that the sequence ammonia, methylamine, and dimethylamine is one of increasing basicity, while the sequence water, methanol, and dimethyl ether is probably one of decreasing basicity (121), makes one doubt the validity of comparison of the ether sequence with the amine sequence.

In solution in isopropyl alcohol the basicity of the alkoxide ion, RO^-, increases in the sequence methoxide, ethoxide, isopropoxide, and probably *tert*-butoxide (121). But complications caused by solvation, hybridization, etc. do not permit one to extrapolate this sequence, apparently dominated by the inductive effect, to ether in the absence of experimental values of the basicities. It is, further, perfectly possible that one sequence might be found in one solvent and another sequence in another.

The only definite measurement of basicity of ethers has been with boron trifluoride as the reference acid (37). Base strengths decreased in the sequence methyl ether, ethyl ether, isopropyl ether. The departure from the sequence of the inductive effect was ascribed to *F*-strain. One should not expect this effect to operate in the addition of a proton to an ether.

Quantities related to basicity have been measured for a series of ethers: the shift of the oxygen–deuterium frequency in CH_3OD consequent to hydrogen bonding to ethers and the heat of mixing of ethers with chloroform, a reaction which also involves hydrogen bonding (245). Both sets of measurements indicate that the basicity increases in the order primary ethers, secondary ethers, tertiary ethers.

The aryl alkyl ethers may be definitely considered as weaker than dialkyl ethers, both from direct experimental considerations and from the strong evidence for contributions to such ethers of structures of the form



The lowered basicity of alkyl phenyl ethers is shown in a study of the effect of ethers upon the rate of etherification of benzhydrol under the catalytic influence of small concentrations of *p*-toluenesulfonic acid (218). The addition of ethers lowers the rate of etherification, presumably by competition with benzhydrol for the acid. Alkyl benzyl ethers are intermediate in basicity between butyl ethers and alkyl phenyl ethers. However, the retarding effects of butyl ether, butyl *sec*-butyl ether, and butyl *tert*-butyl ether are indistinguishable. This absence of structural effect contrasts with that observed in shifts in oxygen–deuterium frequency and in heat of mixing (245).

III. CLEAVAGE BY ACIDS

A. History

Many of the characteristic features of ether cleavage by acids, including structural effects, were discovered during the nineteenth century, although there was some failure to consolidate all of this material into later textbooks.

About the first clear case of cleavage of an ethereal oxygen–carbon bond was that of Butlerow in 1861 (48). He found α-ethoxypropionic acid to react with concentrated aqueous hydriodic acid at about 100°C. to form lactic acid and ethyl iodide. Two years later, his student Saytzeff (237) reported that concentrated aqueous hydriodic acid cleaved *p*-methoxybenzoic acid to *p*-hydroxybenzoic acid and methyl iodide in 12 hr. at 125°C. In following up this work, Graebe in 1866 reported that concentrated hydrochloric acid effected the same reaction under the same conditions (95), although methyl chloride was formed in this case of course, and that both acids effected similar cleavage of *o*-methoxybenzoic acid (94). However, in applying this reaction to anisole, he discovered the greater reactivity of hydriodic acid. In a sealed tube at 135°C. hydriodic acid cleaved anisole to phenol and methyl iodide, but hydrochloric acid would not cleave the ether (95).

The greater ease of cleavage of benzyl ethers was observed by Sinternis in 1872 (252). He found that benzyl phenyl ether was cleaved by concentrated hydrochloric acid at 100°C., with the formation of phenol and benzyl chloride. Another early case of cleavage of alkyl aryl ethers involved the reaction of *p*-propenylanisole and hydriodic acid to form methyl iodide and *p*-propenylphenol (153).

The first study of the cleavage of alkyl ethers was that of Silva (250), who investigated the reaction at 0–4°C. of ether saturated with hydrogen iodide:

$$\text{ROR}' + \text{HI} \rightarrow \text{ROH} + \text{R}'\text{I}$$

He also studied the effect of the molecular weights of the alkyl groups upon their appearance as alkyl iodide or alcohol. The published material is a summary lacking in experimental details. A promised second paper, as so often happens, never appeared. However, in essence, his conclusions are correct and, allowing for his serious analytical problems, the paper must be considered a minor classic.

The following observations are of particular importance: (*a*) Ethers involving a methyl group and a group of higher molecular weight are cleaved cleanly to methyl iodide and the higher alcohol. (*b*) Such ethers react much more rapidly than ethers containing two groups of higher molecular weight. (*c*) In general, the group of higher molecular weight will appear as the alcohol, and that of lower molecular weight as the iodide.

Some of Silva's experiments with ethers of higher molecular weight are probably wrong in detail. For example, he reported that ethyl propyl ether yields ethyl iodide and propyl alcohol cleanly but one would certainly expect, and it has been reported, that both alcohols and both iodides are formed (186).

Silva's work was extended by Lippert (162). In these experiments the ether was saturated with hydrogen iodide at 0°C. The reaction mixture was then heated on a water bath in a sealed tube, although in many cases, particularly those involving more reactive ethers, reaction was observed even during the solution of hydrogen iodide in the ether.

The rate of reaction was observed to decline with molecular weight; propyl ether reacted more slowly than ethyl ether and butyl ether more slowly than propyl.

Lippert studied the products obtained in the cleavage of ethers wlth isomeric radicals such as butyl *sec*-butyl ether. In such cases the identity of the iodide was determined by converting it to the quaternary salt with pyridine and determining the melting point of the platinum complex of this. While this procedure was perhaps the best then available, it is apt to lead one to miss products present in smaller amounts. The products of the cleavage of various ethers are given in table 1.

TABLE 1

Products of ether cleavage

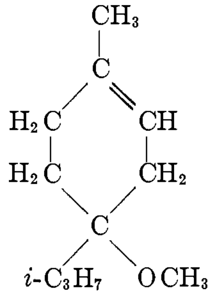
Ether	Iodide	Alcohol
Ethyl isopropyl	Ethyl	Isopropyl
Ethyl isobutyl	Ethyl	Isobutyl
Propyl allyl	Allyl	Propyl
Isopropyl allyl	Allyl	Isopropyl
Propyl isopropyl	Isopropyl	Propyl
Butyl *sec*-butyl	Butyl	*sec*-Butyl
Butyl isobutyl	Butyl	Isobutyl
sec-Butyl isobutyl	*sec*-Butyl	Isobutyl
Glycol dimethyl	Methyl	Glycol
Glycol diethyl	Ethyl	Glycol
Glycol dipropyl	Propyl	Glycol
Glycol diisobutyl	Isobutyl	Glycol

The cleavage products of propyl isopropyl ether seem inconsistent with those of ethyl isopropyl ether and of butyl *sec*-butyl ether, although Silva (250) reported the same products for propyl isopropyl ether. It seems likely that cleavage of the oxygen bond to a normal primary alkyl group is preferred to cleavage of the oxygen bond to a secondary alkyl group or to a primary group like isobutyl with a branch adjacent to the ether linkage.

Lippert also observed that anhydrous hydrogen bromide effected the cleavage of several of these ethers to equivalent products, although the reaction was slower.

Michael and Wilson in 1906 (192) studied the cleavage of ethers with anhydrous hydrogen iodide under conditions resembling those of Lippert. With methyl *n*-alkyl ethers methyl iodide was the principal iodide formed; with methyl *sec*-alkyl ethers, methyl iodide was the only iodide formed; while with methyl *tert*-alkyl ethers, the tertiary iodide was the only iodide obtained. They reported that propyl isopropyl ether cleaved in both ways.

The first observation of the much greater ease of cleavage of tertiary ethers was by Baeyer in 1893 (8), who found that the methyl ether of terpineol,



was rapidly cleaved by aqueous hydriodic acid; cleavage was complete in 15 min. at room temperatures.

The Zeisel method for methoxyl determination was published in 1885 (307). It involves refluxing a sample with concentrated aqueous hydriodic acid and determining the evolved methyl iodide. In so far as ethers are concerned, its success implies the ready cleavage of methyl ethers, particularly methyl aryl ethers. The various developments in the technique of this determination will not be reviewed here, since they are adequately covered elsewhere (125).

B. The mechanism of the cleavage of ethers by anhydrous hydrogen halides

Few papers of interest in regard to the mechanism of the cleavage of ethers by anhydrous hydrogen halides have appeared since the work described in the historical section above. No kinetic data are available for cleavage in approximately equimolar ether–hydrogen halide mixtures. The physical characteristics of the system would make such work difficult, and interpretation of the results would be difficult owing to the large change in the medium which would occur during reaction and which would be occasioned by change in the type of ether.

Kinetic data are available for dilute (0.5 *M*) solutions of hydrogen bromide in ether and for roughly equimolar solutions of ether and hydrogen bromide in chlorobenzene, toluene, and chloroform at room temperatures, but ethyl ether is the only ether which has been so studied (181).

In a large excess of ether, or in chlorobenzene,

$$-\mathrm{d}[(C_2H_5)_2O]/\mathrm{d}t = k[HBr]^2[(C_2H_5)_2O]$$

The reaction is somewhat autocatalytic, owing to acceleration by alcohol. With reasonable alcohol concentrations the rate becomes

$$-\mathrm{d}[(C_2H_5)_2O]/\mathrm{d}t = k'[HBr][(C_2H_5)_2O][C_2H_5OH]$$

The authors suggested that a bimolecular nucleophilic substitution was involved between $(C_2H_5)_2O \cdot HBr$ and HBr. The complex between ether and hydrogen bromide was assumed to be unionized but the ion pair, $(C_2H_5)_2OH^+Br^-$, would lead to the same kinetics.

In chloroform, the rate expression is

$$-\mathrm{d}[(C_2H_5)_2O]/\mathrm{d}t = k[(C_2H_5)_2O]^{3/2}[HBr]^{3/2}$$

which was interpreted as indicating reaction between $(C_2H_5)_2O \cdot HBr$ and Br^-. The bromide-ion concentration is assumed proportional to the square root of $[(C_2H_5)_2O][HBr]$. Thus, the kinetics are satisfied. However, the existence of Br^- implies that of $(C_2H_5)_2OH^+$ and an ion pair would be at least as satisfactory as an unionized complex.

In 1932 (182) Meer and Polanyi proposed that the dialkylhydronium ion decomposed to an alcohol and a carbonium ion which then became hydrated to an alcohol. It was said that this was supported by the following decreasing order of rate of cleavage: tertiary ethers > secondary ethers > *n*-alkyl ethers > methyl ethers; but the third inequality is incorrect and the second is dubious.

Bonhoeffer and Reitz proposed that the reaction of the dialkylhydronium ion with the water of aqueous acids was in essence classifiable as a bimolecular nucleophilic displacement (S_N2) (31).

In interpreting rate measurements in glacial acetic acid containing hydrogen bromide (282), Hughes and Ingold (128) concluded that, if the ether contained a secondary or tertiary group, the reaction was of the carbonium-ion type (S_N1) but that, if both groups were primary, the reaction was a bimolecular nucleophilic displacement (S_N2).

Consideration of the experimental work given above with the additional information in regard to the products and the stereochemistry of the cleavage of optically active methyl *sec*-butyl ether has recently permitted the mechanism to be established with a fair degree of plausibility (45).

An equimolar solution of optically active methyl *sec*-butyl ether and hydrogen bromide at 50°C. yields methyl bromide and *sec*-butyl alcohol of the same configuration as the ether and little if any racemized. No more than a few per cent of *sec*-butyl bromide can have been formed, and some or all of this could have been formed by the action of hydrogen bromide on the alcohol after its formation.

Thus, the bond which was broken was the methyl–oxygen one. There can be little doubt that the reaction is of the S_N2 type between one of the following: the dialkylhydronium ion, the ion pair of this and bromide ion, or less probably an unionized complex of the ether and hydrogen bromide; and either hydrogen bromide or the bromide ion. Data which would permit a definite decision as to the exact reacting species do not exist.

In an ether, ROR′, the same mechanism may be assumed to apply when both alkyls are primary and when R′ is a secondary alkyl group and R is methyl, ethyl, or perhaps any *n*-alkyl group. The reported cleavages of propyl isopropyl ether in disagreement with this are old and need redoing.

When R′ is allyl, one may expect the allyl–oxygen bond to be broken, probably by an S_N2 mechanism (see table 1).

On the other hand, when R′ is tertiary, the bond between the tertiary alkyl group and the oxygen atom is broken (192), with formation of R′X and ROH even when R is methyl. In addition, tertiary ethers are very much more easily cleaved by aqueous acids than ethers containing only primary and secondary alkyl groups (66, 69, 204). This reaction, then, is of the S_N1 type.

$$RR'OH^+ \rightarrow R'^+ + ROH$$

The carbonium ion reacts rapidly with hydrogen halide or halide ion to form the tertiary halide.

When both R and R′ are secondary alkyl groups, it is dubious as to which of the two mechanisms is involved. No data bearing on the problem have been reported. A study of the rotation of *sec*-butyl alcohol formed in the cleavage of optically active *sec*-butyl isopropyl ether would elucidate this point.

If R is primary and R′ is secondary, then as R is progressively hindered, presumably one comes to a case where both carbon–oxygen bonds are broken. With neopentyl, the principal product would most likely be neopentyl alcohol and the secondary halide. It has been reported that cleavage of this type occurs in *sec*-butyl isobutyl ether (table 1).

The relative balance between S_N1 and S_N2 cleavage will also be influenced by the nucleophilic character and the concentration of the ions and molecules in the reaction mixture. Thus the absence of a suitable concentration of species effective in nucleophilic displacement will favor an S_N1 reaction (45).

It would be desirable to run the cleavage of a number of ethers with modern techniques of analysis such as infrared absorption or mass spectroscopy. Determination of the relative yields of alcohols and halides would settle such points and in addition would provide valuable data on the relative ease of bimolecular nucleophilic substitution on various alkyl groups. Such an investigation is in progress in this laboratory.

A mechanism somewhat different from either of the two so far discussed may be involved in the cleavage of benzyl ethers or at least of ethers of α-phenethyl alcohol. The optically active phenyl ether of this alcohol is cleaved by hydrogen chloride at 25–50°C. The rotation of the α-phenethyl chloride so formed shows that the process involves retention of configuration, accompanied by racemization. The loss of optical purity is much greater when benzene is employed as a solvent (105). It was proposed that the reaction proceeds via an oxonium ion pair which decomposes in such a way as to lead to retention of configuration (105). Similar stereochemical anomalies are exhibited in reactions of certain other α-phenethyl derivatives.

C. Further descriptive chemistry of cleavage by hydrogen halides

The general descriptive chemistry of the cleavage of ethers reported in the work described in the historical section has been confirmed and extended in the subsequent period. In particular, it has become clear that while saturation of an ether with anhydrous hydrogen iodide or bromide leads to one mole of alcohol and one of halide, refluxing with excess aqueous hydrogen halides leads to the conversion of the alcohol first formed to halide. In the case of phenols, however, conversion to halide does not occur.

A modification of the use of hydrogen iodide occurs in the use of sodium iodide and phosphoric acid. When an excess of such a mixture is refluxed with alkyl ethers, substantially two moles of alkyl iodide result (271). Phenyl ether is inert to this treatment.

By the use of liquid hydrogen iodide in slight excess one can effect substantially complete conversion of ethyl ether to ethyl iodide. The ether is added to hydrogen iodide cooled by solid carbon dioxide and the mixture allowed to become warm (58).

Lack of rearrangement in the following reaction is consistent with an S_N2 rather than an S_N1 reaction (306). It involves refluxing hydriodic acid.

$$(C_6H_5)_3CCH_2CH_2OC_2H_5 + HI \rightarrow (C_6H_5)_3CCH_2CH_2I + C_2H_5I + H_2O$$

The general resemblance in the behavior of anhydrous hydrogen bromide to that of the iodide which was discovered by Lippert has been confirmed (45, 284).

The general similarity in the behavior of concentrated aqueous hydrobromic acid to that of concentrated hydriodic acid has been established (226, 269), though the former acts somewhat more slowly.

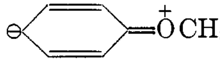
Cleavage of some compounds has been effected by concentrated hydrochloric acid, but its action is slow compared with that of hydrobromic acid (269).

Little examination of the action of hydrogen chloride or of hydrochloric acid has been reported for aliphatic ethers. However, the following reaction presumably involves preliminary cleavage to methyl chloride. The passage of methyl ether and hydrogen chloride at 325°C. over a mixture of silica and copper (previously treated with hydrogen at 1050°C.) results in the formation of methylchlorosilanes (232).

The action of hydrogen fluoride has been reported in one instance. Phenetole is cleaved to phenol and presumably ethyl fluoride by anhydrous hydrogen fluoride in an autoclave at 60–100°C. (238). It is questionable whether hydrogen chloride would effect this reaction under similar conditions. The great acid strength of anhydrous hydrogen fluoride is probably a factor. Conjunct polymerization would probably occur upon similar treatment of secondary or tertiary ethers with the possible exception of isopropyl.

Norris and Rigby (204) measured the relative rates of reaction of ethyl butyl ethers at 25°C. in 35.21 per cent hydrochloric acid in terms of the times required to form 25 per cent of the stoichiometric quantity of alkyl halide. The reaction was followed by the appearance of an upper layer in the initially homogeneous mixture, although the composition of the upper layer in terms of content of ethyl and butyl chlorides was not determined. The times in hours were: ethyl *n*-butyl ether, 768; *sec*-butyl, 105; isobutyl, 1250; *tert*-butyl, too fast to measure. The last reaction is clearly of the S_N1 type but, for reasons previously developed, it is not safe to assign the reactions of the other compounds solely on relative rates.

Concentrated hydriodic acid at reflux removes alkyl groups from alkyl aryl ethers with the formation of phenol and the alkyl iodide. The reaction is apparently slower than with analogous dialkyl ethers (144). This may, in part, result from the reduced basicity of phenyl ethers consequent to contribution to the overall structure of forms such as:



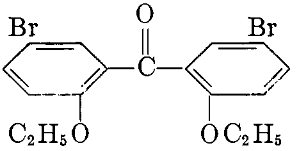
However, the relative rates of attack on the two types of disubstituted hydronium ions would be involved, as well as the relative tendency towards the formation of these ions.

Diphenyl ether is not cleaved by strong acids, for example, by hydriodic acid at 250°C. (123). This ether is very weakly basic and provides no position for ready nucleophilic attack.

In cases where the solubility of an alkyl aryl ether in refluxing hydriodic acid is low, the use of a cosolvent is helpful; for example, phenol (298) and acetic anhydride (120, 126).

Concentrated (48 per cent) hydrobromic acid seems to be effective, although it has been much less used. The action of concentrated hydrochloric acid at reflux is much slower. For example, *o*-benzoylanisole is cleaved by refluxing with 48 per cent hydrobromic acid but similar treatment with concentrated hydrochloric acid is without effect (269).

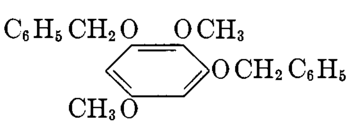
Anhydrous hydrogen chloride has been reported not to split phenolic ethers at 220°C. (220). Refluxing, concentrated hydrochloric acid is without effect on pyrogallol trimethyl ether even if hydrogen chloride gas is passed through the system (144). However, there is slow cleavage in an autoclave at 190°C. When the following compound is heated with concentrated hydrochloric acid at 165°C. there is slow cleavage of *one* ethoxyl group (62).



Ethers in which one group is a tertiary alkyl group are rapidly cleaved not only by concentrated hydriodic acid at room temperature (8) but even by concentrated hydrochloric acid (204). Di-*tert*-butyl ether is also rapidly cleaved by concentrated hydrochloric acid at room temperature to give 2 moles of *tert*-butyl chloride (66). The cleavage may well be helped by the packing strain in this molecule of about 5.4 kcal. (38).

In general, tertiary ethers are easily cleaved by acids (69, 282). Even 10 per cent sulfuric acid at room temperature slowly cleaves ethyl *tert*-butyl ether, although some isobutylene is formed (204). Elimination reactions commonly accompany carbonium-ion reactions.

Ethers containing an allyl group are attacked much more rapidly than the corresponding propyl compounds (282). In allyl alkyl ethers, the allyl group appears as the halide (table 1). Benzyl ethers are also particularly reactive (282). In the following compound both benzyl groups are removed by the action of concentrated hydrochloric acid at 65°C. in 1 hr., but the methyl groups are not touched (12).



The formation of benzyl chloride from benzyl ether by heating the ether with hydrochloric acid at 80–150°C. in the presence of zinc chloride, antimony trichloride, or ferric chloride has been reported (71).

Ethers of benzhydrol are very reactive, presumably via a carbonium-ion process. Benzhydryl ether or methyl benzhydryl ether reacts in the cold with concentrated hydrochloric acid to give benzhydryl chloride (13).

The action of anhydrous hydrogen bromide on the ethyl ether of α-phenethyl alcohol has been investigated (194). No α-phenethyl alcohol was detected in the reaction products, which consisted of ethyl ether, ethyl bromide, ethanol, styrene, and α-phenethyl bromide. No α-phenethyl alcohol should be formed if the reaction is a carbonium-ion reaction or one proceeding via an intermediate involving participation by the phenyl group. However, the reaction was run at 100°C., which is a much more drastic condition than necessary. Secondary reactions appear to have entered in to a considerable extent.

D. Cleavage by action of hydrogen halides in organic acids

In 1898, Fenton and Gostling (70) reported that hydrogen bromide in an organic acid slowly reacts with an ether at room temperature to form an alkyl bromide and an ester:

$$R_2O + HBr + R'COOH \rightarrow RBr + R'COOR + H_2O$$

Presumably, an alkyl bromide and an alcohol are formed first and the alcohol is then esterified. The ester will further react with hydrogen bromide to form an alkyl bromide. If excess hydrogen bromide is employed, substantially two moles of alkyl bromide may be obtained (45, 284). At least in excess ether as the solvent, ethyl acetate reacts with hydrogen bromide about as fast as with ethyl ether (181). However, with hydrogen bromide and ether in a mole ratio of 1:1, the reaction approximates the equation given above, at least for mixed ethers, where the two groups have rather different reactivities (45).

Concentrated hydrobromic acid (48 per cent) may be employed rather than anhydrous hydrogen bromide. Thus, 48 per cent hydrobromic acid in glacial acetic acid reacts with *o*-methoxybenzophenone in 1 hr. at reflux to give good yields of the phenol (269).

Hydrogen chloride has been reported to react similarly (70), but it apparently has been little used.

Tronov and Ladigina (282) reported the rates of reaction of a number of ethers in glacial acetic acid at 20°C. Hydrogen bromide was added as the aqueous solution saturated at 0°C. Its concentration was equal to that of the ether and was 0.065 g./ml. Table 2 gives the relative rates of reaction. The rate constants are apparently second order.

TABLE 2

Relative rate constants (second order) for the reaction of ethers with hydrogen bromide in glacial acetic acid (282)

Ether	Relative k_2	Ether	Relative k_2
Anisole	9.42	Allyl phenyl	156
Phenetole	3.85	Benzyl phenyl	8,140
Propyl phenyl	2.92	Diphenyl	0.03
Butyl phenyl	2.90	Diethyl	6.42
Isobutyl phenyl	1.85	Dipropyl	32.9
Isoamyl phenyl	2.28	Methyl isopropyl	300
Hexyl phenyl	1.00	Diisopropyl	31.4
Isopropyl phenyl	32.9	Ethyl *tert*-butyl	68,600
sec-Butyl phenyl	21.6	Dibenzyl	1,640
Cyclohexyl phenyl	11.6		

Tronov and Ladigina recognized that the differing tendencies of the various ethers to form oxonium salts might distort any simple interpretation. Hughes and Ingold (128) proposed that the data indicated that the reaction was of the S_N2 type for the primary alkyl ethers and for the primary alkyl phenyl ethers and that it was of the S_N1 type for ethers containing secondary or tertiary groups. The decline in rate with the size of the primary alkyl group in the alkyl phenyl ethers is consistent with this, although the decline is rather small compared to many other S_N2 reactions (104, table II, page 154). However, data later obtained (45) place the mixed methyl secondary ethers in the S_N2 category. Optically active methyl *sec*-butyl ether with hydrogen bromide in glacial acetic acid forms methyl bromide and *sec*-butyl acetate of the same configuration as the ether. In excess hydrogen bromide, *sec*-butyl bromide of inverted configuration is formed with little or no racemization. Thus, with methyl *sec*-butyl ether, at any rate, the cleavage is clearly S_N2 on the methyl. Similar stereochemical studies on optically active *sec*-butyl phenyl ether, *sec*-butyl higher alkyl ethers, and *sec*-butyl isopropyl ether would be desirable.

