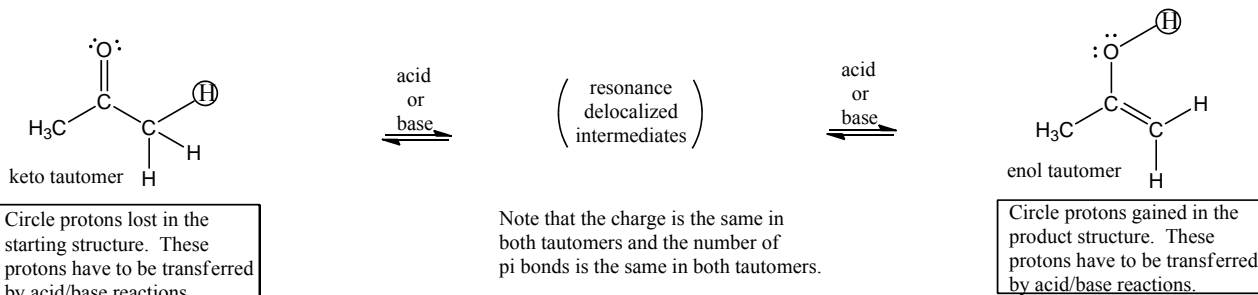
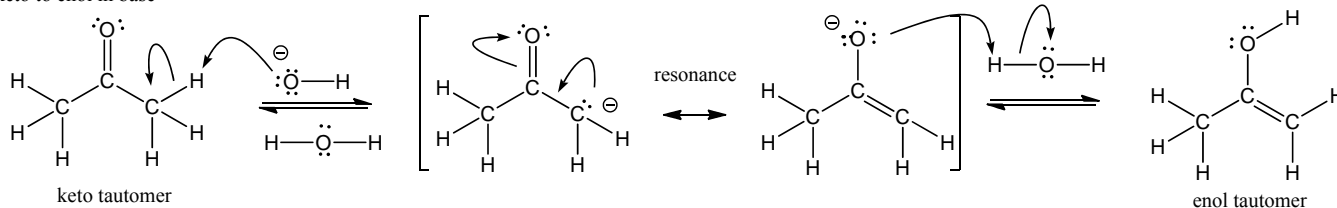


Tautomers are isomers that differ by the location of a proton and a pi bond. These are reactions that can occur in acid or in base. We will use aqueous acid or aqueous base to keep our mechanisms simple, but other acids and bases can cause these changes too. This process can serve as your training tool to learn how to push electron in organic reactions.

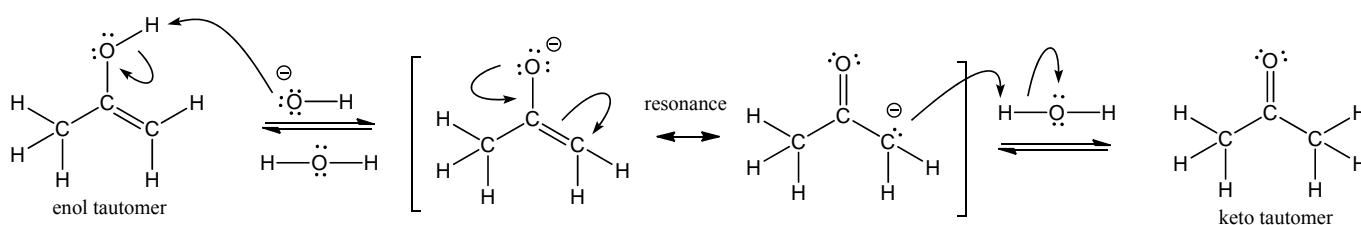
**A simple keto/enol tautomer system** -interconversion of tautomers is possible in one tautomer change in either acid or base. This represents **four** reactions!



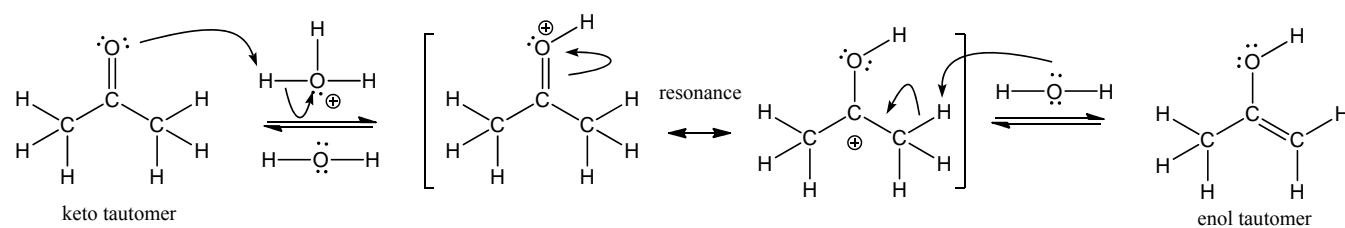
keto to enol in base



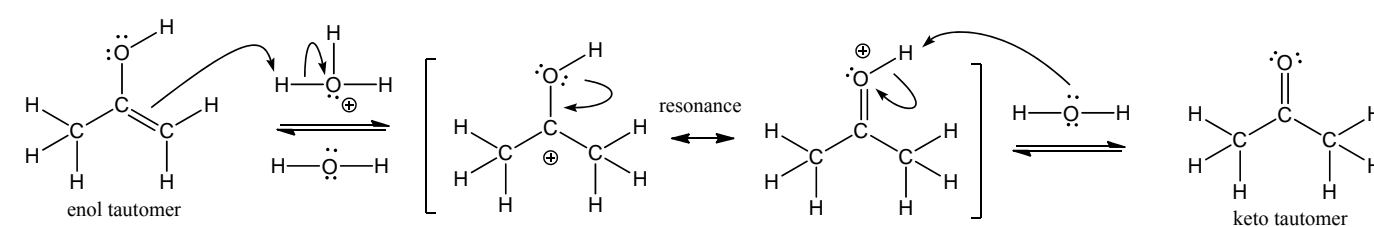
enol to keto in base



keto to enol in acid



enol to keto in acid



**Steps in base for each tautomeric change:**

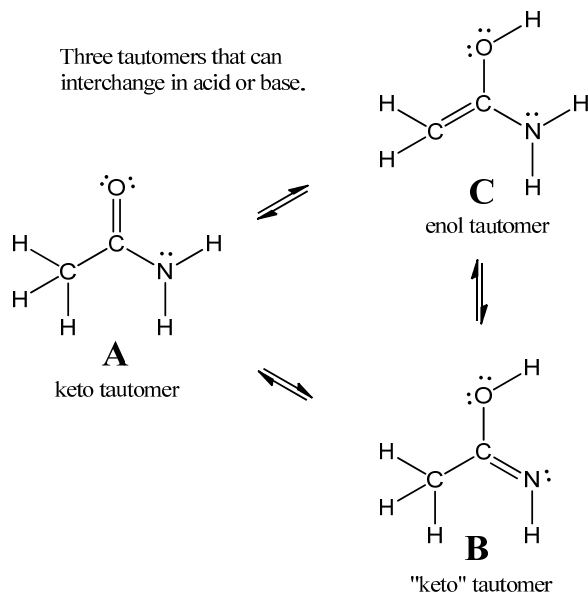
1. proton transfer (proton off, best base =  $\text{HO}^-$ )
2. resonance intermediates
3. proton transfer (proton on, best acid =  $\text{H}_2\text{O}$ )

Remember: each tautomer has the same overall formal charge and the same total number of pi bonds.

**Steps in acid for each tautomeric change:**

1. proton transfer (proton on, best acid =  $\text{H}_3\text{O}^+$ )
2. resonance intermediates
3. proton transfer (proton off, best base =  $\text{H}_2\text{O}$ )

A slightly different tautomeric system.



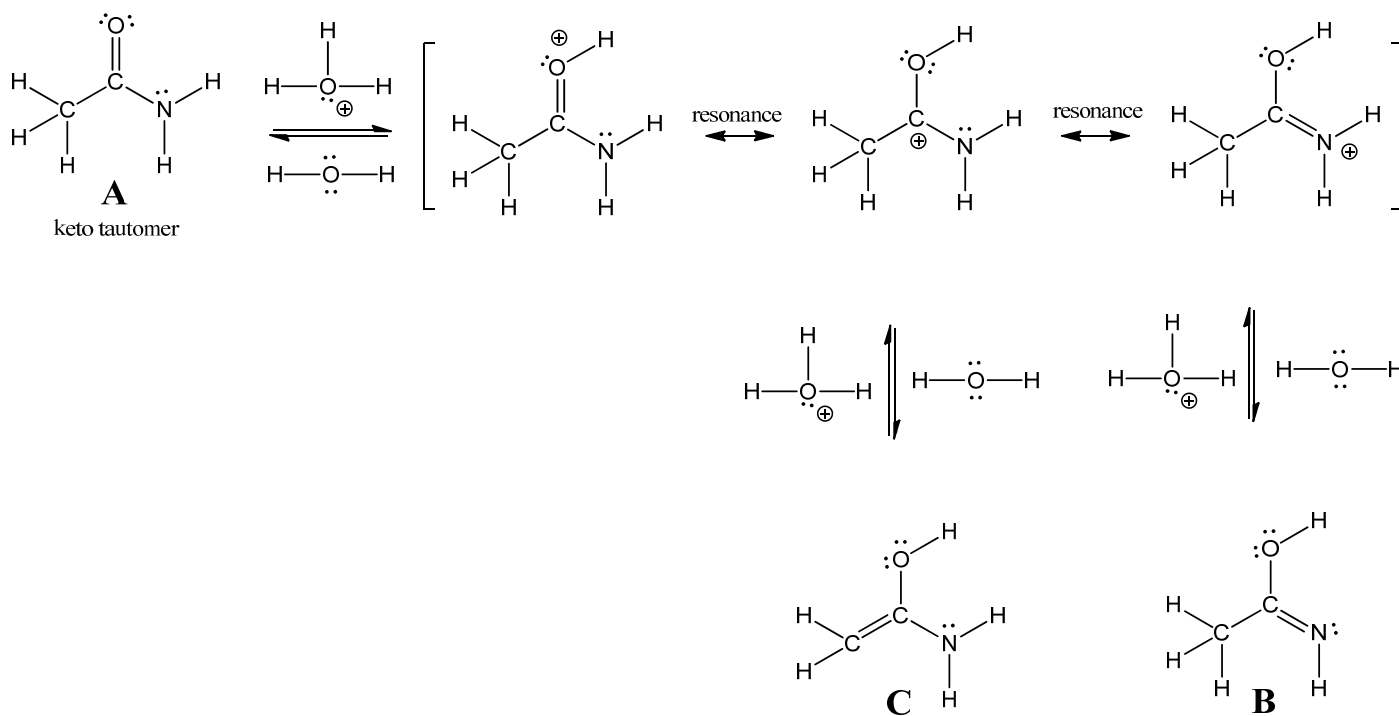
### Tautomers in acid

Circle protons lost and gained.  
These protons have to be transferred by acid/base reactions.

**Steps in acid for each tautomeric change:**

1. proton transfer (proton on, best acid =  $\text{H}_3\text{O}^+$ )
2. resonance intermediates
3. proton transfer (proton off, best base =  $\text{H}_2\text{O}$ )

Note that the charge is the same in both tautomers and the number of pi bonds is the same in both tautomers.



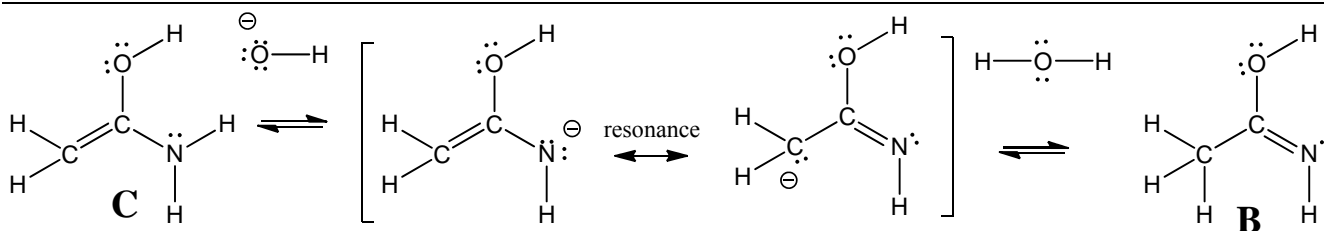
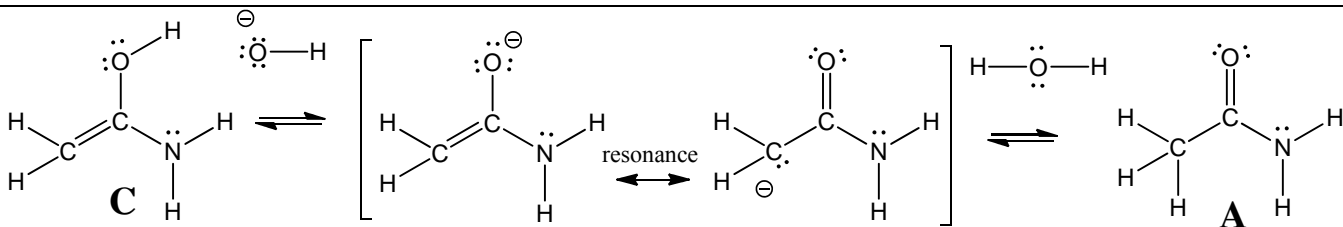
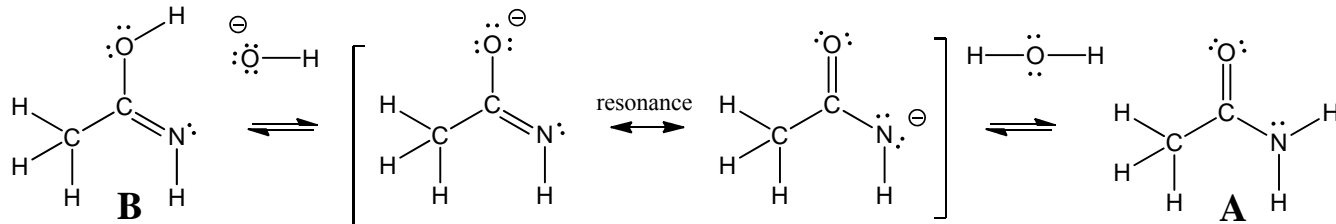
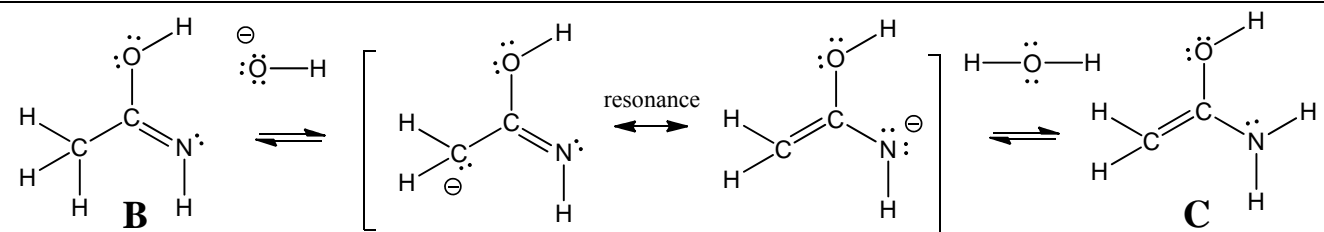
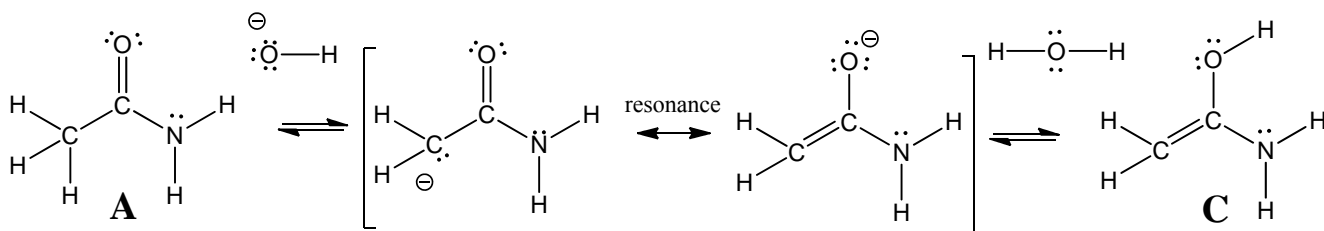
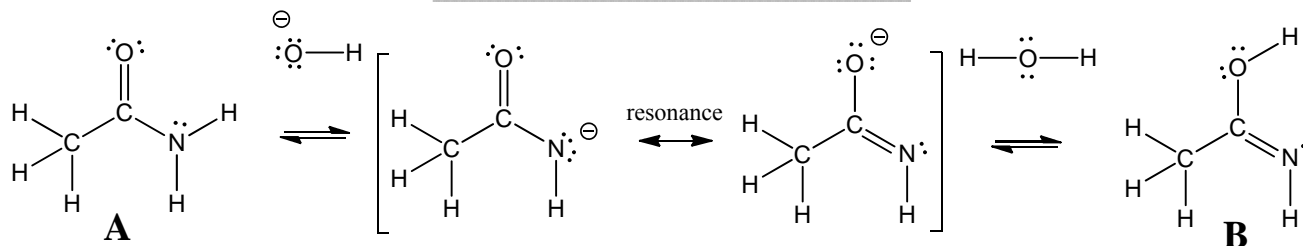
## Tautomers in base

