2.339 Practice Problems

**Basics of Structure and Mechanism**

1. What is the expected site of protonation in an enol ether (ROCH=CHR)? Justify your choice using resonance structures.

2. Rank the following molecules in order of decreasing Bronsted acidity. For each, identify the most acidic H atom. Justify your choice using resonance and/or inductive arguments.

3. Designate each stereogenic centre in the following molecule as (R) or (S).

4. Draw all stereoisomers of 1,2-dichlorocyclohexane. Name them. Which are chiral? If each diastereomer is treated separately with NaI in hot acetone (SN2 reaction), what are the products? How are they related stereochemically? If a chiral stereoisomer of 1,2-dichlorocyclohexane is treated with NaI, will the product be chiral?

5. Chlorosilanes react with alcohols in the presence of tertiary amine bases to give silyl ethers.

   \[ R_3SiCl + ROH \xrightarrow{EtN(i-Pr)_2} CH_2Cl_2 \xrightarrow{ROSiR_3} \]

   If (±)-2-butanol is treated with 0.5 equivalents of (CH₃)₂SiCl₂ and a suitable base, a mixture of 3 products results. Chromatographic analysis of this mixture shows only 2 peaks in a 1:1 ratio. What are the products? Why are there only 2 peaks in the chromatogram? Explain how this could be used to measure the enantiomeric purity of a chiral alcohol.

6. Provide stepwise mechanisms for each of the following reactions. The reactions are taken from a standard introductory organic chemistry textbook, and are not necessarily directly relevant to 2.339, but they are a good reminder of basic principles of mechanism.
Conformations of Organic Molecules

1. Using a conformational argument, predict which of trans-anti-trans-perhydrophenanthrene A or trans-syn-trans-perhydrophenanthrene B is the more stable isomer.

2. Gas-phase and solution studies on 1,4-dimethoxybenzene show the presence of 2 stable conformers. What are they, and why do these geometries represent local energy minima?

3. 2,3-Dibromobutane has both meso and chiral diastereomers. When the meso diastereomer is boiled in acetone with KI, iodide ion attacks one of the bromines, causing an E₂-like elimination and forming trans-2-butene. When
the *chiral* diastereomer is treated in the same way, *cis*-2-butene is obtained. Which process is faster, and why?

4. When cyclohexanols are oxidized to cyclohexanones, large differences in rate between axial and equatorial isomers are observed. Why is the oxidation of the axial isomer so much faster than that of the equatorial isomer?

5. Explain the trends in both the direction and magnitude of the conformational preferences in the 1-hetera-"cis"-decalin equilibria shown below.

![Conformational Preferences Diagram](image)

X = S, $K_{eq} = 1.38$
X = NH, $K_{eq} = \text{ca. 12}$

**Assorted Reactions**

1. The following transformation was attempted:

   ![Reaction 1](image)

   The product was expected to be a carboxylic acid/diol, but the material that was actually isolated was different. NMR showed the disappearance of the alkene, and IR showed the presence of OH and C=O, but not CO$_2$H. A mass spectrum indicated a molecular mass of 144. What was the structure of the product, and why was this obtained instead of the desired compound?

2. Provide the expected major products for each of the following:

   ![Reaction 2](image)

   a. DME = 1,2-dimethoxyethane (a solvent).
3. Provide a stepwise mechanism to explain the following very efficient reaction. Why is only one stereoisomer observed?

![Mechanism Diagram](image)

4. Provide the products of the following reactions. Show stereochemistry where appropriate! All reactions are either specifically discussed in lecture or lab, or are straightforward analogs of such reactions.

![Reactions Diagram](image)

a. 

b. 

c. 

This one is a bit tricky.
d. \( \text{IN}_3 = \text{I} - \text{N} = \text{N} = \text{N} \)  The reagent is a bit odd, but it works like others we have seen.

e. 

f. 

IR shows NO OH group!

h. 

\[ \text{IN}_3 = \text{I} - \text{N} = \text{N} = \text{N} \]

The reagent is a bit odd, but it works like others we have seen.

\[ \text{HCl} \rightarrow \]

\[ \text{Hg(OAc)}_2 \]  \( \text{THF/H}_2\text{O} \)

\[ \text{then} \]

\[ \text{NaBH}_4, \text{NaOH/H}_2\text{O} \]

\[ \text{NaOH (aq.)} \]

\[ \text{then} \]

\[ \text{H}_3\text{O}^{+} \]

\[ \text{IR shows NO OH group!} \]

\[ \text{C}_7\text{H}_8\text{O}_3 \]
2.339 Answers to Practice Problems

**Basics of Structure and Mechanism**

1) An enol ether will be protonated on the C=C rather than on the O atom because the resulting cation can benefit by resonance stabilization. Recall that O is an excellent π donor.

