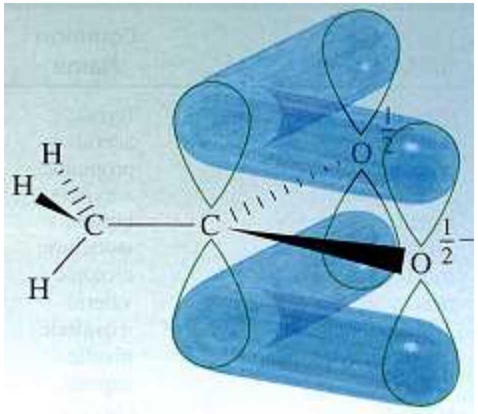
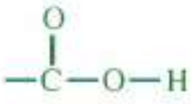
Carboxylic Acids

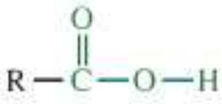


The combination of a **carbo**nyl group and a hydr**oxyl** on the same carbon atom is called a **carboxyl group**. Compounds containing the carboxyl group are distinctly acidic and are called **carboxylic acids**.



$-\overset{\overset{\displaystyle O}{\|}}{C}-O-H$

carboxyl group

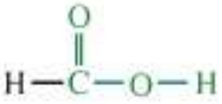


$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-H$

carboxylic acid

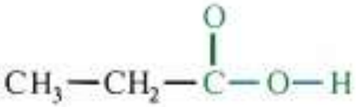
$R-COOH \quad R-CO_2H$

condensed structures



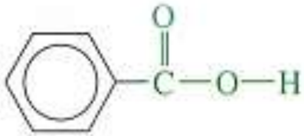
$H-\overset{\overset{\displaystyle O}{\|}}{C}-O-H$

formic acid

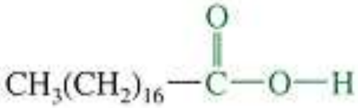


$CH_3-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-O-H$

propionic acid
(an aliphatic acid)



benzoic acid
(an aromatic acid)



$CH_3(CH_2)_{16}-\overset{\overset{\displaystyle O}{\|}}{C}-O-H$

stearic acid
(a fatty acid)

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-H + H_2O \rightleftharpoons R-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + H_3O^+$$

carboxylic acid　　carboxylate ion

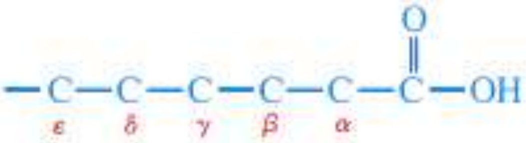
Nomenclature of Carboxylic Acids

Common Names

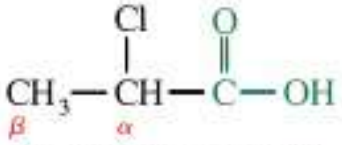
TABLE 20-1 Names and Physical Properties of Some Carboxylic Acids

IUPAC Name	Common Name	Formula	mp (°C)	bp (°C)	Solubility (g/100 g H_2O)
methanoic	formic	$HCOOH$	8	101	∞ (miscible)
ethanoic	acetic	CH_3COOH	17	118	∞
propanoic	propionic	CH_3CH_2COOH	−21	141	∞
2-propenoic	acrylic	$H_2C{=}CH-COOH$	14	141	∞
butanoic	butyric	$CH_3(CH_2)_2COOH$	−6	163	∞

2-methylpropanoic	isobutyric	$(CH_3)_2CHCOOH$	−46	155	23.0
trans-2-butenoic	crotonic	$CH_3-CH=CH-COOH$	71	185	8.6
pentanoic	valeric	$CH_3(CH_2)_3COOH$	−34	186	3.7
3-methylbutanoic	isovaleric	$(CH_3)_2CHCH_2COOH$	−29	177	5.0
2,2-dimethylpropanoic	pivalic	$(CH_3)_3C-COOH$	35	164	2.5
hexanoic	caproic	$CH_3(CH_2)_4COOH$	−4	206	1.0
octanoic	caprylic	$CH_3(CH_2)_6COOH$	16	240	0.7
decanoic	capric	$CH_3(CH_2)_8COOH$	31	269	0.2
dodecanoic	lauric	$CH_3(CH_2)_{10}COOH$	44		i
tetradecanoic	myristic	$CH_3(CH_2)_{12}COOH$	54		i
hexadecanoic	palmitic	$CH_3(CH_2)_{14}COOH$	63		i
octadecanoic	stearic	$CH_3(CH_2)_{16}COOH$	72		i
cis-9-octadecenoic	oleic	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	16		i
cis,cis-9,12-octadecadienoic	linoleic	$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$	−5		i
cyclohexanecarboxylic		$c\text{-}C_6H_{11}COOH$	31	233	0.2
benzoic	benzoic	C_6H_5COOH	122	249	0.3
2-methylbenzoic	*o*-toluic	$o\text{-}CH_3C_6H_4COOH$	106	259	0.1
3-methylbenzoic	*m*-toluic	$m\text{-}CH_3C_6H_4COOH$	112	263	0.1
4-methylbenzoic	*p*-toluic	$p\text{-}CH_3C_6H_4COOH$	180	275	0.03

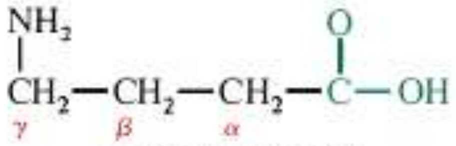


$$-\underset{\varepsilon}{C}-\underset{\delta}{C}-\underset{\gamma}{C}-\underset{\beta}{C}-\underset{\alpha}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$



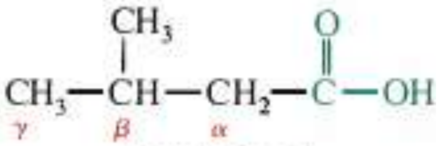
$$\underset{\beta}{CH_3}-\underset{\alpha}{\overset{\overset{\displaystyle Cl}{|}}{CH}}-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

α-chloropropionic acid



$$\underset{\gamma}{\overset{\overset{\displaystyle NH_2}{|}}{CH_2}}-\underset{\beta}{CH_2}-\underset{\alpha}{CH_2}-\overset{\overset{\displaystyle O}{|}}{C}-OH$$

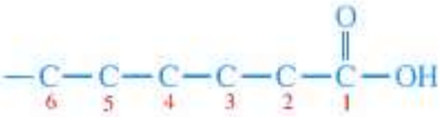
γ-aminobutyric acid



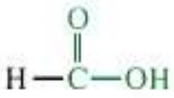
$$\underset{\gamma}{CH_3}-\underset{\beta}{\overset{\overset{\displaystyle CH_3}{|}}{CH}}-\underset{\alpha}{CH_2}-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

isovaleric acid
(β-methylbutyric acid)

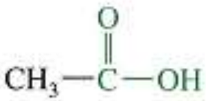
IUPAC Names


$$-\underset{6}{C}-\underset{5}{C}-\underset{4}{C}-\underset{3}{C}-\underset{2}{C}-\underset{1}{\overset{O}{\overset{\|}{C}}}-OH$$

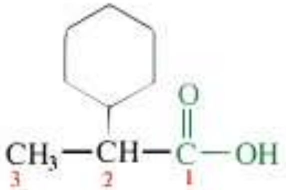
IUPAC name:
common name:


$$H-\overset{O}{\overset{\|}{C}}-OH$$

methanoic acid
formic acid

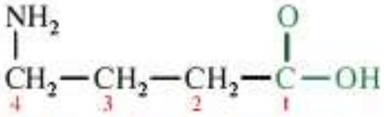

$$CH_3-\overset{O}{\overset{\|}{C}}-OH$$

ethanoic acid
acetic acid

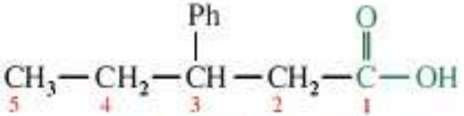


2-cyclohexylpropanoic acid
α-cyclohexylpropionic acid

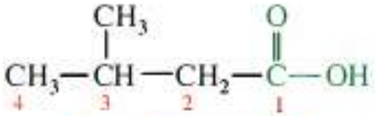
3-oxo-2-propylbutanoic acid
α-acetylvaleric acid


$$\underset{4}{\overset{NH_2}{\overset{|}{CH_2}}}-\underset{3}{CH_2}-\underset{2}{CH_2}-\underset{1}{\overset{O}{\overset{\|}{C}}}-OH$$

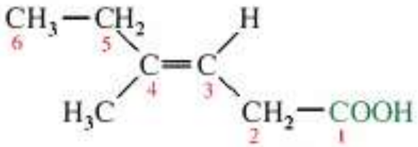
IUPAC name: 4-aminobutanoic acid
common name: *γ*-aminobutyric acid


$$\underset{5}{CH_3}-\underset{4}{CH_2}-\underset{3}{\overset{Ph}{\overset{|}{CH}}}-\underset{2}{CH_2}-\underset{1}{\overset{O}{\overset{\|}{C}}}-OH$$

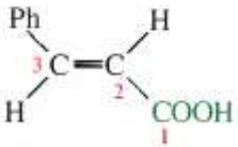
3-phenylpentanoic acid
β-phenylvaleric acid


$$\underset{4}{CH_3}-\underset{3}{\overset{CH_3}{\overset{|}{CH}}}-\underset{2}{CH_2}-\underset{1}{\overset{O}{\overset{\|}{C}}}-OH$$

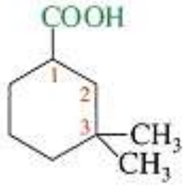
3-methylbutanoic acid
isovaleric acid



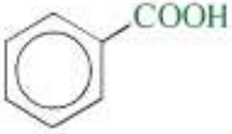
IUPAC name: (*E*)-4-methyl-3-hexenoic acid
new IUPAC name: (*E*)-4-methylhex-3-enoic acid



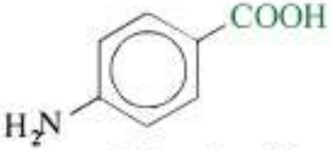
trans-3-phenyl-2-propenoic acid
(*E*)-3-phenylprop-2-enoic acid
(cinnamic acid)



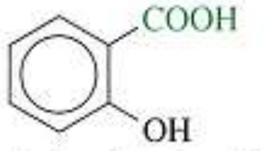
3,3-dimethylcyclohexanecarboxylic acid



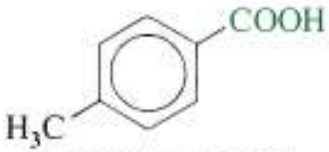
benzoic acid



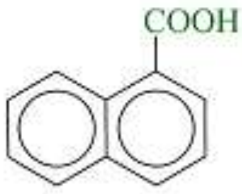
p-aminobenzoic acid



o-hydroxybenzoic acid
(salicyclic acid)



p-methylbenzoic acid
(*p*-toluic acid)



