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2. (20 Marks) STEREOCHEMISTRY AND CONFORMATION

a. The geometry of a terpenoid lactone determined by X-ray crystallography is shown below. With reference to the crystal structure, answer the following questions about this compound. Note that in the perspective, the cyclohexanone carbonyl is projecting towards you.


\[
\text{CH}_3
\]
\[
\text{O} \quad \text{O} \quad \text{O}
\]
\[
\text{CH}_3 \quad \text{CH}_3
\]

i. (2 Marks) There are two stereogenic centres in this molecule. Identify them and designate the absolute configuration (R or S) at each one.

ii. (2 Marks) Taking into account the geometric and conformational properties of esters, what term best describes the conformation of the 5-membered lactone ring?

iii. (6 Marks) The conformation shown is the one present in the solid state, but there are other possible conformers. Would this also be the preferred conformation in solution? If not, what conformation would be preferred? In either case, briefly explain your reasoning.
b. (10 Marks) Consider all the possible structural and configurational isomers of chlorodibromocyclopropane (C₃H₃ClBr₂).

i. Draw all structural isomers of this compound.

ii. Draw all stereoisomers of the structural isomers you drew in part i.

iii. Indicate which of these stereoisomers are chiral and which are achiral. For the chiral stereoisomers, identify all enantiomeric pairs.
3. (20 Marks) Provide the missing product, starting material, or set of reagents to correctly complete each of the following reactions. Indicate stereochemistry as appropriate.


NB: TBDMS = tert-Butyldimethylsilyl.

NB: TBDPS = tert-Butyldiphenylsilyl; Bz = benzoyl.


f. 

\[ \text{Ph} \quad \text{BnO} \quad \text{NH} \quad \text{C}_2\text{H}_5 \quad \text{O} \quad \text{L-Selectride} \quad \text{THF, -78 °C} \]


NB: Bn = CH\(_2\)C\(_6\)H\(_5\); Ph = C\(_6\)H\(_5\) (phenyl).

---

g. 

1. 

2. 

*J. Org. Chem. 2005, 70, 199-206*

HINT: *don’t* use acid!

---

h. 

\[ \text{Ph} \quad \text{SO} \quad \text{O} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{DMSO, CH}_2\text{Cl}_2 \quad -78 \, ^\circ\text{C} \quad \text{then Et}_3\text{N} \quad \text{C}_{14}\text{H}_{14}\text{O} \]

4. (20 Marks) QUESTIONS ABOUT MECHANISMS

a. (4 Marks) Briefly explain why the hydrogenation reaction shown below gives such different stereochemical outcomes in the two solvents noted.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{OH} & \quad \text{H}_2 (\text{g}) \quad \text{Pd/C cat.} \\
\text{solvent} & \quad \text{hexane} & \quad 61 \\
& \quad \text{ethanol} & \quad 6
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{OH} & \quad + & \quad \text{H}_3\text{CO} & \quad \text{OH} \\
\end{align*}
\]


b. (8 Marks) The following reaction gave two rather different products (2 and 3). Provide mechanisms that account for the formation of each of these.

\[
\begin{align*}
\text{COOEt} & \quad \text{mCPBA} & \quad \text{CH}_2\text{Cl}_2 \\
1 & \quad \text{COOEt} & \quad + & \quad \text{COOEt} & \quad \text{OOH} \\
2 & \quad 3
\end{align*}
\]

c. (8 Marks) Here is an interesting reaction that occurred when the researchers attempted to perform a base-catalyzed Baeyer-Villiger reaction on a highly strained ketone. Provide a mechanism to explain the outcome of this process.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

\[
\text{H}_2\text{O}_2, \text{NaOH (aq)} \quad \text{then} \\
\text{acidification to pH 2 during workup}
\]

5. **(20 MARKS)** An organic compound \( \text{A} \) \((C_6H_{10}O_3)\) was treated with KI3 (aq). The product of this reaction was then exposed to \( \text{H}_2 \) (g) \((3 \text{ atm. pressure})\) over a Pd/C catalyst in the presence of NaHCO\(_3\), to form a new compound \( \text{B} \) \((C_4H_6O_3)\). NMR spectra of compound \( \text{A} \) are shown below, and spectra for compound \( \text{B} \) are on the next page. What are the structures of these two compounds?