Circle protons lost and gained.  
These protons have to be transferred by acid/base reactions.

**Steps in base for each tautomeric change:**

1. proton transfer (proton off, best base =  $\text{HO}^-$ )
2. resonance intermediates
3. proton transfer (proton on, best acid =  $\text{H}_2\text{O}$ )

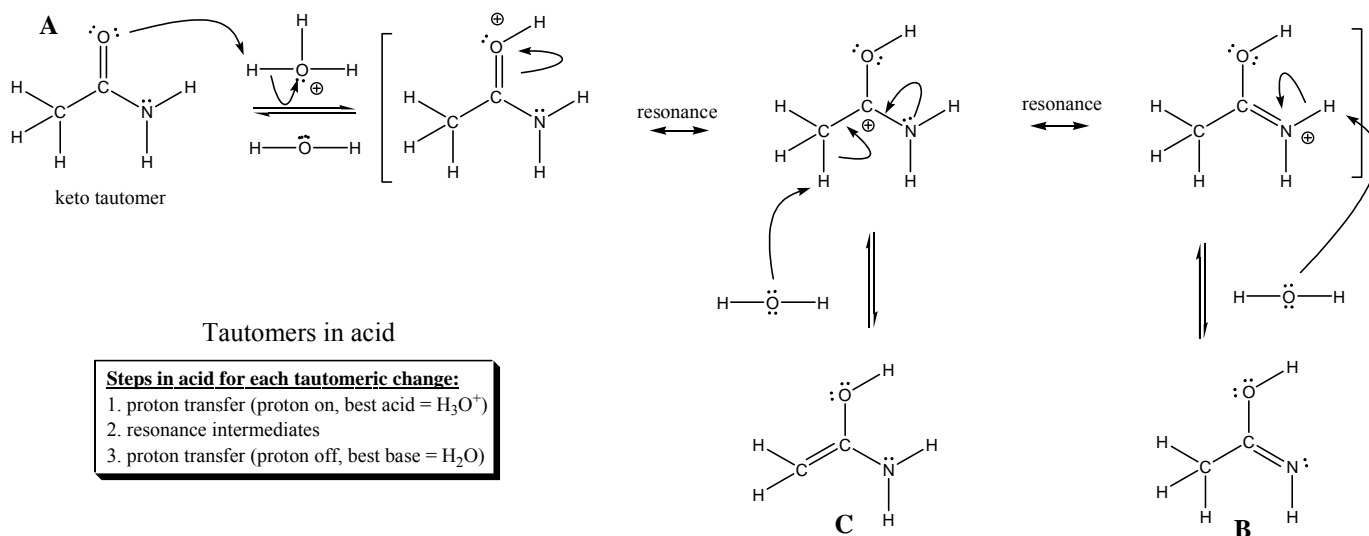
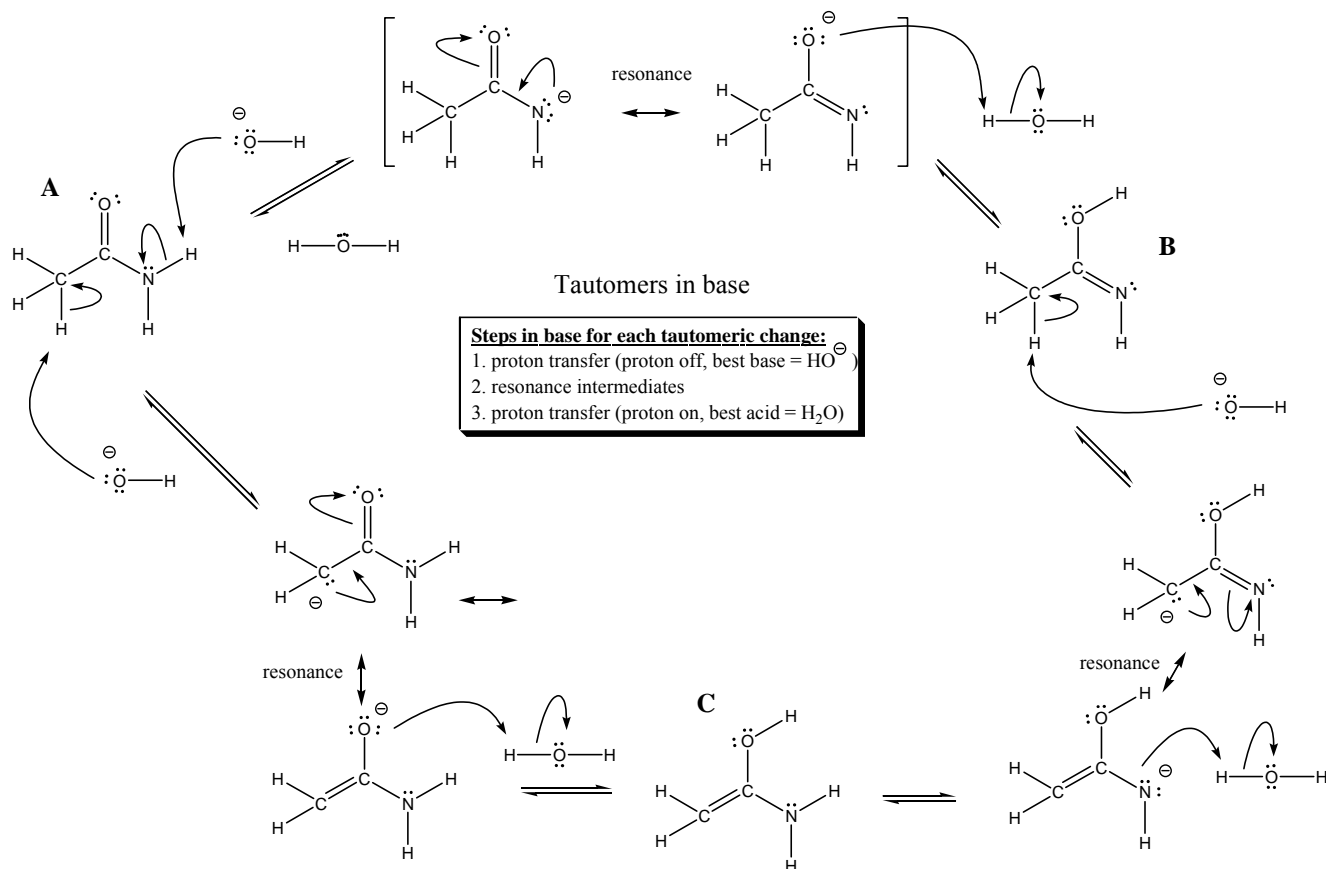
Note that the charge is the same in both tautomers and the number of pi bonds is the same in both tautomers.



Circle protons lost in the starting structure. These protons have to be transferred by acid/base reactions.

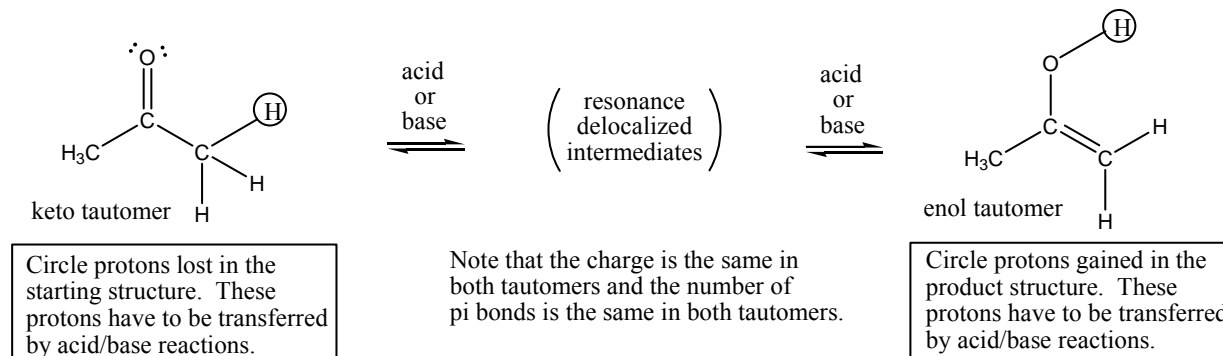
Note that the charge is the same in both tautomers and the number of pi bonds is the same in both tautomers.

Circle protons gained in the product structure. These protons have to be transferred by acid/base reactions.



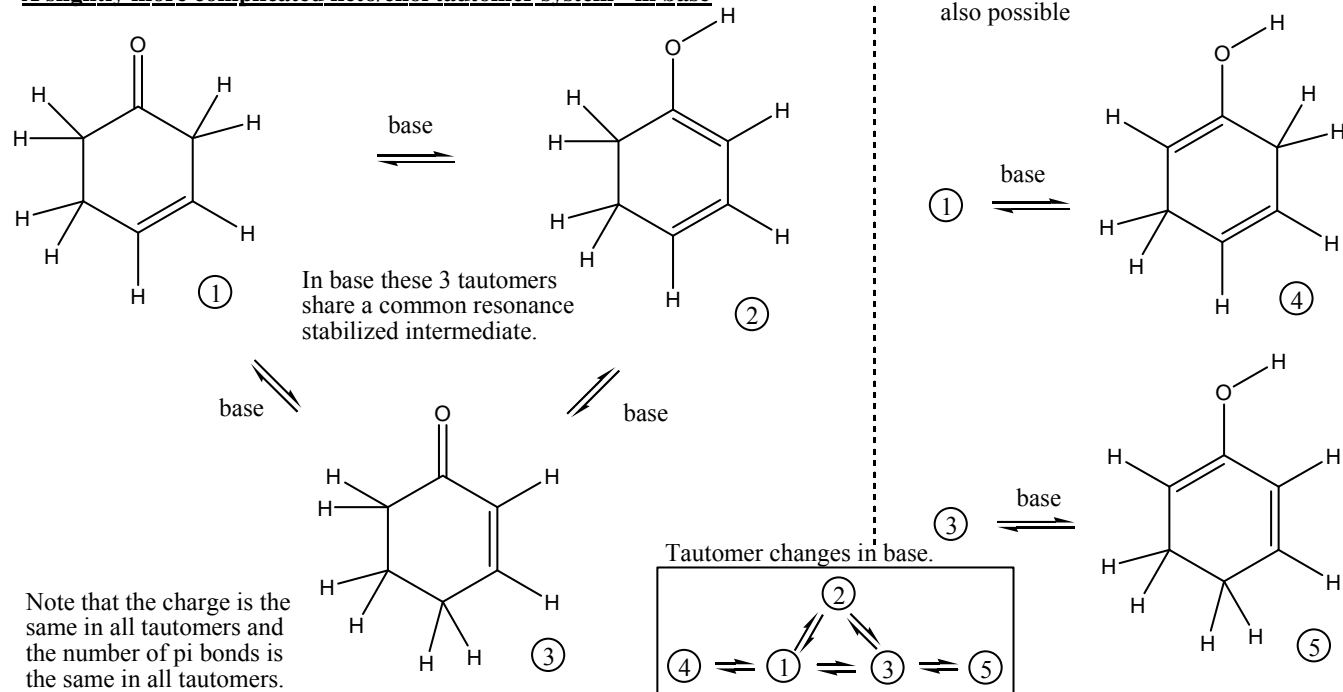
Tautomers are isomers that differ by the location of a proton and a pi bond. To be official tautomers, a heteroatom or atoms (different than carbon, often oxygen or nitrogen or both) is part of the system. In the simplest case, there are at two isomers in equilibrium with one another (there may be many, many more tautomers possible in more complex systems). The tautomers are interchangeable by 1. proton transfer, 2. resonance intermediates and 3. proton transfer. The “keto” isomer, has a heteroatom in a pi bond and in the “enol” tautomer has two carbons forming a pi bond. This simple pattern can occur in an infinite number of systems, from very simple to very complex. A possible approach to figuring out what to do in keto/enol tautomer problems is shown below. Slightly more complex tautomer relationships are shown below the simple example. They are mainly more complicated because there are more than two tautomers and interchanges may require one or more simple tautomer interconversions. Also with more than one pi bond in conjugation, resonance can extend over a longer distance.

