

# 1st Test - CHEM 442/542

200 points total

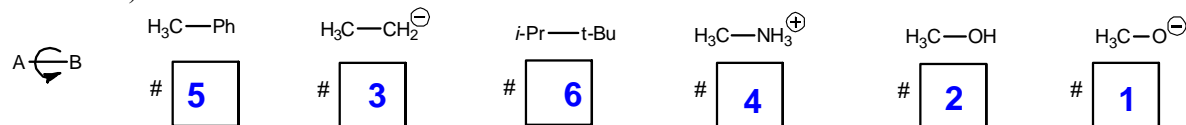
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## Instructions

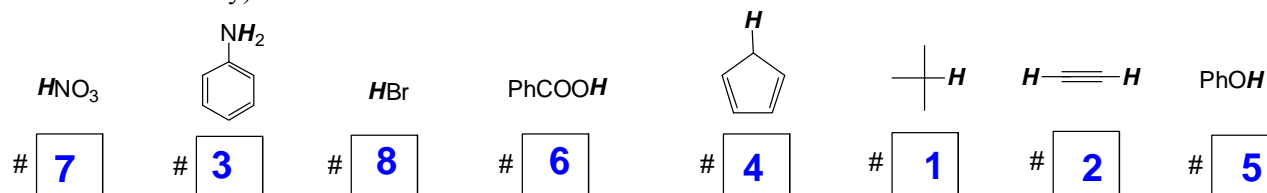
1. Write your answers/solutions directly under the assignment. If you don't have enough space, use the back page of this particular assignment (please, label the continuing answer as such).
2. In your answers be as complete as possible. If you want, however, you may substitute complex substituent as "R", but first you must indicate what the "R" is in a clear unambiguous way.
3. The only tools allowed on this test are your smarts and a pen. All paperwork, books, notes, scratch paper (except the one provided by the proctor) is not allowed.
4. Write/draw in a clear legible manner in permanent ink pen. No pencils or erasable pens, please.
5. Note, that what we cannot find, read or understand will be wrong. Please, help us by writing clearly.
6. If you make a mistake or change your mind, please, cross out clearly the old writing "X" you don't want us to consider. Do not let us choose because we may misunderstand.
7. You have 3:00 p.m. – 6:00 p.m. (3 hours). You should, however, be done in less than 2.5 hrs. If you are done, please, turn in the test to the proctor and quietly leave the classroom.
8. Please, do NOT TALK during the test. Who would talk will have to immediately return the test to the proctor. The official language of the class is English (or broken English). If you need to ask something – you can ask only the proctor, but it must be in English.
9. Explanations require in almost all cases drawing (structures, arrows, cations, anions, etc.). All mechanisms and mechanistic explanations require arrows.
10. Good luck!

1. Consider rotation barrier in the molecule A-B (the axis of rotation is the bond between A and B). Label the following molecules in the order of their decreasing magnitude of the **rotation barrier** (#6 is the highest, #1 is the lowest):



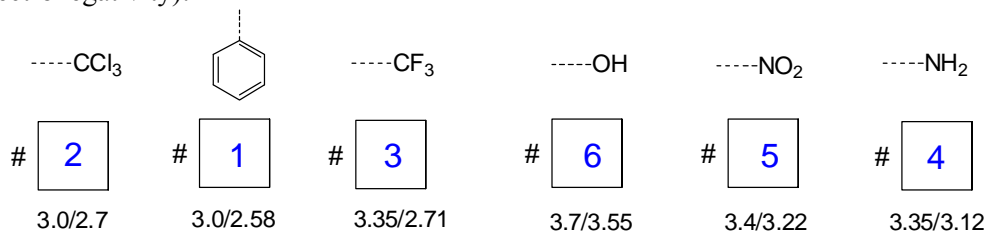
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2. Label the following compounds in the order of the decreasing **acidities** of the highlighted protons (#8 is the highest, #1 is the lowest acidity):



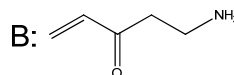
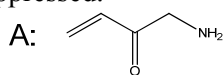
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3. Label the following functional groups in the order of the decreasing **group electronegativities** (#6 is the highest, #1 is the lowest group electronegativity):

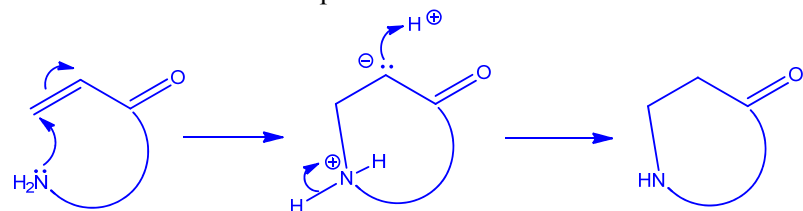


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4. Consider the reactivity of the two following reagents upon heating in a polar non-nucleophilic solvent (e.g. ethanol). Reagent A yields a number of products as well as oligo- and polymers. Reagent B, however, yields mostly one product, while the other products are suppressed.



