16. Epoxidation of Norbornene

A. Introduction

Epoxides, also called oxiranes, are cyclic ethers in a three-membered ring system. Epoxides, while strained, are relatively stable molecules and are commonly found in nature. One example is disparlure, which is the sex pheromone of the female gypsy moth. Another well-known example of naturally occurring epoxides are the epothilones, which have been isolated from the bacterium *Sorangium cellulosum*. The epothilones have been found to exhibit potent anticancer activity. The FDA approved one epothilone B analog, ixabepilone, in 2007 for the treatment of breast cancer.

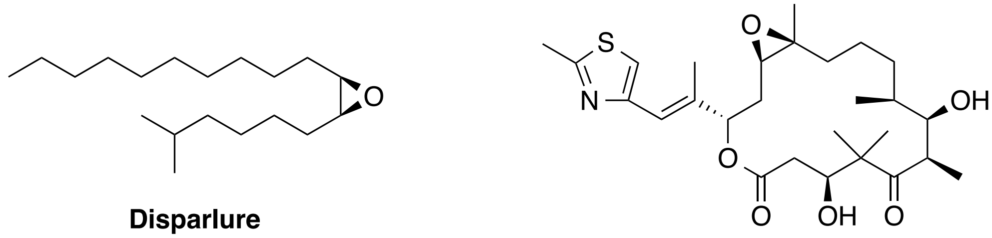

Figure 1. Naturally Occurring Epoxides

There are a number of reactions used in the preparation of epoxides. The majority revolve around the oxidation of an alkene. A reaction discussed in lecture is the mCPBA epoxidation, where *meta*-chloroperoxybenzoic acid is used to add an oxygen atom across the alkene double bond. While mCPBA epoxidations typically work well, it is important to have multiple conditions available to carry out a transformation as oftentimes unintended and unexpected side reactions can occur.

Figure 2. mCPBA Epoxidation

One alternative to the mCPBA epoxidation is epoxidation using dimethyldioxirane (DMDO). The active oxidizing agent, DMDO, is not commercially available due to its instability. It can be prepared for use by the reaction of acetone with oxone ($KHSO_5$ •0.5 $KHSO_4$ •0.5 K_2SO_4) in basic aqueous solution. Typically, sodium bicarbonate ($NaHCO_3$) is used to make the solution basic. (Figure 3)

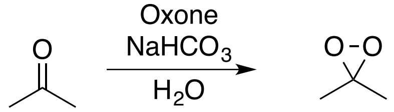

Figure 3. Preparation of Dimethyldioxirane

In the presence of DMDO, alkenes are oxidized to epoxides as shown for cyclohexene in figure 4a. The reaction is thought to proceed through a concerted mechanism as shown in figure 4b. The transition state is spirocyclic in nature. The dotted lines in the transition state in figure 4b represent the partial bonds (bond forming and bond breaking).

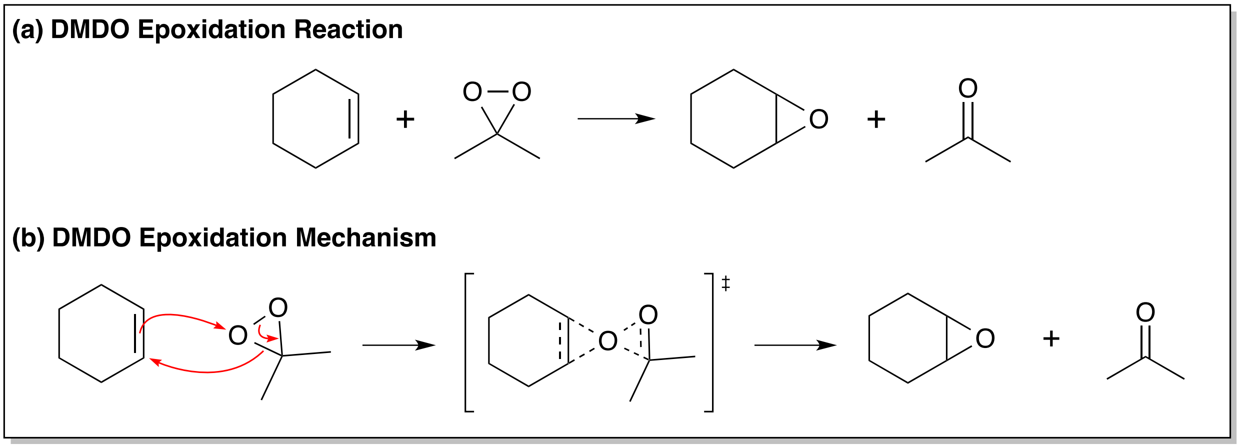

Figure 4. DMDO Epoxidation Reaction and Mechanism

In the laboratory experiment, you will prepare DMDO *in situ* by adding oxone to a solution of the alkene substrate in acetone. As DMDO is formed in the reaction flask, it will subsequently react with the alkene providing the desired epoxide product. The alkene used in this experiment is norbornene which will provide 2,3-epoxynorbornane as the reaction product. (Figure 5)