α-naphthoic acid

Nomenclature of Dicarboxylic Acids

Common Names of Dicarboxylic Acids

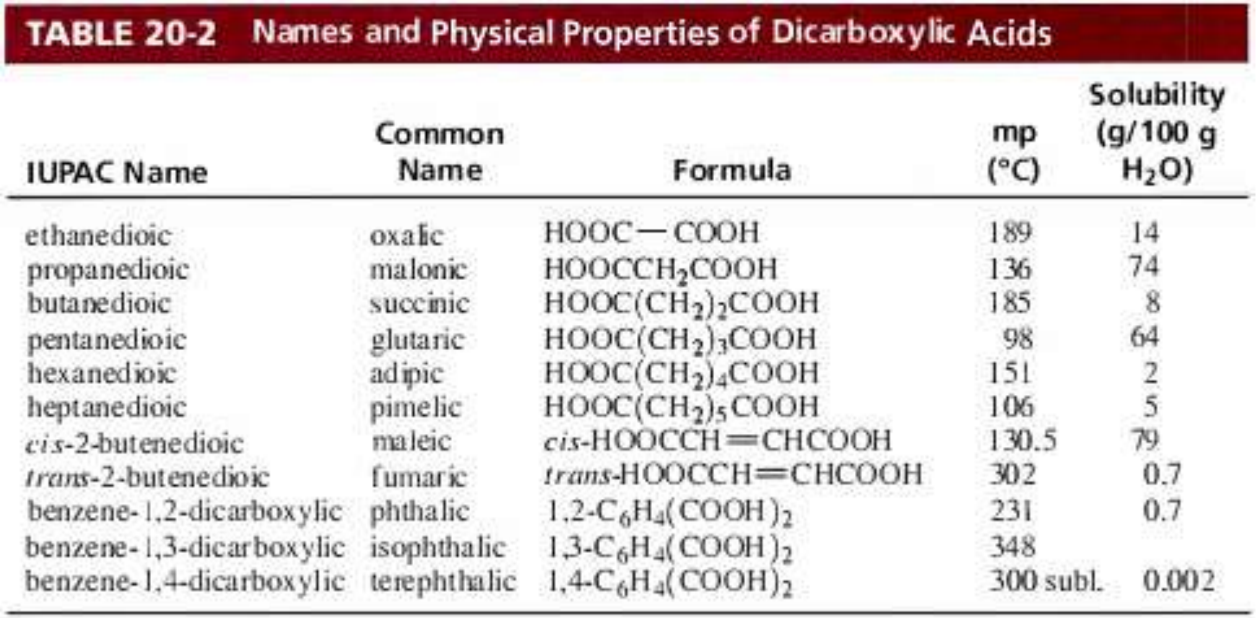
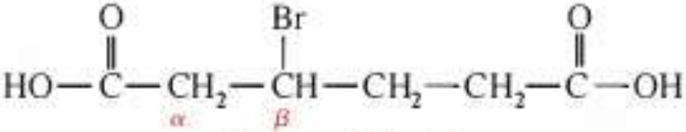


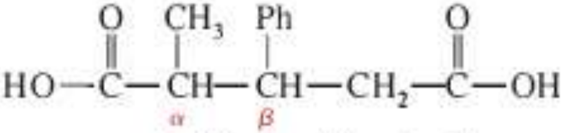
TABLE 20-2 Names and Physical Properties of Dicarboxylic Acids

IUPAC Name	Common Name	Formula	mp (°C)	Solubility (g/100 g H_2O)
ethanedioic	oxalic	$HOOC-COOH$	189	14
propanedioic	malonic	$HOOCCH_2COOH$	136	74
butanedioic	succinic	$HOOC(CH_2)_2COOH$	185	8
pentanedioic	glutaric	$HOOC(CH_2)_3COOH$	98	64
hexanedioic	adipic	$HOOC(CH_2)_4COOH$	151	2
heptanedioic	pimelic	$HOOC(CH_2)_5COOH$	106	5
cis-2-butenedioic	maleic	*cis*-$HOOCCH{=}CHCOOH$	130.5	79
trans-2-butenedioic	fumaric	*trans*-$HOOCCH{=}CHCOOH$	302	0.7
benzene-1,2-dicarboxylic	phthalic	1,2-$C_6H_4(COOH)_2$	231	0.7
benzene-1,3-dicarboxylic	isophthalic	1,3-$C_6H_4(COOH)_2$	348	
benzene-1,4-dicarboxylic	terephthalic	1,4-$C_6H_4(COOH)_2$	300 subl.	0.002



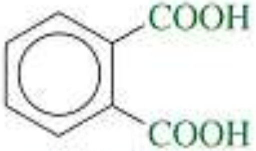
$$HO-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\alpha}{CH_2}-\underset{\beta}{\overset{\overset{\displaystyle Br}{|}}{CH}}-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

β-bromoadipic acid



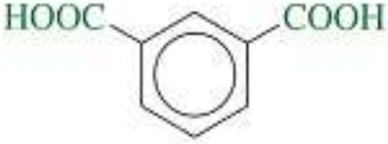
$$HO-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\alpha}{\overset{\overset{\displaystyle CH_3}{|}}{CH}}-\underset{\beta}{\overset{\overset{\displaystyle Ph}{|}}{CH}}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OH$$

α-methyl-β-phenylglutaric acid



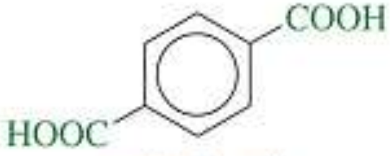
o-phthalic acid

phthalic acid



m-phthalic acid

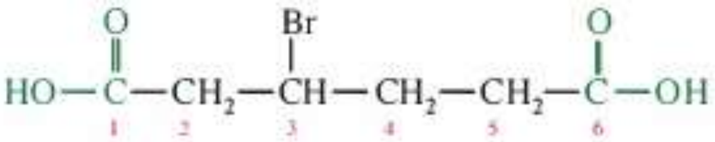
isophthalic acid



p-phthalic acid

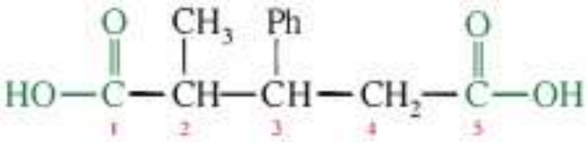
terephthalic acid

IUPAC Names of Dicarboxylic Acids



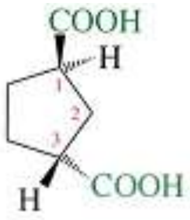
$$\underset{1}{HO-\overset{\overset{O}{\|}}{C}}-\underset{2}{CH_2}-\underset{3}{\overset{\overset{Br}{|}}{CH}}-\underset{4}{CH_2}-\underset{5}{CH_2}-\underset{6}{\overset{\overset{O}{\|}}{C}}-OH$$

3-bromohexanedioic acid

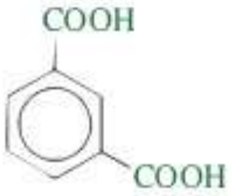


$$HO-\underset{1}{\overset{\overset{O}{\|}}{C}}-\underset{2}{\overset{\overset{CH_3}{|}}{CH}}-\underset{3}{\overset{\overset{Ph}{|}}{CH}}-\underset{4}{CH_2}-\underset{5}{\overset{\overset{O}{\|}}{C}}-OH$$

2-methyl-3-phenylpentanedioic acid



trans-1,3-cyclopentanedicarboxylic acid



1,3-benzenedicarboxylic acid

PROBLEM 20-1

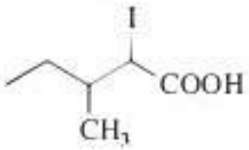
Draw the structures of the following carboxylic acids.

(a) α-methylbutyric acid
(b) 2-bromobutanoic acid
(c) 4-aminopentanoic acid
(d) *cis*-4-phenyl-2-butenoic acid
(e) *trans*-2-methylcyclohexanecarboxylic acid
(f) 2,3-dimethylfumaric acid
(g) *m*-chlorobenzoic acid
(h) 3-methylphthalic acid
(i) β-aminoadipic acid
(j) 3-chloroheptanedioic acid
(k) 4-oxoheptanoic acid
(l) phenylacetic acid

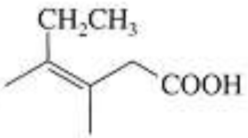
PROBLEM 20-2

Name the following carboxylic acids (when possible, give both a common name and a systematic name).

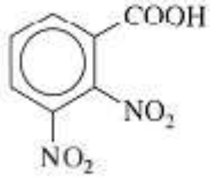
(a)



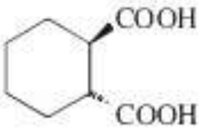
(b)



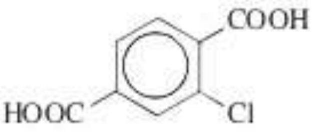
(c)



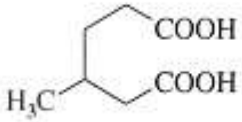
(d)



(e)

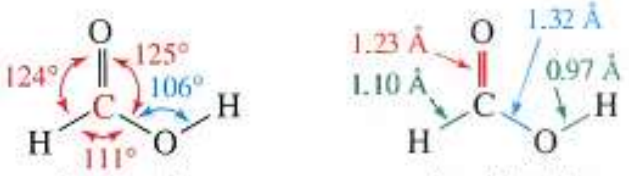


(f)



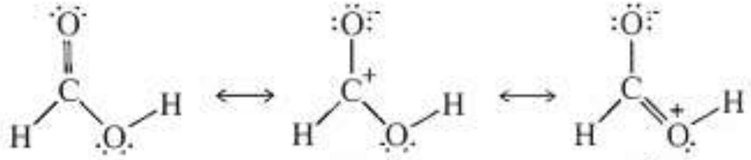
Structure and Physical Properties of Carboxylic Acids

Structure of the Carboxyl Group

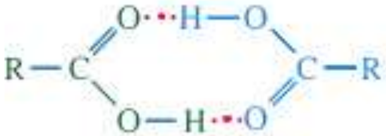


bond angles

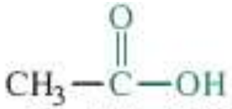
bond lengths



Boiling Points



hydrogen-bonded acid dimer

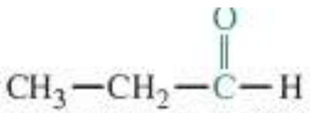


$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-OH$

acetic acid, bp 118°C

$CH_3-CH_2-CH_2-OH$

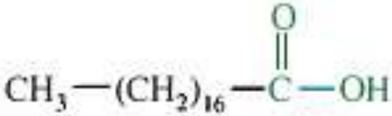
1-propanol, bp 97°C



$CH_3-CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-H$

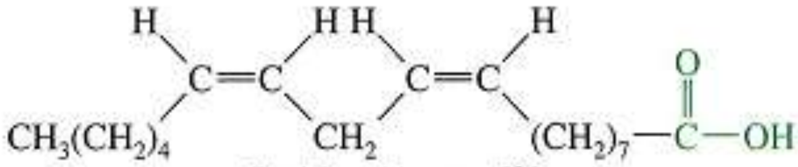
propionaldehyde, bp 49°C

Melting Points



$CH_3-(CH_2)_{16}-\overset{\displaystyle O}{\overset{\|}{C}}-OH$

stearic acid, mp 70°C



linoleic acid, mp −5°C

Solubilities Carboxylic acids form hydrogen bonds with water, and the lower-molecular-weight carboxylic acids (up through 4 carbon atoms) are miscible with water. As the length of the hydrocarbon chain increases, water solubility decreases until acids with more than 10 carbon atoms are essentially insoluble in water. The water solubilities of some simple carboxylic acids and diacids are given in Tables 20-1 and 20-2.