In glacial acetic acid the reaction of ethyl ether with hydrogen bromide is second order. The rate constants fall as the reaction proceeds in a manner consistent with the assumption that each molecule of ethanol removes one of hydrogen bromide. Water and lithium bromide also somewhat retard the rate (181). Mayo proposed that the reaction involved $(C_2H_5)_2OH^+$ and Br^-, probably with solvent participation.

It may be recalled that in spite of its small dielectric constant, 6.2, glacial acetic acid is commonly considered as a good ionizing solvent. The mean ionic activity coefficients of lithium bromide, sodium bromide, and sodium acetate, however, are below those in water (294) and, in general, salts are known to be but slightly dissociated in glacial acetic acid.

Several papers have treated the rates of reaction of variously substituted anisoles (25, 26, 84, 147, 292). In general, rates of reaction decrease with an increasing σ-value of the group; that is, *p*-methylanisole is fast and *p*-nitroanisole is slow. At least in one case (84) Hammett's $\sigma\rho$ relationship seems to be reasonably well followed, with a value of ρ of about -0.8. In this case hydrochloric acid in acetic acid–water solutions (mole ratio = 2) was employed at 120°C. Under these circumstances phenetoles were reported to react a little faster than anisoles, although Tronov and Ladigina reported the opposite (table 2) with hydrogen bromide. Methyl naphthyl ethers have been reported to react more rapidly with hydrogen bromide than the ethyl analogs (147).

The rate of the reaction declines with increasing water content of the acid (84, 147). Hydrogen bromide reacts more rapidly than hydrogen chloride and less rapidly than hydrogen iodide (84, 147). Hydrogen bromide reacts about six times as rapidly as hydrogen chloride (84) while, under these conditions, hydrogen iodide reacts too fast for measurement. According to one study, the rate of reaction increases in the series butyric acid, propionic acid, acetic acid, formic acid (147). Another author (25), however, reports the reaction to be thirteen times as fast in acetic acid as in formic acid.

In methyl and ethyl naphthyl ethers in glacial acetic acid with excess hydrogen bromide, the β-naphthyl ethers are cleaved more rapidly than the α-naphthyl ethers and those more rapidly than the phenyl ethers. The following substituents decrease the rate in the order given: methyl, bromine, chlorine, and nitro (147).

Substituents which place a positive charge on the ethereal oxygen atom might be expected to exert two opposing effects: they would decrease the rate by decreasing the basicity of the oxygen atom with consequent reduction in concentration of the oxonium salt, but the induced positive charge would tend to make the oxonium salt, once formed, more reactive. In the acidity range of hydrogen halides in acetic acid, the first effect seems to predominate in the case of aryl alkyl ethers.

E. Cleavage by other acids

Dilute aqueous acids cleave ethers slowly (save tertiary ones which react relatively rapidly) in the sense of the following equation:

$$R_2O + H_2O \xrightarrow{H^+} 2ROH$$

Rates of reaction of several ethers have been measured in 0.5 *M* *p*-toluenesulfonic acid (255) and found to be proportional to the concentrations of acid and ether (table 3). The second, third, and fourth compounds from the bottom are given in reference 254 and the last in reference 256.

Sulfuric acid: In spite of its high acidity, sulfuric acid is not of much use in the cleavage of ethers, probably because of the relatively slight nucleophilic displacing tendency of the bisulfate ion. Thus, S_N2 reactions are slow and S_N1 reactions are favored. In strong sulfuric acid, conjunct polymerization results.

Eighty-two per cent sulfuric acid at 25°C. does not attack primary ethers. Secondary ethers can be recovered on immediate dilution, but on standing conjunct polymerization occurs. Such polymerization occurs immediately with tertiary ethers. The occurrence of carbonium-ion reactions in the last two cases is supported by the observation that, with concentrated sulfuric acid, secondary ethers can alkylate benzene but primary ones cannot (141). In mixed ethers con-

TABLE 3

Hydrolysis of ethers in dilute aqueous acids

Ether	*k* at 95°C.	*k* at 25°C.
	l. mole⁻¹ min.⁻¹	
Diallyl	32×10^{-6}	
Ethyl allyl	24×10^{-6}	
Isopropyl allyl	61×10^{-6}	
Diethyl	2.63×10^{-6}	1.46×10^{-11}
Ethyl isopropyl	25.1×10^{-6}	15.0×10^{-11}
Diisopropyl	85.6×10^{-6}	66×10^{-11}
Dioxane		Negligible
Furan		Negligible
Ethylene oxide		0.50
Trimethylene oxide		0.060

taining a methyl (or perhaps any *n*-alkyl group) and a secondary or tertiary group, strong sulfuric acid would probably lead to methyl hydrogen sulfate and the conjunct polymer derived from the other group.

Although primary ethers are not attacked rapidly by concentrated sulfuric acid (see Section II,B) at ordinary temperatures, it is reported that passage of methyl ether into sulfuric acid at 160°C. results in the formation of methyl sulfate (27). The first step in its formation is, perhaps, cleavage of the ether into methanol and methyl hydrogen sulfate.

Certain phenolic ethers are cleaved by sulfuric acid. Thus, 2-bromo-4-nitrophenetole with 80 per cent sulfuric acid at 100°C. gives excellent yields of the phenol (62). Dibutyl- and diamylcatechols are rapidly cleaved by concentrated sulfuric acid at room temperature (129). Two somewhat surprising examples are reported. A tetrahydroxymethoxyanthraquinone when heated in concentrated sulfuric acid for 5 min. at 150°C. gave a 54 per cent yield of the demethylated product (146). Anthragallol dimethyl ether upon heating at 100°C. with concentrated sulfuric acid gives the monomethyl ether. When the temperature is raised to 200°C., anthragallol is formed (30).

On the other hand, anisole can be sulfonated at room temperature and disulfonated at 90°C. with little demethylation (272, page 232).

Hydrolysis of ethyl ether at 272°C. by 10 per cent sulfuric acid has been reported (161). In 4 per cent acid at 180°C. no appreciable hydrolysis of ethyl propyl ether occurs in 15 hr. Ethyl isopropyl ether gives ethanol and propylene under these conditions, presumably by a carbonium-ion elimination reaction (186).

Benzhydryl ether does not react with methanol when heated in it. The addition of a few drops of sulfuric acid results in the formation of methyl benzhydryl ether (13). This resembles the behavior of tertiary ethers with dilute sulfuric acid (204).

The reaction of phenyl β-phenethyl ether with glacial acetic acid containing 70 per cent aqueous sulfuric acid (4:1) in 2 days at reflux is reported to give a 70 per cent yield of β-phenethyl acetate (305). On the other hand, *p*-methoxyphenyldiphenylcarbinol in glacial acetic acid containing dilute aqueous sulfuric acid after refluxing for 12 hr. gave *p*-hydroxyphenyldiphenyl carbinol, not the acetate (10).

The reaction of dilute aqueous acids and of dilute solutions of sulfuric acid in particular probably proceeds by the following mechanism in the case of primary ethers:

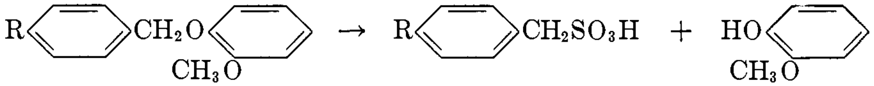
$$H_2O + R_2OH^+ \rightarrow ROH + ROH_2^+$$

The reaction is presumably a bimolecular nucleophilic displacement. It is slow because of the relatively low concentration of dialkylhydronium ions in solutions of dilute acids and because of the relatively low nucleophilic reactivity of water molecules. Tertiary ethers react rather rapidly by a carbonium-ion reaction. The data of table 3 might be taken to indicate the reaction of secondary ethers also by carbonium-ion reactions, although variations in basicity with structure confuse any attempt at analysis. The reaction of ethyl isopropyl ether in an S_N1 reaction diverges from the behavior of methyl *sec*-butyl ether in hydrogen bromide. However, the bromide ion has considerably greater nucleophilic reactivity than the water molecule and the rate of nucleophilic displacement on ethyl is but about one-tenth of that on methyl.

Halosulfonic acids: Fluosulfonic acid reacts with ethyl ether to give ethyl fluosulfonate (190). If chlorosulfonic acid is mixed with ethyl ether, warmed to 55°C., and poured into cold water, ethanol and ethyl chlorosulfonate result (21).

Attempted sulfonation with chlorosulfonic acid leads to the dealkylation of the dibutyl and diamyl ethers of catechol (129).

Sulfurous acid: Certain benzyl ethers are cleaved by sulfurous acid. Thus, where R is nitro or methoxyl, the following reaction proceeds at 135°C. with either aqueous sulfur dioxide or sodium hydrogen sulfite (230). Where R is hydrogen, only sulfur dioxide is effective.



Phosphoric acid: Phosphoric acid cleaves anisole under unstated conditions (222). Diphenyl ether is inert.

Nitric acid: Nitric acid or nitrogen pentoxide reacts with ethyl ether at −15°C. in the sense of the following equations (3):

$$(C_2H_5)_2O + HONO_2 \rightarrow C_2H_5ONO_2 + C_2H_5OH$$
$$(C_2H_5)_2O + N_2O_5 \rightarrow 2C_2H_5ONO_2$$

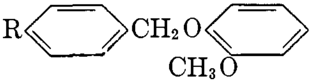
In view of the second reaction it is doubtful whether the first reaction proceeds in the same fashion as other cleavages of ethers by strong acids.

Organic carboxylic acids: These materials are, in general, ineffective. Anisole is not cleaved by formic or acetic acid or even by trichloroacetic acid (222). However, very reactive ethers are cleaved. Thus, methyl benzhydryl ether gives benzhydryl acetate on warming with glacial acetic acid, although benzhydryl ether does not (13).

Cleavage by oxalic acid (293) has not been confirmed (222).

o-Methoxybenzoic acid on heating in water at 200°C. gave phenol (23 per cent), carbon dioxide, methanol, and methyl *o*-methoxybenzoate. Under these same conditions, *o*-hydroxybenzoic acid is decarboxylated to phenol. The corresponding meta and para compounds do not react under these conditions (243). Presumably, the reactivity of the ortho compound results from cyclic hydrogen bonding. *o*-Dimethoxybenzene does not react under these conditions.

Thioglycolic acid: Ethyl ethers of methylphenylcarbinol and of benzhydrol are split by thioglycolic acid plus hydrochloric acid to form the thioether and ethanol (20). Probably the substituted benzyl carbonium ion is an intermediate, but phenyl participation may be involved as in the action of hydrogen chloride on the ethyl ether of methylphenylcarbinol (105). Ethers of the following type do not react with thioglycolic acid at 135°C. (230).



However, substitution of a methyl group on the benzylic carbon atom results in reaction with thioglycolic acid plus hydrogen chloride.

F. Cleavage of cyclic ethers by acids

The first reported cleavage of cylic ethers was that of Bourguignon (35). In brominating tetrahydrofuran he obtained 1,4-dibromobutane formed by the action of hydrogen bromide which resulted from the substitution reaction.

If hydrogen chloride is passed through tetrahydrofuran kept at reflux, a 56 per cent yield of 4-chloro-1-butanol results (265).

If tetrahydrofuran and concentrated hydrochloric acid are exposed to a temperature of 180°C. under pressure in a flow reactor a quantitative yield of tetramethylene chloride may be obtained by recycle. With tetrahydropyran, the corresponding reaction is much more difficult (51).

Treatment of tetrahydrofuran with hydrogen chloride in benzene plus acetic acid results in the formation of the dichlorobutane and of 4-chlorobutyl acetate (102).

The usual order of reactivity of the hydrogen halides is observed; hydrogen iodide is more reactive than hydrogen bromide and hydrogen bromide more reactive than hydrogen chloride (75). Unlike the results with the use of hydrogen chloride, continuous bubbling of hydrogen bromide or of hydrogen iodide through hot tetrahydrofuran gives the 1,4-dihalides in 60–75 per cent yields (75).

With 2,5-dimethyltetrahydrofuran, there is no reaction with hydrogen chloride. Even if zinc chloride is also added, only 8 per cent of the dichloride results in 8 hr. (75). Since addition of these methyl groups would favor a carbonium-ion reaction, cleavage of tetrahydrofuran and tetrahydropyran apparently proceeds by a nucleophilic bimolecular displacement on the conjugate acid of the cyclic ether, as in the cleavage of simple ethers by hydrogen halides.

G. Cleavage by amine salts

Amine salts are weak acids by virtue of the proton attached to the ammonium nitrogen atom. Audrieth and Long have discussed the acidity of pyridine hydrochloride, particularly with reference to inorganic chemistry (4). It is not unexpected that amine hydrohalides should effect ether cleavage under rather drastic conditions.

The reaction was discovered by Klemenc in 1916 (144), who found that aniline hydrochloride in an open flask at 190°C. rapidly cleaves pyrogallol trimethyl ether although it will not react with anisole. Some of the methyl groups come off as methyl chloride, while the rest methylate the nitrogen atoms of the aniline.

The passage of dry hydrogen chloride through the reaction mixture facilitates the reaction (312). The quantity of aniline hydrochloride may be reduced from a mole ratio to ether of 3 down to 0.1. Thus, *o*-methoxyphenol gave a 94 per cent yield of *o*-dihydroxybenzene. Anisole is cleaved, though slowly.

The hydrochlorides of mono-, di-, and trimethylamines and of ethanolamine with an added stream of hydrogen chloride gas may be employed in the temperature range of 180–200°C. (279). Pyridine hydrohalides are probably the materials of choice (219, 220, 221, 222), although it has been reported that, in the cleavage of methyl β-naphthyl ether, quinoline hydroiodide is better than the pyridine analog. Surprisingly, aniline hydroiodide is reported to be ineffective even at 250–270°C. Diphenylamine is a satisfactory amine, although dimethylaniline is not (5).

Heating anisole with pyridine hydrochloride (which when alone melts at 144°C. and "boils" at 218°C.) in a mole ratio of 1:3 for 5–6 hr. at 200°C. results in complete demethylation (219). Phenetole, *o*-methoxyphenol, *o*-dimethoxybenzene, ethyl β-naphthyl ether, and anisaldehyde are similarly cleaved. Pyridine hydrobromide is also effective. Phenyl ether is inert to these reagents.

Passage of dry hydrogen chloride facilitates the reaction in this case also. Under these circumstances only a small per cent of pyridine hydrochloride need be used for most of the ethers mentioned above. With *o*-methoxyphenol and only 1 per cent of pyridine hydrochloride, demethylation is complete in 52 hr. at 200°C. Anisole, however, is not attacked. With 20 per cent pyridine hydrochloride under these conditions, ethyl β-naphthyl ether, *o*-dimethoxybenzene, and *o*-methoxyphenol are rapidly cleaved, while anisole is slowly cleaved (220). Dry hydrogen chloride does not cleave these ethers under these conditions (220).

The reaction products when pyridine hydrochloride alone is employed are the phenol, *N*-methylpyridinium chloride, and methyl chloride. At 220°C. methyl chloride reacts with pyridine hydrochloride to give almost quantitative yields of *N*-methylpyridinium chloride, while treatment of the quaternary salt in pyridine hydrochloride with a stream of dry hydrogen chloride regenerates pyridine and methyl chloride in the course of a few hours. From the slowness of this reaction it appears that methyl chloride is formed directly in the case of the more reactive ethers. With anisole, however, the reaction appears to proceed through *N*-methylpyridinium chloride as an intermediate, followed by reaction of this compound with hydrogen chloride (220) to regenerate pyridine hydrochloride and form methyl chloride.

The conversion of pyridine hydrochloride to *N*-methylpyridinium chloride may be used for the analytical determination of methoxyl groups to an accuracy of 1 per cent (221). Ethyl groups may be similarly determined, but their reaction is slower.

Owing to the faster reaction of methyl groups, it seems probable that the reaction is a bimolecular nucleophilic displacement by halide ion on the conjugate acid of the ether. In the case of anisole, however, the displacement may be by the nitrogen atom of pyridine. Why the displacing species should change is obscure, although one may note that there is more free pyridine present in the anisole reaction owing to the temperature being about 20°C. higher.

The pyridine salt of sulfuric acid cleaves most phenolic ethers, although not phenyl ether. Sulfonation accompanies cleavage (222). The salt with nitric acid does not cleave phenolic ethers but nitrates the ring instead.

The pyridine salts of oxalic acid, formic acid, acetic acid, and trichloroacetic acid at 220°C. will not split phenolic ethers (222).

IV. CLEAVAGE BY ORGANIC ACID HALIDES OR ANHYDRIDES

This section covers the cleavage of ethers by acyl and aroyl halides (including sulfonyl halides) and by anhydrides of carboxylic acids in the presence of Lewis acids (particularly those of the type of stannic chloride) or of strong proton acids. In special cases, a catalyst need not be added. The stoichiometry of the reaction is typified by the following equations:

$$R'COCl + R_2O \rightarrow R'COOR + RCl$$
$$(R'CO)_2O + R_2O \rightarrow 2R'COOR$$

A. Descriptive

In the absence of catalysts, acid fluorides do not react with ethers at 200°C. (259) nor do acid chlorides at 220°C. (222). Acetic anhydride is unreactive at 100°C. (204) and probably at much higher temperatures.

The quantity of Lewis acid required will be discussed later but at least in some cases, for example, stannic chloride, the quantity can be very small (45). With zinc chloride, the still-pot residue can be reused as the catalyst several times (284).

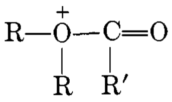
The apparent mechanism of these reactions will be discussed later, but for presentation of the descriptive material, some essential aspects of this mechanism must be presented here.

An ion, RCO^+, derived from acid halides or acid anhydrides, plays much the role that the proton plays in the cleavage of ethers by strong proton acids. The following equation exemplifies the formation of this ion.

$$2RCOCl + SnCl_4 \rightarrow 2RCO^+ + SnCl_6^{--}$$

Acid anhydrides react similarly, giving RCO^+ ions and complexed $RCOO^-$ ions. Strong proton acids, such as sulfuric or perchloric acid, are effective in some cases, apparently by tying up the anion as an undissociated acid.

The Lewis acid, RCO^+, is presumed to add to ethers to form



$$R-\underset{\displaystyle R}{\overset{+}{O}}-\underset{\displaystyle R'}{C}=O$$

which, like R_2OH^+, may react either by giving off one of the R's as a carbonium ion or by undergoing nucleophilic displacement on one of the radicals, R. In either case, an ester and an alkyl halide (or another ester when acid anhydrides are used) result. The occurrence of carbonium-ion reactions is more common than in cleavage by strong acids, very probably owing to the absence from the reaction mixtures of species possessing even fair tendency towards nucleophilic displacement.

Early history: The first reaction of this type was reported by Descudé in 1901 (61). Equimolar mixtures of acetyl chloride and ethyl ether became warm spontaneously at room temperatures in the presence of rather substantial amounts of zinc chloride. An almost quantitative yield of ethyl chloride and ethyl acetate resulted.

$$(C_2H_5)_2O + CH_3COCl \rightarrow CH_3COOC_2H_5 + C_2H_5Cl$$

Methyl amyl ether led to both chlorides and both acetates (61).

Benzoyl chloride and ethyl ether undergo a similar reaction in the presence of rather large amounts of ferric chloride, as reported by Wedekind and Haeussermann in 1901 (296). Reaction of acid anhydrides was first observed by Knoevenagel in 1914 (145) in the reaction of ethyl ether with acetic anhydride as promoted by ferric chloride.

Reactions of alkyl aryl ethers: Cleavage by acyl or aroyl halides or acid anhydrides is generally applicable to alkyl ethers only. Aryl ethers usually give nuclear alkylation to alkoxyaryl ketones (185, 285). For example, acetyl chloride with phenetole and aluminum chloride gives excellent yields of *p*-acetylphenetole; propionyl chloride behaves similarly with anisole. The α- and β-naphthyl methyl ethers and resorcinol diethyl ether behave similarly (80). A similar reaction in the presence of zinc chloride has been reported for acyl halides (285) and for acetic anhydride (43).

It is, perhaps, not surprising that ions of the type of RCO^+ should react preferentially with a benzene ring activated by an alkoxyl group. However, the boron trifluoride–ethyl ether complex and acetyl fluoride in the presence of benzene give ethyl acetate rather than acetophenone, although benzoyl fluoride reacts with aromatic hydrocarbons in the presence of boron trifluoride to give ketones (260). In this case at least, the RCO^+ ion adds preferentially to ether. Of course, benzene is much less basic than alkoxybenzenes.

On the other hand, propyl benzyl ether in acetic anhydride in the presence of benzene and boron trifluoride forms benzylbenzene (196).

The reaction of phenyl benzyl ether (42) with CH_3CO^+ is discussed in the subsection headed *Absence of catalyst* (see page 640).

Sufficiently deactivated benzene rings cannot compete for the RCO^+ ion. Thus benzoyl chloride can be used as a cleavage reagent without being self-benzoylated.

The Lewis acid: In their report of an extensive investigation of reactions of the type described in this section, Meerwein and Maier-Hüser (185) give the yields obtained for a number of Lewis acid halides under the following conditions: 4 moles of ethyl ether; 1 mole of benzoyl chloride; 1 mole of halide; 3 hr. at reflux. The yields were as follows: with zinc chloride and stannic chloride, nearly quantitative; with zirconium chloride, titanium chloride, and antimony pentachloride, about 83 per cent; with ferric chloride and aluminum chloride, about 50 per cent; with antimony trichloride, 17 per cent; with boron trifluoride, cupric chloride, and stannous chloride, traces; with silicon tetrachloride, phosphorus pentachloride, boron trichloride, arsenic trichloride, and magnesium chloride, none. Similar results were obtained with acetyl chloride. With acetic anhydride and similar mole ratios of reactants, the same general order of effectiveness was observed, save that zinc chloride was much less effective and yields were less, ranging downward from 37 per cent. However, this is not the way to run reactions with acid anhydrides, since under the conditions used (1 mole of anhydride per mole of halide) extensive anion interchange occurs and considerable amounts of alkyl halides are formed.

In general, it would appear that stannic chloride or zinc chloride is the reagent of choice. However, there seems to have been no real attempt to determine the conditions which would give the optimum yields for these ether cleavage reactions.

With about 0.25 mole of zinc chloride per mole of acetyl chloride, acetate yields were 30, 68, and 48 per cent from isopropyl, butyl, and isoamyl ethers (285), while with 0.1 mole of zinc chloride the yield was 77 per cent from ethyl ether (284). With methyl cyclohexyl ether, benzoyl chloride, and zinc chloride, a 91 per cent yield resulted (127).

With 0.1 mole of stannic chloride per mole of benzoyl chloride, ethyl ether in 4 hr. at 110°C. gave an 80 per cent yield of ethyl chloride and a 90 per cent yield of ethyl benzoate. With stannic bromide and benzoyl bromide in 3 hr. at 100°C., the corresponding yields were 60 and 77 per cent (259). With acetyl chloride or acetyl bromide and 0.001 mole of stannic chloride acting on *sec*-butyl methyl ether for 1 day at 0°C., the yields of *sec*-butyl halide were about 75 per cent (45). With 0.01 mole of sulfuric acid and acetyl chloride for 3 days at 25°C., the yield of *sec*-butyl chloride was 57 per cent. Similar reaction with acetic anhydride and 0.01 mole of stannic chloride for 3 days at 25°C. resulted in 40 per cent yields of *sec*-butyl acetate.

