

4.7: REACTIONS OF EPOXIDES - RING-OPENING

OBJECTIVES

After completing this section, you should be able to

- write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
 - identify the product formed from the hydrolysis of an epoxide.
 - write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
 - identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
- predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
- write an equation to illustrate the cleavage of an epoxide ring by a base.
 - identify the product formed from the reaction of a given epoxide with given base.
 - explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

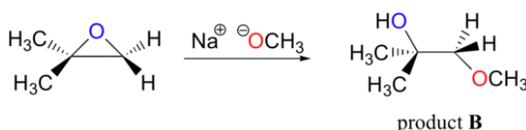
STUDY NOTES

In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2 . While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

EPOXIDE RING-OPENING BY ALCOHOLYSIS

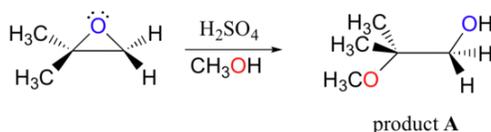
The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes alcoholysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:

basic ring-opening:



Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.

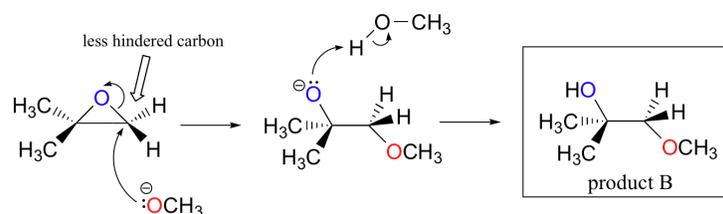
acidic ring-opening:



These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

BASIC EPOXIDE RING-OPENING BY ALCOHOLYSIS

In the basic, S_N2 reaction, the leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group (**Section 11-3**), and thus the ring is unlikely to open without a 'push' from the nucleophile.

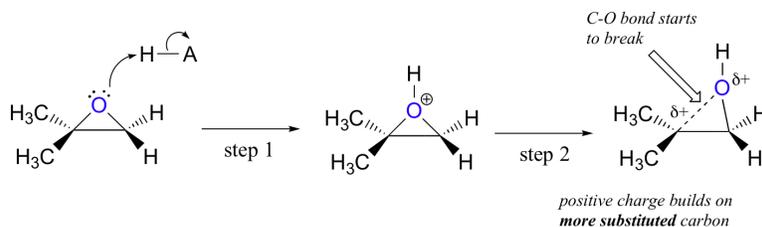


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

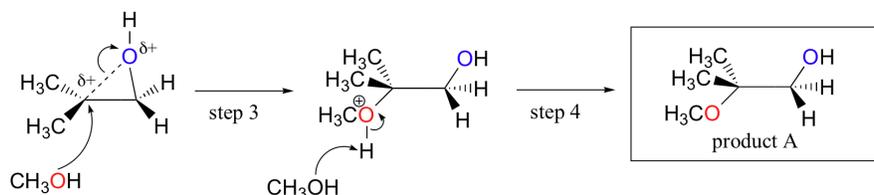
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

ACID-CATALYZED EPOXIDE RING-OPENING BY ALCOHOLYSIS

The best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon. Recall that alkyl substituents can donate electron density through hyperconjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

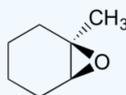


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

✓ EXAMPLE 18.6.1

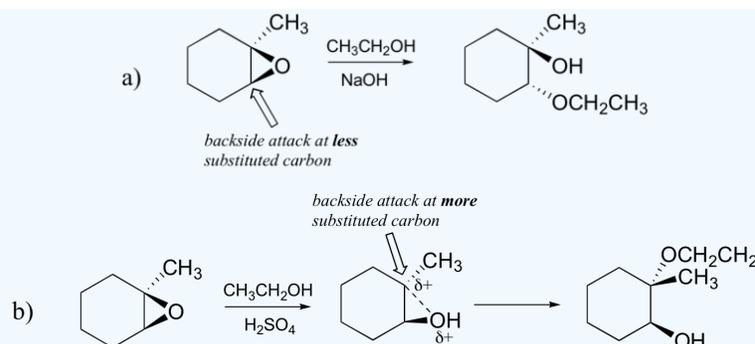
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

- ethanol and a small amount of sodium hydroxide
- ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry **and** stereochemistry!

