Enols and Enolates (and Enamines)

**Carbon Nucleophiles**

- The hydrogen atoms on the carbon that is alpha- to (adjacent to) the carbon of a C=O bond are the ones involved in keto/enol tautomerization and they are unusually acidic for an sp3 hybridized carbon
- These hydrogens are ENOLIZABLE (although we didn't call them that when we first covered enols)

![Enolizable Hydrogens](image)

- Alpha, beta, gamma terminology refers to relative position, alpha means next to, beta means one position further away etc., in THIS CONTEXT, alpha means the carbon next to the C=O bond

### 1 Enolizable Hydrogens: What is it all about?

- We understand that the majority of the reactions we encounter can be understood terms of Lewis acid/base and electrophile/nucleophile theory, the Lewis base/nucleophile provides the electrons to make a new bond
- CARBON nucleophiles/Lewis bases are difficult to make, however, because carbon is not electronegative, it is not possible to have a simple carbon anion, the non-bonding electrons need to be stabilized somehow

Some STABILIZED Carbon Nucleophiles/Lewis Bases we have already seen:

- Acetylide
- Grignard
- Ylid

- The electrons in the acetylide anion are stabilized by sp hybridization, those in the Grignard reagent are stabilized in a weak bond to magnesium, those in the ylid by the positively charged phosphorus

**New NEW Carbon Nucleophiles/Lewis Bases on carbons based on ENOLIZABLE Hydrogen atoms:**

- Enols and enamines (see previously) and the enolate anion

- The electrons on the nucleophilic carbon in the enolate anion are stabilized by RESONANCE
- The nucleophilic carbon in the enamine and enol has a partial negative charge by RESONANCE
- Enolate anions, enamines and enols are Lewis bases with NUCLEOPHILIC carbon atoms in the position next to (alpha to) the carbonyl carbon of an aldehyde or ketone
- Enolates are formed by deprotonation of an enolizable hydrogen using a Bronsted base
- Enamines are formed in reaction between an aldehyde or ketone with a secondary amine (with acid catalysis) and deprotonation of an enolizable hydrogen (we just didn't call it that previously)
- Enols are structural isomers of aldehydes/ketones where the position of ONE ENOLIZABLE hydrogen is changed, we just didn't call it that previously
2 What Kinds of things do Enolizable Hydrogens do?

**Example:** There are FOUR (alpha) enolizable hydrogens in cyclopentanone, these can exchange in presence of acid.

- The mechanism for exchange can be revealed using deuterated (in effect labeled) acidic water, D3O+, involves reversible formation of an enol, ALL enolizable H atoms can be exchanged this way.

![Diagram of enolization mechanism](image)

- There are FOUR enolizable hydrogens in the molecule below, exchange of the hydrogen at the asymmetric center can result in inversion of configuration, i.e., formation of a racemic mixture. The base catalyzed mechanism is shown that proceeds via the enolate anion.

![Diagram of enolate formation](image)

3 Bronsted Acidity of Enolizable Hydrogens

**Which bases can be used to make an enolate anion?**

- Water is a weaker acid, therefore equilibrium lies mostly on ketone side.
- The hydroxide anion can not be used to irreversibly make an enolate, but can be used to produce a SMALL AMOUNT of enolate that is in equilibrium with the neutral aldehyde/ketone.

**Need a Stronger Base:** Recall some strong bases that we know....

- Lithium diisopropylamide is a very strong BULKY base.

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• in the acid/base reaction above, the ketone on the left is a much stronger acid than the amine that is formed on the right, therefore equilibrium lies essentially completely on enolate side
• LDA can be used to IRREVERSIBLY deprotonate an aldehyde/ketone and form an enolate anion

LDA will DEPROTONATE an aldehyde or ketone at a carbon alpha-to the C=O, but it will not ADD to the C=O the same way that other strong nucleophiles do, e.g. the acetylide anion, Grignard reagent etc., because it is BULKY and therefore STERICALLY HINDERED
• where does this base LDA come from??

• LDA is like NaNH₂, but is BULKY BASE, thus less nucleophilic, stronger base than tertiary butoxide
Recall, Bu-Li (butyl lithium) reacts like a carbon anion base, it is the strongest base that we see in second semester organic chemistry

Summary:
• Use OH if you don't care about forming enolate reversibly
• Use LDA if you want to form the enolate irreversibly, using LDA, ALL of the carbonyl is consumed!

3.1 Relative Acidities of Carbonyl Compounds
• Compare an aldehyde, a ketone, an ester, and a new structure, a beta-dicarbonyl
• the acidity order is thus esters (least acidic) < ketones < aldehydes (most acid of these three)
• the beta-dicarbonyl is by far the strongest acid because the enolate anion is DOUBLY resonance stabilized in this case

and so...

• adding a base such as an alkoxide (ethoxide is shown above) or hydroxide results in formation of only a very small amount of the enolate of an aldehyde or a ketone, most of the carbonyl is not deprotonated but......

• adding a base such as an alkoxide to a beta-dicarbonyl results in essentially COMPLETE formation of the enolate anion