Additional references to certain catalysts follow: zinc chloride (204), ferric chloride (145, 296), boron trifluoride (196, 259), sulfuric and perchloric acids with the latter reported more effective (42), and magnesium chloride (relatively ineffective) (301).

Hydrogen chloride and acetic acid led to no reaction under conditions in which traces of stannic chloride led to rapid reaction (45).

Very weak catalytic activity of pyridine has been reported (222).

The behavior of boron trifluoride is rather special. With excess ethyl ether and benzoyl chloride it does not lead to reaction (185). This, presumably, is consequent to the strong bonding between the trifluoride and the ether, which in the case of many ethers can even survive distillation. (A leading reference to the stability of ether–boron trifluoride complexes is reference 46.) In equimolar mixtures, boron trifluoride is effective, although rather drastic conditions (7 hr. at 140°C.) are required and some ethyl fluoride is formed as well as ethyl chloride. Reaction of acetyl chloride under similar conditions is more rapid than with benzoyl chloride (259). Boron trifluoride has a rather weak tendency to abstract chloride or bromide ions from alkyl or acyl halides in alkylation or acylation reactions but great activity in removing fluoride ions (44, 260). Similarly, boron trifluoride is a much more effective reagent in the cleavage of ethers with benzoyl or acetyl fluoride than with the corresponding bromides or chlorides. Yields of 80–90 per cent may be obtained with the acid fluorides (259).

If the organic acid halide and the Lewis acid halide contain different halogen atoms, anion exchange will occur and alkyl halides of both halogens will result: for example, in the action of benzoyl bromide and stannic chloride or of benzoyl chloride and stannic bromide (259). Boron trifluoride exhibits less tendency toward such exchange than stannic chloride. This exchange occasions a problem in dealing with acid anhydrides which can be overcome by the following means: (*a*) employing very little stannic chloride (45); (*b*) employing sulfuric acid (45); (*c*) employing boron trifluoride, which exhibits little anion exchange with acid anhydrides (185). Probably stannic acetate would work with acetic anhydride, but a test of this has not been reported.

Quantity of Lewis acid: Most authors report the use of moderately large quantities of MX_n, in the range of 0.1 to 1 mole per mole of ether or acid chloride or anhydride. There is little data on variation of rate and yield with amount of MX_n. Descudé (61) originally reported that large amounts of zinc chloride were necessary, but this must be wrong since zinc chloride and stannic chloride are effective at a ratio of 0.1 mole per mole (185, 259, 284). Meerwein reported some data on the amount of catalyst required (185). Acetic anhydride was reported to require 1 mole per mole of stannic chloride, although with acetyl chloride 0.1 mole sufficed. These results were for ethyl ether. Meerwein considered that the determining factor was whether the resulting ester formed a complex with the Lewis acid.

The present author suspects that in many cases much more Lewis acid was used than required and that the temperatures of many reactions were needlessly high.

At least with methyl *sec*-butyl ether and acetyl chloride the reaction is rapid at room temperatures with but 0.001 mole of stannic chloride per mole of ether and reasonably rapid at the same temperature with 0.01 mole of stannic chloride with acetic anhydride. A similar quantity of sulfuric acid is also effective (45). When ethyl ether is dropped into benzoyl chloride (a relatively unreactive acid chloride) containing a mole proportion of zinc chloride of 0.004 at 150°C., excellent yields are obtained (152).

Absence of catalyst: Acetyl bromide reacts with ethers at 200°C. in the absence of a catalyst (167, 168, 169, 170, 171, 259).

Methyl *sec*-butyl ether reacted with at least one batch of commercial acetyl bromide without added catalyst, although stannic chloride considerably increased the rate. Distillation of the acetyl bromide reduced the rate. Presumably, some adventitious acidic catalyst was present (45).

Benzoyl iodide reacts without added catalyst only at 100°C. (99, 142). Benzoyl iodide has been reported to react with ethyl ether at room temperatures, but the reaction may have been promoted by mercurous iodide (266).

Acetyl iodide reacts with many alkyl ethers in several days at room temperatures to give yields in the vicinity of 50–75 per cent (99). Chloroacetyl iodide cleaves, though more slowly than acetyl iodide. Trichloroacetyl iodide does not cleave under these conditions. Here, and in other cases, an inverse correlation seems to exist between the acid strength of the acid parent to the acyl halide, RCOOH, and the effectiveness of cleavage. Ease of removal of a proton and of a halide ion might well be inversely correlated.

Free molecular iodine was always present in work with acyl iodides. Iodine possesses acidic characteristics as in the following reaction,

$$I_2 + I^- \rightarrow I_3^-$$

and may function as a catalyst. Molecular iodine does not catalyze cleavage by acetyl chloride at 25°C. (99) but this does not eliminate it as a possible catalyst for acyl or aroyl iodides because the affinity of molecular iodine for the chloride ion is much less than for the iodide ion.

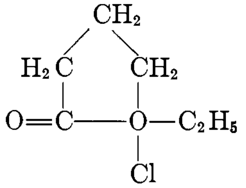
The addition compounds of ethyl ether and magnesium iodide (28, 29) and of zinc iodide react with benzoyl chloride at 100°C. to give ethyl iodide and ethyl benzoate, the latter addition compound the more readily. It was held that the reaction proceeded directly, but since benzoyl chloride and potassium iodide react like benzoyl iodide though more slowly (142), the reactions with the ether complexes probably proceeded through benzoyl iodide as an intermediate.

In the absence of added catalyst, benzoyl chloride and *p*-nitrobenzoyl chloride react with *o*-dimethoxybenzene to form *o*-methoxyphenyl benzoates at 220°C. (222). There is no reaction with anisole.

The following proceed as first-order reactions without added catalyst (218a):

$$C_2H_5O(CH_2)_3COCl \rightarrow Cl(CH_2)_3COOC_2H_5$$
$$C_2H_5O(CH_2)_4COCl \rightarrow Cl(CH_2)_4COOC_2H_5$$

The first reaction proceeds quantitatively at 100°C.; the second requires 150°C. At 150°C. $C_2H_5O(CH_2)_5COCl$ decomposes very slowly to water-insoluble resins. The first two reactions are apparently intramolecular. The following intermediate was suggested:

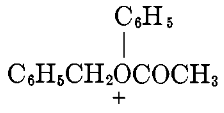


This is the cyclic equivalent of the intermediate of step 2. However, the reaction may be more complicated, since its velocity is influenced by the walls, and the addition of 1 per cent sulfuric acid increases the rate fivefold.

At the opposite extreme are reactions in which the formation of RCO^+ involves stoichiometric consumption of the promoter. The addition of silver perchlorate and acetyl chloride in equimolar ratio to phenyl benzyl ether in nitromethane at 0°C. results in ether cleavage. The phenyl fragment appears as phenyl acetate and acetophenyl acetate. The benzyl fragment appears as benzylphenyl acetate or as polymerized material (42). Under these conditions, acetyl chloride and silver perchlorate react (246, 247) as follows,

$$CH_3COCl + AgClO_4 \rightarrow CH_3CO^+ClO_4^- + AgCl$$

so that acetyl perchlorate is the actual reactant. If benzene is added to the reaction mixture, some diphenylmethane is formed. This is considered to support the idea that the benzyl carbonium ion results from decomposition of



$$C_6H_5CH_2\overset{C_6H_5}{\underset{+}{O}}COCH_3$$

The clearly catalytic reaction involving the ether, acetic anhydride, and perchloric or sulfuric acid leads to similar products save that with excess acetic anhydride, some benzyl acetate also appears.

$CH_3CO^+BF_4^-$ apparently cleaves ethyl ether (246).

The acid halide or anhydride: Reactions of acid halides with ethers have recently been covered in a review on acid halides, but largely from a preparative point of view (262).

Acetyl bromide, acetyl iodide, benzoyl iodide, and chloroacetyl iodide were discussed in connection with their uncatalyzed reactions in the preceding section.

The bulk of the work reported in the literature concerns acetyl chloride, benzoyl chloride, and acetic anhydride. A number of examples of their use have been given.

Acetyl and benzoyl fluorides have been little studied but they seem relatively reactive in the presence of boron trifluoride (246, 259).

3,5-Dinitrobenzoyl chloride and zinc chloride cleave ethyl ether (285). Picryl chloride does not work with zinc chloride, ferric chloride, or aluminum chloride (185).

Oxalyl chloride and ethyl ether give very small yields with zinc chloride under conditions where benzoyl chloride gives 60 per cent yields (285). Under the same conditions, chloroacetyl chloride gives 35 per cent yields and phenylacetyl chloride, 79 per cent.

Succinic anhydride requires a temperature of 150–200°C. under conditions at which acetic anhydride reacts at 100°C. Phthalic acid gives very slight yields at 200°C. (285). However, at 110°C. with small amounts of zinc chloride, phthalyl chloride reacts with ethyl ether to give 2 moles of ethyl chloride and phthalic anhydride (152). With this technique but at 150°C., lauroyl chloride reacts more slowly than benzoyl chloride.

TABLE 4

Cleavage of ethers by acid halides and anhydrides

Ether	References	Ether	References
Isopropyl	(152, 284, 285)	Methyl cyclohexyl	(127)
Butyl	(284, 285)	Ethyl butyl	(204)
Isoamyl	(112, 284, 285)	Ethyl isobutyl	(204)
Methyl *sec*-butyl	(45)	Ethyl *sec*-butyl	(204)
Methyl amyl	(61)	Ethyl *tert*-butyl	(204)
Methyl isoamyl	(28, 29)	Ethyl isoamyl	(142)
2-Methoxy-3-methylbutane	(99)	Propyl benzyl	(196)
Methyl 2-hexyl	(268)	Phenyl benzyl	(42)

The use of carboxylic acids rather than of their anhydrides has been investigated. Acetic acid with zinc chloride is poor, although if it is saturated with hydrogen bromide much better results are obtained (285). Ethyl ether, acetic acid, and boron trifluoride react, but a temperature of 200°C. is necessary to get 20–50 per cent yields of ethyl acetate (112). Since the addition compound of boron trifluoride is a strong acid, both of these sets of reactions may well involve an acid type of cleavage followed by esterification.

The ether: A number of ethers have been cleaved by the methods described in this section. Typical examples of such ethers are given in table 4, with the omission of ethyl ether, which has been sufficiently dealt with, and cyclic ethers, which will be considered later.

B. Mechanism

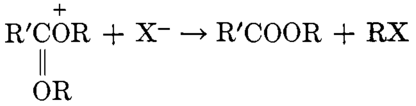
It is proposed that ether cleavage reactions of the type discussed in this section can be accommodated by the following mechanism:

$$2R'COCl + ZnCl_2 \rightarrow 2R'CO^+ + ZnCl_4^{--} \qquad (1)$$

$$R'CO^+ + R_2O \rightarrow R_2\overset{+}{O}COR' \qquad (2)$$

$$R_2\overset{+}{O}COR' \rightarrow ROOCR' + R^+ \qquad (3)$$

$$R^+ + (Cl^-) \rightarrow RCl \qquad (4)$$



$$R'\underset{\underset{OR}{\|}}{\overset{+}{C}}OR + X^- \rightarrow R'COOR + RX \qquad (3')$$

The reactant mixtures in these reactions usually do not contain any appreciable concentration of good nucleophilic displacing species. As will be seen, step 3 occurs when the ether contains a tertiary group and usually when it contains a secondary one. Step 3′ usually appears only with ethers containing only primary alkyl groups.

The exact nature of the anion on the right side of equation 1 cannot be closely specified. For example, $R_2OZnCl_3^-$ might be involved. The source of the chloride ion required in step 4 cannot be closely specified. It might involve either $ZnCl_4^{--}$ or the acid halide.

With a proton acid, step 1 is apparently

$$R'COCl + H_2SO_4 \rightarrow RCO^+ + HSO_4^- + HCl \qquad (1')$$

With an acid anhydride,

$$2(R'CO)_2O + ZnCl_2 \rightarrow 2R'CO^+ + (RCOO)_2ZnCl_2^{--} \qquad (1'')$$

$$(R'CO)_2O + H_2SO_4 \rightarrow R'CO^+ + HOOCR' + HSO_4^- \qquad (1''')$$

$$R^+ + (R'COO^-) \rightarrow R'COOR \qquad (4')$$

Mechanisms involving most of these features have recently been proposed (42, 45). They are new in their use of the RCO^+ ion, but the view that an oxonium salt is an intermediate is old (99, 184, 268).

The ion RCO^+ must be assumed to be a fairly stable intermediate. There is considerable evidence for its existence as a stable species in media in which only very weak Lewis bases are present. The existence, reactions of, and conductivity in liquid sulfur dioxide of acetyl perchlorate, $CH_3CO^+ClO_4^-$, provide rather strong evidence for this (246, 247). Solutions of aluminum chloride in phosgene exhibit similar behavior and ions of this nature were first proposed in connection with this system (81), which is rather close to that of halides such as stannic chloride in acyl chloride–ether mixtures.

The ionization of acetic anhydride in the following sense has been proposed (178):

$$(CH_3CO)_2O \rightleftarrows CH_3CO^+ + CH_3COO^-$$

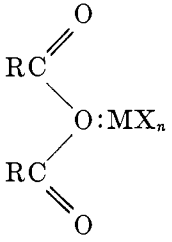
The ionization is very slow and the equilibrium lies far to the left. The degree of ionization is increased by species which combine with the acetate ion. Similar views have been advanced in connection with the behavior of acetyl halides and acetyl benzenesulfonate in acetic anhydride, in which they function as acids (138).

From the cryoscopy in solvent sulfuric acid, the following reaction has been proposed for acetic and benzoic anhydrides (86):

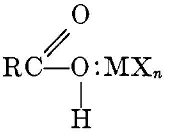
$$(RCO)_2O + 2H_2SO_4 \rightarrow RCO^+ + RCO_2H_2^+ + 2HSO_4^-$$

Acetylsulfuric acid, CH_3COOSO_3H, is very largely dissociated in solvent sulfuric acid. However, it is but slightly dissociated in liquid sulfur dioxide (247).

In regard to step 1″, it may be noted that



can be considered as the anhydride of RCOOH and of the strong acid



$$RC(=O)\text{—}\underset{\substack{|\\H}}{O}:MX_n$$

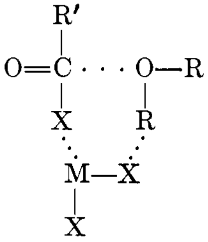
resembling, then, acetylsulfuric acid.

One may question why it is assumed that metallic halides form complexes with and activate acyl halides when such metallic halides are known to form strong complexes with ethers. Complexes with acyl halides are known—for example, $CH_3COCl \cdot AlCl_3$, $CH_3COCl \cdot SbCl_5$, and $CH_3COCl \cdot BF_3$—but these are, in general, rather easily decomposed. Thus, the last compound melts at −70°C. and is completely decomposed by 25°C. (185).

However, complexes between Lewis acid halides and ethers do not usually lead to reaction at moderate temperatures since these complexes are relatively stable, as, for example, the ether–boron trifluoride complexes (46). Ethers can be refluxed with zinc chloride (0.5 mole of chloride per mole of ether) with but slow decomposition (284). The reaction of ethers with such halides is discussed in a separate section of this review.

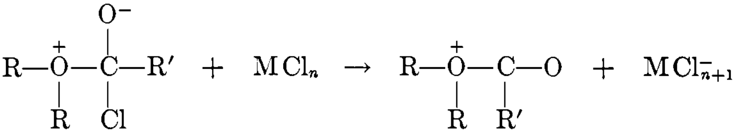
Furthermore, apparently those Lewis acids which form very strong complexes with ethers are not very effective catalysts. Boron trifluoride in a mole ratio to ether of less than one is of this type (185). Aluminum chloride has been little used for this reaction and is apparently not a very effective catalyst (185), although not much evidence exists on this point.

Cleavage of ethers by acyl halides and metallic halides has recently been interpreted in terms of the following intermediate or transition state (195, 259):



In a sense, this telescopes steps 1, 2, and 3 into one concerted step. While its occurrence cannot be excluded in certain cases, it lacks the generality of the mechanism treated above, since the concerted mechanism cannot explain the following facts: the identical behavior of Lewis acids and of proton acids; the cleavage of ethers by acid anhydrides and boron trifluoride; the cleavage of ethers by acetyl perchlorate; the acylation which ordinarily accompanies or predominates in the attempted cleavage of aryl alkyl ethers.

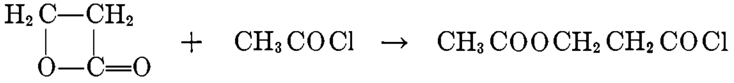
It has been reported that there is a large heat of mixing of ether and acid halide even in cases where ether cleavage does not follow (99) and that, therefore, the catalyst serves to decompose the oxonium salt rather than to form it. In modern structures, the initial complex and its reaction might be written:



$$R-\underset{R}{\overset{+}{O}}-\underset{Cl}{\overset{O^-}{C}}-R' + MCl_n \rightarrow R-\underset{R}{\overset{+}{O}}-\underset{R'}{C}-O + MCl_{n+1}^-$$

The mechanism suffers from the same lack of generality as the one of the previous paragraph to which it is, in fact, closely related.

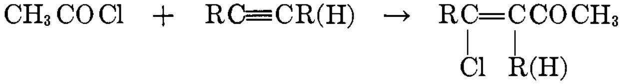
A large number of other types of reactions may be interpreted as involving ions of the type RCO^+. In many, complexes of the nature given above are impossible. Some examples follow.



as catalyzed by sulfuric acid (96).

Acetic anhydride does not react with an aldehyde to form the aldehyde diacetate unless a drop of sulfuric acid (297) or a little boron trifluoride (179) is added.

Stannic chloride serves as a catalyst in the following reaction (150):



$$CH_3COCl + RC\equiv CR(H) \rightarrow \underset{Cl}{RC}{=}\underset{R(H)}{C}COCH_3$$

The addition of ketene to acetaldehyde to give the enol acetate occurs at about 50°C. in the presence of sulfuric acid (103). It may be noted that a proton could add to ketene to form CH_3CO^+. Thus, in a sense, that ion is a conjugate acid of ketene.

C. Cleavage of mixed ethers

The available data on the cleavage of mixed ethers throw light on the problem of whether given types of cleavage involve step 3 or step 3′ of the mechanism.

With acetyl chloride and zinc chloride, butyl ethyl ether gives 34 per cent butyl chloride and 58 per cent butyl acetate at 25°C., while at 60°C. butyl acetate is mainly formed (204). Thus, the ethyl–oxygen bond in the ether is the one preferentially cleaved. With ethyl isobutyl ether at 25°C., one gets mainly isobutyl acetate and ethyl chloride.

These data would indicate that an alkyl group is being removed by a bimolecular nucleophilic displacement in the case of diprimary ethers.

In uncatalyzed cleavage by acetyl bromide at 210°C., ethyl isoamyl ether is cleaved to the extent of 67 per cent between the ethyl group and the oxygen atom and to the extent of 33 per cent between the oxygen atom and the isoamyl group. With ethyl hexyl ether, the corresponding figures are 62 per cent and 38 per cent, and with the ethyl ether of ethyl glycolate, 78 per cent and 22 per cent. In competitive cleavage in mixtures of 1 mole of ether A, 1 mole of ether B, and 1 mole of acetyl bromide, if ethyl ether is ascribed a reactivity of 1.00, that of isoamyl ether is 0.456 and of benzyl ether 9.75. These results are also consistent with an S_N2 reaction and not with an S_N1 one. Lydén (167, 168, 169, 170, 171) ran a large number of similar competitive experiments where one or both ethers were mixed ethers. The results are difficult to interpret. For example, the reactivity of ethyl ether is equal to that of phenetole. The ratio of reactivities of ethyl benzyl ether and of ethyl ether is 1.52. The replacement of ethyl ether by what should be its equivalent, phenetole, gives a ratio of 3.58. Lydén considered that he was measuring some kind of oxygen–carbon bond strength, but other factors clearly enter.

There is doubt that these results should be compared with those in the catalyzed reactions at much lower temperatures. It may be noted that phenyl ethers apparently underwent cleavage without nuclear acylation in Lydén's work.

Rather more data are available where the two groups in the ether are not both primary. Ethyl *sec*-butyl ether and ethyl *tert*-butyl ether with acetyl chloride and zinc chloride at 25°C. (204) give ethyl acetate and *sec*-butyl chloride or *tert*-butyl chloride exclusively. Methyl *sec*-butyl ether gives the *sec*-butyl halide exclusively in cleavage by acetyl chloride and traces of either sulfuric acid or stannic chloride and also in cleavage by acetyl bromide (45).

In cleavage of methyl cyclohexyl ether by zinc chloride and benzoyl chloride with an overall yield of 91 per cent, 92 per cent of the cleavage led to cyclohexyl chloride and methyl benzoate and 8 per cent to methyl chloride and cyclohexyl benzoate (127).

Benzyl groups are cleaved preferentially from propyl benzyl ether (196) and from phenyl benzyl ether (42); if benzene is added they will alkylate it to diphenylmethane.

These results indicate that secondary and tertiary groups are split preferentially to primary ones and, therefore, presumably by a carbonium-ion process (step 3). This is not unreasonable in terms of the mechanism, since species to act as nucleophilic displacing agents in step 3′ are weak or in very low concentration in these reaction mixtures.

One may question whether the rate of formation of $R_2\overset{+}{O}COCH_3$ is rate-determining (steps 1 and 2) or whether its rate of reaction is rate-determining (steps 3 and 3′). There is a lack of rate data, particularly comparative rates of reaction of different types of ethers, which might help to elucidate this problem.

Ethyl *tert*-butyl ether reacts very much faster than the other ethyl butyl ethers with acetyl chloride and zinc chloride (204). It would appear that step 3 occurs much more rapidly here than in the other cases. Acetic anhydride and zinc chloride cleave ethyl *sec*-butyl ether about three times as fast as ethyl butyl ether (204). About the same sort of ratio of reactivities seems to obtain in cleavage by acetyl iodide (99) in comparing diprimary with disecondary alkyl ethers.

Probably, then, in most cases the rate of the cleavage reaction is determined by the concentration of the oxonium salt and by its specific rate of reaction.

Olefin formation accompanying cleavage: Most of the work on ether cleavage of the type covered in this section has involved ethyl ether, for which olefin formation would not be expected. Olefin formation is uncommon in the cleavage of primary alkyl ethers. The only reported case involves the cleavage of butyl ether with zinc chloride and acetyl chloride, in which case 10 per cent of butylene appeared (284). However, with the same reagents under less drastic conditions (25°C.) no butylene was observed with any of the ethyl butyl ethers (204). At 80°C., however, some isobutylene appeared in the cleavage of ethyl isobutyl ether.

At 25°C. cleavage of methyl *sec*-butyl ether with acetyl chloride and stannic chloride resulted in the formation of a little butylene; no quantitative data were given (45).

In the cleavage of methyl cyclohexyl ether by benzoyl chloride and zinc chloride, negligible quantities of cyclohexene were formed (127).

In the cleavage of 2-methoxy-3-methylbutane by acetyl iodide no alkyl iodide was isolated from the heavier radical but only olefin (99).

D. Isomerization accompanying cleavage

Where the oxonium salt reacts by a carbonium-ion process, one would expect isomerization of the fragment separating as the ion to occur in suitable cases. The absence of reported isomerization in the cleavage of normal alkyl ethers supports the assignment of this type to step 3′ (S_N2). Ethyl isobutyl ether with acetyl chloride and zinc chloride gives chiefly isobutyl acetate and ethyl chloride at 25°C., but at 80°C. *tert*-butyl chloride and isobutylene are formed (204). There is, thus, a change from an S_N2 to an S_N1 mechanism.

