Experiment 3 – Epoxidation of Cyclohexene
Students work in pairs

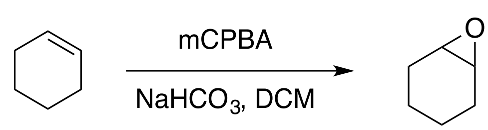
Learning Objectives
- Perform a reaction using a literature procedure
- Understand chemical hazards and take necessary precautions
- Introduction to synthetic methodology: systematic optimization of reaction conditions
- IR, ^{1}H and ^{13}C NMR structural analysis

Epoxides are a versatile functional group in organic synthesis. Readily formed from the reaction of an alkene with a peroxyacid, epoxides react with various nucleophiles to give stereospecific alcohols as well as with $NaIO_4$ to facilitate breaking C-C bonds through oxidative cleavage. In this experiment, students will synthesize cyclohexene oxide from the corresponding alkene using the supplemental information from a journal article.

Experimental methods given at the end of journal articles provide a minimal procedure that should be understood by an experienced synthetic chemist. These instructions 'should' work, however, the first attempt is often less successful than reported (unreacted starting material, lower yield, mixture of products). Students in the Fall '17 offering of CHEM 146A were instructed to follow the procedure given in the article below to synthesize β-pinene oxide from commercially available (-)-β-pinene and *meta*-chloroperoxybenzoic acid (*m*-CPBA). The reactions suffered from poor yields and low conversion. The NMR spectra were difficult to interpret, owing largely to the stereogenic centers in the molecule.

In hindsight, the experiment should have been first attempted with a simpler substrate to optimize the reaction conditions. Students will prepare a solution of *m*-CPBA with varying amounts of $NaHCO_3$ to optimize the reaction conditions for the epoxidation of cyclohexene. IR and NMR spectroscopy will be used to analyze the crude reaction product.

<u>Notebook Preparation</u>
- *Purpose:* To optimize the synthesis of cyclohexene oxide from *m*-CPBA and cyclohexene under basic conditions to exemplify an epoxidation reaction.



- *Reagent table*: List the amounts (mg or mL and mmol), molar equivalents ("equiv."), and physical properties (MW, bp or mp, density, one-word hazard) of each chemical in the reaction scheme. Pay special attention to the 'procedural notes' below to determine the proper amount of base.

- *Hand-written procedure*: step-by-step instructions in your own words. This can be copied almost directly from the literature reference that follows, incorporating the 'procedural notes' on the following page.
  - Constantino, M. G.; Lacerda Jr., V.; Invernize, P. R.; Carlos da Silva Filho, L.; Jose da Silva, G. V. *Synth. Comm.,* **2007**, 37, 3529 – 3539.

- *Safety & Clean-up:* copy the table on page 3 into your notebook.

Procedural Notes – include within the experimental procedure from the literature

- The reaction will be carried out on a 10 mmol scale with respect to cyclohexene. The procedure in the reference above is performed with 14.2 mmol of cyclohexene. Use the molar equivalents (ratios) of other reagents to calculate the proper amounts of each reagent to use, including volumes of solvents and solutions in the reaction and workup. The quantity of $NaHCO_3$ will be optimized as follows:
    - Tu 2pm & W 11am sections use the same amount used in the literature (1.31 eq).
    - T 3:30 & Th 1:30pm sections will use half that amount (0.66 eq).
    - Th 6pm section will use ¼ of the amount in the literature (0.32 eq).
- Stir *m*-CPBA with $NaHCO_3$ in DCM for 10-15 minutes before adding alkene solution.
- Perform the reaction and all steps involving DCM in a fume hood. Space is limited. Please share respectfully.
- A water-ice bath should be carefully maintained. The solution will begin to thicken with an ice bath that approaches 0 °C. Use the black notched rubber stopper in your drawer to securely clamp a thermometer in the bath.
- The reaction will be capped with a rubber septum and needle to equalize pressure. Inert conditions are not required but the solvent will quickly evaporate if left uncapped.
- Do not rush the reaction workup! Transfer the reaction mixture into a separatory funnel after 30 min of stirring with sodium sulfite (Na_2SO_3). In order to minimize presence of by-product (*m*-chlorobenzoic acid or benzoate) in your crude reaction mixture, each aqueous wash should be carried out over approximately 5 minutes with occasional mixing and venting.
- Use a test strip to confirm absence of peroxides before concentrating in the rota-vap.
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- Report the crude yield (mg and %) to the TA.
- Students will not perform column chromatography.
- Each pair will perform IR analysis on starting material and crude reaction products.
- NMR analysis will be performed as follows.

NMR Analysis: Four students will prepare NMR samples under TA supervision. Add 800 μL of $CDCl_3$ to an NMR tube. Use a long stem pipet to transfer one drop of product to the NMR tube and mix (do not invert). Add a clearly written label containing "Last Name, First Initial, Lab Day, Time, and TA." Students will receive an email notification when spectra are available online. If you did not prepare a sample for NMR, you may analyze any one spectra from your section.

