

STUDY GUIDE FOR CHAPTER 18

- Keto – Enol Equilibrium – it exists for any carbonyl compound, with the carbonyl (i.e. the keto) form being the more stable one. The percent of enol form (the so-called *enol content*) is usually very small. Some special cases exist, in which the enol form is favored:
 - Phenols – the enol form has an aromatic system, which is a powerful stabilizing factor;
 - β -dicarbonyl compounds – the enol form is stabilized by both resonance and H-bonding, and becomes preferred;
- Acid – catalyzed enolization – the process involves initial protonation of the carbonyl group, followed by a slower step of proton transfer between C and O.
- Acid-catalyzed halogenation of carbonyl compounds – it was one of the first reactions studied in mechanistic detail. *Arthur Lapworth* studied the process and showed that the reaction rate is INDEPENDENT of the type of halogen, i.e. the rate is identical for chlorination, bromination and iodination of a particular carbonyl compound. The mechanism involves several steps, with enolization being rate-determining. Since halogen does not participate in this step, it does not affect the rate of reaction. Only one halogen atom is introduced in such conditions.
- Base – catalyzed enolization. Enolate ions.
 - Acidity of carbonyl compounds – although the α -carbon is an sp^3 type carbon, it is a center with greatly enhanced acidity, due to the resonance stabilization of the resultant, enolate anion (pK_s in the range 16 – 20). Greater resonance stabilization of β -dicarbonyl compounds' enolates leads to further increase in acidity (pK_s 9 – 14).
 - Base-catalyzed enolization is also a two-step process, the first of which, proton transfer from C to O is the slower.
 - The process is reversible, occurring through a flat enolate anion, resulting in a complete loss of any stereochemical information at the α -carbon atom;
 - Since it is a reversible process, with recurrent deprotonation – reprotonation, it is a convenient way to introduce deuterium (D) labels at the α -carbon(s);
 - The deprotonation of carbonyl compounds can be done two different ways:
 - Reversible deprotonation – the carbonyl compound is reacted with a base, whose conjugate acid has acidity comparable with that of the carbonyl compound;
 - Irreversible deprotonation – done with very strong bases;
- Base-catalyzed halogenation of carbonyl compounds – unlike acid-catalyzed halogenation, the process does not stop with the introduction of a single halogen atom; it is actually accelerated upon introduction of each subsequent halogen atom. With methyl ketones the process eventually leads to cleavage of the molecule and formation of haloform (*Haloform reaction!*!).
- Alkylation of enolate anions – the enolate anions are nucleophiles that can interact with a variety of substrates, including alkyl halides. The reaction occurs via S_N2 mechanism. Its practical significance, with simple aldehydes and ketones is somewhat limited, due to the fact that the enolate anions enter into another, competing reaction: *aldol condensation*.
- Aldol Condensation.
 - In conditions of reversible deprotonation, e.g. with OH^- , the carbonyl compound exists as a mixture of neutral and enolate versions. The enolate ion is nucleophilic, so a reaction is possible with a neutral molecule of the carbonyl compound, giving a product known as *aldol* (*aldehyde + alcohol*). This is the so-called *aldol reaction*.
 - The aldol can be dehydrated in the reaction conditions, giving a product with a C=C bond, conjugated to the C=O bond. Such compounds are known as α,β -unsaturated carbonyl compounds. Since this process is associated with formation of one molecule of water, it is known as aldol condensation. It involves elimination of a hydroxide anion, a rather unfavorable process. However, in this particular case the reaction is driven forward by the stability of the product of

dehydration: A conjugated $C=C-C=O$ system. Dehydration of the aldol is an irreversible step, thus driving the equilibrium of the aldol reaction towards products.

- C. Mixed aldol condensations – if one employs a mixture of TWO carbonyl compounds, then both self-coupling and cross-products are possible. The reaction has practical value when one of the components has no enolizable protons.
8. Reactions of α,β -unsaturated carbonyl compounds.
- A. 1,2- and 1,4 – addition. Kinetic and Thermodynamic control – α,β -unsaturated compounds have two potential site for nucleophilic attack: The carbonyl carbon as well as the β -carbon. Either of them can participate in reactions of nucleophilic addition. This leads to two distinct products of addition: 1,2- and 1,4-addition product. Which route is realized often depends on the nucleophile and the mode of addition (reversible or irreversible). As it turns out, the 1,2-addition product is obtained faster (kinetic control), while the 1,4-addition product is more stable (thermodynamic control). 1,2-additions are realized with strong nucleophiles that are also strong bases (Grignard reagents, hydrides). 1,4-addition takes place with strong nucleophiles that are weaker bases (thioate, cyanide, azide, enolate ions, lithium dialkylcuprates).
 - B. Michael addition and the Robinson annulation.