More data bearing on isomerization would be desirable, particularly with secondary ethers. It appears probable that isomerization of the following type accompanies all reactions properly described as typical carbonium-ion reactions (47, 50, 214, 215).

$$\text{C—C—}\overset{+}{\text{C}}\text{—C—C} \rightleftharpoons \text{C—C—C—}\overset{+}{\text{C}}\text{—C}$$

It would be of interest to examine the products of the cleavage of 3-methoxypentane for such isomerization.

E. Stereochemistry

Methyl *sec*-butyl ether is cleaved by acetyl chloride and small amounts of either stannic chloride or sulfuric acid to give methyl acetate and *sec*-butyl chloride almost exclusively. If an optically active ether is used, the *sec*-butyl chloride is of inverted configuration and of an optical purity one-half that of the ether (45). Similar results are obtained with acetyl bromide. With acetic anhydride and stannic chloride, the *sec*-butyl acetate is of inverted configuration and of but 19 per cent optical purity.

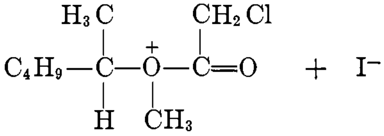
In general, this stereochemistry is similar to that of solvolytic reactions assigned to the carbonium-ion type, although the racemization in the case of the halides is a little less than often observed. It is clear that the carbonium ion cannot be "free" for any substantial period of time. One may assume either a "shielded" carbonium ion (104, page 172) or some sort of concerted process. These two assumptions are closely related (104, page 172).

In addition, the following isomerization may be involved, in part, in the loss of optical purity:

$$\text{C—}\overset{+}{\text{C}}\text{—C—C} \rightleftharpoons \text{C—C—}\overset{+}{\text{C}}\text{—C}$$

Investigation of the cleavage of 3-methoxypentane as mentioned in the preceding subsection would clarify this problem.

The cleavage of optically active 2-methoxyhexane by chloroacetyl iodide without added catalyst has also been investigated (268). After a reaction period of 17 days at room temperatures, 2-iodohexane in 29 per cent yield and 2-hexyl chloroacetate in 52 per cent yield were obtained. The latter compound was of the original configuration; the former was of inverted configuration and about one-half racemized. It was proposed that the oxonium salt reacted with iodine in two ways:



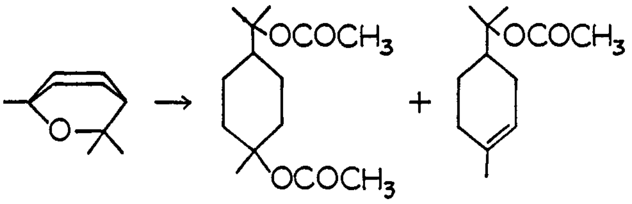
$$\mathrm{C_4H_9}-\underset{\mathrm{H}}{\overset{\mathrm{H_3C}}{\mathrm{C}}}-\underset{\mathrm{CH_3}}{\overset{+}{\mathrm{O}}}-\overset{\mathrm{CH_2Cl}}{\mathrm{C}}=\mathrm{O} \quad + \quad \mathrm{I^-}$$

(*1*) by nucleophilic displacement on methyl to give methyl iodide and hexyl chloroacetate and (*2*) by displacement on the 2-carbon atom of hexyl to give 2-iodohexane and methyl chloroacetate. It is, however, improbable that nucleophilic displacement would occur on *sec*-hexyl more than half as rapidly as on methyl. It is more likely that two different types of reaction occur, S_N2 by iodide on methyl as suggested and S_N1 fission of the *sec*-hexyl group. It cannot be definitely ascertained whether any isomerization of 2-hexyl to 3-hexyl occurred.

The entrance of S_N2 displacement with chloroacetyl iodide where none existed detectably with acetyl bromide or chloride is probably associated with the greater nucleophilic displacing tendency of iodide ion and possibly with higher concentrations of iodide ion.

F. Cleavage of cyclic ethers

Although almost all of the work on the cleavage of cyclic ethers has dealt with tetrahydrofuran and tetrahydropyran and their derivatives, the first reported cleavage was of cineole by Knoevenagel in 1914 (145).



With acetic anhydride and a little sulfuric acid or ferric chloride in 1–3 days at 20–50°C. good yields of a 50:50 mixture of the diacetate and of terpineol acetate resulted.

The reaction of tetrahydrofuran and tetrahydropyran with acetic anhydride and 1 per cent of zinc chloride requires much higher temperatures (190°C.) for convenient rates than does the ditertiary ether, cineole. Both form pure diacetates but tetrahydropyran reacts more slowly than tetrahydrofuran (210), as it does in cleavage by hydrogen halides. If methyl or ethyl is substituted in the α-position, the reaction goes at a lower temperature but largely to the olefin acetate with the acetate at the primary carbon atom. With methyltetrahydrofuran, 24 per cent of the diacetate and 70 per cent of the olefinic acetate result; with ethyltetrahydrofuran, 10 per cent and 84 per cent, respectively. Similar results are obtained with tetrahydropyrans.

Generally similar results were obtained in a similar study of a large number of substituted tetrahydrofurans (122).

More rapid reaction occurs with acyl halides. Benzoyl chloride reacts with tetrahydrofuran at reflux in the presence of titanium chloride or stannic chloride to give an 80 per cent yield of the chlorobutyl benzoate plus a little diester. A similar but slower reaction occurs with dioxane (92).

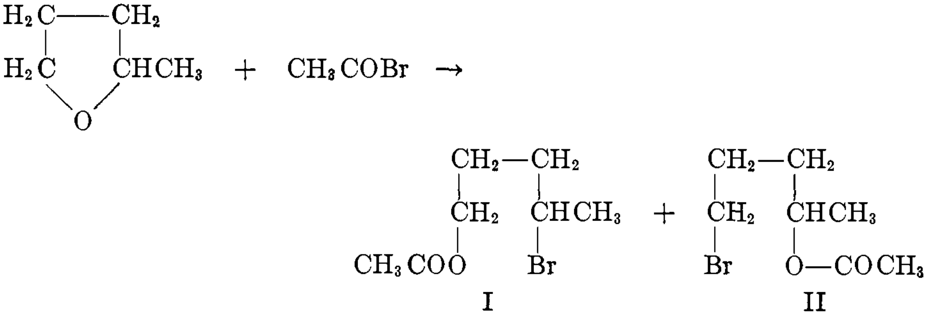
The preparation of 4-chlorobutyl benzoate in 80 per cent yield by the action of benzoyl chloride and zinc chloride on tetrahydrofuran is described in *Organic Syntheses* (275). Tetrahydropyran gives a similar yield (274).

Without added catalyst, acetyl chloride and tetrahydrofuran refluxed for 12 hr. gave a 45 per cent yield of 4-chlorobutyl acetate plus some $CH_3CO(CH_2)_4$-$O(CH_2)_4Cl$ and the analogous trimer (56). The addition of 0.25 mole of zinc chloride per mole of ether gave tars but, with traces of zinc chloride, refluxing for 30 min. gave a 71 per cent yield of the chlorobutyl acetate. Propionyl chloride, butyryl chloride, and benzoyl chloride gave similar results. Acetyl bromide behaved similarly, although the product was contaminated with dibromide. 2,5-Dimethyltetrahydrofuran was cleaved similarly in similar yield.

When a mixture of tetrahydrofuran, glacial acetic acid, phosphorus trichloride, and a trace of zinc chloride is refluxed for 2 hr. at 120°C., an 80 per cent yield of the chlorobutyl acetate results (36). Acetyl chloride is probably an intermediate.

The use of other acid chlorides has been reported. *p*-Nitrobenzoyl chloride with stannic chloride results in an 85 per cent yield of the chloroester with tetrahydrofuran (261). *p*-Nitrobenzoyl bromide and acetyl bromide give similar yields of the analogous compounds.

Acetyl bromide is reported to react spontaneously with 2-methyltetrahydrofuran at 50°C. or above to give both bromoacetates (197). In view of the results with acetyl bromide and methyl *sec*-butyl ether, adventitious catalysis may be involved.



T	Yield of I	Yield of II
°C.	*per cent*	*per cent*
50–60	61	39
70–80	54	46
90–100	37	63
121	12	88

In the analogous open-chain ether, methyl *sec*-butyl ether, bromide appeared only at the secondary position in reaction with acetyl bromide at 25°C. without added catalyst (45). The results resemble those with chloroacetyl iodide acting on methyl 2-hexyl ether (268). Apparently an S_N1 reaction is accompanied by an S_N2 reaction of higher activation energy.

G. Cleavage by sulfonyl halides and related acid chlorides

p-Toluenesulfonyl chloride in the presence of ferric chloride cleaves ethyl ether at 25°C. (185) to form ethyl chloride and ethyl *p*-toluenesulfonate. Aluminum chloride also effects this reaction, but boron trifluoride and zinc chloride do not. Zinc chloride is also reported to be ineffective in leading to the reaction of benzenesulfonyl chloride and *p*-toluenesulfonyl chloride with ethyl ether at reflux (285).

However, sulfonyl halides react with dimethoxybenzenes in the presence of zinc chloride at 125°C. (40). Two types of reaction occur, one leading to phenyl dimethoxyphenyl sulfones and the other to cleavage of one of the methoxyl groups with formation of methoxyphenyl sulfonates. The latter reaction is the more common, particularly with alkylsulfonyl chlorides. In some cases both reactions occur, particularly with arylsulfonyl chlorides. Dimethoxybenzenes are stable to either zinc chloride or sulfonyl chlorides alone at 150°C.

It was proposed (41) that RSO_2^+ is an intermediate in this reaction resembling RCO^+. It was assumed to add to the ethereal oxygen, from which methyl carbonium ion was then eliminated. It seems questionable that the methyl carbonium ion is involved. The reaction may well involve S_N2 attack on the methyl radical in the oxonium salt.

Ethyl ether and thionyl chloride react when warmed in the presence of stannic chloride or titanium tetrachloride. The reaction seems largely to occur in the sense of the equation:

$$(C_2H_5)_2O + SOCl_2 \rightarrow 2C_2H_5Cl + SO_2$$

The yield of ethyl chloride was 75 per cent in terms of the equation (90, 91).

The authors proposed that alkyl chlorosulfites were intermediates and that these decomposed under the catalytic action of stannic chloride. Perhaps the ion $ClSO^+$ is involved in a reaction similar to the others of this section. Its adduct with ether, R_2OSOCl^+, would react to form RCl and ROSOCl.

A similar reaction was observed with higher alkyl ethers, but there were side reactions. With isoamyl ether, some hydrogen chloride was evolved and sulfur-containing substances occurred in the reaction products. Phenyl and benzyl ethers gave side reactions. Some isomerization was reported: from propyl to isopropyl; from butyl and isobutyl to *tert*-butyl and perhaps *sec*-butyl. Carbonium-ion reactions are apparently involved in some degree for ethers of molecular weight above ethyl.

At water bath temperatures, thionyl chloride and tetrahydrofuran with stannic chloride react to give 1,4-dichlorobutane (92).

Sulfuryl chloride and anisole at 220°C. react very slowly to give a little cleavage and some nuclear chlorination. The addition compound of pyridine and sulfuryl chloride cleaves anisole under these conditions, again with accompanying chlorination (222).

V. CLEAVAGE BY INORGANIC ACID ANHYDRIDES

If the anhydride of a strong acid is a strong Lewis acid, it will form complexes with ethers which may then rearrange to esters of the acid derived from the anhydride.

Ether cleavage by sulfur trioxide, phosphorus pentoxide, nitrogen pentoxide, and nitrogen dioxide may be placed in this class, although the reaction is reasonably clear-cut only in the first case.

Sulfur trioxide forms a complex with chloroethyl ether which may be represented thus:

$$(ClCH_2CH_2)_2O{:}SO_3$$

The compound has not been isolated in the pure form and is not very stable, but its chemical properties accord with this formula. If it is heated to about 125°C. under a pressure of 2–3 mm., chloroethyl sulfate, $(ClCH_2CH_2O)_2SO_2$, distills in 91 per cent yield (273). It is not clear whether the isomerization is inter- or intramolecular.

In 1837 Regnault found that methyl ether reacts very rapidly with sulfur trioxide in the vapor phase at room temperatures to give methyl sulfate. No evidence of an addition compound, $(CH_3)_2O{:}SO_3$, was reported but, of course, none was sought (228).

The same reaction may be run more conveniently by passing methyl ether into oleum (101) or by passing sulfur trioxide into a solution of methyl ether in methyl sulfate at room temperatures or at slightly lower ones (110).

The following similar reactions have also been reported (272, page 50):

$$(CH_3)_2O + Na_2S_2O_7 \rightarrow (CH_3)_2SO_4 + Na_2SO_4$$
$$(CH_3)_2O + CH_3OSO_2Cl \rightarrow (CH_3)_2SO_4 + CH_3Cl$$

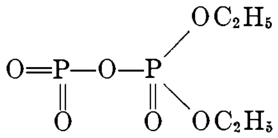
With higher aliphatic ethers such as ethyl (101) and propyl (273), charring and other side reactions supervene.

Langheld first reported a reaction between ethyl ether and phosphorus pentoxide (154). Upon refluxing the anhydride in an excess of ether for 3 days he obtained reaction in the sense of the following equation:

$$(C_2H_5)_2O + P_2O_5 \rightarrow 2C_2H_5OPO_2$$

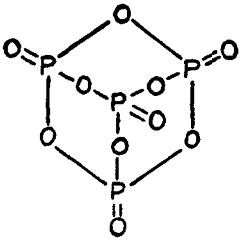
The reaction is run more conveniently and in better yields in chloroform at reflux (267, 299).

The earlier workers considered that they had obtained ethyl metaphosphate, but cryoscopy indicated that the material was at least dimeric (216, 291), being perhaps (216) as shown in the formula below:

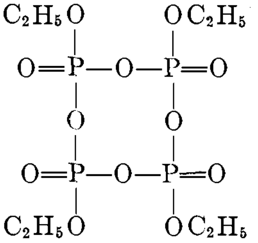


$$O{=}\underset{\underset{O}{\|}}{P}{-}O{-}\underset{\underset{O}{\|}}{P}(OC_2H_5)_2$$

The reaction appears simpler if one considers the probable structure of phosphoric anhydride (211).

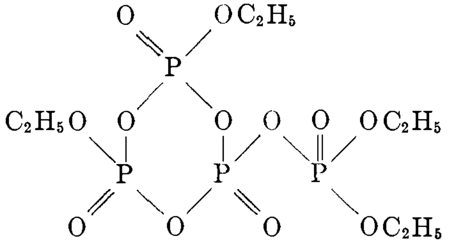


As suggested by Rätz and Thilo (225), reaction with this might lead to either



I

or

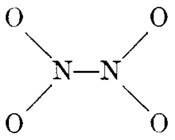


II

By aqueous hydrolysis of Langheld's ester, one gets the following compounds in the listed mole per cent: $C_2H_5OPO_3H_2$, 46.7; $(C_2H_5O)_2PO_2H$, 20.0; H_3PO_4, 21.5; $(C_2H_5)_2P_2O_7H_2$, 12 (225). This is consistent with Langheld's ester being mostly II with a little I. Possible stereoisomers have not been considered.

At the temperature of refluxing chloroform, ethyl ether does not react beyond the stage represented by $C_2H_5PO_3$ (225). Phenyl ether is unreactive under these conditions (291). However, alkyl ethers are reported to react to trialkyl phosphates under more drastic conditions (132), for example, ethyl ether at 100–150°C. Phenyl ether is reported to form triphenyl phosphate at 130–150°C.

Simple alkyl ethers form complexes with nitrogen dioxide which melt at rather low temperatures with considerable, though apparently not complete, dissociation (233). Nitrogen dioxide



may be considered as the mixed anhydride of nitrous and nitric acids for the present purpose.

Isoamyl ether in petroleum ether reacts with nitrogen dioxide at room temperatures to give isoamyl nitrite, isoamyl nitrate, and the analogous nitro compound, 3-methyl-1-nitrobutane (64). Some further oxidation products also appear. Phenyl ether under similar treatment leads to nitrodiphenyl ether and oxidation products (64), while isoamyl phenyl ether gives isoamyl nitrophenyl ether and isovaleric acid (65).

The addition compound $Zn(NO_3)_2 \cdot 2N_2O_4$ reacts rapidly with ethyl ether to form acetaldehyde and acetic acid among other oxidation products (1).

Nitrogen pentoxide reacts with ethyl ether at −15°C. to form ethyl nitrate (3).

VI. CLEAVAGE BY LEWIS ACID HALIDES

Ethers may react with certain halides which are Lewis acids as exemplified by reaction with aluminum chloride.

$$R_2O + AlCl_3 \rightarrow R_2O{:}AlCl_3 \rightarrow ROAlCl_2 + RCl$$

In general, the required temperatures are rather high, higher than those at which reaction occurs in the same system when an acid chloride is added. Boron chloride and boron bromide are exceptions to this, as they react even at room temperatures.

In general, halides which are Lewis acids form addition compounds with ethers. Some examples of such addition compounds are given in table 5.

TABLE 5

Examples of addition compounds of ethers and Lewis acid halides

Addition Compound	References	Addition Compound	References
$AlCl_3{:}[O(CH_3)_2]_2$	(188)	$TiCl_4$:anisole	(59)
$AlCl_3{:}O(C_2H_5)_2$	(188)	$VOCl_3{:}O(C_2H_5)_2$	(16)
$AlCl_3$:anisole	(6, 106)	$SnCl_4{:}[OC_2H_5)_2]_2$	(283)
$AlBr_3{:}O(C_2H_5)_2$	(202, 213, 217)	$BCl_3{:}O(C_2H_5)_2$	(302)
$TiCl_4{:}O(C_2H_5)_2$	(16)		

A. Descriptive

Aluminum halides: Of the various halides, the aluminum ones have been most investigated. They have received some preparative use, particularly in the cleavage of methoxyl and ethoxyl groups in aromatic ethers. This reaction with aluminum chloride was discovered in 1892 by Hartmann and Gattermann (106) in cleaving anisole. Aluminum chloride and anisole form a crystalline addition compound which on heating at 120°C. for 3 hr. (2 hr. at 100°C. would have sufficed (6)) evolved methyl chloride and left $Cl_2AlOC_6H_5$.

Similar results were obtained with phenetole and isobutyl phenyl ether. *o*-Nitroanisole and *o*-nitrophenetole react readily in boiling carbon disulfide.

When the mole ratio of aluminum chloride to anisole is 1, good yields are obtained. If the ratio is 0.5, one-half of the anisole is converted. If the ratio exceeds 1, the ring is alkylated by some of the methyl chloride. Tolyl ethers exhibit a greater tendency to alkylation than do phenyl ethers (6).

If the complex $(C_2H_5)_2O{:}AlCl_3$ (m.p. 35°C.) is heated to 160–170°C., it decomposes to ethyl chloride, hydrogen chloride, and ethylene. About 10 per cent of the reaction involves elimination. A residue of AlOCl and polymer remains. $[(CH_3)_2O]_2AlCl_3$ melts at 57°C. with the elimination of 1 mole of methyl ether. On heating to 190°C., an 85 per cent yield of methyl chloride results, accompanied by a little hydrogen chloride. When the addition complex of ethyl ether and aluminum bromide is heated, the yield of ethyl bromide is 95 per cent. Much less elimination occurs than with aluminum chloride (188).

Cleavage of alkyl aryl ethers results from refluxing the ether and aluminum bromide in a 1:1 mole ratio in benzene. With anisole, $C_6H_5OAlBr_2$ and methyl bromide result. When the reaction mixture is hydrolyzed, phenol is obtained in an overall yield of 90 per cent. *p*-Ethoxybenzophenone, *p*-methoxybenzoic acid, and *p*-methoxyphenylacetic acid behave similarly. Diaryl ethers are unattacked (213).

In heating 5,5′-dibromo-2,2′-diethoxydiphenylmethane with aluminum chloride in a mole ratio of one-third for 90 min. at 130–140°C., only one ethoxyl group was cleaved (62).

The 1:1 addition complex of aluminum bromide and pyridine splits anisole at 220°C. but not diphenyl ether (222).

Reaction of aluminum bromide and phenyl benzyl ether in chlorobenzene results (after hydrolysis) in phenol and *o*-benzylphenol. Reaction is accompanied by interchange of aryl groups. The reaction is very fast; it occurs in less than 5 sec. at −40°C. Unlike the situation in the cleavage of other ethers, $C_6H_5OAlBr_2$ also cleaves. The appearance of only the *o*-isomer of benzylphenol suggests that it is formed by an intramolecular rearrangement rather than via a benzyl carbonium ion (277). This contrasts with the view expressed in regard to the somewhat similar cleavage of the same ether by acetyl perchlorate (42), in which case the identity of the benzylphenol was not determined (see page 640 under the heading *Absence of catalyst*).

Cleavage of ethyl triphenylmethyl ether by aluminum chloride in carbon disulfide solution is also fast (205).

Titanium chloride: The first example of the general type of ether cleavage here under examination was reported by Bedson in 1876 (16). The complex $(C_2H_5)_2O:TiCl_4$ can be distilled at 180 mm. without decomposition but, on heating at higher temperatures, ethyl chloride and $TiCl_3OC_2H_5$ result.

Magnesium bromide: Phenyl benzyl ether does not react with anhydrous magnesium bromide in ethyl ether. If ethyl ether is distilled off and replaced by benzene, then reaction occurs during a reflux period of 1 day. Unchanged ether, benzyl bromide, phenol, and higher-boiling materials are recovered (87). Butoxymagnesium bromide is unreactive under these conditions. In view of the slow reaction of phenyl benzyl ether with magnesium bromide, one would not expect most other types of ethers to react with this material under practicable conditions.

As judged by its reaction with anisole, magnesium iodide probably cleaves more rapidly than magnesium bromide (98).

Phosphorus pentachloride: Phosphorus pentachloride reacts with ethers at 110°C. (300). Chlorides are formed in small yield. There is apparently accompanying direct chlorination.

Ethyl ether is reported to react with phosphorus pentachloride during a reflux period of 2 days. The products apparently consist of oxidation products derived from chlorination at the α-carbon atom. Any ethyl chloride formed would have been lost (100).

The action of sulfuryl chloride has been entered with those of acid chlorides, but it gives some chlorination like phosphorus pentachloride (222).

Stannic chloride: The 2:1 complex of ethyl ether and stannic chloride melts at 87°C. At 100°C. it decomposes into its constituents, but on heating to 113°C. some ethyl chloride is formed (283). The complex may be purified by vacuum sublimation. It is reversibly dissociated in benzene and virtually completely dissociated in the vapor phase (258). Thus, the complex between ether and stannic chloride can hardly, in general, be the reactive intermediate in the cleavage of ethers by acid chlorides and stannic chloride.

The similar complex of isoamyl ether and stannic chloride melts at 32–35°C. and is decomposed to its constituents on heating (283).

However, the corresponding complex with ethyl benzyl ether gives polymeric material on heating. On heating in benzene, diphenylmethane and dibenzylbenzenes are formed. This is reminiscent of the reactions of this ether with boron trifluoride (196) and of acetyl perchlorate with phenyl benzyl ether (42). If water is added to the stannic chloride complex soon after formation, the ether is regenerated. Thus, the reaction is much slower than that involving aluminum bromide and phenyl benzyl ether (277).

Zinc chloride: The refluxing of ethyl ether, isopropyl ether, butyl ether, or isoamyl ether for 2 hr. with zinc chloride in a mole ratio of 2:1 results in the formation of only traces of products (284). Heating the addition compound of pyridine and zinc chloride with anisole at 220°C. gives a very little splitting (222). Here again, there is considerable contrast in the conditions under which zinc chloride attacks ethers and those under which it catalyzes the reaction of acid chlorides with ethers.