[Diagram showing chemical reaction and NMR spectra for \( \text{A} \) and \( \text{B} \)]
Structure for compound B
C_{4}H_{6}O_{3}
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Unmatched items in column B are highlighted.
2. (20 Marks) STEREOCHEMISTRY AND CONFORMATION

a. The geometry of a terpenoid lactone determined by X-ray crystallography is shown below. With reference to the crystal structure, answer the following questions about this compound. Note that in the perspective, the cyclohexanone carbonyl is projecting towards you.


i. (2 Marks) There are two stereogenic centres in this molecule. Identify them and designate the absolute configuration (R or S) at each one.

ii. (2 Marks) Taking into account the geometric and conformational properties of esters, what term best describes the conformation of the 5-membered lactone ring?

iii. (6 Marks) The conformation shown is the one present in the solid state, but there are other possible conformers. Would this also be the preferred conformation in solution? If not, what conformation would be preferred? In either case, briefly explain your reasoning.

I will accept any reasonable and supported argument on either side of this issue. It is noteworthy that the crystal conformation certainly forces significant synaxial steric interactions, in particular between the axial H atoms on the cyclohexanone ring and the methyl groups of the lactone ring. There is also a synaxial interaction involving the axial methyl group. Furthermore, this geometry probably has a larger dipole moment than is necessary. If the cyclohexanone ring were to flip to the other chair, all these interactions would be significantly relieved. Thus, one could anticipate that the crystal conformation would not be preserved in solution. This would be my own answer to this question, but if you can make a good argument for why this conformation would be stable in solution I am open to being convinced.

Obviously you could not perform any calculations during the exam, but this is the "other" chair conformation. Molecular mechanics suggests that it is about 3.7 kcal mol\(^{-1}\) more stable than the observed crystal geometry. Presumably the intermolecular interactions in the crystal favour the observed geometry despite its intramolecular problems.
b. (10 Marks) Consider all the possible structural and configurational isomers of chlorodibromocyclopropane \( (\text{C}_3\text{H}_3\text{ClBr}_2) \).

i. Draw all **structural** isomers of this compound.

There are only three structural isomers

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

ii. Draw all **stereoisomers** of the structural isomers you drew in part i.

There are a total of 10 distinct stereoisomers of the three structural isomers for chlorodibromocyclopropane. See below.

iii. Indicate which of these stereoisomers are **chiral** and which are **achiral**. For the chiral stereoisomers, identify all enantiomeric pairs.

Stereoisomers 1 – 6, 9 and 10 are chiral. The enantiomer pairs are 1 and 2, 3 and 5, 4 and 6, and 9 and 10.

Stereoisomers 7 and 8 are both meso compounds and are hence achiral.
3. (20 Marks) Provide the missing product, starting material, or set of reagents to correctly complete each of the following reactions. Indicate stereochemistry as appropriate.

a.

\[
\begin{align*}
\text{Hg(OAc)}_2 & \quad \text{THF} \\
\text{NaCl}, \text{NaBH}_4 & \quad \text{H}_2\text{O}
\end{align*}
\]

You could also have suggested 1. NIS or NBS or KI\textsubscript{3} or KBr\textsubscript{3}; 2. Bu\textsubscript{3}SnH, AIBN, toluene

b.

\[
\begin{align*}
\text{TBDMSO} & \quad \text{TBDMSO} \\
\text{9-BBN, THF} & \quad \text{H}_2\text{O}_2, \text{NaOH (aq.)}
\end{align*}
\]

Note that the hydroboration occurs on the “back” face to avoid approach across the ring system — this is essentially like equatorial approach to a cyclohexanone.


NB: TBDMS = tert-Butyldimethylsilyl.

c.

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OsO}_4 \,(\text{cat.}) \\
\text{NMO} & \quad \text{THF/H}_2\text{O}
\end{align*}
\]

Note that the conformation of the starting material leaves the “front” face of the alkene exposed.


NB: TBDPS = tert-Butyldiphenylsilyl; Bz = benzoyl.

d.

\[
\begin{align*}
\text{MnO}_2 & \quad (\text{s}) \\
\text{CH}_2\text{Cl}_2
\end{align*}
\]

Notice that vigorous acid conditions will also eliminate the tertiary hydroxyl group.


e.

\[
\begin{align*}
\text{Li} & \quad (\text{s}) \\
\text{NH}_3, (\text{l}), \text{BuOH} \\
\text{HCl (aq.)} & \quad \text{MeOH, reflux}
\end{align*}
\]

Birch reduction followed by vigorous acid hydrolysis forms the thermodynamically preferred ketone.

L-Selectride is a bulky and non-chelating reagent. The NHCBz group is bigger than CH$_2$Ph. Thus, the syn alcohol is the major product.

Any source of positive halogen could have been used. I would also accept oxymercuration conditions, with the appropriate reduction, although in fact the N-O bond probably would be susceptible to reductive cleavage by NaBH$_4$.