### A simple keto/enol tautomer system

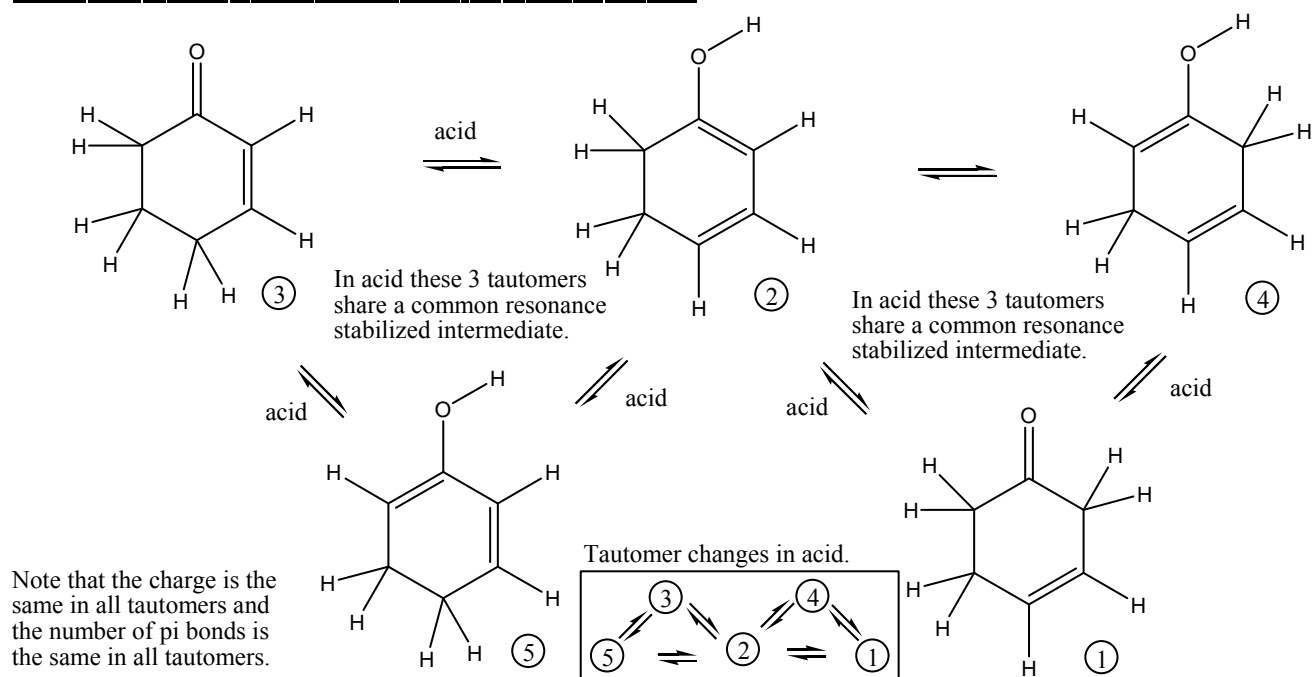


Interconversion of tautomers is possible in one tautomer change in either acid or base.

### A slightly more complicated keto/enol tautomer system - in base



The “single conversion” tautomer interconversions that are shown above are possible because of shared resonance intermediates.

**A slightly more complicated keto/enol tautomer system - in acid**

The “single conversion” tautomer interconversions that are shown above are possible because of shared resonance intermediates.

There are actually 40 tautomer problems in all the possible combinations ( $5 \times 4 \times 2 = 40$ ). The total number of tautomer changes required to change any tautomer into any other tautomer are shown below for base (on the left) and acid (on the right). The number of tautomer changes in parentheses was worked out in my head, not on paper, so there may be some wrong estimates (please let me know if you find errors).

Number of tautomer changes to transform one tautomer into another in base.

①	$\rightleftharpoons$	②	③	④	⑤
		(1x)	(1x)	(1x)	(2x)
②	$\rightleftharpoons$	①	③	④	⑤
		(1x)	(1x)	(2x)	(2x)
③	$\rightleftharpoons$	①	②	④	⑤
		(1x)	(1x)	(2x)	(1x)
④	$\rightleftharpoons$	①	②	③	⑤
		(1x)	(2x)	(2x)	(3x)
⑤	$\rightleftharpoons$	①	②	③	④
		(2x)	(2x)	(1x)	(3x)

Number of tautomer changes to transform one tautomer into another in acid.

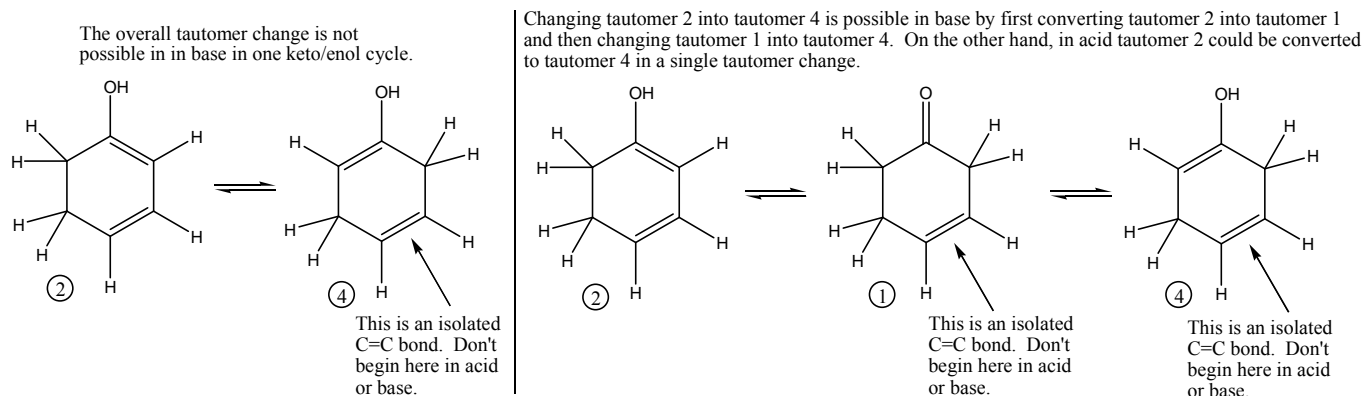
①	$\rightleftharpoons$	②	③	④	⑤
		(1x)	(2x)	(1x)	(1x)
②	$\rightleftharpoons$	①	③	④	⑤
		(1x)	(1x)	(1x)	(1x)
③	$\rightleftharpoons$	①	②	④	⑤
		(2x)	(1x)	(2x)	(1x)
④	$\rightleftharpoons$	①	②	③	⑤
		(1x)	(1x)	(2x)	(2x)
⑤	$\rightleftharpoons$	①	②	③	④
		(2x)	(1x)	(1x)	(2x)

Possible Approach to Solving Tautomer Problems

1. Circle the protons lost (in the starting tautomer) and the protons gained (in the product tautomer). Circled protons have to be moved, either taken off (with the best base available) or put on (with the best acid available). There is always resonance delocalization in the intermediate. Circling the protons that change is always a good idea, but may not show every tautomer change, because sometimes an early tautomer sequence is reversed later and becomes invisible in the overall tautomer process.

Best acid in  $\text{H}_3\text{O}^+/\text{H}_2\text{O}$  is  $\text{H}_3\text{O}^+$ , and the best base in  $\text{H}_3\text{O}^+/\text{H}_2\text{O}$  is  $\text{H}_2\text{O}$   
 Best base in  $\text{H}_2\text{O}/\text{HO}^-$  is  $\text{HO}^-$  and the best acid in  $\text{H}_2\text{O}/\text{HO}^-$  is  $\text{H}_2\text{O}$

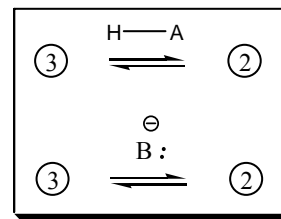
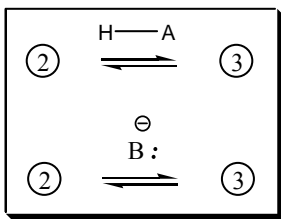
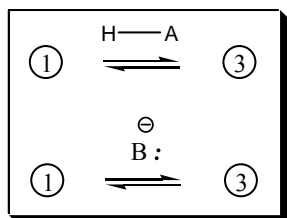
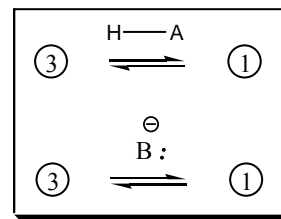
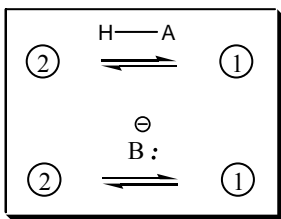
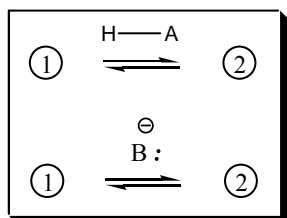
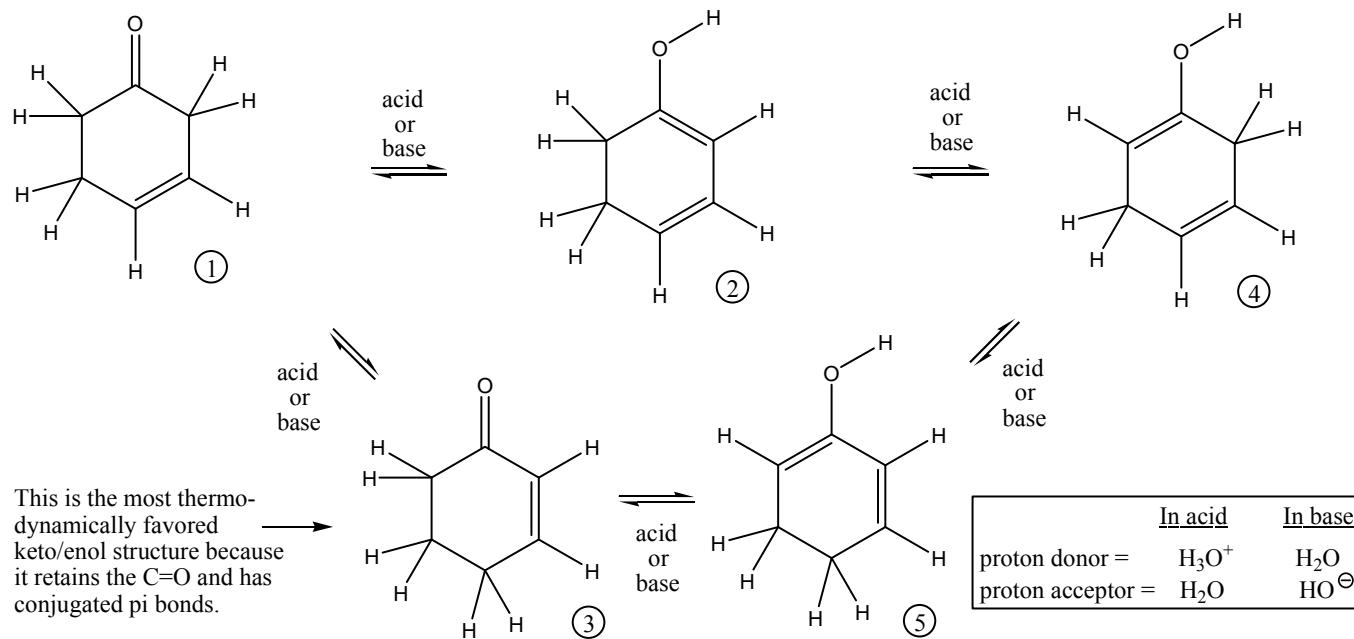
2. Always work from a "keto" part ( $\text{CH}-\text{C}=\text{O}$  or  $\text{CH}-\text{C}=\text{N}-$ ) or "enol" part ( $\text{C}=\text{C}-\text{OH}$  or  $\text{C}=\text{C}-\text{NH}-$ ) of the molecule. Do not use isolated pi bonds ( $\text{C}=\text{C}$ ) to initiate change in the structure. With an allowed change, an isolated pi bond may become conjugated with a "keto" or "enol" part of another tautomer, and then can be used to invoke further changes. Any keto or enol part will be the better base or the better acid, because it will form a resonance stabilized intermediate with the oxygen (or nitrogen, or...) greatly assisting in the resonance structures.



3. If in acid, use the strongest acid ( $\text{H}_3\text{O}^+$  in our examples) to put on a "gained" proton first and take off a "lost" proton second, with a weak base (usually the solvent =  $\text{H}_2\text{O}$  in our examples).
4. If in base, use the strongest base ( $\text{HO}^-$  in our examples) to take off a "lost" proton first and put on a "gained" proton second with a weak acid (usually the solvent =  $\text{H}_2\text{O}$  in our examples).
5. In all tautomer mechanisms there will be resonance structures in the intermediate formed. The intermediate structure will show the way to all other reasonable tautomers from that intermediate. You may have to repeat the tautomer process once, twice, etc. until you accomplish an overall indicated transformation. Counting the number of protons lost or the number of protons gained will give you an indication of how many times you may have repeat the tautomerization process. This may not always match however because sometimes a tautomer sequence is reversed and hidden from the overall change indicated (See rule 2.). Finally, there is **always** the same number of pi bonds in each tautomer and same overall formal charge.

