

# CFQ & PP: Carbonyl Chemistry: 1,3-Dicarbonyl Compounds

## Reading

Brown and Foote: Sections 17.9, 19.3D and 19.6

## Suggested Text Exercises

Brown and Foote: Chapter 17: 6

Chapter 19: 11 – 13, 46 - 50

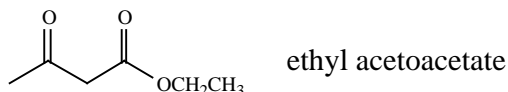
## Optional Interactive Organic Chemistry CD and Workbook

Mechanisms: Decarboxylation of a  $\beta$ -Dicarboxylic Acid (p. 23)

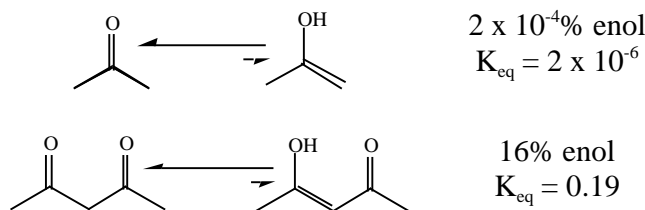
Decarboxylation of a  $\beta$ -Ketocarboxylic Acid (p. 24)

## Concept Focus Questions

1. Name and illustrate each of the three fundamental carbonyl mechanism steps using ethyl acetoacetate, a typical 1,3-dicarbonyl compound. Explain why a particular site within the molecule is preferred for this mechanism step.



2. A carbonyl compound exists in equilibrium with the corresponding enol form. In water, this equilibrium for acetone contains only  $2 \times 10^{-4}$  % enol, whereas the enol content for 2,4-pentanedione is 16%. Explain this difference.

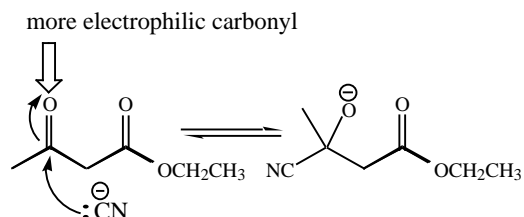


3. Condensation reactions are the most important synthetic routes to 1,3-dicarbonyl compounds. Illustrate the synthesis of ethyl acetoacetate with a Claisen condensation.
4. What is the synthetic advantage of the acetoacetic ester synthesis? Give a specific example and include a complete mechanism.
5. Briefly discuss the role of the retro-aldol reaction and keto-enol tautomerism in glycolysis. (You may skip this question if glycolysis was not covered in lecture.)

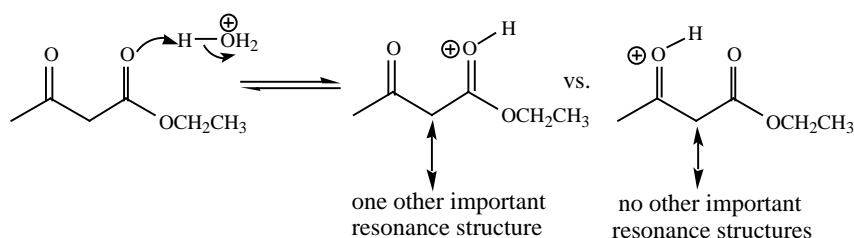
## Concept Focus Questions Solutions

1. Review the three fundamental carbonyl mechanism steps from the Fundamentals of Carbonyl Chemistry CFQ if needed.

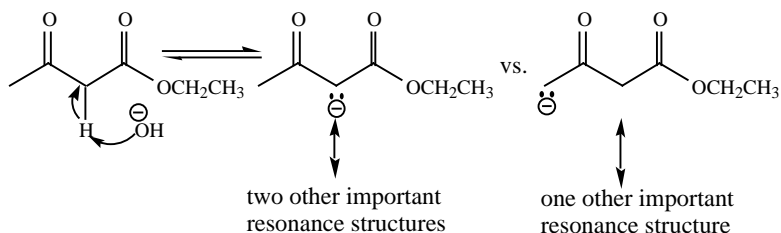
**Nucleophilic addition:** The nucleophile will add preferentially to the more electrophilic carbonyl first. A ketone carbonyl has a greater charge on the carbonyl carbon, and is thus more electrophilic. (Alternately, the ketone does not lose any resonance when it accepts a nucleophile, whereas the ester loses the minor resonance contributor.)