Draw a mechanism and explain:



**A:** 5-Endo-Trig = Forbidden

**B:** 6-Endo-Trig = Allowed

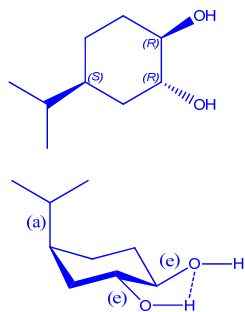
**5-Endo-Trig = Forbidden** does not undergo an intramolecular reaction to a 5-membered cyclic product in a high yield. This leads to inter-molecular reactions, oligomers and polymers.

**6-Endo-Trig = Allowed** and does yield a good yield of the product of intra-molecular cyclization.

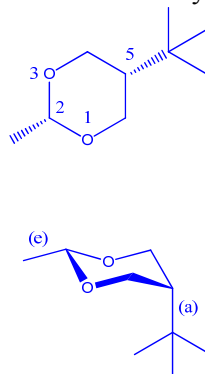
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5. Consider (1R,2R,4S)-1,2-dihydroxy-4-isopropyl cyclohexane. A) Use the normal dash/wedge zig-zag representation to draw the molecule and indicate the isomerism. B) Re-draw the same molecule as a conformational drawing (to include chair, boat, etc.) in the most stable conformation of this chemical when dissolved in a non-polar solvent such as benzene. Indicate (a) and (e) positions. Do the same for cis-5-<sup>t</sup>butyl-2-methyl-1,3-dioxane. For both molecules, add a brief verbal explanation for the conformational drawing.

(1R,2R,4S)-1,2-dihydroxy-4-isopropyl cyclohexane



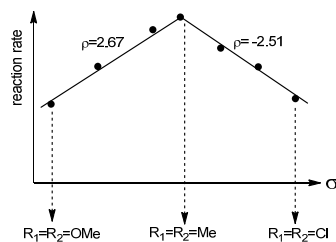
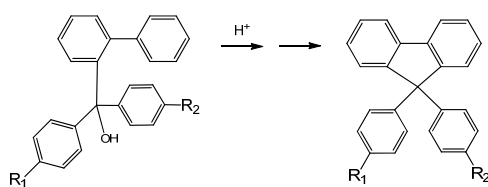
5-<sup>t</sup>Butyl-2-methyl-1,3-dioxane



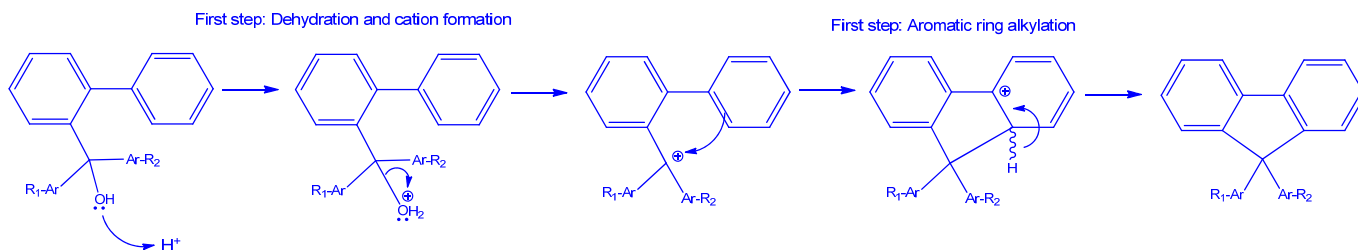
Explanation: In both cases, the 6-membered ring adopts seemingly unfavorable conformations with large substituents (isopropyl and <sup>t</sup>butyl) in axial positions. These are, however, favored because the dihydroxycyclohexane forms in a non-polar environment an additional 5-membered ring due to hydrogen bonding. In 1,3-dioxane, the oxygen atoms do not constitute the unfavorable 1,3-diaxial interaction with the <sup>t</sup>butyl group.

