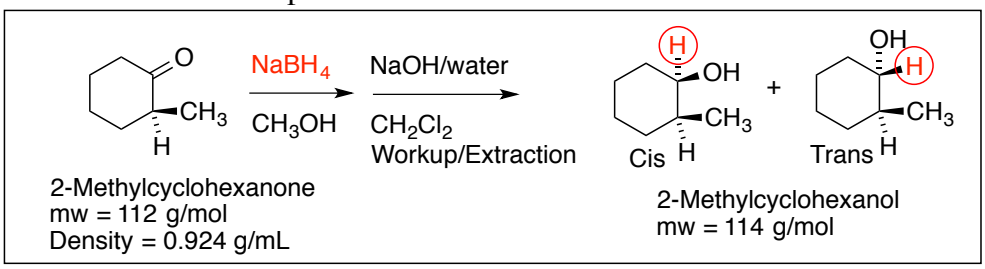
$NaBH_4$ Reduction of 2-Methylcyclohexanone. Use of H-NMR Integration for Analysis of Isomeric Product Ratios

BACKGROUND Hydrogen-NMR is useful for analyzing pure samples, and one of the pieces of information is the **integration** of hydrogen signal sets. Integration of hydrogen signal sets measures the signal areas, and these areas are proportional to the number of hydrogens causing the particular signals. Thus in a pure compound, a 3:2 integral ratio would be observed for a CH_3 signal set versus a CH_2 signal set.

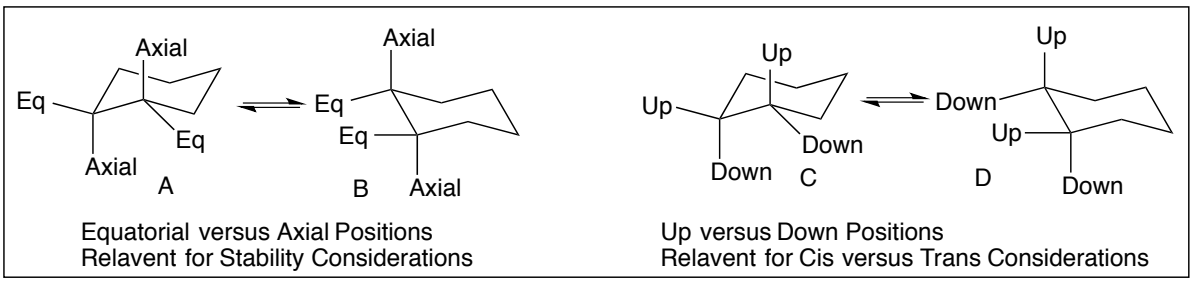
In today's experiment, we will apply integration in a related but different way: to measure the ratio of two **different products formed in a single reaction mixture**. The chemical experiment will be a standard $NaBH_4$ reduction of a ketone to produce alcohol. Due to the chirality of the starting ketone, 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, in which the hydride approaches 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 the product ratio.



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

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

- To review some of the considerations regarding cyclohexane chairs, you might review the pre-lab video.
- You might also wish to review some Organic I notes about cyclohexane chairs, and/or the video discussing them:
  - Notes: http://web.mnstate.edu/jasperse/Chem365/Cyclohexane%20Chairs%20Review.pdf
  - Video: https://mediaspace.minnstate.edu/media/Cyclohexane+Chairs+and+Cis-Trans+Diastereomers/0_qmuhyoez



- 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.
- You will want to determine which is better overall, the best chair conformation for the cis isomer or the best chair conformation for the trans isomer.

- In the "best cis", you'll want to identify whether the "feature hydrogen" on the hydroxyl carbon is axial or equatorial.

