A Mixed Aldol Condensation/Michael Addition Reaction


**Introduction:**

Reactions of aldehydes and ketones, particularly the aldol reaction and the Michael addition, are extremely important in both synthetic chemistry and the chemistry of living systems as they lead to the making or breaking of carbon-carbon and carbon-oxygen bonds. In this experiment, you will examine the aldol and Michael reactions between 3-pentanone, 1, and *p*-chlorobenzaldehyde, 5. There are many different ways in which these two compounds can react with themselves or each other so that one can hypothesize that many different products are possible. First, reaction of the ketone 1 with itself can yield the aldol product 2 or, if this eliminates water, the enone 3 (eq 1). Pentanone 1 could do a Michael addition to 3 to yield the C_{15} diketone 4 (eq 2). Since the benzaldehyde 5 does not have any H’s to the carbonyl, we do not need to worry about aldol reactions with itself. The mixed aldol reaction of 1 with 5 gives 6 which can eliminate water to give 7 (eq 3).

Alternatively, 6 could react with aldehyde 5 to give the double diol 8 (eq 4). Equation 5 shows the possible aldol reaction of 7 with 5 to give the enone alcohol 9 or the dienone 10 if 9 loses water. Equations 6, 7, and 8 show various Michael addition possibilities of 1 to the enones 7, 9, and 10. Formation of 13 involves the internal Michael addition of the alcohol –OH to the C=C (eq 8).

Under the conditions used in the experiment, the symmetrical ketone 10 is the product normally isolated. However, as is all too common in organic chemistry, an exception is found for the 3-pentanone/*p*-chlorobenzaldehyde combination used here. Instead of 10, the cyclic keto ether 13 is isolated. Given this information, after you have carried out its synthesis, you will be asked to determine the actual stereochemistry of product 13 by NMR spectroscopy. In the molecular modeling component of this experiment, you will show whether this stereochemistry is indeed the lowest energy structure possible for 13.
Prelaboratory Exercises:

Give the mechanism of the aldol addition/water elimination reaction of acetone and benzaldehyde. Then show the mechanism of the Michael addition of CN\textsuperscript{-} to this product.

Using R to represent the \textit{p}-chlorophenyl group, draw all possible stereochemical possibilities for keto-ether 13. Where there are enantiomeric possibilites only draw one enantiomer and say “+ other enantiomer”. This should yield 6 structures. In preparation for the molecular modeling portion, confirm this with Spartan using all the atoms and saving results on zip disk. Turn in a printout of one of the structures with your PreLab.

Cautions:

2N sodium hydroxide is very caustic. Avoid contact with skin.

Synthesis:

Fill a 400-mL about one-tenth full of water and heat to about 70 to 80°C on a hot plate. In a 125-mL Erlenmeyer flask are placed 0.86 g (10 mmol) of 3-pentanone, 50 mL of 95% ethanol, and 3.5 g of \textit{p}-chlorobenzaldehyde. After the aldehyde dissolves, 15 mL of 2 N NaOH solution is added and the reaction mixture is heated in the warm water bath for 30 min.

Isolation:

Upon cooling in ice, white crystals separate and can be collected on a Buchner funnel suing a 125-mL filter flask. Wash with a few mL of cold ethanol using a Pasteur pipet. Set aside a small amount of crude product for a mp and recrystallize the rest from ethanol. The pure product has a mp of 189-191°C. Typical yields are on the order of 30%, although higher yields can be achieved if longer reaction times are used or if the \textit{p}-chlorobenzaldehyde is freshly distilled.

Cleaning Up:

The filtrates should be concentrated by evaporation in the hood and then disposed of in the proper waste container.

Molecular Modeling:

Using Spartan, draw and minimize the structures for the six isomers you derived in the PreLab. Do a geometry optimization using an appropriate semi-empirical algorithm to determine the energies of each. Molecular modeling will involve determining the dihedral angles in the pyran ring and comparing them to those derived experimentally from a Karplus analysis of the NMR spectrum.

Use MacSpartan Pro (or PC Spartan) to draw the structures. (HINT: use “rings” in the Model Kit.) Do a molecular mechanics minimization. Next, set up a PM3 semi-empirical calculation for equilibrium geometry. This is located under the “setup” menu. Select “calculations.” Choose “equilibrium geometry” and “PM3.” Under “setup,” choose “surfaces” and add surface “density,” property “potential.” By selecting for potential, a color-coded electrostatic potential map is created for the molecule. Under “setup,” submit the task. It may take a couple of minutes for the calculations to finish. Do this once for each conformer. Make a chart like the one below to record the specified dihedral angles for each conformer.

Karplus and Equilibrium Analysis

Putting in your values for \(\theta\) use the modified Karplus equation below to calculate the theoretical coupling constants for \(H_a\) and \(H_b\) based on the calculated dihedral angles. Record these coupling constants (J values) into your chart.

\[
J = 7.76\cos^2\theta - 1.1\cos\theta + 1.4
\]

Final Report:

How do your experimental and computational results match? Is the calculated lowest energy isomer geometry the same as that of the isomer isolated? Are the dihedral angles between the methine H’s on the carbon atoms attached to the methyl and phenyl groups as calculated by Spartan comparable to the angles determined from NMR and the Karplus relationship?
<table>
<thead>
<tr>
<th>Conformer</th>
<th>Dihedral Angle</th>
<th>J/Hz</th>
<th>Width of multiplet, W/Hz</th>
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<td>HINT: draw it</td>
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