2) The order of acidity is shown below. The most acidic H atom is highlighted in each structure. In all cases except the alkyne, the acidity can be rationalized in terms of resonance stabilization of the conjugate base, combined with consideration of the relative electronegativities of the atom(s) bearing formal negative charges in the canonical forms. The alkyne acidity arises from the high degree of s orbital character on the terminal carbon atom, which lowers the energy of the nonbonding electron pair in the conjugate base, relative to an electron pair in an sp³ orbital. Note that the C-H bond adjacent to a nitrile is also relatively acidic, due to the electron-withdrawing nature of the CN group and its ability to delocalize negative charge. However, this H atom is not as acidic as the alkyne and so the first deprotonation would occur on the alkyne.

3) There are 17 stereogenic centres in inostamycin. Note that this means that there are $2^{17} = 131,072$ stereoisomers for this structure!

4) There are three stereoisomers of 1,2-dichlorocyclohexane. Note that the structure in which both Cl groups are “down” is identical to the meso structure shown.
b) Boiling a primary or secondary alkyl chloride with NaI in acetone leads to $S_{N2}$ displacement of Cl– by I–. If only one molar equivalent of NaI is used, the major products will be mixed dihalides, along with some unreacted dichloride, and the diiodide. In the presence of an excess of NaI, the products will be the diiodides.

\[
\begin{align*}
&\text{Cl} \quad \text{Cl} \\
&\text{NaI} \\
&\text{acetone} \\
&\Delta \\
&\text{Cl} \quad \text{Cl} \\
&\text{I} \\
&\text{I} \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

Assuming that each C-Cl bond reacts independently, these materials will be formed in a ratio of 1:1:1:1.

\[
\begin{align*}
&\text{I} \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

These diiodides are enantiomers.

The mixed halides are also enantiomers. Note that the displacement of chloride from a chiral dichloride leads to chiral mixed halides, and chiral diiodides. You should also note that these results assume that once iodide has replaced chloride, no displacement of iodide by iodide occurs. If it does, then the stereochemistry of the products will become scrambled.
5) Note that the silyl chloride has two leaving groups, and so it will react twice, linking two molecules of the chiral alcohol. Because the \((R,S)\) and \((S,R)\) combinations are *meso* compounds, they are identical. Only *two* peaks are observed in the chromatogram because the \((R,R)\) and \((S,S)\) compounds are enantiomers, and therefore have identical physical and chemical properties. This means that they will move through a chromatography column at the same rate.

\[
\begin{align*}
&\text{HO} \quad \text{H} \quad \text{HO} \quad \text{H} \\
\text{Base} \quad \text{(CH}_3\text{)}_2\text{SiCl}_2 \quad \rightarrow \quad \text{CH}_3 \quad \text{OSiO} \quad \text{CH}_3 \quad + \quad \text{CH}_3 \quad \text{OSiO}^{\bullet} \quad \text{CH}_3 \quad + \quad \text{CH}_3 \quad \text{OSiO}^{\bullet} \quad \text{CH}_3 \\
&\quad \text{identical} \\
&\quad \text{identical}
\end{align*}
\]

\((R,S)\) and \((S,R)\)

b) If the alcohol is racemic, then the *meso* and *chiral* compounds will be formed in equal proportions, and the chromatogram will show two equal peaks. If (for example) the alcohol is the pure \(R\) enantiomer, then there will be *no meso* compound formed, and only the \((R,R)\) chiral compound. Only *one* peak will be visible in the chromatogram. A pure sample of \(S\) alcohol will behave in a similar way, giving the same chromatographic peak (recall \(R,R\) and \(S,S\) elute together). For any mixture of \(R\) and \(S\) in between, varying amounts of *meso* compound will be formed, and the enantiomeric excess can be determined from the ratio of *meso* to *chiral* compounds formed.

6) Mechanisms.

a) This is an example of an *aldol condensation* followed by elimination. Note that in this case, all steps are reversible, although the final product is very much more stable than the \(\beta\)-hydroxyketone (aldol) intermediate and thus is the only product isolated.

b) This is the Benzilic Acid Rearrangement. Note the similarity to the Pinacol Rearrangement, although the benzilic acid process occurs under basic conditions, while the Pinacol is a cationic, acid catalyzed rearrangement.
c) This is the *Iodoform Reaction*. When methyl ketones are treated with diiodine or dibromine and aqueous sodium hydroxide, they rapidly halogenate, and then split off the trihalomethyl anion. This C–C bond cleavage may seem odd, but note that the three halogens are good electron-withdrawing groups, and stabilize the carbanion.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

(on acidifying during workup)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

The same process of enolate formation and iodination occurs two more times by a similar mechanism. Note that the remaining H atoms become more acidic as more I atoms are added.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]
d) There are two processes occurring here. The first is the acid-catalyzed hydrolysis of an ester, while the second is the spontaneous decarboxylation of a β-ketoacid. Note that while β-ketoesters are quite stable, the corresponding carboxylic acids are not. Loss of CO2 occurs essentially instantly, by a cyclic mechanism. The resulting enol tautomerizes to the ketone.

\[
\begin{align*}
\text{OEt} & \quad \text{H}_3\text{C} \quad \text{H} \quad \text{O} \\
\text{H}_3\text{C} \quad \text{O} & \quad \text{EtOH} + \quad \text{H}_3\text{C} \quad \text{H} \quad \text{OH} \\
\text{H}_3\text{C} \quad \text{O} & \quad \text{H} \\
\text{H}_3\text{C} \quad \text{O} & \quad \text{OH} \\
\end{align*}
\]

\[
\text{+ CO}_2
\]

Conformations of Organic Molecules

1) Trans-anti-trans-perhydrophenanthrene A is the more stable isomer. You can see that it is able to assume a chair-chair-chair conformation, whereas trans-syn-trans-perhydrophenanthrene B must put one of its three cyclohexane rings into a boat conformation. This will raise its energy considerably, not to mention other unfavorable van der Waals' interactions that occur in this structure.

