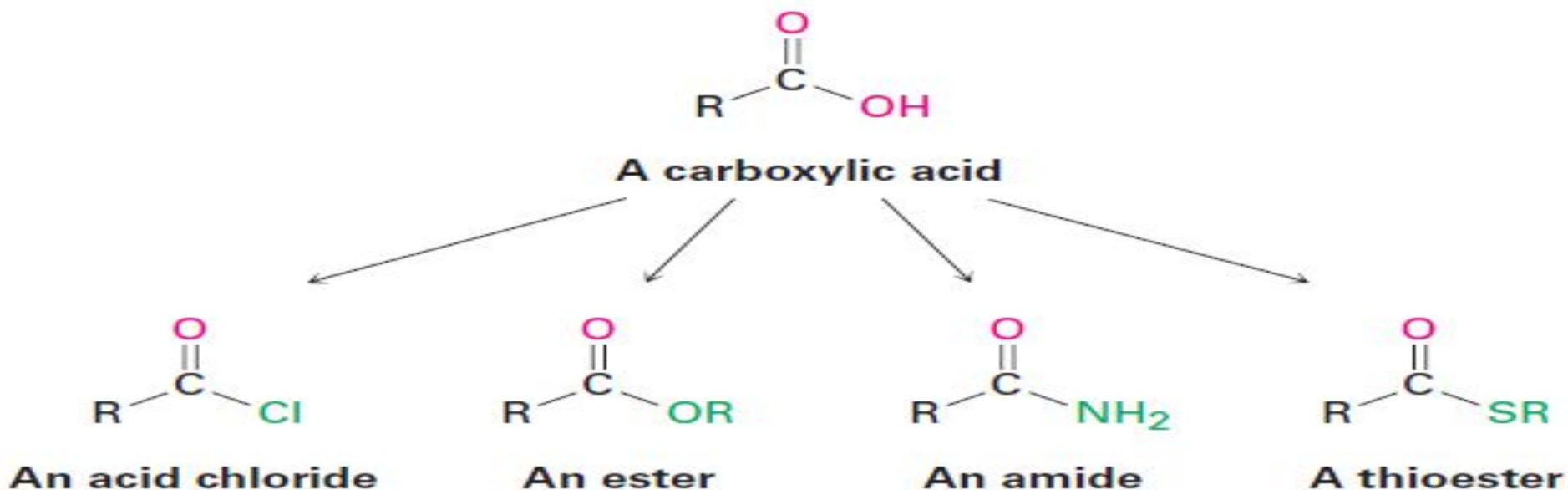


Organic Chemistry

Lec:2

Carboxylic acids

Carboxylic acids, RCO_2H , occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous carboxylic acid derivatives such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways.

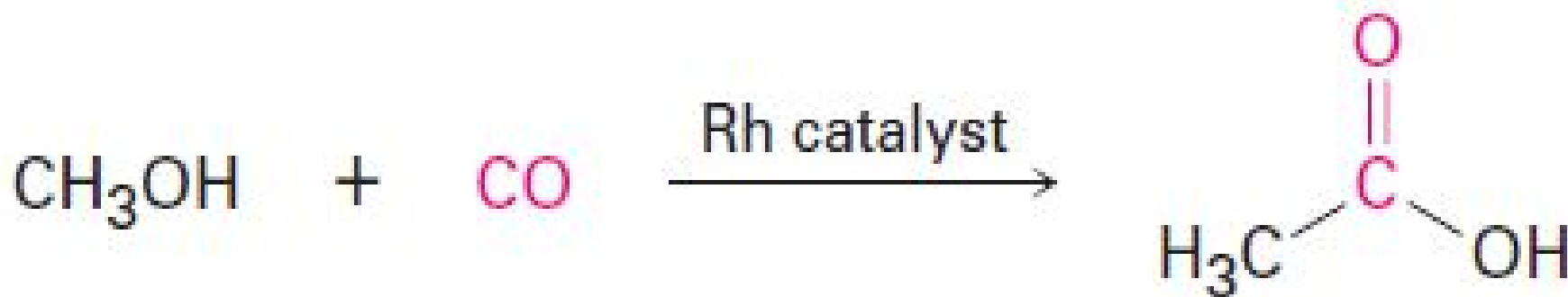


many carboxylic acids are found in nature:

acetic acid, $\text{CH}_3\text{CO}_2\text{H}$, is the chief organic component of vinegar; butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$, is responsible for the unmistakable aroma of goats and dirty gym socks. Other examples are cholic acid, a major component of human bile, and long-chain aliphatic acids such as palmitic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, a biological precursor of fats and vegetable oils.

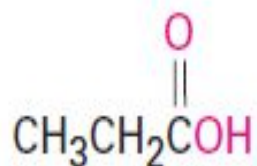
acetic acid is produced worldwide each year for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives.

About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.

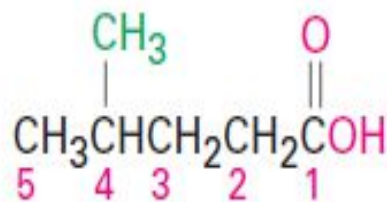


Naming of carboxylic acid

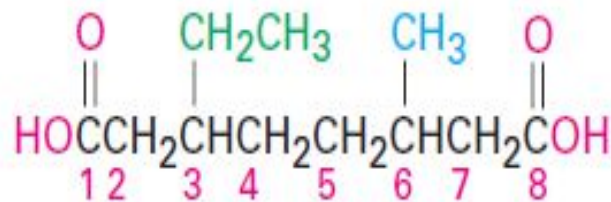
Simple carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. The $-\text{CO}_2\text{H}$ carbon atom is numbered C1.



