Small Heterocyclic Rings
(Epoxides)

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Reference Textbook:

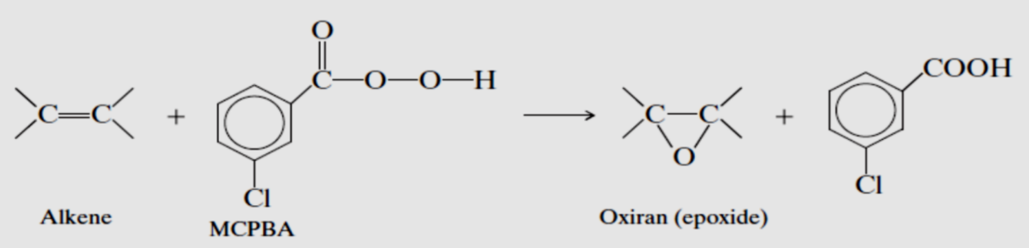
- R.T. Morrison, R.N. Boyd, and S.K. Bhattacharjee "Organic Chemistry" 7th ed. Pearson Education Inc. India (**2011**).

Epoxides are compounds containing a three-membered ring with oxygen as a heteroatom. The IUPAC name of such rings is oxiran. They are cyclic ethers, but the three-membered ring gives them unusual properties that make them exceedingly important class of compounds having numerous synthetic applications.

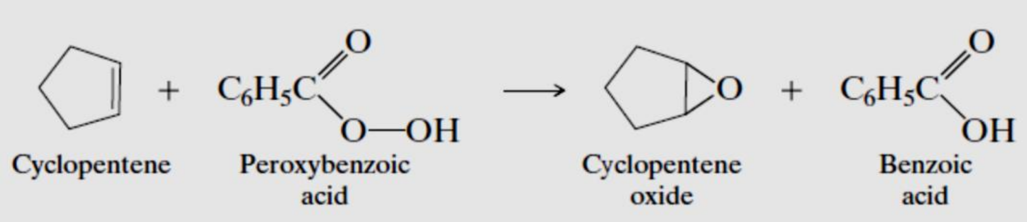
Preparation of Epoxides

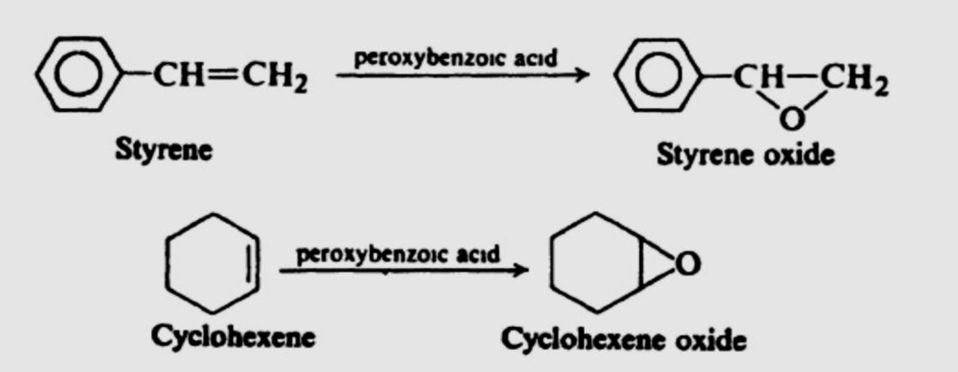
Peroxidation of carbon-carbon double bonds.

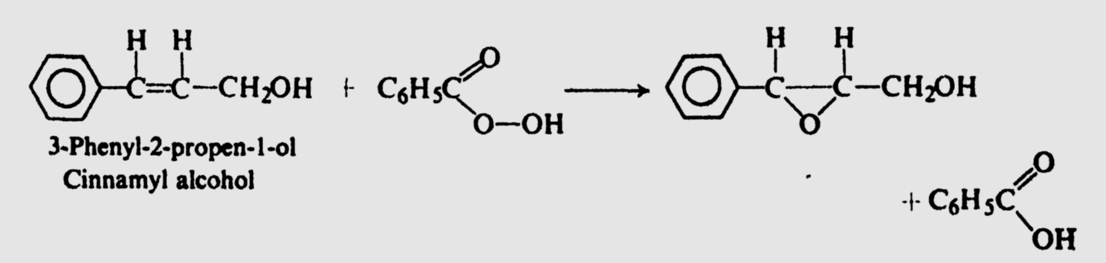
Such a ring is generally synthesized by the oxidation of a C=C bond of alkenes with peracids like peroxybenzoic acid and *m*-chloroperbenzoic acid (MCPBA).



