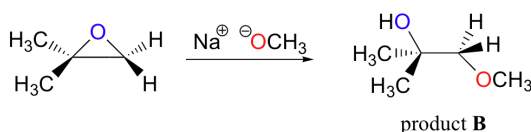


15.8: OPENING OF EPOXIDES

EPOXIDE RING-OPENING REACTIONS - S_N1 VS. S_N2, REGIOSELECTIVITY, AND STEREOSELECTIVITY

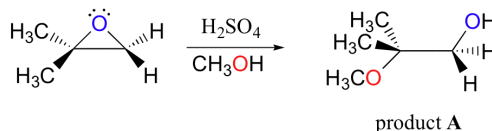
The ring-opening reactions of epoxides provide an excellent review of the differences between S_N1 and S_N2 reactions. Both mechanisms are good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively). 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. For the S_N1 mechanism, the stability of the charged intermediate determines the regioselectivity. For the concerted S_N2 mechanism, sterics are the dominating consideration. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic reaction, leading to what we will refer to as product B:

basic ring-opening:

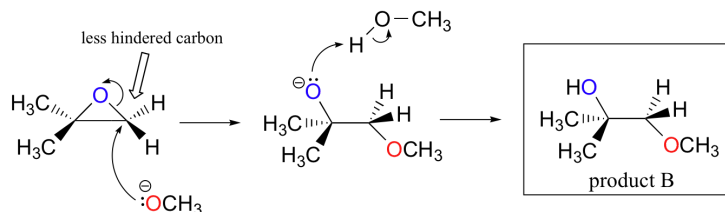


Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of reaction. As a result, product A predominates.

acidic ring-opening:



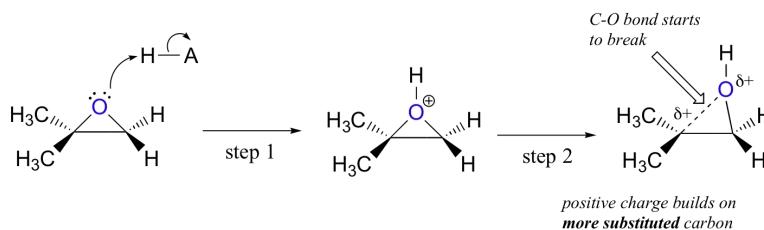
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



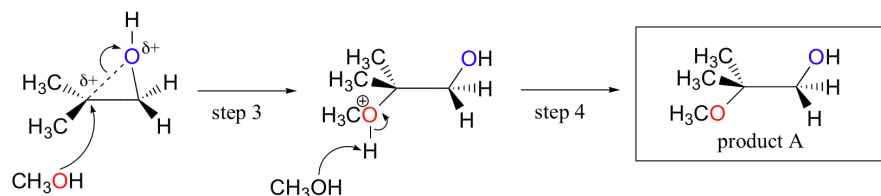
The nucleophile itself is a potent, deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? 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, bimolecular, nucleophilic substitution reactions take place from the backside, resulting in inversion at the electrophilic carbon.

The acid-catalyzed epoxide ring-opening reaction mechanism is analogous to the formation of the bromonium ion in halogenation of alkenes and mercurium ion formation in oxymercuration/demercuration or alkoxymercuration/demercuration. 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 carbocation stability).



Unlike in an S_N2 reaction, the nucleophile reacts with the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

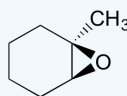


The reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the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

Example

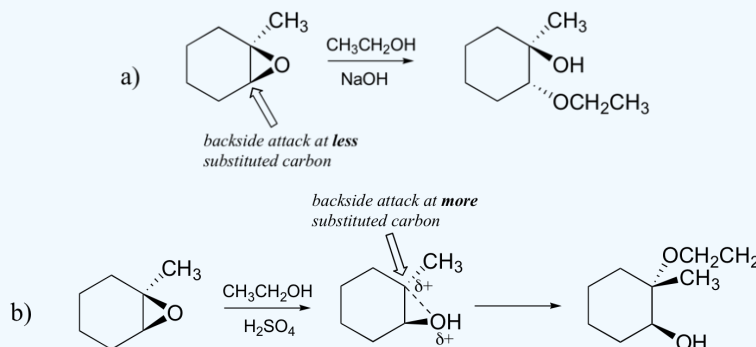
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