HINT: don’t use acid!
4. (20 Marks) QUESTIONS ABOUT MECHANISMS

a. (4 Marks) Briefly explain why the hydrogenation reaction shown below gives such different stereochemical outcomes in the two solvents noted.

\[
\text{H}_3\text{CO} \quad \text{OH} \quad \text{H}_3\text{CO} \quad \text{OH} \quad + \quad \text{H}_3\text{CO} \quad \text{OH} \\
\text{hexane} \quad 61 \quad \text{ethanol} \quad 69
\]


This is an example of the haptophilic effect in action. In hexane, the only thing that can coordinate to the metal catalyst is the hydroxyl group of the substrate, and so the hydrogenation is predominantly controlled by this coordination. In ethanol, however, the solvent is present in a far greater concentration than the substrate and it out-competes the substrate for coordination sites on the metal. Thus, the hydrogenation occurs under purely steric control in this solvent.

b. (8 Marks) The following reaction gave two rather different products (2 and 3). Provide mechanisms that account for the formation of each of these.

\[
\text{COOEt} \quad \text{mCPBA} \quad \text{CH}_2\text{Cl}_2 \quad \text{COOEt} + \text{CH}_2\text{Cl}_2
\]


Note that epoxide 2 does not open under these conditions because this would have to occur via an *equatorial* ring opening pathway. The other epoxide opens readily because it can do so by the favoured *diaxial* mechanism.
c. **(8 Marks)** Here is an interesting reaction that occurred when the researchers attempted to perform a base-catalyzed Baeyer-Villiger reaction on a highly strained ketone. Provide a mechanism to explain the outcome of this process.

\[
\text{Ph} \quad \text{H}_2\text{O}_2, \text{NaOH (aq)} \quad \text{then acidification to pH 2 during workup}
\]


Standard Baeyer-Villiger, followed by base hydrolysis of the resulting lactone to reveal a \(\beta\)-keto acid. As you learned in your introductory course, \(\beta\)-keto acids readily decarboxylate.
5. **(20 MARKS)** An organic compound \( A \) (\( C_6H_{10}O_3 \)) was treated with \( KI_3 \) (aq). The product of this reaction was then exposed to \( H_2 \) (g) (3 atm. pressure) over a \( \text{Pd/C} \) catalyst in the presence of \( \text{NaHCO}_3 \), to form a new compound \( B \) (\( C_4H_6O_3 \)). NMR spectra of compound \( A \) are shown below, and spectra for compound \( B \) are on the next page. What are the structures of these two compounds?

The formula indicates 2 degrees of unsaturation. The \( ^{13}C \) NMR shows six distinct signals, so there is no symmetry. There are three downfield signals, and one at ca. 158 ppm might be a carbonyl. The other two are definitely alkene.

The \( ^1H \) NMR shows the characteristic 3:2 tr:q pattern of an ethyl group, and the chemical shift of the quartet indicates that it is attached to O. Note the remaining \( ^1H \) signals are in a 1:1:2 m:m:m:d pattern, and the chemical shift of the multiplet signals is consistent with alkene. The doublet suggests \( \text{CH-CH}_2\text{-O} \).

These ideas are not the only possibilities, but taken all together the only consistent solution is as shown.

In addition to the purely spectroscopic approach, you are told that this compound reacts with \( KI_3 \) to form a new substance. The only thing we have seen \( KI_3 \) do in this course is react with alkenes as a source of iodonium ion. This should strongly suggest to you some kind of halolactonization process, and that compound \( A \) must contain an alkene and some carboxyl equivalent.
The formula again has 2 degrees of unsaturation, and notice that although compound A was treated with iodonium ion, compound B has no halogen. This suggests that the hydrogen treatment served to hydrogenolyse a C-I bond. There are 4 $^{13}$C signals, so again there is no internal symmetry. We again see the peak at about 158 ppm, but the alkene signals of compound A are gone. In the $^1$H NMR, the ethyl group is likewise not present, but we see a clear 3H doublet suggesting CH$_2$-CH. The remaining $^1$H signals are in a 1:1:1 ratio and lie between 4 and 5 ppm – likely all are adjacent to O. The pair of double doublets suggests a heterotopic CH$_2$-CH pattern.

Putting these together gives us CH$_3$CHCH$_2$ and with CO$_3$ left to install there is only one possibility.

The hydrogen treatment might have reduced the alkene of compound A, but then what was the purpose of the KI$_3$ treatment? Also, if a terminal alkene was reduced, it would form a CH$_3$CH$_2$ fragment, which is clearly absent. All the evidence suggests that the alkene was altered in step 1 by reaction with iodonium ion, and then the C-I bond was reduced in step 2.