

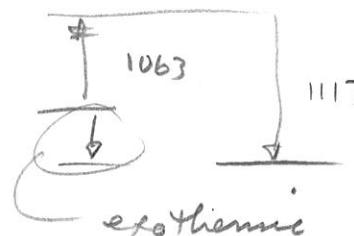
1. Consider the following reaction.

Given: $\Delta G = \Delta H - T\Delta S$ and $K_{eq} = e^{-\Delta G/RT}$

(10 points)



| Bond Dissociation | |
|-------------------|-------------------------|
| Bond | Enthalpy (BDE) - kJ/mol |
| C=C | 632 |
| C-C | 368 |
| C-Cl | 339 |
| C-H | 410 |
| H-Cl | 431 |



a. Using the BDE values in the table, calculate the estimated enthalpy (ΔH) for the above reaction. Clearly show your calculation.

$$\Delta H = 1063 - 1117 = -54 \text{ kJ/mol}$$

bond broken

$$\begin{array}{l} \text{C}=\text{C} \quad 632 \\ \text{H}-\text{Cl} \quad 431 \end{array} \left. \vphantom{\begin{array}{l} \text{C}=\text{C} \\ \text{H}-\text{Cl} \end{array}} \right\} 1063 \text{ kJ/mol}$$

bonds made

$$\begin{array}{l} \text{H}-\text{C} \quad 410 \\ \text{C}-\text{C} \quad 368 \\ \text{C}-\text{Cl} \quad 339 \end{array} \left. \vphantom{\begin{array}{l} \text{H}-\text{C} \\ \text{C}-\text{C} \\ \text{C}-\text{Cl} \end{array}} \right\} 1117$$

(6 points)

b. Predict the sign of the entropy (ΔS). Explain your answer.

Because 2 molecules combine to make one molecule

$$\Delta S = \ominus$$

(2 points)

c. How is the equilibrium of this reaction dependent on temperature? Explain your answer.

$$\Delta G = \Delta H - T\Delta S$$

the enthalpy term is \ominus and the entropy term is \ominus

So,

$$\Delta G = \ominus - T(\ominus) = \ominus \text{ at low temperatures}$$

\oplus

$$= \oplus \text{ at high temperatures}$$

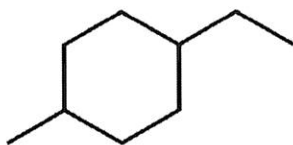
at high temperatures
 the reaction is favored
 in reverse - at low

where $-T\Delta S$ becomes larger
 than ΔH

temperatures, the forward direction is favored.

2. Consider both the *trans* and *cis* isomers of 1-ethyl-4-methylcyclohexane.

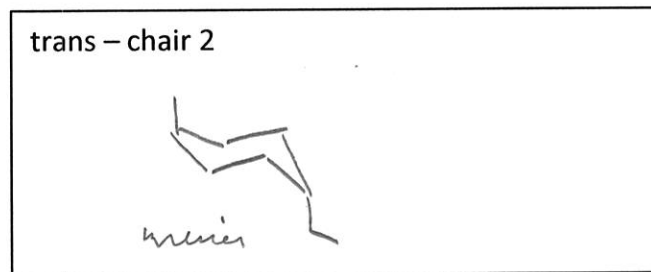
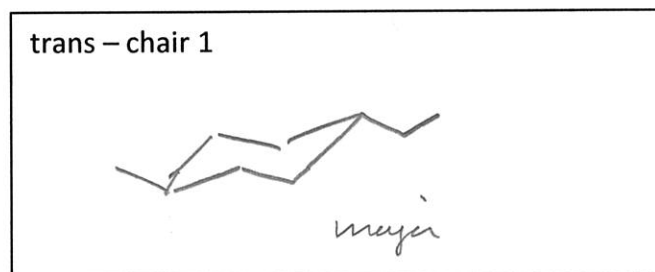
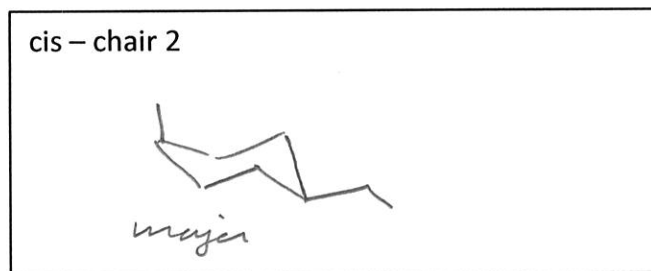
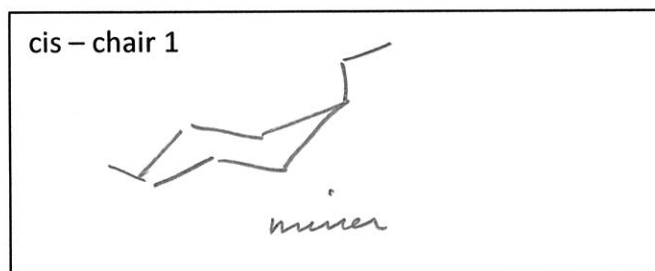
(40 points)