When allowed to stand in ether or chloroform solution, the peroxy acid and the unsaturated compound (which need not be a simple alkene) react to yield benzoic acid and the epoxide. For examples:





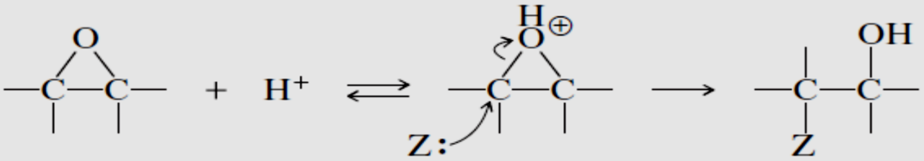


Reactions of epoxides

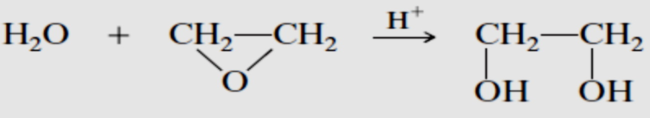
Epoxides owe their importance to the ease of opening of the highly strained three-membered ring. They undergo acid-catalyzed reactions with extreme ease and -unlike ordinary ethers- can even be cleaved by bases. Some of their important reactions are outlined below.

1) Acid-catalyzed cleavage of epoxides. *anti*-Hydroxylation

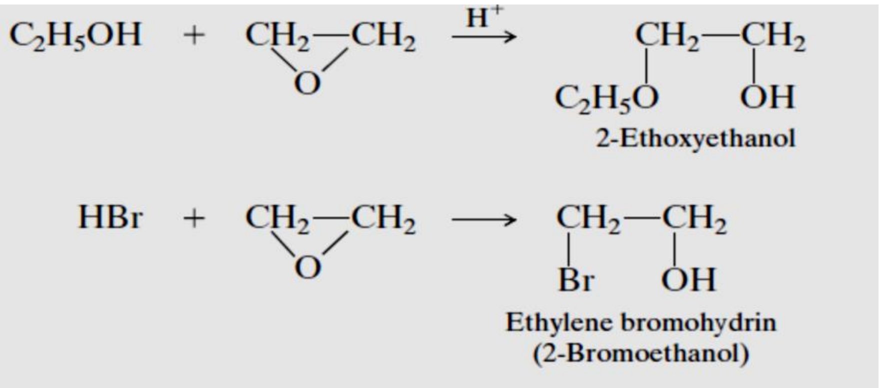
Like other ethers, an epoxide is protonated by acid; the protonated epoxide can then undergo attack by any of several nucleophilic reagents.

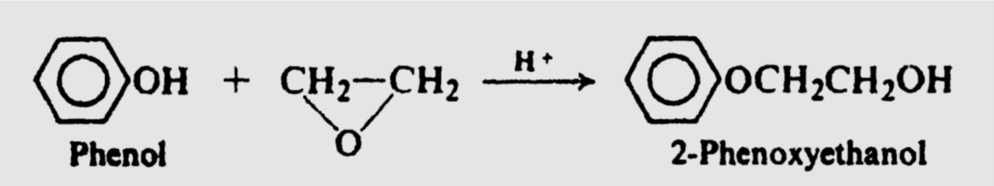


Examples:

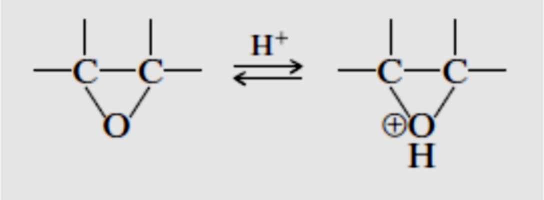


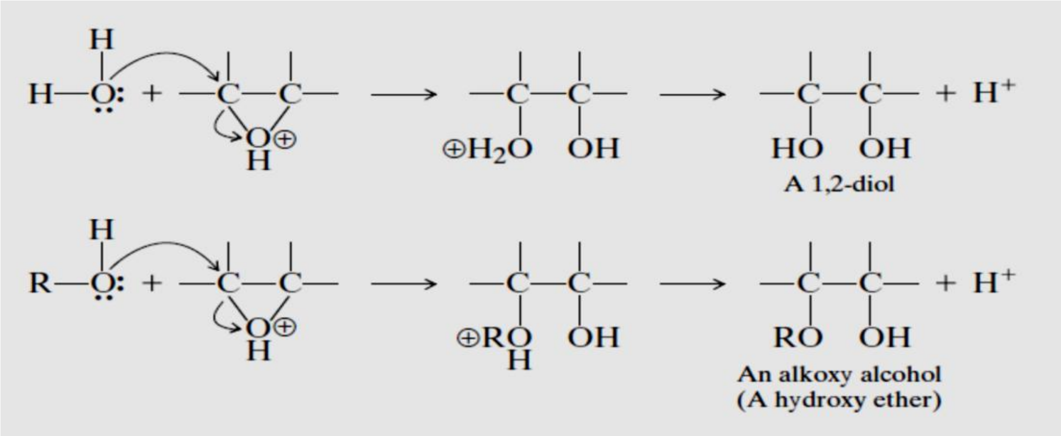
Ethylene oxide 1,2-Ethanediol





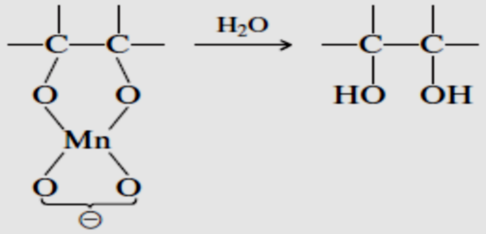
An important feature of the reactions of epoxides is the formation of compounds that contain ***two*** functional groups. Thus, reaction with water yields a 1,2-diol; reaction with an alcohol yields a compound that is both ether and alcohol.





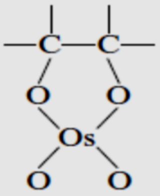
The two-stage process of epoxidation followed by hydrolysis is stereoselective and gives 1,2-diols corresponding to ***anti-***addition to the carbon-carbon double bond. The same stereochemistry was observed for hydroxylation of alkenes by peroxyformic acid—and for good reason: an epoxide is formed there, too, but is rapidly cleaved in the acidic medium, formic acid. The interpretation is the same as that given to account for ***anti***-addition of halogens; indeed, epoxides and their hydrolysis served as a model on which the halonium ion mechanism was patterned.

Hydroxylation with permanganate gives ***syn***-addition. To account for this stereochemistry, it has been suggested that an intermediate like **I** is involved:



I

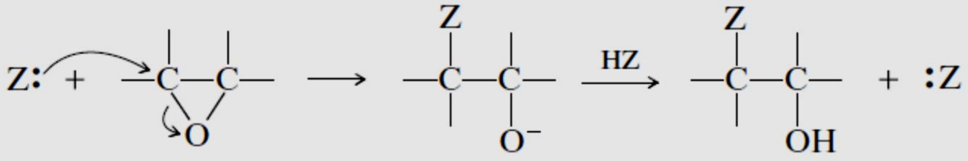
Hydrolysis of such an intermediate would yield the ***cis*** diol. This mechanism is supported by the fact that osmium tetroxide, OsO_4, which also yields the ***cis*** diol, forms stable intermediates of structure II.



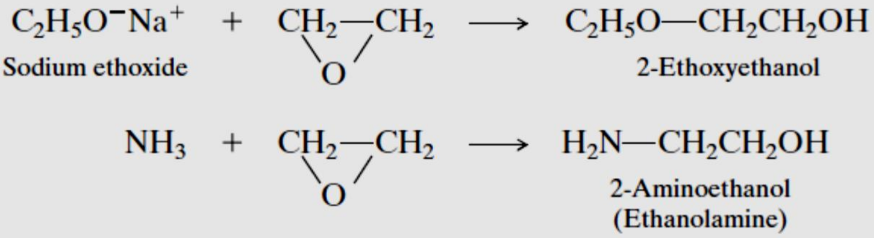
II

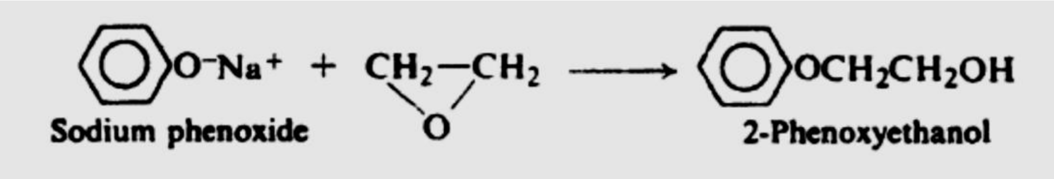
Thus, the two methods of hydroxylation—by peroxy acids and by permanganate- differ in stereochemistry because they differ in mechanism.