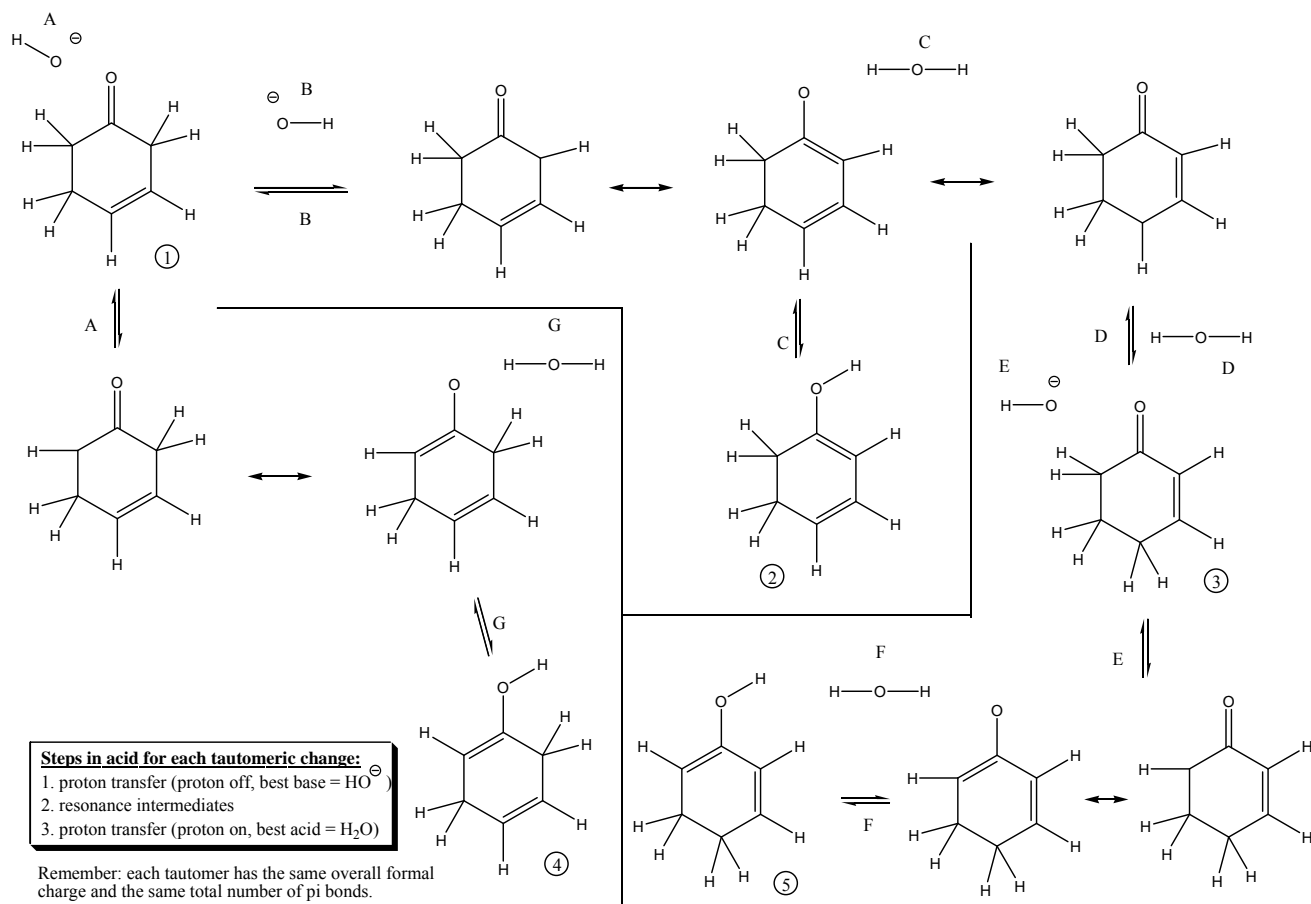
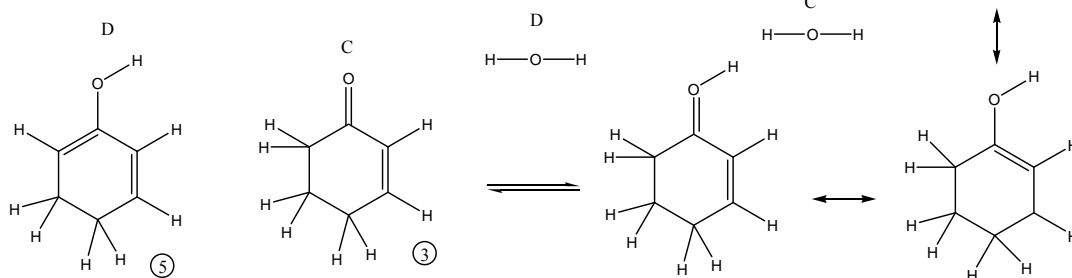
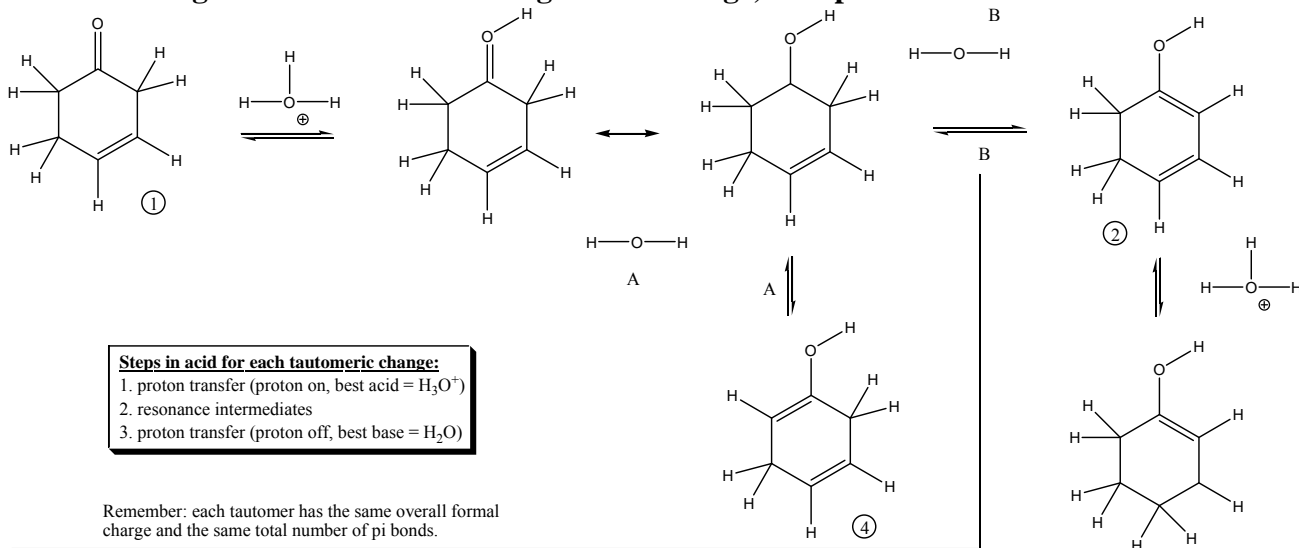
## Acids and Bases and Tautomerism

The following transformations can be done in base or acid. Intermediate resonance structures lead to stable structures.

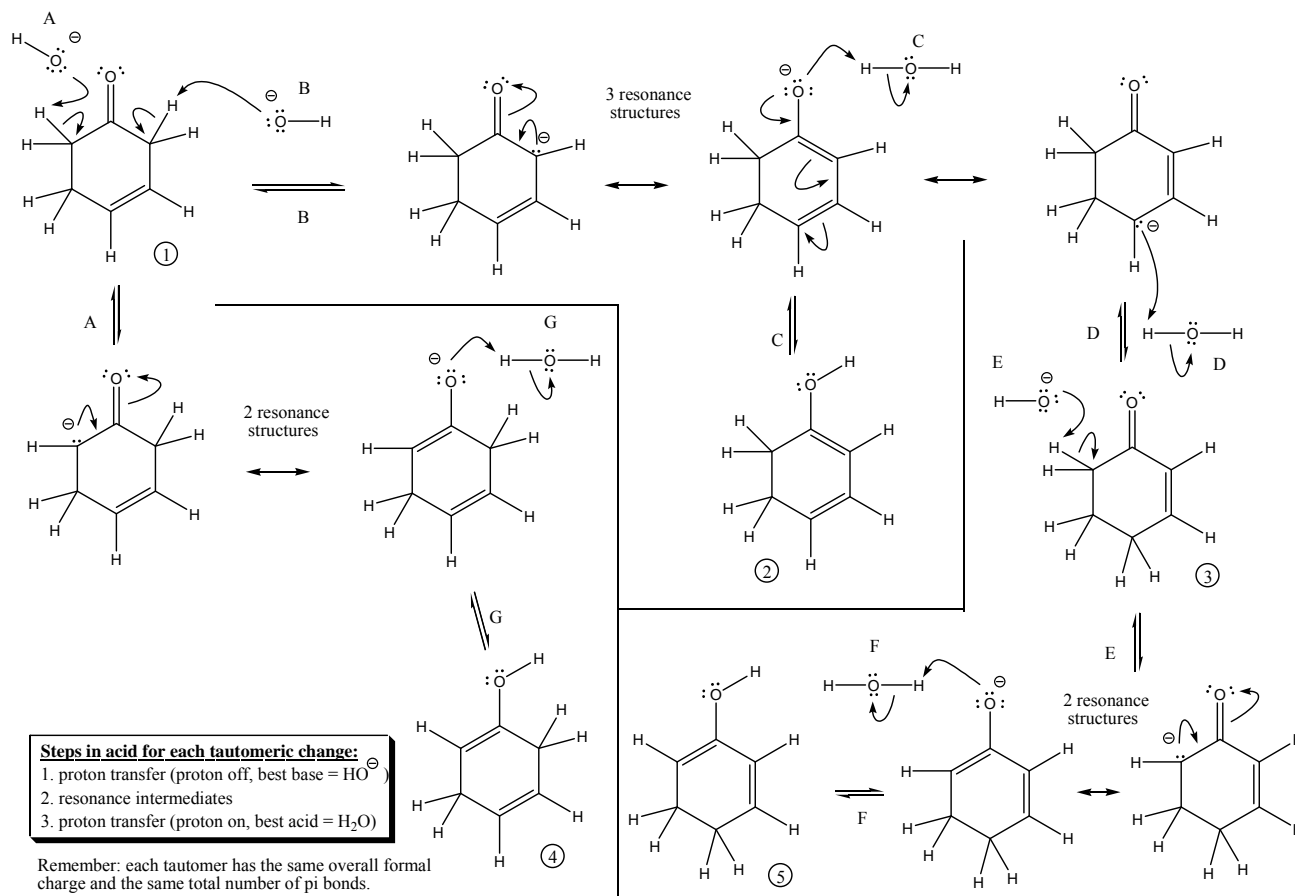
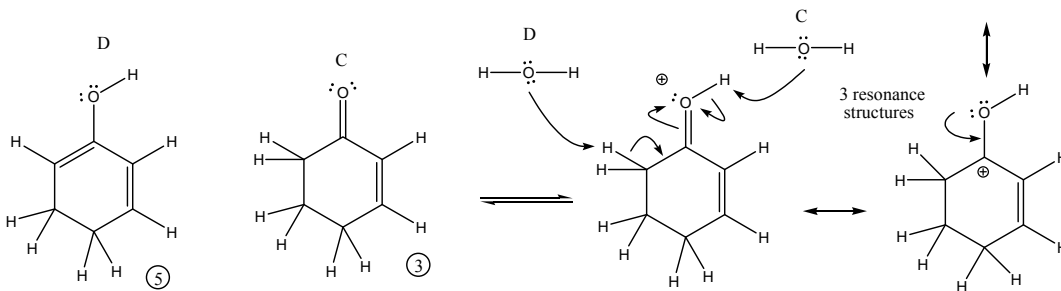
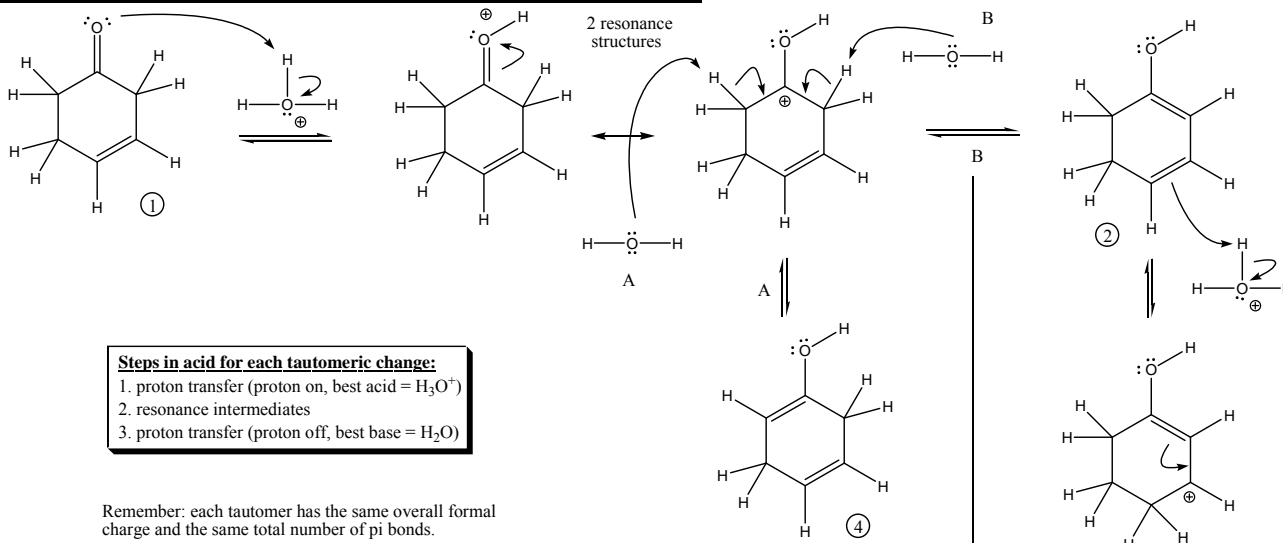


See page 2 for the number of tautomer changes needed to accomplish these transformations in acid or base.



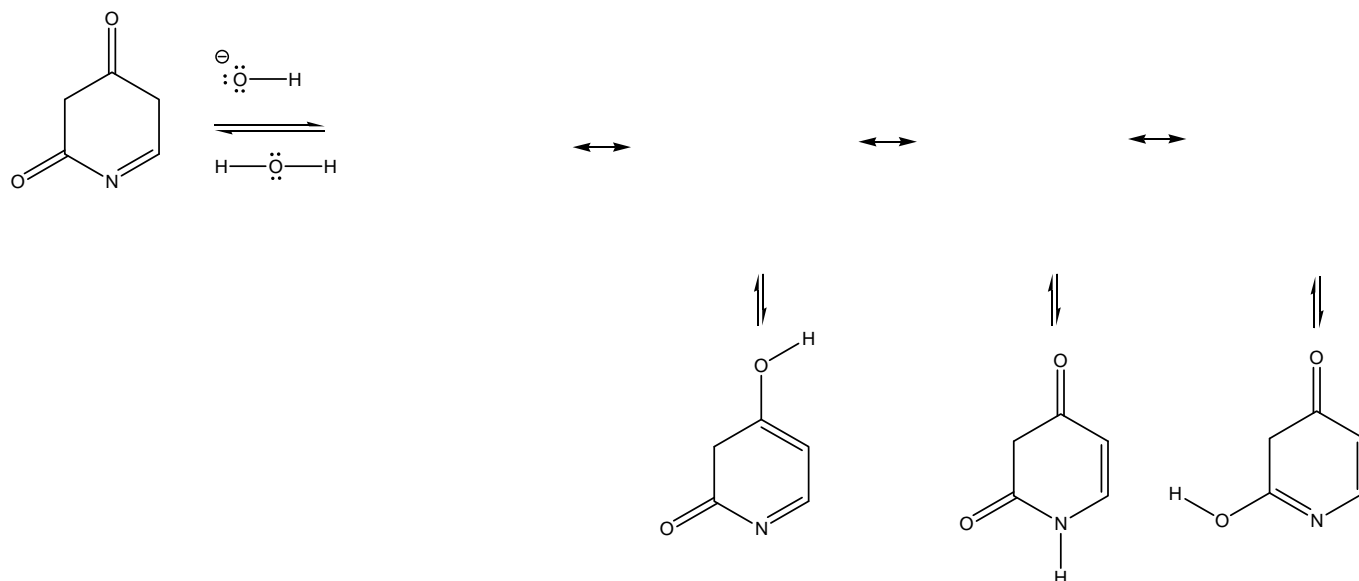
**Arrow-Pushing Practice – Fill in missing formal charge, lone pairs and curved arrows.**

**Possible Key for arrow-pushing in "tautomer" problems**

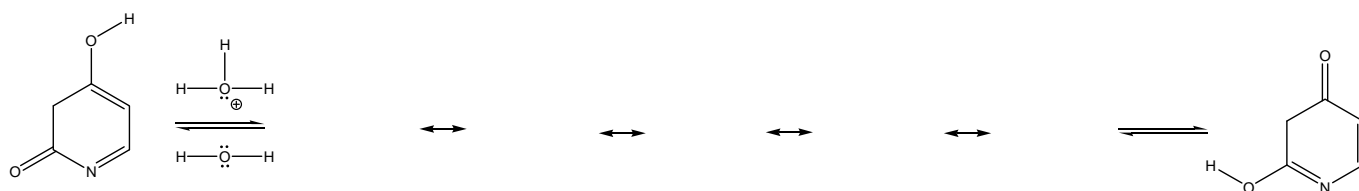


## Tautomer Problems

1. a. Rationalize the formation of the 4 tautomeric forms indicated from a single intermediate generated from the given starting structure (show an arrow pushing mechanism). (Hint: Where was a proton lost?)