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6. **Hammett correlation.** Consider the following two-step reaction and the Hammett correlation plot and provide answers to the following assignments.



A) Draw the mechanism (indicate the two most important steps):



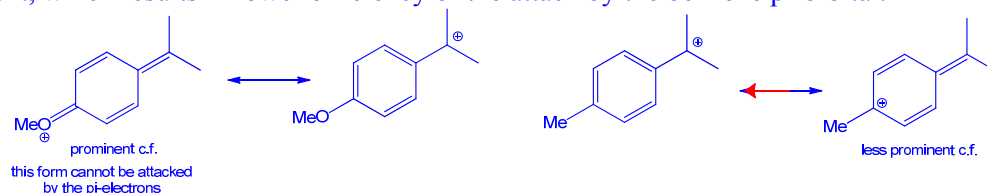
B) Because there are two steps, you must decide which step is the rate-limiting one. Is the mechanism the same for all the compounds with varying  $R_1/R_2$ ? Is the rate-limiting step always the first/second regardless of the substituents  $R_1/R_2$ ? Provide a detailed explanation:

The Hammett correlation plot shows a break in the trend suggesting a change in the mechanism of two different rate-limiting steps. Because the mechanism appears to be the same (Friedel-Crafts type alkylation), what must change is the nature of the rate-limiting step. We have 2 important steps:  $S_N1$ -type spontaneous ionization of the substrate, and  $S_E+Ar$  alkylation. The attack of the benzene pi-orbital of the triphenylmethyl cation does not depend on the substituents  $R_1/R_2$ , but the stability of the triphenylmethyl cation does.

Thus, in the left part of the correlation plot there are ERG substituents (e.g. OMe) that stabilize the triphenylmethyl cation. In the right part of the plot there are EWG substituents (e.g. Cl) that make the cation less stable. A less stable cation means higher energy and also higher activation energy (slower rate) of the process. This suggests that the right part of the plot corresponds to the  $S_N1$ -type ionization of the substrate as a rate-limiting step. Conversely, the substituents that stabilize the triphenylmethyl cation actually make the formation of this cation very fast (c.f. Hammond postulate - the intermediate energy is close to the transition state when we are going from C-C to  $C(\delta^+)---X(\delta^-)$  and  $C(+)$  and  $X(-)$ ). Rapid formation of the triphenylmethyl cation implies that the rate-limiting step in the left part of the correlation is actually the attack of the cation by the pi-system of the aromatic ring.

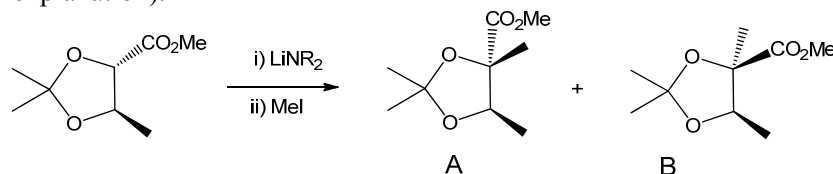
C) What remains to be explained is the following: If you look at the Hammett plot, you can see that the OMe substituent yields a lower reaction rate than the Me substituents. Suggest an explanation:

This is most likely due to the fact that the OMe substituents stabilize the cation too much! In fact the resonance hybrid comprises more prominent canonical forms  $MeO(+)=C$  than the  $Me-C(+)$ . This is known, c.f. the stability of triphenylmethyl (trityl, Tr) cation vs. the dimethoxytrityl (DMTr) cation. In the case of the DMTr-type cation, the  $C^+$  is much less prominent, which results in lower efficiency of the attack by the benzene pi-orbital.

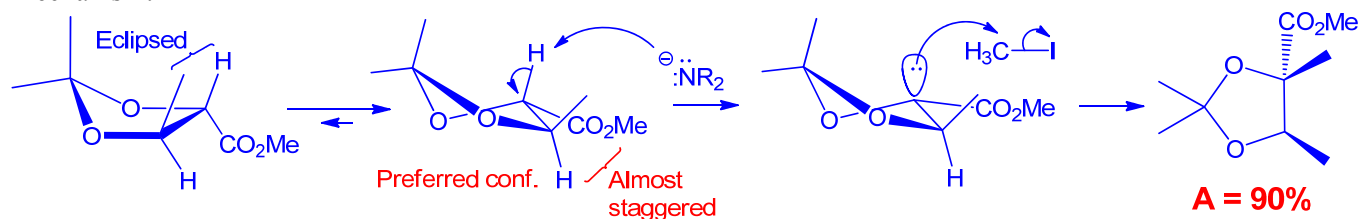


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**7. Conformation and stereochemistry.** Predict which product isomer A/B is formed preferentially. Explain (drawing a mechanism + brief verbal explanation).