2) Base-catalyzed cleavage of epoxides



Examples:





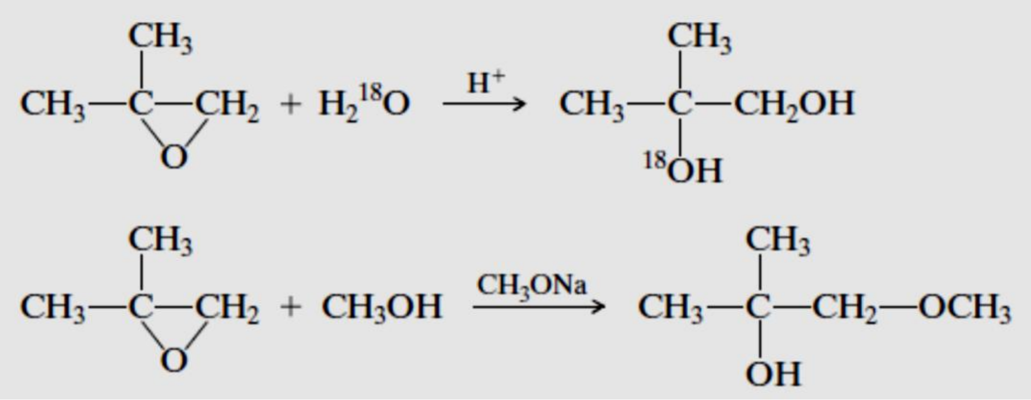
Unlike ordinary ethers, epoxides can be cleaved under alkaline conditions. Here it is the epoxide itself, not the protonated epoxide, that undergoes nucleophilic attack: The lower reactivity of the non-protonated epoxide is compensated for by the more basic, more strongly nucleophilic reagents that are compatible with the alkaline solution: alkoxides, phenoxides, ammonia, etc.

Like alkyl halides and sulfonates, and like carbonyl compounds, epoxides are an important source of ***electrophilic*** carbon: of carbon that is highly susceptible to attack by a wide variety of nucleophiles. (Epoxides generated from carcinogenic hydrocarbons are even attacked by the nucleophilic portion of the genetic material DNA and thereby induce mutation and tumors.)

Orientation of cleavage of epoxides

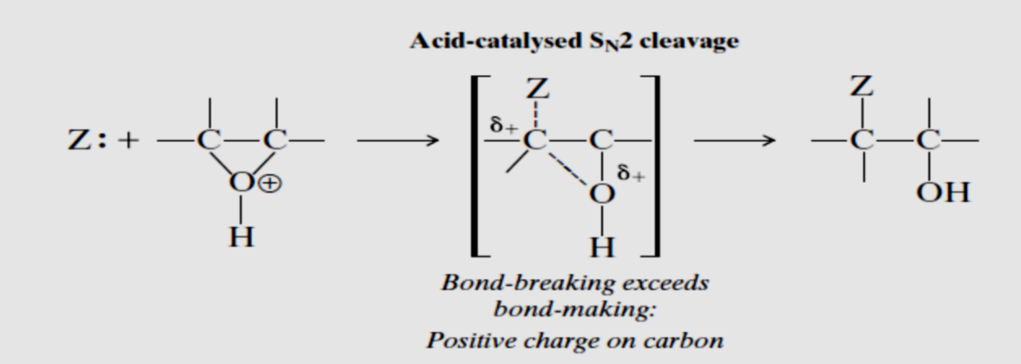
There are two carbon atoms in an epoxide ring and, in principle, either one can suffer nucleophilic attack. In a symmetrical epoxide like ethylene oxide, the two carbons are equivalent, and attack occurs randomly at either. But in an unsymmetrical epoxide, the carbons are *not* equivalent, and the product we obtain depends upon which one is preferentially attacked. Just what is the orientation of cleavage of epoxides, and how does one account for it?

The preferred point of attack, it turns out, depends chiefly on whether the reaction is acid-catalyzed or base-catalyzed. Consider, for example, two reactions of isobutylene oxide:



Here, as in general, the nucleophile attacks the more substituted carbon in acid catalyzed cleavage, and the less substituted carbon in base-catalyzed cleavage. Our first thought is that two different mechanisms are involved here, S_N^1 and S_N^2. But the evidence indicates clearly that both are of the S_N^2 type: cleavage of the carbon-oxygen bond and attack by the nucleophile occur in a single step. (There is not only stereochemical evidence -complete inversion- but also evidence of several kinds that we cannot go into here.) How, then, are we to account for the difference in orientation-in, for S_N^2 attack at the *more hindered* position in acid-catalyzed cleavage?