Acidity of Carboxylic Acids

Measurement of Acidity

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O-H + H_2O \rightleftarrows R-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + H_3O^+$$

$$K_a = \frac{[R-CO_2^-][H_3O^+]}{[R-CO_2H]}$$

$$pK_a = -\log_{10} K_a$$

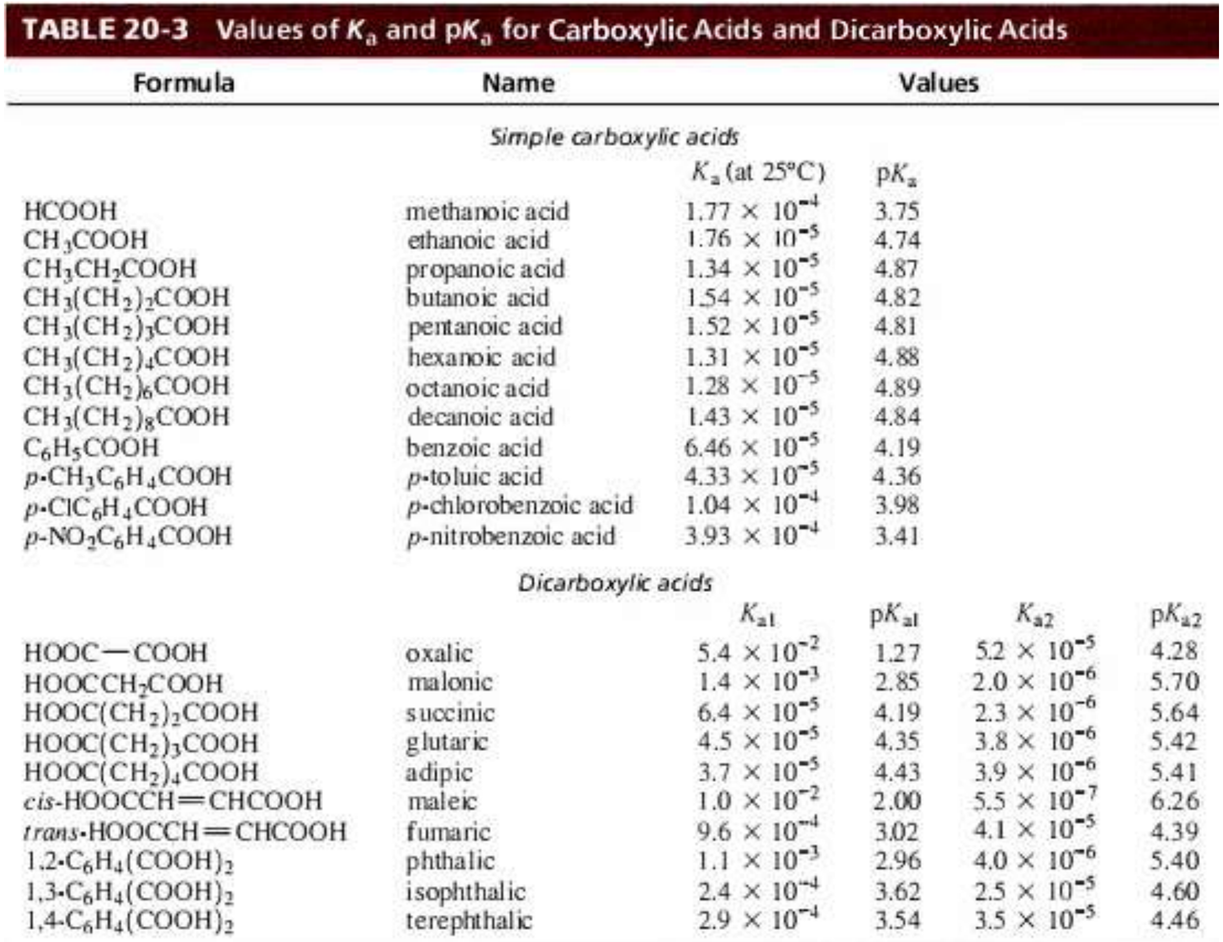
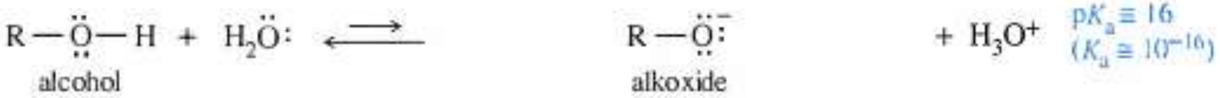
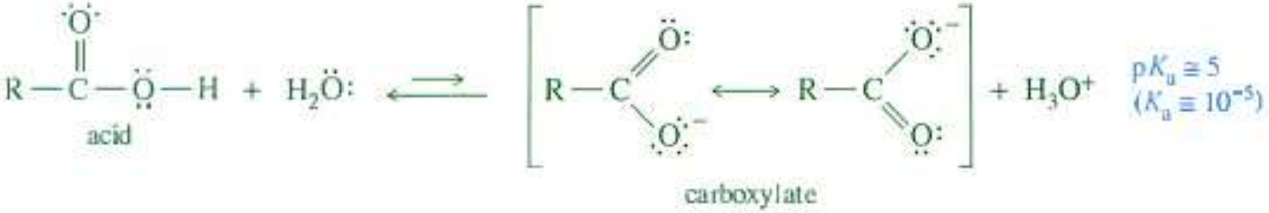


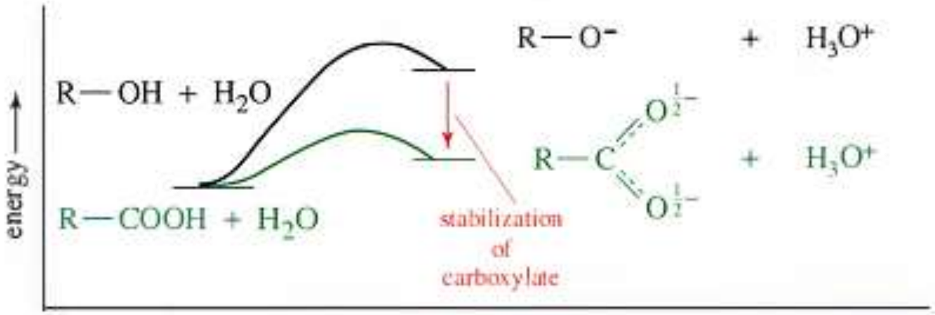
TABLE 20-3 Values of K_a and pK_a for Carboxylic Acids and Dicarboxylic Acids

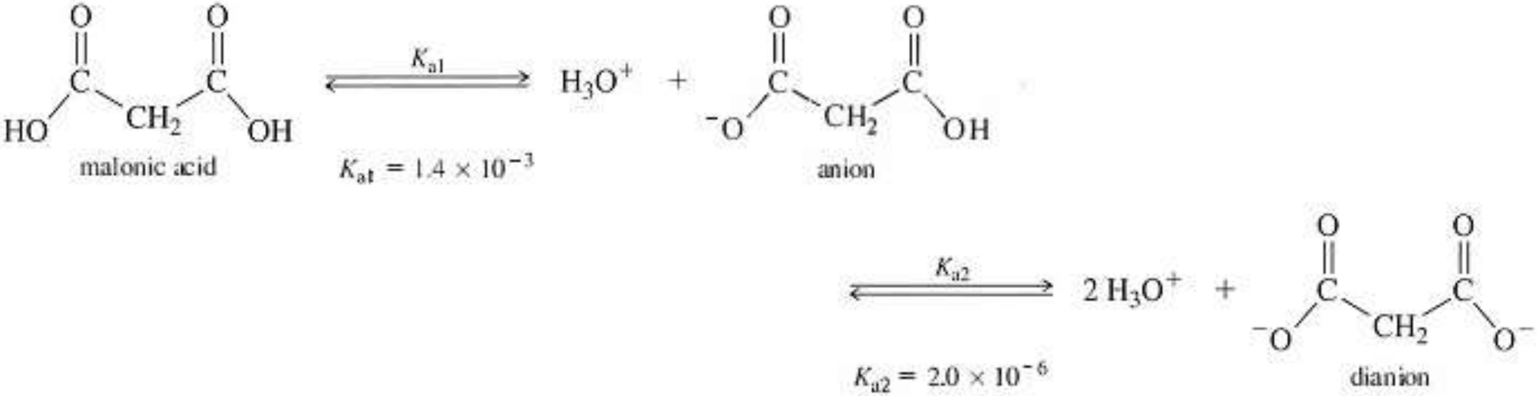
Formula	Name	Values			
		Simple carboxylic acids			
		K_a (at 25°C)	pK_a		
HCOOH	methanoic acid	1.77×10^{-4}	3.75		
CH_3COOH	ethanoic acid	1.76×10^{-5}	4.74		
CH_3CH_2COOH	propanoic acid	1.34×10^{-5}	4.87		
$CH_3(CH_2)_2COOH$	butanoic acid	1.54×10^{-5}	4.82		
$CH_3(CH_2)_3COOH$	pentanoic acid	1.52×10^{-5}	4.81		
$CH_3(CH_2)_4COOH$	hexanoic acid	1.31×10^{-5}	4.88		
$CH_3(CH_2)_6COOH$	octanoic acid	1.28×10^{-5}	4.89		
$CH_3(CH_2)_8COOH$	decanoic acid	1.43×10^{-5}	4.84		
C_6H_5COOH	benzoic acid	6.46×10^{-5}	4.19		
p-$CH_3C_6H_4COOH$	*p*-toluic acid	4.33×10^{-5}	4.36		
p-ClC_6H_4COOH	*p*-chlorobenzoic acid	1.04×10^{-4}	3.98		
p-$NO_2C_6H_4COOH$	*p*-nitrobenzoic acid	3.93×10^{-4}	3.41		
		Dicarboxylic acids			
		K_{a1}	pK_{a1}	K_{a2}	pK_{a2}
HOOC—COOH	oxalic	5.4×10^{-2}	1.27	5.2×10^{-5}	4.28
$HOOCCH_2COOH$	malonic	1.4×10^{-3}	2.85	2.0×10^{-6}	5.70
$HOOC(CH_2)_2COOH$	succinic	6.4×10^{-5}	4.19	2.3×10^{-6}	5.64
$HOOC(CH_2)_3COOH$	glutaric	4.5×10^{-5}	4.35	3.8×10^{-6}	5.42
$HOOC(CH_2)_4COOH$	adipic	3.7×10^{-5}	4.43	3.9×10^{-6}	5.41
cis-HOOCCH═CHCOOH	maleic	1.0×10^{-2}	2.00	5.5×10^{-7}	6.26
trans-HOOCCH═CHCOOH	fumaric	9.6×10^{-4}	3.02	4.1×10^{-5}	4.39
1,2-$C_6H_4(COOH)_2$	phthalic	1.1×10^{-3}	2.96	4.0×10^{-6}	5.40
1,3-$C_6H_4(COOH)_2$	isophthalic	2.4×10^{-4}	3.62	2.5×10^{-5}	4.60
1,4-$C_6H_4(COOH)_2$	terephthalic	2.9×10^{-4}	3.54	3.5×10^{-5}	4.46