Propanoic acid

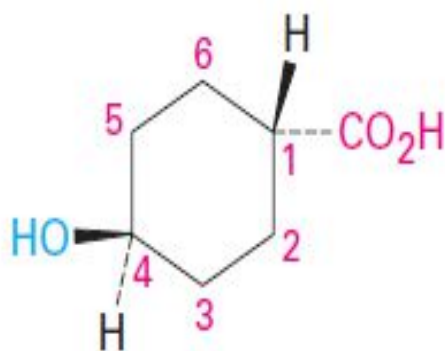


4-Methylpentanoic acid

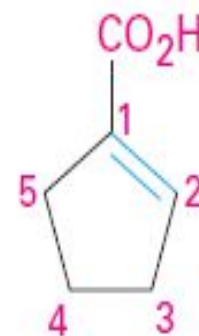


3-Ethyl-6-methyloctanedioic acid

Compounds that have a $-\text{CO}_2\text{H}$ group bonded to a ring are named using the suffix *-carboxylic acid*. The CO_2H carbon is attached to C1 in this system and is not itself numbered. As a substituent, the CO_2H group is called a **carboxyl group**.



trans-4-Hydroxycyclohexanecarboxylic acid



1-Cyclopentenecarboxylic acid

Table 20.1 Common Names of Some Carboxylic Acids and Acyl Groups

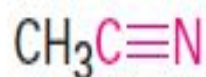
Structure	Name	Acyl group
HCO_2H	Formic	Formyl
$\text{CH}_3\text{CO}_2\text{H}$	Acetic	Acetyl
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	Propionic	Propionyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Butyric	Butyryl
$\text{HO}_2\text{CCO}_2\text{H}$	Oxalic	Oxalyl
$\text{HO}_2\text{CCH}_2\text{CO}_2\text{H}$	Malonic	Malonyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Succinic	Succinyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Glutaric	Glutaryl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Adipic	Adipoyl
$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	Acrylic	Acryloyl
$\text{HO}_2\text{CCH}=\text{CHCO}_2\text{H}$	Maleic (cis)	Maleoyl
	Fumaric (trans)	Fumaroyl
$\text{HOCH}_2\text{CO}_2\text{H}$	Glycolic	Glycoloyl

Nitriles, $\text{RC}\equiv\text{N}$

Compounds containing the $-\text{C}\equiv\text{N}$ functional group are called **nitriles** and undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.

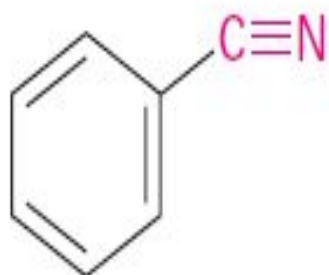


Nitriles can also be named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile*, or by replacing the *-carboxylic acid* ending with *-carbonitrile*. The nitrile carbon atom is attached to C1 but is not itself numbered.



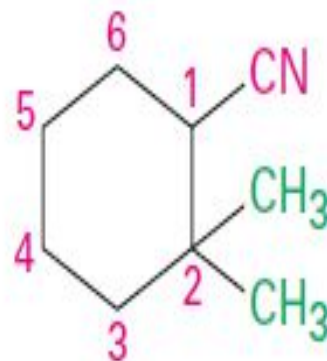
Acetonitrile

(from acetic acid)



Benzonitrile

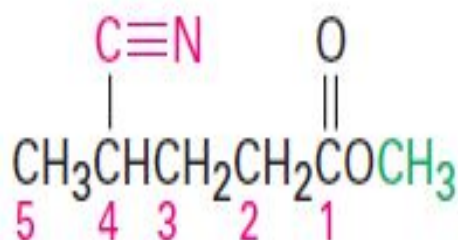
(from benzoic acid)



2,2-Dimethylcyclohexanecarbonitrile

(from 2,2-dimethylcyclohexane-carboxylic acid)

If another carboxylic acid derivative is present in the same molecule, the prefix *cyano-* is used for the $\text{C}\equiv\text{N}$ group.

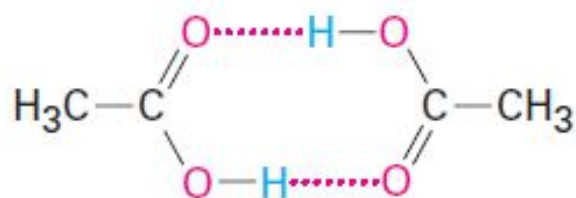


Methyl 4-cyanopentanoate

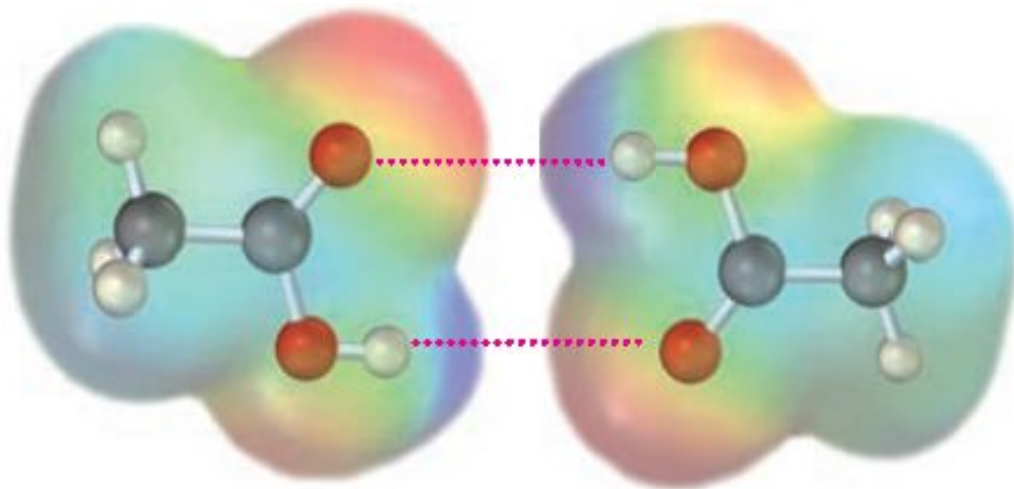
Properties of carboxylic acid

Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2 -hybridized, and carboxylic acid groups are therefore planar with C – C=O and O=C – O bond angles of approximately 120° .

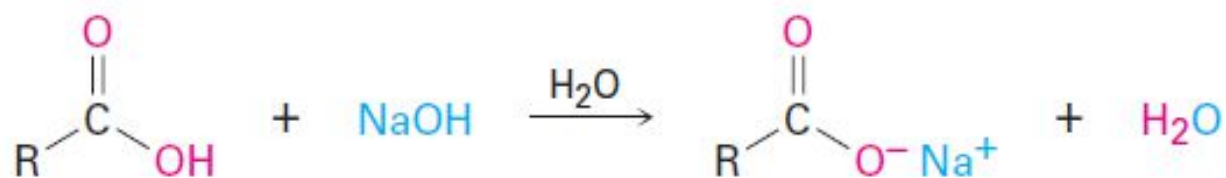
Like alcohols, carboxylic acids are strongly associated because of hydrogen bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding alcohols. Acetic acid, for instance, has a boiling point of 117.9°C , versus 78.3°C for ethanol, even though both compounds have two carbons.



