Chem 633: Advanced Organic Chemistry 2011 ... Midterm 1

Please answer the following questions clearly and concisely. In general, use pictures and less than 10 words in your answers.

Write your answers in the space provided.

Write your initials on each page you want graded.

There are 11 total pages to this exam. The last 2 pages were intentionally left blank and may be used for scratch paper. Please be sure your copy has 11 pages before you begin.

Molecular models are allowed.

Calculators are unnecessary and prohibited.

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Averages shown

**TOTAL** 49/100

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![Comic Strip](https://phdstanford.edu)

Jorge Cham @ The Stanford Daily
4 pts each.

1. (20 points) Please clearly depict the lowest energy conformations of the following molecules. No explanation is necessary.

- [Chemical structure 1]
- [Chemical structure 2]
- [Chemical structure 3]
- [Chemical structure 4]
- [Chemical structure 5]

(equal energies)
2. (18 points) (a) Please draw the lowest energy conformations for both the *cis* and *trans* configurations of the following acetal. If there is more than one lowest energy conformation, please draw both.

\[ \Delta G^o = +0.17 \text{ kcal/mol} \]

**cis** (6 pts):

(trans 6 pts)

(2 equal lowest energy conformations)

(6 pts) (b) Please explain why the *cis* conformation is more stable than the *trans* conformation.

Anomeric effect beats steric effect.
3. (6 points) In nucleophilic additions to nitrilium ions (e.g., 1), the major product is the one in which the nitrogen substituent is cis to the incoming nucleophile. Please rationalize why the cis product is favored. Hint: You may find it easier to consider the reverse of the reaction, which is a reasonable approach given the Principle of Microscopic Reversibility.

Reverse: Breaking C-Nuc bond.

4. (6 points) Please explain why the equatorial C–H bond is longer than the axial one in 1,3-dioxolane.

3 effects on Equatorial C–H:

- [Diagram showing the effects on C–H bond]

5. (10 points) (a) Please draw a reasonable arrow-pushing mechanism for the following transformation (Coxon *Tetrahedron Lett.* 1990, 5357).

(b) Is the starting material chiral or achiral? **achiral**
6. (10 points) (a) Baldwin has reported that under a variety of basic conditions, alcohol 1 does not cyclize to form ether 2 (Baldwin et al. JCS Chem. Commun. 1976, 736). Why doesn’t this reaction occur?

5-endo-trig - disfavored by Baldwin’s Rules.

(b) In contrast, this reaction does occur under acidic conditions (p-toluene sulfonic acid). Why does the use of acidic conditions now make this reaction feasible?
7. (10 points) Please propose a reasonable arrow-pushing mechanism for the following transformation. Please note that there is no work-up between steps. (Grossman, Ch 2, #2k)
8. (20 points) Husson has reported a method for the preparation of 2-cyanopiperideines (3) from the corresponding N-oxides (1).

(a) Please draw a reasonable arrow-pushing mechanism for the transformation of 1 to 3.

(b) Surprisingly, in the observed conformation of 3, the nitrile (CN) substituent is pseudo-axial, although the A-value of CN predicts a slight equatorial preference (A value = 0.2 kcal/mol). Please explain why the conformation with a pseudo-axial nitrile is more stable.

Anomeric effect! ("α-amino nitrile anomeric effect")
CN ≈ halide or heteroatom.

† better acceptor than θ^*_{C-H}.
(8 – continued)
(c) In the cyanation of iminium ion 4, two products (5A and 5B) are observed in a 3:2 ratio. What is the stereochemical relationship between 5A and 5B?

\[
\begin{array}{c}
\text{Ph} \\
\text{C} \\
\text{N} \\
\text{Me} \\
\end{array} 
\xrightarrow{\text{KCN}} 
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{C} \\
\text{Me} \\
\end{array} + 
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{C} \\
\text{Me} \\
\end{array} 
\text{57\% (combined)} 
\frac{5A}{5B} = 3:2 
\]

Diastereomers

(d) Will the Me substituent be in a pseudo-equatorial or pseudo-axial position in the most stable conformation of 4? Please clearly illustrate/explain your reasoning.

\[ \text{pseudo-axial.} \]

Also \( \rightarrow \) no axial H's on bottom face, so not so bad to be pseudo-axial.

(e) Use your predicted conformation of 4 to rationalize why both 5A and 5B are observed. Hint: You may assume that stabilizing effects present in the products will also be present in the transition states leading to the products.

ECN wants to be axial in transition state (\( \alpha \)-amino nitrile anomeric effect)

But CH₃ is on bottom face.

so...

\[ \text{equatorial attack} \]

\[ \text{1,3-diaxial interaction with CH₃, but no anomeric effect} \]

\[ \text{anomeric effect} + \]

\[ \text{favored by anomeric effect} \]

(also: both pseudo-axial)