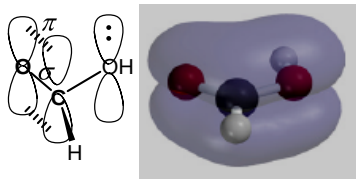
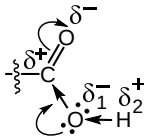
№ 28. CARBOXYLIC ACIDS. STRUCTURE OF CARBOXYLIC GROUP AND CHARACTERISTIC CHEMICAL REACTIONS FOR CARBOXYLIC ACIDS. REPRESENTATIVES.

I. Structure and bonding of the carboxyl group. The essential structural features of carboxylic acids can be illustrated by referring to the simples one – formic acid. Formic acid is a planar molecule, with one of its carbon-oxygen bonds significantly shorter than the other. The trigonal planar geometry is due to sp^2 hybridization of the carbon atom and shortened bond distance arises from multiple bonding of σ+π type. By analogy to aldehydes and ketones, the orbital description of bonding in carboxylic acids is shown as:

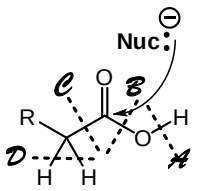


The two groups >C=O and –OH affect strongly each other so that they behave as a new functional group. The functional group of carboxylic acids is the carboxyl group –COOH. Notice that one p orbital (with electron pair) of the hydroxyl oxygen can be oriented in such way to permit orbital overlap with the π orbital of the carbonyl group. This overlap generates an extended and therefore more stable π system, which includes the carbon and both oxygen atoms of formic acid.

The carbonyl bond is polar, the carbon atom is considerably positively charged. The lone pair donation from the hydroxyl group, however, stabilizes the carbonyl group and renders it less electrophilic than that of an aldehyde or a ketone. Electron density is increased at the carbonyl oxygen, as shown:. This donation effect increases the polarity of -O–H bond and makes the bond between carbon and the hydroxyl group with a degree of "double bond character" due to delocalization of an electron pair. The effect is strong because of the conjugation between the carbonyl π electrons and the unshared electron pair at the oxygen of –OH group.



II. General scheme of the chemical properties of carboxylic acids. The chemical reactions of carboxylic acids may be classified according to the portion of –COOH or its surroundings they affect. They can be divided into four groups as indicated in the scheme:



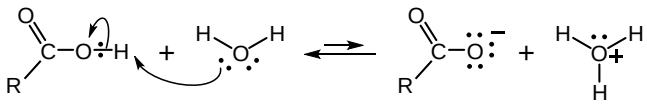
A - breaking the chemical bond between oxygen and hydrogen in OH of a carboxylic acid - dissociation and formation of salts;

B - Nucleophilic reactions leading to esters, acyl halides, amides, and acid anhydrides;

C - decarboxylation;

D - reactions after deprotonation of an α-hydrogen due to its acidity. (Its much higher in β-keto esters/acids.) These reactions are used for preparation of α-substituted carboxylic acids.

III. Acidity of carboxylic acids. The acidity is the most notable property of carboxylic acids, which are the most acidic class of compounds that contain only carbon, hydrogen, and oxygen. Although much weaker than mineral acids, carboxylic acids with ionization constants K_a on the order of 10^{-5} (pK_a~5), are much stronger acids than water and alcohols. Aqueous solutions of carboxylic acids are weakly acidic, pH<7. Though, the carboxylic acids are poor proton donors toward water and do not ionize completely. A 0.1 *M* solution of acetic acid in water, for example, is only 1.3 % ionized. An aqueous solution of carboxylic acid contains the following species in equilibrium:



$$K_a = \frac{[RCOO^-]\,[H_3O^+]}{[RCOOH]}$$

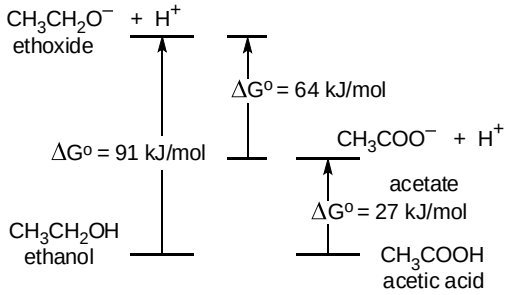
$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

carboxylic acid (weaker acid) | water (weaker base) | carboxylate ion (stronger base) | hydronium ion (stronger acid)

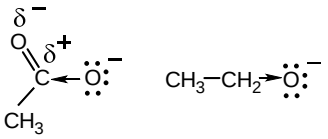
$$pK_a = -\lg K_a$$

In order to understand the greater acidity of carboxylic acids compared with water and alcohols, the structural changes that accompany the ionization of representative ethanol and acetic acid should be considered. The ethanol gives ethoxide anion with an ionization constant $K_a = 10^{-16}$. The negative charge in this ion is localized