Answer



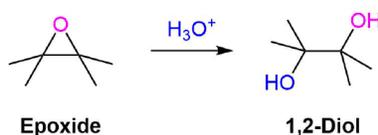
EPOXIDE RING-OPENING BY HYDROLYSIS

Epoxides may be cleaved by hydrolysis to give **trans-1,2-diols** (1,2 diols are also called **vicinal diols** or **vicinal glycols**). The reaction can be performed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

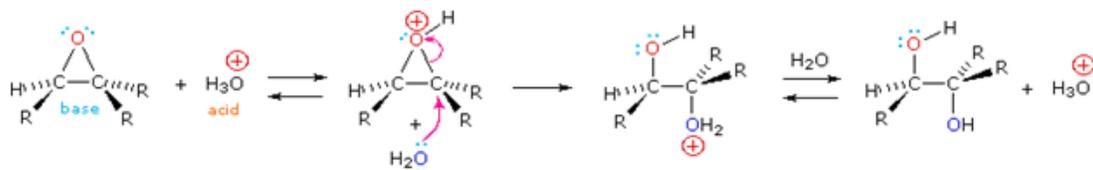
ACID CATALYZED HYDROLYSIS

Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

GENERAL REACTION



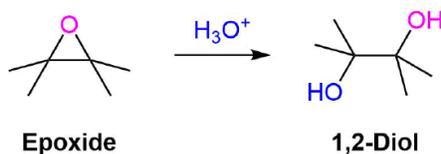
MECHANISM



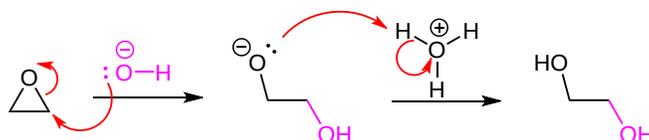
BASIC HYDROLYSIS

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferably attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

GENERAL REACTION



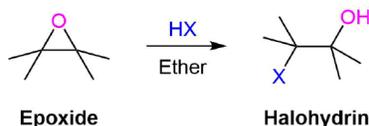
MECHANISM



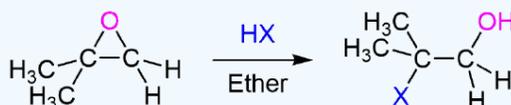
EPOXIDE RING-OPENING BY HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

GENERAL REACTION

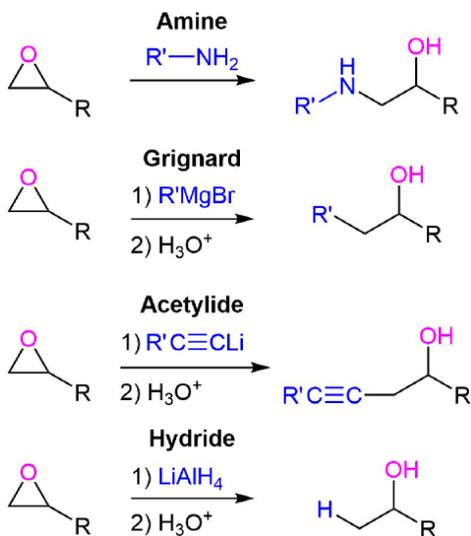


✓ EXAMPLE 18.6.2



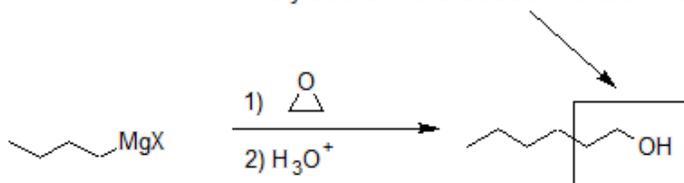
EPOXIDE RING-OPENING BY OTHER BASIC NUCLEOPHILES

A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.