Acetic acid dimer



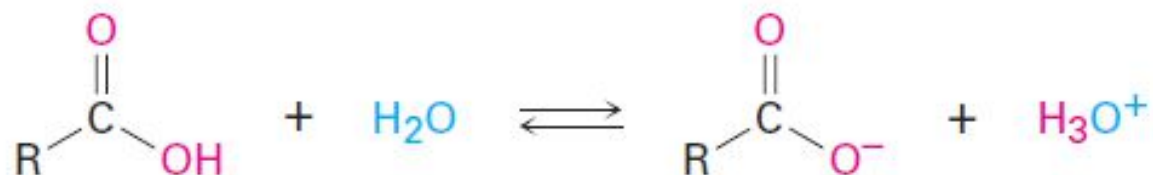
The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. They therefore react with bases such as NaOH and NaHCO₃ to give metal carboxylate salts, RCO₂⁻ M⁺. Carboxylic acids with more than six carbons are only slightly soluble in water, but the alkali metal salts of carboxylic acids are often highly water-soluble. In fact, it's often possible to purify an acid by extracting its salt into aqueous base, then reacidifying and extracting the pure acid back into an organic solvent.



A carboxylic acid
(water-insoluble)

A carboxylic acid salt
(water-soluble)

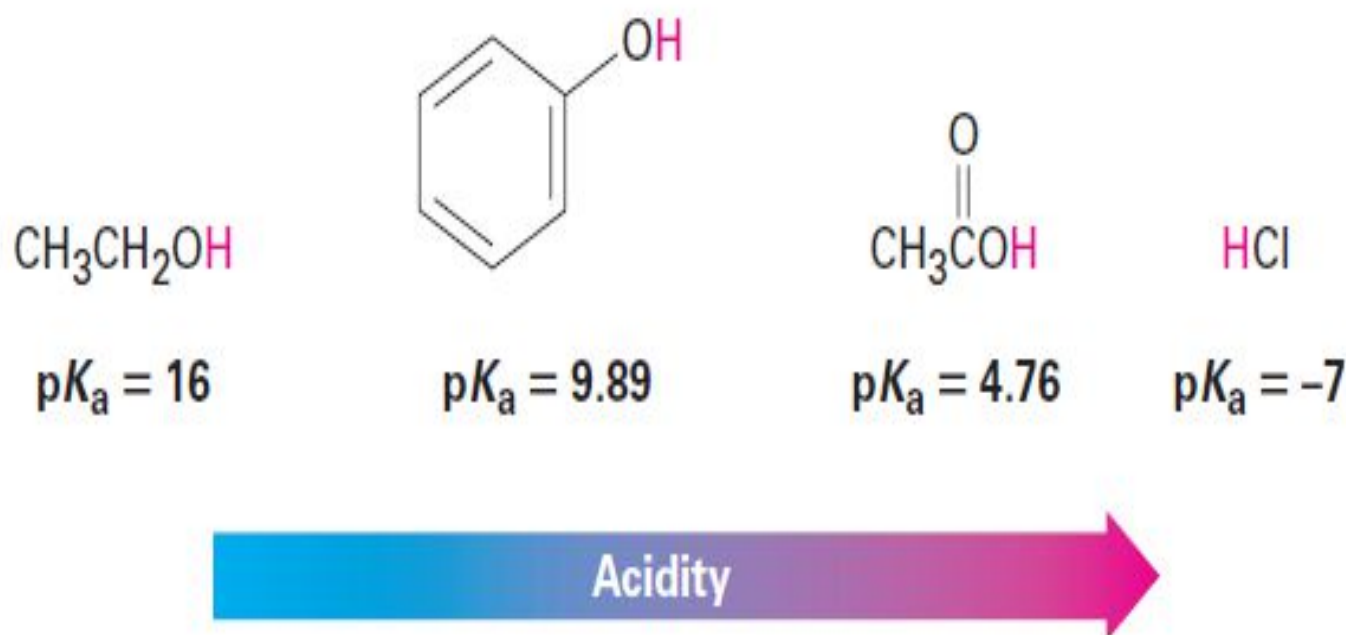
Like other Brønsted–Lowry acids, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ and the corresponding carboxylate anions, RCO_2^- . The extent of dissociation is given by an acidity constant, K_a .



$$K_a = \frac{[\text{RCO}_2^-][\text{H}_3\text{O}^+]}{[\text{RCO}_2\text{H}]} \quad \text{and} \quad \text{p}K_a = -\log K_a$$

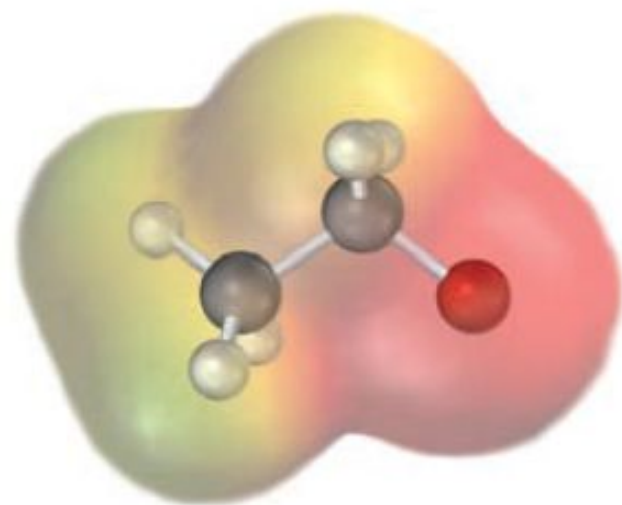
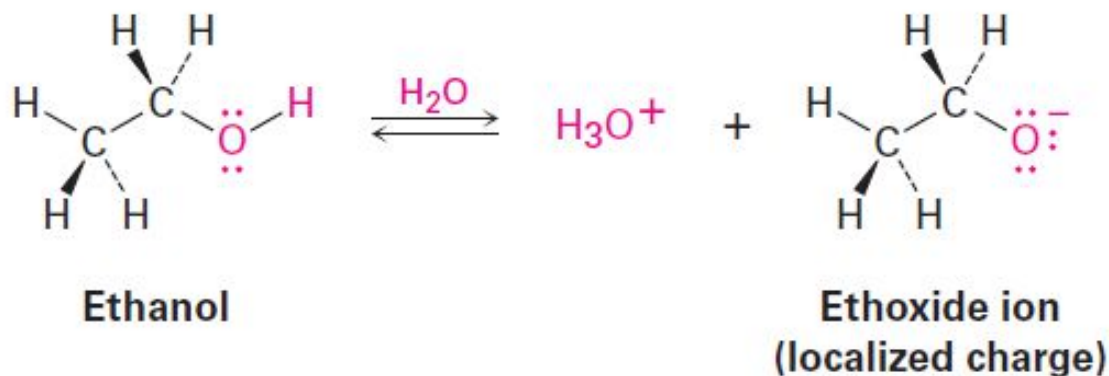
A list of K_a values for various carboxylic acids is given in Table 20.3. For most, K_a is approximately 10^{-4} to 10^{-5} . Acetic acid, for instance, has $K_a = 1.75 \times 10^{-5}$ at 25°C , which corresponds to a $\text{p}K_a$ of 4.76. In practical terms, a K_a value near 10^{-5} means that only about 0.1% of the molecules in a 0.1 M solution are dissociated, as opposed to the 100% dissociation found with strong mineral acids like HCl.

