**NaBH$_4$ 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 CH$_3$ group would give an integral 3/2 as large as a CH$_2$ 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. Due to the chirality of the starting ketone, two diastereotopic cis/trans alcohols are produced. The circled hydrogens in the products will give NMR signals with different chemical shifts. (Because they are on oxygenated carbons, the circles hydrogens will both have chemical shifts in the 3's.) By integrating the sizes of their signals, we will be able to determine a product ratio.
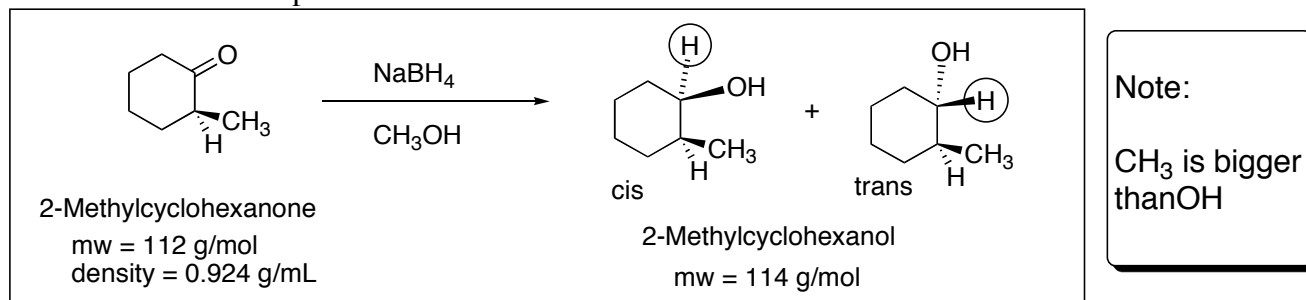
Chair Conformations and NMR Interpretation Summary: How do we know which signal in the 3's comes from the cis product and which from the trans?
a. Key: One product will have its circled hydrogen **axial**, while the other will have it's circled hydrogen **equatorial.**
b. Fact: **An axial hydrogen has a chemical shift further to the right ("upfield", lower number) relative to an 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.)
c. **If you can figure out which product has the axial and which product has the equatorial hydrogen, then by NMR integration of the axial vs equatorial hydrogens, you can measure the trans/cis product ratio.**

How do I know whether the axial hydrogen comes from the cis product and the equatorial hydrogen from the trans product, or vice versa?
- Draw both chair forms for the cis isomer, and identify which is the more stable.
- **Does the best cis chair have the circled hydrogen equatorial or axial?**
- Draw both chair forms for the trans isomer, and identify which is more stable.
- **Does the best cis chair have the circled hydrogen equatorial or axial?**
- By comparing the best cis chair with the best trans chair, you should also be able to recognize which of the two products is more stable overall, cis or trans.

 "Thermodynamic Product-Stablity 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 "kinetic control".
a. "Product Stability Control":
- the most stable product forms preferentially.
- "Product stability" control usually applies, because factors that stabilize the product often stabilize the transition state as well (the "product stability-reactivity principle").
b. "kinetic control".
- The less stable product forms preferentially.
- When this happens, it always results from the transition state leading to the more stable product being less stable for some reason than the transition state leading the less stable product.
- This is not the normal situation, but when it occurs it usually involves some steric factors.
  o Sometimes steric crowding can destabilize a transition state but not the final product.
  o Might the methyl group obstruct the front face and thus destabilize the transition state leading to the trans product?
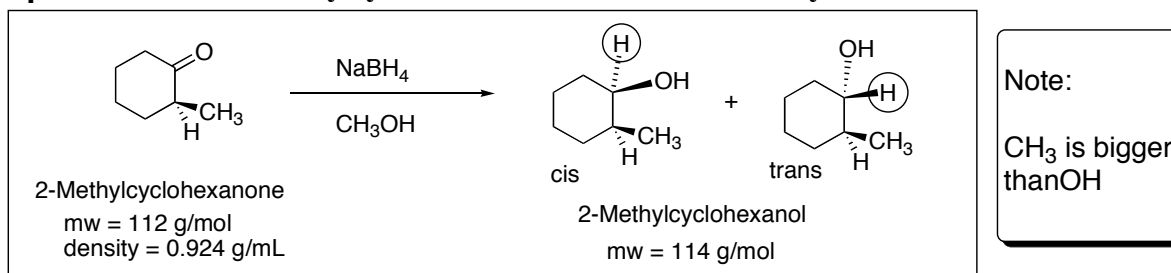
Experimental Procedure