$$R-\ddot{O}-H + H_2\ddot{O}: \rightleftharpoons R-\ddot{O}:^- + H_3O^+$$







Substituent Effects on Acidity

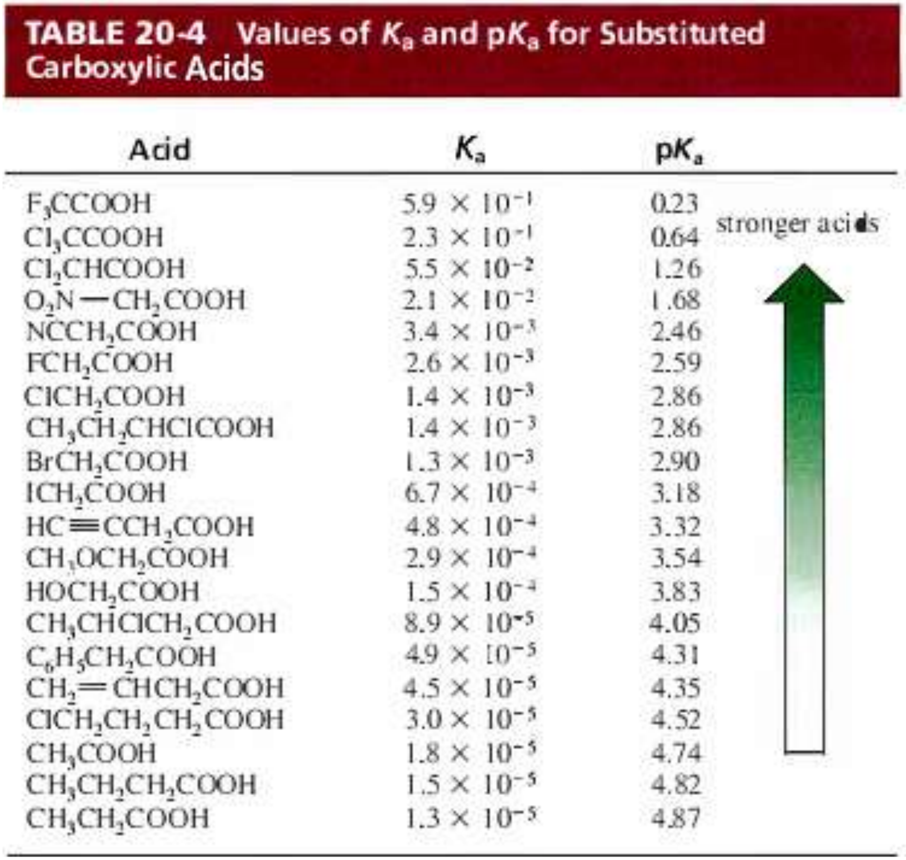
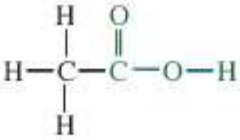


TABLE 20-4 Values of K_a and pK_a for Substituted Carboxylic Acids

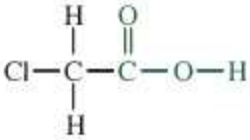
Acid	K_a	pK_a
F_3CCOOH	5.9×10^{-1}	0.23
Cl_3CCOOH	2.3×10^{-1}	0.64
$Cl_2CHCOOH$	5.5×10^{-2}	1.26
O_2N-CH_2COOH	2.1×10^{-2}	1.68
$NCCH_2COOH$	3.4×10^{-3}	2.46
FCH_2COOH	2.6×10^{-3}	2.59
$ClCH_2COOH$	1.4×10^{-3}	2.86
$CH_3CH_2CHClCOOH$	1.4×10^{-3}	2.86
$BrCH_2COOH$	1.3×10^{-3}	2.90
ICH_2COOH	6.7×10^{-4}	3.18
$HC\equiv CCH_2COOH$	4.8×10^{-4}	3.32
CH_3OCH_2COOH	2.9×10^{-4}	3.54
$HOCH_2COOH$	1.5×10^{-4}	3.83
$CH_3CHClCH_2COOH$	8.9×10^{-5}	4.05
$C_6H_5CH_2COOH$	4.9×10^{-5}	4.31
$CH_2=CHCH_2COOH$	4.5×10^{-5}	4.35
$ClCH_2CH_2CH_2COOH$	3.0×10^{-5}	4.52
CH_3COOH	1.8×10^{-5}	4.74
$CH_3CH_2CH_2COOH$	1.5×10^{-5}	4.82
CH_3CH_2COOH	1.3×10^{-5}	4.87

stronger acids



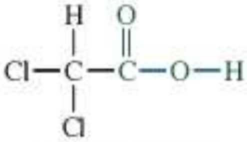
$H-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

acetic acid
pK_a = 4.74



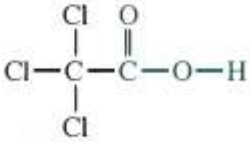
$Cl-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

chloroacetic acid
pK_a = 2.86



$Cl-\overset{H}{\underset{Cl}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

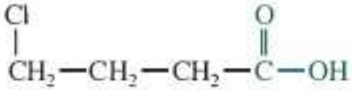
dichloroacetic acid
pK_a = 1.26



$Cl-\overset{Cl}{\underset{Cl}{C}}-\overset{O}{\overset{\|}{C}}-O-H$

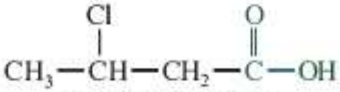
trichloroacetic acid
pK_a = 0.64

stronger acids



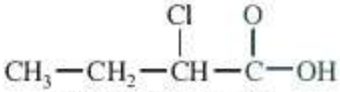
$\overset{Cl}{CH_2}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-OH$

4-chlorobutanoic acid
pK_a = 4.52



$CH_3-\overset{Cl}{CH}-CH_2-\overset{O}{\overset{\|}{C}}-OH$

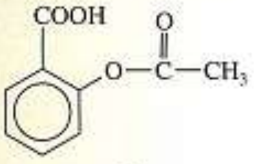
3-chlorobutanoic acid
pK_a = 4.05



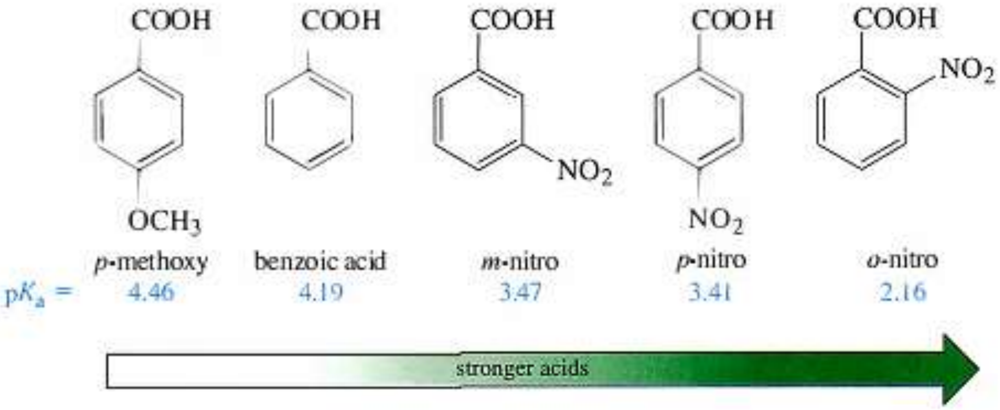
$CH_3-CH_2-\overset{Cl}{CH}-\overset{O}{C}-OH$

2-chlorobutanoic acid
pK_a = 2.86

The absorption of many orally administered drugs containing carboxylic acids depends on their pK_a values. Aspirin, for example, is largely absorbed from the acidic environment of the stomach because it is present as the acid, which readily passes through the membranes into the blood.



aspirin



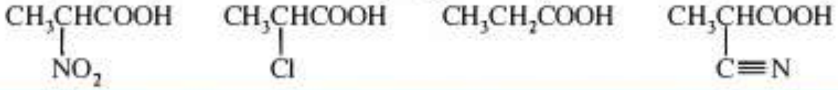
PROBLEM 20-3

Rank the compounds in each set in order of increasing acid strength.