**Electrophilic addition (usually protonation):** An ester is more readily protonated than a ketone because the protonated ester that results has more resonance contributors than the protonated ketone.

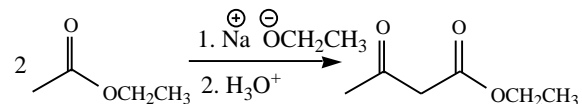


**Form an enolate:** The most acidic hydrogen is removed first. The most acidic hydrogen atom, upon removal, affords the most stable conjugate base. Deprotonation of the carbon between the two carbonyls yields an enolate with three resonance structures. Deprotonation on the other side of the ketone carbonyl leads to an enolate that has but one other important resonance form, and is thus less stable and harder to form.

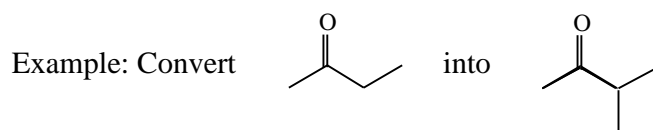


- The sum of the bond energies for the keto form of acetone is greater than the bond energy sum for the enol form. Thus the keto form is more stable. Conjugation and intramolecular hydrogen bonding are not present in the enol form of acetone, but do stabilize the enol form of 2,4-pentanedione. Because of this, the energy difference between the enol and keto forms of the dione is less than the energy difference between the enol and keto forms of acetone. The keto-enol equilibrium contains a greater percentage of enol when the energy difference between the keto and enol forms is less.

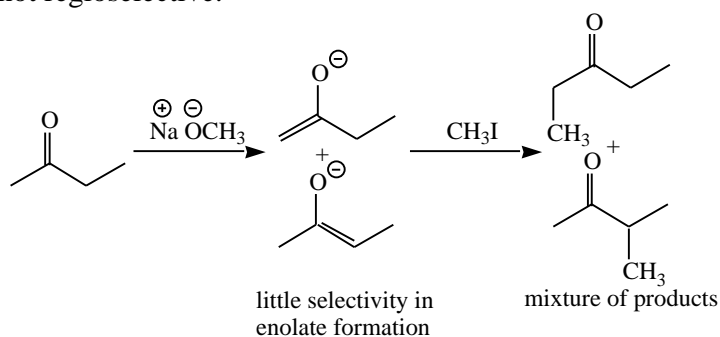
3. A condensation reaction is a reaction in which two or more molecules combine to make a larger molecule with the loss of a small neutral molecule, often water. A condensation of two esters is called the Claisen condensation. Claisen condensation between two molecules of ethyl acetate (via the ester enolate) affords ethyl acetoacetate.



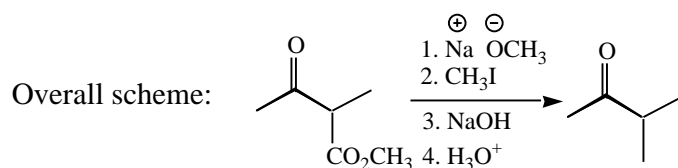
4. The acetoacetic ester synthesis is a protocol for regioselective alkylation of a ketone. That is, it provides a way to form a new carbon-carbon bond specifically on one side of a ketone carbonyl. The procedure involves a  $\beta$ -ketoester. The ester group serves to direct enolate formation (and thus carbon-carbon bond formation) exclusively to one site, due to differences in acidity. Once the new carbon-carbon bond has been formed, the ester is removed by hydrolysis to the carboxylic acid, and decarboxylation of the  $\beta$ -keto acid.



