Reactions of the Oxirane Group[1]

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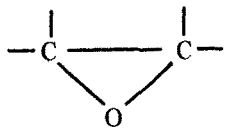
Abstract

Epoxidized oils and esters have been used commercially for about two decades; their consumption is now of the order of 100 million lb./year, mainly as stabilizer-plasticizers for vinyl chloride polymers. Yet in spite of their low price and ready availability, chemical derivatives of these substances have not achieved similar commercialization. It has long been known that the oxirane group is highly reactive and undergoes a wide variety of ring-opening reactions with a broad range of electrophiles and nucleophiles. During the past ten years, in particular, new and interesting reactions of the oxirane group have been described that provide new routes to other heterocyclic ring systems and functional groups. After a brief background survey, recently published and unpublished reactions from the author's laboratory, as well as reactions published by other groups, are described.

Introduction

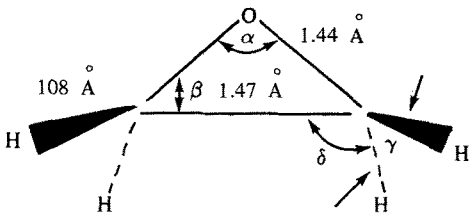
Organic chemistry is, to a large extent, the study of reactions of functional groups with important contributions of polar, steric, conformational and neighboring group effects. One of the most versatile, reactive and interesting functional groups that continues to provide exciting chemistry is the oxirane group, a three-membered heterocyclic ring:



Oxirane Group

Compounds containing the oxirane group are frequently called epoxides and that term, as well as oxiranes, will be used interchangeably in this discussion. Oxiranes are at present the simplest known oxygen-containing heterocycles.

Electron diffraction and microwave spectroscopic studies have been extremely useful tools for elucidating the molecular geometry of epoxides (1). A detailed structure of ethylene oxide, the lowest and parent member of oxiranes, is shown below. Each CH_2 group is in a plane at right angles to the plane of the ring and the angle between each CH_2 plane and the carbon-carbon bond is about 158° 6′.

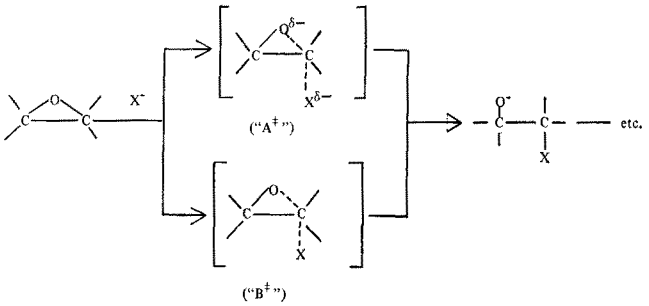


α = 61° 24′
β = 59° 18′
γ = 116° 15′
δ = 158° 6′

The figure shows that the plane formed by the carbon and hydrogen atoms is approximately perpendicular to that of the ring. The hydrogens are situated above and below the ring, and the two carbons are raised above the plane formed by the four hydrogens. The C–C bond length is intermediate between that of a normal C–C bond (1.54 Å) and that of a C = C bond (1.33 Å), while the H–C–H bond angle is intermediate between the tetrahedral (109° 28′) and trigonal (120°) configuration. It can thus be imagined that the oxygen atom is somehow lifting the two carbons out of the plane formed by the four hydrogens, the plane in which they would lie if they were genuine olefinic sp^2-hybridized carbons. The molecule, therefore, is strained; the strain energy, taken as the difference between the experimental and the calculated heats of formation, has been found to be 13 kcal/mole for ethylene oxide. The corresponding values for cyclopropane, ethyleneimine and ethylene sulfide are estimated to be 25, 14 and 9 kcal/mole, respectively. Structural and strain energy considerations indicate that oxiranes, in common with other three-membered ring compounds, should be highly reactive and should undergo ring-opening reactions with facility, as is well known, thereby relieving the strain energy of the ring.

Oxiranes react in solution with a wide variety of electrophilic, nucleophilic and neutral reagents (2). Although the lability of epoxides in the presence of an enormous variety of reagents has been known and exploited for many years, much confusion has surrounded the mechanism of these reactions. The direction and stereochemistry of ring opening are governed largely by three factors: (a) structure of epoxide; (b) structure of reagent; and (c) reaction conditions, such as temperature, solvent polarity and catalysts.