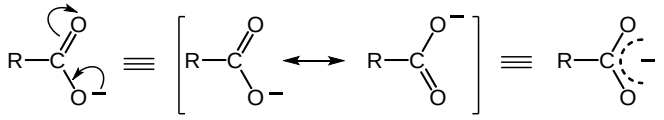
on oxygen and stabilized only by solvation forces. The ionization constant of acetic acid is $K_a = 1.8 \times 10^{-5}$. From these K_a values one can calculate the free energies of ionization according to the relationship: $\Delta G° = -RT\ln K_a$. Since it is *equilibria*, not *rates*, of ionization that are being compared, the following diagram shows only the initial and final states. It is not necessary to be concerned about the energy of activation, since that affects only the rate of ionization, not the extend of ionization. The large difference in the respective free energies of ionization is generally attributed to a greater stabilization of acetate anion relative to ethoxide anion. The former is also stabilized by solvation but has two additional mechanisms for dispersing its negative charge that are not available to ethoxide ion. The more stable ion means that it is formed easier.

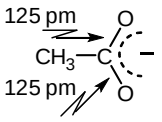


A) *The inductive effect of the carbonyl group*. The carbonyl group is electron-withdrawing, and by attracting electrons away from the negatively charged oxygen, acetate ion is stabilized. This is an inductive effect, transmitted through σ bond. The effect is absent in the ethoxide, even the +I effect of the alkyl group makes the charge more localized.



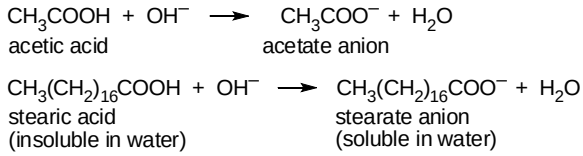
B) *The conjugation effect of the carbonyl group*. Electron delocalization causes the negative charge in acetate to be shared equally by both oxygens. This effect can be expressed with two border structures:

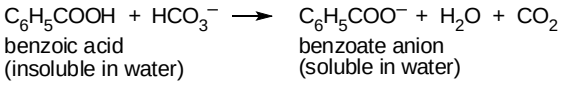




Electron delocalization is supported by structural, experimental studies that have shown significant differences in the carbon-oxygen bond lengths of carboxylic acids and their anions. As expected, in acetic acid the C=O double bond is shorter than the C-O single bond distance. In ammonium acetate, the two C-O bond distances are equal, as they should be according to the molecular orbital picture of bonding in carboxylate anions.

Toward relatively strong bases, such as the hydroxide, carbonate, and bicarbonate ions, carboxylic acids are good proton donors. The reactions are called neutralization reactions and are usually quantitative for alkali hydroxides and carbonates.



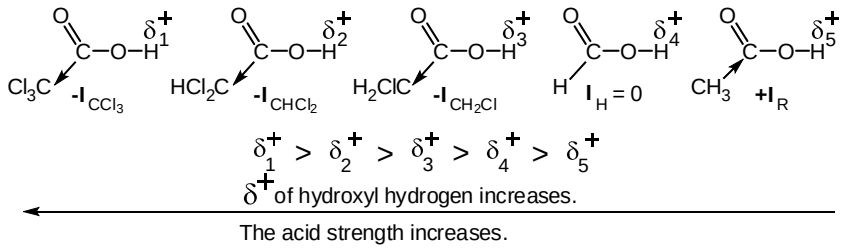


Bicarbonate ion serves a crucial role in the physiological pH buffering system. The bicarbonate ion in the body fluids helps to neutralize the carboxylic acids produced by normal metabolism. The buffer system provides prompt resistance to drastic pH changes (as small as 0.2 pH units), e.g. blood may become too acidic that threatens life.

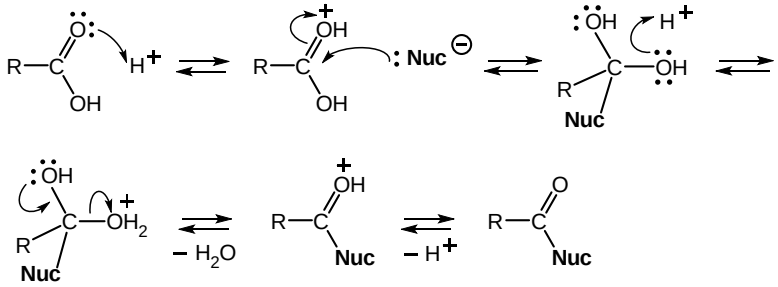
Some of the equations above show that an H^+ makes decisive difference in solubility of several species. The COOH can be considered a "solubility switch" for an entire molecule because a water-insoluble carboxylic acid (with more than 6 carbon atoms) almost instantly dissolves in aqueous base and RCOOH changes into $RCOO^-$. Analogously, a water-soluble carboxylate salt ($RCOO^-$) instantly changes to much less soluble RCOOH when aqueous strong acid is added. For this reason, by adjusting pH of an aqueous solution, a substance containing COOH group can be made more soluble or less soluble in water. These reversible changes have application in isolation and purification of compounds with COOH groups.