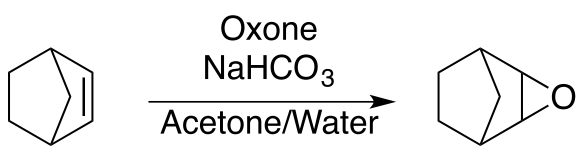

Figure 5. DMDO Epoxidation of Norbornene

B. Experimental Procedure – **You can work in pairs in this experiment**

Reagent	Mol. Wt.	Equiv.	Mmol	Mass	Volume
Norbornene	94.2 g/mol	1.0	1.06	100. mg	
Acetone	--	--	--	--	1.5 mL
$NaHCO_3$	84 g/mol	4.8	5.09	427 mg	--
Oxone	307 g/mol	1.7	1.80	553 mg	--
Water	--	--	--	--	2.5 mL

Product	Mol. Wt.	Mass Isolated	% Yield	Melting Point Range
2,3-epoxynorbornane	110 g/mol			

Measure 100. mg of norbornene into a 10 mL round bottomed flask or a large test-tube. Next, add 1.5 mL of reagent grade acetone. Clamp the flask or test tube above the magnetic stir plate, add a spin vane and commence stirring. To the solution, add 427 mg of sodium bicarbonate ($NaHCO_3$). The bicarbonate will not completely dissolve so ensure vigorous mixing to keep the solid well suspended in the solution. Weigh out 553 mg of oxone in a weighing boat and add the solid to a small test tube supported in a 50 mL beaker. Add 2.5 mL of distilled water. Use a pipet to withdrawal and expel the solution several times to affect dissolution of the oxone in the water. Do not use the solution until is becomes clear. Next, add the Oxone solution dropwise via pipet in three portions to the norbornene solution.

- 1st addition – Add ~0.5 mL of the oxone solution dropwise then let the reaction mixture stir for 2-3 min.
- 2nd addition – Add ~1 mL of the oxone solution dropwise then let the reaction mixture stir for 2-3 min.
- Final addition – Add the remaining ~1 mL of the oxone solution.

Once oxone addition is complete, allow the reaction to stir at room temperature for 25 min.

Workup and Product Isolation: If the reaction was carried out in a round-bottomed flask, transfer the reaction mixture to a large test-tube.

- Add 2 mL of water and mix thoroughly to dissolve the salts in the solution.
- Add 2.5 mL of ether and mix the solution thoroughly to extract the desired product into the ether layer. Allow the layers to separate and transfer the ether layer to a small test-tube supported in a 5 mL beaker. *If the two layers do not separate out, add 0.5-1 mL of brine and re-mix the solution.*
- Add a second 2 mL portion of ether to the aqueous layer and mix thoroughly to extract the remaining product. Allow the layers to separate and combine the upper ether layer with the first ether extract. Discard the lower aqueous layer.
- Put the combined ether extracts back into the large test-tube and wash the solution with 2 mL of brine. Once the solution has been mixed thoroughly and the layers are allowed to separate, pipet out and discard the lower aqueous layer.
- Pass the ether extracts through a sodium sulfate drying column and collect the solution in a clean, **pre-weighed** 5 mL conical vial.
- Evaporate the ether using a steady stream of nitrogen[1] until a solid or semi-solid product results. Weigh the vial containing the solid to get a mass of the isolated product.

Calculate the percent yield and if possible obtain a melting point.

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[1] Connect a length of rubber tubing to the nitrogen valve under the hood. Place a small pipet into the end of the tubing and clamp the pipet in the hood above the conical vial. The pipet will direct a stream of nitrogen into the flask to rapidly evaporate the ether.

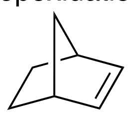
C. Pre-Lab Questions

1. Go to www.sigmaaldrich.com and look up Oxone. Find the safety data sheet (SDS) for oxone on the website. Read over the SDS and list any major safety hazards that you should be aware of.

2. Calculate the theoretical yield of 2,3-epoxynorbornane based on using 100. mg of of norbornene.

3. Why is it important that you not dump any oxone waste into the acetone waste container?

4. A more three-dimensional structure of norbornene is shown below.
   a. Using this structure, show the two diastereomeric products that can result from epoxidation.

   b. Which the diastereomers do you think predominates in the reaction? Explain.
   c. Identify all of the chiral centers in one of the 2,3-epoxynorbornane stereoisomers.
   d. Is 2,3-epoxynorbornane chiral or achiral? Explain.

D. Post-Lab Questions

1. Look up the literature melting point value for epoxynorbornane at www.sigmaladrich.com. How does your experimental melting point compare?

2. What was the percent yield of your reaction? List a few things that you possibly could have done differently to improve the yield?