1,3-Diaxial Interactions

| | |
|----------------------------------|------------|
| -CH ₃ | 7.6 kJ/mol |
| -CH ₂ CH ₃ | 8.0 kJ/mol |

a. Draw the chair conformations of both isomers.



b. Which isomer is expected to be more stable? Clearly explain your choice.

The *trans* isomer - the *major* chair form has all equatorial groups and has zero observable strain. Both of the *cis* chairs have one axial substituent which introduces 1,3-diaxial strain.

c. The enthalpy of combustion (ΔH_c) has been measured for both isomers. The ΔH_c values for the two isomers differ by 8.0 kJ/mol. Which isomer is predicted to have a greater (i.e., more exothermic) ΔH_c value?

greatest value

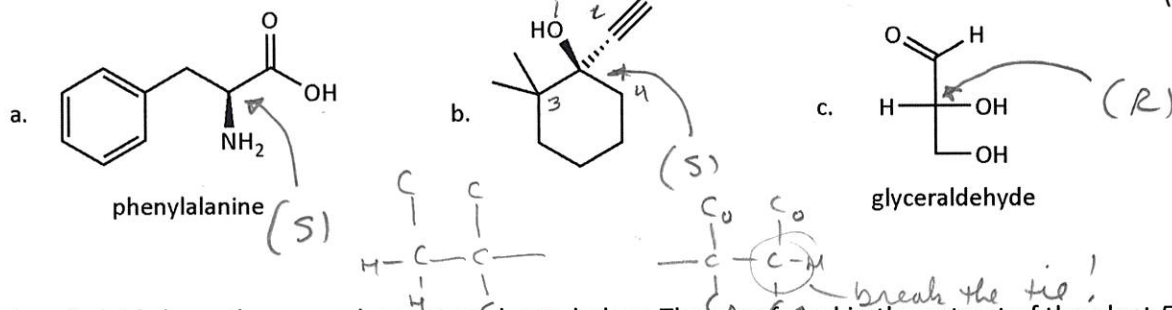
The *cis* isomer always has a 1,3-diaxial interaction in both conformations, even in the *major* form. The *trans* isomer has no 1,3-diaxial interactions in the *major* chair.

d. Does the 8.0 kJ/mol difference in enthalpy of combustion values seem reasonable in light your analysis of the conformations of the two isomers? Clearly explain your response.