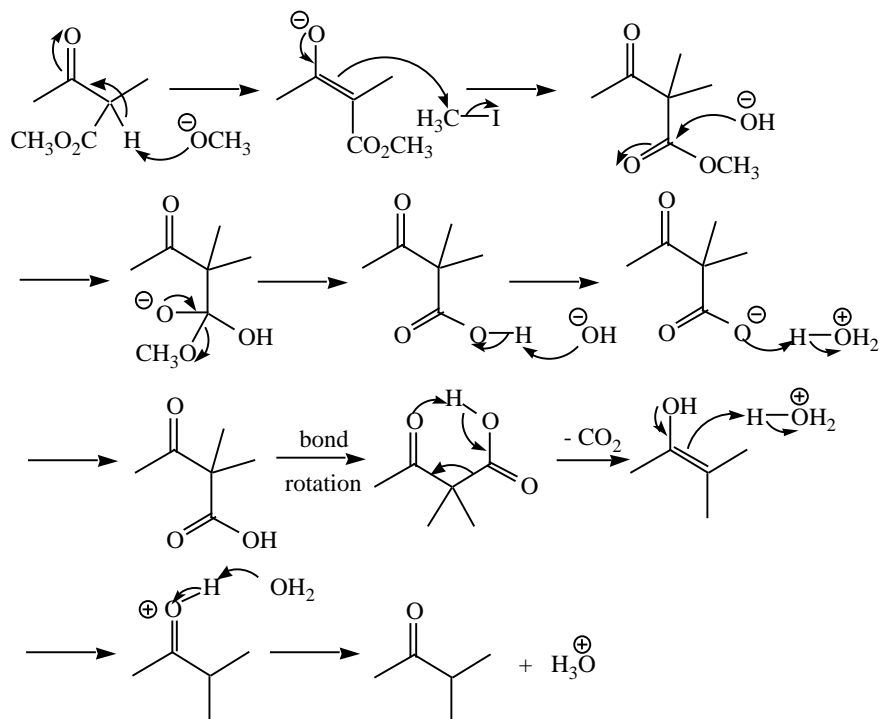
Normal ketone enolate formation and alkylation yields a mixture of products. The reaction is not regioselective.



Application of the acetoacetic ester synthesis allows regioselective formation of the desired product.



Mechanism details:

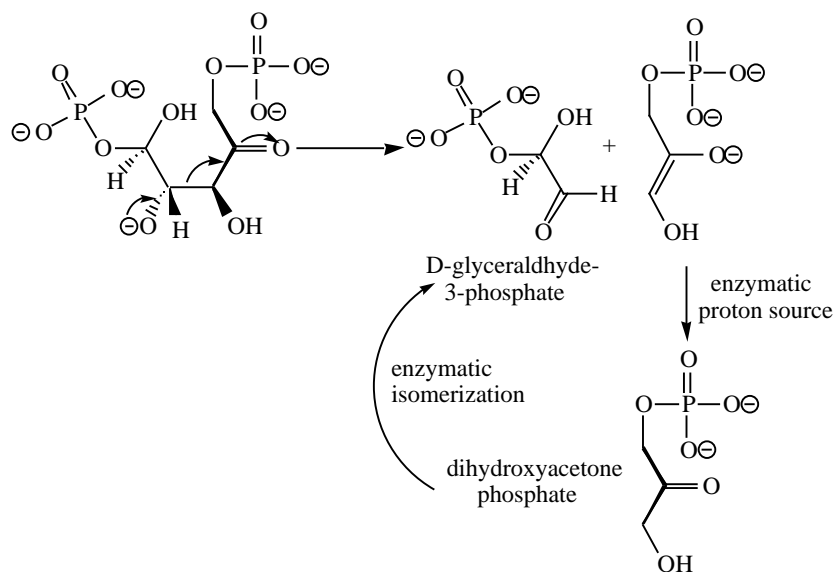


The deprotonation of the intermediate  $\beta$ -ketoacid followed by protonation with  $\text{H}_3\text{O}^+$  (second line of mechanism scheme) may appear pointless. However, hydroxide is a strong base and carboxylic acid deprotonation cannot be stopped. Thus it is necessary to protonate with acid prior to decarboxylation.

The malonic ester synthesis proceeds in a very similar manner, affording a carboxylic acid product.

The main synthetic advantages of the acetoacetic ester and malonic ester syntheses are mild reaction conditions and excellent control of position of new C-C bond.

