Experiment 8: Reduction of 4-t-Butylcyclohexanone with Sodium Borohydride

Introduction: In this experiment you will investigate the facial selectivity of the sodium borohydride reduction of 4-t-butylcyclohexanone by determining axial/equatorial ratio of the resulting alcohol using NMR.

Background:

Ketones are converted to alcohols by reduction with sodium borohydride followed by hydrolysis in an aqueous acidic workup. In this reaction, a hydride anion from the borohydride is transferred to the electropositive carbon of the carbonyl group. The reaction of cyclohexanone with sodium borohydride is demonstrated in the following equation:

\[
\text{NaBH}_4 + \text{C}_6\text{H}_5\text{COCH}_3 \rightarrow \text{C}_6\text{H}_5\text{CH(OH)}\text{CH}_3 + \text{Na}^+ + \text{H}_2\text{O}.
\]

The product, cyclohexanol, exists as a mixture of two rapidly interconverting chair cyclohexane conformations. In one conformation, the hydroxyl group is in an equatorial position and in the other conformation, the hydroxyl group is in an axial position. The conformations interconvert by a ring flip.

Reduction of 4-t-butylcyclohexanone with sodium borohydride affords two 4-t-butylcyclohexanol diastereomers which differ in their relative stereochemistry, cis-4-t-butylcyclohexanol and trans-4-t-butylcyclohexanol.
The very bulky tertiary butyl group at the 4 position of the cyclohexane ring strongly prefers to be in the equatorial position. This effectively locks the conformations of the cyclohexanols. The hydroxyl group in cis-4-t-butylcyclohexanol is held in the axial position and the hydroxyl group in trans-4-t-butylcyclohexanol is held in the equatorial position.

Axial and equatorial hydrogens exhibit different NMR splitting patterns. This makes it possible to determine the product ratio in this reaction. Remember that the axial alcohol was formed by adding a hydrogen to the equatorial position and vice versa.

**Techniques: Extraction**

**Solubility**

Solubility is the property of a substance which describes the ability of the substance to form chemically and physically homogeneous mixtures with other substances. More simply: Will the substance dissolve in a particular solvent? How much of it will dissolve?

You have already seen differences in solubility used to purify compounds by recrystallization. **Extraction** is another common way that chemists use differences in solubility to separate or purify compounds. Our ability to predict if a compound will be more soluble in organic solvent (ether, hexane, dichloromethane), water, acid or base allows

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**Diagram:**

1. $\text{O}$
2. $\text{C(CH}_3\text{)}_3$
3. $\text{1) NaBH}_4$
4. $\text{2) H}_2\text{O, HCl}$
5. $\text{C(CH}_3\text{)}_3$
6. $\text{OH}$
7. $\text{C(CH}_3\text{)}_3$
8. $\text{OH}$

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us to separate mixtures easily. Often, this may be predicted fairly easily by examining the functional groups of the molecule.

Extraction

**Aqueous and Organic Phases:** “Oil and water do not mix.” This common knowledge describes the behavior of water and most organic liquids, such as hexane, ether, and dichloromethane. Liquids that mix to form a homogeneous liquid phase are said to be **miscible**, meaning that the two substances are mutually soluble in all proportions. Most organic liquid used as solvents for manipulations in an organic chemistry laboratory are not significantly soluble in water. Organic liquids and water are said to be **immiscible** in one another.

When water and an organic liquid are shaken together and then allowed to stand, the liquids separate into two layers or “phases” with the more dense liquid on the bottom. *As a general rule of thumb, if the organic solvent is halogenated (dichloromethane) it will be more dense than water and thus on the bottom. If it is non-halogenated (ether, hexane, ethyl acetate) it will be less dense than water and on the top.* If there is any doubt about the identity of a layer, there is a quick test which can be performed to determine its identity. A drop of the layer in question is added to a small amount (approx. 0.5 mL) of water in a small test tube or vial. If the drop dissolves in the water, the layer in question is the aqueous layer. If the drop does not dissolve, but forms a new layer of its own the layer is the organic layer.

**Extraction vs. Washing:** Usually in a reaction there is one “compound of interest” or “desired product” that you care about, and by-products, extra reagents, or remaining starting material that you want to separate from it. Extracting and washing involve exactly the same procedure, they differ in which compounds change layers. In **Extraction the desired product changes layers**, in **Washing, the impurities change layers.**

**Partition Coefficient:** Many compounds are at least slightly soluble in both the aqueous layer and the organic layer. The partition coefficient describes how a particular substance will be distributed between the two layers at equilibrium.

The theory of the process can best be illustrated by considering the common task of extracting an organic compound from an aqueous solution with an immiscible organic solvent. The distribution law or partition law states that if a substance is added to a system of two liquid layers, made up of two immiscible or slightly miscible components, then the substance will distribute itself between the two layers so that the ratio of the concentration in one solvent to the concentration in the second solvent remains constant. At equilibrium, the partition coefficient is described by the mathematical expression:

\[ K = \frac{\text{concentration in solvent A}}{\text{concentration in solvent B}} \]
The constant K is termed the **distribution** or **partition coefficient**. As a very rough approximation, the distribution coefficient may be assumed equal to the ratio of the solubilities of the compound in the two solvents.

Organic compounds are usually relatively more soluble in organic solvents than in water, hence they may be extracted from aqueous solutions. Several extractions may be needed to remove “all” of the organic compound from the aqueous layer, depending on the partition coefficient. If salts, such as sodium chloride, are added to the aqueous solution, the solubility of the organic substance is lowered. This is called **salting out** and can assist in the extraction of organic compounds that are partially soluble in water.