Parker and Isaacs (3) have formulated a theoretical model to account for the enormous variety of reactions of epoxides. Epoxides react by either or both of two limiting processes, which are of the true S_N2 and of the 'borderline S_N2' type, respectively.



Unlike the classical S_N1 and S_N2 mechanisms of nucleophilic substitution, these processes both involve Walden inversion at the reaction site. It appears, moreover, that both are bimolecular. Where they do differ, however, is in the relative proportions of bond forming and bond breaking in the transition states involved. The latter may be depicted as shown for the general case, where X^- is a nucleophilic anion but

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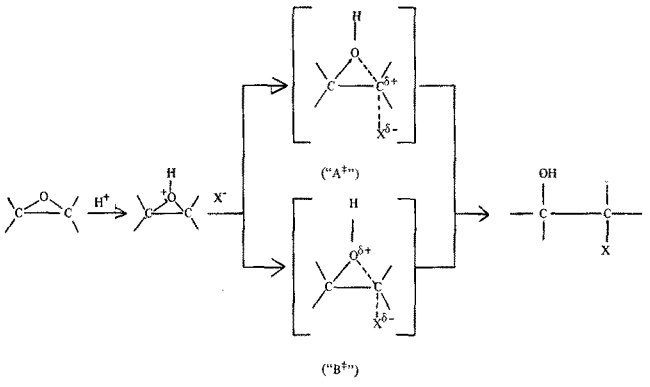
could equally well be replaced by some neutral species X.

Of the two transition states ("A‡") and ("B‡"), the first clearly entails less bond forming than does the second, and therefore more nearly resembles a conventional S_N1 transition state in that respect. Somewhat like a S_N1 transition state also, ("A‡") is stabilized by inductive or resonance electron release from nearby substituents. That a fully developed carbonium ion is not generated, however, has been firmly established by numerous stereochemical studies demonstrating inversion (not racemization) at the reaction site. There appears, generally, to be sufficient evidence to justify the designation of transition state ("A‡") as a 'borderline S_N2' transition state.

The second transition state ("B‡") evidently resembles rather closely the true S_N2 transition state, increasing alkyl substitution, for example, causes a corresponding increase in the activation energy required to form it. Non-polar solvents, on the other hand, lower the activation energy, in line with their recognized ability to accommodate dispersal of like change. Where ("B‡") does presumably differ from a pure S_N2 transition state, however, is that the geometry of the epoxide ring renders unattainable one of the conditions of a classical S_N2 transition state, namely, linear disposition of the incoming nucleophile, the carbon atom undergoing substitution and the departing epoxide oxygen atom.

Acid-catalysis promotes epoxide ring cleavage to a singular degree. Protonation of the epoxide oxygen atom gives an oxonium ion, in which C–O bond rupture is facilitated by the electron-demanding positive charge on the oxygen atom. As in the uncatalyzed case, epoxide reactions may be considered to proceed by one or both of two limiting pathways in the presence of acid, involving the transition states ("A‡") and ("B‡").



With low molecular weight oxiranes, such as ethylene oxide, propylene oxide, epichlorohydrin, glycidyl ethers, and styrene oxide, a wide variety of industrially important compounds are prepared on a large scale, as the starting oxiranes and the reagents are of relatively low cost. The situation with respect to the preparation of chemical derivatives is considerably different with epoxidized oils and epoxidized fatty acid esters. Although epoxidized oils and epoxidized fatty acid esters are almost universally employed as components of polyvinyl chloride formulations, derivative products from these long chain oxiranes have not achieved any large commercial utilization.

Since two excellent reviews of oxirane chemistry have appeared that cover the literature through about 1964 (2,3), the discussion in this paper will be devoted to work conducted since that time primarily in the author's laboratory; much of the work to be described is still largely unpublished. To present a balanced picture, however, reactions that are of general interest or of unusual character reported from other laboratories will also be described. Naturally, with limited time available the major emphasis will be on work that has been carried out in the author's laboratory at Temple University.