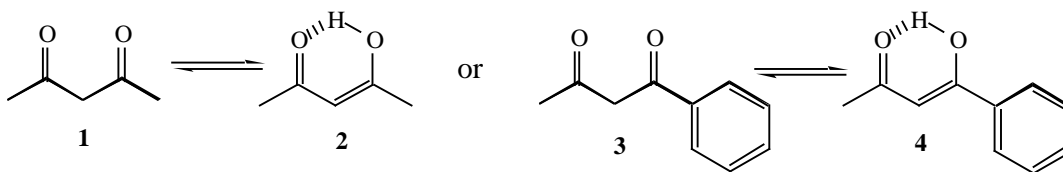
- Glycolysis is the biological process in which glucose is metabolized. The overall source of energy is the oxidation of C-H and C-C bonds to stronger C-O bonds. A retro-aldol reaction is used to cleave a carbon-carbon bond, affording one molecule each of D-glyceraldehyde-3-phosphate and dihydroxyacetone phosphate.



Further oxidation of D-glyceraldehyde-3-phosphate provides some energy. The dihydroxyacetone phosphate cannot be metabolized as is, and thus represents a waste of half the carbons in a molecule of glucose. However, dihydroxyacetone and glyceraldehyde are isomers. Isomerization of the useless dihydroxyacetone into glyceraldehyde allows this half of the glucose to be used for energy as well. On the surface, this isomerization appears to occur by a simple keto-enol tautomerization process, but in reality, involves a more complex enzymatic mechanism involving the enamine of dihydroxyacetone.

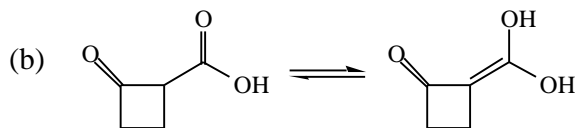
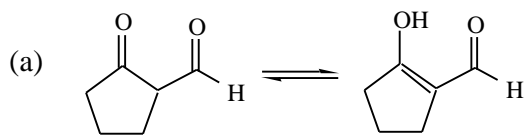
### Practice Problems

- Which of the two equilibria shown below will lie furthest to the right? Briefly explain your answer.

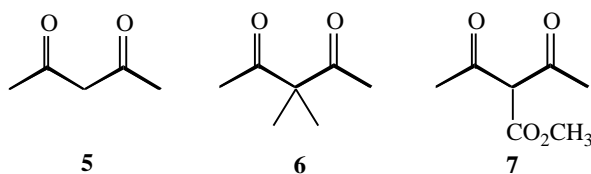


- Provide a detailed curved arrow mechanism that shows how enol **2** forms from dione **1** in aqueous acid.
- Provide a detailed curved arrow mechanism that shows how enol **4** forms from dione **3** in aqueous base.

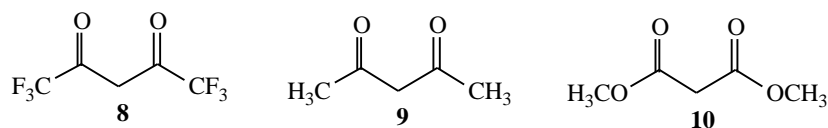
4. Determine if these equilibria favor the left or right side. Briefly explain.



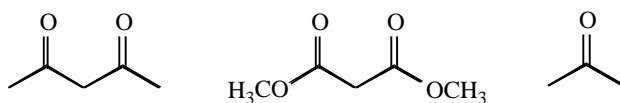
5. Rank these 1,3-dicarbonyl compounds by increasing  $pK_a$ . Briefly explain.



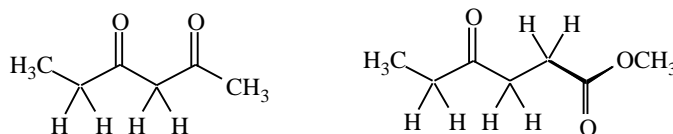
6. Rank these structures in order of increasing acidity. Provide the structure of a dicarbonyl compound which is clearly more acidic than any of these compounds.



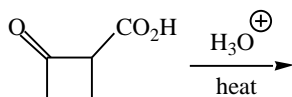
7. Assign a  $pK_a$  value of 20, 13 or 9 for each structure. Briefly explain your reasoning.



