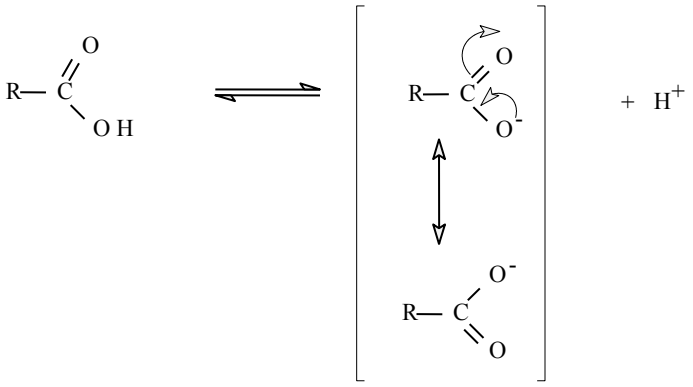
Lecture 16

Carboxylic Acids and Derivatives



March 10, 2016

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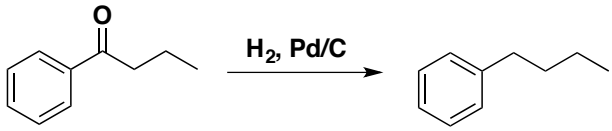
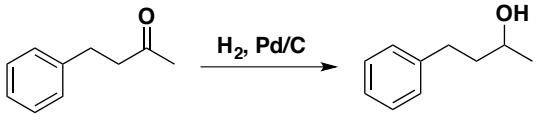
Hydrogenolysis of benzylic carbonyls

- Benzyl ethers, aldehydes and alcohols are also reduced to the corresponding methylene group





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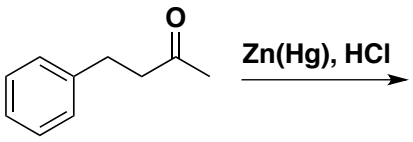
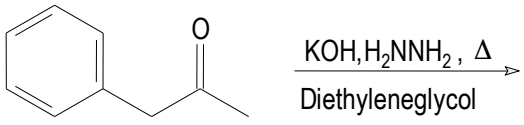
Clemmensen Reduction

- Refluxing an aldehyde or ketone with amalgamated zinc in concentrated HCl converts the carbonyl group to a methylene group
- Limitations…??



Wolff-Kishner Reduction

- If aldehydes or ketones are refluxed with hydrazine and KOH in a high-boiling solvent, the reaction converts carbonyls into methylenes

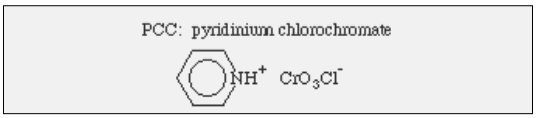


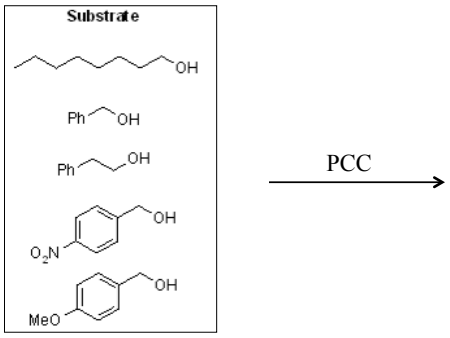
Oxidation Reactions

- **Jones Reagent** (H_2CrO_4 in acetone) takes primary alcohols to acids and secondary alcohols to ketones

PCC Oxidations

$C_5H_5N + HCl + CrO_3 \rightarrow [C_5H_5NH][CrO_3Cl]$

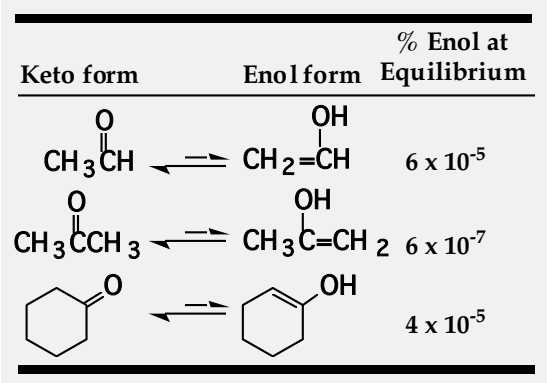




PCC →

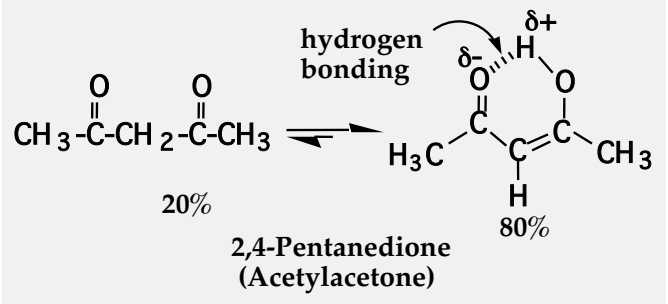
Keto-enol Tautomerism

- Keto-enol equilibria for simple aldehydes and ketones lie far toward the keto form