Boron halides: The 1:1 addition complex of boron trifluoride and ethyl ether may be distilled at its boiling point, 124°C. (37), without decomposition. The analogous complex with isopropyl ether decomposes slowly at 50°C., probably to isopropyl fluoride and isopropoxyboron difluoride. Polymeric materials then result, probably from the action of boron trifluoride on the isopropyl fluoride (37). Because of the great tendency for boron trifluoride to abstract a fluoride ion from alkyl fluorides (44), one would expect difficulty in isolating alkyl fluorides in the presence of free boron trifluoride.

Boron trichloride and boron tribromide cleave ethers much more readily than does boron trifluoride. Their reaction is of considerable potential utility but the reaction has been little applied.

The 1:1 addition compound of ethyl ether and boron trichloride melts at 56°C. and decomposes slowly to ethoxyboron dichloride and ethyl chloride at that temperature (227). The ethoxyboron dichloride can add 1 mole of ether to form an addition compound which undergoes disporportionation.

$$2C_2H_5OBCl_2 + (C_2H_5)_2O \rightarrow (C_2H_5OBCl_2)_2O(C_2H_5)_2 \rightarrow BCl(OC_2H_5)_2 + BCl_3{:}O(C_2H_5)_2$$

Diethoxyboron chloride does not add ether (302).

TABLE 6

Products of reaction of mixed ethers and boron trichloride (83)

Ether	RCl	$ROBCl_2$
Butyl isobutyl	Isobutyl + *tert*-butyl	Butyl
Butyl *sec*-butyl	*sec*-Butyl	Butyl
Isobutyl *sec*-butyl	*sec*-Butyl	Isobutyl
Butyl *tert*-butyl	*tert*-Butyl	Butyl
Isobutyl *tert*-butyl	*tert*-Butyl	Isobutyl
sec-Butyl *tert*-butyl	*tert*-Butyl	*sec*-Butyl
Ethyl octyl	Octyl	Ethyl
Ethyl 2-octyl	2-Octyl	Ethyl
Anisole	Methyl	Phenyl
Phenetole	Ethyl	Phenyl

Table 6 gives the products isolated from a mixture of an ether and boron trichloride after a reaction period of a few hours at 20°C. In most cases the mole ratio of reactants was about 1. The ratio of butyl isobutyl ether to boron trichloride was 3, but the reaction seemed to have proceeded normally (83).

Ethyl (+)-2-octyl ether and boron trichloride under similar conditions give nearly quantitative yields of ethoxyboron dichloride and (−)-2-chlorooöctane (82). The configuration of the latter compound is inverted from that of the ether, and it is racemized to the extent of at least 60 per cent (140). Optically active ethyl α-phenethyl ether gives completely racemic α-phenethyl chloride. However, the chloride itself is racemized under the same conditions by boron trichloride. 2-Chlorooöctane is not.

When 3 moles of ethyl ether, butyl ether, or isopropyl ether is heated on the water bath with 1 mole of boron tribromide, the following reaction occurs:

$$R_2O + RBr_3 \rightarrow (RO)_3B + 3RBr$$

Under the same conditions anisole, butyl phenyl ether, and isopropyl phenyl ether give (after hydrolysis) phenol and the alkyl halide. Phenyl benzyl ether gives phenol and benzyl bromide. Mesityl methyl ether is cleaved without difficulty. The yields with the above ethers are 70 ± 15 per cent. Butyl ether and butyl phenyl ether give butyl bromide without isomerization, as judged by refractive index and boiling point (19).

B. Mechanism

The first step in the reaction is clearly the formation of an addition compound of the type $R_2\overset{+}{O}:\overset{-}{M}X_n$. Like the other conjugate acids of ethers this might be presumed to react in two possible ways, S_N1 and S_N2.

$$R_2O:MX_n + [X^-] \rightarrow RX + ROMX_n^- \qquad (S_N2)$$

$$R_2O:MX_n \rightarrow R^+ + ROMX_n^- \qquad (S_N1)$$

$$R^+ + [X^-] \rightarrow RX$$

The apparent ready cleavage of anisole suggests that it reacts by an S_N2 process. Lack of apparent rearrangement in the formation of any primary alkyl halides suggests that they are formed by an S_N2 process. Against such an assumption is the reported cleavage of ethyl octyl ether to give octyl chloride rather than mainly ethyl chloride (table 6), although no isomerization was noted here. Gerrard and Lappert (82, 83) have suggested that the S_N1 process obtains in all cases, even in the cleavage of anisole. The lack of rearrangement of primary alkyl groups and the ready cleavage of anisole would suggest the absence of a typical carbonium-ion reaction.

Since anisoles and phenetoles can be cleaved in benzene solution by aluminum bromide without alkylating the benzene (213), cleavage cannot involve carbonium-ion intermediates in this case. Anisole and phenetole are cleaved by boron trichloride (table 6), and alkyl aryl ethers and benzyl phenyl ether are cleaved by boron tribromide (19) without accompanying alkylation. Since in the latter case there were three times as many moles of ether as of bromide, all of the ether cannot have been deactivated by complex formation. This raises some doubts that typical carbonium-ion reactions are involved.

On the other hand, where one of the alkyl groups is secondary or tertiary the products of cleavage of mixed ethers (table 6) accord with the view that a carbonium-ion process is operating, as does the stereochemistry of the cleavage of ethyl *sec*-octyl ether (82).

Unlike cleavage by proton acids, cleavage of alkyl aryl ethers by halides seems, at least in some instances, as fast as that of dialkyl ethers. Cleavage with aluminum halides occurs more readily with the alkyl aryl ethers. The apparent accelerating effect of a nitro group substituted on a benzene ring (106) constitutes another difference in the case of aluminum chloride. Perhaps in such cases all of the ethers behave as strong bases so that relative basicity is of no consequence. The relative positive charge induced on the ethereal oxygen atom by the phenyl would then serve to augment reactivity.

The origin of the inversion of relative reactivity of the boron halides from that usually observed is somewhat obscure. The considerable stability of boron trifluoride etherates has been mentioned. Owing to the lack of alkylation by such etherates in the presence of a slight excess of ether, the following ionization has been proposed (46):

$$R_2O{:}BF_3 \rightarrow R_2OBF_2^+ + F^-$$
$$F^- + BF_3 \rightarrow BF_4^-$$

Such a process is favored by the high stability of the BF_4^- ion. The positive charge would cause greater reactivity of the species $R_2OBF_2^+$ than of $R_2O{:}BF_3$.

By analogy with the lesser stability of tetrachloroborates compared with tetrafluoborates, one might suggest that the first step of the ionization of the etherate would proceed more easily with boron trichloride and boron bromide. Such a process would also give a higher concentration of anion and an anion of much greater nucleophilic character than would result with boron trifluoride.

Similar ionization of aluminum bromide etherates was proposed by Plotnikov

(217) to account for their conductivity in carbon disulfide or chloroform. However, the conductivity of such etherates in nitrobenzene is reported to be slight (289).

VII. CLEAVAGE BY ALKYLATION

In the presence of strong proton acids or Lewis acids, ethers alkylate aromatic hydrocarbons. The initial reaction may be represented thus:

$$R_2O + C_6H_6 \rightarrow RC_6H_5 + ROH$$

The alcohol may, of course, bring about alkylation in its turn.

In general, alkylation by ethers closely resembles alkylation by alcohols. Although alkylation by ethers is a cleavage reaction, it is more appropriately reviewed under the heading of alkylation. It will not be treated extensively in this review, but in any case it has not been much investigated.

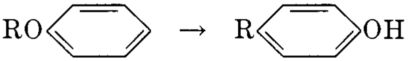
As with alcohols, alkylation is not easily effected by ethers containing only primary alkyl groups. Thus, with concentrated sulfuric acid at moderate temperatures, secondary ethers alkylate benzene but primary ethers do not (141). With boron trifluoride, drastic conditions are necessary to effect alkylation by primary ethers (206). Secondary ethers react much more readily. Even secondary ethers, however, do not alkylate readily unless boron trifluoride is present in a mole ratio to the ether of one or better, or unless small amounts of promoters such as water or sulfuric acid are present (46). This is a consequence of the comparative stability of boron trifluoride etherates, as discussed in the subsection on boron halides in Section VI.

When benzene is alkylated by optically active methyl *sec*-butyl ether in the presence of boron trifluoride, the *sec*-butylbenzene produced is of inverted configuration but of an optical purity of only about 1 per cent (47).

Apparently, alkylations of the types mentioned above proceed by the carbonium-ion reactions typical of Friedel–Crafts reactions (46, 47).

The easily cleaved benzyl ethyl and benzyl phenyl ethers alkylate aromatic hydrocarbons readily. Such alkylation has been discussed in connection with their cleavage by acetyl perchlorate (42), boron trifluoride and acetic anhydride (196), aluminum bromide (277), stannic chloride (283), and phosphorus pentoxide (291).

Self-alkylation constitutes a special case, thus:



Although the reaction appears to be intramolecular in the case of phenyl benzyl ether in the presence of aluminum bromide (277), in other cases it appears to be at least in part intermolecular because of the formation of $R_2C_6H_3OH$ and because of transfer of the group, R, to other aromatic compounds when these are added (249, 257). Phenyl benzyl ether behaves in this way with dry hydrogen chloride at 100°C. and with zinc chloride at 160°C. (249).

Optically active *sec*-butyl phenyl ether rearranges to *sec*-butylphenol in the presence of zinc chloride or of sulfuric acid in glacial acetic acid. The product has considerable optical activity but is partially racemized (264). Here the reaction is at least partly intramolecular. However, *sec*-butyl mesityl ether when treated with either of the above reagents in the presence of *p*-cresol gives completely racemic *sec*-butyl-*p*-cresol (85). Here the reaction is intermolecular. The considerable literature on rearrangements of this nature will not be reviewed further. Reference is made to the cited papers and to Hurd and Pollack (133) for further references.

VIII. CLEAVAGE BY NUCLEOPHILIC REAGENTS ALONE

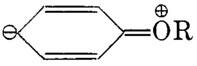
For reasons developed in Section II, ethers are much less reactive in substitution reactions than are their conjugate acids, i.e.:

$$R_2O + X^- \rightarrow RX + OR^- \textit{ vs. } R_2OH^+ + X^- \rightarrow RX + ROH$$

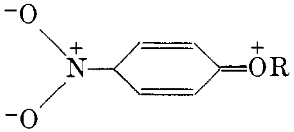
However, in the absence of strong acids, the species X^- can be chosen to have much greater nucleophilic character, since there is some correlation between basicity and such character. Thus, in the absence of strong acids one can use an alkoxide rather than an alcohol. Displacement by the strongest of such bases, carbanions, is discussed separately in the following section.

The possible increase in nucleophilic character does not compensate for loss of positive charge. No useful cleavage reactions of alkyl ethers by basic reagents alone have been reported. When the bases are strong enough to attack alkyl ethers (as for example, carbanions), elimination and transmetalation reactions largely supervene.

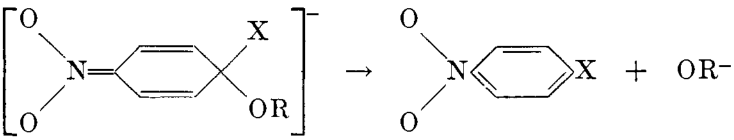
Alkyl aryl ethers are more reactive than alkyl ethers consequent to the relative positive charge transferred to the oxygen atom by contributions of such structures as the following:



Such ethers approach in some degree the character of R_3O^+ (see oxonium salts, page 618). Electron-withdrawing substituents, such as the nitro group, particularly in the ortho or para position, increase this effect by contributions to the resonance hybrid of such forms as



However, another possible reaction is also favored by such substituents.



The bracketted species might be either a true transition state or an intermediate. Substitution reactions of this type are known for ethers and for a number of other types of compounds, such as aryl halides. Such reactions and their mechanisms have recently been reviewed by Bunnett and Zahler (39) and discussed also by Miller (114, 193). Their mechanism will not, accordingly, be treated at any length.

For displacement on either the alkyl or the phenyl group of these ethers to occur easily, one or better two activating substituents are necessary. Both types of displacement, S_N2 on phenyl and S_N2 on alkyl, are favored by activating groups. As will be seen, either may predominate and the factors which decide which are rather obscure.

A. Reaction with OH^-, OR^-, *and* SR^-

Phenyl ether reacts with aqueous sodium hydroxide slowly at 300°C. (191).

At 180–200°C. anisole and phenetole in mixtures containing twice as much potassium hydroxide as ether and four times as much ethanol react slowly to form phenol (270). In 15 hr. the reaction proceeds to an extent of the order of 15 per cent.

When anisole is heated in a 20 per cent solution of potassium hydroxide in ethanol for 7 hr. at 200°C. about 7 per cent of *phenol* results. Since phenetole is not formed, the reaction is apparently S_N2 on methyl (130, 131).

$$C_6H_5OCH_3 + OC_2H_5^- \rightarrow C_6H_5O^- + C_2H_5OCH_3$$

If thiophenol is added to the mixture with consequent formation of thiophenoxide ion, the following reaction goes to completion in 6 hr. at 200°C.

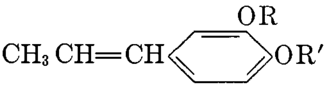
$$C_6H_5OCH_3 + SC_6H_5^- \rightarrow C_6H_5O^- + CH_3SC_6H_5$$

This also works for hexestrol and stilbestrol dimethyl ethers. This is an instance of the greater reactivity in nucleophilic displacement of ions of the type SR^- as compared with OR^-.

If a mixture of anisole and thiophenol is treated with hydrogen iodide, the products are phenol and methyl iodide (131). Here, no thiophenoxide ions are present but rather iodide ion, a species with a relatively large tendency toward nucleophilic displacing.

Another example of the slow reaction of unactivated ethers with hydroxide or alkoxide ions is that of tris(*p*-methoxyphenyl)ethylene in 15 per cent potassium hydroxide in 90 per cent ethanol at 195°C. (248).

If the compound,



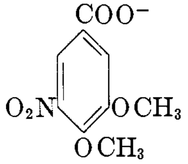
when R and R′ are methyl, is heated with sodium ethoxide or methoxide in dry ethanol or dry methanol, reaction is substantially complete in 110 min. at 190°C. The reaction proceeds to the monomethyl ether and stops. Presumably the negative charge on this species hinders further attack. If either R or R′ is methyl and the other ethyl, the methyl is cleaved 5–10 times as rapidly as the ethyl (290). In view of the relative reactivity of methyl and ethyl and since the free phenolic group is the product, this reaction is of the S_N2 type on alkyl.

In general, the methyl and ethyl ethers of dihydric and polyhydric phenols appear more reactive than anisole or phenetole, as in the hydrolysis of *o*-dimethoxybenzene to *o*-methoxyphenol in alcoholic or aqueous alkali (189) or in the hydrolysis of pyrogallol trimethyl ether in alcoholic caustic potash, in which the middle methoxyl group is cleaved (15). In some more complicated cases, demethylation occurs even more easily. Thus, the α-monomethyl ether of alizarin is cleaved on prolonged boiling with aqueous barium hydroxide, although no such reaction occurs with the β-monomethyl ether (212).

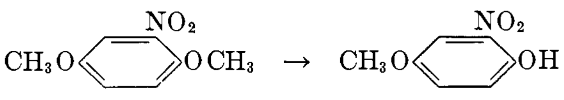
p-Chloroanisole reacts with a solution of sodium methoxide in absolute methanol at 180°C. to form *p*-chlorophenol and, presumably, methyl ether. Thus, displacement on the methyl is faster than on the ring. Consequent to this, *p*-dichlorobenzene in the same solution at 180°C. reacts to form *p*-chlorophenol, since the chloroanisole first formed reacts in a faster step to chlorophenol (60).

In the hydrolysis of methyl naphthyl ethers in alcoholic potassium hydroxide, chlorine, bromine, and a nitro group substituted on the ring accelerate the reaction in that order. This is the inverse of the order obtaining in the cleavage with hydrogen bromide and acetic acid (147). Presumably the accelerating effect of nitro groups is present in the second reaction but is overbalanced by the decrease in the basicity of the ether occasioned by substitution of a nitro group.

Nitro groups are much more effective in the ortho or para position than in the meta position. Three examples illustrate this nicely. In the cleavage of the following compound with potassium hydroxide, only the methoxyl group ortho to the nitro group is cleaved (143).



The following reaction occurs on 12 hr. refluxing in an ethanol–water solution of potassium hydroxide (139):



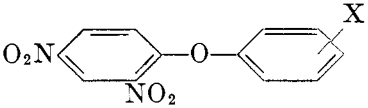
Refluxing with 10 per cent potassium hydroxide for 24 hr. hydrolyzes *o*- and *p*-nitroanisoles and phenetoles to the extent of about 18 per cent but the meta analogs undetectably (209).

With the substitution of nitro groups and particularly with that of more than one, the rate of the reaction, S_N2 on phenyl, overtakes that of S_N2 on alkyl, although with certain entering groups the latter reaction is observed. Examples of reactions which are S_N2 on phenyl follow.

Refluxing *o*- and *p*-nitroanisoles in a 10 per cent solution of potassium hydroxide in aqueous ethanol largely converts them to the phenetoles. With the analogous phenetoles, anisoles result on heating with potassium hydroxide in methanol at 100°C. (209).

When solutions of 2,4-dinitroanisole in alcohols containing 0.8 per cent of potassium hydroxide are refluxed for 10 hr., good yields of the exchanged ether are obtained when the alcohol is a simple aliphatic one. Allyl and benzyl alcohols and phenol are unsatisfactory. Similar reaction occurs with phenyl 2,4-dinitrophenyl ether and with α- or β-naphthyl 2,4-dinitrophenyl ether. In these cases an alkyl dinitrophenyl ether and either phenol or naphthol result. The following ethers do not react detectably under these conditions: *p*-nitroanisole, *p*-acetylanisole, *p*-chloroanisole, 2,4,6-tribromoanisole, potassium *p*-methoxybenzenesulfonate (207).

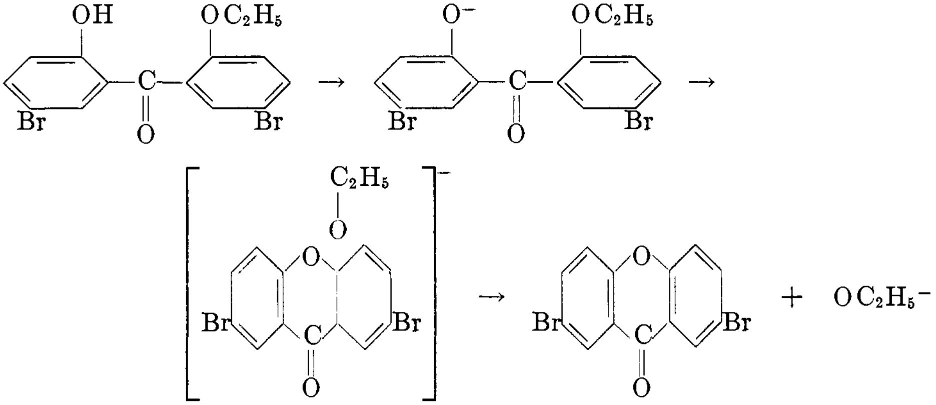
In reaction of the following under similar conditions



the Hammett σp relation is obeyed for X = *p*-nitro, *p*-chloro, and *p*- and *m*-methyl. The value of ρ is +1.46 (208).

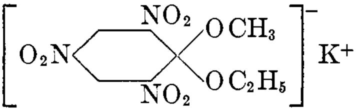
4-Methoxy-3-nitroazobenzene is converted to the corresponding ethoxy compound upon 9 hr. refluxing in ethanol containing sodium ethoxide and to the corresponding phenol upon refluxing with potassium hydroxide in aqueous methanol. However, 4-methoxyazobenzene does not react under these conditions nor does the corresponding azoxy compound nor *o*-nitroanisole (79).

The following reaction occurs upon refluxing a solution of the compound and potassium hydroxide in aqueous ethanol (62), perhaps via the intermediate shown.



When 4-methoxy-3,5-dinitrobenzoic acid is heated in water for 5 hr. at 150°C., it is cleaved to the corresponding phenol (235). This cleavage may well belong to the category considered here, owing to the low basicity to be expected of the oxygen atom in such an ether.

Picryl ethyl ether with potassium methoxide and picryl methyl ether with potassium ethoxide form the same addition compound. For example, the addition of picryl methyl ether to a solution of potassium ethoxide in ethanol at 5°C. results in rapid crystallization of the addition compound as red needles. If a suspension of this compound in water is treated with dilute sulfuric acid, a mixture of the two ethers is formed with the ethyl ether in excess. Similar results are obtained with the ethyl and isobutyl picryl ethers (187). Every evidence indicates that the structure of the addition compound is:



In the case of less activated ethers, for example a mononitroanisole, it is not clear whether a true intermediate such as the above is formed or whether the structure analogous to this is a transition state.

Although the following compounds fall mostly somewhat outside the kinds of ethers considered in this review, they will be mentioned because they exemplify the precarious balance which can exist between S_N2 on the aryl ring and S_N2 on alkyl. Only particularly reactive ethers are cleaved by treatment with thiophenol for 1–2 days at 160°C. Even ethyl benzyl ether is cleaved but to an extent of 2.5 per cent by such treatment with thiocresol to give benzyl tolyl sulfide. Ethyl β-naphthyl ether does not react. 2-Ethoxyquinoline, however, is cleaved to give ethyl phenyl sulfide and 2-hydroxyquinoline. 2-Benzyloxyquinoline behaves similarly. 2-Phenoxyquinoline also cleaves readily but gives phenol and phenyl 2-quinolyl sulfide. Also, if the ethoxyl group is in the 7-position on the quinoline ring, the reaction is S_N2 on aryl (134).

With potassium *tert*-butoxide as a catalyst, benzhydryl ether is quantitatively decomposed at 150°C. in 30 min. to diphenylmethane and benzophenone. A carbanion intermediate is presumably involved (157):

$$(C_6H_5)_2HCOCH(C_6H_5)_2 \rightarrow (C_6H_5)_2HCOC(C_6H_5)_2^- \\ \rightarrow (C_6H_5)_2HC^- + (C_6H_5)_2CO$$

There is equivalent cleavage of benzyl ether at 200°C., although the benzaldehyde which is formed undergoes the Cannizzaro reaction. The reaction is also accompanied by rearrangement to desoxybenzoin (see Section VIII,D).

B. Reaction with the sodium salt of acetoacetic ester

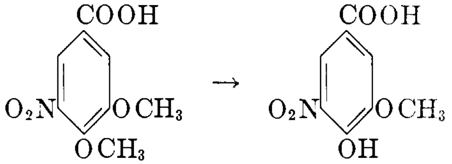
Reaction for 7 days at 25°C. with 2,4-dinitroanisole gives a small yield; phenyl 2,4-dinitrophenyl ether gives a 40 per cent yield. Both reactions form 2,4-dinitrophenylacetoacetic ester (33).

C. Reaction with amines

The rate of reaction of amines with unsubstituted alkyl aryl ethers is very low. For example, methyl β-naphthyl ether and methyl diphenyl ether are not cleaved in refluxing piperidine nor moist pyridine, although partial demethylation occurs when these are heated in a sealed tube at 250–300°C. (5). Diphenyl ether is not cleaved by refluxing piperidine (155). No cleavage of alkyl ethers has been reported and even the amide ion does not cleave ethyl *l*-menthyl ether (127).

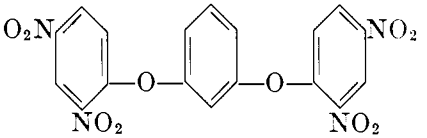
The effect of nitro groups in facilitating ether cleavage was first observed by Salkowski in 1874 (234). He observed that methyl and ethyl picryl ethers react with aqueous ammonia on warming to give picramide. In alcoholic solution this reaction occurs rapidly at room temperatures. 4-Methoxy-3,5-dinitrobenzoic acid is cleaved rapidly also. With 2,4- and 2,6-dinitroanisoles and phenetoles, aqueous ammonia requires 120°C. for complete reaction in 6 hr. *o*- and *p*-Nitroanisoles require a temperature of nearly 200°C. for reasonable rates. In all cases nitroanilines (and presumably methanol or ethanol) result.