Substituents and acid strength. The nature of the group bonded to a COOH group affects its properties, e.g. the acid strength. The acidity of a carboxylic acid is little affected by alkyl substituents. Electronegative substituents, particularly when they are attached to the α-carbon atom, significantly increase the acidity of a carboxylic acid. Multiple halogen substitution increases the acidity even more; trichloroacetic acid is 7000 times more acidic than acetic acid. The effect can be explained with the increased polarity of O-H

bond and increased stability of the resulting ion after dissociation. The acid-strengthening effect of electronegative atoms or groups is attributed to an inductive (–I) effect of the substituent transmitted through the σ bonds of the molecule. The σ electrons in the carbon-chlorine bond of chloroacetate anion are drawn toward chlorine, leaving the α carbon with a slight positive charge. Because of this character, the α carbon attracts electrons from the negatively charged carboxylate, thus dispersing the charge and stabilizing the anion. The more stable the anion, the greater is the equilibrium constant for its formation, hence the greater is the acidity. Inductive effects diminish rapidly as the number of σ bonds between the reaction center and the polar substituent increases. The acid-strengthening effect of a halogen decreases as it becomes more remote from the carboxyl group.



IV. Nucleophilic acyl substitution – conversion into derivatives. The already described inductive and conjugation effects in the carboxyl group cause decreased polarity of the carbonyl group. As a result, unlike typical carbonyl compounds (aldehydes and ketones), the carboxylic acids and their derivatives undergo nucleophilic acyl substitution which begins with nucleophilic addition but it is followed by elimination. In order to replace an -OH group which is a poor leaving group, often acidic catalysis is necessary.



The mechanism of nucleophilic acyl substitution comprises the following steps that are common for all cases of such reactions:

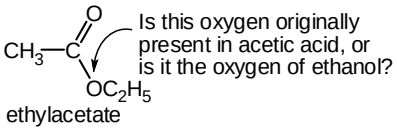
1) Protonation of the carbonyl oxygen activates the carboxylic acid;

2) A nucleophilic attack follows that yields a tetrahedral intermediate (the nucleophile **Nuc** can be not only negatively charged but also R-OH, R-NH_2, R-SH).

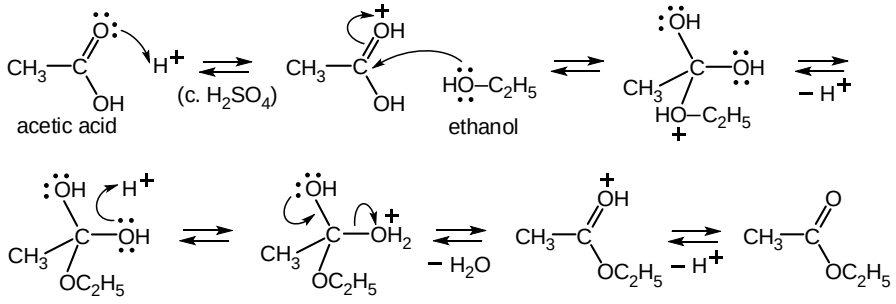
3) Transfer of another proton converts the OH group into good leaving group in another tetrahedral intermediate.

4) Elimination of water.

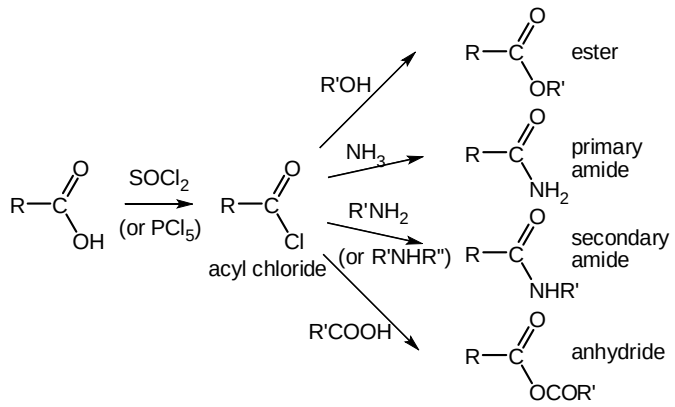
5) Loss of proton regenerates the carbonyl group in trigonal shape.