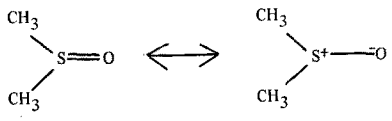
Discussion

I should like to begin with a very brief description of some of the philosophy behind our research program on new reactions of the oxirane ring. We have been concerned for some time that large scale commercialization of chemical derivatives from epoxidized oils and epoxidized fatty acid esters has not been realized even though, as already noted, many chemical reactions of the oxirane group are well known. We decided therefore, to study new reactions of the oxirane group, from both the mechanistic and preparative viewpoint, in the hope of sparking renewed interest in long chain oxirane chemistry. Although our interest is primarily in lipids, we have found it much more expedient to study simple model compounds so that reaction conditions and product isolation can be perfected before applying new reactions to the more complicated epoxidized oils and esters. Furthermore, with model systems we are in a position to work with pure compounds of known stereochemistry and we have been able to use instrumental (NMR, IR, UV) and microseparation techniques (thin layer chromatography and gas liquid chromatography) more efficiently in working out structure and composition of products.

Two new reactions of the oxirane group under investigation in our laboratory will be described. The first of these is the reaction of dimethyl sulfoxide (DMSO) and amine oxides with oxiranes in the presence of strong acid catalysts. Since DMSO and amine oxides have a connected pair of atoms with formal charges, we have named this area of research 1,2 dipolar additions to the oxirane group.

1,2 Dipolar Additions to the Oxirane Group

Dimethyl Sulfoxide. Although DMSO has achieved preeminence as a solvent during the past decade, its use as a chemical reagent is relatively recent (4). DMSO is a highly polar molecule usually written as a resonance hybrid of the two limiting forms A and B.



A B

Although 2p-3d overlap between oxygen and sulfur is certainly a reasonable possibility (A), the high dipole moment of DMSO coupled with its facility for complexing cations suggests that there is considerable contribution from the dipolar form (B). The dipolar form indicates a high level of nucleophilicity for the oxygen atom; this was first demonstrated by Kornblum et al. in 1957 when they showed that tosylates and phenacyl halides are readily con-

verted to carbonyls by reaction with DMSO and base (5). The reaction is illustrated below:

$$ArCOCH_2X + DMSO \xrightarrow{NaHCO_3} ArCOCHO + (CH_3)_2S + NaX$$

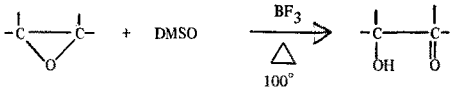
(X, Halide or tosylate) (50-90%)

(a) $ArCOCH_2X + DMSO \longrightarrow ArCOCH_2\overset{+}{O}S(CH_3)_2\ X^-$

(b) $ArCOCH_2\overset{+}{O}S(CH_3)_2\ X^- \xrightarrow{NaHCO_3} ArCOCHO + (CH_3)_2S + NaX$

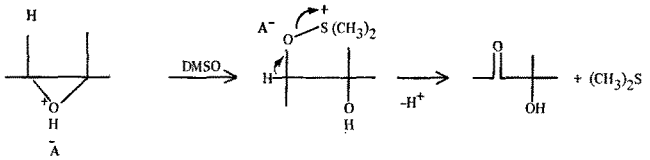
As the equations show, DMSO first (a) performs a nucleophilic displacement on the substrate to yield an intermediate alkoxysulfonium salt which is then converted to the carbonyl product and dimethyl sulfide (b) (4).

The oxidation of epoxides by DMSO was first reported by Cohen and Tsuji (6), who obtained fair to good yields of α-ketols from styrene oxide, a steroidal epoxide and cyclohexene epoxide with boron fluoride as catalyst.



The reaction does not have general applicability, as we have shown, because of the isomerizing tendency of epoxides in the presence of BF_3. Later Tsuji (7) reported that the oxidation can also be effected without boron fluoride if air is passed through the reaction mixture of epoxide and DMSO or if a catalytic amount of *t*-butyl hydroperoxide is present. Tsuji concluded that the boron fluoride-catalyzed reaction is ionic but that free radicals are involved in the presence of air or hydroperoxide. This reported dichotomy of mechanism did not seem reasonable to us and we undertook not only a mechanistic study of the reaction but also an investigation of its scope and limitations from the preparative side.