(a) CH_3CH_2COOH $CH_3CHBrCOOH$ CH_3CBr_2COOH

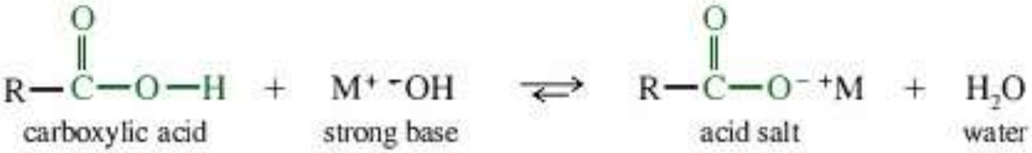
(b) $CH_3CH_2CH_2CHBrCOOH$ $CH_3CH_2CHBrCH_2COOH$ $CH_3CHBrCH_2CH_2COOH$

(c)



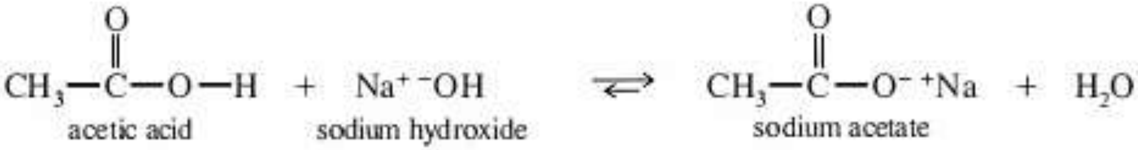
$CH_3\underset{NO_2}{\underset{|}{C}}HCOOH$ $CH_3\underset{Cl}{\underset{|}{C}}HCOOH$ CH_3CH_2COOH $CH_3\underset{C\equiv N}{\underset{|}{C}}HCOOH$

Salts of Carboxylic Acids



$$R-\overset{\overset{O}{\|}}{C}-O-H + M^{+}\,{}^{-}OH \rightleftharpoons R-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}M + H_2O$$

carboxylic acid, strong base, acid salt, water



$$CH_3-\overset{\overset{O}{\|}}{C}-O-H + Na^{+}\,{}^{-}OH \rightleftharpoons CH_3-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}Na + H_2O$$

acetic acid, sodium hydroxide, sodium acetate

$$\underset{\text{acid salt}}{R-\overset{\overset{O}{|}}{C}-O^{-}\,{}^{+}M} + H^{+} \rightleftharpoons \underset{\text{regenerated acid}}{R-\overset{\overset{O}{|}}{C}-O-H} + M^{+}$$

Example

$$\underset{\text{sodium acetate}}{CH_3-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}Na} + H^{+}\,Cl^{-} \rightleftharpoons \underset{\text{acetic acid}}{CH_3-\overset{\overset{O}{\|}}{C}-O-H} + Na^{+}\,Cl^{-}$$

Nomenclature of Carboxylic Acid Salts

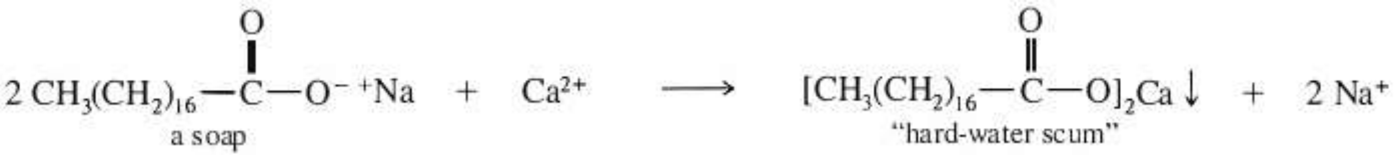
$$CH_3CH_2CH_2CH_2-\overset{\overset{O}{\|}}{C}-OH + LiOH \longrightarrow CH_3CH_2CH_2CH_2-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}Li$$

IUPAC name:	pentanoic acid	lithium hydroxide	lithium pentanoate
common name:	valeric acid		lithium valerate

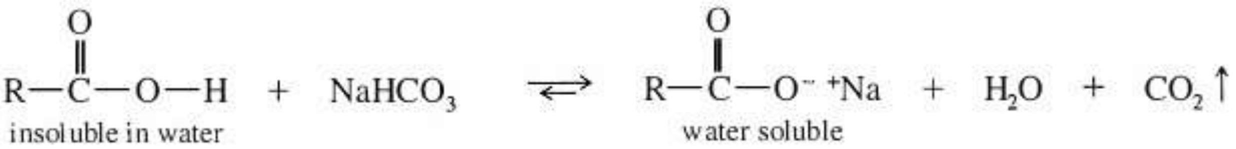
$$CH_3CH_2CH_2-\overset{\overset{O}{\|}}{C}-OH + {:}NH_3 \longrightarrow CH_3CH_2CH_2-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}NH_4$$

IUPAC name:	butanoic acid	ammonia	ammonium butanoate
common name:	butyric acid		ammonium butyrate

Properties of Acid Salts

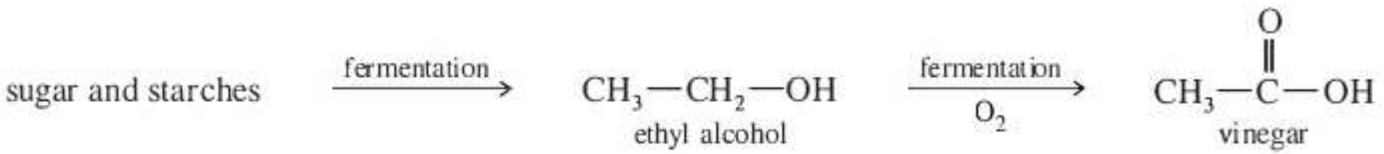


$$\underset{\text{a soap}}{2\,CH_3(CH_2)_{16}-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}Na} + Ca^{2+} \longrightarrow \underset{\text{“hard-water scum”}}{[CH_3(CH_2)_{16}-\overset{\overset{O}{\|}}{C}-O]_2Ca\downarrow} + 2\,Na^{+}$$

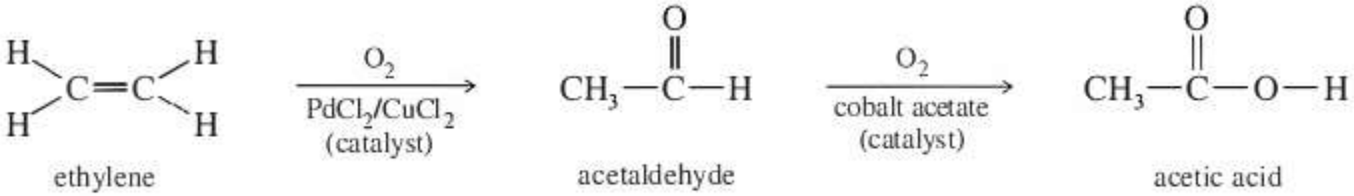


$$\underset{\text{insoluble in water}}{R-\overset{\overset{O}{\|}}{C}-O-H} + NaHCO_3 \rightleftharpoons \underset{\text{water soluble}}{R-\overset{\overset{O}{\|}}{C}-O^{-}\,{}^{+}Na} + H_2O + CO_2\uparrow$$

Commercial Sources of Carboxylic Acids

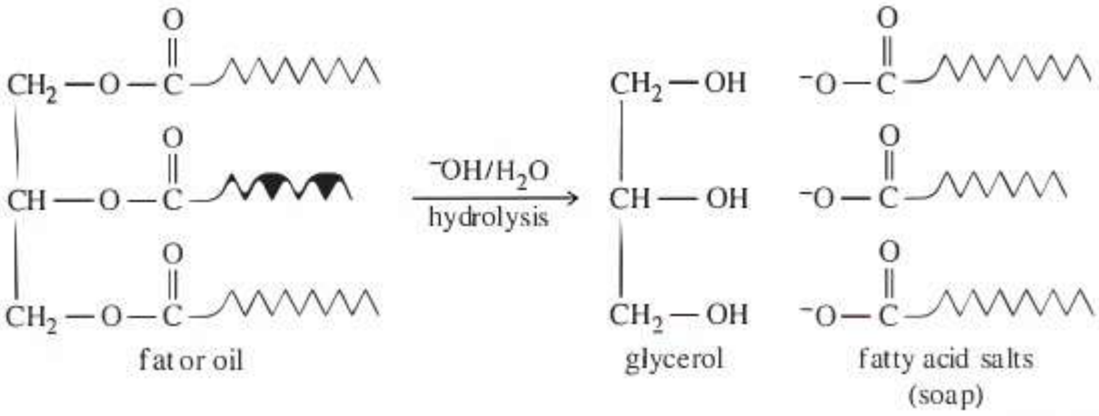


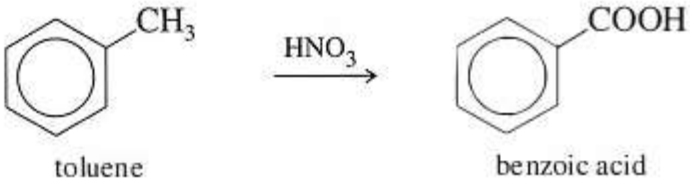
$$\text{sugar and starches} \xrightarrow{\text{fermentation}} CH_3-CH_2-OH \xrightarrow[O_2]{\text{fermentation}} CH_3-\overset{\overset{O}{\|}}{C}-OH$$

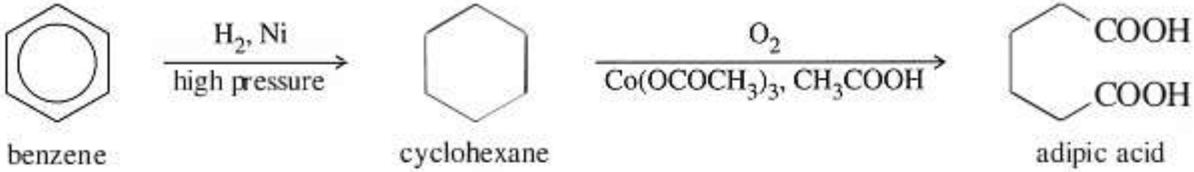


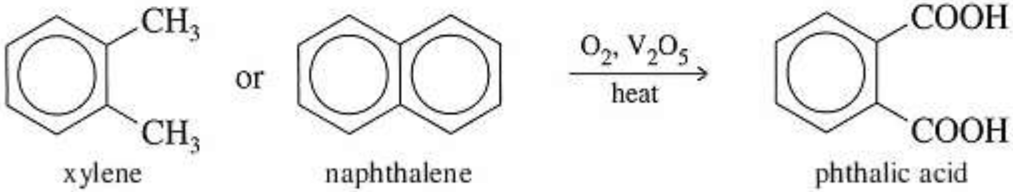
$$CH_3OH + CO \xrightarrow[\text{heat, pressure}]{\text{Rh catalyst}} CH_3COOH$$

methanol — acetic acid





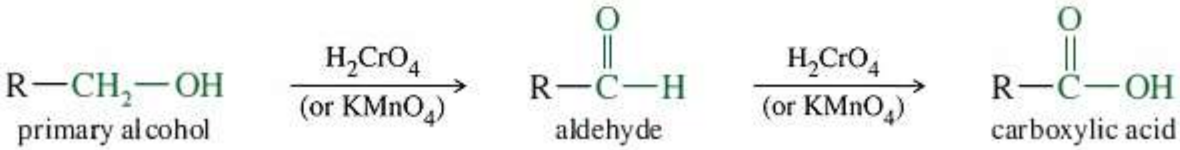




Synthesis of Carboxylic Acids

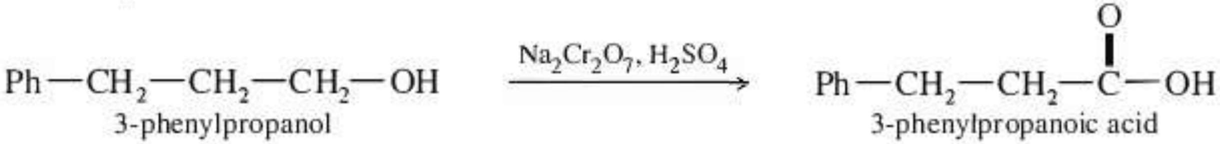
Review of Previous Syntheses

1. Primary alcohols and aldehydes are commonly oxidized to acids by chromic acid (H_2CrO_4, formed from $Na_2Cr_2O_7$ and H_2SO_4). Potassium permanganate is occasionally used, but the yields are often lower (Sections 11-2B and 18-20).