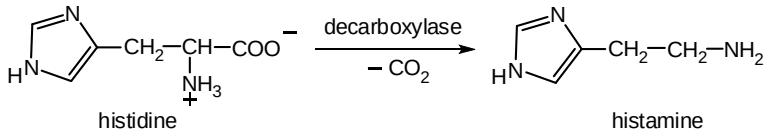
Acid-catalyzed esterification of carboxylic acids is one of the fundamental reactions of organic chemistry. The proposed above general mechanism for nucleophilic acyl substitution gives answer to the question "Does the alkoxy oxygen in an ester originate from the alcohol or it is present in the original acid?". The clear-cut answer was provided by experiments using ^{18}O labeled alcohol. The resulting ester was found to contain all the label from the alcohol. The mechanism consistent with this finding includes breaking of C-O bond that is without the isotopic label in the tetrahedral intermediate, and preserving C-O bond with the label.



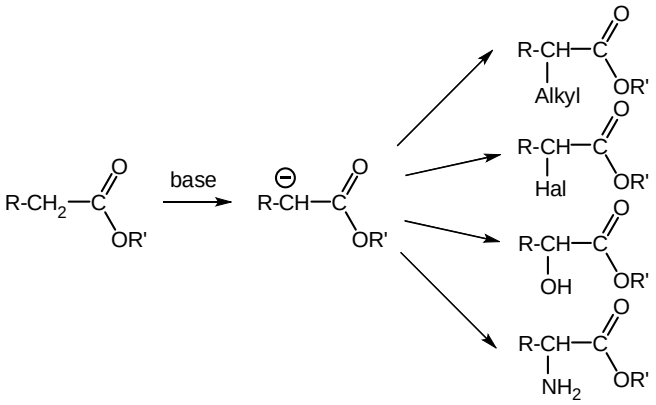
Carboxylic acids can be converted into variety of derivatives using the corresponding acyl chlorides. They are readily prepared from the acids and thionyl chloride or phosphorus pentachloride. The acid chlorides are much more reactive than acids in nucleophilic acyl substitution reactions. This is due to the easiness with which the tetrahedral intermediate loses chloride ion. It is better leaving group than hydroxide and its loss restores the conjugated carbonyl group in the derivative. All chemical reactions on the left proceed via similar mechanism described in the general scheme (see previous page). They differ with respect to the nucleophile that attacks the carbonyl group in the acyl chloride.



V. Decarboxylation. The loss of a molecule of carbon dioxide (CO_2) from a carboxylic acid is known as decarboxylation reaction. Decarboxylation of simple carboxylic acids takes place with great difficulty and is rarely encountered. Much easier is the decarboxylation of carboxylic acids that have second carbonyl group at β position relative to COOH and such decarboxylations have synthetic value. Besides synthesis, biochemical reaction that amino acids can undergo is decarboxylation to an amine. For example, decarboxylation of histidine gives histamine. It is a powerful vasodilator, normally present in tissue. Histamine is responsible for many of the symptoms associated with hay fever and other allergies.



VI. Substitution of the α hydrogen atoms. The α hydrogen atoms of carboxylic acids (and their derivatives) are more acidic than the rest (β, γ etc) due to influence of the carboxyl group that can delocalize a negative charge on the α carbon when such is generated. Because of higher reactivity, the α hydrogen atoms can be replaced by a number of functional groups, often under basic conditions, to give α substituted carboxylic acids.



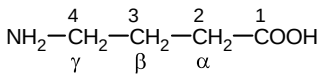
VII. Representatives of unsubstituted carboxylic acids

1. Saturated monocarboxylic acids

Acid		Name	Number of C atoms
HCOOH		**Formic** (methanoic)	1
CH_3COOH		**Acetic** (ethanoic)	2
CH_3CH_2COOH	C_2H_5COOH	**Propionic** (propanoic)	3
$CH_3(CH_2)_2COOH$	C_3H_7COOH	**Butyric** (butanoic)	4
$CH_3(CH_2)_3COOH$	C_4H_9COOH	**Valeric** (pentanoic)	5
$CH_3(CH_2)_4COOH$	$C_5H_{11}COOH$	**Caproic** (hexanoic)	6
			With even number of C atoms
$CH_3(CH_2)_6COOH$	$C_7H_{15}COOH$	**Caprylic** (octanoic)	8
$CH_3(CH_2)_8COOH$	$C_9H_{19}COOH$	**Capric** (decanoic)	10
$CH_3(CH_2)_{10}COOH$	$C_{11}H_{23}COOH$	**Lauric** (dodecanoic)	12