Students will be provided with an NMR worksheet for the second week of this lab, in addition to using that time to work on the lab report (ex. Experimental Methods section).

Table 1. Clean-up & Safety – copy into notebook

Cleaning Instructions	Safety Hazards
Clean and return all shared equipment in an organized manner. Wipe bench tops.	*m*-CPBA is a strong **oxidizer** – measure with plastic spoon, test for peroxides before using rota-vap – peroxides are potentially **explosive** when concentrated
Rinse glassware with provided solvent wash bottle into *liquid waste* before washing glassware in the sink	Cyclohexene is **flammable**
Clean IR plates using acetone saturated with NaCl and store in desiccator when not in use	Methylene chloride (dichloromethane, DCM) is a potential **carcinogen** – handle in fume hood only
Liquid waste – aqueous washes, product after analysis, solvent from rota-vap trap Solid waste - Filter paper, $MgSO_4$, and contaminated pipets	Na_2CO_3 is an **irritant**
Drawer Check (week 2): Use the equipment list and check that each item in the drawer is clean and present. Points will be removed for any items that are dirty, missing, broken, or extra.	

Pre-lab Questions

1. Read the *m*-CPBA article posted on the course website and the table on the previous page. Reproduce the reaction scheme for the synthesis of *m*-CPBA (leave space and draw by hand) using the full structures of *m*-chlorobenzoyl chloride, dioxane, and product. Comment on the safety hazards associated with using this reagent and precautions taken.

2. What is the mass and volume of 10 mmol of cyclohexene? What are the molar equivalents of *m*-CPBA and $NaHCO_3$ to be used? Considering *m*-CPBA is 70% pure, what quantity of *m*-CPBA and $NaHCO_3$ will be used (mmol and mg)? What is the theoretical yield of cyclohexene oxide (mmol and mg)? Show your work. Ignore $NaHCO_3$ as a possible limiting reagent.

3. Complete two tables using the format below - one for cyclohexene and another for cyclohexene oxide. How will IR spectroscopy be used to determine whether the reaction was complete / successful?

Table x. IR Analysis of (Compound Name)

Functional Group	Bond	Expected from tables (cm^{-1})

4. Using the NMR table of values on the CHEM 110L website, report the expected ^{1}H NMR chemical shifts, integration values, and splitting patterns for both cyclohexene and cyclohexene oxide. Do the same for expected chemical shift values in the ^{13}C NMR spectrum. Use the format below along with labeled structures.

Table x. ^{1}H NMR Analysis of (Compound Name)

Signal	Integration (#H's)	Splitting	Chemical Shift, Expected
A			

Table x. ^{13}C NMR Analysis of (Compound Name)

Signal	Chemical Shift, Expected
A'	

Post-Lab Questions

1. Report the crude yield of product (mg and %). Identify and briefly discuss three potential sources of product loss (not including human error).

2. The average yield for each section will be posted online by the end of the week. What was determined to be the optimal amount of $NaHCO_3$? Briefly comment on this finding, given your experience with this reaction.

3. Report the data from IR analysis of cyclohexene and its epoxide. Add an "Observed Value (cm^{-1})" column to the table from pre-lab #4. Attach the spectrum to the back of the report.

4. The NMR spectra will be posted online in the shared folder with an email notification. Add a "Chemical Shift, Observed" column to each of the tables from pre-lab #5 to complete NMR analysis. Indicate which spectrum you analyzed (file name only, printing not required). Was the epoxide formed and were any impurities observed? Explain.

Exp 3 - Synthesis of Cyclohexene Oxide Name ______________________________

Section Day _____ Time _____ TA Name ___________________________

CHEM 110L GRADING RUBRIC - Use as cover page for report

SECTION	INSTRUCTOR COMMENTS	POINTS ASSIGNED
IN-LAB QUIZ		**/ 5**
LAB REPORT		
NMR PROBLEMS Completed by the end of the second lab period. Checked for completeness & correctness by TA at the end of the second Exp 3 lab period (preferred) or turned in with the lab report.		**/ 50**
INTRODUCTION Original responses to pre-lab questions with TA initials		**/ 45**
RESULTS The main results are stated, as outlined in the in-lab questions, using complete sentences.		**/ 35**
EXPERIMENTAL METHODS The experimental details (including final amount used and obtained) are *briefly* described in a few sentences. Compound characterization is included.		**/ 25**
NOTEBOOK PAGES Proper format: reaction scheme, chemical info table, procedure, waste and clean-up procedure.		**/ 20**
NEATNESS, ORGANIZATION, & LAB TECHNIQUE Proper order and format; spelling & grammar. Safety rules followed, equipment used properly. Student made efficient use of down-time during lab. Week 2 drawer check.		**/ 20**
	LAB REPORT TOTAL	**/ 200**