Topics Discussed on Sept. 16
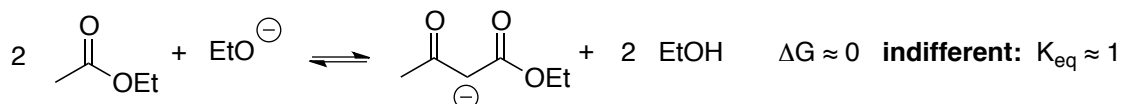
Importance of carbonyl-based transformations in organic synthesis

Carbonyl-based reactions as ideal starting points to explore modern synthetic methodology, *as well as physicochemical aspects of chemical reactivity.*

Overall Stoichiometry of the Claisen condensation of EtOAc

$\Delta G \approx 0$ **indifferent:** $K_{eq} \approx 1$

Kinetic aspects of the Claisen condensation: the addition of the enolate to an intact molecule of ester as the rate-limiting step of the reaction:

rate-limiting step
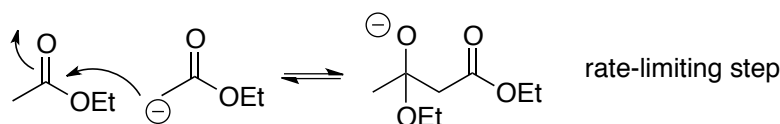
consequently, we may infer that the overall rate of the Claisen condensation
depends on the instant concentration of intact ester and on that of enolate:

rate = k [ester] • [enolate]

Thermodynamic aspects of individual steps of the Claisen condensation of EtOAc

Principle: because changes in pKa are associated with ΔG's (see below), one may generally use ΔpKa's to estimate whether a reaction that forms a Bronsted base at the expense of another Bronsted base will be thermodynamically favorable or unfavorable:

Reminder: a step that produces a weaker base at the expenses of a stronger base is thermodynamically favorable (because $\Delta G < 0$)

A step that produces a stronger base at the expenses of a weaker base is thermodynamically unfavorable (because $\Delta G > 0$)

Step 1: Use of pKa's to estimate the position of the equilibrium in a proton transfer reaction

for the deprotonation of CH$_3$-COOEt with EtONa (consult the handouts on pKa's   posted on the course website for details):

$pK_{eq} \approx 25 - 17 = 8 \quad K_{eq} \approx 10^{-8}$
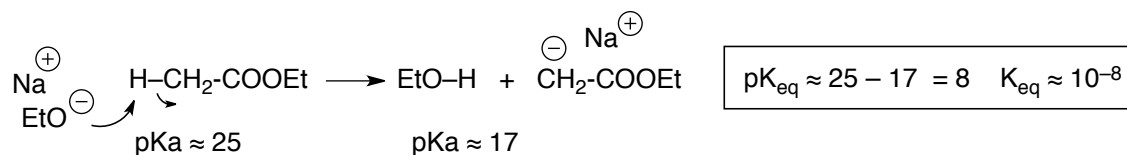
Relationship between equilibrium constants and $\Delta G°$: the Gibbs equation:

$$\Delta G° = - n\, RT\, \ln K_{eq}$$

where n = number of moles, R = gas constant (=$1.98 \cdot 10^{-3}$ kcal/°K mol)

For the deprotonation of ethyl acetate by EtONa, $\Delta G° = - n\, RT\, \ln 10^{-8} > 0$

the process is thermodynamically unfavorable

Extent of deprotonation of ethyl acetate under the above conditions (crude – but useful) estimate:

equilibrium constants / pKa differences provide an estimate of the extent of   deprotonation. For the above reaction,

$$K_{eq} = \frac{[EtOH]\,[\,^{\ominus}CH_2COOEt]}{[EtO^{\ominus}]\,[CH_3COOEt]} = 10^{-8}$$

Suppose that the instant concentrations of CH_3COOEt and EtO^- are identical and = 1 M. To which extent will EtOAc be deprotonated?