We now believe that in all cases previously described the oxidation is an acid-catalyzed ionic process (8, unpublished results from Temple University). Oxygen or hydroperoxide does not initiate a free radical chain oxidation, but instead serves to generate an acid catalyst in situ prior to the DMSO interaction with epoxide. The mechanism we now propose for the acid-catalyzed oxidation of oxiranes by DMSO is as follows:



Evidence for the necessity of an acid catalyst is as follows: the air-catalyzed or *t*-butyl hydroperoxide catalyzed oxidation of styrene oxide by DMSO produces a small amount of a strong acid, which we have determined by titration. When these reactions are attempted in the presence of excess sodium carbonate, oxidation does not take place. If the hydroperoxide and DMSO are heated under the usual conditions of the epoxide oxidation (90–100 C) but in the absence of epoxide, the hydroperoxide is consumed and the strong acid is still formed. If heating is continued until the hydroperoxide is completely decomposed and styrene oxide is then introduced, oxidation of the epoxide begins almost immediately. The addition of benzoquinone has no effect.

Thus an acid is required for the oxidation and with hydroperoxide, it is the acid produced by reaction of hydroperoxide with DMSO that catalyzes the oxidation and not the hydroperoxide itself.

The catalytic activity of oxygen can be explained by suggesting that autoxidation of a small amount of epoxide to a hydroperoxide occurs, which then reacts with DMSO to form the acid catalyst. This explanation is supported by the observation that oxygen, DMSO and epoxide all together are necessary for the production of an efficient catalyst. Thus, if styrene oxide is heated in air under the usual conditions but in the absence of DMSO, the system purged of oxygen and DMSO then added, no strong acid is produced and essentially no oxidation is noted. Similarly, heating DMSO in air followed by purging the system of oxygen and then adding styrene oxide in the absence of air does not produce the acid catalyst; oxidation is not observed.

Further evidence that the oxidation is not a free radical one is the failure of *t*-butyl peroxide to catalyze it. This dialkyl peroxide does not form an acid on reaction with DMSO at 100 C although the peroxide is largely destroyed. However, it would be expected to initiate a free radical oxidation if such a process were operative. Since the peroxide fails to catalyze the reaction, it seems unlikely that DMSO oxidation of epoxides is a free radical process.

Finally, in the reaction of DMSO with hydroperoxides, we have in fact isolated methanesulfonic and sulfuric acids (as their phenylhydrazine salts).

In all cases, therefore, involving the reaction of DMSO with oxiranes, we believe an alkoxydimethylsulfonium salt is the requisite intermediate. On reaction with base, the sulfonium salt is converted to the α-ketol; on reaction with water or preferably methanol as the nucleophile, the sulfonium salt is converted in good yield to the α-glycol. The formation of glycol from oxiranes occurs with clean stereochemical inverstion; *cis*-epoxides yield *threo*-glycols and *trans*-epoxides yield *erythro*-glycols. It is thus possible to convert oxiranes to α-glycols in essentially quantitative yields within a few minutes without the use of water. The option exists, therefore, of converting an oxirane to an α-ketol (reaction of alkoxysulfonium salt with base) or to α-glycol (reaction of alkoxysulfonium salt with nucleophile) depending upon the reaction conditions. These reactions are illustrated with *cis*- and *trans*-9,10-epoxystearic acids in which no BF_3 is used but the presence of an equivalent amount of carboxyl function relative to oxirane catalyzes the reaction (9):

cis or *trans* $CH_3(CH_2)_7CH{-}CH(-CH_2)_7CO_2H \xrightarrow[\Delta,\ 100°]{DMSO}$

$CH_3(CH_2)_7\overset{O}{\overset{\|}{C}}{-}\overset{OH}{\overset{|}{C}}H{-}(CH_2)_7CO_2H +$

(60–65% yield; two isomers)

$CH_3(CH_2)_{7(8)}{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_{8(7)}{-}CO_2H +$

(15–20%)

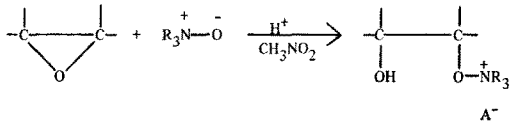
$CH_3(CH_2)_7\overset{OH}{\overset{|}{C}}H{-}\overset{OH}{\overset{|}{C}}H{-}(CH_2)_7CO_2H$

threo from *cis*-oxirane; *erythro* from *trans* oxirane (15–20%)

To assure ourselves that alkoxysulfonium salts are readily prepared intermediates from oxiranes, we have currently been preparing a series of alkoxysulfonium salts from oxiranes, DMSO and strong acids. In all cases studied the sulfonium salts are obtained in excellent yields and these isolated salts can either be con-

verted to α-ketol by reaction with base or to α-glycol by reaction with methanol. All the reactions are very rapid; conversion of oxiranes to sulfonium salts is complete at room temperature within a few minutes to a few hours.