In the transition state of most S_N^2 reactions, bond-breaking and bond-making have proceeded to about the same extent, and carbon has not become appreciably positive or negative; as a result, steric factors, not electronic factors, chiefly determine reactivity. But in acid-catalyzed cleavage of an epoxide, the carbon-oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation: the leaving group is a very good one, the weakly basic alcohol hydroxyl. The nucleophile, on the other hand, is a poor one (water, alcohol). In the transition state bond-breaking has proceeded further than bond-making, and carbon has acquired a considerable positive charge.

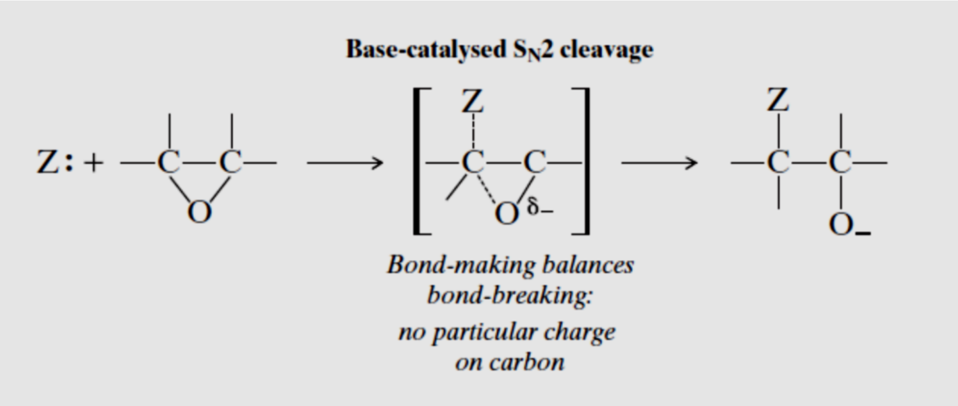

Acid-catalysed S_N2 cleavage

Bond-breaking exceeds bond-making: Positive charge on carbon

Since both leaving group and nucleophile are far away, crowding is relatively unimportant. The stability of the transition state is determined chiefly by electronic factors and not steric factors, and the reaction has considerable S_N^1 character. *Attack occurs at the carbon that can best accommodate the positive charge.*

In base-catalysed cleavage, the leaving group is a poorer one (a strongly basic alkoxide oxygen) and the nucleophile is a good one (hydroxide, alkoxide).

Bond breaking and bond-making are more nearly balanced, and reactivity is controlled in the more usual way, by steric factors. *Attack occurs at the less hindered carbon.*



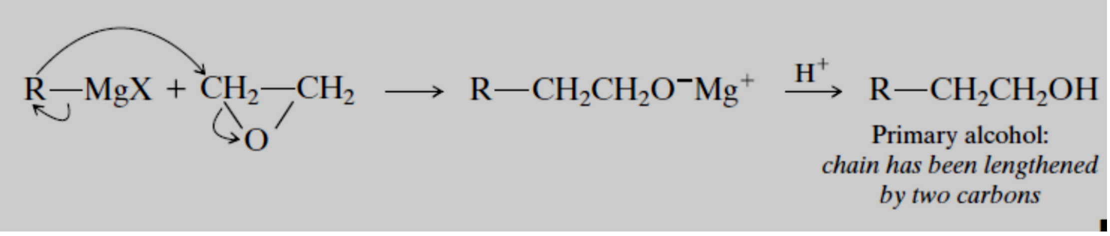
Base-catalysed S_N2 cleavage

Bond-making balances bond-breaking:

no particular charge on carbon

3) Reaction with Grignard reagents.

Reaction of Grignard reagents with ethylene oxide is an important method of preparing primary alcohols since the product contains two carbons more than the alkyl or aryl group of the Grignard reagent. As in reaction with the carbonyl group, we see the nucleophilic (basic) alkyl or aryl group of the Grignard reagent attach itself to the relatively positive carbon and the electrophilic (acidic) magnesium attach itself to the relatively negative oxygen. Use of higher epoxides is complicated by rearrangements and formation of mixtures.



Primary alcohol:
chain has been lengthened by two carbons

Examples