Keto-enol tautomerism in β-diketones and β-ketoesters

- Open-chain β-diketones are further stabilized by intramolecular hydrogen bonding

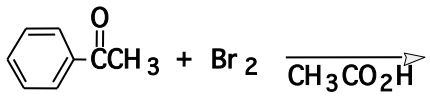


Enolate anions

Hydrogens α to carbonyls are "acidic"

α-Halogenation

- α-Halogenation: aldehydes and ketones with at least one α-hydrogen react at an α -carbon with Br_2 and Cl_2 and the reaction is catalyzed by both acid and base



Acetophenone

- Acid catalysis gives the most substituted product
- Mono-substitution occurs with acid catalysis
- Poly-halogenation occurs with base promoted halogenation goes "all the way" because the product is more acidic than the starting material

Acid Catalyzed α-Halogenation

Step 1: Acid-catalyzed enolization

Step 2: Nucleophilic attack of the enol on halogen

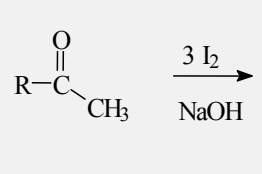
Base Catalyzed α-Halogenation

Step 1: formation of an enolate anion

Step 2: nucleophilic attack of the enolate anion on halogen

Iodoform Reaction

- A qualitative test for **methyl ketones**
- A decent way to synthesize carboxylic acids

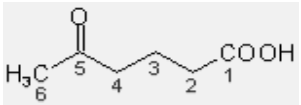


Carboxylic Acid Nomenclature

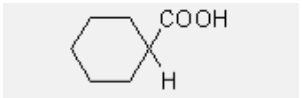
- IUPAC names: drop the -e from the parent alkane and add the suffix -oic acid
- If the compound contains a carbon-carbon double bond, change the infix -an- to -en-

CH_4	Methane	Methanoic acid	Formic Acid
CH_3CH_3	Ethane	Ethanoic acid	Acetic acid
$CH_3CH_2CH_3$	Propane	Propanoic acid	Propionic acid
$CH_3CH_2CH_2CH_3$	Butane	Butanoic acid	Butyric acid

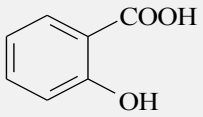
Naming acids



5-Oxohexanoic acid

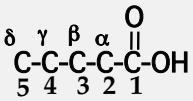


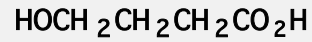
Cyclohexanecarboxylic acid



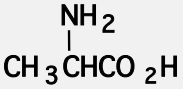
2-hydroxybenzoic acid
Salicylic acid

- When common names are used, the letters δ, etc. are often used to locate substituents





4-Hydroxybutanoic acid
(γ-Hydroxybutyric acid)

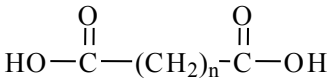


2-Aminopropanoic acid
(α-Aminopropionic acid; Alanine)

Naming the Salts

- To name the salt of the carboxylic acid, name the cation followed by the name of the anion (two words).
- The anion is named by removing -oic acid and adding ate

The Simple Dibasic Acids

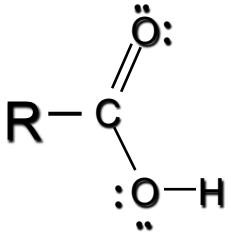


n	*Total C's*	*Name* (acid)
0	2	Oxalic
1	3	Malonic
2	4	Succinic
3	5	Glutaric
4	6	Adipic
5	7	P???