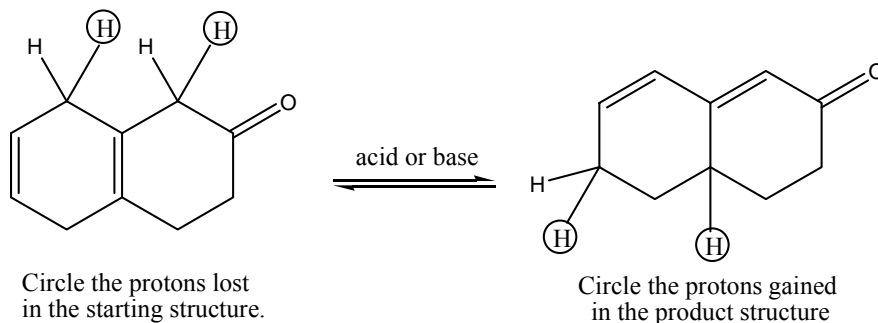


- b. Provide a mechanism for the indicated transformation. (Hint: Where does the new proton appear?)



Remember all of your tautomers must have the same total formal charge and same number of pi bonds.

Another example of keto/enol tautomer problems.

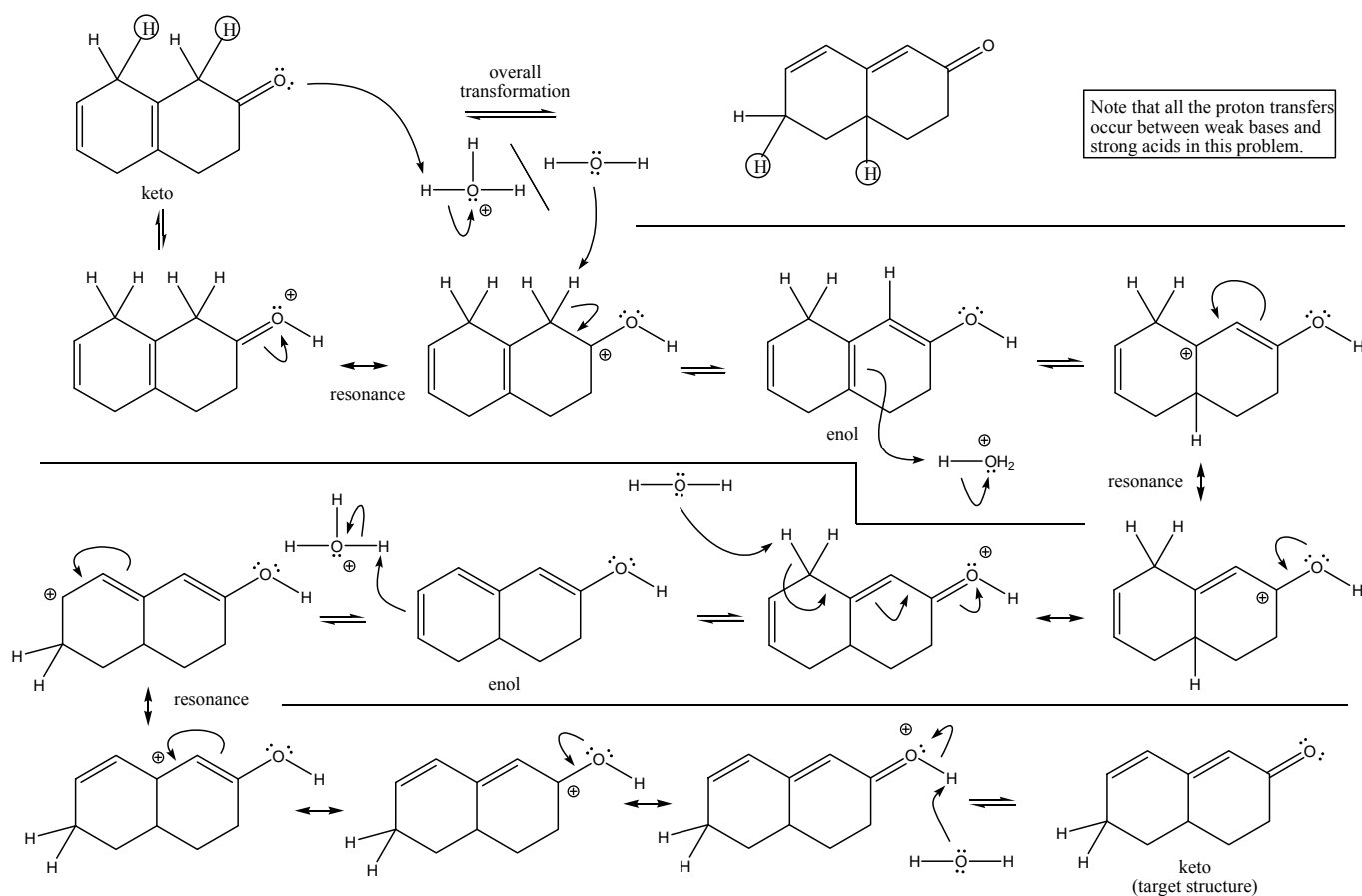


1. The circled protons have to be moved, either taken off (with the best base available) or put on (with the best acid available).

Best acid in  $\text{H}_3\text{O}^+/\text{H}_2\text{O}$  is  $\text{H}_3\text{O}^+$ , best base in  $\text{H}_3\text{O}^+/\text{H}_2\text{O}$  is  $\text{H}_2\text{O}$   
 best base in  $\text{H}_2\text{O}/\text{HO}^-$  is  $\text{HO}^-$  and the best acid in  $\text{H}_2\text{O}/\text{HO}^-$  is  $\text{H}_2\text{O}$

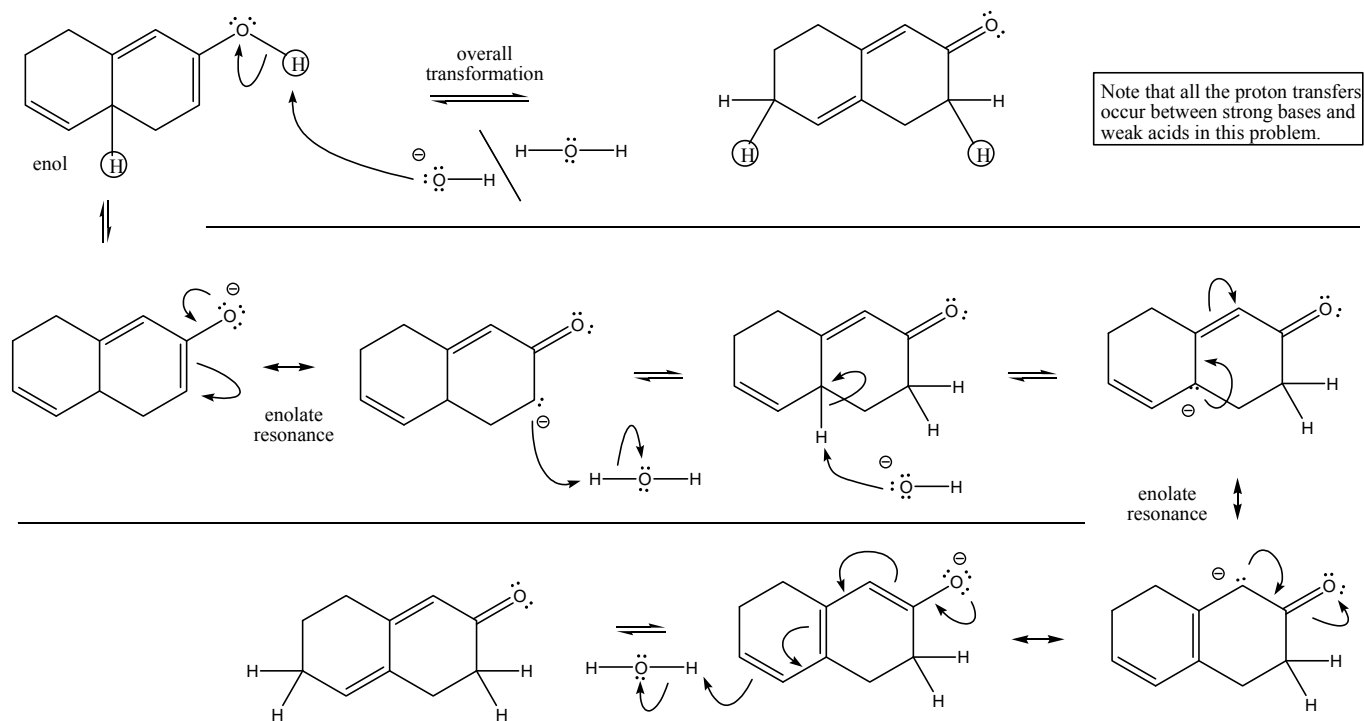
2. Always work from a "keto" or "enol" part of the molecule. Do not use isolated pi bonds to change the structure. The keto or enol part will be the better base or the better acid, because it will form a very good resonance stabilized intermediate with the oxygen (or nitrogen, or...) assisting in the resonance structures.
3. If in acid, use the strongest acid to put on a "gained" proton first (in our course =  $\text{H}_3\text{O}^+$ ) and take off a "lost" proton second, usually by a weak base (solvent =  $\text{H}_2\text{O}$ ).
4. If in base, use the strongest base to take off a "lost" proton first (in our course =  $\text{HO}^-$ ) and put on a "gained" proton second usually by a weak acid (solvent =  $\text{H}_2\text{O}$ ).
5. In all mechanisms there will be resonance structures in the intermediate formed. The intermediate structure will show the way to all reasonable tautomers of that intermediate. You may have to repeat the process once, twice, etc. until you accomplish the overall indicated transformation. Counting the number of protons lost or the number of protons gained will give you an indication of how many times you may have repeat the tautomerization process. This may not always match however because sometimes a tautomer sequence is reversed and hidden from the overall change indicated (See rule 2.). Finally, there is **always** the same number of pi bonds in each tautomer and same overall formal charge.

Example 1 (in strong acid): In acid a proton goes on first, then a different proton comes off. In this example, there is no enol, only a keto, so begin there and make it into an enol (do not use the isolated C=C pi bonds). In this example it is difficult to see this because the proton added to the oxygen will be lost later, at the end, and will not show up in the overall transformation. Rule 2 requires that we begin at a keto or an enol, so this is our only option. In the second step we remove the proton that allows conjugation between the middle, isolated  $\pi$  bond and the newly formed enol. Once conjugated, the middle, formerly isolated double bond can be protonated (look for the circled proton in the product) forming a new cationic intermediate having resonance structures, including the oxygen with full octets. This then allows you to take off the second lost protons to form a different extended enol. This new enol can gain a proton at the other "gained" position and then the "invisible" proton transfer occurs when a proton is taken off the oxygen. Try to think these steps through on your own after studying the problem.



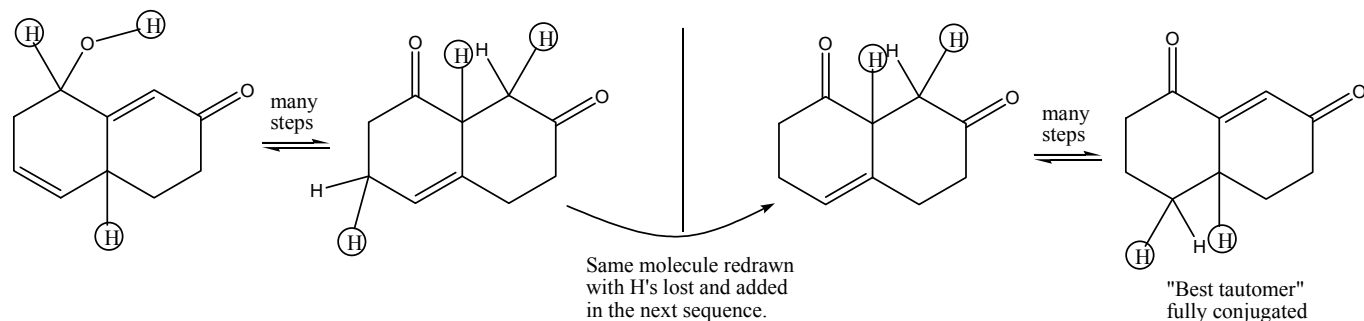
**Redo this problem using a base solution.**

Example 2 (in strong base): Begin at the enol portion and remove one of the lost protons (on oxygen) and generate an enolate using the best base,  $\text{HO}^-$ . Draw the other resonance form and reprotonate at the carbanion site using the weak acid (water). Pull off a proton from the other "lost" position, which is now tied into the keto structure (negative charged pushed to oxygen). This will form a resonance delocalized extended enolate. There are several "negative" sites that could be protonated. You need to protonate the site that the problem tells you picked up a new proton. That generates the final structure. Try this same transformation in acid, or do it in reverse. The possibilities are almost endless.