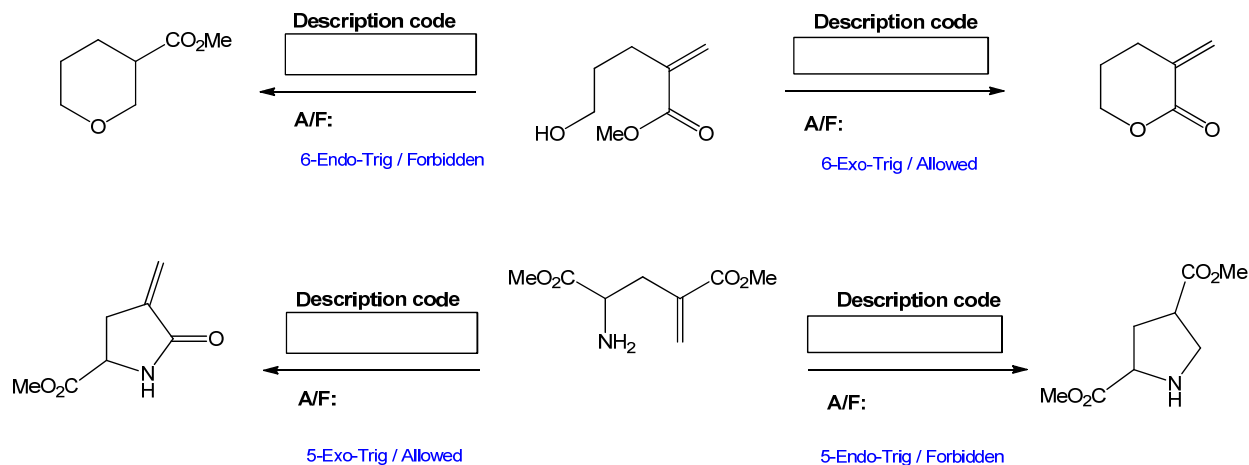
Mechanism:



Cp ~ 2 puckered conformations: Envelope and half-chair. However, in this case, the half-boat with the quasi-staggered substituents (and a larger substituent in eq.-like position) is more stable (= preferred) and is major contributor to the product formation.

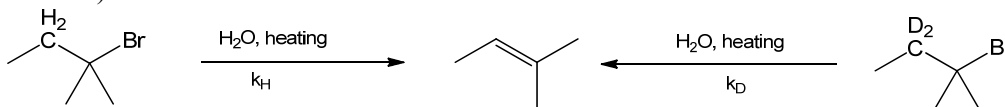
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8. **Baldwin rules** of cyclization #2. Fill in the reaction codes and indicate allowed/forbidden (A/F) transformation. An example of a description code: 4-Endo-Dig



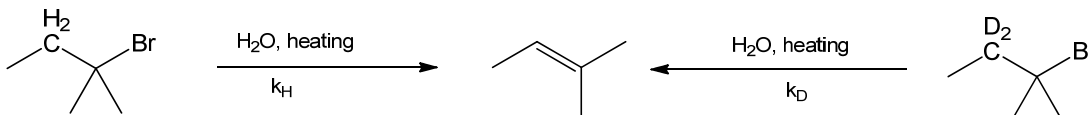
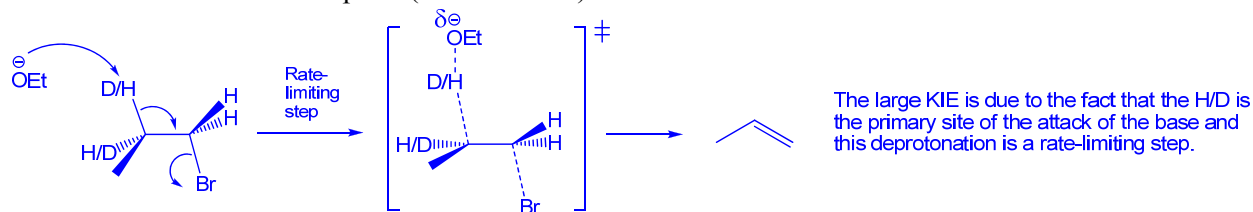
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9. Consider the following two eliminations (dehydrohalogenations) and make a qualitative prediction regarding the magnitude of the **primary kinetic isotope effect** ( $1^\circ$  KIE  $k_H/k_D$  value) and provide a mechanistic explanation (yes, you must draw the mechanism).



