

9.14: OPENING OF EPOXIDES - ACIDIC VERSUS BASIC CONDITIONS

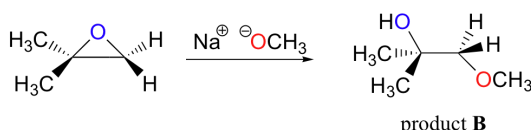
Learning Objective

- predict the products/specify the reagents for dihydroxylation of alkenes

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

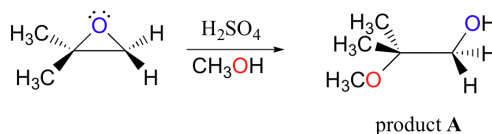
The nonenzymatic ring-opening reactions of epoxides provides an opportunity to review the nucleophilic substitution mechanisms. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon reacts with the nucleophile under steric considerations and produces product B in the example below.

basic ring-opening:



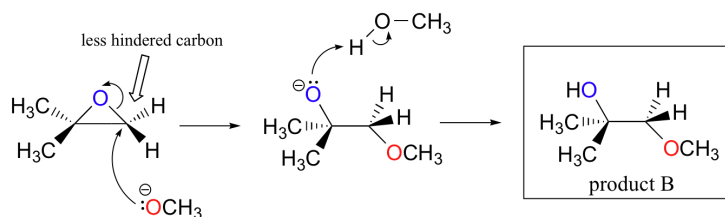
Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon reacts with the nucleophile under electrostatic considerations and produces product A in the example below.

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).

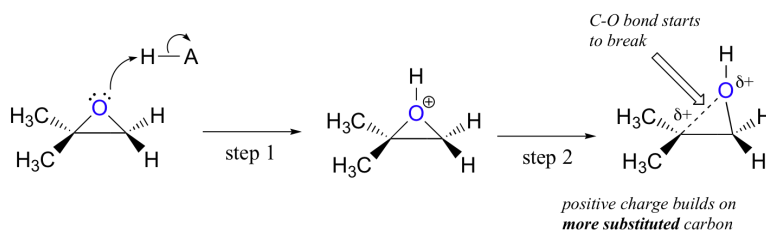
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



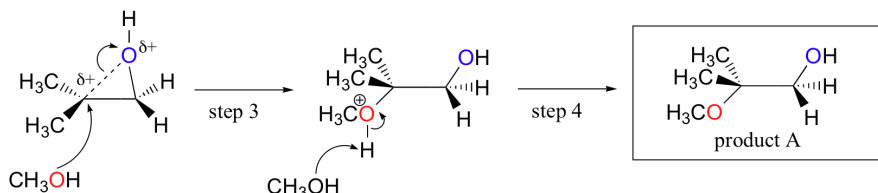
The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

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, nucleophilic reactions take place with backside orientation relative to the leaving group, resulting in inversion at the electrophilic carbon.

Probably 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). Electrostatic considerations have greater importance with a protonated intermediate. As the carbon-oxygen bond begins to break (step 2), positive charge builds on the more substituted carbon with greater carbocation stability.



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

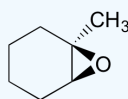


Reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, the regiochemical outcome is different from the base-catalyzed reaction. In the acid-catalyzed process, the nucleophile reacts with the more substituted carbon because it is this carbon that holds a greater degree of positive charge and electrostatics (carbocation stability) take a dominant role in determining the mechanism.

Example 9.14.1

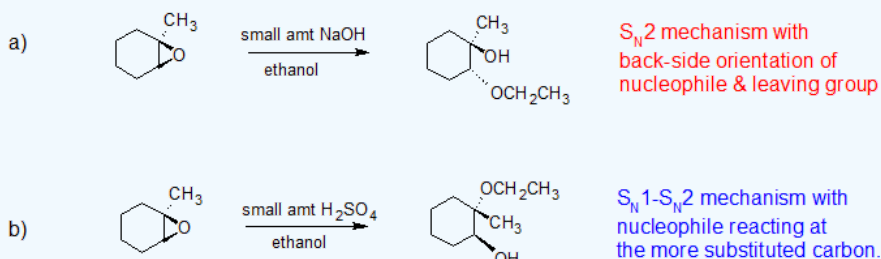
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

