Solvent Effects and Stereochemical Analysis of the Reduction of 2,6-Dimethylcyclohexanone with Sodium Borohydride

Note: This is from Chem 36H. You do not need to do Prelab & PostLab exercises as such but you should discuss the ideas therein. Molecular modeling is optional.

Introduction

One of the most common routes to secondary alcohols is the reduction of ketone compounds. One such reaction is the reduction of 2,6-dimethylcyclohexanone (Isomers 1 and 2) to 2,6-dimethyl-cyclohexanol (isomers 3-5) using sodium borohydride (NaBH₄). In this reaction the NaBH₄ adds a nucleophilic hydride ion to the electrophilic carbon of the carbonyl yielding an sp³ hybridized alkoxide intermediate. This intermediate is then protonated by water or acid yielding the secondary alcohol.

Each BH₄⁻ has four hydrides capable of participating in four such reductions. Such reactions are typically done with NaBH₄ because of its relative safety and ease of handling. Alternatively, a stronger reductant such as lithium aluminum hydride (LiAlH₄) may be used. This reagent is more reactive than NaBH₄ however, it is also more dangerous. Lithium aluminum hydride reacts violently with water and is unstable at elevated temperatures. Consequently, it is best to avoid this reagent unless it is really necessary to use it.

Several stereochemical questions are raised by the above reactions. First, on the ketone, there are two possible arrangements of the methyl groups at positions 2 and 6: cis and trans. What is the ratio of these isomers in commercially available 2,6-dimethylcyclohexanone? Second, once the ratio of these isomers is known, several possible isomers of to 2,6-dimethylcyclohexanol are possible upon reduction. The cis isomer of the ketone, 1, gives two distinct products: trans,trans-2,6-dimethylcyclohexanol, 3, and cis,cis-2,6-dimethylcyclohexanol, 4. The chromatogram above is from a paper by Garner who claims the major isomer is the trans, trans alcohol 3. The trans isomer of the ketone, 2, on the other hand, gives only one product, cis,trans-2,6-dimethyl-cyclohexanol, 5.

What are the isomeric ratios of all of the above products? Because each isomer has a different arrangement of closely spaced functional groups, each will be characterized by unique thermodynamic stability (heat of formation). Presumably, the empirically observed ratios should parallel the thermodynamic trends, but how can these ratios be determined? One possibility is that the transition states involving the borohydride attack from either the axial or equatorial direction is critical. Alternatively, the energies of the possible intermediate borates determines the favorability of formation of one isomer over the other. For the cis starting ketone, 1, the two possible intermediates arising from axial or equatorial attack are shown below:
Hathaway has used NMR of the isomers to show that the major isomer is not 3 as Garner claims, but 4. You will use computational chemistry to try to understand why this is the case. You will also try to explain a solvent effect, that is, the variation in ratio of 3 to 4 when the reduction is carried out in methanol, ethanol and 2-propanol.

The variation in stereochemistry of the products results in slightly different polarities for each. This small difference allows separation of the products by capillary gas chromatography. Using the integrated peak areas generated by the gas chromatograph and the pattern of relative retention times previously published, it is possible to determine the initial isomer ratio of the commercially available ketone, as well as the isomer ratios of all of the products upon reduction.

**Prelaboratory Exercise**

1. Using the number of isomers possible from cis and trans 2,6-dimethylcyclohexanone, explain how the peak areas in the chromatograms of Garner shown above are consistent with the cis starting ketone being the major isomer in the commercially available starting material.

2. Build the structure of 2 in Spartan, do a geometry optimization, and print out a picture that shows that 2 is or is not a true chair conformation.

**Caution**

Sodium borohydride is a strong reducing agent. Gloves must be worn while handling this reagent.

**Analysis of the 2,6-dimethylcyclohexanone isomer ratio:**

Dilute 1.0 uL of 2,6-dimethylcyclohexanone (mixture of isomers) in 1.0 mL CH$_2$Cl$_2$ and pipet-mix thoroughly. Inject 1 uL of this mixture into the GC with a temperature program of 60-100°C at 4°C/min. The isomer ratios of the starting ketone can be determined from the integrated peak areas.

**Synthesis Reduction of 2,6-dimethylcyclohexanone**

Combine 2.0 uL of 2,6-dimethylcyclohexanone (a mixture of isomers) and approximately 10 drops of methanol in a small reaction tube. Add a tiny granule of NaBH$_4$ to the reaction tube and pipet-mix thoroughly.

**Product Isolation**

Add 0.5 mL of saturated NaHCO$_3$ and 2.0 mL of hexanes, and pipet-mix thoroughly. Allow the emulsion to settle and draw off the organic (upper) phase via pipet, and transfer it to a shorty vial. Add sufficient anhydrous Na$_2$SO$_4$ to cover the bottom of the vial.

To study the effect of solvent on isomer ratio, do the same reaction, but in place of the methanol solvent, use 95% ethanol. Repeat a 3rd time using 2-propanol as the solvent.
Analysis of 2,6-dimethylcyclohexanol isomer ratio

Inject 1 μL of this mixture into the GC with a temperature program of 60-100°C at 4°C/min. The isomer ratios of the alcohol product can be determined from the integrated peak areas.

Cleaning-Up

The starting ketone solution in CH₂Cl₂ should be disposed of in the "Halogenated Organic Waste" receptacle. The aqueous layer used in the alcohol extraction can be disposed of down the drain. The solution of the alcohol in hexanes should be placed in the "Non-Halogenated Organic Waste" receptacle. The used Na₂SO₄ should be dried in the hood, and can then be disposed of in the waste basket.

Final Report

Tabulate the GC data by retention times, peak areas and % ratios of the three peaks on the chromatogram for all three reactions in different solvents. The relative isomer ratios can be determined from the absolute integrated peak areas generated by the GC integrator. Compare the values obtained in your experiment to the reported literature values³. Discuss any significant differences. Based on your molecular modeling results, comment on possible explanations of the observed isomer ratios in the alcohol product and give answers to the questions on the next page. Discuss the effect of solvent on the ratio. You might look at Hathaway’s article² and references cited therein.

³ Hathaway reports a ratio of 4 to 3 in 95% ethanol of 1.28, and in 2-propanol of 0.97.