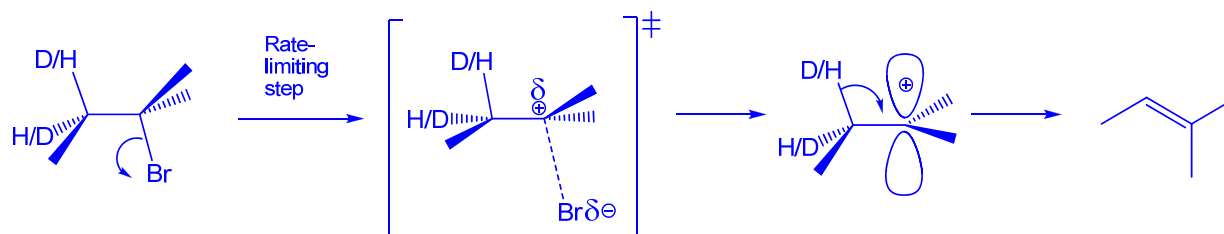
The expected value of the primary KIE is: \_\_\_\_\_ (possible answers <1, 1-2, 2-5, >5).

Draw the mechanism and explain (1-2 sentences):



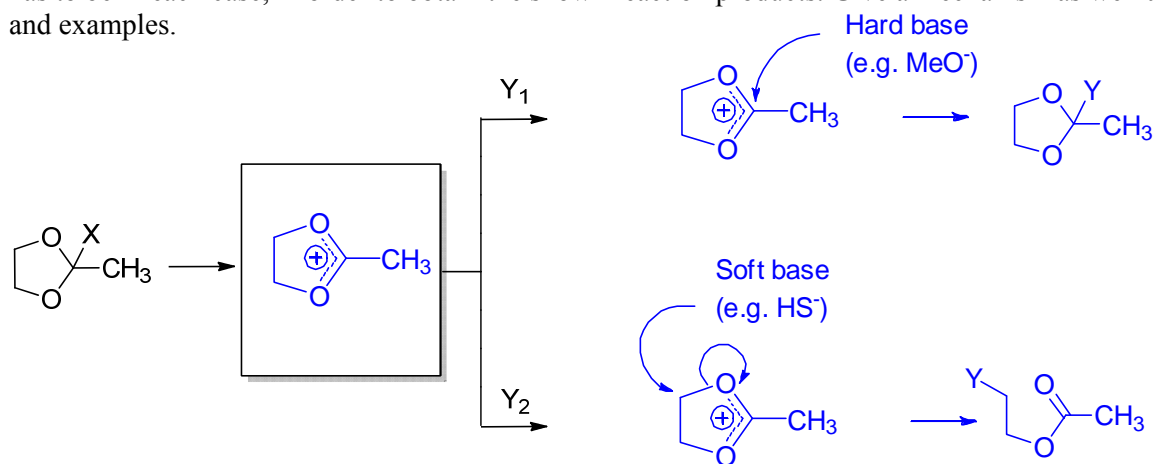
The expected value of the primary KIE is: \_\_\_\_\_ (possible answers <1, 1-2, 2-5, >5).

Draw the mechanism and explain (1-2 sentences):



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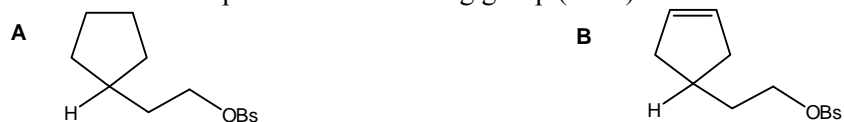
**10. HSAB theory.** In the scheme below, draw the correct intermediate structure and explain what kind of Lewis base Y has to be in each case, in order to obtain the shown reaction products. Give a mechanism as well as a verbal explanation and examples.