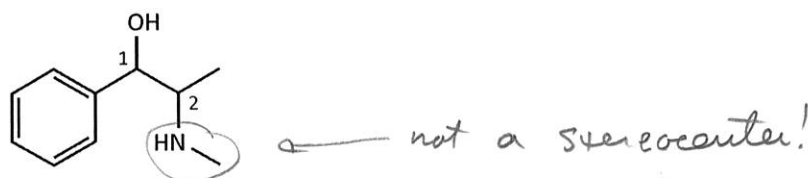
In either chair conformation of the *cis* isomer there is a substituent in an axial position. Both of these chairs are $\sim 7.6 - 8.0$ kJ/mol higher in energy than the "best" *trans* chair - the difference in observed strain is approximately equal to the difference in ΔH_c .

see explanation document at end

3. Assign the configurations of each stereocenter in the following compounds using the appropriate notation. (15 points)



4. Ephedra alkaloids have the general structure shown below. They are found in the extract of the plant *Ephedra sinica*, which has been used to treat many medical conditions (such as asthma) and has been used in traditional Chinese Herbal Medicine for over 2000 years. The IUPAC name is provided for the structure but none of the stereochemistry is shown. (20 points)

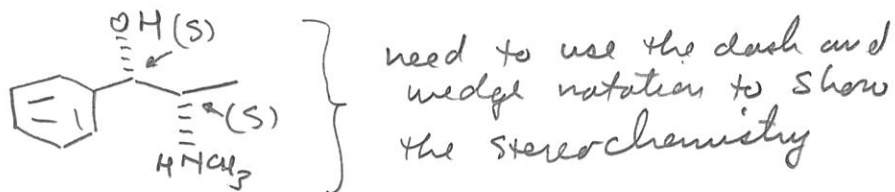


2-(methylamino)-1-phenylpropan-1-ol

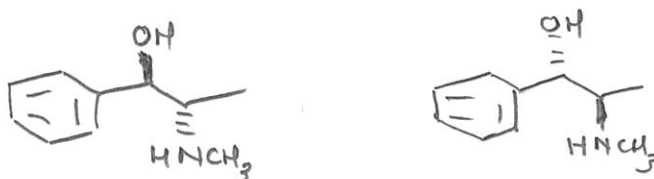
- a. How many stereoisomers are possible for the ephedra alkaloids (shown above)?

there are two stereocenters, $2^2 = 4$ isomers

- b. The decongestant known as Sudafed[®] contains one of these alkaloids and is called **pseudoephedrine** and has the *absolute configuration* of (1S,2S). Draw this isomer using appropriate notation (line, dash, and wedge).



- c. The alkaloid called **ephedrine** is a *diastereomer* of **pseudoephedrine**. Draw a possible structure for **ephedrine** and label each stereocenter with appropriate notation.



- d. Write the complete IUPAC name for the *enantiomer* of **pseudoephedrine** using the correct notation for stereochemistry (and in the correct format).

(1R,2R)-2-(methylamino)-1-phenylpropan-1-ol

5. Indicate whether the following statements are *absolutely* true or false. (25 points)

a. All *enantiomers* are optically active.

T

b. (2*R*,3*R*)-pentane-2,3-diol is the *enantiomer* of (2*S*,3*R*)-pentane-2,3-diol.

F

c. If a molecule lacks a sigma plane of symmetry (σ) then it is chiral.

F (could have i)

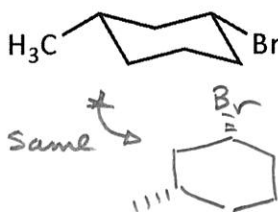
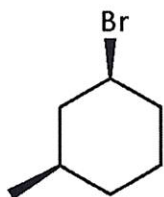
d. All *meso* compounds are optically active.

F

e. *cis*-1,3-dimethylcycloheptane is achiral.

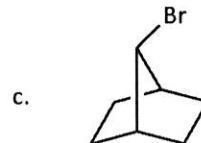
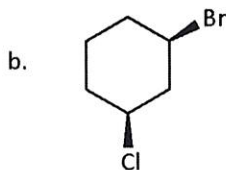
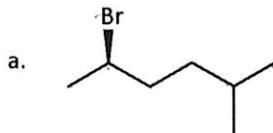
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6. What is the relationship between the following two structures? Are they *enantiomers*, *diastereomers*, *constitutional isomers*, or *identical*? (5 points)