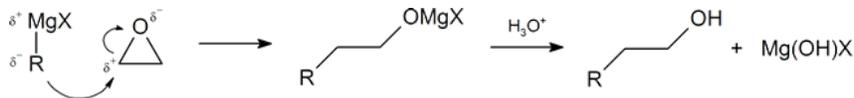


Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.

Primary alcohol with a 2-carbon increase in chain.

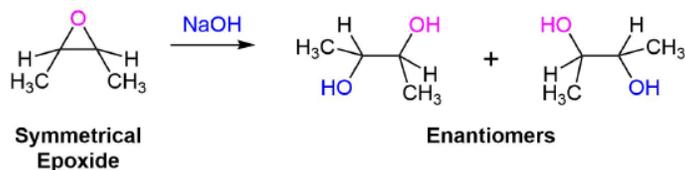


This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



ADDITIONAL STEREOCHEMICAL CONSIDERATIONS OF RING-OPENING

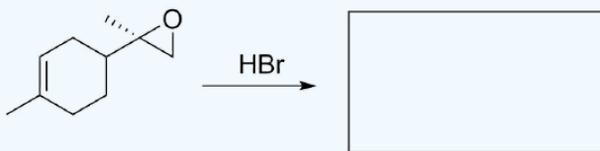
During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.



EXERCISES

? EXERCISE 4.7.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)



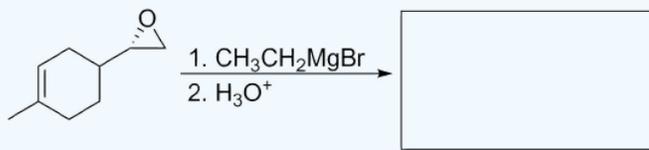
Answer



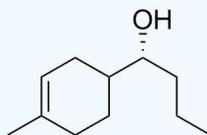
Note that the stereochemistry has been inverted

? EXERCISE 4.7.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

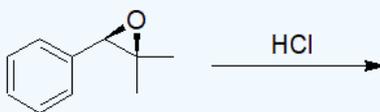


Answer

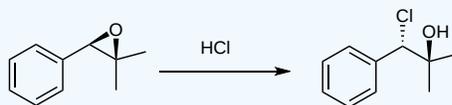


? EXERCISE 4.7.3

Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



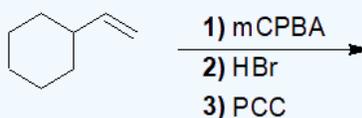
Answer



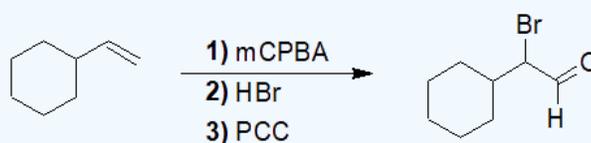
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

? EXERCISE 4.7.4

Predict the product of the following reaction.

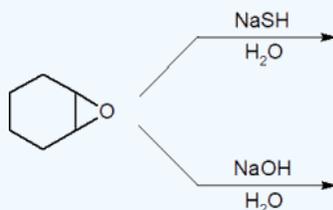


Answer

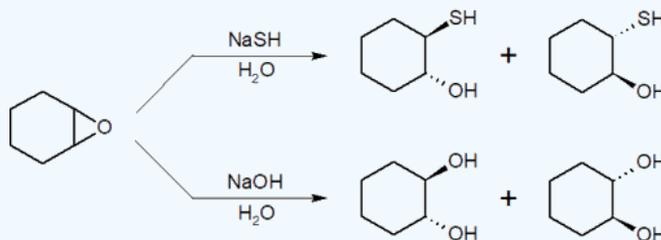


? EXERCISE 4.7.5

Provide the final products of the following reactions.



Answer



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