Amine oxides also have high dipole moments and we would anticipate that they would react with oxiranes in the presence of strong acid to yield alkoxyammonium salts, strictly analogous to the alkoxysulfonium salts already described (10):



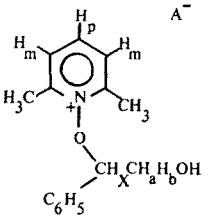
We have now shown by NMR studies in solution and also by isolation of products that aromatic amine oxides react readily at ambient temperatures with oxiranes in the presence of strong acids to give alkoxyammonium salts. In this discussion, I will describe (a) the use of NMR to demonstrate the formation in solution of an alkoxyammonium salt from 2,6-lutidine N-oxide, styrene oxide, and trifluoroacetic or perchloric acid, and (b) the isolation of the analytically pure salt in good yield.

The NMR spectral changes occurring with time in a mixture of 2,6-lutidine N-oxide, styrene oxide and trifluoroacetic acid in nitromethane (molar ratio 1:1:5, respectively) were investigated first. Trifluoroacetic acid, and later perchloric acid, was selected as the acid because of low nucleophilicity of the anion. Nitromethane was used because of its high polarity, inertness and simple NMR spectrum. 2,6-Lutidine N-oxide was selected because the signal from its methyl groups could be monitored to show whether the lutidine ring was being incorporated into any new species. Styrene oxide was chosen for comparison of the results with those previously obtained with DMSO.

At 37 C in the absence of a strong acid no reaction is observed. Addition of the acid causes the lutidine oxide methyl singlet (δ 2.5) to diminish at exactly the rate of development of a new singlet slightly downfield (δ 2.8). In 40 min the δ 2.8 signal reaches 43% of the total area of the δ 2.5 and δ 2.8 signals. Accompanying the development of the δ 2.8 signal and always exactly ⅙ its area, a doublet of doublets appears at δ 5.8. (When 2-picoline N-oxide is used in place of 2,6-lutidine N-oxide, a similar NMR pattern develops; as expected, the doublet of doublets this time is ⅓ the area of the new methyl signal.) Since these new signals are comparable to those observed for the $(CH_3)_2S^+OCH(C_6H_5)CH_2OH$ species they are assumed to be those of an analogous alkoxyammonium ion intermediate (A). Protonated styrene oxide would be expected to undergo nucleophilic attack at the benzylic carbon due to the partial S_N1 character of this process.

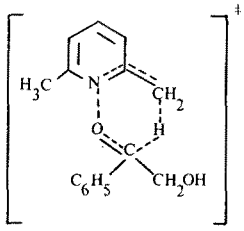
Furthermore, just as in the DMSO case, quenching of the reaction mixture with base causes the disappearance of the signals assigned to the salt. When the methyl groups of lutidine oxide are labeled with deuterium, the NMR spectrum of the base-quenched reaction indicates that the protium on the benzylic carbon atom of the salt has been transferred to a methyl group during this decomposition. This suggests that the decomposition may proceed via initial abstraction of a methyl hydrogen (ylid formation), followed by intramolecular abstraction of the benzylic hydrogen through a sterically favorable transition state shown (B).

(A)



$A^- = CF_3CO_2^-$ or ClO_4^-

(B)

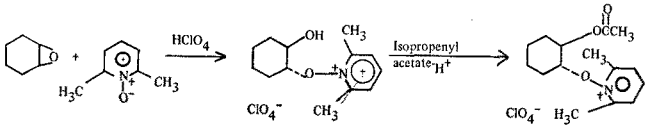


This proposal is similar to that of Fenselau and Moffatt (4) for the decomposition of alkoxydimethylsulfonium salts. Decomposition via the transition state shown above (B) then yields lutidine and phenacyl alcohol.

