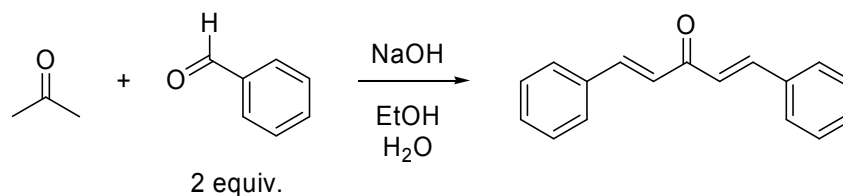


Aldol Condensation

Overall Reaction



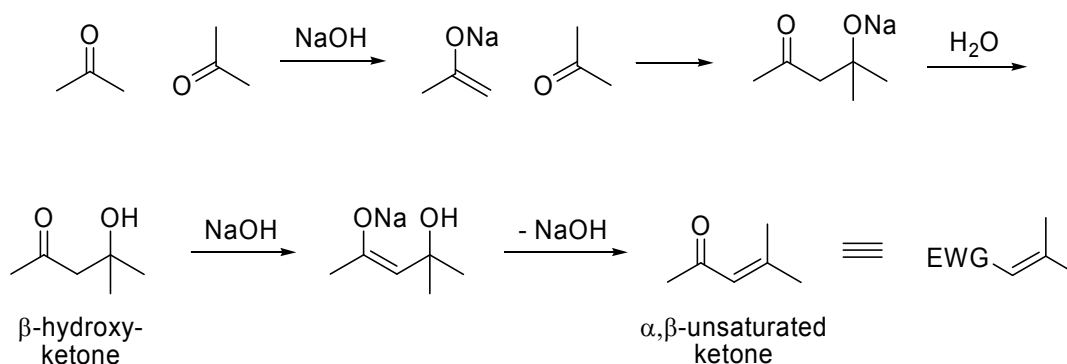
Purpose

This experiment has the following goals:

- (1) provide exposure to a classic reaction – the aldol condensation
- (2) demonstrate the utility of molecular modeling
- (3) show a simple purification method (crystallization).

Background

The aldol condensation is one of the all-time classic organic reactions. The reaction involves addition of a ketone or aldehyde enolate (nucleophile) onto another ketone or aldehyde (electrophile) to give a tetrahedral intermediate. Protonation of the alkoxide, deprotonation at the α -carbon, and elimination of the alcohol gives an α,β -unsaturated ketone (Scheme 1). Although they lie beyond the traditional definition of the “aldol condensation” proper, variations of the reaction abound. In practice, the carbonyl on the enolate serves as an electron-withdrawing group (EWG). Any strong EWG can be used in place of the ketone, and examples include esters, nitriles, and nitro groups. Once deprotonated next to the EWG, these enolate equivalents can react to give alkenes bearing EWGs. Ketones, esters, and nitriles are readily available, and a huge variety of alkenes can potentially be accessed through the aldol condensation and its variants.

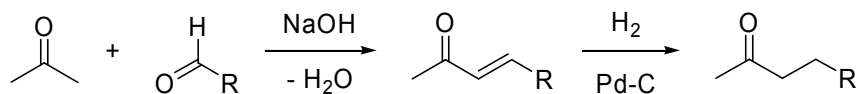


Scheme 1. The aldol condensation.

The value of aldol condensation products is often in the formation of a new alkene, one of the most flexible functional groups. Alkenes can undergo additions (H₂O, HX, hydroboration/oxidation), oxidations (epoxidation, dihydroxylation, halogenation), and reductions (H₂ and many important transition metal catalyzed processes). Because alkenes are useful, methods for preparing alkenes, like the aldol condensation, are very important.

A specific application of the aldol condensation is to alkylate a ketone. The ketone reacts with an aldehyde in the presence of base to form an α,β -unsaturated ketone. This product may be

reduced with $\text{H}_2/\text{Pd-C}$ to a new ketone with an alkyl group on the α -carbon. Other ways to alkylate ketones are known (e.g. LDA deprotonation and reaction of the resulting enolate with an alkyl halide), but the aldol route is simple to perform and typically high yielding.



Scheme 2. Overall ketone alkylation by an aldol condensation.