**Redo this problem using an acid solution.**

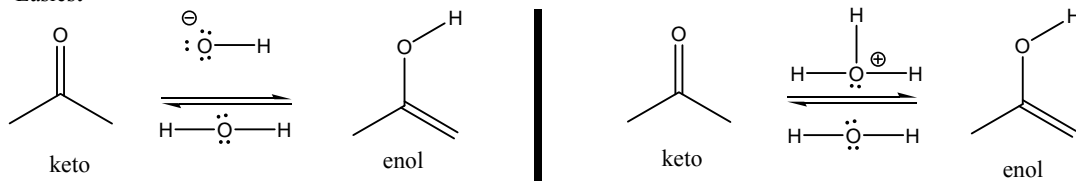
Additional problems: Try to approach each tautomer problem in some systematic manner similar to the above (in acid and/or base). An extra oxygen (or nitrogen) makes things a little more complicated. Note, there are always the same number of pi bonds and the same overall charge in each tautomer.



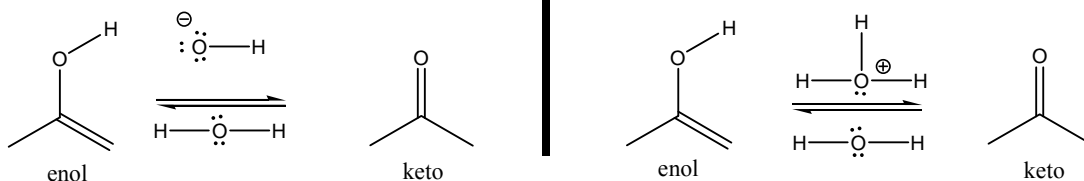
**More Examples of Tautomer Problems**

A progression from easier to harder. Work each tautomer equilibrium forward and backwards, in acid and in base (4 problems).

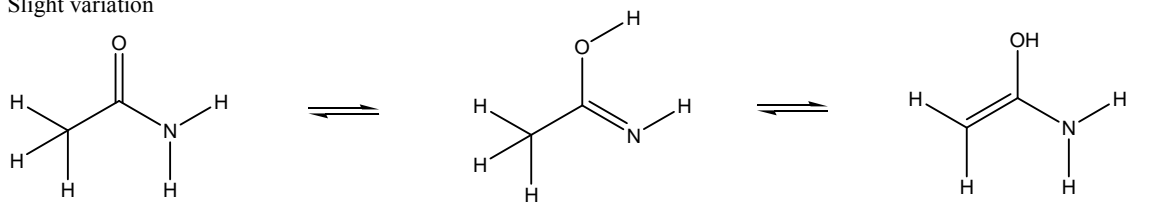
Easiest

**Tautomer sequence**

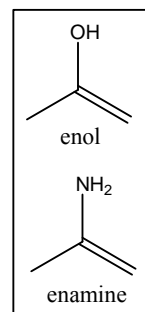
1. proton transfer
2. resonance
3. proton transfer

**In Acid:  $\text{H}_3\text{O}^+/\text{H}_2\text{O}$** acid =  $\text{H}_3\text{O}^+$   
base =  $\text{H}_2\text{O}$ **In Base:  $\text{H}_2\text{O}/\text{HO}^-$** acid =  $\text{H}_2\text{O}$   
base =  $\text{HO}^-$ 

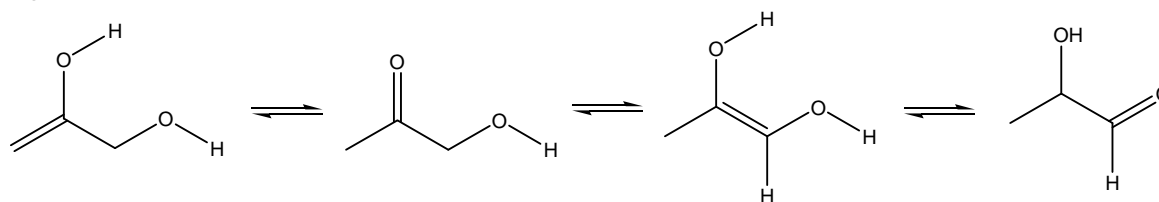
Slight variation

**Tautomer electron pair donor**

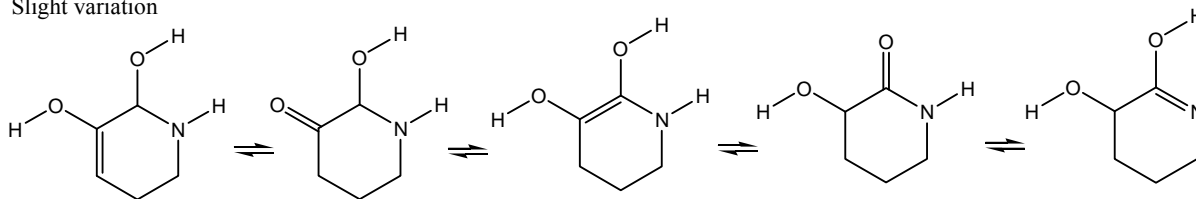
- a. lone pair of  $\text{C}=\text{O}$  or  $\text{C}=\text{N}$
- b.  $\text{C}=\text{C}$  pi electrons of enol or enamine