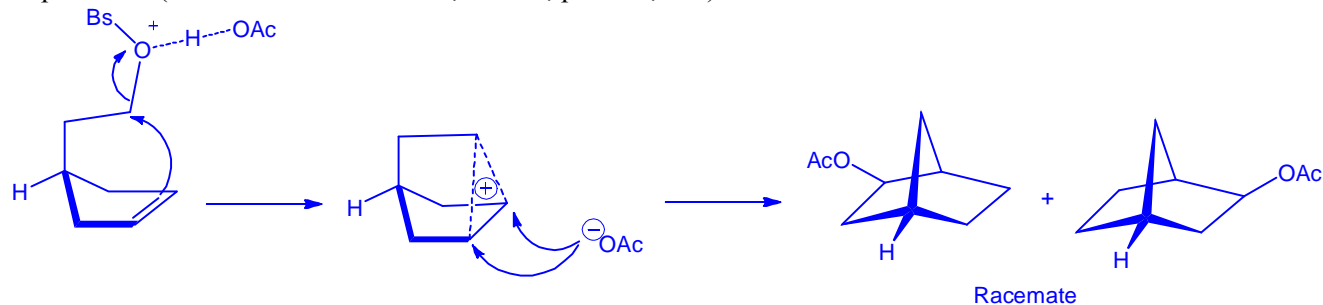
**Explanation:** The explanation: formation of the carbocation intermediate results in rehybridization of the central carbon atom from sp<sup>3</sup> to sp<sup>2</sup>. Therefore the carbocation has more s-character, and becomes a hard species. If Y is a hard Lewis base (i.e. EtO<sup>-</sup>) the attack will be performed at the hard center, the carbocation. On the other hand, if Y is a soft Lewis base (i.e. I<sup>-</sup>) the attack will be done at the softest center which is any of the σ<sub>C-O</sub>\* orbitals.

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**11. Predict which isomer A/B is reacting faster in acetolysis at 25 °C. Explain (drawing + brief verbal explanation). It is a solvolysis - assume that in both cases the departure of the leaving group (BsO<sup>-</sup>) is the rate-limiting step.**



**Explanation (must draw a mechanism, arrows, product, etc.):**



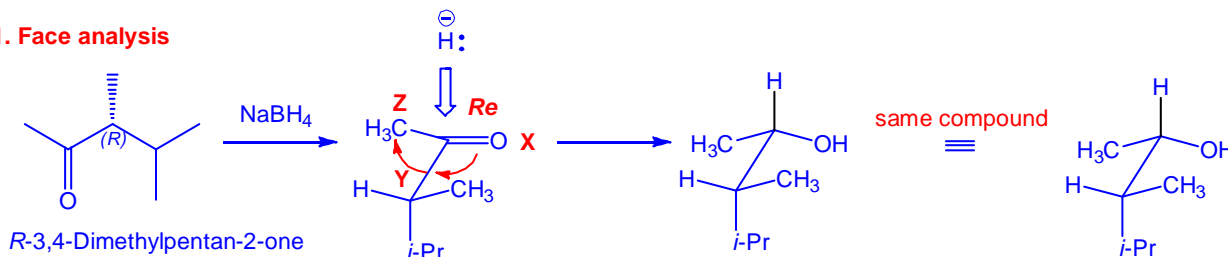
D reacts faster because of the anchimeric assistance from the double bond to help the nucleofuge to leave the primary carbon.

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**12. Conformations and stereochemistry of a nucleophilic attack:** *R*-3,4-dimethylpentan-2-one is reduced by sodium borohydride to the corresponding alcohol. The analysis of the product revealed that the attack by the hydride donor proceeded from *Re*-face.

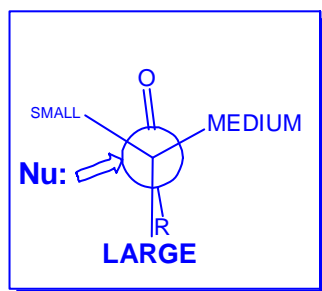
Draw the presumed preferred conformation of the starting ketone in Newman projection, as well as the proposed transition state, and the “textbook” interpretation of the Cram’s rule reasoning (S/M/L substituents + attacking nucleophile). Compare with the Felkin-Ahn model of nucleophile attack.