The aldol condensation is a reversible reaction. Energetically, the reaction does favor the products, but the ΔG° of the reaction is negative by only a few kcal/mol. ΔG° is properly determined by taking the difference between the G_f° of products and reactants (eq. 1). G_f° values are not always easy to determine with entropy being a complicating factor. Often entropy can be ignored without introducing too much error into ΔG° (eq. 2).

$$\Delta G^\circ = \sum G_f^\circ(\text{products}) - \sum G_f^\circ(\text{reactants}) \quad (1)$$

$$\Delta G^\circ \cong \sum H_f^\circ(\text{products}) - \sum H_f^\circ(\text{reactants}) \quad (2)$$

Because the aldol condensation is often not strongly favored energetically, the reaction does not have nearly the scope that is implied in most organic chemistry texts. Successful aldol condensations (i.e., aldol condensations with high yields) almost always require tweaking of the equilibrium by Le Chatlier's principle. Removal of one of the products can drive the reaction to the right and affect a complete, high-yielding reaction.

The aldol condensation has two products – water and the α,β -unsaturated ketone. Removal of water can be accomplished by adding a desiccant to absorb the water or by distilling the water out as it forms. The most common method of removing the ketone product is by precipitation. This requires the product to be a solid with low solubility in the reaction solvent. Aromatic substitution normally increases crystallinity and decreases solubility. For this reason, the most common aldol condensations have products with at least one aromatic substituent.

Without a means of removing the product, the reaction would drift aimlessly along the reaction coordinate as a mixture of starting materials, products, and intermediates. The reaction would never go to completion with two important consequences. First, the reaction yield would be low. Second, the reaction would be full of impurities and difficult to purify.

Any reaction that forms alkenes can potentially generate either the *E*- or *Z*-isomer. If the alkene is 1,2-disubstituted (as in our reaction), then ^1H NMR is an excellent method for determining the geometry of the alkene. In 1963 Karplus published a communication on the prediction of coupling constants based on the dihedral angle (ϕ) of vicinal hydrogens (Karplus *J. Am. Chem. Soc.* **1963**, 85, 2870) (eq. 3). Many variations of the original Karplus equation have been developed depending on the system being analyzed. Equation 4 is as good as any. Aside from determining the stereochemistry of an alkene, Karplus equations can be used to determine relative stereochemistry of aliphatic hydrocarbons as well (as we shall see in a later experiment).

$$J_{\text{HH}'} = A - B \cos \phi + C \cos 2\phi \quad (3)$$

$$J_{\text{HH}'} = 0.2 - 1.3 \cos \phi + 10.2 \cos^2 \phi \quad (4)$$

Experiment (modified from Fairlamb *Org. Lett.* **2004**, 6, 4435-4438)

Monday/Wednesday (week 1): Dissolve NaOH (125 mmol) into EtOH (50 mL) and H₂O (30 mL) in a 250 mL beaker with stirring. Cool the solution to 0° in an ice bath. In a 20 mL scintillation vial dissolve acetone (20 mmol) and benzaldehyde (45 mmol) in EtOH (5 mL). To the cold NaOH solution, add the aldehyde/ketone solution dropwise with a Pasteur pipet. Rinse the vial with additional EtOH (2 mL). Remove the reaction from the ice bath, and allow the reaction to stir at room temperature. After 1 h, cool the reaction to 0° and filter with a Buchner funnel (fits 5.5 cm paper). Wash the filter cake with H₂O. Spread the solid on a tared watch glass to air dry.

Friday (week 1), Monday/Wednesday (week 2): Determine your percent yield and gather the following data: melting point, ¹H NMR spectrum, ¹³C NMR spectrum, GC-MS spectrum, and *R_f* value (20% EtOAc/80% Hex).

Lab Report

Aside from the standard lab report items, your report should include the following items in the Discussion Section.

- Use the Karplus equation (eq. 4) to make a plot of *J*-value vs. dihedral angle (ϕ) and determine the stereochemistry of the alkenes in the reaction product. You will need to use expansion plots of the alkene protons to determine the coupling constants. Remember that our magnet runs at 400 MHz (400 Hz/ppm).
- Approximate the ΔG for the aldol condensation of acetone with itself (Scheme 1). You will need to model the starting materials and products with Spartan to determine the H_f for each compound. Be sure to account for all the products and starting materials by writing out the balanced equation for the reaction. Determine the ΔG by ignoring entropy and using H_f values in place of G_f . We have lots of assumptions here. First, we're ignoring entropy. Second, the energy in Spartan is *internal energy* (*U*) and not enthalpy. Enthalpy and internal energy differ by a work term (usually small). Based on the calculated ΔG , what would *K* be for this reaction? What would be the extent of reaction?
- List at least two side products that might be seen in this reaction. These should be other aldol-type products. Provide any evidence that you have for side products.