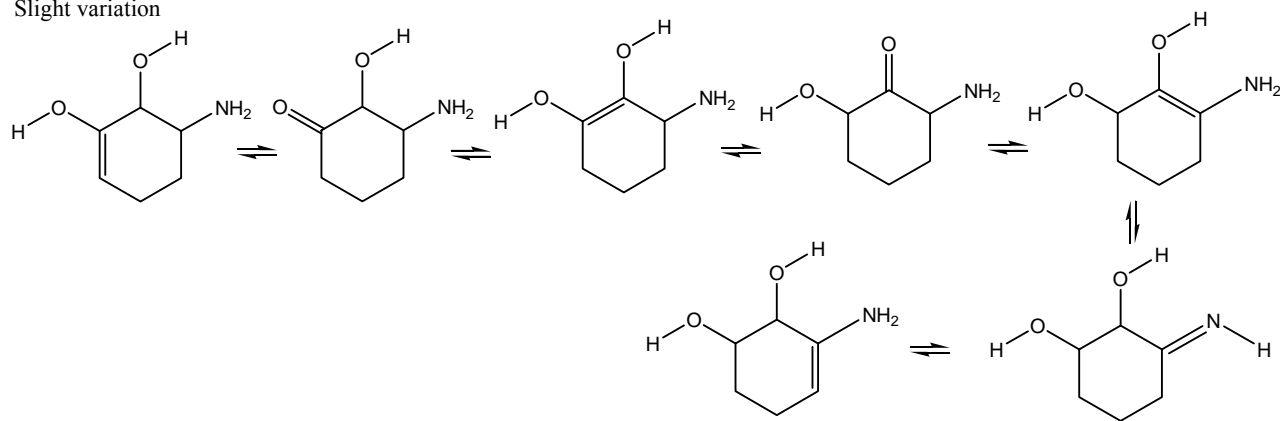
Slight variation



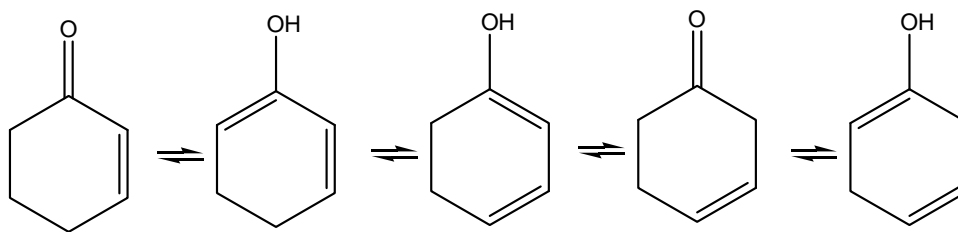
Slight variation



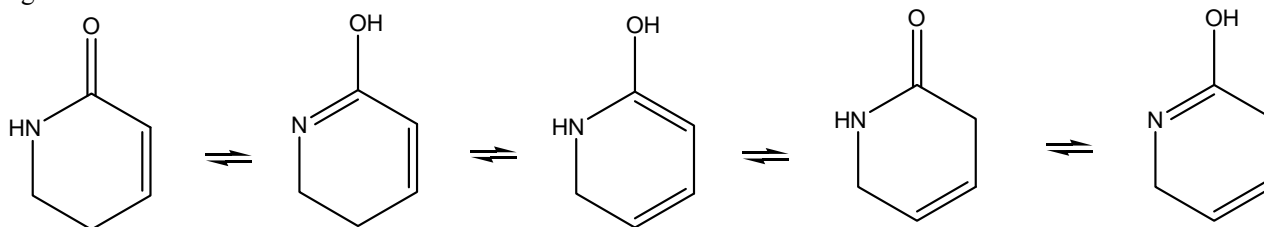
Slight variation



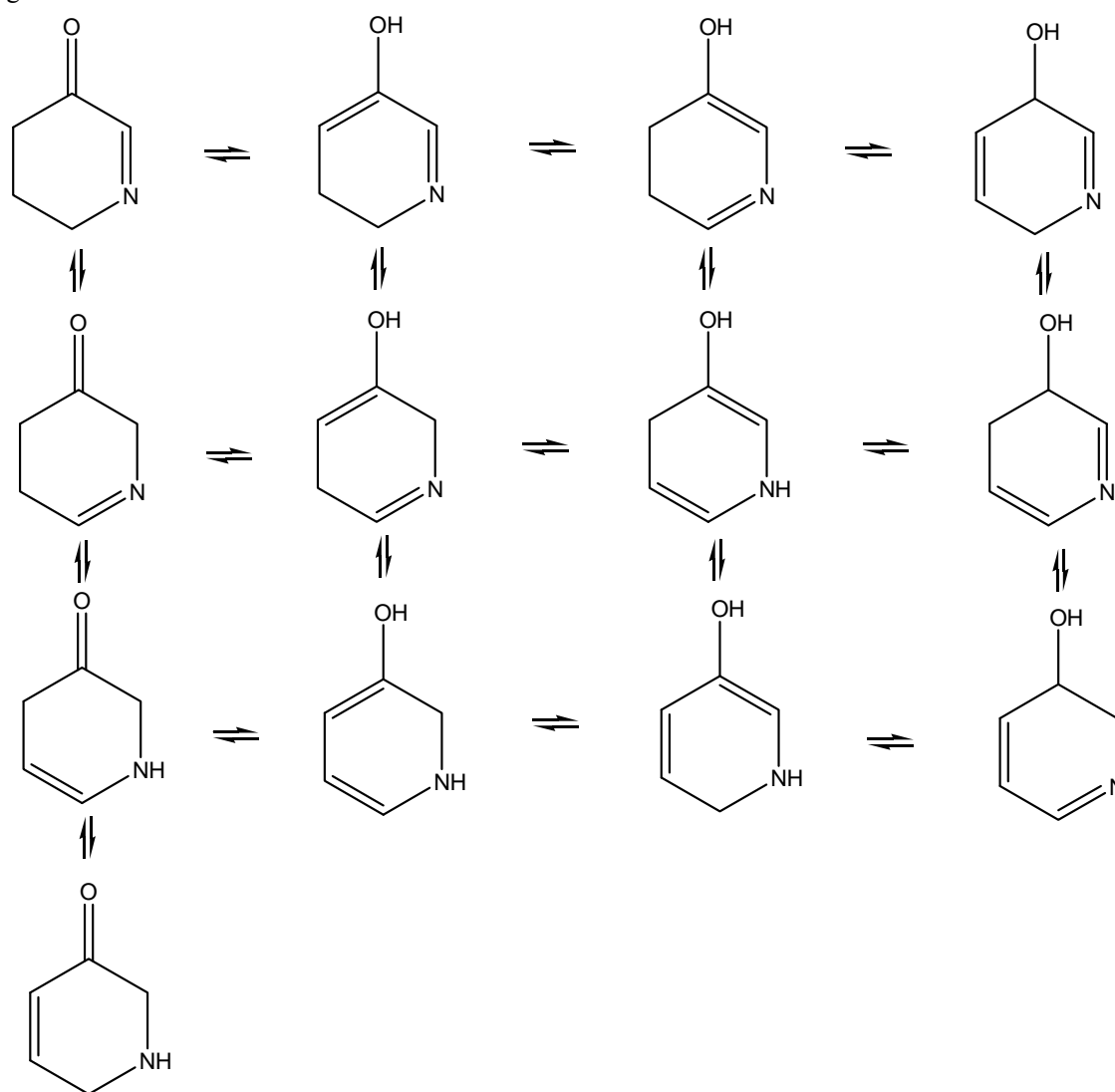
presented earlier



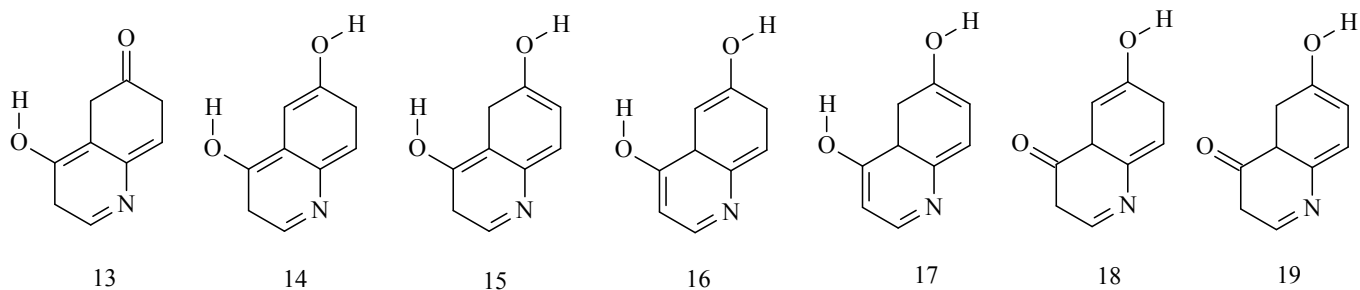
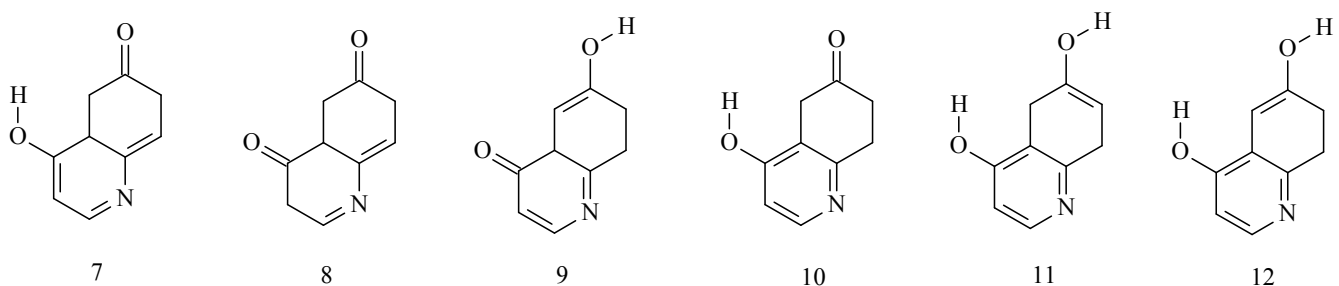
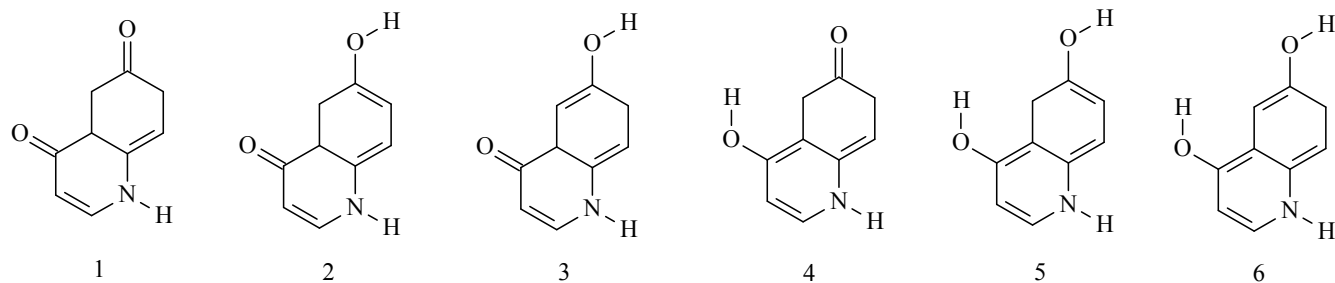
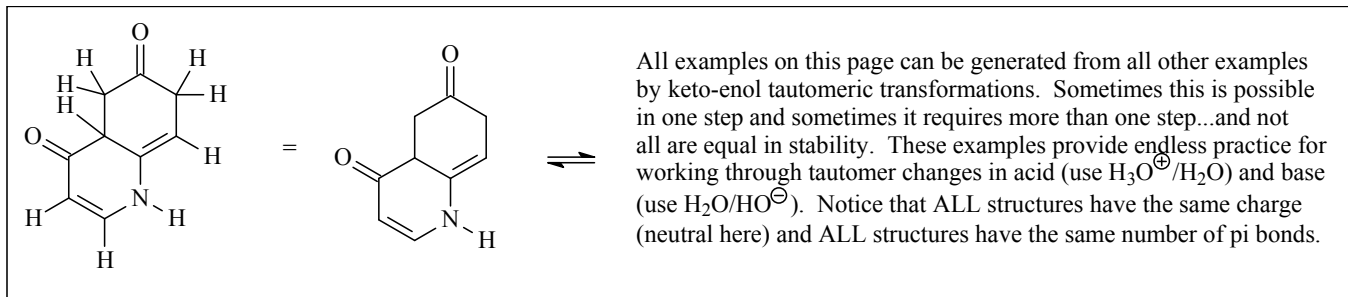
slight variation



slight variation







Almost certainly there are more tautomers, but this is all my brain could think of at the moment. Remember the general strategy for each tautomeric transformation:

1. proton transfer
2. resonance delocalized intermediates
3. proton transfer

**In acid**

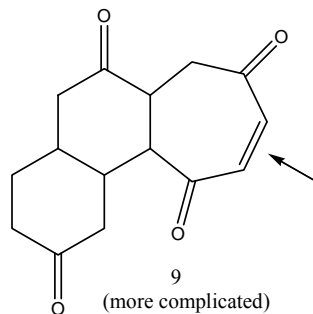
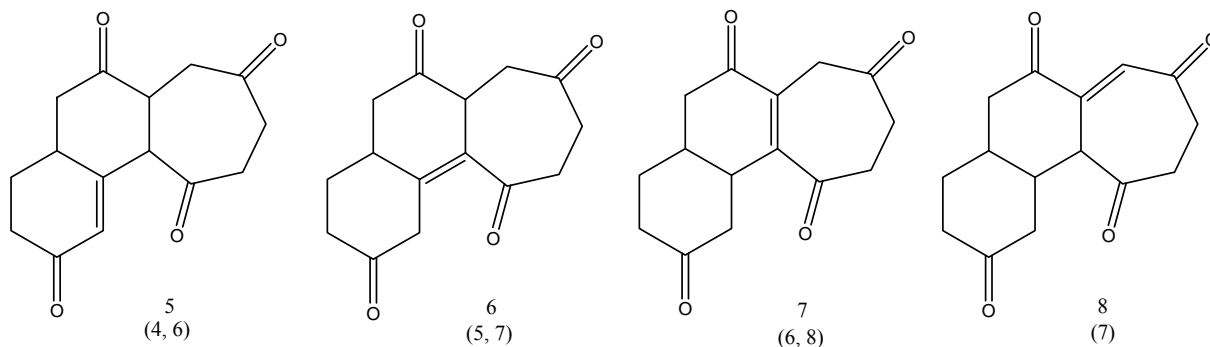
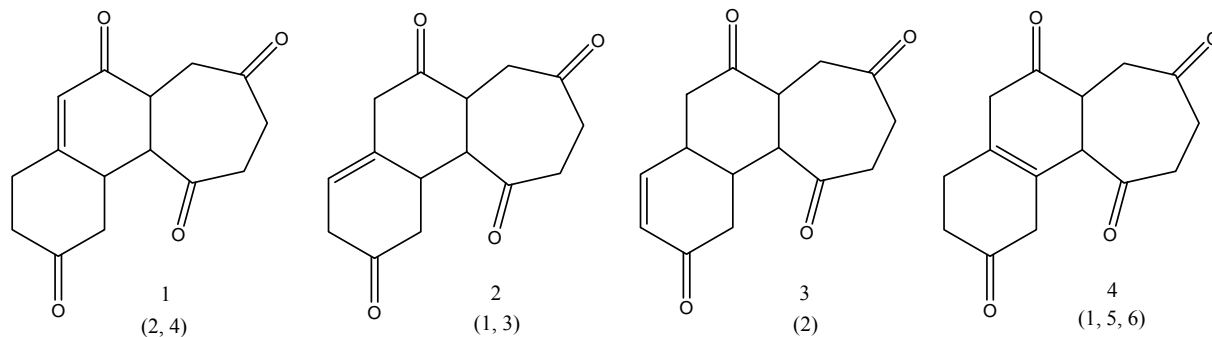
1. proton on (from  $\text{H}_3\text{O}^{\oplus}$ )
2. resonance
3. proton off (with  $\text{H}_2\text{O}$ )

**In base**

1. proton off (with  $\text{HO}^{\ominus}$ )
2. resonance
3. proton on (with  $\text{H}_2\text{O}$ )

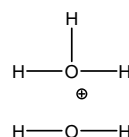
Note – There is the same number of pi bonds and same total charge in each tautomer. Every tautomer can be mechanistically converted into every other tautomer. Also,  $1 \rightarrow 2$  is a different problem than  $2 \rightarrow 1$ . These interconversions can be done in acid or in base, which means there are  $(19 \times 18 \times 2) = 684$  problems just on this page. This isn't the kind of topic you can memorize. You need to develop a systematic approach and practice your strategy until it becomes a workable tool for you.

Problem – The C=C pi bond can be moved around to all possible positions. Show how this might be done in acid and base conditions. You will have to use “enols” (in acid) or “enolates” (in base) to help in these transformations. Consider how many C-H positions are enolizable. The answers may surprise you. Only “keto” tautomer forms are shown below. There are many, many “enol” variations of those “keto” forms (see some of these on the next page). The numbers in parentheses show other “keto” tautomers that can be made in a single keto/enol tautomer change (connected by resonance) **in base**. For example, in base, tautomer 1 can make (or be made from) tautomers 2 and 4 in a single tautomer change. Other changes, for example 1 to 3, would require more tautomer cycles. The steps for 9 → 7 are shown at the bottom of this page (could be done in acid or base). Notice that every tautomer below has the same charge (neutral here) and the same number of total pi bonds (5 here).

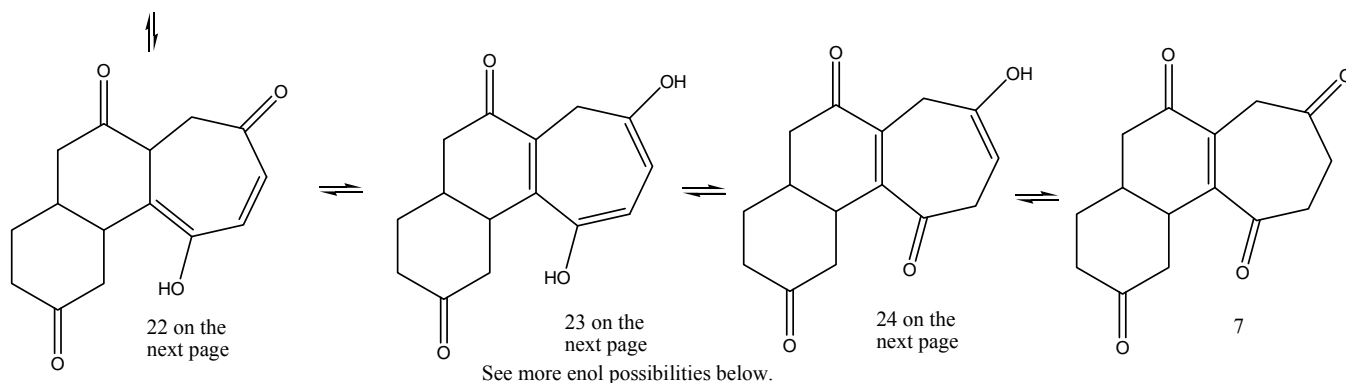
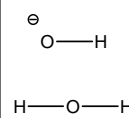


No easy way to move this double bond to another position. It would require multiple tautomer changes.

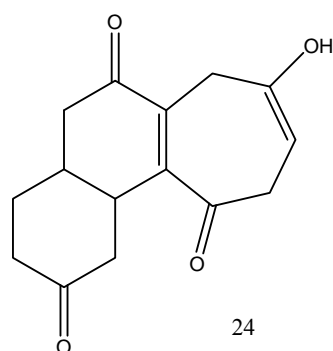
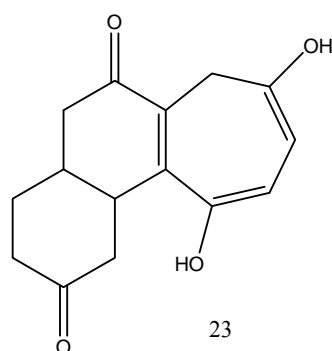
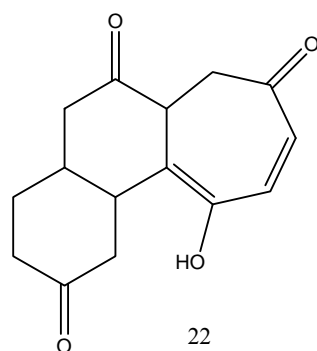
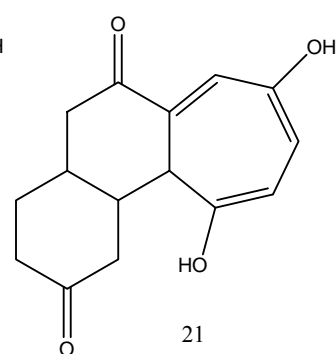
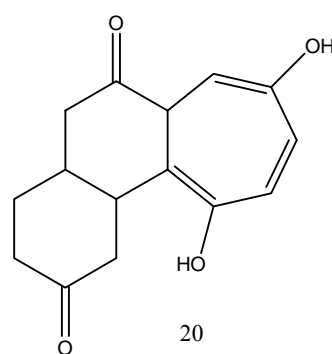
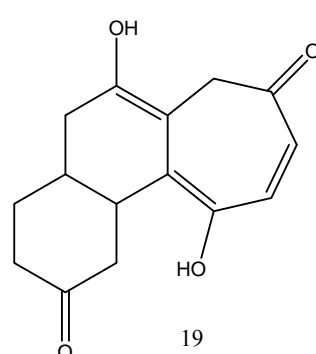
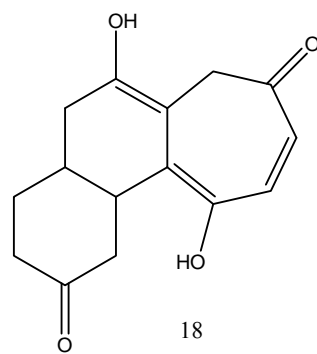
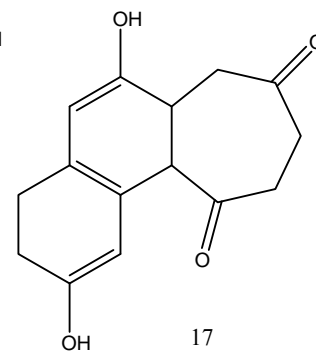
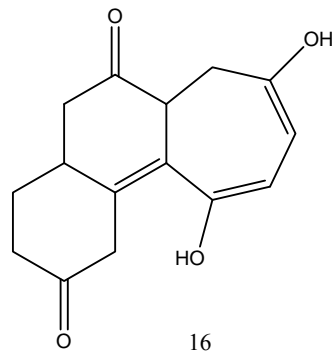
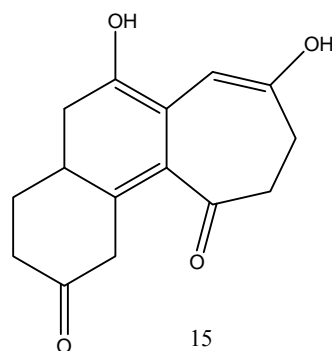
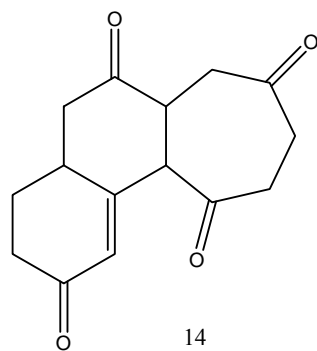
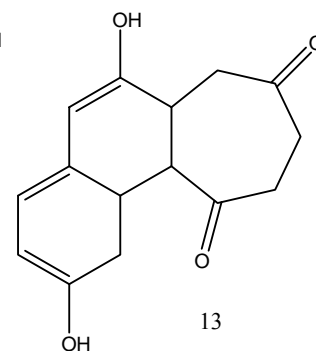
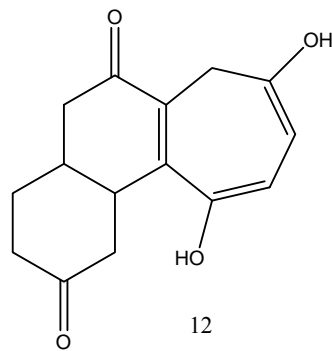
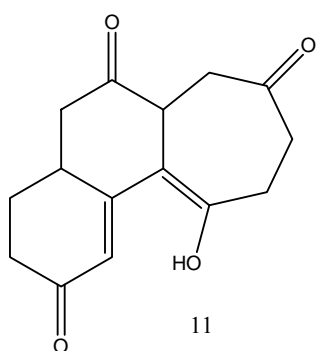
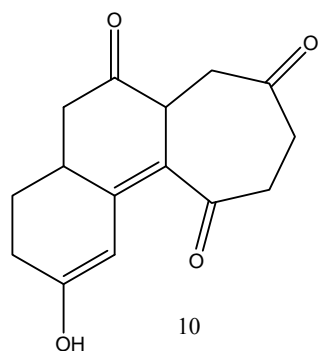
acid conditions



