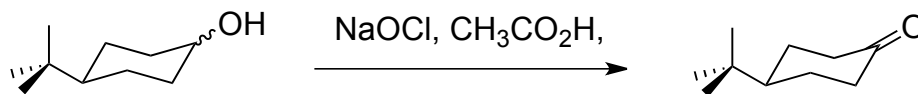


CHEM51LC OXIDATION-REDUCTION PROJECT BACKGROUND
THE INTERCONVERSION OF
4-*tert*-BUTYLCYCLOHEXANOL AND 4-*tert*-BUTYLCYCLOHEXANONE¹

OUTLINE AND GOALS OF THE PROJECT: This is a three week project that will evaluate the stereochemistry of the oxidation-reduction interconversion of 4-*tert*-butylcyclohexanol and 4-*tert*-butylcyclohexanone. In week 1 you will oxidize the commercially available 4-*tert*-butylcyclohexanol, which is mixture of the *cis* and *trans* stereoisomers. You will then perform two different reduction procedures using sodium borohydride and the Meerwein-Ponndorf-Verley (MPV) conditions to reduce the ketone you made in week 1. Using NMR spectroscopy you will evaluate the outcome of both reactions and determine and compare the diastereomeric ratios of the 4-*tert*-butylcyclohexanol you started with and the products you obtained after the oxidation-reduction sequences. A third NMR spectrum will be provided for analysis from the L-Selectride (lithium tri-*sec*-butylborohydride) reduction process.

OXIDATION

In this experiment, we will explore the oxidation of a secondary alcohol to a ketone using an oxidizing reagent, sodium hypochlorite, which is a readily available and commonly used household cleaning product. We will use thin layer chromatography (TLC) to monitor the progress of oxidation reaction.



Sodium hypochlorite solutions (approximately 2 M) sold commercially as liquid bleach are often described as having 11.5-12.5% available chlorine. The term “available chlorine” compares the oxidizing capacity of the solution relative to that of the same weight of chlorine, Cl₂. Sodium hypochlorite solutions are used extensively in swimming pool sanitation, and as bleach in the pulp and textile industries. A less-concentrated product (5% available chlorine) is used in laundry and as household bleach. It is reported that 210,000 tons of sodium hypochlorite were consumed in the United States in 1982. The reaction described in this experiment illustrates the use of liquid bleach as an oxidizing agent in the organic laboratory.²

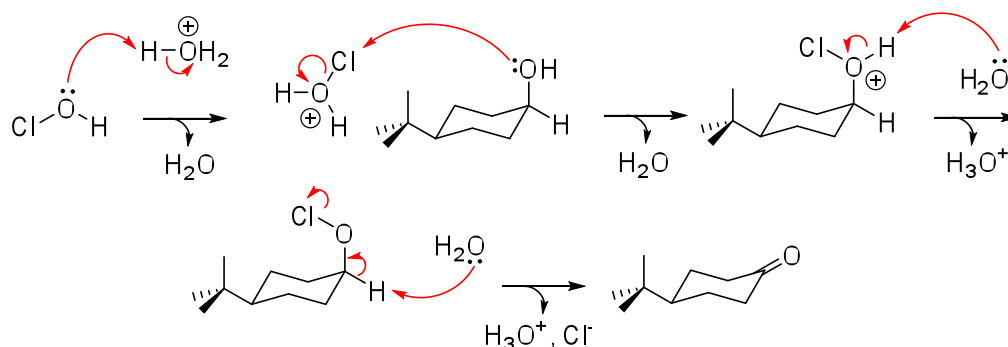
Sodium hypochlorite is prepared commercially by passing chlorine gas through a solution of aqueous sodium hydroxide (eq 1). In acidic condition, a rapid equilibrium is established between hypochlorite anion and hypochlorous acid (HOCl), which produces a Cl⁺ ion equivalent (eq 2). Do note that Cl⁺ is not actually generated by the reaction.