enantiomers

7. Provide names for the following alkyl halides. (15 points)

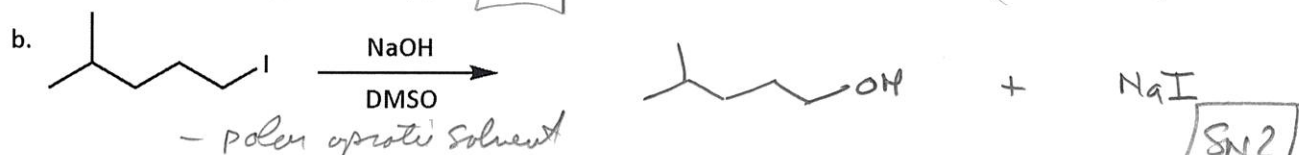
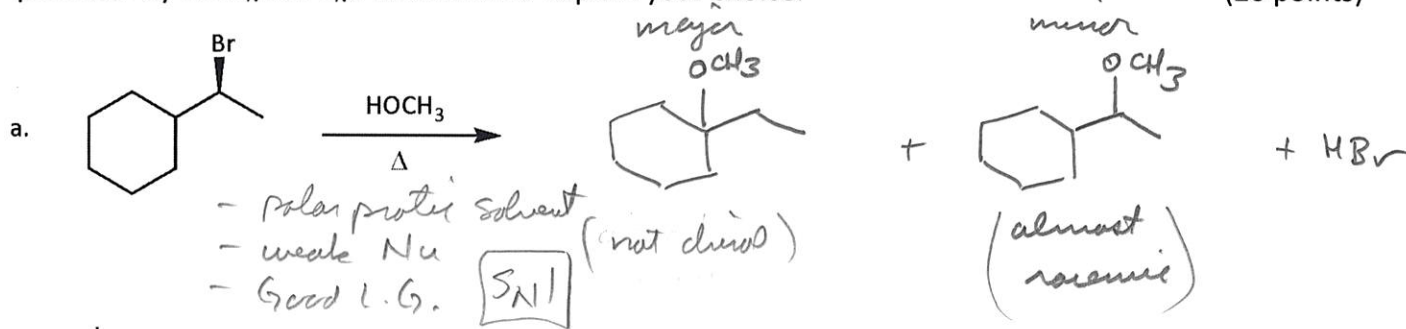


a. (R)-2-bromo-5-methylhexane

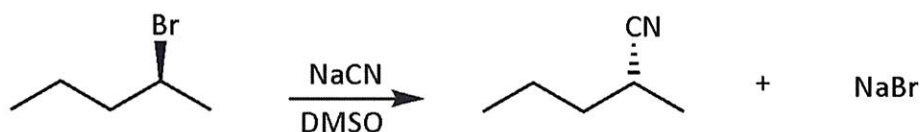
b. (1*R*,3*S*)-1-bromo-3-chlorocyclohexane

c. 7-bromobicyclo[2.2.1]heptane

8. For the following substitution reactions show the product (or products). Indicate whether the reaction proceeds by the S_N1 or S_N2 mechanism. Explain your choice. (20 points)



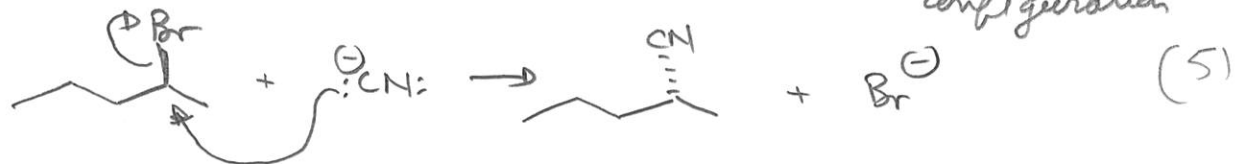
9. Consider the following reaction: - good Nu / good L.G. 1° -substrate (30 points)



- a. Indicate whether this reaction proceeds via an S_N1 or S_N2 process. Explain your answers. (5)