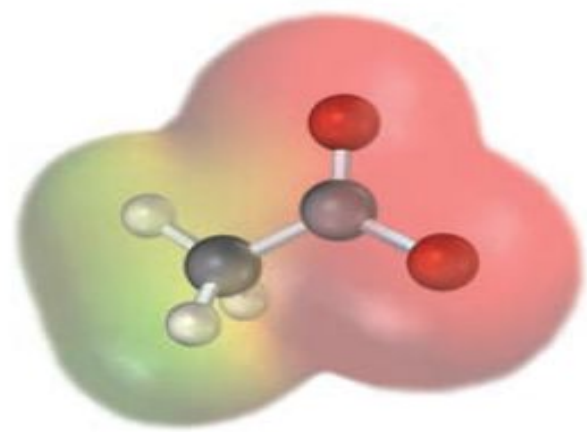
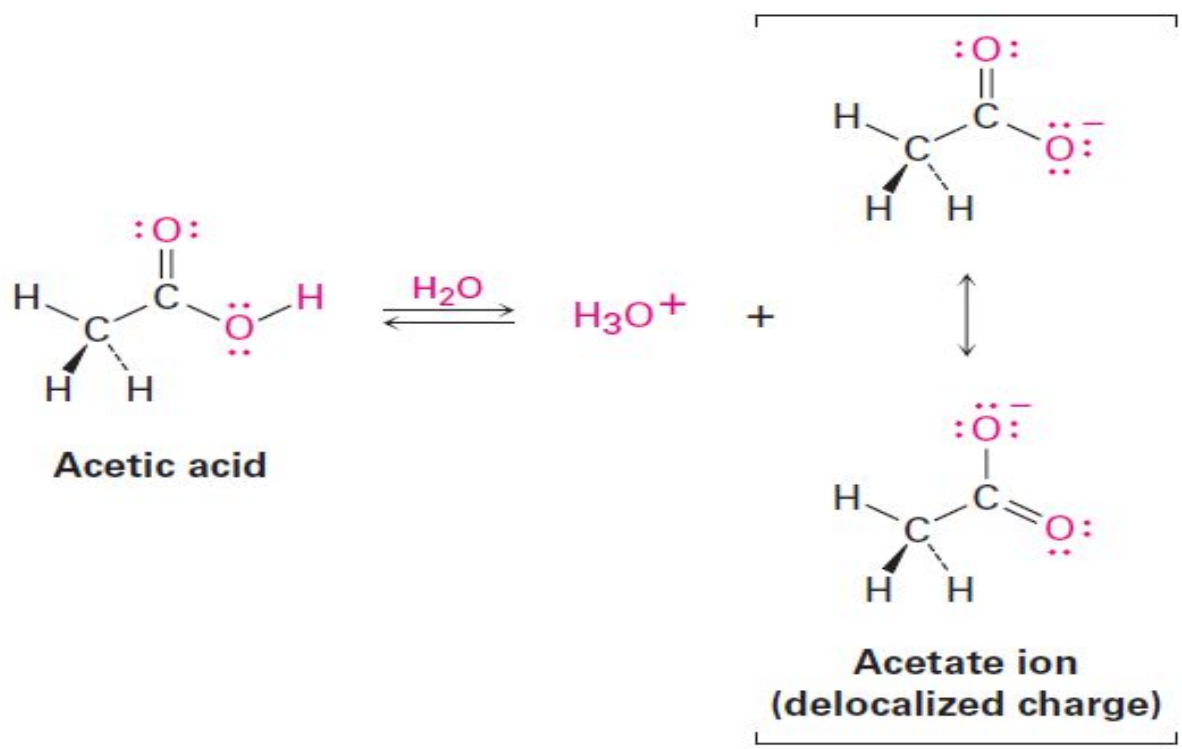
Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16} , making ethanol a weaker acid than acetic acid by a factor of 10^{11} .



Why are carboxylic acids so much more acidic than alcohols, even though both contain $-OH$ groups? An alcohol dissociates to give an alkoxide ion, in

which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge is delocalized over two equivalent oxygen atoms. In resonance terms, a carboxylate ion is a stabilized resonance hybrid of two equivalent structures. Since a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and more favored in the dissociation equilibrium.





Biological Acids and the Henderson–Hasselbalch Equation

In acidic solution, at low pH, a carboxylic acid is completely undissociated and exists entirely as RCO_2H . In basic solution, at high pH, a carboxylic acid is completely dissociated and exists entirely as RCO_2^- . Inside living cells, however, the pH is neither acidic nor basic but is instead buffered to nearly neutral pH—in humans, to $\text{pH} = 7.3$, a value often referred to as *physiological pH*. In what form, then, do carboxylic acids exist inside cells? The question is an important one for understanding the acid catalysts so often found in biological reactions.

If the pK_a value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using the Henderson–Hasselbalch equation. For any acid HA, we have

$$\begin{aligned} pK_a &= -\log \frac{[H_3O^+][A^-]}{[HA]} = -\log [H_3O^+] - \log \frac{[A^-]}{[HA]} \\ &= pH - \log \frac{[A^-]}{[HA]} \end{aligned}$$

which can be rearranged to give

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Henderson–Hasselbalch equation

so
$$\log \frac{[A^-]}{[HA]} = pH - pK_a$$

This equation says that the logarithm of the concentration of dissociated acid $[A^-]$ divided by the concentration of undissociated acid $[HA]$ is equal to the pH of the solution minus the pK_a of the acid. Thus, if we know both the pH of the solution and the pK_a of the acid, we can calculate the ratio of $[A^-]$ to $[HA]$. Furthermore, when $pH = pK_a$, the two forms HA and A^- are present in equal amounts because $\log 1 = 0$. As an example of how to use the Henderson–Hasselbalch equation, let's find out what species are present in a 0.0010 M solution of acetic acid at $pH = 7.3$.