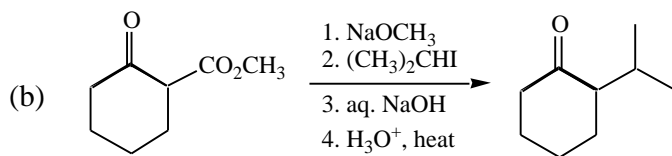
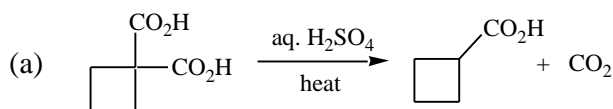
8. Select the single most acidic hydrogen in each molecule.



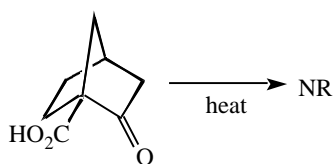
9. Write the organic product(s) and reaction mechanism.



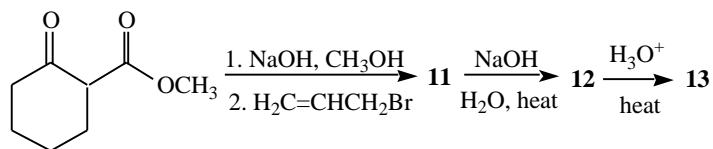
10. Provide mechanisms.



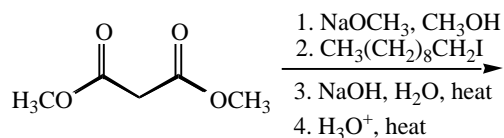
11. The  $\alpha$ -ketoacid shown below is stable to heating; it does not lose  $\text{CO}_2$ . Explain.



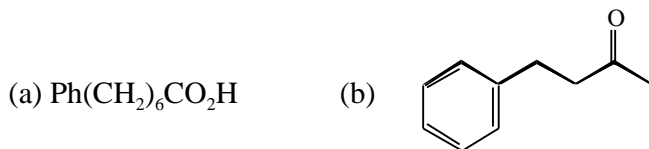
12. Provide the structures of products **11** – **13**.



13. Provide the organic product(s) of the following reaction. If more than one product is formed, indicate which is the major product. If no reaction occurs, write "NR."

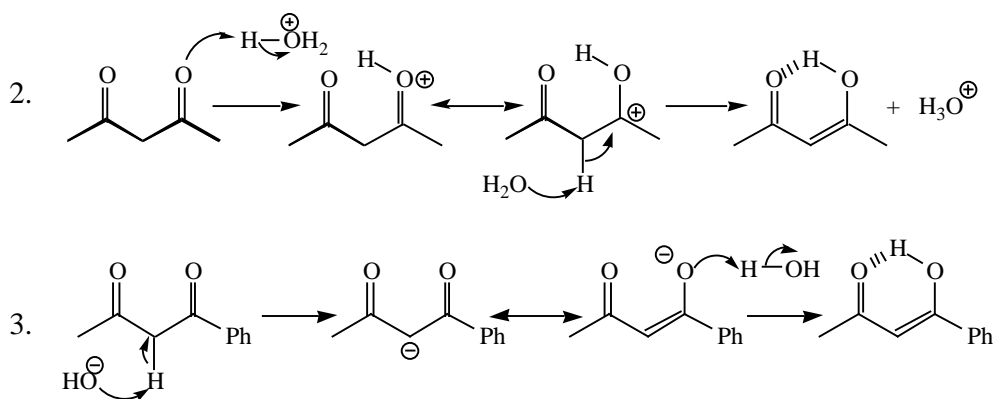


14. Show how the following compounds could be synthesized starting with dimethyl malonate or ethyl acetoacetate, and any other needed reagents.

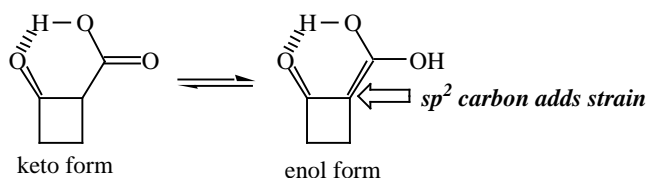


## Practice Problems Solutions

1. The formation of an enol from a 1,3-dicarbonyl compound is driven by gain of intramolecular hydrogen bonding and conjugation. Enols **2** and **4** both have one intramolecular hydrogen bond, so this will not be useful in differentiating them. Enol **2** has two conjugated functional groups (the carbonyl and the alkene), whereas enol **4** has three conjugated functional groups (carbonyl, alkene, and benzene ring). Increasing conjugation increases stability. Thus, we predict the second equilibrium to favor the enol more than the first equilibrium.