Because K_{eq} is so small, the equilibrium will be strongly shifted to the *left*, meaning that   the reaction will have progressed very, very little. But then, $[CH_3COOEt]$ and $[EtO^-]$ are   very   nearly   = 1M. Moreover, the stoichiometry of the reaction requires that for every   molecule of enolate that is formed, one molecule of EtOH must also form. Therefore, $[^-CH_2COOEt]$ and [EtOH] are numerically equal. But then:

$$K_{eq} \approx \frac{[^{\ominus}CH_2COOEt]^2}{1 \cdot 1} = 10^{-8} \quad \text{and} \quad [^{\ominus}CH_2COOEt] \approx \sqrt{10^{-8}} = 10^{-4}$$
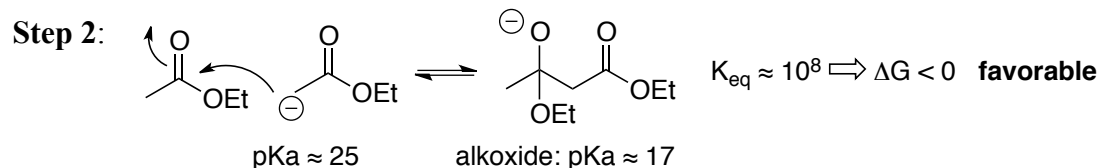
So, the extent of deprotonation of EtOAc under these conditions is roughly equal to the   square root of K_{eq}, meaning that approximately 1 part in 10,000 of the quantity of EtOAc will be present as the enolate under these conditions.

Reversibility of the deprotonation of ethyl acetate with NaOEt as a consequence of its thermodynamically unfavorable nature:
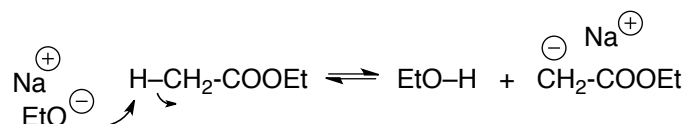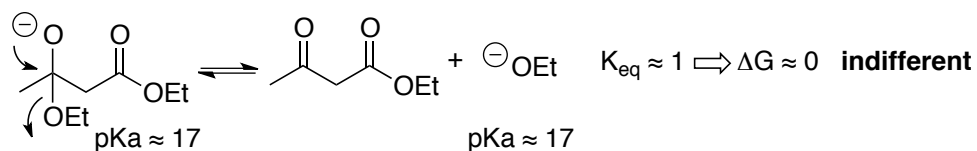

Principle: the rate of a reaction is a function of the instant concentration of reactive species. Useful rates are commonly achieved if the concentration of such agents is greater that ca. $10^{-5} - ^-$ ^{6} M (more about this later)
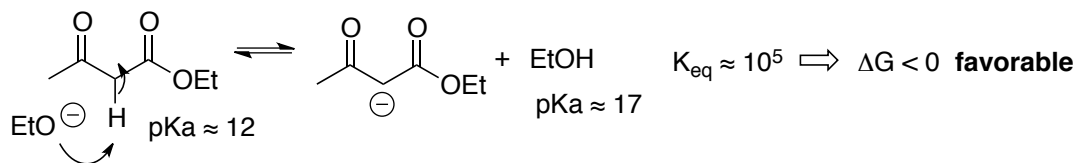
Principle: a base stronger than EtONa would convert a greater proportion of EtOAc into the enolate; i.e., it would cause an increase in the instant concentration of enolate.   As a consequence, the reaction would proceed at a faster rate

Step 2:

$K_{eq} \approx 10^8 \Rightarrow \Delta G < 0$ **favorable**

pKa ≈ 25   alkoxide: pKa ≈ 17

Step 3:

$K_{eq} \approx 1 \implies \Delta G \approx 0$ **indifferent**

pKa ≈ 17   pKa ≈ 17

Step 4:

+ EtOH $K_{eq} \approx 10^5 \implies \Delta G < 0$ **favorable**

pKa ≈ 17

EtO⊖ H pKa ≈ 12

Reminder: the thermodynamically favorable deprotonation of ethyl acetoacetate by ethoxide ion approximately cancels out the thermodynamic disadvantage incurred in the earlier stages of the process. Consequently, the overall ΔG for the reaction is nearly zero

Principle: if the above reaction were to occur under conditions of thermodynamic equilibrium, only a portion of the starting materials would advance to the products

The Claisen condensation as a readily reversible process when carried out under the above conditions