The pK_a of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\log \frac{[A^-]}{[HA]} = \text{pH} - \text{pK}_a = 7.3 - 4.76 = 2.54$$

$$\frac{[A^-]}{[HA]} = \text{antilog}(2.54) = 3.5 \times 10^2 \quad \text{so} \quad [A^-] = (3.5 \times 10^2) [HA]$$

In addition, we know that

$$[A^-] + [HA] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives $[A^-] = 0.0010 \text{ M}$ and $[HA] = 3 \times 10^{-6} \text{ M}$. In other words, at a physiological pH of 7.3, essentially 100% of acetic acid molecules in a 0.0010 M solution are dissociated to the acetate ion.

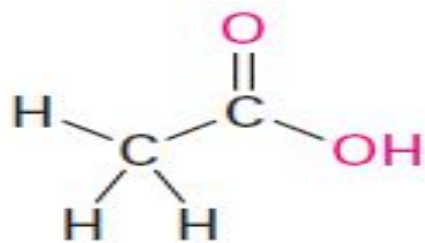
What is true for acetic acid is also true for other carboxylic acids: at the physiological pH that exists inside cells, carboxylic acids are almost entirely dissociated. To reflect this fact, we always refer to cellular carboxylic acids by the name of their anion—acetate, lactate, citrate, and so forth, rather than acetic acid, lactic acid, and citric acid.

Substituent Effects on Acidity

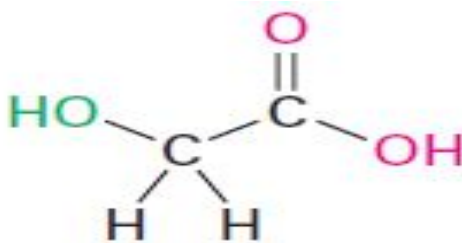
There are substantial differences in acidity from one carboxylic acid to another.

For example, trifluoroacetic acid ($K_a = 0.59$) is 33,000 times as strong as acetic acid ($K_a = 1.75 \times 10^{-5}$). How can we account for such differences? Because the dissociation of a carboxylic acid is an equilibrium process, any factor that stabilizes the carboxylate anion relative to undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity.

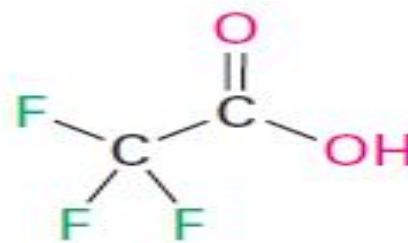
For instance, three electron-withdrawing fluorine atoms delocalize the negative charge in the trifluoroacetate anion, thereby stabilizing the ion and increasing the acidity of $\text{CF}_3\text{CO}_2\text{H}$. In the same way, glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$; $\text{p}K_a = 3.83$) is stronger than acetic acid because of the electron withdrawing effect of the electronegative oxygen atom.



$\text{p}K_a = 4.76$



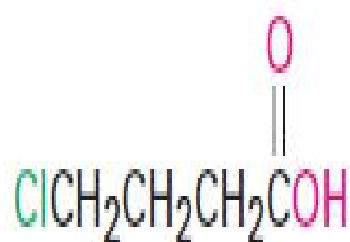
$\text{p}K_a = 3.83$



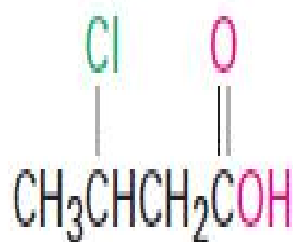
$\text{p}K_a = -0.23$



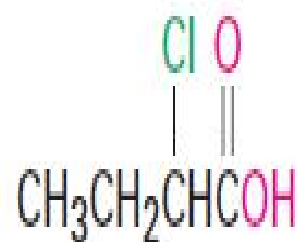
Because inductive effects operate through σ bonds and are dependent on distance, the effect of halogen substitution decreases as the substituent moves farther from the carboxyl. Thus, 2-chlorobutanoic acid has $pK_a = 2.86$, 3-chlorobutanoic acid has $pK_a = 4.05$, and 4-chlorobutanoic acid has $pK_a = 4.52$, similar to that of butanoic acid itself.



$$pK_a = 4.52$$



$$pK_a = 4.05$$



$$pK_a = 2.86$$



Substituent effects on acidity are also found in substituted benzoic acids. We said during the discussion of electrophilic aromatic substitution, that substituents on the aromatic ring strongly affect reactivity. Aromatic rings with electron-donating groups are activated toward further electrophilic substitution, and aromatic rings with electron-withdrawing groups are deactivated. Exactly the same effects are noticed on the acidity of substituted benzoic acids.

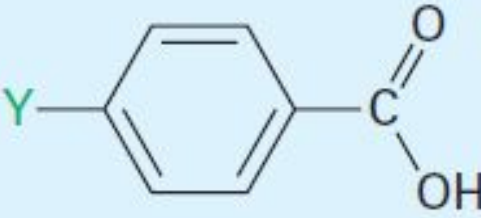
an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion and an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion.

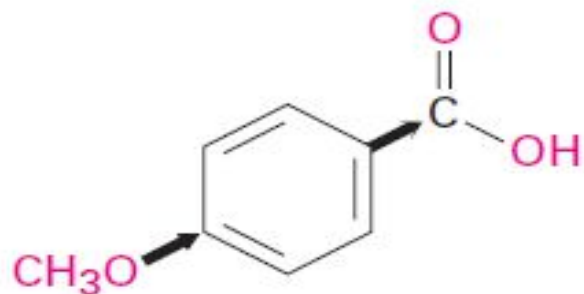
Table 20.4 Substituent Effects on Acidity of *p*-Substituted Benzoic Acids

Stronger acid

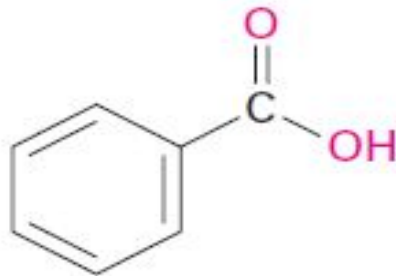


Weaker acid

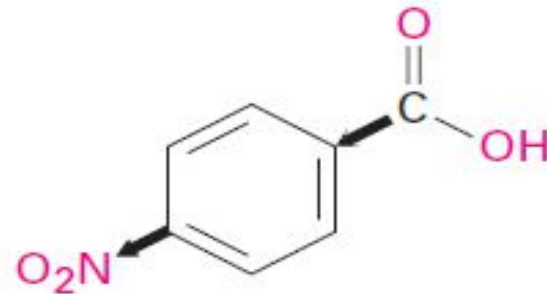
			
Y	$K_a \times 10^{-5}$	p <i>K</i> _a	
-NO ₂	39	3.41	Deactivating groups
-CN	28	3.55	
-CHO	18	3.75	
-Br	11	3.96	
-Cl	10	4.0	
-H	6.46	4.19	
-CH ₃	4.3	4.34	Activating groups
-OCH ₃	3.5	4.46	
-OH	3.3	4.48	



p-Methoxybenzoic acid
($pK_a = 4.46$)