Synthesis of Carboxylic acids

1) Oxidation of benzyl positions

2) Oxidation of 1˚ alcohols



3) Oxidation of Aldehydes

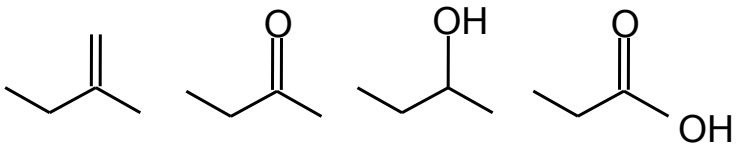
4) Cleavage of alkenes

Synthesis of Carboxylic acids

5) Hydrolysis of Nitriles:

6) Carboxylation of Organometallic Reagents:

Boiling Points

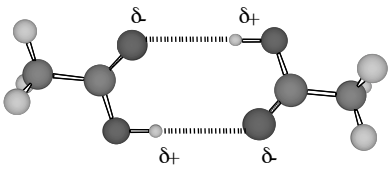


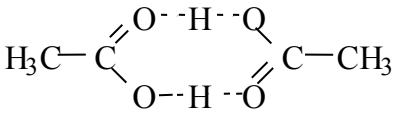
bp (1 atm)	**31°C**	**80°C**	**99°C**	**141°C**
Molar mass	70	72	74	74

- Intermolecular forces, especially hydrogen bonding, are stronger in carboxylic acids than in other compounds of similar shape and molecular weight

Physical Properties

- In the liquid and solid states, carboxylic acids are associated by hydrogen bonding into dimeric structures

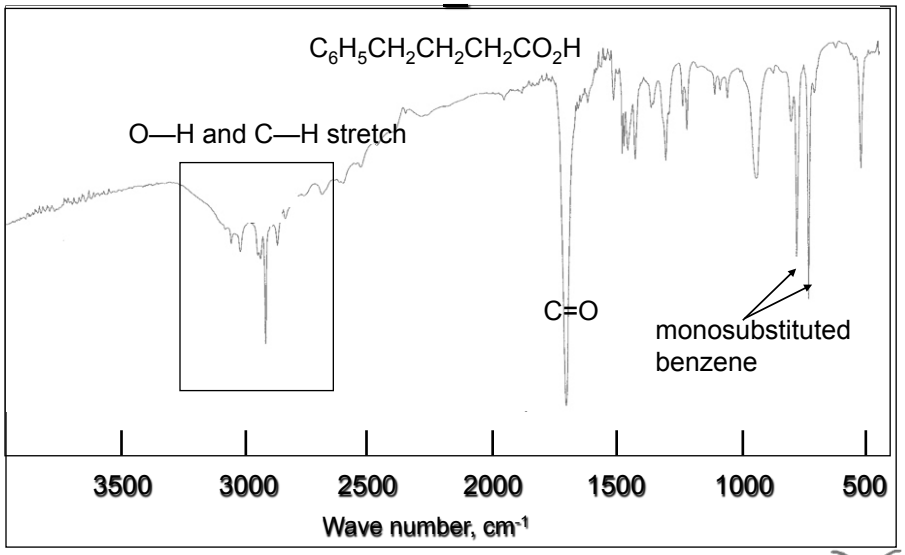




Infrared Spectroscopy

- **A carboxylic acid is characterized by peaks due to OH and C=O groups in its infrared spectrum.**
- **C=O stretching gives an intense absorption near 1700 cm^{-1}.**
- **OH peak is broad and overlaps with C—H absorptions.**

Infrared Spectrum of 4-Phenylbutanoic acid



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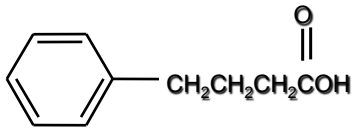
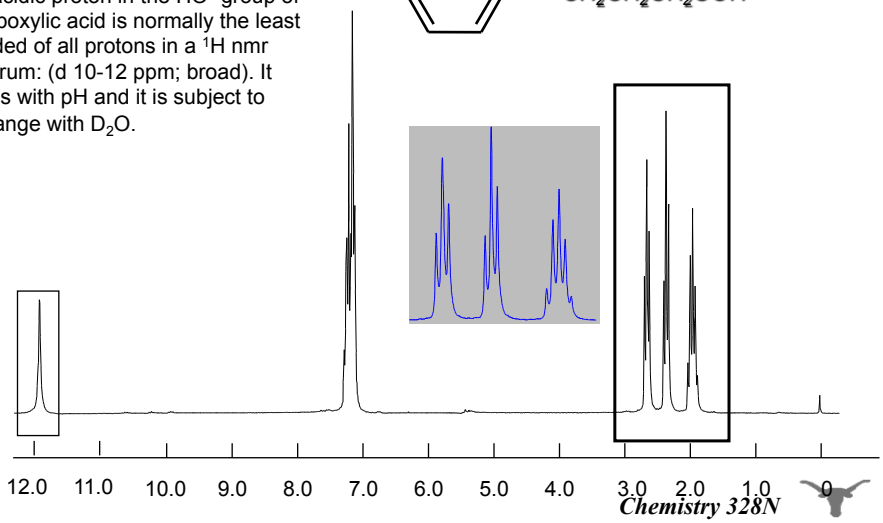
^1H NMR of Carboxylic acids

The acidic proton in the HO- group of a carboxylic acid is normally the least shielded of all protons in a ^1H nmr spectrum: (d 10-12 ppm; broad). It moves with pH and it is subject to exchange with D_2O.