1. ethanol and a small amount of sodium hydroxide
2. ethanol and a small amount of sulfuric acid



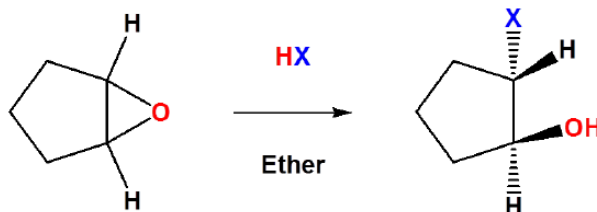
*Hint: be sure to consider both regiochemistry **and** stereochemistry!*

Solution

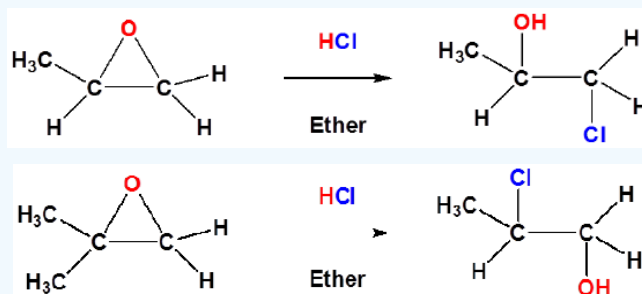


ADDITION OF HX

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 attack the less substituted carbon and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in a S_N1 like reaction.

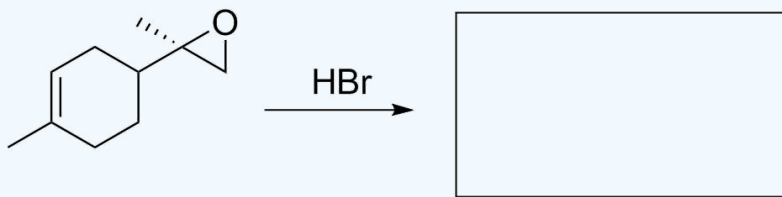


Example 9.14.1

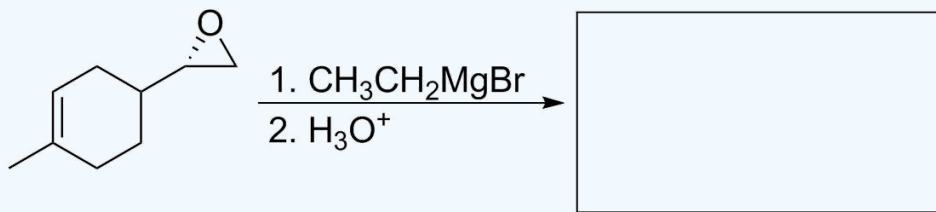


Exercise

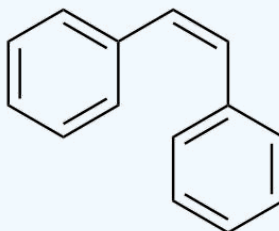
1. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



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

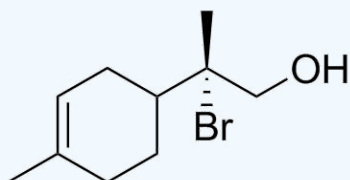


3. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



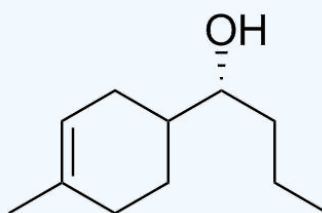
Answer

1.



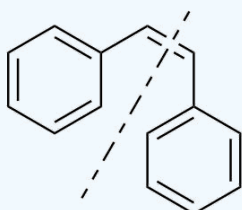
Note that the stereochemistry has been inverted

2,

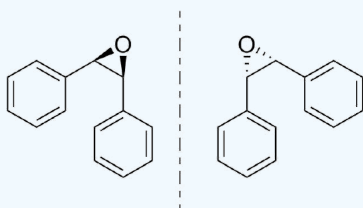


3.

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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