The best geometry for B is shown. Notice that the two-dimensional structure gives no hint of this fact – it appears to contain two trans-decalin fragments, just as A does. However, closer inspection shows a problem. In a normal chair-chair trans-decalin, the bridgehead substituents are axial. Start with the H-atom at the “12-o’clock” position, and assume it is axial. Its neighbor (“up”) will also be axial. The next “up”
H-atom shown must be equatorial, and the “down” H-atom adjacent will be equatorial as well, if all rings are chairs – but this is impossible because for this to be true, the C–C bonds of the ring fusion must be diaxial, which is geometrically impossible for chair conformers.

2) The ring in 1,4-dimethoxybenzene must be planar, so any conformational differences can only involve the methoxyl groups. Rotations around the O–CH₃ bonds are of no consequence, but rotation around the Cₓsp²–O bonds gives rise to distinctly different geometries. The fact that there are two and only two stable minima suggests the “cis” and “trans” structures shown at right. We would expect there to be a strong preference for coplanar conformers to permit delocalization of the lone-pair electrons of the O atoms into the ring π system. Note that, as in aniline derivatives, amides, and esters, the best VB description of the O atom is sp², with one lone pair in a p orbital (rather than the sp³ tetrahedral geometry usually shown in first-year books).

3) In order for an E₂-like elimination to occur, the Br atoms must be antiperiplanar. For the meso diastereomer, this geometry corresponds to its preferred conformation. Reaction from this low-energy state leads to the trans alkene and should be relatively fast. In contrast, the reactive conformer of the chiral diastereomers requires a gauche relationship between the methyl groups. This conformation will be destabilized relative to the CH₃-anti conformer (at least in a relatively polar solvent like acetone). This means that the concentration of the reactive conformer will be quite low, and the corresponding rate will be relatively small.

4) In an axial cyclohexanol, there are unfavorable 1,3-synaxial interactions between the OH group and the axial substituents on positions 3 and 5. When the alcohol is oxidized to a C=O group, these interactions are relieved. In contrast, equatorial cyclohexanols do not have these synaxial interactions. If we assume that the transition states for the oxidation processes have roughly the same absolute energy,
we can see that the reaction from the higher-energy conformer has the smaller activation energy, and should be faster. Destabilization of the ground state is another way of looking at kinetics, but it is important to keep everything relative to some fixed reference. In this case, the fact the that same ketone is formed from both oxidations allows a direct comparison, but you cannot compare processes that have both different starting and ending points quite so easily.

5) Notice that although these structures look quite different, they are simply two different chair-chair conformations of the cis decalin skeleton. Consider the left-hand

structure, which is the disfavored one in both equilibria. Note that there are two 1,3-synaxial interactions between H-atoms of the heterocyclic ring and the C–C bond of the carbocyclic ring. In contrast, the preferred (right-hand) structure has only one such synaxial interaction, because of the location of the heteroatom X. This explains why the right-hand structure is always favored. The reason that the equilibrium constant is so much larger when X=NH can be seen from the C-X bond lengths. The C-N bond is much shorter than the C-S bond (1.47 Å vs. 1.82 Å), and hence the synaxial interactions are more severe in the amine than in the sulfide. This shifts the equilibrium to the right for the amine.

X = S, $K_{eq} = 1.38$
X = NH, $K_{eq} = \text{ca. 12}$
**Assorted Reactions**

1) The desired reaction was the vicinal cis-hydroxylation of the alkene by cold alkaline permanganate. However, in order to isolate the product, it is necessary to acidify the mixture to re-protonate the carboxylate salt. Under acidic conditions, a carboxylic acid and an alcohol will form an ester, especially when they are in the same molecule and can form a lactone. From the information given, we can’t determine whether the product was the 5- or 6-membered ring lactone. Recall that 5-membered rings generally form fastest, but that 6-membered rings are more stable. Under the conditions of acidic workup and isolation, the system probably will equilibrate to form the more-stable isomer, but the question did not make this clear.

![Chemical diagram](image1)

2) a) ![Chemical diagram](image2)

b) ![Chemical diagram](image3)
3) This is a variation on the oxymercuration, in which the cationic centre is relayed from one tertiary position to another. The process mimics the actual mechanism of the biosynthesis of cholesterol and other steroids. Because each tertiary cation is similar
in stability, the C–C bond forming reactions are reversible. This means that the most stable isomer is formed. The diagram in the box shows that cyclization to a trans-decalin proceeds through a very reasonable chair-like geometry that produces the observed stereochemistry.