Chapter 16-1, 3-5: Acidity and Basicity; Enolization/Enolate Formation
I. Solvation, Inductive, and Resonance Effects in Acidity and Basicity

(1) Solvation effect: More effective solvation on the conjugate base increases the acidity of the original acid.

Alcohols: \[ R-\text{OH} \rightleftharpoons R-\text{O}^- + \text{H}^+ \]

\[
\begin{array}{cccc}
\text{H}_2\text{C}-\text{OH} & \text{CH}_3\text{CH}_2-\text{OH} & (\text{CH}_3)_2\text{CH}-\text{OH} & (\text{CH}_3)_3\text{C}-\text{OH} \\
pK_a & 15.5 & 15.9 & 17.0 & 19.2
\end{array}
\]

Carboxylic acids:

\[
\begin{array}{cccc}
\text{OH} & \text{HO}_2\text{C} & \text{CH}_3\text{CH}_2-\text{O}_2\text{C} & (\text{CH}_3)_2\text{CH}-\text{O}_2\text{C} & (\text{CH}_3)_3\text{C}-\text{O}_2\text{C} \\
pK_a & 3.75 & 4.76 & 4.88 & 4.85 & 5.05
\end{array}
\]

(2) Hybridization effect on R-C(=O)OH - Inductive effect by the \( \alpha \)-carbon

\[
\begin{array}{cc}
\text{CH}_2\text{CH}_2-\text{OH} & \text{CH}_2=\text{CH}-\text{O}_2\text{C} & \text{Cl} & \text{C} \text{C}-\text{C}-\text{O}_2\text{C} \\
pK_a & 4.88 & 4.20 & \sim 4.2 & 1.84
\end{array}
\]

\( \alpha \)-C: \( \text{sp}^3 \text{C} \) \( \text{sp}^2 \text{C} \) \( \text{sp}^2 \text{C} \) \( \text{sp} \text{C} \)

(3) Halogenated Carboxylic Acids

\[
\begin{array}{cc}
\text{H} & \text{Cl} & \text{Cl} & \text{Cl} \\
pK_a & 4.8 & 2.8 & 1.3 & 0.64 \\
\text{F} & \text{Cl} & \text{Cl} & \text{F} \\
\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl} \\
\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl}
\end{array}
\]

Examples of the Inductive Effect

- more Cl atoms
- Cl closer to the C(=O)OH
- \( \text{sp}^2 \) C
- \( \text{sp}^2 \) C
- \( \text{sp} \) C

more acid

\[
\begin{array}{cc}
\text{Cl} & \text{Cl} \\
pK_a & 4.52 & 4.05 & 2.86
\end{array}
\]

\[
\begin{array}{cc}
\text{F} & \text{Cl} \\
pK_a & 0.23
\end{array}
\]

electrons are withdrawn more to the O atom of the O-H bond by the halogen atom(s)

electrons are withdrawn more to the O atom of the O-H bond by the halogen atom(s)

charge more stabilized by the presence of the halogen atom(s)

\[
\begin{array}{cc}
\text{R-\text{O}^-} & \text{H^+} \\
\text{R-\text{O}^-} & \text{H^+}
\end{array}
\]
(4) Aromatic Carboxylic Acids

- Inductive effect in aromatic carboxylic acids

\[
\begin{align*}
\text{pKa} & \quad 4.2 \\
& \quad 4.1 \\
& \quad 3.9 \\
& \quad 3.3
\end{align*}
\]

*note: Inductive effect through the $\sigma$-bond framework*

- Combination of inductive and resonance effects

\[
\begin{align*}
\text{pKa} & \quad 3.4 \\
& \quad 3.5 \\
& \quad 2.2
\end{align*}
\]

*weak inductive effect & strong resonance effect*  
*mostly inductive effect*  
*strong inductive effect & extremely strong resonance effect*

Resonance structures of the conjugate base of 4-nitrobenzoic acid:

(5) Aromatic amines (or anilines)

Instead of using the basicity scale (pKb), the dissociation acidity (pKa) of the conjugate acids is typically used. So, a stronger base has a higher pKa of its conjugate acid.

\[
\begin{align*}
\text{BH}^+ & \quad \text{pKa} \\
\text{H}_3C\text{N}-\text{H} & \quad \text{pKa} 10.6 \\
\text{pKa} 4.6
\end{align*}
\]

Because of the delocalizable N lone pair in aniline (as a result of resonance with the benzene $\pi$-system), the aniline N atom is considerably less basic compared with that of R-NH$_2$.