Benzoic acid
($pK_a = 4.19$)



p-Nitrobenzoic acid
($pK_a = 3.41$)

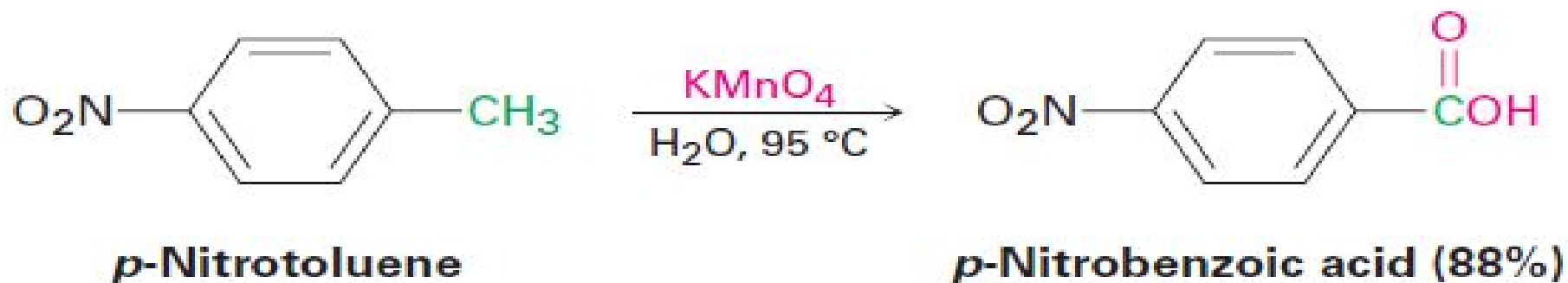


Because it's much easier to measure the acidity of a substituted benzoic acid than it is to determine the relative reactivity of an aromatic ring toward electrophilic substitution, the correlation between the two effects is useful for predicting reactivity. If we want to know the effect of a certain substituent on electrophilic reactivity, we can simply find the acidity of the corresponding benzoic acid.

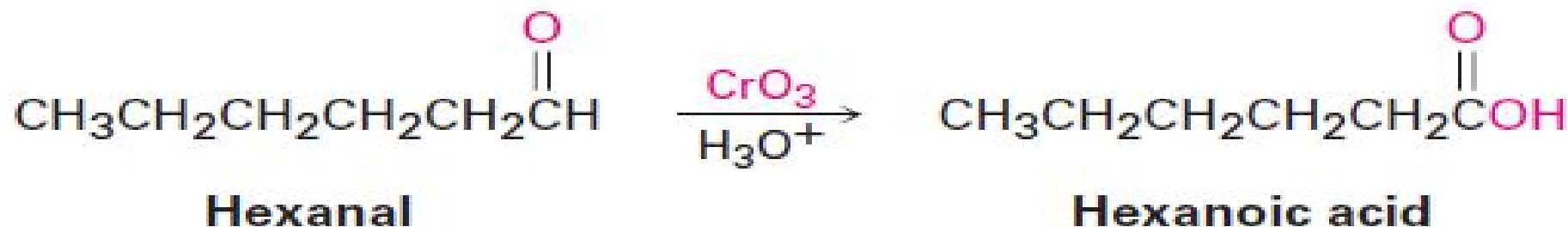
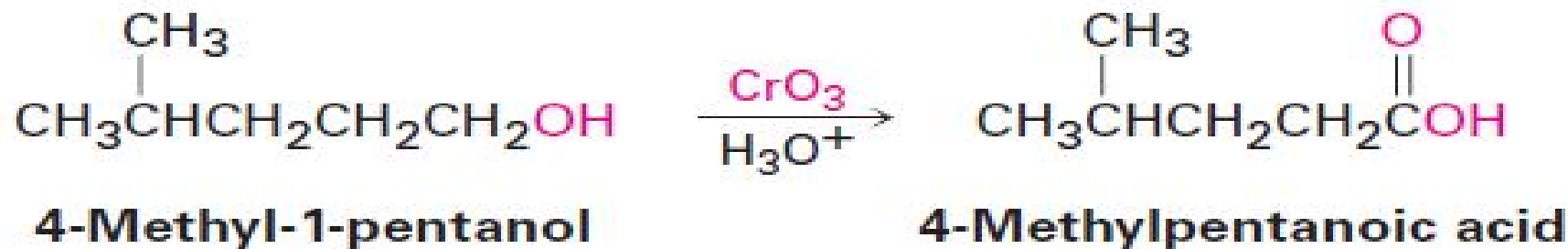
Preparing Carboxylic Acids

Some of the methods for preparing carboxylic acids

- Oxidation of a substituted alkylbenzene with KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ gives a substituted benzoic acid. Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