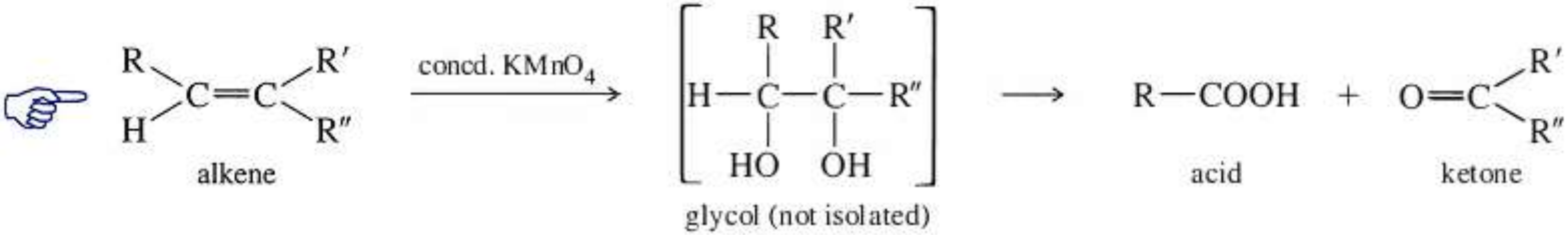
$$R-CH_2-OH \xrightarrow[\text{(or KMnO}_4\text{)}]{H_2CrO_4} R-\overset{\overset{O}{\|}}{C}-H \xrightarrow[\text{(or KMnO}_4\text{)}]{H_2CrO_4} R-\overset{\overset{O}{\|}}{C}-OH$$

Example

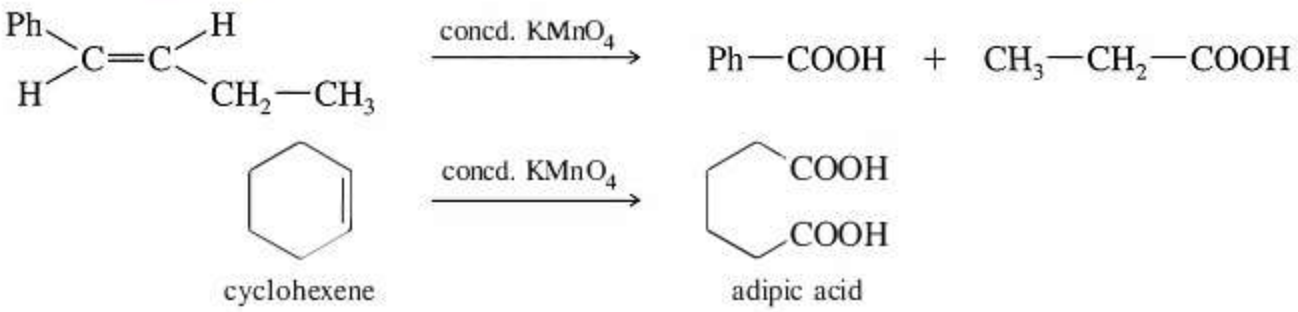


$$Ph-CH_2-CH_2-CH_2-OH \xrightarrow{Na_2Cr_2O_7,\ H_2SO_4} Ph-CH_2-CH_2-\overset{\overset{O}{\|}}{C}-OH$$

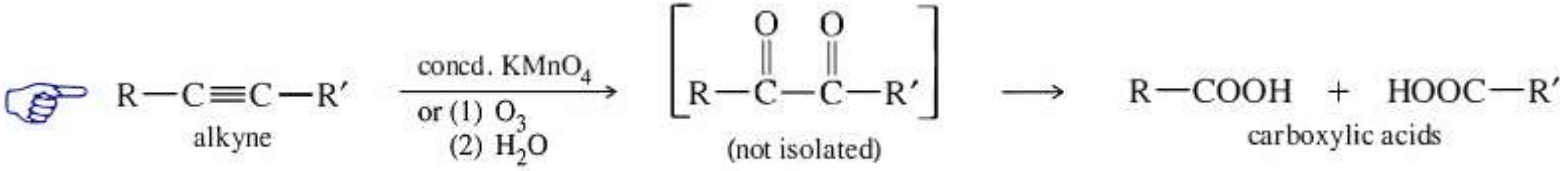
2. Cold, dilute potassium permanganate reacts with alkenes to give glycols. Warm, concentrated permanganate solutions oxidize the glycols further, cleaving the central carbon–carbon bond. Depending on the substitution of the original double bond, ketones or acids may result (Section 8-15A).



Examples



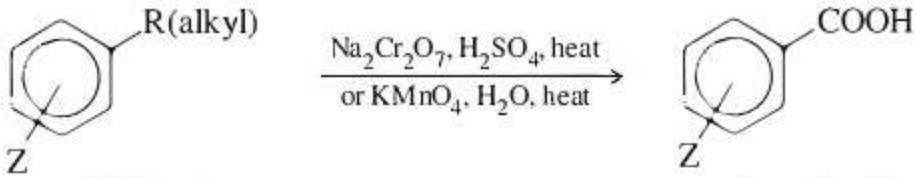
With alkynes, either ozonolysis or a vigorous permanganate oxidation cleaves the triple bond to give carboxylic acids (Section 9-10).



Example

$$CH_3CH_2CH_2—C{\equiv}C—Ph \xrightarrow[(2)\ H_2O]{(1)\ O_3} CH_3CH_2CH_2—COOH + Ph—COOH$$

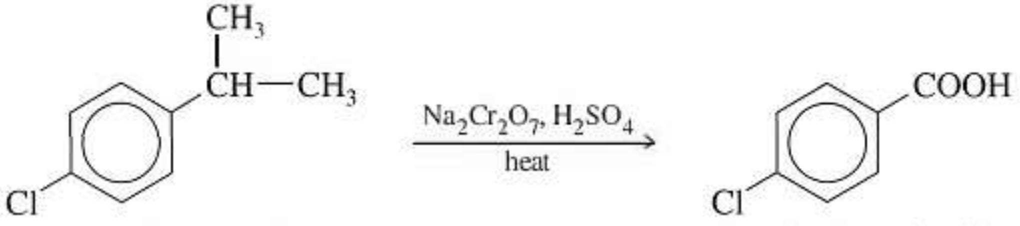
3. Side chains of alkylbenzenes are oxidized to benzoic acid derivatives by treatment with hot potassium permanganate or hot chromic acid. Because this oxidation requires severe reaction conditions, it is useful only for making benzoic acid derivatives with no oxidizable functional groups. Oxidation-resistant functional groups such as $—Cl$, $—NO_2$, $—SO_3H$, and $—COOH$ may be present (Section 17-14A).



an alkylbenzene
(Z must be oxidation-resistant)

a benzoic acid

Example

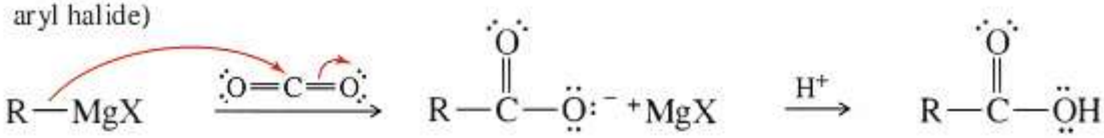


p-chloroisopropylbenzene

p-chlorobenzoic acid

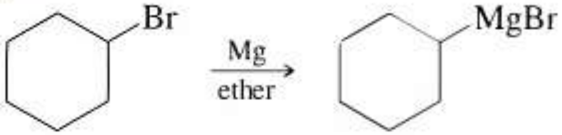
Carboxylation of Grignard Reagents

$$\underset{\text{(alkyl or aryl halide)}}{R-X} \xrightarrow[\text{ether}]{\text{Mg}} R-MgX$$

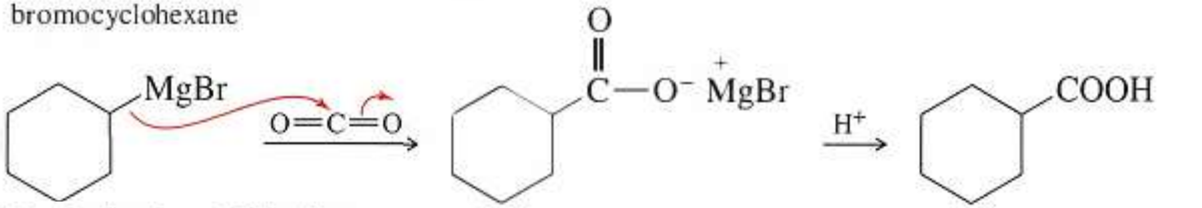


$$R-MgX \xrightarrow{O=C=O} R-\overset{O}{\overset{\|}{C}}-O^{-}\ {}^{+}MgX \xrightarrow{H^+} R-\overset{O}{\overset{\|}{C}}-OH$$

Example



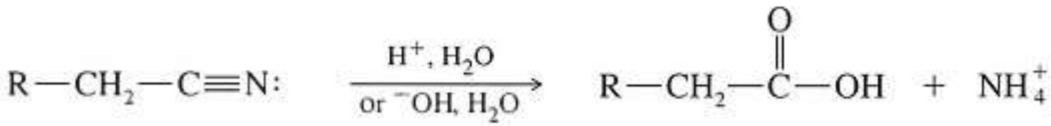
bromocyclohexane



cyclohexanecarboxylic acid

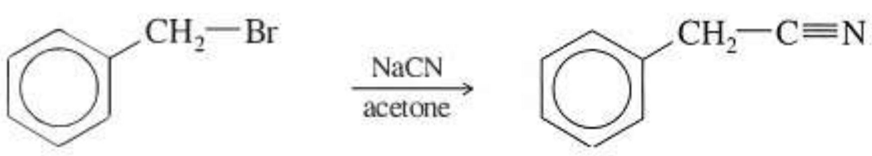
Formation and Hydrolysis of Nitriles

$$R-CH_2-X \xrightarrow[\text{acetone}]{\text{NaCN}} R-CH_2-C\equiv N:$$



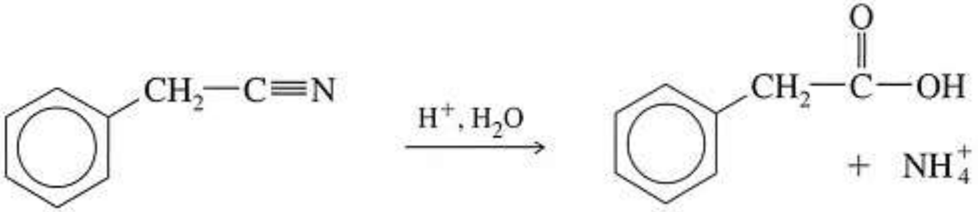
$$R-CH_2-C\equiv N: \xrightarrow[\text{or }^{-}OH,\ H_2O]{H^+,\ H_2O} R-CH_2-\overset{O}{\overset{\|}{C}}-OH + NH_4^+$$

Example



benzyl bromide

phenylacetonitrile



phenylacetonitrile

phenylacetic acid

PROBLEM 20-11

Show how you would synthesize the following carboxylic acids, using the indicated starting materials.