As with cleavage by hydroxide and alkoxide ions, *o*- and *p*-nitro groups are much more effective than *m*-nitro groups. For example, in the cleavage of the following compound with refluxing aniline, only the methoxyl group ortho to the nitro group reacts (143).



Since the phenol is formed and presumably methylaniline, this reaction is a nucleophilic displacement on methyl.

In similar treatment of the following compound, the displacement is on the ring, since dinitrodiphenylamine results (203).



In addition to aniline a wide variety of amines can effect similar cleavage, as shown in table 7 derived from the work of Borsche (33, 34).

The cyano group is also activating. Thus phenyl 4-cyano-2-nitrophenyl ether is cleaved by hydrazine in 5 min. at 100°C. (33). In the reactions of table 7 the nitroanisoles all are cleaved by displacement on the ring. The nitrodiphenyl ethers described above and also in all cases described subsequently are cleaved by substitution on the ring containing the nitro groups, i.e., phenol and *N*-substituted nitroanilines result.

Refluxing piperidine is also a good cleavage reagent in suitable cases. Phenyl 2- and 4-nitrophenyl ethers react slowly in refluxing piperidine. Phenyl 2,4-dinitrophenyl ether and bis(2,4-dinitrophenyl) ether react slowly in the cold and rapidly at 100°C. (155). Cleavage of a variety of more complicatedly substituted diphenyl ethers with piperidine and pyridine has been described (32, 72, 111).

Refluxing piperidine and pyridine both cleave nitroanisoles, although reaction with the former is much faster. In 1 hr. with piperidine, *o*-nitroanisole is 40 per

TABLE 7

Cleavage of nitroaryl ethers by amines

Reagent	Conditions	Yield from A*	Yield from B*
Dilute alcoholic NH_3	50°C., 1 day	Trace	Fair
Aniline	2 hr., 180°C.	Trace	Good
Hydrazine	30 min., 100°C.	100 per cent	100 per cent in a few minutes
Phenylhydrazine	Less reactive than hydrazine		
Hydroxylamine	½ day, 100°C.	100 per cent	100 per cent in 2 hr.
Sodium salt of acetoacetic ester	7 days, 25°C.	Small	40 per cent

* A = 2,4-dinitroanisole; B = phenyl 2,4-dinitrophenyl ether.

cent cleaved, whereas cleavage with pyridine is negligible. Under similar conditions, reaction of piperidine with 2,4-dinitroanisole proceeds to completion, and with pyridine to 70 per cent. 3,5-Dinitroanisole reacts negligibly with both. The reaction of piperidine with 2,4,6-trinitroanisole is complete in 1 min. With 2,4-dinitroanisole, the nitrophenylpiperidine resulted. The other ethers gave the nitrophenols. Methylpiperidinium and methylpyridinium ions were presumably formed also, but their salts were not isolated (49). It was suggested that traces of water were responsible for the formation of phenols, but in the total context of reactions of these ethers with nucleophilic species, it seems more probable that displacement on methyl occurred. The addition of water to pyridine slowed the reaction.

A series of papers by Hertel presents data on the cleavage of picryl ethers which are of particular interest. At room temperatures, picryl methyl ether reacts with dimethylaniline to give trimethylanilinium picrate (115), thus with cleavage of the aryl–oxygen bond. When the reaction of para-substituted dimethylanilines is studied in acetone solution with this ether, the kinetics are found to be first order in the ether and first order in the aniline. Relative rates at 35°C. for various para-substituents follow (116, 117):

Substituent	$N(CH_3)_2$	OCH_3	CH_3	H	Br	CN	NO_2
k_{35}	0.7	0.65	0.27	0.108	0.0250	0.00046	0.00012

Increased electron density on the nitrogen atom of the aniline favors reaction. Reactivity is exactly correlated with basicity, since the data given above obey the $\sigma\rho$ relation with log $k^0 = -4.500$ and $\rho = -2.383$ (104, page 189, example 21).

The effect of substituents on the nucleophilic reagent is, of course, exactly opposite that on the ether. If the ether is a 4-substituted-2,6-dinitroanisole and the amine is *p*-methyldimethylaniline, the relative rates *decrease* with the 4-substituent in the following order: nitro, cyano, halogen, hydrogen, methyl, methoxy, dimethylamino (118).

In the case of these cleavages with tertiary amines, the ethers react as rather strong alkylating agents. Side reactions are negligible. The reaction is clearly a nucleophilic displacement on methyl.

On the other hand, the reaction of ammonia or of aniline with picryl methyl ether or the picryl ether of ethyl lactate cleaves the aryl–oxygen bond, forming picramide or phenylpicramide and, presumably, methanol or ethyl lactate. As a contrast to the more usual reactivities of ethers, one may note that these ethers are soluble in concentrated hydrochloric acid without reaction at the same temperature at which they react readily with amines (119).

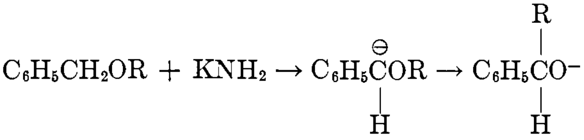
N,*N*-Dimethyl-α- and *N*,*N*-dimethyl-β-naphthylamines react like dimethylaniline but higher temperatures, about 100°C., are required (115). The naphthylamines similarly require higher temperatures than aniline (119). Diphenylamine is unreactive (119).

D. Reaction with the amide ion

Reaction with such reagents as potassium amide has been little investigated. Potassium amide in liquid ammonia demethylates 3,4-dimethoxybenzoic acid but not nearly so well as elementary potassium in liquid ammonia. The phenol is formed and, presumably, methylamine (73).

Sodium amide is reported to react with monomethyl ethers of dihydric phenols when stirred in an autoclave with tetralin at 200°C., but anisole and the dimethoxybenzenes are reported to be unreactive (198). *l*-Menthyl ethyl ether is not cleaved by sodium amide apparently under the same conditions (127). Optically active methyl *sec*-butyl ether is unaffected by lithium amide at 80°C. in 20 hr. (45). Other basic reagents, sodium hydride and lithium aluminum hydride, are also without effect under similar conditions.

Strong bases may cause rearrangement of some benzyl ethers like those resulting from organometallic reagents (109). The following reaction occurs in some cases:



$$C_6H_5CH_2OR + KNH_2 \rightarrow C_6H_5\underset{\displaystyle H}{\overset{\ominus}{C}}OR \rightarrow C_6H_5\underset{\displaystyle H}{\overset{\displaystyle R}{C}}O^-$$

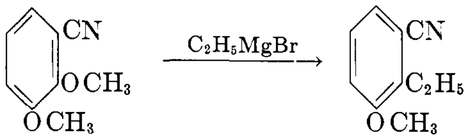
When R is ethyl, elimination occurs.

E. Displacement on the ring with organometallic reagents

As described in Section IX, anisole reacts with Grignard reagents by displacement on methyl.

$$C_6H_5OCH_3 + RMgX \rightarrow C_6H_5OMgX + CH_3R$$

However, with activating groups on the ring, instances of displacement on phenyl are known, as, for example (231):



Nitro groups cannot be used because of their reactivity with Grignard reagents; in many cases the cyano group reacts preferentially with Grignard reagents (77). Owing to steric hindrance mesitoyl groups activate without reacting. Apparently an ortho pair of methoxyl groups is necessary and there must be a cyano or a hindered keto group in the ortho or para position to one of the methoxyl groups (76). In view of the generally important role of addition compounds of Grignard reagents and ethers and in view of the requirement of the ortho pair of methoxyl groups, the reaction is probably not a simple nucleophilic displacement on the ring, but it does seem to have some of this character.

There is a report that traces of isoamylbenzene result from the action of isoamylmagnesium bromide on anisole (263).

This general type of cleavage by Grignard reagents has been reviewed by Gaertner (78).

Triphenylmethylsodium cleaves phenyl ether. After a reaction period of 2 weeks at 80°C., phenol (44 per cent), tetraphenylmethane (16 per cent), and the isomerization product, *o*-hydroxybiphenyl (4 per cent), were isolated (166). This reaction apparently constitutes a case of nucleophilic displacement on an aromatic ring carbon atom.

F. Summary of relative tendency to displacement on alkyl and on the ring

The data are inadequate to firm conclusions but the following generalizations appear likely: (*1*) Unactivated alkyl aryl ethers react by nucleophilic displacement on the alkyl carbon atom adjacent to the oxygen atom. (*2*) Activating groups such as nitro or cyano more greatly augment the rate of displacement on the ring than that on alkyl. (*3*) When two or more nitro groups are substituted on the ring, hydroxide and alkoxide ions, ammonia, and primary amines react by substitution on the ring but secondary and tertiary amines react by displacement on alkyl. The behavior of secondary and tertiary amines may be largely a matter of steric hindrance, since models show that the transition state or intermediate for displacement on the ring involves crowding when nitro groups are present in the 2- and 6-positions.

IX. CLEAVAGE BY ORGANOMETALLIC COMPOUNDS

A. Grignard reagents

The reaction of Grignard reagents with ethers was discovered by Grignard (97). At 160°C. amylmagnesium bromide reacted with phenetole. Hydrolysis of the reaction mixture resulted in a good yield of phenol, but the products of the aliphatic portion of the ether were not examined. Grignard assumed, apparently by analogy with the results of Schorigin with sodium alkyls (239), that the reaction proceeded thus:

$$C_6H_5OC_2H_5 + C_5H_{11}MgBr \rightarrow C_6H_5OMgBr + C_2H_4 + C_5H_{12}$$

On the other hand, Simonis and Remmert (251) found that similar reaction occurred under the same conditions between anisole and methylmagnesium iodide. They assumed the reaction to be a coupling:

$$C_6H_5OCH_3 + CH_3MgI \rightarrow C_6H_5OMgI + CH_3CH_3$$

Since phenetole behaved similarly, they assumed that propane was the product, though they did not show that the evolved gas was not methane and ethylene.

Actually, both reactions apparently occur simultaneously with phenetole and methyl- or ethylmagnesium halide (98), although the relative degrees of the two reactions have not been reported.

The reactions may be represented as second-order displacement and second-order elimination reactions by a carbanion:

$$C_6H_5OCH_2CH_3 + R^- \rightarrow C_6H_5O^- + RCH_2CH_3$$

$$C_6H_5OC_2H_5 + R^- \rightarrow C_6H_5OCH_2CH_2^- + RH \rightarrow C_6H_5O^- + CH_2{=}CH_2 + RH$$

The second reaction might, of course, be concerted rather than two-stage. In any case, the representation must be oversimplified and the reacting species, as Grignard himself suggested (97), is most likely the Grignard reagent–ether complex.

Ordinary aliphatic ethers are very unreactive with Grignard reagents. Thus, isoamyl ether is only very slightly cleaved in 2.5 days at 200–215°C. by methylmagnesium iodide (263), although 5-ethoxy-2-methylhexane is about 10 per cent decomposed in 4 hr. at 180°C., giving some heptylenes.

In alkyl aryl ethers the oxygen atom is relatively more positively charged. The relative positive charge induced on R should increase the ease both of the displacement and of the elimination reaction.

At about 170°C. both anisole and *o*-dimethoxybenzene are demethylated to give good yields of the appropriate phenols (263).

Phenyl ether is partially cleaved in 15 hr. at 180°C. to give phenol and *o*-hydroxybiphenyl (263). Anisole and isoamylmagnesium iodide under similar conditions yield phenol (78 per cent) plus a little isoamylbenzene (263). Any isohexane would have been lost under the conditions of the reaction. If the reported identification of isoamylbenzene is correct, its formation would constitute a particularly simple example of nucleophilic displacement on a benzene ring carbon atom. Such reaction of simple aryl ethers is uncommon (see Section VIII).

Ethyl benzyl ether reacts with propylmagnesium iodide at reflux to give butylbenzene, 1,2-diphenylethane, and ethanol (after hydrolysis) (54). Ethyl benzhydryl ether gives corresponding products.

Ethyl benzyl ether is also reported to react with methylmagnesium bromide at 170°C. to give a 40 per cent yield of ethylbenzene together with some benzyl ether. Under the same conditions, benzyl ether reacts to give roughly 60 per cent yields of ethylbenzene and benzyl alcohol (263). Phenyl benzyl ether with ethylmagnesium bromide gives propylbenzene and phenol.

Apparently the benzyl group enters into a coupling reaction much more readily than alkyl or aryl groups with consequent disappearance of the elimination reaction.

Allyl ethers are more reactive than benzyl ethers. Thus, allyl phenyl ethers react in boiling ethyl ether solution with aryl and alkyl Grignard reagents to give good yields of the coupling product, $CH_2{=}CHCH_2R$, whereas phenyl benzyl ether does not react at 80°C. (165). Butyl- and phenylmagnesium bromides cleave phenyl allyl ether at room temperatures, although the reaction takes several days (164).

It might be supposed that the cleavage occurs by action of MgX_2 produced by disproportionation of the Grignard reagent,

$$2RMgX_2 \rightarrow R_2Mg + MgX_2$$

Reaction with an allyl ether, $R'OCH_2CH{=}CH_2$, would form $R'OMgX$ and $CH_2{=}CHCH_2X$. The latter compound would then react with R_2Mg. However, this possibility is excluded by the fact that pure diphenylmagnesium reacts with allyl phenyl ether as well as phenylmagnesium bromide does (166).

In such allyl ether cleavage, bromides and chlorides were reported to give better results than iodides (165), but iodides were reported to give better results in reaction with alkyl phenyl ethers (98).

B. Alkali metal alkyls

Reaction between ethers and organometallic compounds was first reported by Schorigin in 1910 (239). He found that ethylsodium attacked ethyl ether at room temperature in the sense of the following equation:

$$C_2H_5Na + (C_2H_5)_2O \rightarrow C_2H_5H + CH_2{=}CH_2 + NaOC_2H_5$$

Phenetole and anisole led to sodium phenoxide. The reaction is thus equivalent to the elimination reaction in the case of reaction with Grignard reagents.

The only definite case of coupling reported for alkyl ethers is in the interaction of ethylsodium with ethyl *l*-menthyl ether in cyclohexane solution. The products were reported to be menthol in 70 per cent yield and ethylmenthane in 33 per cent. Ethyl *d*-neomenthyl ether behaved similarly (127).

In most of the cases described below, attention has been primarily directed to the olefin and little attention has been given to the detection of possible coupling products. The literature indicates that olefin formation predominates over coupling more than in the case of Grignard reactions, but this generalization may entirely result from lack of attention to possible coupling products.

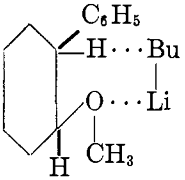
With 2-methoxyoctane, amylsodium yields an octene which is very largely 1-octene (159).

Cholesteryl ethyl, isopropyl, or tertiary butyl ethers and amylsodium at 10°C. form cholesterol (after hydrolysis) and the olefin derived from the alkyl group. Small amounts of cholestadiene also appear. If the alkyl groups lack a β-hydrogen atom (methyl or benzyl), then cholestadiene is formed exclusively. No trace of alkylcholestenes could be detected (93).

Sodium alkyls split alkyl aryl ethers mainly to phenoxide and olefin (166). Exactly what happens to the methyl radical in the cleavage of anisole is not clear from existing data.

Lithium alkyls also attack the simpler alkyl ethers but much more slowly. For example, although the action of amylsodium and isopropyllithium on 2-methoxyoctane leads to the same products, reaction with the first is complete in a few hours at 0°C. while reaction with the second requires many hours at 35°C. (159).

Methyl *trans*-2-phenylcyclohexyl ether is attacked by butyllithium about eight times faster than the *cis* analog. Since methyl cyclohexyl ether does not react detectably under the same treatment, the hydrogen atom in the 2-position—which is activated by the phenyl group—is probably the one lost. Thus, elimination occurs more rapidly when the methoxyl radical and a hydrogen atom are *cis* to one another (158). Letsinger has proposed that a transition state of the following nature is involved:



The following reaction proceeds satisfactorily in ethyl ether

$$RCl + 2Li \rightarrow RLi + LiCl$$

and the lithium alkyl can be used for further reactions in the same solvent (88, 308). However, ethyl ether is slowly attacked by lithium alkyls (308).

Methyllithium is the most stable lithium organometallic compound. In a year at room temperatures, the titer in carbanion of an ethyl ether solution declined to about one-quarter, whereas in a few days at 35°C. butyllithium had completely disappeared (108). The order of increasing rate of cleavage by organolithium compounds is aryl, ethyl, isopropyl, *tert*-butyl.

Methyl ether is less reactive than ethyl ether by a factor of 10–20 in rate (309). In reaction between ethyl ether and butyllithium, the following reaction is the only one observed:

$$C_4H_9Li + (C_2H_5)_2O \rightarrow CH_2{=}CH_2 + C_2H_5OLi + C_4H_{10}$$

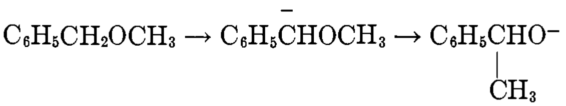
With methyl ether, however, butane, pentane, hexane, heptane, and octane are formed in addition to a quantitative yield of lithium methoxide.

$LiCH_2OCH_3$, formed by transmetalation by butyllithium, was proposed as the origin of the higher alkanes.

Methyl butyl ether behaves like methyl ether in giving a mixture of higher alkanes.

In 1 hr. at 50°C. phenyllithium almost completely cleaves allyl phenyl ether although, under similar conditions, no reaction occurs with anisole, butyl ether, *sec*-butyl phenyl ether, and phenyl ether (164). With phenyl benzyl ether, the simple coupling product, diphenylmethane, is isolated but four times as much 1,1,2-triphenylethane is formed, apparently by exchange of lithium between phenyllithium and a hydrogen atom in the α-position of phenyl benzyl ether. Reference 166 may be cited for a comprehensive coverage of such side reactions.

In addition, the aromatic ring may be transmetallated (86a) and ether rearrangement may occur in certain benzyl ethers (109, 304), as, for example:



$$C_6H_5CH_2OCH_3 \rightarrow C_6H_5\overset{-}{C}HOCH_3 \rightarrow C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HO^-$$

X. CLEAVAGE BY ALKALI METALS

Under suitable conditions aryl ethers are cleaved by alkali metals:

$$ROR' + 2Na \rightarrow RONa + NaR'$$

Aliphatic ethers are resistant to such attack at temperatures below 200°C. Isoamyl ether suffers only slight decomposition at 275°C. in a sealed tube (240). This ether may be boiled for hours with sodium-potassium alloy in an atmosphere of hydrogen without decomposition (241). Heating with sodium-potassium alloy for several days at 190–200°C. is without effect upon aliphatic ethers such as propyl isobutyl ether, isopropyl butyl ether, and methyl isopropyl ether (113). Terpineol methyl ether (b.p. 212°C.) can be distilled from the alloy without reaction, as can the ether of camphene hydrate (310).

An early report that aliphatic ethers readily react with sodium or the liquid potassium-sodium alloy (63) must have resulted from the use of impure ethers.

Ethyl ether heated with sodium at temperatures reaching 340°C. yields ethylene, a trace of sodium ethoxide, and perhaps ethane and hydrogen. Isoamyl ether similarly treated at up to 360°C. gives amylenes but no sodium isoamoxide (241).

Even if aliphatic ethers should cleave under such drastic conditions in the sense of the equation given above, one could not expect to isolate sodium alkoxides or sodium alkyls. Sodium amoxide decomposes at 275°C. (201). Sodium alkyls would be expected to attack unreacted ether thus (159):

$$RNa + \text{—}CH_2CH_2OR' \rightarrow RH + NaOR' + \text{—}CH{=}CH_2$$

Aliphatic ethers resist other treatments which cleave aryl, benzyl, and allyl ethers. Isoamyl ether is not cleaved by treatment with sodium in liquid ammonia (244) nor is ethyl *l*-menthyl ether (127). Isoamyl ether is not cleaved by the pyridine-sodium addition compound at temperatures of refluxing pyridine (223).

On the other hand, diphenyl ether, one of the most resistant of ethers to acidic (proton or Lewis) reagents, is cleaved by sodium at 180°C. (240) or by the liquid potassium-sodium alloy at room temperatures (199). In the latter case the reaction proceeds nearly quantitatively according to the equation:

$$(C_6H_5)_2O + 2Na \rightarrow C_6H_5ONa + C_6H_5Na$$

In the former case some biphenyl, some rearrangement products, and resinous substances are also formed. Treatment with bulk sodium requires too high a temperature, owing to the small area and the coating of insoluble substances which form on the metal. Sodium powder or "sand" is effective at room temperatures, at least in certain cases (160, 310, 311).

Phenyl naphthyl ethers are cleaved by bulk sodium at 140°C. (241). With both α- and β-naphthyl, the cleavage proceeds about five to seven times more rapidly to form phenol than to form naphthol.

Ethers in which one of the radicals consists of benzyl or α-substituted benzyl also cleave readily. With bulk sodium, phenyl benzyl ether is cleaved slowly at 39°C. and readily at 100°C. The oxygen–benzyl bond is broken exclusively, though there is some rearrangement to benzhydrol, probably by the action of sodium benzyl (see Section IX). Ethyl benzyl ether is cleaved at 140°C. The benzyl–oxygen bond is mainly cleaved, but a little sodium ethoxide is also formed (241). *o*-Tolyl triphenylmethyl ether is cleaved at 100°C., again with exclusive cleavage of the benzyl–oxygen bond but with some rearrangement to *o*-triphenylmethylphenol, while phenyl benzhydryl ether is cleaved principally to sodium phenoxide and benzhydrylsodium, but considerable tetraphenylethane and the sodium salt of triphenylcarbinol are also formed (242).

Ethers of this type are more readily cleaved by the liquid potassium–sodium alloy or sodium or potassium powder. Methyl and phenyl triphenylmethyl ethers are readily cleaved at room temperatures to form triphenylmethylpotassium (or sodium) and the alkali metal methoxide or phenoxide (311). Benzhydryl ether and ethyl benzhydryl ether react similarly (311), as do ethyl 1,1-diphenylethyl ether and methyl 2-phenyl-2-propyl ether (310).

Allyl ether is readily cleaved by sodium powder in hexane at 35°C. to form allylsodium and sodium alloxide. This appears to be the method of choice for preparing allylsodium (160).

Alkyl phenyl ethers apparently are cleaved with more difficulty. Thus, phenetole reacts with bulk sodium only at 200°C. Under these drastic conditions one gets sodium phenoxide and a trace of sodium ethoxide and ethane, ethylene, and high-boiling materials (241).

Sodium in liquid ammonia at −33°C. cleaves a wide variety of diaryl ethers (236), phenyl benzyl ethers (244), and alkyl aryl ethers (23, 74). The aryl ethers are cleaved more rapidly than the alkyl aryl ethers. For example, methoxyphenyl phenyl ethers which are both diaryl ethers and alkyl aryl ethers are cleaved exclusively at the aryl–oxygen–aryl linkage (236).

A blue solution of alkali metal in ammonia is essential. After such a solution reacts to one of the alkali metal amides it becomes ineffective (74, 295). The effective reactant is therefore the solvated electron and the reaction may be written as follows (236):

$$\mathrm{ROR'} + 2e \rightarrow \mathrm{R^-} + \mathrm{R'O^-}$$

This reaction, owing to the acidic nature of ammonia, is followed by

$$\mathrm{R^-} + \mathrm{NH_3} \rightarrow \mathrm{RH} + \mathrm{NH_2^-}$$

for alkyl and aryl carbanions, though not for conjugate bases of more acidic hydrocarbons such as triphenylmethane.