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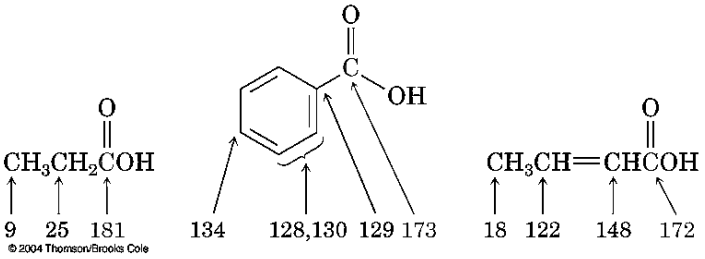
^{13}C NMR of Carboxylic acids

The Carbonyl carbon on the carboxylic acid group is at low field (δ 165-185 ppm), but not quite as deshielded as the carbonyl carbon of an aldehyde or ketone (δ 190-215 ppm).



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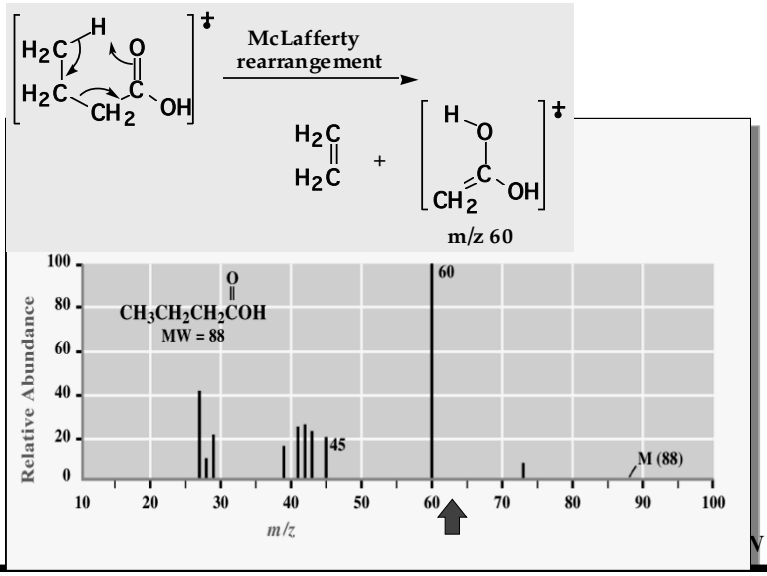
Mass Spectrometry of Carboxylic Acids

- The McLafferty rearrangement gives a characteristic peak at **m/z = 60**

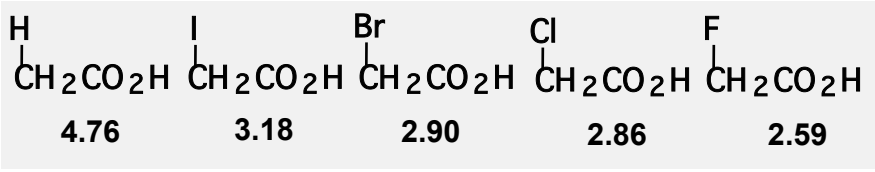


Acidity

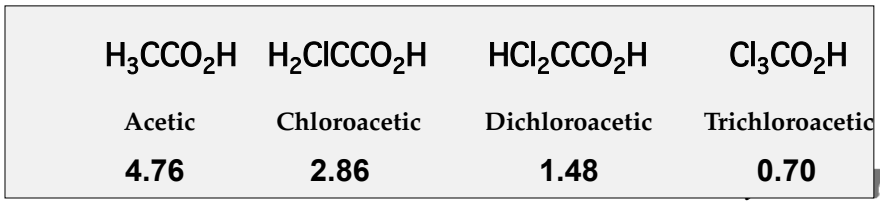
- Carboxylic acids are weak acids
  - The pK_a of typical aliphatic and aromatic carboxylic acids falls within the range 4 to 5

Acidity

- Electron-withdrawing substituents near the carboxyl group increase acidity through their inductive effect

