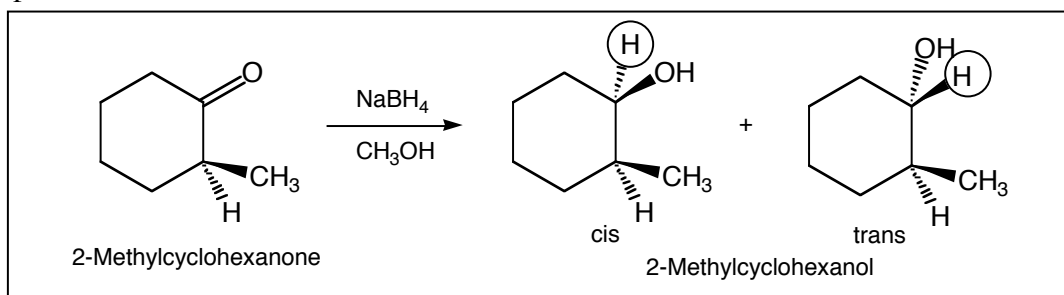


NaBH₄ Reduction of 2-Methylcyclohexanone. H-NMR for Analysis of Isomeric Product Ratios

BACKGROUND Hydrogen-NMR is useful for analyzing a pure sample, and one of the pieces of information is the **integration** of hydrogen signal sets. Integration of hydrogen signal sets measures the area, and this area is proportional to the number of hydrogens causing the particular signal. Thus in a pure compound, a CH₃ group would give an integral 1.5 times as large as a CH₂ group.

In today's experiment, we will apply integration in a related but different way: to measure the ratio of two different products formed in a single reaction mixture. The chemical experiment will be a standard NaBH₄ reduction of a ketone to produce alcohol. Due to the chirality of the starting ketone, two diastereotopic cis/trans alcohols are produced. Attack of the hydride from the back face, trans to the methyl group, produces the cis product alcohol. Attack of the hydride from the front face, cis to the methyl group, produces the trans alcohol. The labeled hydrogens on the oxygen-bearing carbons of the alcohol products give NMR signals with different chemical shifts. By integrating the sizes of their signals, we will be able to determine a product ratio.

**Chair Conformations and NMR Interpretation Summary: How do we know which product is cis and which is trans?**

We know that a cyclohexane ring has two chair conformations of unequal energy.

- You will want to draw both chairs for the cis isomer, and identify which is the more stable.
- You will then want to draw both chairs for the trans, and identify which of those is more stable.
- **By comparing the best cis chair with the best trans chair, you should be able to recognize which of the two products is more stable overall, cis or trans.**
- **By looking at your models/drawings, you should also be able to recognize whether the best cis chair has an axial or equatorial “feature H” (the hydrogen attached to the oxygen bearing carbon, which will give a signal in the 3’s.)**
- **Likewise you can determine whether the trans isomer should have its “feature H” equatorial or axial. (It will be axial in one of the isomers and equatorial in the other.)**

Fact: An axial hydrogen has a chemical shift further to the right (“upfield”, lower number) relative to otherwise analogous equatorial hydrogens in an H-NMR spectrum. (The reason for this is that an axial hydrogen is more crowded, and closer to electron clouds around other atoms. The greater crowding/proximity to electron clouds causes the upfield shift.)

Application: Your drawing/model-building should tell you whether the axial “feature H” correlates to the cis or trans product.

- By integrating the axial (upfield) to equatorial (downfield) signals, you will thus be measuring the ratio of the two isomers.

“Thermodynamic Product-Stability Control” versus “Kinetic Control”

When the same starting material can give two different products, we say that the reaction is either under “product stability” control or under “kinetic control”. “Product stability” control usually applies, because factors that stabilize the product often stabilize the transition state as well. But this is not always true: sometimes steric crowding can destabilize a transition state without destabilizing a product. If a reaction does not preferentially produce the most stable product, the reaction is said to be under “kinetic control” rather than product stability control. In today's experiment, might the methyl group obstruct the front face and thus destabilize the transition state leading to the trans product?