¹ Parts of this procedure were adopted from an article published by C.S. Jones and K. Albizati in the *Journal of Chemical Education* **1994**, *71*, A271 and from Novak, M.; Gung, B. W.; Hershberger, J. W.; Taylor, R. T.; Emenike, B.; Chakraborty, M.; Scioneaux, A. N.; Ponsot, A. E.; Daka, P. *Chem. Educator* **2009**, *14*, 232–235. <http://chemeducator.org/sbibs/s0014006/spapers/14090232mn.pdf>

² As a general reference for the use of sodium hypochlorite as an oxidant, see: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol I, p. 1084.



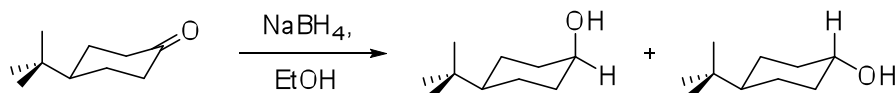
The actual oxidizing agent in the present experiment is believed to be $[\text{Cl}]^+$, which is reduced in the reaction to chloride ion (Cl^-). The alcohol acts as a reducing agent, and thus becomes oxidized to a ketone. The most likely operating mechanism is shown below.



This oxidation procedure is more efficient than the chromic acid-amberlite procedure, which is a heterogeneous solid-liquid reaction that proceeds poorly due to the requirement of very efficient agitation.

REDUCTION

In this portion of experiment, the facial selectivity for the reduction of 4-*tert*-butylcyclohexanone with different reducing agents will be explored through the use of ^1H NMR spectroscopy. Reduction of 4-*tert*-butylcyclohexanone affords two possible 4-*tert*-butylcyclohexanol diastereomers, *cis*-4-*tert*-butylcyclohexanol, and *trans*-4-*tert*-butylcyclohexanol.

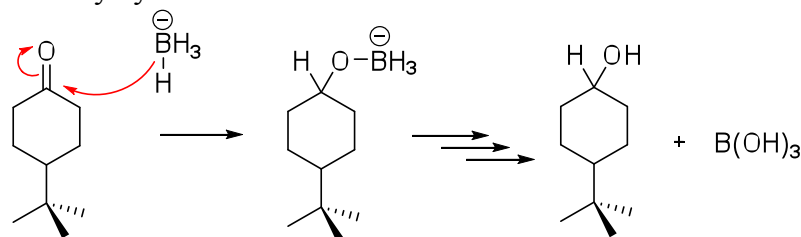


Due to the large size of the *tert*-butyl group, 4-*tert*-butylcyclohexanone exists almost exclusively in one chair conformation, the one in which the *tert*-butyl group is in the equatorial position. Likewise, the size of the *tert*-butyl group effectively locks the conformations of the two possible cyclohexanol products. The hydroxyl group in *cis*-4-*tert*-butylcyclohexanol is held in the axial position, and the hydroxyl group in *trans*-4-*tert*-butylcyclohexanol is held in the equatorial position. Axial and equatorial hydrogens exhibit different ^1H NMR splitting patterns. This makes it possible to determine the *cis-trans* product ratio in this reaction.

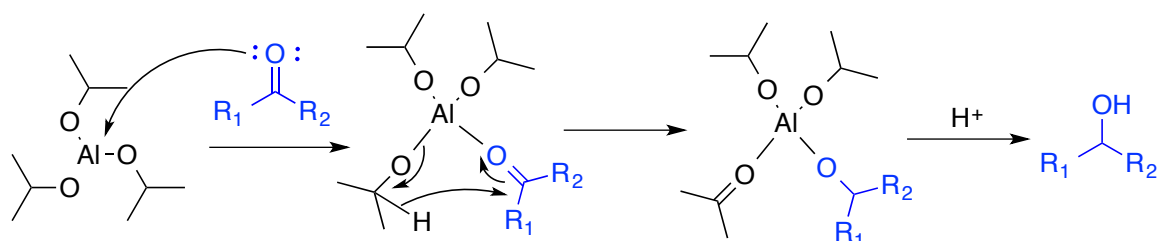
Background on Reduction Processes:

Sodium borohydride (NaBH_4) is a reagent that performs an *irreversible* reduction of aldehydes and ketones. Therefore, the ratio of *cis* to *trans* diastereomeric alcohol products from NaBH_4 reduction is determined by their relative rates of formation, with the fastest-forming product predominating. Other reducing reagents, such as lithium aluminum hydride, react violently with water and alcohols to produce hydrogen gas while NaBH_4 reactions commonly are run in methanol or ethanol as solvent. This is because NaBH_4 is

significantly less basic and the acid-base reaction is much slower. The mechanism of the reduction of 4-*tert*-butylcyclohexanone is shown below:

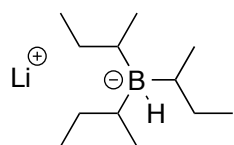


The Meerwein-Ponndorf-Verley (MPV) reaction using aluminum isopropoxide in the presence of isopropyl alcohol provides a **reversible** reduction of ketones and aldehydes.³ In the MPV reduction, the *cis* or *trans* diastomeric alcohol products can revert back to starting ketone. Each step in the mechanism is reversible (equilibrium mixture) and so the reaction is driven by formation of the most stable product. The thermodynamically more stable product will eventually be favored with time.



Aluminum isopropoxide

More bulky species such as lithium tri-*sec*-butylborohydride (L-Selectride) generate the *cis* isomer by equatorial attack on the carbonyl.⁴ Consider the reasons why this occurs.



L-Selectride

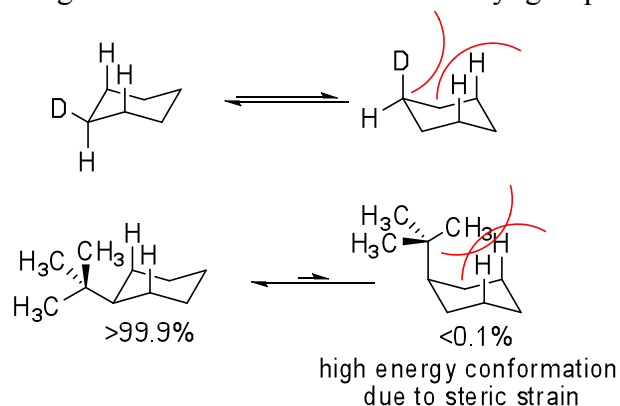
STEREOCHEMICAL CONSIDERATIONS

4-*Tert*-butylcyclohexane can exist in two conformations: one where the *tert*-butyl group is equatorial and the other where it is axial. Most substituted cyclohexane rings will rapidly interconvert between the two conformations, so at any given time the solution will be a mixture of both conformers. When the substituent is small, like in the case of deuterium, the two conformers are almost equal in energy so it is practically a 50:50 mixture of the axial and equatorial conformers. The bigger the substituent, however, the higher in energy the axial conformer becomes and, therefore, the ratio of equatorial to axial increases. When the substituent is a *tert*-butyl group, the axial conformer has severe steric interactions that make it very high energy and therefore very unfavorable. In the case of *tert*-

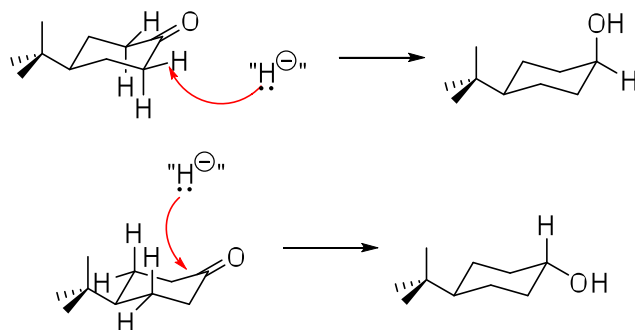
³ Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796.

⁴ Brown, H. C.; Krishnamurthy, S., *J. Am. Chem. Soc.* **1972**, *94*, 7159.

butylcyclohexane, the axial conformation is practically not observed and the cyclohexane ring is “locked” into a single conformation with the *tert*-butyl group equatorial.