base conditions

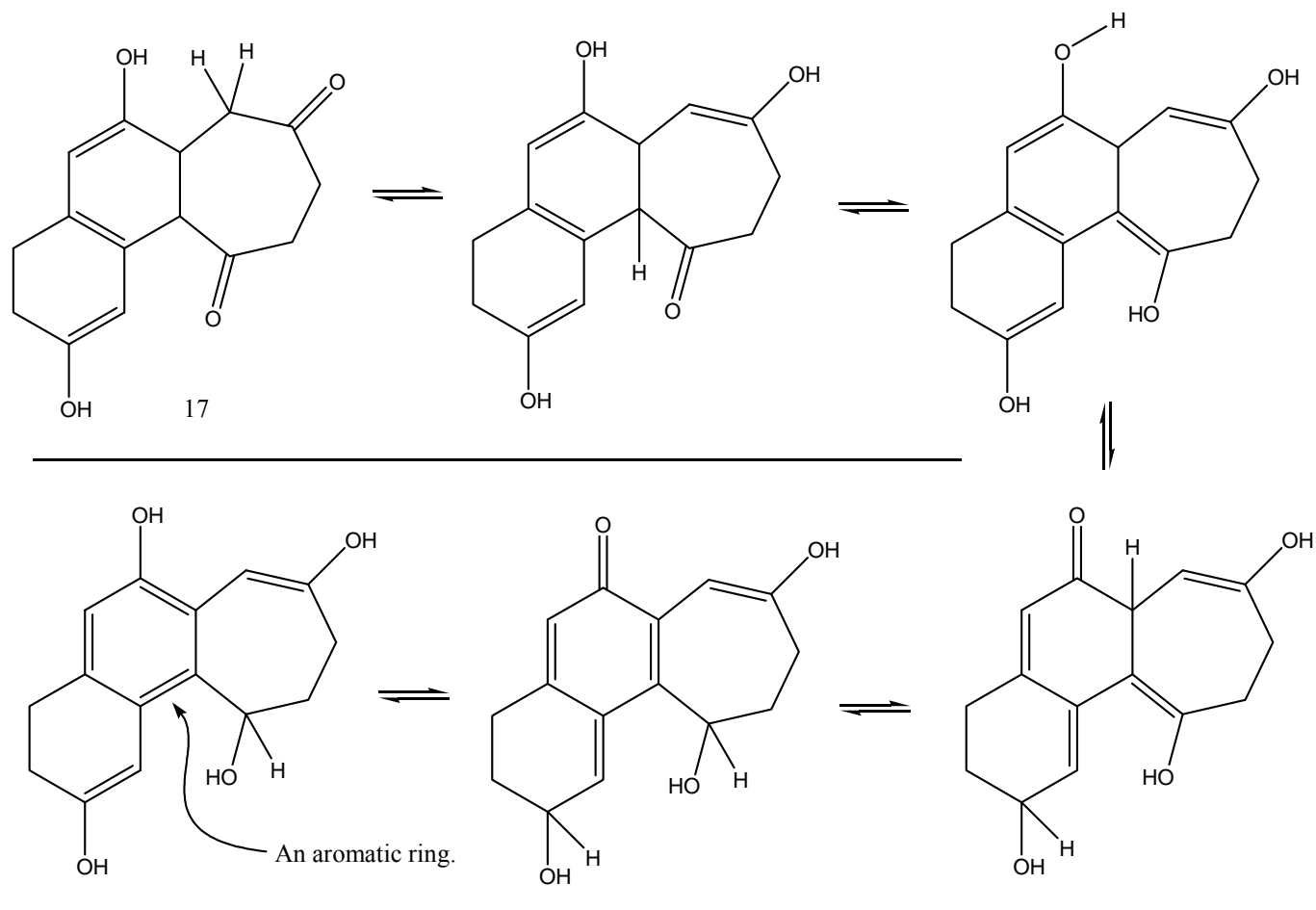


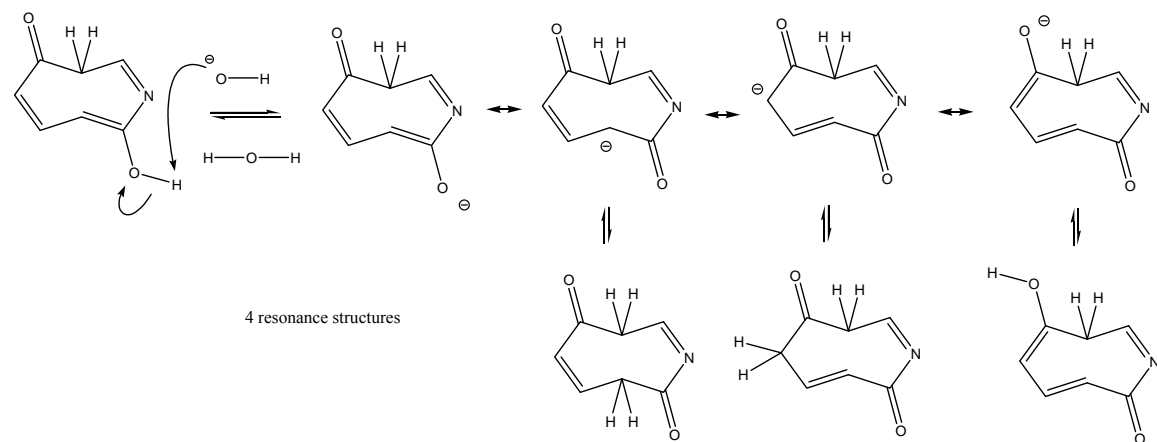
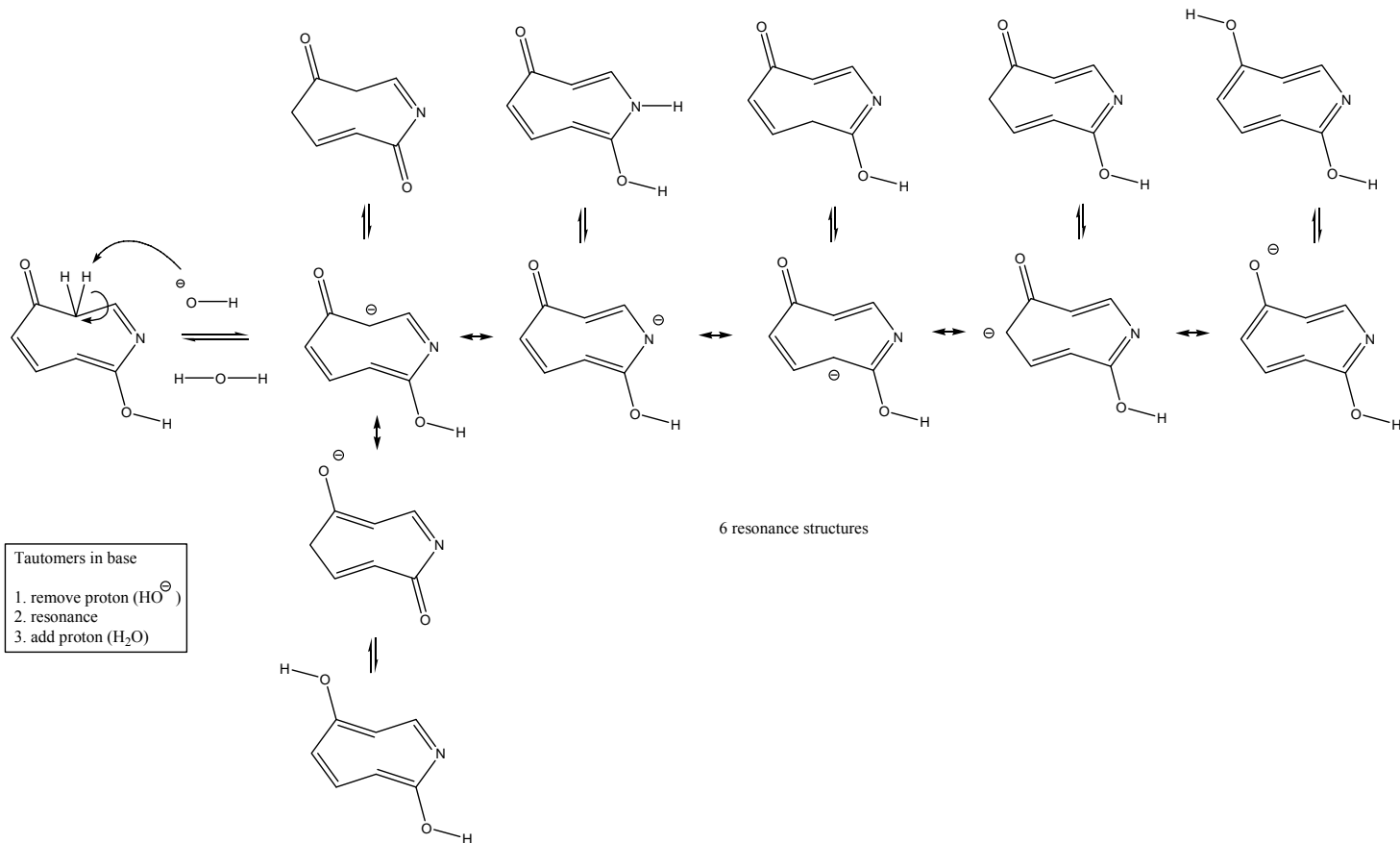
Here are a few additional helpful "enol" tautomers connecting one "keto/enol" system to another "keto/enol" system. There should be four "keto/enol" pi systems in this problem, plus one extra C=C pi bond in conjugation with one or more of them. If a tautomer below does not have that, it is wrong. Not all enol tautomers are shown below.

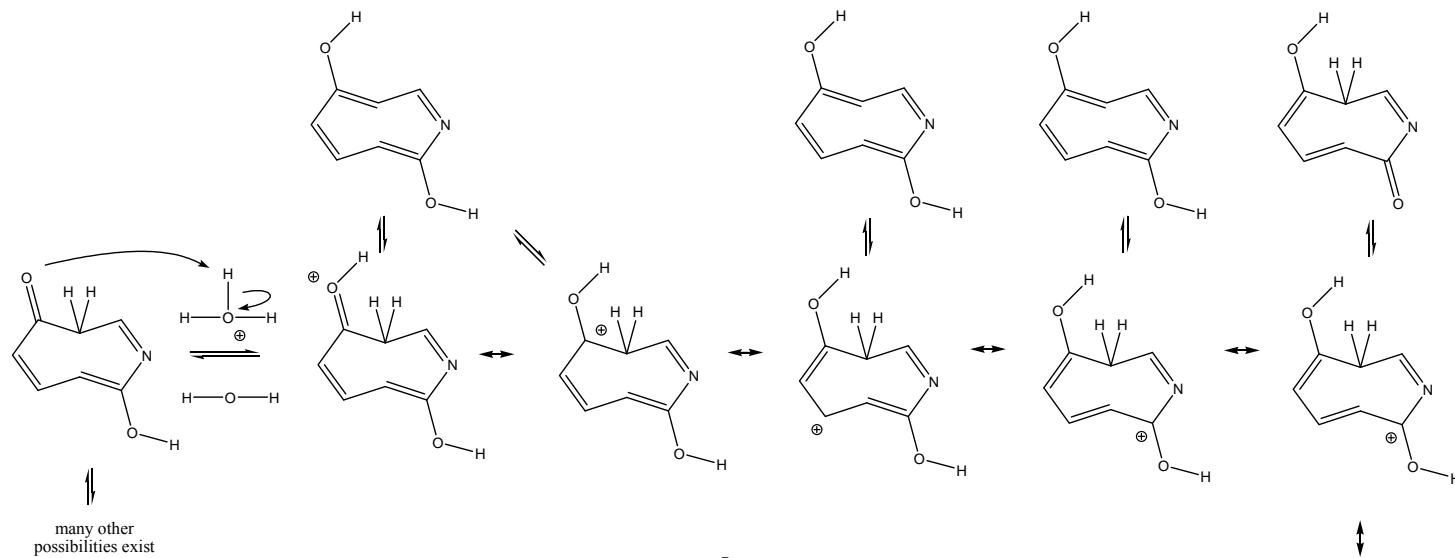


There are lots more we could draw.

We can even make an aromatic ring by moving pi bonds around. These transformations can be done in acid or in base.





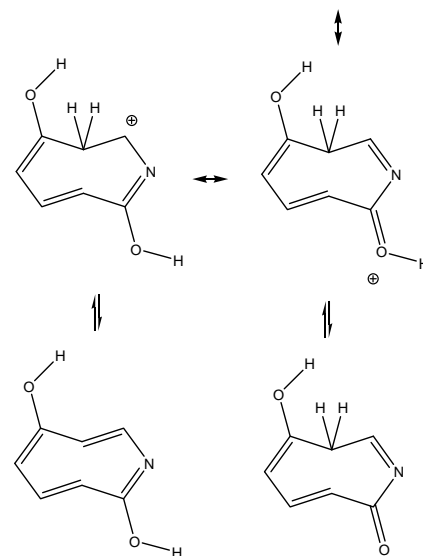
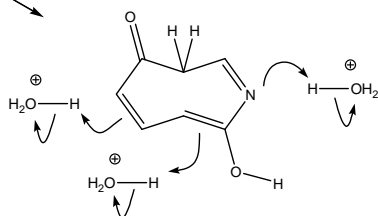


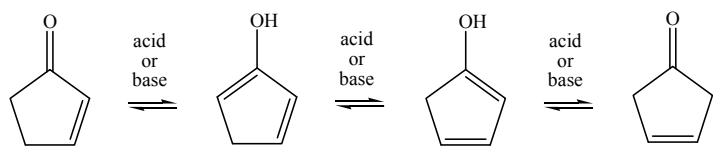
many other possibilities exist

7 resonance structures

Tautomers in acid

1. add proton ( $\text{H}_3\text{O}^+$ )
2. resonance
3. remove proton ( $\text{H}_2\text{O}$ )





Other considerations = R/S and E/Z