S_N2 - 2° substrate + good L.G. + good Nu (CN^-) + polar aprotic solvent

- b. Draw the mechanism of this reaction. + 100% inversion of configuration



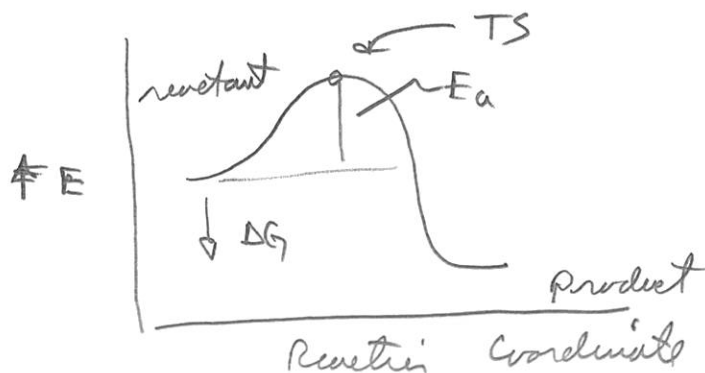
- c. What is the rate equation of this reaction? (5)

$$\text{Rate} = k [R-Br] [CN^-]$$

- d. Would the reaction occur at a faster rate if the concentration of cyanide were doubled? Explain. (5)

The rate would double since the nucleophile is 1st order in the rate equation

- e. Draw an energy diagram of the reaction above. (10 points)



10. The table below (Table 9.5) shows the rate constants for the reaction of select nucleophiles from Group 6A and 7A with methyl iodide (CH₃I). (40 points)

a. What is the trend in nucleophile strength for each of the groups of elements, 6A and 7A? Explain your answer.

15 the rate constant gets bigger in each series as the element gets bigger (which is going down the periodic table)

b. What type of solvent is this reaction run in, polar protic or polar aprotic?

5 polar protic due to $\text{CH}_3\text{O}-\text{H}$ hydrogen bond donor acid

c. What does the pK_a of the conjugate base tell you about the nucleophile strength in this case? Explain your answer.

15 In this case, the stronger the acid the better the conjugate base is a nucleophile AND only in CH₃OH.

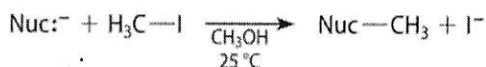
(Note the trend in the 2nd row elements is opposite!)

d. What effect would switching the solvent of the reaction to DMSO have on the rate of reaction of the nucleophiles in Group 7A with methyl iodide?

5 In group 7A, using DMSO reverses the nucleophile strength

F[⊖] would be a stronger nucleophile and thus would react faster

TABLE 9.5 Dependence of S_N2 Reaction Rate on the Basicity of Nucleophiles from Different Periods of the Periodic Table in Methanol



| Nucleophile | pK _a of conjugate acid* | k (second-order rate constant, M ⁻¹ s ⁻¹) | log k |
|------------------------------|------------------------------------|--|-------|
| Group 6A Nucleophiles | | | |
| PhS ⁻ | 6.52 | 1.1 | +0.03 |
| PhO ⁻ | 9.95 | 7.9 × 10 ⁻⁵ | -4.1 |
| Group 7A Nucleophiles | | | |
| I ⁻ | -10 | 3.4 × 10 ⁻³ | -2.5 |
| Br ⁻ | -8 | 8.0 × 10 ⁻⁵ | -4.1 |
| Cl ⁻ | -6 | 3.0 × 10 ⁻⁶ | -5.5 |
| F ⁻ | 3.2 | 5.0 × 10 ⁻⁸ | -7.3 |

* pK_a values in water

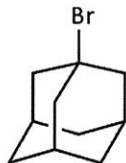
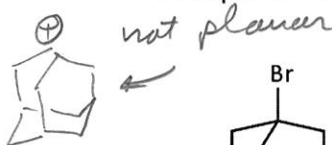
(Source: Marc Loudon *Organic Chemistry* 6th edition, Roberts and Co., 2016, p. 399)

unlike the 2nd row elements and the "hydrides" (CH₄, NH₃, H₂O, HF) where higher pK_as indicate stronger Nu for the conjugate base, periodic columns have the opposite trend in protic solvents (groups)