The presence of the alkoxyammonium salt (perchlorate) was unequivocally confirmed by actual isolation. A reaction mixture of 2,6-lutidine N-oxide, perchloric acid, styrene oxide and nitromethane (1.0:0.5:1.0:7.5 molar ratio, respectively) was allowed to stand for 1 hr at 37 C and then poured into a large excess of ether. The precipitated oil solidified overnight in a vacuum desiccator. NMR analysis showed it to be about 80% intermediate and about 20% lutidine oxide. Recrystallization by dissolving it in acetone, adding ether until the cloud point was reached, followed by adding one drop of acetone to redissolve the incipient precipitate and cooling in a freezer to −10 C yielded the analytically pure salt, 1-(α-phenyl-β-hydroxyethoxy)-2,6-dimethylpyridinium perchlorate (colorless sheets, 62% yield), mp 104.0–104.5 C. Analysis Calculated for $C_{15}H_{18}NO_6Cl$: C 52.41; H 5.28; N 4.08; Cl 10.31. Found: C 52.68; H 5.32; N 4.33 (D); Cl 10.49. The NMR spectrum is consistent with the assigned structure, and its interpretation follows: Signals in DMSO-d_6 (and in acetone-d_6) were found at δ 8.4 (8.3) (1H, multiplet, H_p); δ 7.9 (7.9) (2H, doublet, H_m); δ 7.5 (7.5) (5H, singlet, C_6H_5); δ 5.7 (5.8) (1H, doublet of doublets, J_{xa} = 3.2 cps, J_{xb} = 7.9 cps, H_x); δ 5.3 (5.1) (variable δ) (1H, singlet, OH); δ 4.4 (4.5) (1H, doublet of doublets, J_{bx} = 7.9 cps, J_{ba} = 13.6 cps, H_b); δ 3.9 (4.1) (1H, doublet of doublets, J_{ax} = 3.2 cps, J_{ab} = 13.6 cps, H_a); and δ 2.7 (2.8) (6H, singlet, CH_3).

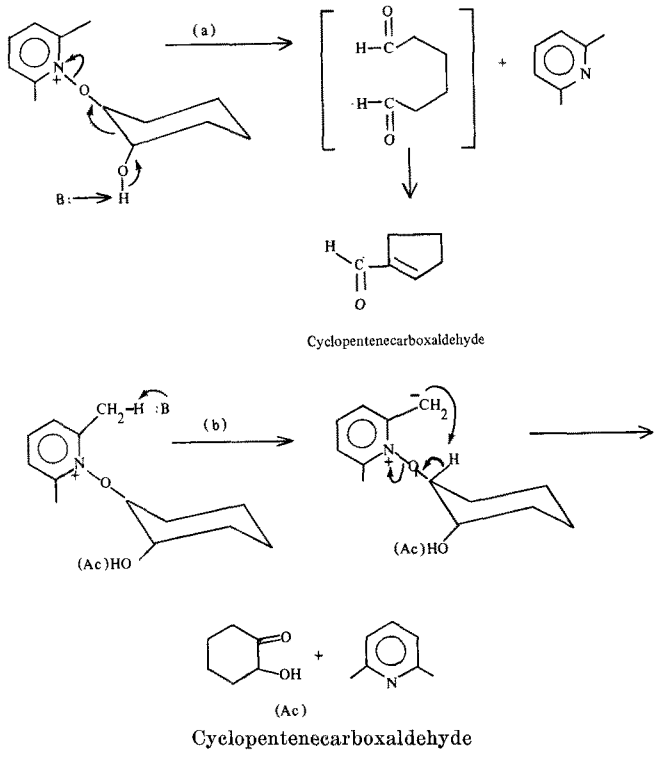
Major IR absorptions (in KBr) were found at 3500, 3100, 1620, 1600, 1500, 1460, 1385, 1240, 1080–1100, 1040, 1000, 886, 842, 816, 770 and 705 cm^{-1}.

Most of the experiments just described were focussed on the mechanism by which alkoxyammonium salts are prepared and decompose and the reactions were done in NMR tubes in solution with no actual isolation of products. We therefore decided to scale up the reactions to be sure of all of the reaction products proposed. Since alkoxyammonium salts containing a free hydroxy group can decompose in several different ways, we studied the acetylated adduct of 2,6-lutidine N-oxide, 1,2-epoxycyclohexane and perchloric acid, a species that is readily synthesized.