Substituted anilines

\[
\begin{align*}
pKa & \quad 4.60 \\
pK_a & \quad 1.00 \\
pK_a & \quad 5.31
\end{align*}
\]
Explanation based upon resonance structures of the conjugate acids:

The BH⁺ form is destabilized by the presence of the 4-nitro group. → more acidic than PhNH₃⁺

The BH⁺ form is stabilized by the presence of the 4-OCH₃ group. → less acidic than PhNH₃⁺

Alternatively, these pKa values can be explained by using the resonance structures of substituted anilines (i.e., B instead of BH⁺).

II. Carbon Acids

(1) Carbanions

\[
\begin{align*}
\text{sp}^3 & = 25\% \text{ s character} \quad \text{pKa} > 50 \\
\text{sp}^2 & = 33\% \text{ s character} \quad \text{pKa} \approx 40
\end{align*}
\]

extremely strong nucleophiles and bases

Inductive effect:

\[
\begin{align*}
\text{Cl} - & \text{C} + \text{Cl} - \text{H} + \Theta \text{OH} \quad \text{pKa} \approx 25 \\
\text{Cl} - & \text{C} + \Theta \text{OH} \quad \text{pKa} 15.7
\end{align*}
\]

much weaker base than \( \text{C}^{-} \)

But, note: \( \text{H}_3\text{CO} - \text{C} - \text{H} \) not acidic at all!

(2) Electron-withdrawing groups (in terms of resonance) & pKa

\[
\begin{align*}
\text{pKa} > 50 & \quad \text{pKa} 19 & \quad \text{pKa} 10.2
\end{align*}
\]

both inductive effect & resonance stabilization of the carbanion
III. Enols and Enolates (16-4, 5)

(1) Deprotonation of an α-Hydrogen by a Base

\[ \text{α-carbons} \quad (i.e., \text{alpha or the first C's from C=O}) \]

\[ \text{α-hydrogens} \]

Note: \( \text{OH} \) is also a nucleophile.

So, \( \text{OH} \) takes place as well.

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Ambident Nucleophilic Nature of Enolates: can react at either anionic center (i.e., C' and O').

C': more nucleophilic site

C: less electronegative and will share electrons with electrophiles more easily

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pKa’s of carbonyl compounds:

ketone

\[ \text{H}_2\text{C}=\text{C}(-\text{CH}_3) \rightarrow \text{H}_2\text{C}=\text{C}(-\text{CH}_3) \]

The presence of unshared pairs of electrons on the O of the alkoxy group diminishes the effectiveness of the carbonyl group of the ester in delocalizing the \( \text{O}^- \) charge.
(2) Protonation of an enolate anion

(3) Keto-Enol Tautomerization (see: p 338 of the textbook for tautomerism)

(4) Acid catalyzed-Enol Formation (Enolization)
(5) Active methylene compounds

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{C} \quad \text{H}_3 \\
& \quad \text{H} \quad \text{H} \quad \text{or active methylene Hs} \\
pK_a & = 9
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \quad \text{C} \quad \text{H}_3 \\
& \quad \text{H} \quad \text{H} \\
pK_a & = 11
\end{align*}
\]

These Hs are highly acidic as the corresponding carbanions are doubly stabilized by resonance with the two C=O groups.

(6) Racemization/epimerization of Stereocenters at the \( \alpha \)-C Atoms

(a) Racemization
\( \alpha \)-Hydrogen atoms can be deprotonated by a base or ketones can form enols under acidic conditions, thus losing the original stereochemistry. In the example shown below, treatment of the \( R \)-enantiomer with \( \text{NaOCH}_3/\text{HOCH}_3 \) results in the formation of a racemic mixture.

(b) Epimerization
\( \text{(b) epimerization} \)

\[\text{Epimers}: \text{ Diastereomers differing in configuration at only one of two or more chiral centers.}\]

\[\text{Epimerize}: \text{ To interconvert diastereomers by changing a configuration at only one of two or more chiral centers.}\]