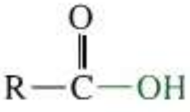
- (a) 4-octyne → butanoic acid
- (b) *trans*-cyclodecene → decanedioic acid
- (c) bromobenzene → phenylacetic acid
- (d) 2-butanol → 2-methylbutanoic acid
- (e) *p*-xylene → terephthalic acid
- (f) allyl iodide → 3-butenoic acid

Reactions of Carboxylic Acids and Derivatives; Nucleophilic Acyl Substitution

Nucleophilic acyl substitution

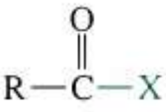
$$R-\overset{\overset{\ddot{O}:}{\|}}{C}-X + Nuc:^- \rightleftharpoons R-\overset{\overset{\ddot{O}:}{\|}}{C}-Nuc + :X^-$$

Acid derivatives



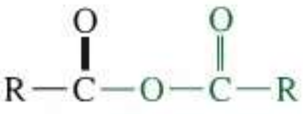
$$R-\overset{\overset{O}{\|}}{C}-OH$$

carboxylic acid



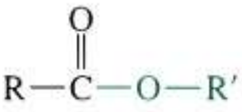
$$R-\overset{\overset{O}{\|}}{C}-X$$

acyl halide



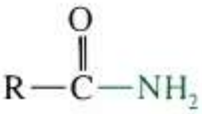
$$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R$$

anhydride



$$R-\overset{\overset{O}{\|}}{C}-O-R'$$

ester

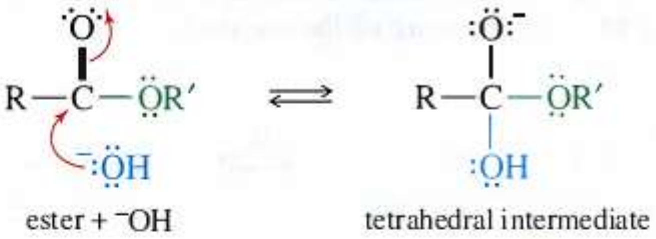


$$R-\overset{\overset{O}{\|}}{C}-NH_2$$

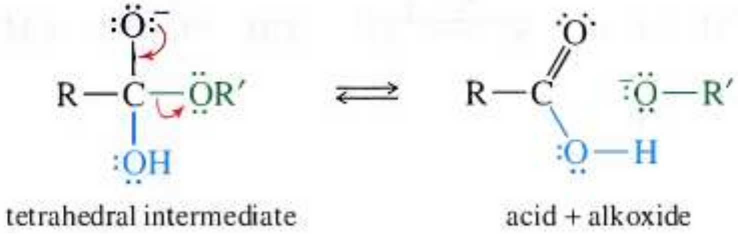
amide

MECHANISM 20-1 Nucleophilic Acyl Substitution in the Basic Hydrolysis of an Ester

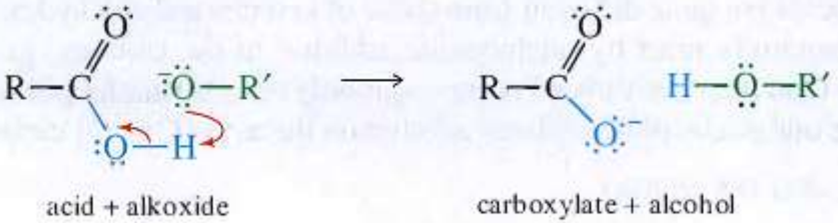
Step 1: Hydroxide ion (strong nucleophile) adds to the carbonyl group, forming a tetrahedral intermediate.



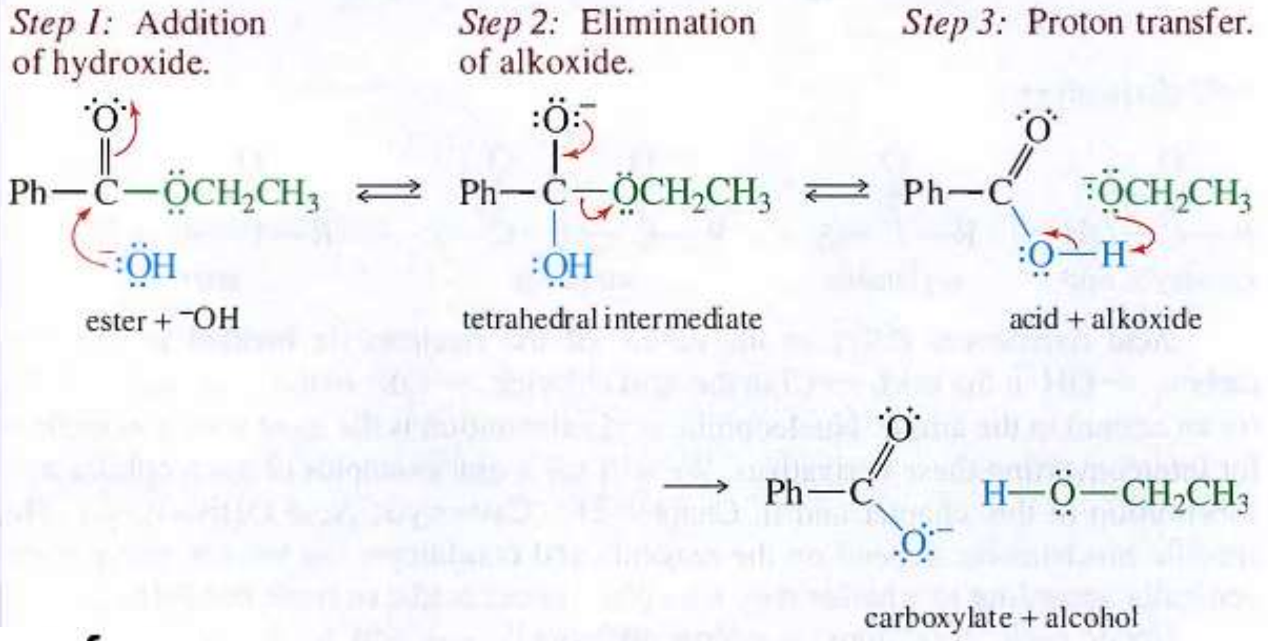
Step 2: An alkoxide ion leaves, regenerating the C=O double bond.



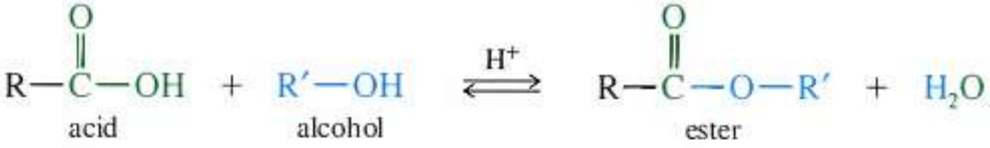
Step 3: A fast, exothermic proton transfer drives the reaction to completion.



Example: Basic hydrolysis of ethyl benzoate.

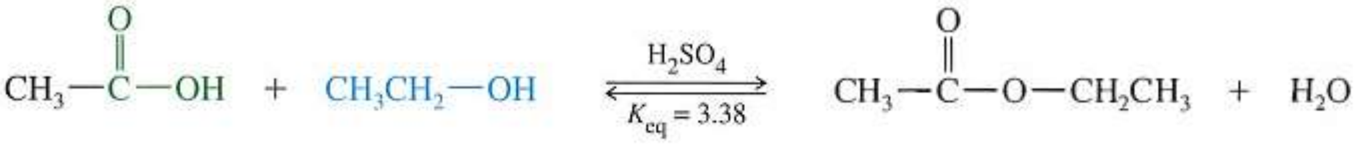


Condensation of Acids with Alcohols: The Fischer Esterification

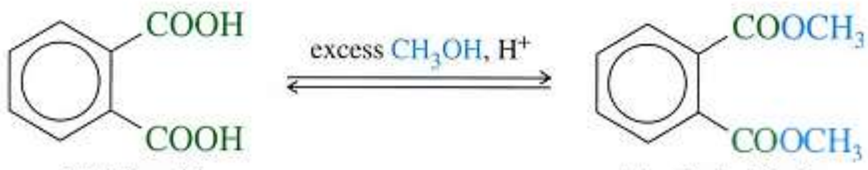


$$\underset{\text{acid}}{R-\overset{O}{\overset{\|}{C}}-OH} + \underset{\text{alcohol}}{R'-OH} \overset{H^+}{\rightleftharpoons} \underset{\text{ester}}{R-\overset{O}{\overset{\|}{C}}-O-R'} + H_2O$$

Examples



$$CH_3-\overset{O}{\overset{\|}{C}}-OH + CH_3CH_2-OH \underset{K_{eq}=3.38}{\overset{H_2SO_4}{\rightleftharpoons}} CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 + H_2O$$



phthalic acid

dimethyl phthalate

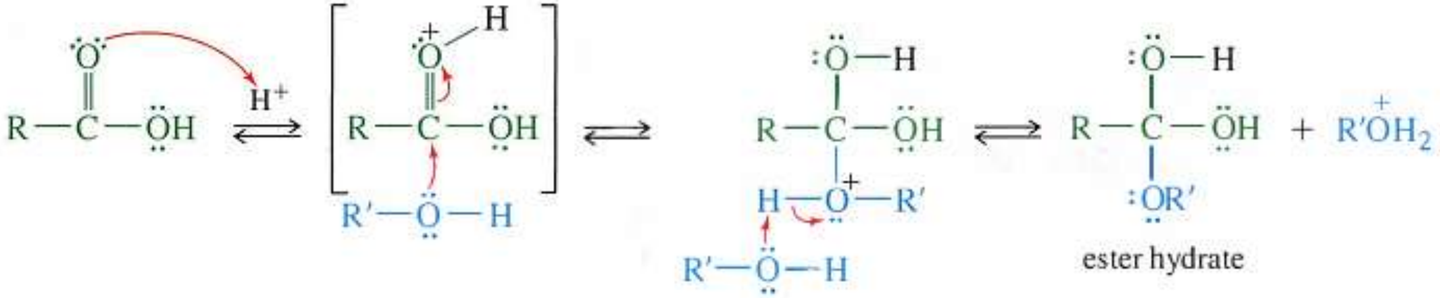
KEY MECHANISM 20-2 Fischer Esterification

Part 1: *Acid-catalyzed addition of the alcohol to the carbonyl group.*

Protonation activates the carbonyl.