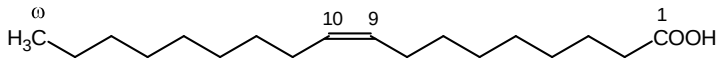
$CH_3(CH_2)_{12}COOH$	$C_{13}H_{27}COOH$	**Myristic** (tetradecanoic)	14
$CH_3(CH_2)_{14}COOH$	$C_{15}H_{31}COOH$	**Palmitic** (hexadecanoic)	16
$CH_3(CH_2)_{16}COOH$	$C_{17}H_{35}COOH$	**Stearic** (octadecanoic)	18
$CH_3(CH_2)_{18}COOH$	$C_{19}H_{39}COOH$	**Arachidic** (eicosanoic)	20

Note on nomenclature: The trivial and more common names above are given in bold. When using them and the chain has substituents, their position is shown by Greek letters, α, β, γ, etc., excluding the carbon of COOH group. Thus, the α-carbon is adjacent to the carboxyl group, as illustrated with γ-aminobutyric acid. If the IUPAC name is used, then the carboxyl carbon is always numbered 1, and the adjacent to it is 2. The IUPAC nomenclature for carboxylic acids uses the alkane name that corresponds to the longest carbon chain in the acid. The ending –e in the alkane name is replaced by suffix –ioc acid.

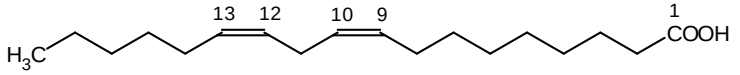


4-aminobutanoic acid
γ-aminobutyric acid

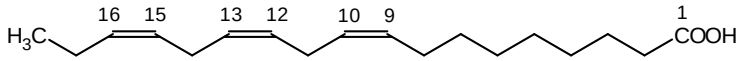
2. Unsaturated monocarboxylic acids



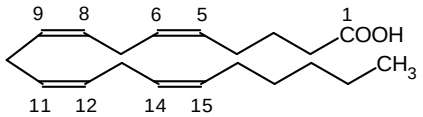
$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Oleic acid (*cis*-9-octadecenoic acid)



$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$
Linoleic acid (*cis,cis*-9,12-octadecadienoic acid)



$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COOH$
Linolenic acid (*cis,cis,cis*-9,12,15-octadeca-trienoic acid)

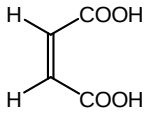


$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COOH$
Arachidonic acid (*cis,cis,cis,cis*-5,8,11,14-eicosatetraenoic acid)

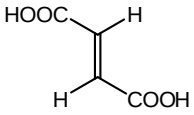
3. Saturated dicarboxylic acids

Acid		Name
HOOC-COOH	($H_2C_2O_4$)	**Oxalic acid** (ethanedioic acid)
$HOOC\text{-}CH_2\text{-}COOH$		**Malonic acid** (propanedioic acid)
$HOOC\text{-}(CH_2)_2\text{-}COOH$		**Succinic acid** (butanedioic acid)
$HOOC\text{-}(CH_2)_3\text{-}COOH$		**Glutaric acid** (pentanedioic acid)
$HOOC\text{-}(CH_2)_4\text{-}COOH$		**Adipic acid** (hexanedioic acid)
$HOOC\text{-}(CH_2)_5\text{-}COOH$		**Pimelic acid** (heptanedioic acid)

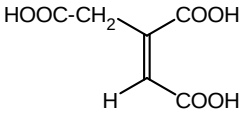
4. Unsaturated dicarboxylic acids



maleic acid
(*Z*)-butenedioic acid

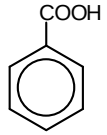


fumaric acid
(*E*)-butenedioic acid

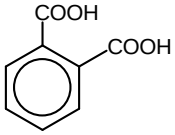


***cis*-aconitic acid**

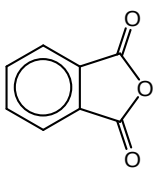
5. Aromatic carboxylic acids



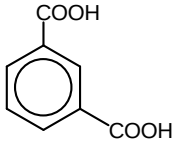
benzoic acid



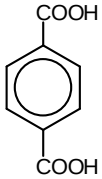
phthalic acid
(benzene-1,2-dicar-boxylic acid)



phthalic anhydride



isophthalic acid
(benzene-1,3-dicar-boxylic acid)



terephthalic acid
(benzene-1,4-dicar-boxylic acid)