The scheme below outlines two routes (a and b) of basic decomposition of an intermediate containing a free hydroxyl group; these routes are quite competitive and occur to an almost equal extent. However, NMR analysis and product isolation show that

the acetylated adduct decomposes only by Route b. Decomposition of the acetylated adduct in pyridine gives only lutidine and adipoin acetate in essentially quantitative yield.

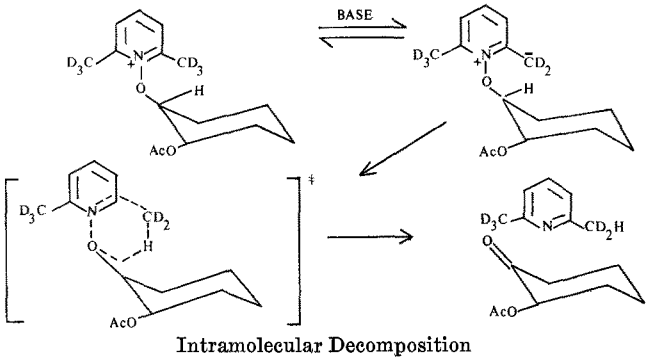


Cyclopentenecarboxaldehyde

Cyclopentenecarboxaldehyde

2,6-Lutidine N-oxide with fully deuterated methyl groups is necessary for mechanistic studies and was used to confirm pathway (b). Such a compound is readily prepared by refluxing the undeuterated amine oxide with excess deuterium oxide and NaOD for 2 hr followed by removal of the water by distillation. Several repetitions of the deuterium exchange procedure yields an N-oxide with 98% of its methyl groups containing deuterium instead of protium, as shown by NMR analysis. The deuterated amine oxide is then used for reaction with epoxycyclohexane and perchloric acid followed by acetylation with isopropenyl acetate. When the intermediate (1 μmole) is treated for 1 min with Na_2CO_3 (5 μmoles) in deuterium oxide (300 μmoles) at 100 C and then the resulting 2,6-lutidine extracted by CCl_4, the NMR methyl signal of this lutidine indicates the incorporation of almost exactly one protium. The hydrogen atoms of the methyl groups of the formed 2,6-lutidine do not exchange under these reaction conditions. It is reasonable to assume therefore that the observed hydrogen transfer proceeds intramolecularly by a favorable six-centered transition state, as shown below:

Intramolecular Decomposition

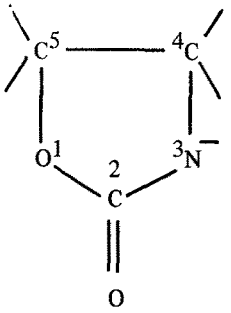


Intramolecular Decomposition

Thus DMSO and amine oxides are extremely useful reagents for converting the oxirane group to other interesting and useful functional groups.

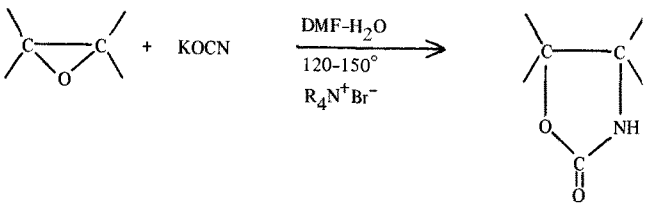
2-Oxazolidones (11)

Next I should like to discuss the conversion of the oxirane group to the 2-oxazolidone heterocyclic ring system.

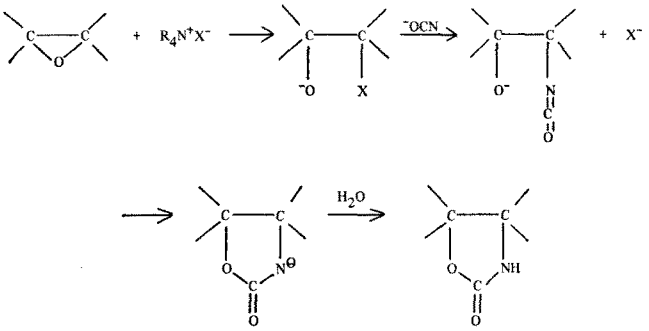


2-Oxazolidone Ring

Although the reaction of many nucleophiles with the oxirane group had been studied up to 1960, no work had been reported on the reaction of oxiranes with cyanate ion, a relatively weak nucleophile. Reaction of terminal epoxides with sodium or potassium cyanate in dimethyl formamide (DMF) at 120–150 C in the presence of a small quantity of water and tetraalkyl ammonium halide as catalyst gives 2-oxazolidones in fair to good yields, as the equation shows (12):