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



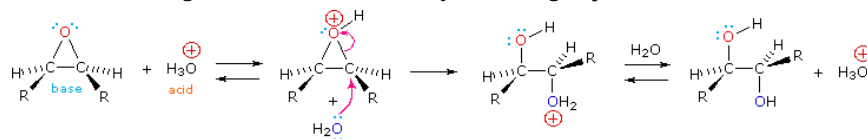
*Hint: be sure to consider both regiochemistry **and** stereochemistry!*

Answer



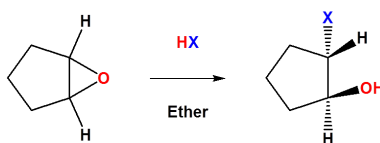
ANTI DIHYDROXYLATION

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which can be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



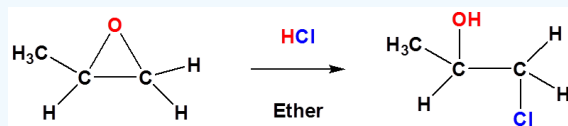
ADDITION OF HX

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

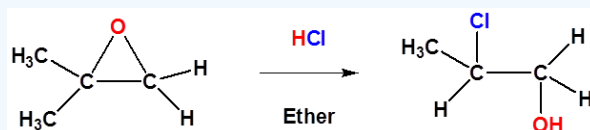


Example

In the first example, the epoxide is formed by a secondary and primary carbon. The reaction with the Cl^- nucleophile proceeds via the $\text{S}_{\text{N}}2$ mechanism and reacts with the least substituted carbon.

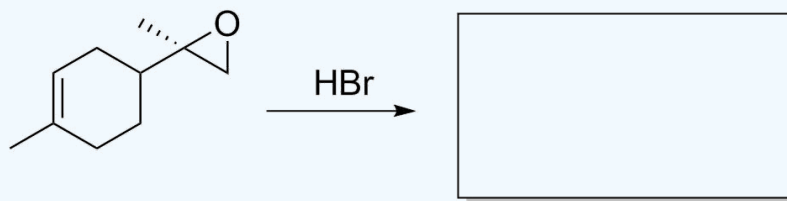


In the second example, the epoxide is formed by a tertiary and primary carbon. The reaction with Cl^- nucleophile proceeds via the $\text{S}_{\text{N}}1$ like mechanism and reacts with the most substituted carbon because it carries the greater partial positive charge.

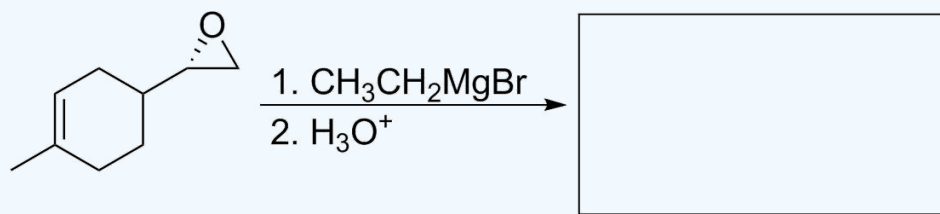


Exercise

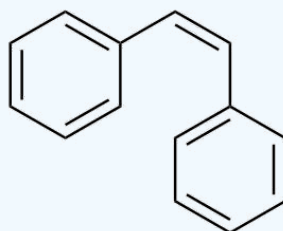
9. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



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

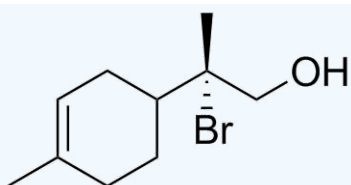


11. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be an enantiomerically pure? If not, what would it be?



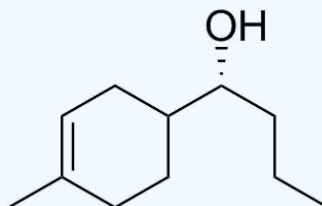
Answer

9.



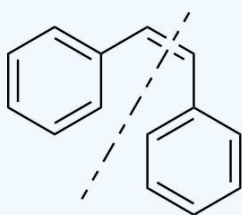
Note that the stereochemistry has been inverted

10.

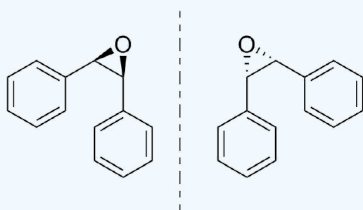


11.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer ([Sonoma State University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)

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