11. Explain (clearly) why fluoride (F^-) is a better nucleophile in DMSO than in ethanol. (10 points)

In DMSO, F^- doesn't get solvated as well as in ethanol so it is more reactive

12. Adamantyl bromide is completely unreactive toward nucleophiles in either the S_N1 or the S_N2 reaction. Suggest an explanation for this lack of reactivity. (10 points)



adamantyl bromide

adamantyl bromide is not susceptible to S_N2 reaction not only because the substrate is 3° but also the backside is completely inaccessible (the Nu would have to approach from the inside)

The tertiary halide is also not able to ionize for an S_N1 reaction because the substrate cannot produce a stable, planar carbocation due to the constraint of the adamantyl ring system

13. **EXTRA CREDIT CHALLENGE PROBLEM.** The Finkelstein reaction is a widely used reaction to prepare alkyl iodides (R-I). The reaction converts alkyl chlorides (R-Cl) and alkyl (R-Br) to their corresponding iodides in excellent yield. Given the "normal" order of nucleophilic strength of the halides in protic vs. aprotic solvents and noting that the only alkali metal salt that is soluble in acetone is NaI, suggest an explanation for the success of this popular reaction.

(20 EC points)



R = methyl, primary, or secondary
X = Cl or Br

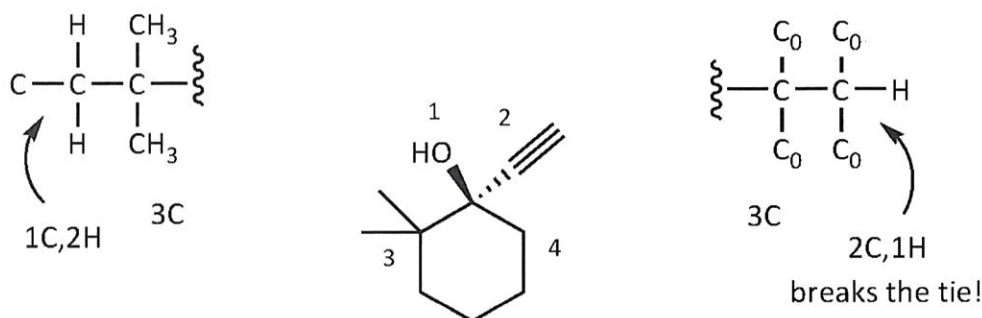
1. NaI is soluble in acetone and delivers I^- as a nucleophile
2. acetone is a polar aprotic solvent which would normally make Cl^- and Br^- stronger nucleophiles than I^-
3. The reaction succeeds since the NaCl or NaBr produced is insoluble in acetone and precipitates from the mixture — this is an example of Le Chatelier's principle where removing one of the formed products drives the reaction forward.

Exam 2, Question 3b, Final answer

Many of you were surprised that your answer was marked incorrect for Question 3b on Exam 2. Even more surprised were those who also found that a computer program (that I recommended) agreed with the incorrect absolute configuration and put the same answer on the make-up exam.

Fortunately, the correct answer has nothing to do with the computer program, but merely the application of the CIP rules to determine priorities and then assign absolute configuration by viewing the structure in the correct way.

The correct name is shown below with the correct absolute configuration. The expanded views of the two substituents in question must be viewed with all of the attached elements "visible," noting that multiple bonds count for more attachments to carbon, which in case breaks the tie. The resulting priorities for the four groups around the asymmetric carbon are shown – this leads to the configuration as (S).



(S)-1-ethynyl-2,2-dimethylcyclohexanol

I must admit that it was surprising to find the configuration from ChemDoodle to be wrong (ChemDraw and ChemSketch give the correct answer), so I wrote to the company and this is what they said:

"Hi Stephen,

Topic: ChemDoodle
Ticket #: 401823

Thanks for this report. Our CIP system was overhauled about 2 months ago in our development version and these incorrect assignments are now correct. The new CIP system in ChemDoodle is very accurate and reliable, and will be made available with the release of ChemDoodle 9, tentatively in Q1 2017.

Sincerely,
iChemLabs Customer Service"