Le Chatelier's principle: in a system at equilibrium, addition of reactant(s) or removal of product(s) shifts the equilibrium to the right; removal of reactants(s) or addition of product(s) shifts the equilibrium to the left

Removal EtOH from the medium as a possible way to drive the reaction to the right

Removal of EtOH produced during a Claisen condensation by:

> (a) continuous fractional distillation (old method, painstaking)
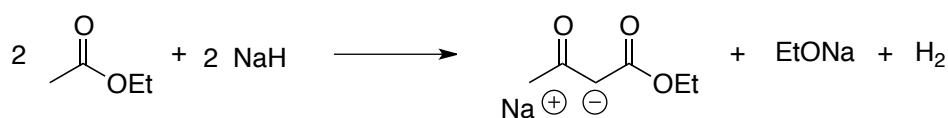> (b) chemical reaction with an appropriate agent

Sodium hydride (NaH), potassium hydride (KH) as carriers of hydride ion, H⁻

H⁻ as the conjugate base of H_2

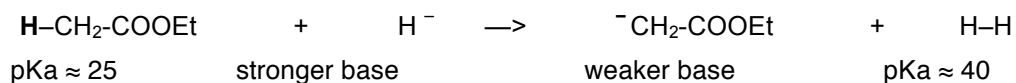Estimated pKa of $H_2 \approx 40$, therefore, H⁻ is a very strong base

Rapid and irreversible deprotonation of EtOH with NaH (pKa of $H_2 \approx 40$)

Stoichiometry of the Claisen condensation promoted by NaH:

no EtOH present → no opportunity for reversal

Thermodynamically favorable deprotonation of an ester by hydride ion:

$$\textbf{H}–CH_2\text{-COOEt} \quad + \quad H^- \quad \longrightarrow \quad {}^-CH_2\text{-COOEt} \quad + \quad H–H$$

pKa ≈ 25   stronger base   weaker base   pKa ≈ 40

$$\Delta pKa = -15 \;\rightarrow\; Keq \approx 10^{15}\;; \quad \Delta G_{25°C} \approx -20 \text{ kcal/mol} \ll 0$$

However: kinetic effects cause H^- in NaH to react very slowly with an ester.

Rapid reaction of NaH with hydroxylic agents such as alcohols or water, leading to formation of alkoxides or of hydroxide. Such reactions evolve flammable H_2 gas:

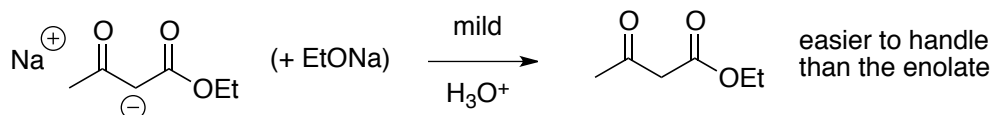$$R–OH \;+\; NaH \;\longrightarrow\; R–ONa \;+\; H_2 \qquad (R = H,\ alkyl)$$

Use of catalytic amounts of EtOH in Claisen condensations promoted by NaH:
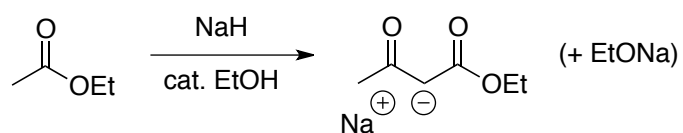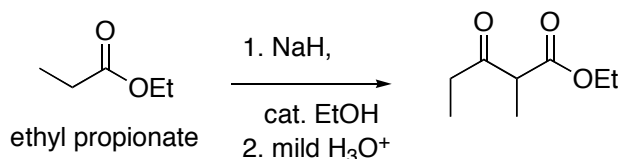

Principle: it is generally easier to isolate organic substances as electrostatically neutral species, rather than in ionic form

Protonation of the enolate of the 1,3-dicarbonyl product of a Claisen condensation by treatment with mild aqueous acid (e.g., 1N aq. HCl):

Claisen condensation of esters other than ethyl acetate, e.g:

Failure of Claisen condesations carried out under the above conditions and leading to non-deprotonatable dicarbonyl products; e.g.:

not possible under such conditions