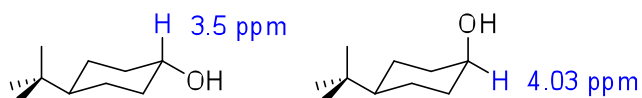
Analogously, 4-*tert*-butylcyclohexanone is locked in the conformation with the *tert*-butyl group equatorial and, thus, the two faces of the carbonyl group become non-equivalent. This means that when the hydride source attacks the ketone it could result in the formation of two different diastereomers of product, depending on which face of the carbonyl the hydride attacks. Furthermore, because the two ketone faces are non-equivalent, one can expect to see stereoselectivity in the reduction, meaning one diastereomer will be more prevalent than the other. For each set of reduction conditions, predict which diastereomer will be the major product and explain the basis of your prediction. Additionally, compare the diastereomer ratio of the products from each reduction reaction to the ratio in the commercial sample (provided on class website) and determine whether the commercial sample was prepared by reduction of the ketone under one of the set reduction conditions explored in this project.



SPECTROSCOPY

NMR

The product of each of these reductions, mixtures of *cis* and *trans*-4-*tert*-butylcyclohexanol, has a very complicated ^1H NMR spectrum. In spite of this, it is easy to use the spectrum to analyze the ratio of *cis* and *trans* isomers because the methine hydrogen on the carbon bearing the hydroxyl group is shifted downfield of the other signals. In addition, in studies of many substituted cyclohexane rings, it has been found that equatorial hydrogens generally appear about 0.5 ppm downfield of the corresponding axial hydrogens. In this mixture of *cis* and *trans*-4-*tert*-butylcyclohexanol, there is a signal at approx. 3.5 ppm for the methine hydrogen of the *trans* isomer (this H is axial), and a signal at approx. 4.03 ppm for the methine hydrogen of the *cis* isomer (this H is equatorial). The integration values for these two signals correspond to the relative amounts of the two isomers.



You can easily calculate the *cis:trans* diastereomers ratio by using the integration on your ^1H NMR spectrum.

$$\% \text{ cis isomer} = \frac{\text{area of 4.03 ppm signal}}{\text{area of 4.03 ppm signal} + \text{area of 3.5 ppm signals}} \times 100$$

This way you will be able to determine whether under each set of reduction conditions the hydride preferentially attacks one face of the ketone, and if so, which one it is. Use thermodynamic, kinetic and stereochemical arguments to explain the selectivity.

IR

How would you expect the IR spectra of 4-*t*-butylcyclohexanone and 4-*t*-butylcyclohexanol to differ? Would you expect the diastereomers of 4-*t*-butylcyclohexanol to differ? If so, how?

ADDITIONAL BACKGROUND READING:

- Sodium borohydride reduction: Chapter 20, pgs 728-731 Smith, 2nd Ed.
- Thermodynamic vs kinetic control: Chapter 6, Smith, 2nd Ed. (Thermodynamics Section 6.5, Kinetics Section 6.9)

A note about diastereomers⁵: The word diastereomer describes any spatial isomer that is not an enantiomer. A pair of diastereomers can be a set of molecules with stereocenters that are not enantiomers. A pair of diastereomers can also be a pair of cis-trans isomers as in alkene isomers or the 4-*t*-butylcyclohexanol isomers in this project. Think of “diastereomers” as a big umbrella term used to describe relationships between any set of molecules that are stereoisomers but not enantiomers. In other words, all cis-trans isomers are diastereomers, but not all diastereomers are cis-trans isomers. Normally you want to be as specific as possible when describing the relationship between a pair of isomers. We are using terms like diastereomer and diastereomeric ratio in this handout because they are easier to write and say than cis-trans isomer or cis-trans isomeric ratio.

⁵ Eliel, E. L. Stereochemistry of Organic Compounds; McGraw-Hill: New York, 1962.