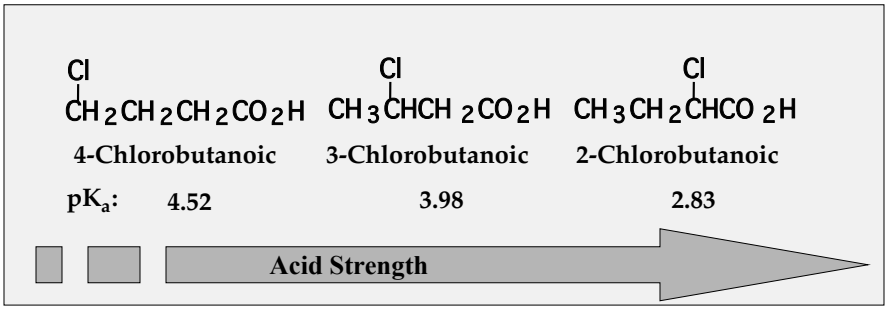


- Substitution by multiple electron-withdrawing groups further increases acidity



Acidity

- The inductive effect of an electron-withdrawing substituent falls off rapidly with its distance from the carboxyl group



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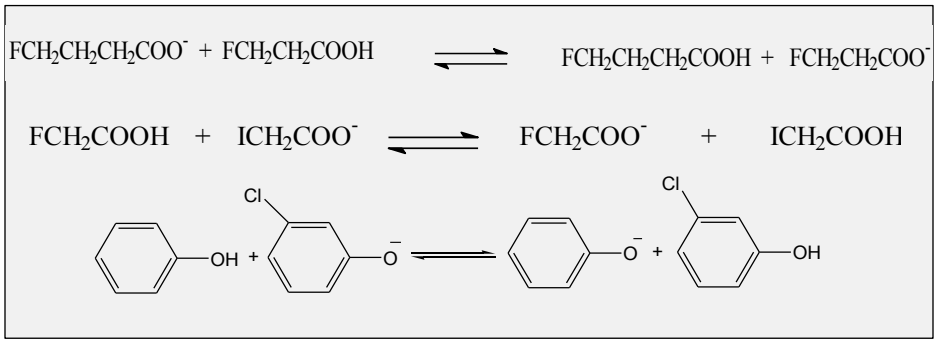
Be Sure to Study Trends in Acid Strength



Which way does the equilibrium lie??

Please Practice This Game

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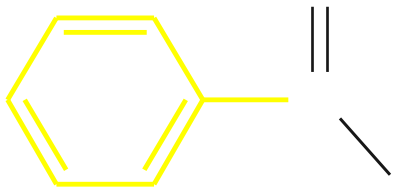
Reactions of Carboxylic acids

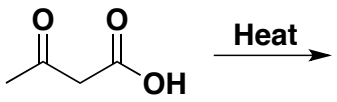


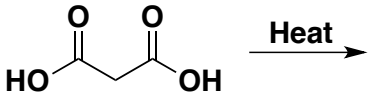
Decarboxylation

- Decarboxylation: loss of CO_2 from a carboxyl group
- Most carboxylic acids, if heated to a very high temperature (fried), undergo thermal decarboxylation
- Most carboxylic acids, however, are quite resistant to reasonable heat and melt or even boil without decarboxylation

Decarboxylation

- Exceptiogroup beta to the carboxyl group
  - ketocarboxylic acid undergoes decarboxylation on mild heating
- ns are carboxylic acids that have a carbonyl





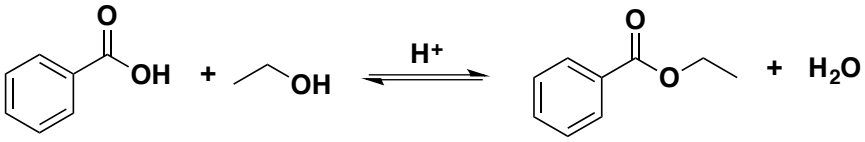
Decarboxylation Mechanism

Nucleophilic Acyl Addition Elimination

This is a very IMPORTANT general reaction. Understanding the mechanism allows one to explain and predict a large body of organic chemistry!

Acid-catalyzed Esterification

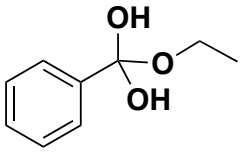
(also called Fischer esterification)



- Important fact: the oxygen of the alcohol is incorporated into the ester as shown.

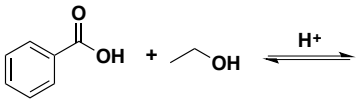
Mechanism of Fischer Esterification

- The mechanism involves two stages:
- 1) formation of tetrahedral intermediate (3 steps)
- 2) dissociation of tetrahedral intermediate (3 steps)



tetrahedral intermediate

First stage: formation of tetrahedral intermediate



Second stage: conversion of tetrahedral intermediate to ester