**Technique of Extraction:** The objective of a simple extraction is to partition one or more substances between two immiscible solvents. This is usually accomplished with the use of a **separatory funnel**. If the separatory funnel has a glass stopcock, prepare the funnel for use by making sure that the stopcock is lightly greased and will turn without difficulty. Teflon stopcocks need not be greased.

With the separatory funnel supported in a ring, check to make sure that the stopcock is closed and pour in the solution to be extracted. Then add the extracting solvent (the funnel should not be filled to more than about three-fourths of its height), replace the
stopper after wetting it with water (to keep the organic solvent from creeping out around the stopper), and swirl or shake the contents to mix them. **Vent the separatory funnel often to release any built up pressure.** Shake the separatory funnel by placing the palm of your hand over the stopper and holding it large end down so that the liquid has more space to mix. Vent through the stopcock. With vigorous shaking, a total mixing period of ten to thirty seconds is usually considered adequate to establish equilibrium. Replace the separatory funnel in the ring, remove the stopper and allow the mixture to settle.

After allowing the mixture to stand in the separatory funnel until the two immiscible layers have separated cleanly, draw off part of the lower layer through the stopcock at the bottom. Wait a little while for the remainder of the lower layer to settle down (gentle swirling of the separatory funnel can speed this up), and draw this off also. Then pour the upper layer out the top.

It is dangerous to try to extract a solution if its temperature is near or above the boiling point of the extracting solvent. Thus if you plan to extract with pentane, ether, or dichloromethane, you may need to cool the solution. When these solvents are used, it is also a good idea to hold the separatory funnel by the ends so that the contents will not be warmed by your hands.

If a strong acid is to be extracted with carbonate or bicarbonate solution, the carbon dioxide produced can cause a large build-up in pressure unless mixing is done very cautiously with frequent release of pressure. In cases where much carbon dioxide production is anticipated, it is best to do the mixing in a flask or beaker and then to transfer the mixture to the separatory funnel for separation.

**Procedure:**

Dissolve 0.5 g (0.0032 mole) of 4-t-butylocyclohexanone in 5 mL of 95% ethanol in a 25 mL Erlenmeyer flask. Slowly add 0.4 g (0.01 mole) of sodium borohydride. The mixture may become warm, so have a cold-water bath handy. Keep the reaction temperature between 25-35°C (if it feels warm to the touch, you need to cool it, you are 37°C). You may see a slow evolution of hydrogen gas during the reaction. Allow the reaction to stand for 20 minutes, then carefully add 3 mL of water. Dropwise, and with caution add 1 mL of 3M hydrochloric acid solution **Caution: This will generate hydrogen gas. Gas evolution may be vigorous and should be controlled. Hydrogen gas is flammable.** After about 10 minutes, when the evolution of hydrogen gas becomes very slow or ceases, heat the mixture to boiling and then allow the mixture to cool to room temperature. A white, inorganic solid sometimes forms at this point. If this happens in your reaction mixture, decant the liquid off into a separatory funnel. The white solid may be discarded.

Extract the reaction mixture twice using 5 mL of diethyl ether each time. **Caution:** Make sure the reaction solution is cool before adding ether. Wash the combined ether layers with two 5 mL portions of water in order to remove most of the ethanol that remains dissolved in the ether layer. Dry the combined ether layers over anhydrous magnesium sulfate.
and gravity filter the mixture to remove the drying agent. Transfer the filtrate to a tared beaker and isolate the product by evaporating it to dryness on a hotplate in the fume hood. Weigh your product after all of the ether has been evaporated. Calculate your percent yield.

Prepare and submit a $^1$H NMR sample to analyze your product.

**In your lab report:**

From your NMR spectrum, determine the relative amounts of *cis* and *trans* isomers in your product. Use the spectrum and directions provided below. Do not fully assign the spectrum. Locate the tertiary butyl group and the key hydrogens on the carbon bearing the alcohol.

Discuss the purpose of the t-butyl group.

Write a mechanism for the reaction.

Show which side the hydride prefers to attack from, given the results of your experiment.

As always, report your yield, evaluate the quality of your product and discuss possible sources of error.

**Analysis of cis/trans Product Isomer Ratio by $^1$H NMR**

Your product, which is a mixture of *cis* and *trans* 4-t-butyl cyclohexanol, has a complicated $^1$H NMR spectrum. However, you can easily use the spectrum to analyze the ratio of *cis* to *trans* isomers in your product because the methine hydrogen, the hydrogen on the carbon bearing the hydroxyl group, is shifted downfield of the other signals. In a mixture of *cis* and *trans* 4-t-butylicyclohexanol there is a signal at about $\delta = 3.5$ ppm for the methine hydrogen of the *trans* isomer and a signal at about $\delta = 4.0$ ppm for the methine hydrogen of the *cis* isomer. The integration values for these two signals correspond to the relative amounts of the two isomers.

The methine hydrogen of the *trans* isomer is axial whereas the methine hydrogen of the *cis* isomer is equatorial. Studies of many different substituted cyclohexanes have shown that it is generally true that axial hydrogens appear at about 0.5 ppm higher field than the corresponding equatorial hydrogens when cis and trans isomers are compared.

Use the integration values for the two methine signals in your $^1$H NMR spectrum to determine the ratio of *cis* to *trans* 4-t-butyl cyclohexanol in your product. Report this ratio in your lab report.