1. To a large test tube, add 4 mL (or two full pipet squirts) of methanol
2. Add a small stirring bar
3. Add 0.90 mL of 2-methylcyclohexanone. **Note: This is the limiting reagent**.
   - Use density and molecular weight information to calculate how many moles are involved
   - density = 0.924 g/mL
   - mw = 112 g/mol)
4. Prepare an ice-water bath in your 150-mL beaker and set it on your stirring plate.
5. Place the test tube into the ice-water bath and turn the stirrer on
6. Weigh out 0.15 g of $NaBH_4$ (mw = 38 g/mol)
7. 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).
   - Note: While this gives fewer moles of $NaBH_4$ than there are of the ketone, the $NaBH_4$ is still excess. This is due to the fact that one $NaBH_4$ can provide four hydrides.
8. After two minutes, remove the test tube from the ice-water and let it stir at room temperature for 20 minutes.
9. Clamp your smallest iron ring to a vertical rod, and insert your separatory funnel
10. Pour your test tube solution into the separatory funnel
11. Rinse test tube with an additional two pipets of dichloromethane and add this to the separatory funnel
12. 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
13. Shake the mixture <u>vigorously</u>, for at least 3 minutes, then let it settle
    - Question: which layer is organic and which is aqueous?
    - If in doubt, add some additional water and watch to see which layer it falls into, and which layer grows!
14. Drain the dichloromethane layer into a 50-mL Erlenmeyer flask
15. 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.
16. Repeat the last step again.
17. 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.
18. Pre-weigh a 50-mL round-bottomed flask, and then clamp it onto a vertical rod.
19. Take your long stem funnel and push a little glass wool into the neck.
20. 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.
21. Rinse the Erlenmeyer with additional dichloromethane, and pour the rinse through the funnel into the round-bottomed flask.
22. At this point, there should be only dichloromethane and alcohol products in your flask.
23. 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.
24. Once most of the solvent has evaporated, add an additional two pipets of dichloromethane, and reconcentrate again by rotary evaporation.
    - Purpose: after one concentration cycle, a significant amount of methanol still "sticks" to the product, and interferes with the NMR. Reconcentration helps to ensure there isn't enough methanol left to mess up the experiment.
25. Once the sample has concentrated to a residual oil, weight the flask and calculate your mass yield.
26. Prepare and run an NMR. Use one or two drops of sample, and dilute the NMR tube to 1/3 full with $CDCl_3$.
    - Use the experiment ah1-tune
    - Print an expansion of the region between 4.0 and 3.0 (or perhaps a little wider) to focus in on the equatorial and axial hydrogens of interest.

Sodium Borohydride Lab Report Requirements

1. Get yield information

2. Take H-NMR
   - Print the full spectrum
   - Print horizontal expansion from about 4.0-3.0
   - The axial hydrogen will appear at about 3.1 ppm
   - The equatorial hydrogen will appear at about 3.8 ppm
   - The integration is **not** the height of the signal sets themselves. It is the areas of the signal sets, as reflected by the integral markers
   - There will be some numbers printed out underneath the signals. These reflect the integration areas.
   - To get your product ratio, just take the integration of these two numbers. (For example, if one is 3.84 and the other is 2.35, the ratio would be 3.84/2.35 = 1.6:1)
   - Note: CH_2Cl_2 solvent, if not evaporated completely, will give a singlet at 5.3
   - Note: Methanol, if not completely evaporated will give a signal around 3.5 or so, in between the two important signals.

NaBH$_4$ Reduction of 2-Methylcyclohexanone. H-NMR for Analysis of Isomeric Product Ratios

2-Methylcyclohexanone
mw = 112 g/mol
density = 0.924 g/mL

cis   trans

2-Methylcyclohexanol
mw = 114 g/mol

Note:

CH$_3$ is bigger thanOH

1. Mass yield:

2. Percent yield:

Cis Chairs
3. Draw both chair-flip forms of the **cis** isomer shown above.
4. Circle the more stable cis chair
5. Write "equatorial" or "axial" to describe whether the circled hydrogen is axial or equatorial in the more stable cis chair.

Trans Chairs
6. Draw both chair-flip forms of the **trans** isomer shown above.
7. Circle the more stable trans chair
8. Write "equatorial" or "axial" to describe whether the circled hydrogen is axial or equatorial in the more stable cis chair.

9. Would the cis chair or the trans chair be more stable overall?

10. What is your ratio of axial/equatorial hydrogens?

11. What is your trans/cis product ratio?

12. Did this reaction proceed under "product stability control" or under "kinetic control"?