

16. Epoxidation of Cyclooctene

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.

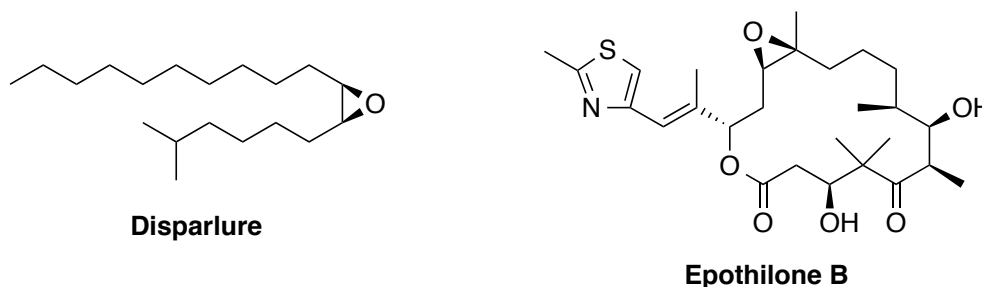


Figure 1. Naturally Occurring Epoxides

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 ($\text{KHSO}_5 \cdot 0.5 \text{KHSO}_4 \cdot 0.5 \text{K}_2\text{SO}_4$) in basic aqueous solution. Typically, sodium bicarbonate (NaHCO_3) is used to make the solution basic. (Figure 3)

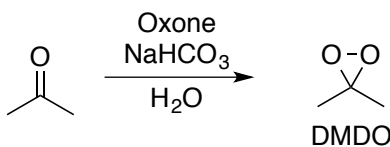


Figure 3. Preparation of Dimethyldioxirane

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).

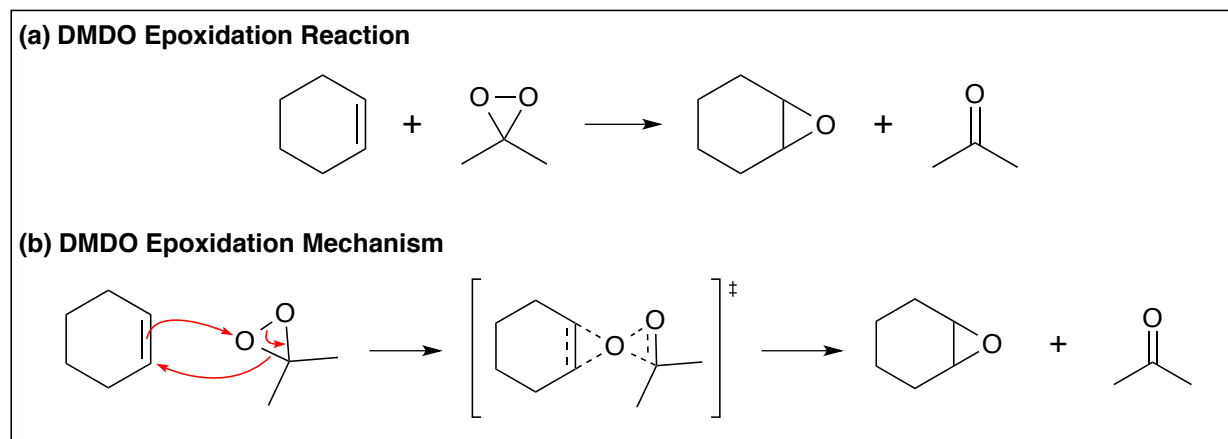


Figure 4. DMDO Epoxidation Reaction and Mechanism

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 will be cyclooctene which will provide cyclooctene oxide as the reaction product.

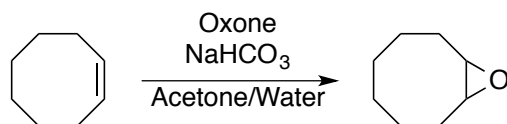


Figure 5. Epoxidation of Cyclooctene to Provide Cyclooctene Oxide

B. Experimental Procedure

Reagent	Mol. Wt.	<i>d</i> (g/mL)	Equiv.	Mmol	Mass	Volume
Cyclooctene	110 g/mol	0.848	1.0	0.578	63.6 mg	0.075 mL
Acetone	--	--	--	--	--	1.5 mL
NaHCO ₃	84 g/mol	--	4.8	2.77	233 mg	--
Oxone	307 g/mol	--	1.7	0.983	302 mg	--
Water	--	--	--	--	--	1.5 mL
Product	Mol. Wt.	Mass Isolated	% Yield	Melting Point Range		
Cyclohexene oxide	126 g/mol					

Measure 0.075 mL of cyclooctene into a 5 mL conical reaction vial¹ using a 1 mL syringe. Dilute the cyclooctene with 1.5 mL of reagent grade acetone. *You can use the marks on the vial to estimate 1.5 mL.* Add a spin vane and commence stirring on the magnetic stir plate. To the

¹ You will be working near the upper volume limits of the conical vial. Be sure to not add a larger volume of any solvent than what is instructed.

solution, add 233. 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 302 mg of oxone in a weighing boat and add the solid to a small test tube supported in a 50 mL beaker. Add 1.5 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 it becomes clear. Next, add the Oxone solution dropwise via pipet over 2-3 min to the cyclooctene solution. If the reaction becomes too vigorous, slow the addition rate. Once addition is complete, allow the reaction to stir at room temperature for 25 min.

Workup and Product Isolation: When the reaction is complete, add 2 mL of ether and stir the solution rapidly to extract the cyclohexene oxide product into the ether layer. Stop stirring and allow the layers to separate. Carefully pipet the ether layer into a small test-tube supported in a 50 mL beaker. Extract the aqueous layer with a second 1.5 mL portion of ether. Combine this ether extract with the first ether extract in the test tube. Discard the aqueous layer and rinse the vial with distilled water. Next, transfer the ether extracts to the 5 mL conical vial. Add 1 mL of water and stir rapidly to wash the organic layer. Pipet out and discard the lower aqueous layer. Pass the ether layer through a sodium sulfate drying column and collect the dried solution in a clean **weighed** 5 mL conical vial. Evaporate the ether a steady stream of nitrogen² until a solid product results. Scrape the product onto a pre-weighed watch glass. Weigh the vial containing the solid to get a mass of the isolated product. Calculate the percent yield and obtain a melting point. *The mp should be less than 70 °C.*

C. Pre-Lab Questions

1. Go to www.sigmaldrich.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 cyclooctene oxide based on using 63.6 mg of cyclooctene.
3. If the starting material for this reaction was 1-methylcyclohexene, what would the reaction product look like?
4. Why is it important that you not dump any oxone waste into the acetone waste container?

D. Post-Lab Questions

1. Look up the literature melting point value for cyclohexene oxide at www.sigmaldrich.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?

² 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.