Experimental Procedure

1. To a large test tube, add 4 mL (or two full pipet squirts) of dichloromethane
2. Add 0.9 mL of 2-methylcyclohexanone.
 - Use density and molecular weight information to calculate how many moles are involved
 - density = 0.924 g/mL
 - mw = 112 g/mol)
3. Prepare an ice-water bath in your 150-mL beaker
4. Place the test tube into the ice-water bath
5. Weigh out 0.15 g of NaBH_4 (mw = 38 g/mol)
6. Carefully add the NaBH_4 to the test-tube. (The NaBH_4 is in excess, so if some sticks on the walls of the tube, it isn't a problem).
7. After the vigorous bubbling subsides, remove the test tube from the icewater and let it stand at room temperature for 20 minutes.
8. Clamp your smallest iron ring to a vertical rod, and insert your separatory funnel
9. Pour your test tube solution into the separatory funnel
10. Rinse test tube with an additional pipe of dichloromethane and add this to the separatory funnel
11. Add two pipets of tap water, and then two full pipets of 3 M sodium hydroxide solution (purpose: to decompose the borate salts and move them into the aqueous phase)
12. Shake the mixture, then let it settle
 - Question: which layer is organic and which is aqueous? If in doubt, add some addition water and watch to see which layer it falls into, and which layer grows!
13. Drain the dichloromethane layer into a 50-mL Erlenmeyer flask
14. Wash the aqueous layer in the sep funnel with an additional pipet of dichloromethane, let settle, and drain the organic layer into the Erlenmeyer flask.
15. Repeat the last step again.
16. Add a large scoop of anhydrous sodium sulfate to the Erlenmeyer flask to "dry" your organic solvent. If the sodium sulfate all clumps, add more until at least some does not clump up.
17. Pre-weigh a 50-mL round-bottomed flask, and then clamp it onto a vertical rod.
18. Take your long stem funnel and push a little glass wool into the neck.
19. Pour the organic solution from the Erlenmeyer through the funnel into the round-bottomed flask. The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask.
20. Rinse the Erlenmeyer with additional dichloromethane, and pour the rinse through the funnel into the round-bottomed flask.
21. At this point, there should be only dichloromethane and alcohol products in your flask.
22. Concentrate the organic solution by rotary evaporation. Be sure the aspirator power is on; that the top air valve is closed; and that you have an adapter for a good glass seal. Make sure that the spinner is also turned on.
23. Once the sample has concentrated to a residual oil, weight the flask and calculate your mass yield.
24. Prepare and run an NMR.

Model Building (Can share this groups of students.)

1. Build a model of both cis and trans 2-methylcyclohexanol.
2. Chair-flip both
3. For the cis isomer, which chair if more stable?
4. In the more stable cis chair, is the "feature hydrogen" axial or equatorial?
5. For the trans isomer, which chair is more stable?
6. In the more stable trans chair, is the "feature hydrogen" axial or equatorial?
7. Which is more stable, the best cis chair or the best trans chair?
8. Draw your best cis and best trans chairs.

Name:

Sodium Borohydride Lab Report

1. Use Standard Synthesis Format:
 - a. Illustrate the Chemical Reaction
 - b. Summarize the Chemicals Used
 - Include mole Calculation for 2-methylcyclohexanone
 - c. Calculate the theoretical yield
 - d. Write up the procedure, **including observations**
 - e. Analysis:
 - Include actual yield, and percent yield
2. Take H-NMR
 - Print full spectrum
 - Print horizontal expansion from about 4.0-2.8
 - Notes: CH₂Cl₂ solvent, if not evaporated completely, will give a singlet at 5.3; and methanol, if not completely extracted/evaporated will give a singlet around 3.5.
3. Discussion/interpretation
 - Draw both cis chairs
 - Identify the better of the two
 - is the “feature” H axial or equatorial?
 - Draw both trans chairs
 - Identify the better of the two
 - is the “feature” H axial or equatorial?
 - Would the cis chair or the trans chair be most stable overall?
 - From the NMR integration and chemical shifts, determine the trans/cis ratio.
 - Was the major product formed via “product-stability control” (the most stable product is formed preferentially) or “kinetic control” (for some steric reason, the fastest reaction/lowest transition state did not lead to the most stable product)?