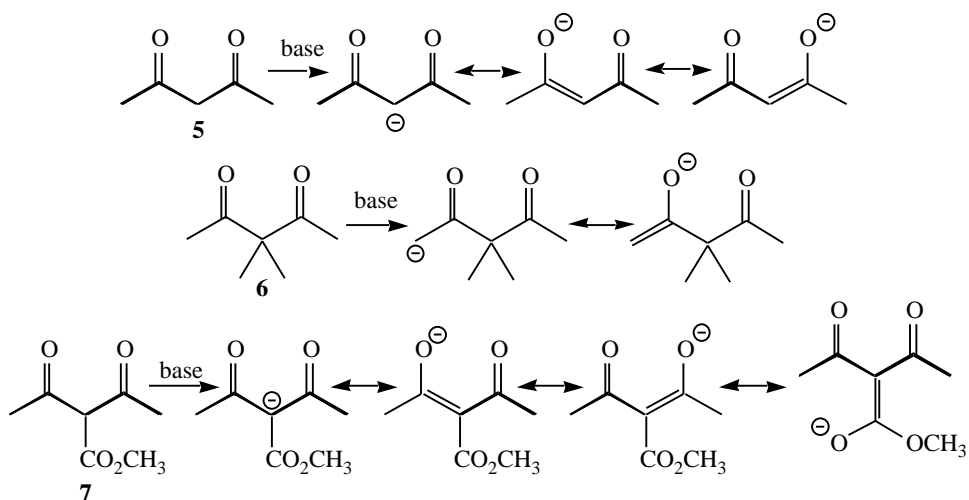


4. (a) The driving force for the formation of the enol tautomer (right side of the equilibrium) is the addition of an intramolecular hydrogen bond, and conjugation of the C=C and C=O. Neither of these stabilizing factors is present in the keto tautomer (left side of the equilibrium). Therefore the equilibrium lies to the right.



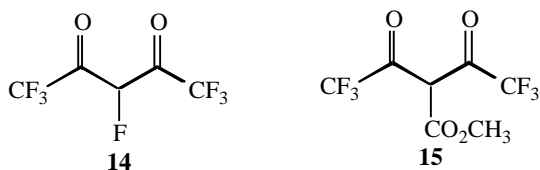
- (b) The enol form of the carboxylic acid (structure on the right) is conjugated. This is a stabilizing factor that favors the right side of the equilibrium. Both the keto and enol forms of a  $\beta$ -ketoacid can undergo intramolecular hydrogen bonding, so hydrogen bonding will not have a major effect on the position of this equilibrium. However, there is an increase in ring strain due to the addition of a second  $sp^2$  carbon in the cyclobutane ring. If this added strain is greater than the added stability due to conjugation and hydrogen bonding, the equilibrium lies to the left. (Molecular modeling calculations suggest the equilibrium lies to the right by several  $\text{kcal mol}^{-1}$ , and that the intramolecular  $=\text{O}\cdots\text{H}$  bond distance is too long (about 2.5 Å) to play a significant role. Typical H-bonding distances are 2.0 Å or less.)
5.  $\text{pK}_a$  is determined by the stability of the conjugate base. Stability of the conjugate base is determined in this case by the number of resonance contributors. More

resonance contributors result in more stability of conjugate base and thus lower  $pK_a$ . The conjugate bases have the following resonance forms:



The enolate from dione **5** has three resonance contributors, the enolate from dione **6** has two resonance contributors, and the enolate from dione (actually trione) **7** has four resonance contributors. Using the reasoning stated above, the  $pK_a$  order is: **7** (lowest  $pK_a$ ) < **5** < **6**.

6. The conjugate bases of all three diones will have the same number of resonance contributors, so resonance is not expected to be a significant difference. The  $CF_3$  group is electron withdrawing. This stabilizes the conjugate base of **8**, making this dione more acidic. Methyl is a mild electron-donating group, causing a small destabilization of the conjugate base of **9**. Methoxy is a strong electron-donating group, causing a greater destabilization of the conjugate base of **10**. Thus, the order of acidity is: (least acidic) **10** < **9** < **8** (most acidic). Any 1,3-dicarbonyl compound with a conjugate base which is more stable than the most stable conjugate base from part (a) will be more acidic. For example, adding more electron-withdrawing groups (compound **14**) or more resonance contributors for the conjugate base (compound **15**) can achieve this.