**1. Face analysis**

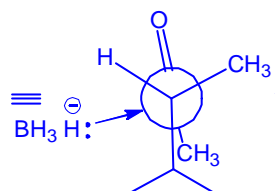


**1. Transition state analysis** (In both models the TSs are defined by the sizes of substituents)

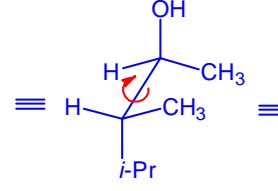
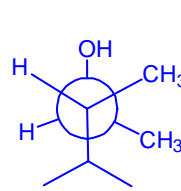
**1a Cram's model**



Nucleophile attacks from *Re* face

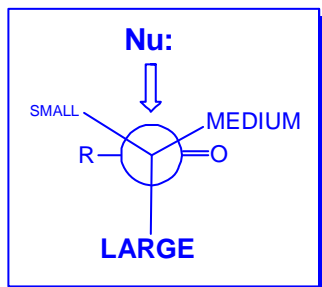


Felkin-Ahn product

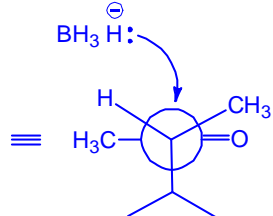


same (just different) compound conformation

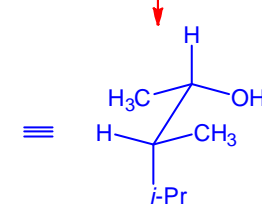
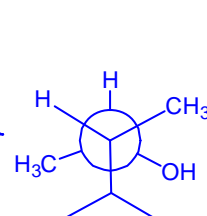
**1b Felkin-Ahn model**



Nucleophile attacks from *Re* face



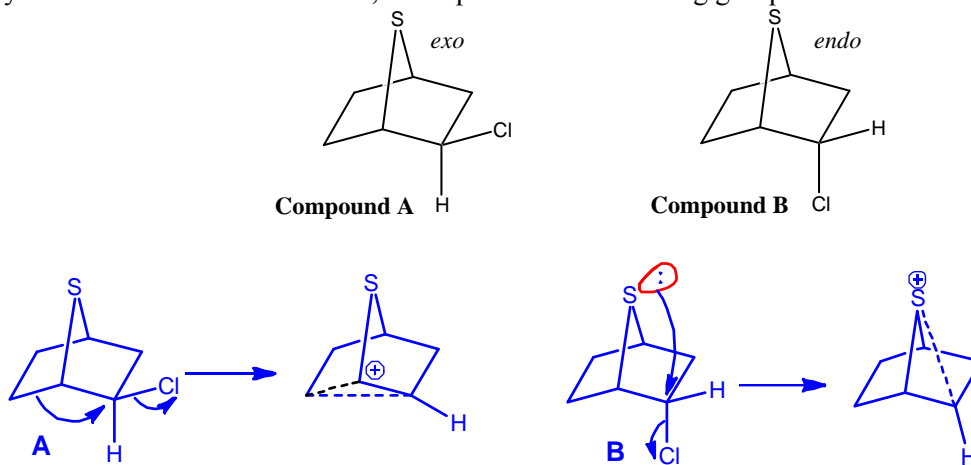
Cram product



**YES!** The Cram's rule corresponds to the nucleophilic attack from the *Re*-face.

Did the reaction follow the Cram’s rule? Y/N: \_\_\_\_\_

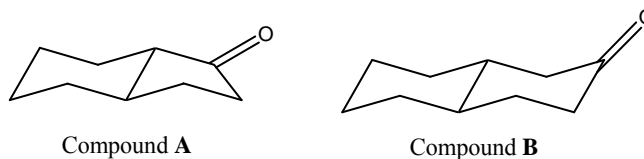
13. Predict which isomer *endo*/*exo*- is reacting faster in acetolysis at 25 °C. Explain (drawing + brief verbal explanation). It is a solvolysis - assume that in both cases, the departure of the leaving group is the rate-limiting step.