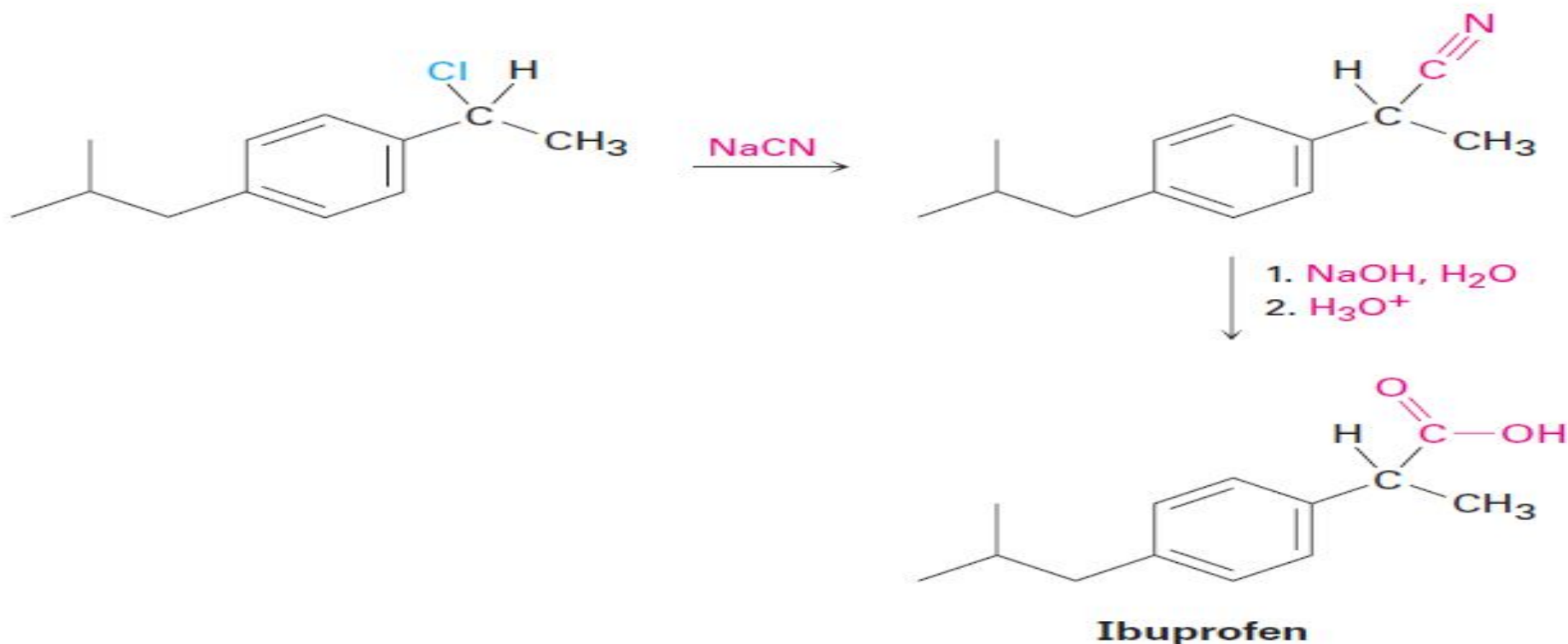
- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid. Primary alcohols are often oxidized with CrO_3 in aqueous acid, and aldehydes are similarly oxidized.



Hydrolysis of Nitriles

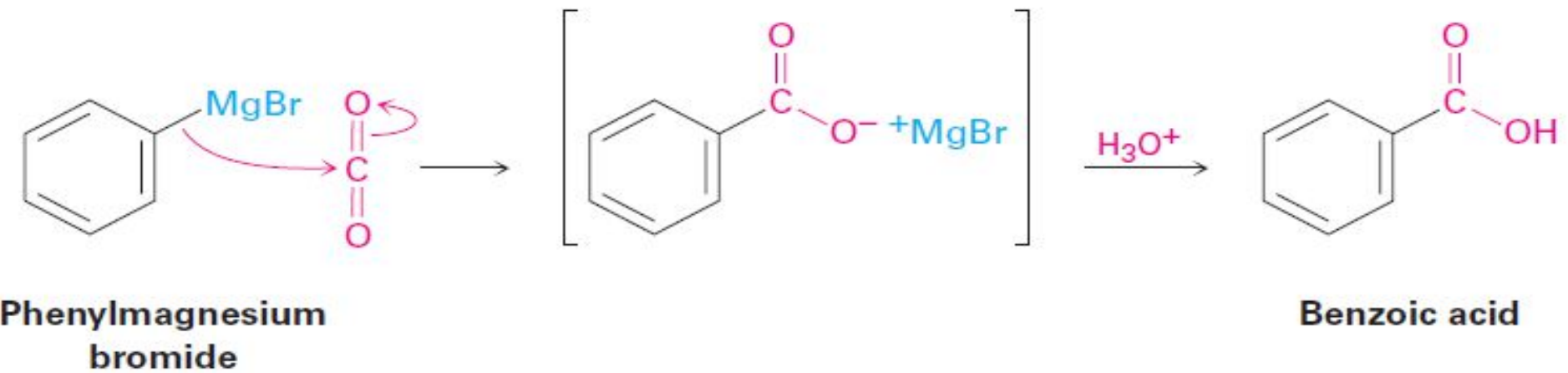
Carboxylic acids can be prepared from nitriles on heating with aqueous acid or base by a mechanism. Since nitriles themselves are usually made by $\text{S}_\text{N}2$ reaction of a primary or secondary alkyl halide with CN^- , the two-step sequence of cyanide displacement followed by

nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($\text{RBr} \rightarrow \text{RC} \equiv \text{N} \rightarrow \text{RCO}_2\text{H}$). Note that the product acid has one more carbon than the starting alkyl halide. An example occurs in one commercial route for the synthesis of the nonsteroidal anti-inflammatory drug ibuprofen.