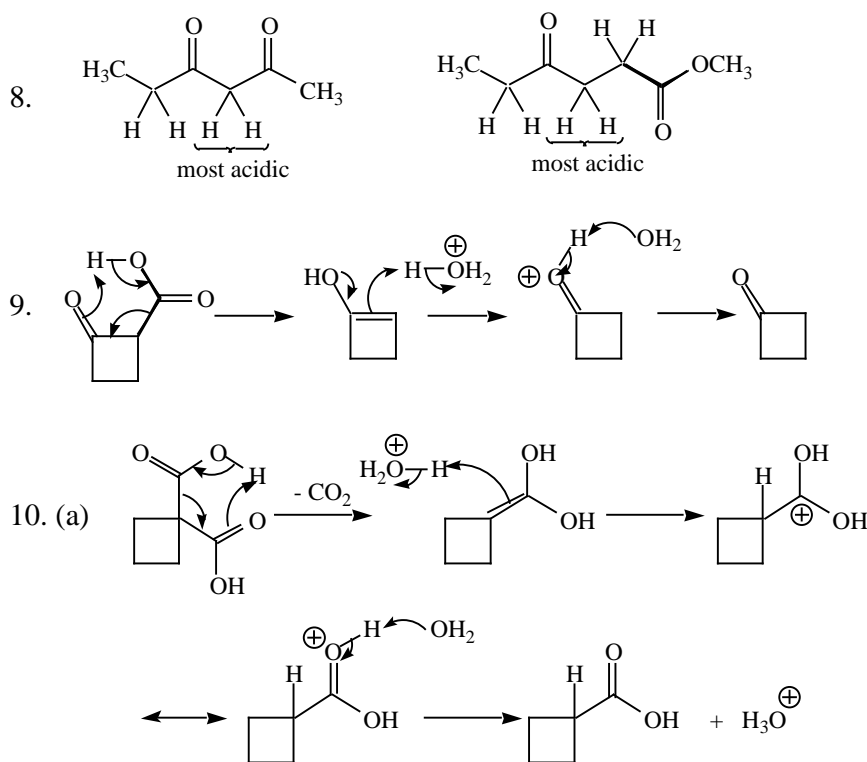


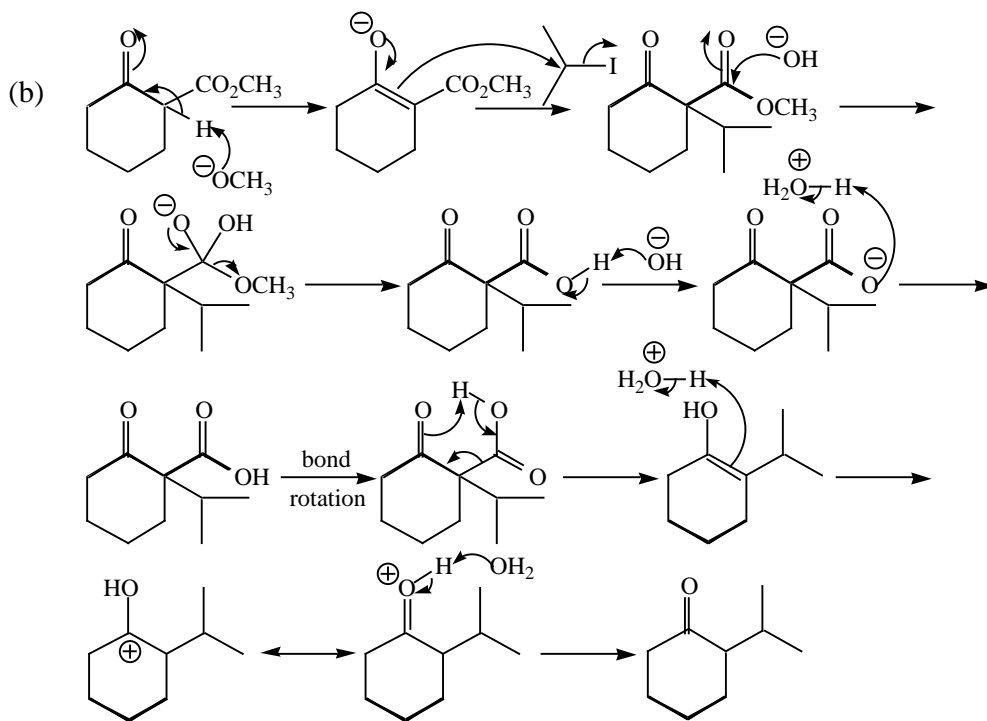
7. A convenient way to consider  $pK_a$  is by examining the stability of the conjugate bases. The more stable the conjugate base, the more readily the acid will lose a proton to form it, and thus acid will be more acidic. Factors that stabilize the negative charge of the conjugate base (more resonance contributors, electron-withdrawing groups) will lower  $pK_a$ .