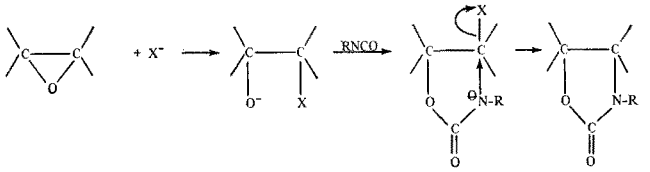
A reasonable mechanism for this reaction that rationalizes the role of water and catalyst is as follows (11):



(A)

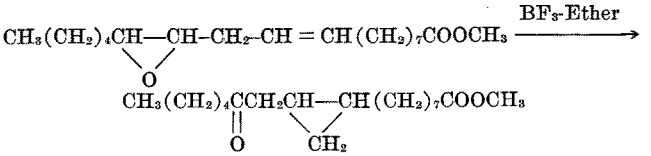
In the absence of water the nitrogen-containing anion (A) can react with another molecule of oxirane in a typical nucleophilic reaction to yield dimeric products. If a small amount of water is present it serves as an acid and neutralizes the anion. Excess water, however, hydrolyzes the inorganic cyanate and oxazolidones are not obtained. The reaction, unfortunately, is not applicable to internal oxiranes, as distinguished from reactions of DMSO and amine oxides with oxiranes that are quite generally applicable.

The 2-oxazolidones just described are unsubstituted on the nitrogen atom. Reaction of oxiranes with organic isocyanates in DMF solution under anhydrous conditions at 120–150 C in the presence of a nucleophilic catalyst produces N-substituted 2-oxazolidones (12,14). A suggested mechanism for this reaction is shown below:



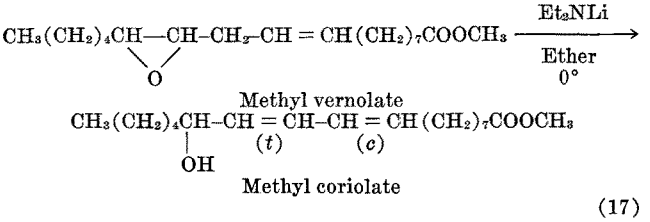
This reaction is of particular interest because dioxiranes and diisocyanates yield polymeric 2-oxazolidones.

I should now like to conclude by briefly describing several other new reactions of the oxirane group that have appeared in the literature within the past ten years, with emphasis on long chain or internal oxiranes. Owing to time limitations, these reactions will be presented by an equation and references.



Methyl 12,13-epoxy-9-octadecenoate
(*cis* + *trans* mixture)

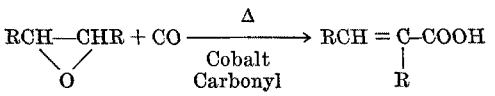
(15,16)



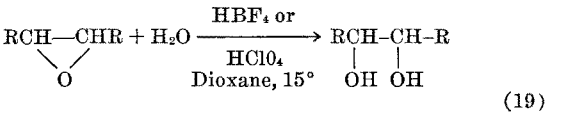
Methyl vernolate

Methyl coriolate

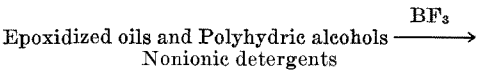
(17)



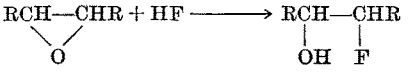
(18)



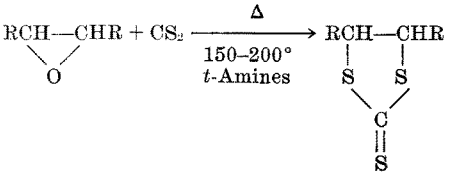
(19)



(20)



(21)



(22,23)

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