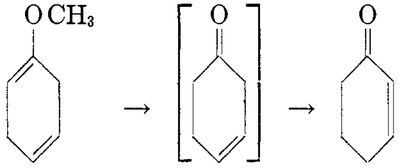
Substituents attached to the benzene ring strongly affect which phenyl–oxygen linkage is cleaved in diaryl ethers. Thus, phenyl *p*-carboxyphenyl ether gives a 100 per cent yield of phenol, whereas phenyl *p*-aminophenyl gives a 100 per cent yield of *p*-aminophenol (236).

Phenyl 1-naphthyl and phenyl 2-naphthyl ethers cleave both ways but the three dinaphthyl ethers (1,1-, 1,2-, and 2,2-) give resinous substances (281).

Phenyl benzyl ether yields phenol and bibenzyl but no benzhydrol (244) in contrast to the case of bulk sodium at 100°C. (241). *o*-Tolyl triphenylmethyl ether yields *o*-cresol and triphenylmethane.

Potassium in liquid ammonia cleaves anisole substantially quantitatively to phenol and presumably methane. Veratrole forms guaiacol and catechol (74). One would expect the second stage of ether cleavage to proceed more slowly than the first, since the negative charge on the ion, $CH_3OC_6H_4O^-$, should oppose further electron addition. The methoxyl groups in lignin are largely but not completely converted to hydroxyl by potassium in liquid ammonia (73).

In the presence of ethanol, the action of sodium in liquid ammonia on alkyl aryl ethers is accompanied by reduction of the aryl group. About 10 per cent of phenol is obtained by demethylation as in the absence of ethanol. In addition, 20–40 per cent of an unsaturated ketone is formed, as a result, presumably, of reduction by hydrogen atoms rather than by electrons (22).



In special cases, cleavage of methyl aryl ethers can be effected by the action of metallic sodium on a hot alcoholic solution of the ether. Pyrogallol trimethyl ether is cleaved to resorcinol dimethyl ether. Ethers of monohydric phenols are unaffected by this procedure, while ethers of dihydric phenols are cleaved but slightly (278).

Sodium in pyridine cleaves ethers by a process probably related to that with sodium in ammonia (223). Sodium and pyridine form an addition compound which is partially soluble in pyridine and which upon the addition of water yields tetrahydrodipyridyls. When the addition compound in pyridine is refluxed with phenyl ether, a 90 per cent yield of phenol and benzene results. Potassium and lithium behave similarly. Phenyl *o*-hydroxyphenyl ether gives both phenol and catechol although, with phenyl *p*-hydroxyphenyl ether, sodium in liquid ammonia gives further reduction products of an unidentified nature (295). The sodium–pyridine addition compound cleaves phenyl benzyl ether to phenol and presumably toluene, and also cleaves anisole and phenetole to phenol, all in good yields.

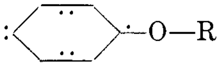
Although the mechanism of ether cleavage by alkali metals cannot be worked out in detail, certain aspects seem clear. The fission of the carbon–oxygen bond presumably occurs either from a species with a single negative charge or from a species with a double negative charge,

$$ROR^- \rightarrow RO^- + R\cdot$$

or

$$ROR^{--} \rightarrow RO^- + R^-$$

although the ready mobility of electrons in ammonia (metallic conductivity) makes exact location of the charge rather tenuous. The electron affinity of free radicals appears sufficiently favorable (224) to assure that any reaction occurring according to the first equation would be rapidly followed by $R\cdot + e \rightarrow R^-$. In either case, if one or both of the R groups are aryl, an electron can enter the first vacant molecular orbital to which a resonance hybrid of twelve forms similar to the one given below is equivalent. Only the π electrons are shown.



Substituents which tend to place a positive charge on the ring will facilitate such addition. Such substituents would, furthermore, stabilize both R^- and RO^-. However, owing to the relatively high free energy of the carbanion (in the sense of $RH \rightarrow R^- + H^+$ *vs.* $ROH \rightarrow RO^- + H^+$) stabilizing substituents should preferentially lead to formation of the more stabilized carbanion (23, 24).

From competitive cleavage of unsymmetrically substituted diphenyl ethers (148, 236, 295), it is found that substituents increase the relative ease of cleavage of the bond between oxygen and the ring to which the substituent is attached in the following order of increasing effect: *p*-amino, *o*-amino, *m*-amino, *p*-methoxy, *p*-*tert*-butyl, *p*-methyl, *m*-methyl, *o*-methyl, no substituent, *m*-methoxy, *o*-methoxy, *m*-carboxy, *o*-carboxy, and *p*-carboxy. A similar order exists for the effect on the absolute rate of cleavage of phenyl-substituted alkyl phenyl ethers (23). This order is nearly the same as that of substituent constants, σ, in Hammett's $\sigma\rho$ relationship (104, page 188), although *m*-amino and *p*-methoxy are inverted and the wide separation of *o*- and *p*-methoxy seems odd.

For variation in the alkyl part of alkyl phenyl ethers, the order of increasing rate is isopropyl, propyl, methyl, —CH_2COOH, benzyl (23). For example, the methyl group was removed first from *o*-methoxyamoxybenzene.

The order given is that of increasing stability of carbanions and not that of free radicals. Birch (24) has contended that this indicates that a species with a double negative charge is involved in the transition state. The occurrence of bibenzyl as a product in the cleavage of benzyl ethers may then be ascribed to the following reaction (see Section IX) rather than to free-radical combination:

$$C_6H_5CH_2^- + C_6H_5CH_2OR \rightarrow C_6H_5CH_2CH_2C_6H_5 + RO^-$$

XI. HETEROGENEOUS CATALYTIC CLEAVAGE

There are not many examples of the application of heterogeneous catalysis to ether cleavage reactions. Perhaps the most interesting is the hydrogenolytic cleavage of benzyl ethers in the sense of the equation:

$$C_6H_5CH_2OR + H_2 \rightarrow C_6H_5CH_3 + HOR$$

Benzylation with later debenzylation has received some application as a means of protecting hydroxyl groups during reaction.

The carbon–oxygen bond is as readily cleaved in similar alcohols and ketones as in ethers. Therefore, no attempt will be made to cover the subject exhaustively, particularly since the general subject of the hydrogenolysis of benzyl groups is the subject of a recent review (107).

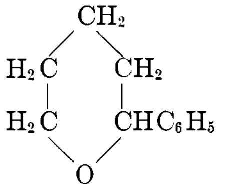
Simple aliphatic ethers are unaffected by Raney nickel at 200°C. and a pressure of 200 atm. of hydrogen. In fact, the hydrogenolysis of the carbon–oxygen bond in such molecules is probably nearly as difficult as that of the carbon–carbon bond (288).

At temperatures of 100–150°C. benzyl ethers react readily and somewhat more easily when R is aryl than when it is alkyl. It is usually possible to cleave aryl benzyl ethers without hydrogenating R.

At 200°C. hydrogenolysis of phenyl alkyl ethers occurs but usually at a rate much slower than that of hydrogenation of the benzene ring. An alkyl cyclohexyl ether will be stable at 200°C.

With nickel (148) or nickel oxide (138), high pressures of hydrogen, and temperatures of about 240°C., phenyl ether is largely cleaved and hydrogenated to benzene and cyclohexanol.

Cleavage of benzyl ether can be effected with spongy palladium at 50°C. and a pressure of 1 atm. (52) and with palladium on charcoal in glacial acetic acid in the presence of small amounts of sulfuric or perchloric acid (11). Cyclic ethers may also be hydrogenolyzed as, for example (11):



$$\rightarrow HOCH_2CH_2CH_2CH_2CH_2C_6H_5$$

Since alumina catalyzes the formation of ethers from alcohols, as, for example, methyl ether from methanol (135), alumina should catalyze the hydrolysis of ethers. Hydrolysis of methyl ether, occurs, in fact, at a convenient rate at 330–370°C. (2). Hydrolysis of ethyl ether has also been reported at 320–330°C. and a pressure of 7–13 atm. (180). The last reaction is complicated by olefin formation, as might be expected, since alumina catalyzes the dehydration of alcohols. Similar hydrolytic reactions have been patented for acid-treated clays of the type of Super-Filtrol at 200–250°C. (280) and aluminum fluoride at about 260°C. (176). The last two catalysts are known to be acidic. The cleavage reactions may somewhat resemble those occurring in homogeneous systems in the presence of acids. This is particularly true for a catalyst of sulfuric acid promoted by copper sulfate and deposited on silica gel with which equilibrium constants for the dehydration of ethanol to ethyl ether were measured (286).

The hydrolysis of allyl ether may be effected at 190°C. on a catalyst of copper sulfate deposited on alumina (55).

The following reaction occurs quantitatively at 280°C. on activated alumina to yield a product of high purity (68):

$$C_6H_5NH_2 + (CH_3)_2O \rightarrow C_6H_5N(CH_3)_2 + H_2O$$

Use of methyl ether is preferred to that of methanol because of higher yield and purity and lower operating temperatures.

"Solid phosphoric acid" (which appears to be representable as a condensation polymer of silicic and phosphoric acids) catalyzes the formation of methyl ether from methanol at 350°C. and of methyl ethyl ether and methyl benzyl ether from the mixed alcohols (136). The reverse reactions could presumably be effected but would be complicated in the case of ethyl groups by the formation of ethylene and in the case of benzyl groups by the formation of polymer. The following reaction was effected on this catalyst in batch operation at 150°C.:

$$(CH_3)_2O + (C_2H_5)_2O \rightarrow 2CH_3OC_2H_5$$

XII. CLEAVAGE OF THIOETHERS

A cursory treatment of the cleavage of thioethers follows.

Comparisons of certain aspects of the cleavage of ethers and of thioethers have recently been presented (131, 276). The two types seem to be cleaved by similar processes in most cases, although thioethers are cleaved very much less readily both with acidic and with basic reagents, as is illustrated by a table taken from Hughes and Thompson (131).

Phenyl benzyl sulfide is cleaved by aluminum bromide and by hydrogen bromide in glacial acetic acid but much less readily than phenyl benzyl ether. However, less nuclear alkylation seems to occur with the benzyl fragment with

TABLE 8

Comparison of the cleavage of anisole and thioanisole

Reagent	Reaction Conditions	Yield of Demethylated Product	
		Anisole	Thioanisole
		per cent	*per cent*
Hydriodic acid, hydrobromic acid	2 hr., 130°C.	100	0
Pyridine hydrochloride	6 hr., 200°C.	100	0
Magnesium iodide	1 hr., 200°C.	58	0
Aluminum chloride	2 hr., 100°C.	100	20
Potassium hydroxide in ethanol	7 hr., 200°C.	7	0
Sodium in pyridine	5 hr., 120°C.	94	62
Sodium in liquid ammonia	15 hr.	100	100

the thioether than with the ether. The ease of cleavage by aluminum bromide of alkyl phenyl sulfides increases in the series methyl < isopropyl < *tert*-butyl. The rates are very much slower than with the oxygen analogs. Phenyl benzhydryl and phenyl trityl sulfides are cleaved by aluminum bromide more readily than phenyl benzyl sulfide. In these cases some diphenyl disulfide is formed. The analogous side reaction does not occur with any ether, of course (276).

Acetyl iodide cleaves thioethers, although much more slowly than ethers (99).

Phenyl 2-nitrophenyl sulfide is untouched by refluxing piperidine under conditions under which the analogous ether reacts slowly (155).

In so far as proton acids are concerned, sulfides are much less basic than the corresponding ethers. Although sulfonium salts, R_3S^+, form more readily and are more stable than oxonium salts, R_3O^+, contributions of the following structure to the resonance hybrid are greater in ethers (7).

$$R—\overset{+}{O}=R^-$$

Apparently, then, the S—R bond is less easily cleaved by nucleophilic displacement and the conjugate acid of the thioether is less easily formed.

On the other hand, alkyl aryl sulfides and diaryl sulfides are at least as easily cleaved by alkali metals as the ether analogs (131, 241a, 311). Furthermore, while dialkyl ethers are very resistant to alkali metals and in particular to sodium in liquid ammonia, dialkyl sulfides such as ethyl sulfide, propyl sulfide, and isoamyl sulfide are readily split (303),

$$R_2S + 2Na + NH_3 \rightarrow RSNa + RH + NaNH_2$$

presumably via the reaction:

$$R_2S + 2Na \rightarrow RS^- + R^- + 2Na^+$$

Perhaps, unlike the case with an ether, an electron (or perhaps two) can be added to the sulfur atom to form R_2S^- or R_2S^{--}, which then dissociates. Sulfur can probably have more than eight electrons in the outer shell, while oxygen cannot. This situation may be connected with ready desulfurization by Raney nickel. Analogous reaction with ethers occurs only with benzyl ethers.

XIII. REFERENCES

(1) Addison, C. C., Lewis, J., and Thompson, R.: J. Chem. Soc. **1951**, 2829.
(2) Adkins, H., and Perkins, P. D.: J. Phys. Chem. **32**, 221 (1928).
(3) Alphen, J. van: Rec. trav. chim. **49**, 492 (1930).
(4) Audrieth, L. F., Long, A., and Edwards, R. E.: J. Am. Chem. Soc. **58**, 428 (1936).
(5) Baddar, F. G.: Nature **153**, 377 (1944).
(6) Baddeley, G.: J. Chem. Soc. **1944**, 330.
(7) Baddeley, G.: J. Chem. Soc. **1950**, 663.
(8) Baeyer, A.: Ber. **26**, 2560 (1893).
(9) Baeyer, A., and Villiger, V.: Ber. **34**, 2679 (1901).
(10) Baeyer, A., and Villiger, V.: Ber. **36**, 2791 (1903).
(11) Baker, R. H., Cornell, K. H., and Cron, M. J.: J. Am. Chem. Soc. **70**, 1490 (1948).
(12) Baker, W., Nodzu, R., and Robinson, R.: J. Chem. Soc. **1929**, 74.

(13) Balfe, M. P., Doughty, M. A., Kenyon, J., and Poplett, R.: J. Chem. Soc. **1942,** 605.
(14) Bamberger, E.: Ber. **19**, 1818 (1886).
(15) Basler Chemische Fabrik: German patent 162,658; Chem. Zentr. **1905, II**, 1061.
(16) Bedson, P. P.: Ann. **180,** 235 (1876).
(17) Belov, V. N., and Finkelshtein, M. Z.: J. Gen. Chem. (U. S. S. R.) **16,** 1248 (1946); Chem. Abstracts **41,** 3066 (1947).
(18) Belov, V. N., and Shepelenkova, E. I.: J. Gen. Chem. (U. S. S. R.) **11,** 757 (1941); Chem. Abstracts **36,** 419 (1942).
(19) Benton, F. L., and Dillon, T. E.: J. Am. Chem. Soc. **64,** 1128 (1942).
(20) Berg, G. A., and Holmberg, B.: Svensk Kem. Tidskr. **47,** 257 (1935).
(21) Bert, L.: Compt. rend. **222,** 898 (1946).
(22) Birch, A. J.: J. Chem. Soc. **1944,** 430.
(23) Birch, A. J.: J. Chem. Soc. **1947,** 102.
(24) Birch, A. J.: Quart. Revs. (London) **4,** 69 (1950).
(25) Birosel, D. M.: J. Am. Chem. Soc. **52,** 1944 (1930).
(26) Birosel, D. M.: J. Am. Chem. Soc. **53,** 1408 (1931).
(27) Blackler, M. B.: Chem. News **83,** 303 (1901).
(28) Blaise, E. E.: Compt. rend. **139,** 1211 (1904).
(29) Blaise, E. E.: Compt. rend. **140,** 661 (1905).
(30) Böck, F.: Monatsh. **23,** 1017 (1902).
(31) Bonhoeffer, K. F., and Reitz, O.: Z. physik. Chem. **179A,** 143 (1937).
(32) Borrows, E. T., Clayton, J. C., Hems, B. A., and Long, A. G.: J. Chem. Soc. **1949,** S190.
(33) Borsche, W.: Ber. **56B,** 1488 (1923).
(34) Borsche, W.: Ber. **56B,** 1494 (1923).
(35) Bourguignon, A.: Bull. soc. chim. Belg. **22,** 87 (1908).
(36) British Celanese Ltd.: British patent 642,489; Chem. Abstracts **46,** 132 (1952)
(37) Brown, H. C., and Adams, R. M.: J. Am. Chem. Soc. **64,** 2557 (1942).
(38) Brown, H. C., Barbaras, G. K., Berneis, H. L., Bonner, W. H., Johannesen, R. B., Grayson, M., and Nelson, K. L.: J. Am. Chem. Soc. **75,** 1 (1953).
(39) Bunnett, J. F., and Zahler, R. E.: Chem. Revs. **49,** 273 (1951).
(40) Burton, H., and Hoggarth, E.: J. Chem. Soc. **1945,** 14.
(41) Burton, H., and Hopkins, H. B.: J. Chem. Soc. **1952,** 4457.
(42) Burton, H., and Praill, P. F. G.: J. Chem. Soc. **1951,** 522.
(43) Burton, H., and Praill, P. F. G.: J. Chem. Soc. **1951,** 726.
(44) Burwell, R. L., Jr., and Archer, S.: J. Am. Chem. Soc. **64,** 1032 (1942).
(45) Burwell, R. L., Jr., Elkin, L. M., and Maury, L. G.: J. Am. Chem. Soc. **73,** 2428 (1951).
(46) Burwell, R. L., Jr., Elkin, L. M., and Shields, A. D.: J. Am. Chem. Soc. **74,** 4567 (1952).
(47) Burwell, R. L., Jr., Elkin, L. M., and Shields, A. D.: J. Am. Chem. Soc. **74,** 4570 (1952).
(48) Butlerow, A.: Ann. **118,** 325 (1861).
(49) Cahn, R. S.: J. Chem. Soc. **1931,** 1121.
(50) Cason, J., and Mills, R. H.: J. Am. Chem. Soc. **73,** 1354 (1951).
(51) Cass, O. W.: Ind. Eng. Chem. **40,** 216 (1948).
(52) Cavallito, C. J., and Buck, J. S.: J. Am. Chem. Soc. **65,** 2140 (1943).
(53) Chelinzev, V., and Koslow, N.: J. Russ. Phys. Chem. Soc. **46,** 708 (1914); Chem. Zentr. **1915, I,** 828.
(54) Chelinzev, V., and Pavlov, B.: J. Russ. Phys. Chem. Soc. **45,** 289 (1913); Chem. Zentr. **1913,** 1962.
(55) Cheney, H. A., Dagley, R., and McAllister, S. H.: U. S. patent 2,434,394; Chem. Abstracts **42,** 3425 (1948).

(56) Cloke, J. B., and Pilgrim, F. J.: J. Am. Chem. Soc. **61,** 2667 (1939).
(57) Collie, J. N., and Tickle, T.: J. Chem. Soc. **75,** 710 (1899).
(58) Cottrell, F. G., and Rogers, R. R.: Am. Chem. J. **21,** 64 (1899).
(59) Cullinane, N. M., Chard, S. J., and Leyshon, D. M.: J. Chem. Soc. **1952,** 4106.
(60) De Lange, P. W.: Rec. trav. chim. **38,** 101 (1919).
(61) Descudé, M.: Compt. rend. **132,** 1129 (1901); Ann. chim. phys. [7] **29,** 497 (1903).
(62) Diels, O., and Bunzl, F.: Ber. **38,** 1486 (1905).
(63) Durand, J. F.: Compt. rend. **172,** 70 (1921).
(64) Egorova, O. I.: Ukrains. Khem. Zhur. **4,** Sci. Pt. 193 (1929); Chem. Zentr. **1930, I,** 359.
(65) Egorova, O. I.: J. Russ. Phys. Chem. Soc. **62,** 1097 (1930); Chem. Zentr. **1930, II,** 3548.
(66) Erickson, J. L. E., and Ashton, W. H.: J. Am. Chem. Soc. **63,** 1769 (1941).
(67) Erlenmeyer, E., and Kriechbaumer, A.: Ber. **7,** 699 (1874).
(68) Evans, T. H., and Bourns, A. N.: Can. J. Technol. **29,** 1 (1951).
(69) Evans, W., and Edlund, K. R.: Ind. Eng. Chem. **28,** 1186 (1936).
(70) Fenton, H. J. H., and Gostling, M.: J. Chem. Soc. **73,** 554 (1898).
(71) Fisher, L. H.: U. S. patent 2,108,937; Chem. Abstracts **32,** 2958 (1938).
(72) Fox, D. L., and Turner, E. E.: J. Chem. Soc. **1930,** 1115.
(73) Freudenberg, K., Engler, K., Flickinger, E., Sobek, A., and Klink, F.: Ber. **71B,** 1810 (1938).
(74) Freudenberg, K., Lautsch, W., and Piazolo, G.: Ber. **74B,** 1879 (1941).
(75) Fried, S., and Kleene, R. D.: J. Am. Chem. Soc. **63,** 2691 (1941).
(76) Fuson, R. C., and Gaertner, R.: J. Org. Chem. **13,** 496 (1948).
(77) Fuson, R. C., Gaertner, R., and Chadwick, D. H.: J. Org. Chem. **13,** 489 (1948).
(78) Gaertner, R.: Chem. Revs. **45,** 493 (1949).
(79) Galmarini, O.: Anales assoc. quím. argentina **38,** 19 (1950); Chem. Abstracts **45,** 572 (1951).
(80) Gattermann, L., Ehrhardt, R., and Maisch, H.: Ber. **23,** 1199 (1890).
(81) Germann, A. F. O.: J. Am. Chem. Soc. **47,** 2461 (1925).
(82) Gerrard, W., and Lappert, M. F.: J. Chem. Soc. **1951,** 1020.
(83) Gerrard, W., and Lappert, M. F.: J. Chem. Soc. **1952,** 1486.
(84) Ghaswalla, R. P., and Donnan, F. G.: J. Chem. Soc. **1936,** 1341.
(85) Gilbert, W. I., and Wallis, E. S.: J. Org. Chem. **5,** 184 (1940).
(86) Gillespie, R. J.: J. Chem. Soc. **1950,** 2997.
(86a) Gilman, H., Meikle, W. J., and Morton, J. W., Jr.: J. Am. Chem. Soc. **74,** 6282 (1952).
(87) Gilman, H., and Schulze, F.: Rec. trav. chim. **47,** 752 (1928).
(88) Gilman, H., Zoellner, E. A., and Selby, W. M.: J. Am. Chem. Soc. **54,** 1957 (1932).
(89) Gladishev, A. T., and Syrkin, Ya. K.: Compt. rend. acad. sci. U. R. S. S. **20,** 145 (1938); Chem. Abstracts **33,** 1578 (1939).
(90) Goldfarb, Ya. L., and Smorgonskiĭ, L. M.: Bull. acad. sci. U. R. S. S., Classe sci. math. nat., Sér. Chim. **1936,** 553; Chem. Abstracts **31,** 6613 (1937).
(91) Goldfarb, Ya. L., and Smorgonskiĭ, L. M.: Ber. **69B,** 1036 (1936).
(92) Goldfarb, Ya. L., and Smorgonskiĭ, L. M.: J. Gen. Chem. (U. S. S. R.) **8,** 1516 (1938); Chem. Abstracts **33,** 4593 (1939); Chem. Zentr. **1939, II,** 4233.
(93) Gould, D. H., Schaaf, K. H., and Ruigh, W. L.: J. Am. Chem. Soc. **73,** 1263 (1951).
(94) Graebe, C.: Ann. **139,** 134 (1866).
(95) Graebe, C.: Ann. **139,** 149 (1866).
(96) Gresham, T. L., Jansen, J. E., and Shaver, F. W.: J. Am. Chem. Soc. **72,** 72 (1950).
(97) Grignard, V.: Compt. rend. **151,** 322 (1910).
(98) Grignard, V., and Ritz, J.: Bull. soc. chim. France [5] **3,** 1181 (1936).
(99) Gustus, E. L., and Stevens, P. G.: J. Am. Chem. Soc. **55,** 378 (1933).
(100) Guthmann, W. S.: J. Am. Chem. Soc. **54,** 2938 (1932).

(101) Guyot, J., and Simon, L.-J.: Compt. rend. **169,** 795 (1919).