Comparing 2,4-pentanedione (first structure) with acetone (third structure): Removal of hydrogen atoms from the CH<sub>2</sub> between the two carbonyl groups yields an enolate with three resonance contributors. Deprotonation of acetone affords an enolate with two resonance forms. The enolate derived from 2,4-pentanedione is more stable than the enolate derived from acetone, so the pK<sub>a</sub> of 2,4-pentanedione is less than the pK<sub>a</sub> of acetone.

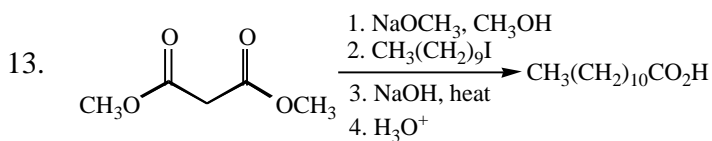
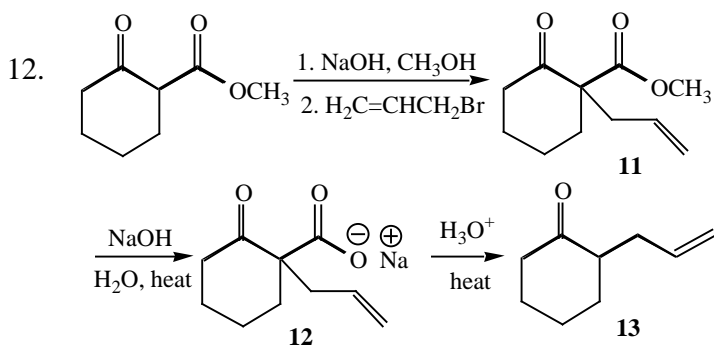
Comparing 2,4-pentanedione with dimethyl malonate (center structure): Both afford enolates with three resonance contributors. The CH<sub>3</sub> groups of 2,4-pentanedione are weak electron donors, so they will reduce the conjugate base stability by a small amount. The methoxy groups of dimethyl malonate are strong electron donors by resonance, so they reduce the stability of the conjugate base by a larger amount.

Therefore the enolate of 2,4-pentanedione is more stable than the enolate of dimethyl malonate, so the pK<sub>a</sub> of 2,4-pentanedione is lower than the pK<sub>a</sub> of dimethyl malonate. The pK<sub>a</sub> assignments are: Acetone pK<sub>a</sub> 20, dimethyl malonate pK<sub>a</sub> 13, and 2,4-pentanedione pK<sub>a</sub> 9.

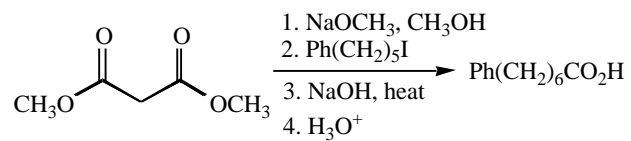




11. Decarboxylation of a  $\beta$ -ketoacid proceeds through an enol. In this case, the enol intermediate shown below has a very strained alkene (make a model). This strain raises the energy of activation leading to the enol enough so that it cannot easily form.



14. (a) Synthesis of a carboxylic acid can be achieved via the malonic ester synthesis.



(b) Synthesis of a ketone can be achieved via the acetoacetic ester synthesis.