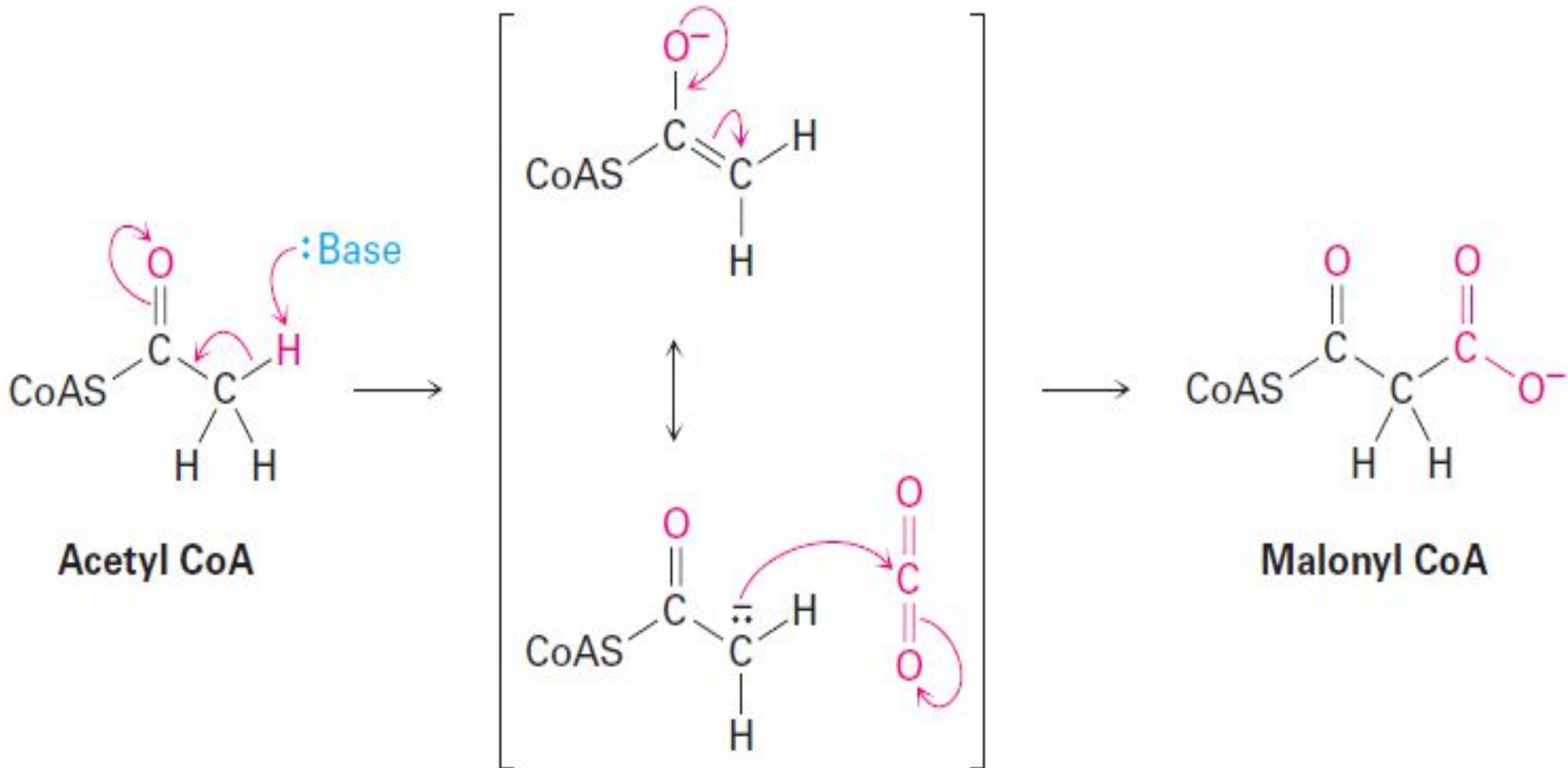
Carboxylation of Grignard Reagents

Another method for preparing carboxylic acids is by reaction of a Grignard reagent with CO_2 to yield a metal carboxylate, followed by protonation to give the carboxylic acid. This carboxylation reaction is usually carried out by bubbling a stream of dry CO_2 gas through a solution of the Grignard reagent. The organomagnesium halide adds to a C=O bond of carbon dioxide in a typical nucleophilic carbonyl addition reaction, and protonation of the carboxylate by addition of aqueous HCl in a separate step then gives the free carboxylic acid. For example



there are no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated.

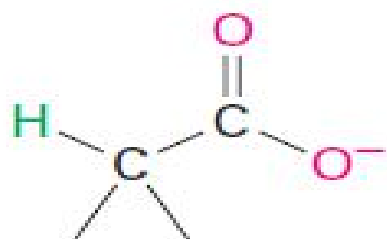
One of the initial steps in fatty-acid biosynthesis, for instance, involves formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.



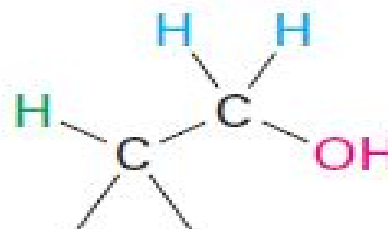
Reactions of Carboxylic Acids:

carboxylic acids are similar in some respects to both alcohols and ketones. Like alcohols, carboxylic acids can be deprotonated to give anions, which are good nucleophiles in S_N2 reactions. Like ketones,

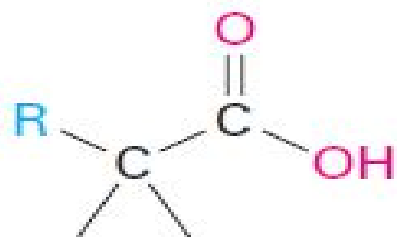
carboxylic acids undergo addition of nucleophiles to the carbonyl group. In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones.



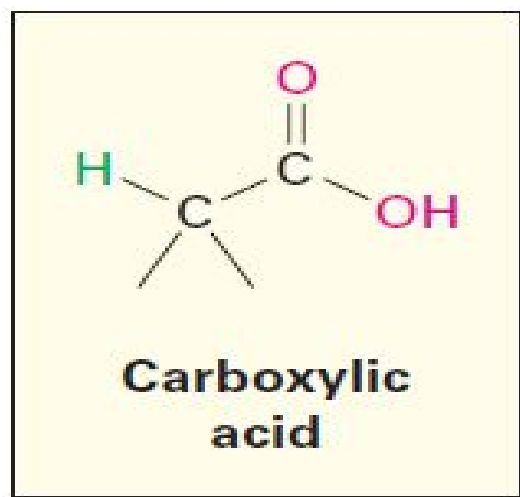
Deprotonation



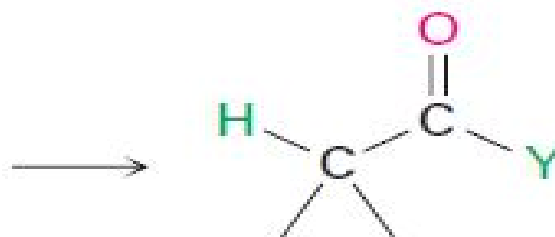
Reduction



**Alpha
substitution**



**Carboxylic
acid**



**Nucleophilic acyl
substitution**

Vitamin C

The word *vitamin*, despite its common usage, is actually an imprecise term. Generally speaking, a vitamin is an organic substance that a given organism requires in small amounts to live and grow but is unable to synthesize and must obtain in its diet. Thus, to be considered a vitamin, only a *small* amount of the substance is needed—anywhere from a few micrograms to 100 mg or so per day. Dietary substances needed in larger amounts, such as some amino acids and unsaturated fats, are not considered vitamins. Furthermore, different organisms need different vitamins.

More than 4000 species of mammals can synthesize ascorbic acid in their bodies, for instance, but humans are not among them. Ascorbic acid is therefore a human vitamin—what we all know as vitamin C—and must be obtained in our diet. Small amounts of more than a dozen other substances are similarly required by humans: retinol (vitamin A), thiamine (vitamin B1), and tocopherol (vitamin E), for instance. Vitamin C is surely the best known of all human vitamins. combined. In addition to its use as a vitamin supplement, vitamin C is used as a food preservative, a “flour improver” in bakeries, and an animal food additive.

Vitamin C is perhaps most well known for its antiscorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high.

In more recent times, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in acquired immunodeficiency syndrome (AIDS), and inhibit the development of gastric and cervical cancers. None of these claims have been backed by medical evidence. Vitamin C does appear to decrease the cold's duration by perhaps a day.