(102) Hachihama, Y., Imoto, M., Mao, C., and Kishimoto, I.: J. Soc. Chem. Ind. Japan **47,** 220 (1944).

(103) Hagemeyer, H. J., Jr.: Ind. Eng. Chem. **41,** 765 (1949).

(104) Hammett, L. P.: *Physical Organic Chemistry.* McGraw-Hill Book Company, New York (1940).

(105) Hart, H., and Eleuterio, H. S.: J. Am. Chem. Soc. **76,** 1379 (1954).

(106) Hartmann, C., and Gattermann, L.: Ber. **25,** 3531 (1892).

(107) Hartung, W. H., and Simonoff, R.: *Organic Reactions*, Vol. VII, edited by Roger Adams, Chap. V. John Wiley and Sons, Inc., New York (1953).

(108) Haubein, A. H.: Iowa State Coll. J. Sci. **18,** 48 (1943).

(109) Hauser, C. R., and Kantor, S. W.: J. Am. Chem. Soc. **73,** 1437 (1951).

(110) Haworth, W. N., and Irvine, J. C.: U. S. patent 1,401,693; Chem. Zentr. **1923, II,** 856.

(111) Henley, R. V., and Turner, E. E.: J. Chem. Soc. **1930,** 928.

(112) Hennion, G. F., Hinton, H. D., and Nieuwland, J. A.: J. Am. Chem. Soc. **55,** 2857 (1933).

(113) Henstock, H.: J. Chem. Soc. **1931,** 371.

(114) Heppolette, R. L., and Miller, J.: J. Am. Chem. Soc. **75,** 4265 (1953).

(115) Hertel, E., and van Cleef, J.: Ber. **61B,** 1545 (1928).

(116) Hertel, E., and Dressel, J.: Z. physik. Chem. **B23,** 281 (1933).

(117) Hertel, E., and Dressel, J.: Z. physik. Chem. **B29,** 178 (1935).

(118) Hertel, E., and Lührmann, H.: Z. Elektrochem. **45,** 405 (1939).

(119) Hertel, E., and Römer, G. H.: Ber. **63B,** 2446 (1930).

(120) Herzig, J.: Monatsh. **9,** 544 (1888).

(121) Hine, J., and Hine, M.: J. Am. Chem. Soc. **74,** 5266 (1952).

(122) Hinz, A., Meyer, G., and Schücking, G.: Reichsamt Wirtschaftsausbau, Chem. Ber. Prüf-Nr. **093** (PB 52020), 1043 (1942); Chem. Abstracts **41,** 6559 (1947).

(123) Hoffmeister, W.: Ber. **3,** 747 (1870).

(124) Horner, L.: Angew. Chemie **62,** 359 (1950).

(125) Houben, J.: *Die Methoden der organischen Chemie*, 4th edition, Vol. 2, p. 401. Verlag G. Thieme, Leipsig (1953).

(126) Howell, W. N., and Robertson, A.: J. Chem. Soc. **1936,** 588.

(127) Hückel, W., and Bretschneider, H.: J. prakt. Chem. [N. F] **151,** 61 (1938).

(128) Hughes, E. D., and Ingold, C. K.: J. Chem. Soc. **1935,** 251.

(129) Hughes, G. K., and Lions, F.: J. Proc. Roy. Soc. N. S. Wales **71,** 103 (1938); Chem. Zentr. **1938, I,** 4033.

(130) Hughes, G. K., and Thompson, E. O. P.: Nature **164,** 365 (1949).

(131) Hughes, G. K., and Thompson, E. O. P.: J. Proc. Roy. Soc. N. S. Wales **83,** 269 (1950).

(132) Hull, D. C., and Snodgrass, J. R.: U. S. patent 2,407,279; Chem. Abstracts **41,** 3114 (1947).

(133) Hurd, C. D., and Pollack, M. A.: J. Org. Chem. **3,** 550 (1938).

(134) Illuminati, G., and Gilman, H.: J. Am. Chem. Soc. **71,** 3349 (1949).

(135) Ipatieff, V. N.: Ber. **37,** 2961 (1904).

(136) Ipatieff, V. N., and Burwell, R. L., Jr.: J. Am. Chem. Soc. **63,** 969 (1941).

(137) Ipatieff, V. N., and Philipov, O.: Ber. **41,** 1001 (1908).

(138) Jander, G., Rüsberg, E., and Schmidt, H.: Z. anorg. Chem. **255,** 238 (1948).

(139) Kauffmann, H., and Fritz, I.: Ber. **43,** 1214 (1910).

(140) Kenyon, J., Phillips, H., and Pittman, V. P.: J. Chem. Soc. **1935,** 1075.

(141) Kirrmann, A., and Graves, M.: Bull. soc. chim. France [5] **1,** 1497 (1934).

(142) Kishner, N.: J. Russ. Phys. Chem. Soc. **41,** 651 (1909); Chem. Zentr. **1909, II,** 1132.

(143) Klemenc, A.: Monatsh. **33,** 375 (1912).

(144) Klemenc, A.: Ber. **49,** 1371 (1916).

(145) Knoevenagel, E.: Ann. **402,** 133 (1914).

(146) Kögl, F., and Postowsky, J. J.: Ann. **444,** 6 (1925).

(147) Kolhatkar, G. B., and Bapat, V. V.: J. Univ. Bombay **7,** Pt. 3, 157 (1938); Chem. Abstracts **33,** 5268 (1939); Chem. Zentr. **1940, II,** 2000.

(148) Komatsu, S., and Masumoto, M.: Bull. Chem. Soc. Japan **5,** 241 (1931).

(149) Kranzfelder, A. L., Verbanc, J. J., and Sowa, F. J.: J. Am. Chem. Soc. **59,** 1488 (1937).

(150) Kroeger, J. W., Sowa, F. J., and Nieuwland, J. A.: J. Org. Chem. **1,** 163 (1936).

(151) Kursanov, D. N., and Setkina, V. N.: Doklady Akad. Nauk S. S. S. R. **65,** 847 (1949); Chem. Abstracts **43,** 6622 (1949).

(152) Kyrides, L. P.: J. Am. Chem. Soc. **55,** 1209 (1933).

(153) Ladenburg, A., and Leverkus, C.: Ann. **141,** 260 (1867).

(154) Langheld, K.: Ber. **43,** 1857 (1910).

(155) Le Févre, R. J. W., Saunders, S. L. M., and Turner, E. E.: J. Chem. Soc. **1927,** 1168.

(156) Lemaire, H., and Lucas, H. J.: J. Am. Chem. Soc. **73,** 5198 (1951).

(157) Leskowitz, S.: Dissertation, Columbia University, 1950; Dissertation Abstracts **13,** 13 (1953).

(158) Letsinger, R. L., and Bobko, E.: J. Am. Chem. Soc. **75,** 2649 (1953).

(159) Letsinger, R. L., Schnizer, A. W., and Bobko, E.: J. Am. Chem. Soc. **73,** 5708 (1951).

(160) Letsinger, R. L., and Traynham, J. G.: J. Am. Chem. Soc. **70,** 3342 (1948).

(161) Lewis, W. K.: U. S. patent 2,045,785; Chem. Abstracts **30,** 5589 (1936).

(162) Lippert, W.: Ann. **276,** 148 (1893).

(163) Lowe, C. W.: Ann. **241,** 374 (1887).

(164) Lüttringhaus, A., and v. Sääf, G.: Angew. Chem. **51,** 915 (1938).

(165) Lüttringhaus, A., v. Sääf, G., and Hauschild, K.: Ber. **71B,** 1673 (1938).

(166) Lüttringhaus, A., v. Sääf, G., Sucker, E., and Borth, G.: Ann. **557,** 46 (1945).

(167) Lydén, R.: Finska Kemistsamfundets Medd. **35,** 19 (1926); Chem. Zentr. **1927, I,** 1814.

(168) Lydén, R.: Finska Kemistsamfundets Medd. **37,** 53 (1928); Chem. Zentr. **1928, II,** 2133.

(169) Lydén, R.: Finska Kemistsamfundets Medd. **38,** 19 (1929); Chem. Abstracts **24,** 335 (1930).

(170) Lydén, R.: Finska Kemistsamfundets Medd. **38,** 68 (1929); Chem. Abstracts **24,** 1620 (1930).

(171) Lydén, R.: Finska Kemistsamfundets Medd. **38,** 72 (1929); Chem. Abstracts **24,** 1628 (1930).

(172) Maass, O., and McIntosh, D.: J. Am. Chem. Soc. **34,** 1273 (1912).

(173) Maass, O., and McIntosh, D.: J. Am. Chem. Soc. **35,** 535 (1913).

(174) Maass, O., and Morrison, D. M.: Trans. Roy. Soc. Can. **17,** Sect. III, 47 (1923); Chem. Abstracts **18,** 968 (1924).

(175) Maass, O., and Morrison, D. M.: J. Am. Chem. Soc. **45,** 1675 (1923).

(176) McAteer, J. H.: U. S. patent 2,547,766; Chem. Abstracts **45,** 8033 (1951).

(177) McIntosh, D.: J. Phys. Chem. **12,** 167 (1908).

(178) McKenzie, H. A. E., and Winter, E. R. S.: Trans. Faraday Soc. **44,** 159 (1948).

(179) Man, E. H., Sanderson, J. J., and Hauser, C. R.: J. Am. Chem. Soc. **72,** 847 (1950).

(180) Mason, R. B.: U. S. patent 2,519,061; Chem. Abstracts **45,** 635 (1951).

(181) Mayo, F. R., Hardy, W. B., and Schultz, C. G.: J. Am. Chem. Soc. **63,** 426 (1941).

(182) Meer, N., and Polanyi, M.: Z. physik. Chem. **19B,** 171 (1932).

(183) Meerwein, H., Battenberg, E., Gold, H., Pfeil, E., and Willfang, G.: J. pr Chem. **154,** 83 (1939).

(184) Meerwein, H., Hinz, G., Hofmann, P., Kroning, E., and Pfeil, E.: J. pra **147,** 257 (1936).

(185) Meerwein, H., and Maier-Hüser, H.: J. prakt. Chem. **134,** 51 (1932)

(186) Meerwein, H., Rathjen, H., and Werner, H.: Ber. **75B,** 1618 (1942).

(187) Meisenheimer, J.: Ann. **323**, 205 (1902).

(188) Menzel, W., and Froehlich, M.: Ber. **75B**, 1055 (1942).

(189) Merck, E.: German patent 78,910; Chem. Zentr. **1895, I,** 719.

(190) Meyer, J., and Schramm, G.: Z. anorg. u. allgem. Chem. **206,** 24 (1932).

(191) Meyer, K. H., and Bergius, F.: Ber. **47**, 3158 (1914).

(192) Michael, A., and Wilson, F. D.: Ber. **39**, 2569 (1906).

(193) Miller, J.: J. Chem. Soc. **1952**, 3550.

(194) Mislow, K.: J. Am. Chem. Soc. **73,** 4043 (1951).

(195) Mislow, K., and Brenner, J.: J. Am. Chem. Soc. **75**, 2318 (1953).

(196) Monacelli, W. J., and Hennion, G. F.: J. Am. Chem. Soc. **63,** 1722 (1941).

(197) Morell, S. A.: U. S. patent 2,424,184; Chem. Abstracts **41,** 7411 (1947).

(198) Mottier, M.: Helv. Chim. Acta **18,** 840 (1935).

(199) Müller, E., and Bunge, W.: Ber. **69B,** 2171 (1936).

(200) Nef, J. U.: Ann. **298**, 233 (1897).

(201) Nef, J. U.: Ann. **318**, 137 (1901).

(202) Nicklès, J.: Compt. rend. **52**, 869 (1861).

(203) Nietzki, R., and Schündelen, B.: Ber. **24,** 3585 (1891).

(204) Norris, J. F., and Rigby, G. W.: J. Am. Chem. Soc. **54**, 2088 (1932).

(205) Norris, J. F., and Young, R. C.: J. Am. Chem. Soc. **52,** 753 (1930).

(206) O'Connor, M. J., and Sowa, F. J.: J. Am. Chem. Soc. **60,** 125 (1938).

(207) Ogata, Y., and Okano, M.: J. Am. Chem. Soc. **71,** 3211 (1949).

(208) Ogata, Y., and Okano, M.: J. Am. Chem. Soc. **71,** 3212 (1949).

(209) Oliverio, A.: Atti X° congr. intern. chim. **3,** 258 (1938); Chem. Zentr. **1939, II,** 3977.

(210) Paul, R.: Bull. soc. chim. France [5] **6,** 1162 (1939).

(211) Pauling, L.: *The Nature of the Chemical Bond*, p. 249. Cornell University Press, Ithaca, New York (1945).

(212) Perkin, A. G.: J. Chem. Soc. **91,** 2069 (1907).

(213) Pfeiffer, P., and Loewe, W.: J. prakt. Chem. [N. F.] **147,** 293 (1937).

(214) Pines, H., Huntsman, W. D., and Ipatieff, V. N.: J. Am. Chem. Soc. **73,** 4483 (1951).

(215) Pines, H., Rudin, A., and Ipatieff, V. N.: J. Am. Chem. Soc. 74, 4063 (1952).

(216) Plimmer, R. H. A., and Burch, W. J. N.: J. Chem. Soc. **1929**, 292.

(217) Plotnikov, V.: Z. anorg. Chem. **56,** 53 (1907).

(218) Pratt, E. F., and Matsuda, K.: J. Am. Chem. Soc. **75**, 3739 (1953).

(218A) Prelog, V., and Heimbach-Juhász, S.: Ber. **74B,** 1702 (1941).

(219) Prey, V.: Ber. **74B**, 1219 (1941).

(220) Prey, V.: Ber. **75B**, 350 (1942).

(221) Prey, V.: Ber. **75B**, 445 (1942).

(222) Prey, V.: Ber. **75B,** 537 (1942).

(223) Prey, V.: Ber. **76B**, 156 (1943).

(224) Pritchard, H. O.: Chem. Revs. **52**, 556 (1953).

(225) Rätz, R., and Thilo, E.: Ann. **572,** 173 (1951).

(226) Raiford, L. C., and Colbert, J. C.: J. Am. Chem. Soc. **48,** 2652 (1926).

(227) Ramser, H., and Wiberg, E.: Ber. **63B**, 1136 (1930).

(228) Regnault, V.: Ann. **27,** 11 (1837); Chem. Zentr. **9,** 653 (1838).

(229) Rice, F. O., and Rice, K. K.: *The Aliphatic Free Radicals*, p. 114. The Johns Hopkins Press, Baltimore, Maryland (1935).

(230) Richtzenhain, H.: Ber. **72B,** 2152 (1939).

(231) Richtzenhain, H., and Nippus, P.: Ber. **77B,** 566 (1944).

2) Rochow, E. G.: U. S. patent 2,459,539; Chem. Abstracts **43,** 3025 (1949).

(Rubin, B., Sisler, H. H., and Schechter, H.: J. Am. Chem. Soc. **74,** 877 (1952).

kowski, H.: Ann. **174,** 257 (1874).

wski, H., and Rudolph, C.: Ber. **10**, 1254 (1877).

retto, P. A., and Sowa, F. J.: J. Am. Chem. Soc. **59,** 603 (1937).

eff, C.: Ann. **127**, 129 (1863).

(238) Schmerling, L.: U. S. patent 2,289,886; Chem. Abstracts **37**, 387 (1943).

(239) Schorigin, P.: Ber. **43**, 1931 (1910).

(240) Schorigin, P.: Ber. **56B**, 176 (1923).

(241) Schorigin, P.: Ber. **57B**, 1627 (1927).

(241a) Schorigin, P.: Ber. **58B**, 2028 (1925).

(242) Schorigin, P.: Ber. **59**, 2510 (1926).

(243) Schorigin, P., Issaguljanz, W., and Below, W.: Ber. **64B**, 274 (1931).

(244) Schorigin, P., and Skoblinskaya, S. A.: Compt. rend. acad. sci. U. R. S. S. **14**, 505 (1937).

(245) Searles, S., and Tamres, M.: J. Am. Chem. Soc. **73**, 3704 (1951).

(246) Seel, F.: Z. anorg. allgem. Chem. **250**, 331 (1943).

(247) Seel, F., and Bauer, H.: Z. Naturforsch. **2b**, 397 (1947).

(248) Shelton, R. S., Van Campen, M. G., Jr., Meisner, D. F., Parmerter, S. M., Andrews, E. R., Allen, R. E., and Wyckoff, K. K.: J. Am. Chem. Soc. **75**, 5494 (1953).

(249) Short, W. F., and Stewart, M. L.: J. Chem. Soc. **1929**, 553.

(250) Silva, R.: Ber. **8**, 1352 (1875); Ann. chim. phys. [5] **7**, 429 (1876).

(251) Simonis, H., and Remmert, P.: Ber. **47**, 269 (1914).

(252) Sintenis, F.: Ann. **161**, 343 (1872).

(253) Sisler, H. H., Batey, H. H., Pfahler, B., and Mattair, R.: J. Am. Chem. Soc. **70**, 3821 (1948).

(254) Skrabal, A., and Skrabal, R.: Z. physik. Chem. **A181**, 449 (1938).

(255) Skrabal, R.: Z. physik. Chem. **A185**, 81 (1939).

(256) Smith, L., Wode, G., and Widhe, T.: Z. physik. Chem. **130**, 154 (1927).

(257) Smith, R. A.: J. Am. Chem. Soc. **56**, 717 (1934).

(258) Smith, W. C., and Laubengayer, A. W.: Paper presented at the 124th Meeting of the American Chemical Society, Chicago, Illinois, September 7, 1953.

(259) Smorgonskiĭ, L. M.: J. Gen. Chem. (U. S. S. R.) **17**, 416 (1947); Chem. Abstracts **42**, 858 (1948).

(260) Smorgonskiĭ, L. M.: J. Gen. Chem. (U. S. S. R.) **21**, 655 (1951); Chem. Abstracts **45**, 9504 (1951).

(261) Smorgonskiĭ, L. M., and Goldfarb, Ya. L.: J. Gen. Chem. (U. S. S. R.) **10**, 1113 (1940); Chem. Zentr. **1940**, **II**, 3472.

(262) Sonntag, N. O. V.: Chem. Revs. **52**, 353 (1953).

(263) Späth, E.: Monatsh. **35**, 319 (1914).

(264) Sprung, M. W., and Wallis, E. S.: J. Am. Chem. Soc. **56**, 1715 (1934).

(265) Starr, D., and Hixon, R. M.: J. Am. Chem. Soc. **56**, 1595 (1934).

(266) Staudinger, H., and Anthes, E.: Ber. **46**, 1424 (1913).

(267) Steinkopf, W., and Schubart, I.: Ann. **424**, 19 (1921).

(268) Stevens, P. G.: J. Am. Chem. Soc. **62**, 1801 (1940).

(269) Stoermer, R.: Ber. **41**, 321 (1908).

(270) Stoermer, R., and Kahlert, B.: Ber. **34**, 1812 (1901).

(271) Stone, H., and Shechter, H.: J. Org. Chem. **15**, 491 (1950).

(272) Suter, C. M.: *Organic Chemistry of Sulfur.* John Wiley and Sons, Inc., New York (1944).

(273) Suter, C. M., and Evans, P. B.: J. Am. Chem. Soc. **60**, 536 (1938).

(274) Synerholm, M. E.: J. Am. Chem. Soc. **69**, 2581 (1947).

(275) Synerholm, M. E.: Org. Syntheses **29**, 30 (1949).

(276) Tarbell, D. S., and Harnish, D. P.: J. Am. Chem. Soc. **74**, 1862 (1952).

(277) Tarbell, D. S., and Petropoulous, J. C.: J. Am. Chem. Soc. **74**, 244 (1952).

(278) Thoms, H., and Siebeling, W.: Ber. **44**, 2134 (1911).

(279) Tinker, J. M., and Weinmayr, V. M.: U. S. patent 2,100,228; Chem. Zentr. **1938**, **I**, 1660.

(280) Tollefson, R. C.: U. S. patent 2,413,802; Chem. Abstracts **41**, 2429 (1947).

(281) TOMITA, M., FUJITA, E., AND ABE, T.: J. Pharm. Soc. Japan **72**, 384 (1952); Chem. Abstracts **47**, 7453 (1953).

(282) TRONOV, B. V., AND LADIGINA, L. V.: Ber. **62B**, 2844 (1929).

(283) TSONEV, N. S.: J. Russ. Phys. Chem. Soc. **48**, 550 (1916); Chem. Abstracts **11**, 585 (1917).

(284) UNDERWOOD, H. W., JR., AND TOONE, G. C.: J. Am. Chem. Soc. **52**, 391 (1930).

(285) UNDERWOOD, H. W., JR., AND WAKEMAN, R. L.: J. Am. Chem. Soc. **52**, 387 (1930).

(286) VALENTIN, F. H. H.: J. Chem. Soc. **1950**, 498.

(287) VANDONI, R., AND CHÉDIN, J.: Mém. services chim. état (Paris) **31**, 101 (1945); Chem. Abstracts **42**, 4425 (1948).

(288) VAN DUZEE, E. M., AND ADKINS, H.: J. Am. Chem. Soc. **57**, 147 (1935).

(289) VAN DYKE, R. E., AND KRAUS, C. A.: J. Am. Chem. Soc. **71**, 2694 (1949).

(290) WACEK, A. V., AND MORGHEN, I.: Ber. **70B**, 183 (1937).

(291) WAGNER-JAUREGG, T., AND GRIESSHABER, H.: Ber. **70B**, 1 (1937).

(292) WALVEKAR, S. P., PHALNIKAR, N. L., AND BHIDE, B. V.: J. Indian Chem. Soc. **20**, 131 (1943).

(293) WASER, E., AND SANDER, K.: Helv. Chim. Acta **8**, 106 (1925).

(294) WEBB, T. J.: J. Am. Chem. Soc. **48**, 2263 (1926).

(295) WEBER, F. C., AND SOWA, F. J.: J. Am. Chem. Soc. **60**, 94 (1938).

(296) WEDEKIND, E., AND HAEUSSERMANN, J.: Ber. **34**, 2081 (1901).

(297) WEGSCHEIDER, R., AND SPÄTH, E.: Monatsh. **30**, 825 (1909).

(298) WEISHUT, F.: Monatsh. **33**, 1165 (1912).

(299) WERTYPOROCH, E., AND KIEKENBERG, H.: Biochem. Z. **268**, 8 (1934).

(300) WHITMORE, F. C., AND LANGLOIS, D. P.: J. Am. Chem. Soc. **55**, 1518 (1933).

(301) WHITMORE, F. C., AND WHEELER, W. R.: J. Am. Chem. Soc. **60**, 2899 (1938).

(302) WIBERG, E., AND SÜTTERLIN, W.: Z. anorg. allgem. Chem. **202**, 22 (1931).

(303) WILLIAMS, F. E., AND GEBAUER-FÜLNEGG, E.: J. Am. Chem. Soc. **53**, 352 (1931).

(304) WITTIG, G., AND LÖHMANN, L.: Ann. **550**, 260 (1942).

(305) WOHL, A., AND BERTHOLD, E.: Ber. **43**, 2177 (1910).

(306) WOOSTER, C. B., SEGOOL, H. D., AND ALLAN, T. T., JR.: J. Am. Chem. Soc. **60**, 1666 (1938).

(307) ZEISEL, S.: Monatsh. **6**, 989 (1885).

(308) ZIEGLER, K., AND COLONIUS, H.: Ann. **479**, 135 (1930).

(309) ZIEGLER, K., AND GELLERT, H.-G.: Ann. **567**, 185 (1950).

(310) ZIEGLER, K., AND SCHNELL, B.: Ann. **437**, 227 (1924).

(311) ZIEGLER, K., AND THIELMANN, F.: Ber. **56B**, 1740 (1923).

(312) ZOFIN, E. A., AND SCHCHIKOVADSE, K. A.: Khim. Farm. Prom. **10**, 376 (1932); Chem. Zentr. **1933**, **II**, 3118.