- Several reminders for cyclohexane chair conformations:
  1. When a chair flips, a substituent that was equatorial in the first figure will be axial in the second, while a substituent that is axial in the first will be equatorial in the second. See figures **A** and **B** in the figure.
  2. The most stable chairs have larger-than-hydrogen substituents equatorial. Thus, between the cis and the trans diastereomers, the one in which both the methyl and the hydroxyl are equatorial will be the more stable of the two.
  3. A methyl group is larger than a hydroxyl group. So in the cis/trans conformation in which both can't be equatorial at the same time, the preferred conformation will keep the methyl group equatorial while placing the hydroxyl group axial.
  4. In terms of cis-trans assignment, remember that "**cis**" would involve having both the methyl and the hydroxyl substituents relatively "**up**", whereas "trans" would have one of the methyl/hydroxyl groups "up" and the other "down" (see figures **C** and **D**.)
- **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.)**

NMR Facts: **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.
- Remember that the C-H hydrogen on an oxygen-bearing carbon appear in the 3's. So the "feature H" in both the cis and the trans diastereomers should appear in the 3's.
- The methanol CH3 group also shows up in the 3's. Hopefully the concentration process will remove most or all of the methyl signal, but perhaps check with instructor.

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 in the 3's, you will thus be measuring the ratio of the two isomers.

"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 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, then 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 a teensy stir bar, and add 4 mL (or two full pipet squirts) of methanol
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, place it on your stir plate, and stir
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. Stir the mixture for five minutes, then after the vigorous bubbling subsides, remove ice-water bath and stir the test-tube mixture 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 8mL of dichloromethane and add this to the separatory funnel
11. Rinse test tube with ~15 mL of tap water, and add to the sep funnel.
12. Then add 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, then let it settle
    - Question: which layer is organic and which is aqueous? If in doubt, add 10 more mL of 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 5 mL of dichloromethane, let it settle, and drain the organic layer into the Erlenmeyer flask.
16. Repeat step 14 again; use another 5 mL of dichloromethane to extract any remaining product out of the water layer.
    - Notes: In today's lab, we are doing three dichloromethane extractions to try to get all of the organic product out of the water layer. Being an alcohol, the product has hydrogen-bonding capacity and non-trivial solubility in water. So, if we had just done a single separation, an unnecessarily large amount of product would remain dissolved in the water layer.
    - When doing repeat extractions, it is practical to have the "extracting" solvent be the heavier, denser liquid that sinks to the bottom of the separatory funnel. Thus we are using dichloromethane rather than ether, because relative to water dichloromethane sinks but ether floats.
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. Add a small stir-bar to a 50-mL round-bottomed flask
19. Pre-weigh the combined flask-plus-stirbar, then clamp it.
20. Take your long stem funnel and push a little glass wool into the neck.
21. 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.
22. Rinse the Erlenmeyer with additional dichloromethane, and pour the rinse through the funnel into the round-bottomed flask.
23. At this point, there should be only CH_2Cl_2, methanol, and alcohol products in your flask.

24. 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.
25. If the rotovap is too busy, you could do the concentration in your hood, using your vacuum adapter. If so, make sure you have your stir-bar stirring vigorously, and that you very gradually/carefully open your vacuum. You may wish to have the instructor come over to help. It may also provide some extra precaution to include a dry reflux condenser to prevent boil-over.
26. Once the sample has concentrated to a residual oil, (shouldn't take 10 minutes), re-dilute with an additional 10-mL of dichloromethane, then re-concentrate again. The purpose here is to help ensure that all of the methanol distills away.
27. Weigh the flask and calculate your mass yield.
28. Prepare and run an NMR.

<u>Model Building</u> (Optional.)

1. Build a model of both cis and trans 2-methylcyclohexanol.
2. Either chair-flip both, or else build both flip-forms of each
3. For the cis isomer,
    a. which chair-flip conformation is more stable?
    b. In the more stable cis chair, is the "feature hydrogen" axial or equatorial?
4. For the trans isomer,
    a. which chair is more stable?
    b. In the more stable trans chair, is the "feature hydrogen" axial or equatorial?
5. Which is more stable overall, the best cis chair or the best trans chair?

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. (Assume $NaBH_4$ is excess.)
    c. Calculate the theoretical yield
    d. Write up the procedure, **including observations**
    e. Analysis:
        - Include actual yield, and
        - percent yield
        - Attach NMR

2. Take H-NMR
    - Print full spectrum, with integrals for the two diagnostic signal sets in the 3's.
    - Solvent 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)?