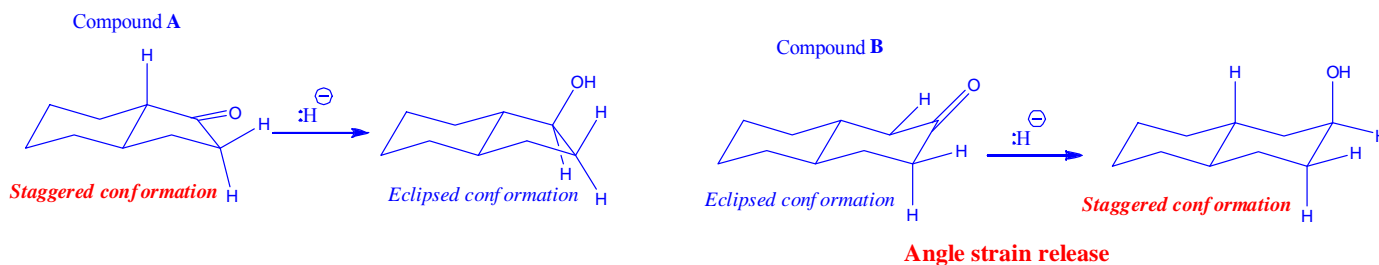
Compound **B** reacts faster than **A** due to the favored geometric arrangement of the sulfur's non-bonding  $e^-$  pair to attack the  $\sigma_{C-Cl}$  in the *endo* isomer. This geometric arrangement is similar in the *exo* isomer (A) for the interaction between  $\sigma_{C-C}$  and  $\sigma_{C-Cl}^*$ . However, the high polarizability (softness) of sulfur allows for the deformation of the unshared S: electron pair which favors the C-Cl bond rupture and consequent departure of the chloride from this thianorbornene system B. JACS 1975, 97, 2886

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14. Predict, which isomer reacts faster in the reduction by sodium borohydride. Explain (drawing + brief verbal explanation).



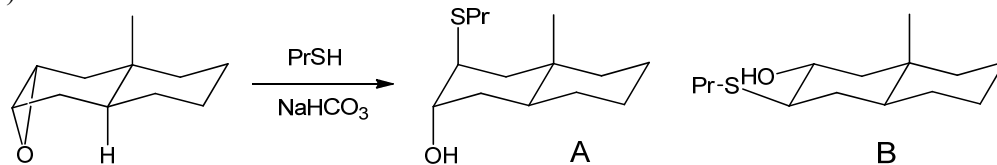
Answer:



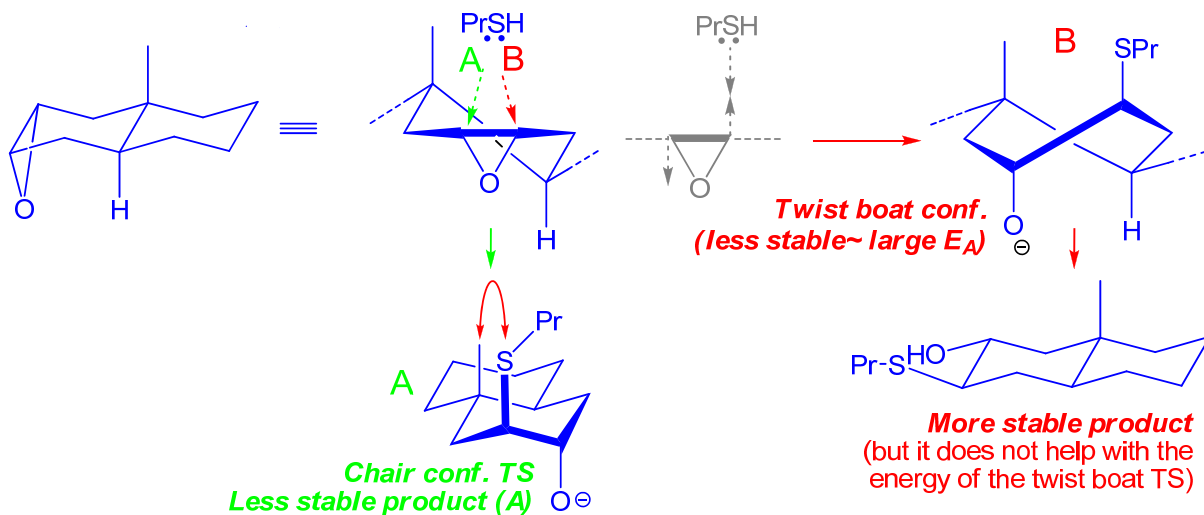
Compound B reacts faster. Attack reduction of the carbonyl group will give rise to an eclipsed conformation in A, opposite to the case of B where the product will have a staggered conformation. Therefore, the 5-membered ring alcoholate will have more ring strain than the one with 6 members.

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**15. Furst-Plattner.** Predict which product isomer A/B is formed preferentially. Explain (drawing a mechanism + brief verbal explanation).



**Mechanism:**



**In reality, only the product A is formed.**

Product ratio depends on  $\Delta\Delta G^\ddagger$  (i.e. relative energy of the respective transition states): Route to product A proceeds through a stable chair conformation and the destabilizing 1,3-diaxial interaction is of lower energy than the route to product B, which involves twist boat transition state.