The alcohol adds.

Deprotonation completes the reaction.

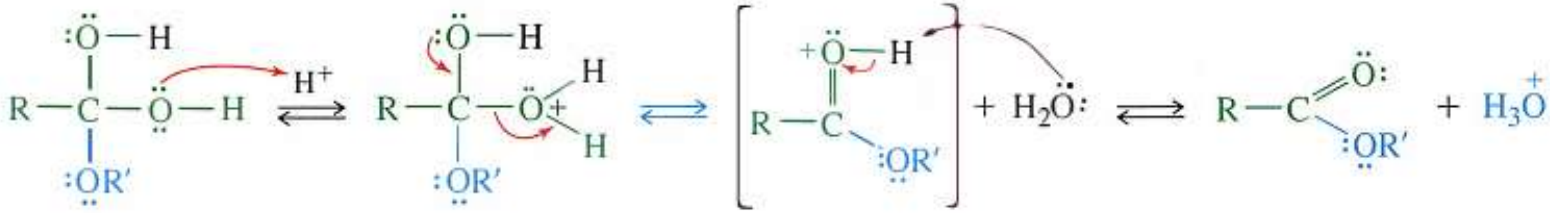


Part 2: *Acid-catalyzed dehydration.*

Protonation prepares the OH group to leave.

Water leaves.

Deprotonation completes the reaction.



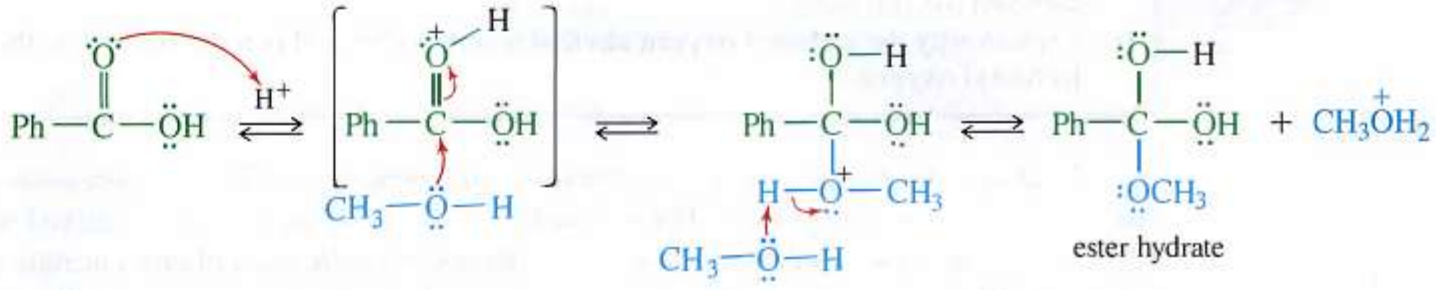
EXAMPLE: Acid-catalyzed formation of methyl benzoate from methanol and benzoic acid.

Part 1: *Acid-catalyzed addition of methanol to the carbonyl group.*

Protonation activates the carbonyl.

Methanol adds.

Deprotonation completes the reaction.

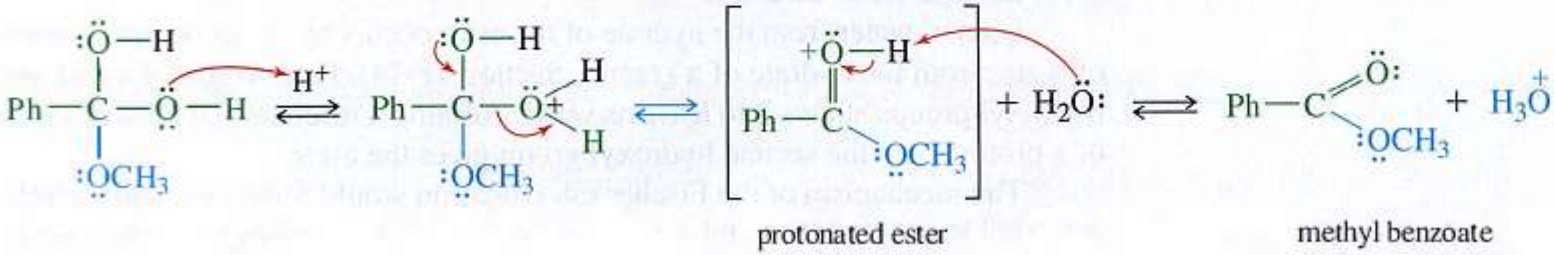


Part 2: Acid-catalyzed dehydration.

Protonation prepares the OH group to leave.

Water leaves.

Deprotonation completes the reaction.



QUESTION: Why can't the Fischer esterification take place under basic catalysis?

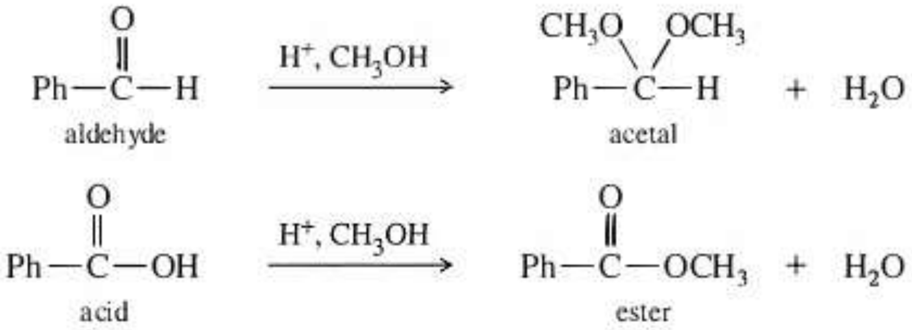
PROBLEM 20-12

(a) The Key Mechanism for Fischer Esterification omitted some important resonance forms of the intermediates shown in brackets. Complete the mechanism by drawing all the resonance forms of these two intermediates.

(b) Propose a mechanism for the acid-catalyzed reaction of acetic acid with ethanol to give ethyl acetate.

PROBLEM 20-13

Most of the Fischer esterification mechanism is identical with the mechanism of acetal formation. The difference is in the final step, where a carbocation loses a proton to give the ester. Write mechanisms for the following reactions, with the comparable steps directly above and below each other. Explain why the final step of the esterification (proton loss) cannot occur in acetal formation, and show what happens instead.



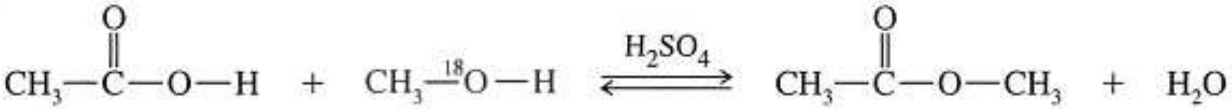
PROBLEM 20-15

Show how Fischer esterification might be used to form the following esters. In each case, suggest a method for driving the reaction to completion.

(a) methyl salicylate **(b)** methyl formate (bp 32°C) **(c)** ethyl benzoate

PROBLEM 20-16

The mechanism of the Fischer esterification was controversial until 1938, when Irving Roberts and Harold Urey of Columbia University used isotopic labeling to follow the alcohol oxygen atom through the reaction. A catalytic amount of sulfuric acid was added to a mixture of 1 mole of acetic acid and 1 mole of special methanol containing the heavy ^{18}O isotope of oxygen. After a short period, the acid was neutralized to stop the reaction, and the components of the mixture were separated.

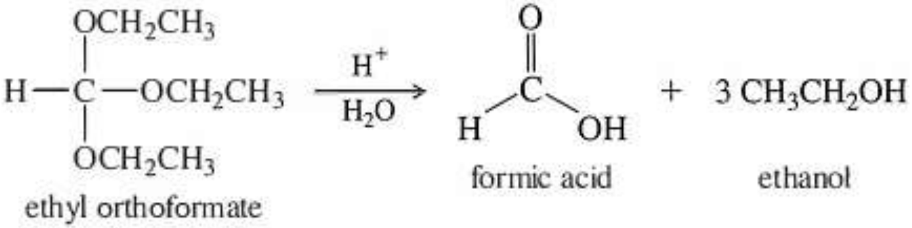


$$CH_3-\overset{O}{\overset{\|}{C}}-O-H + CH_3-{}^{18}O-H \xrightleftharpoons{H_2SO_4} CH_3-\overset{O}{\overset{\|}{C}}-O-CH_3 + H_2O$$

(a) Propose a mechanism for this reaction.

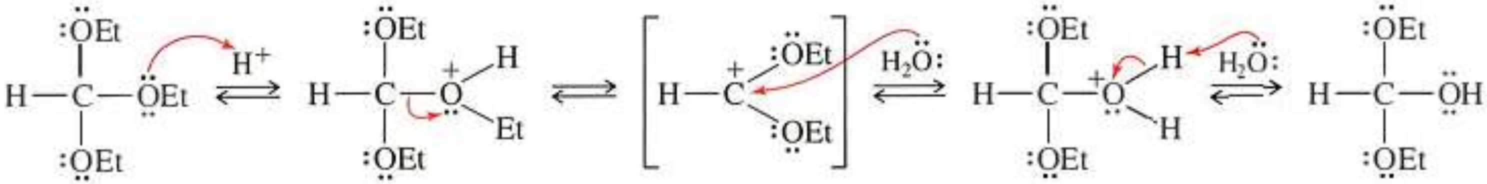
SOLVED PROBLEM 20-1

Ethyl orthoformate hydrolyzes easily in dilute acid to give formic acid and three equivalents of ethanol. Propose a mechanism for the hydrolysis of ethyl orthoformate.

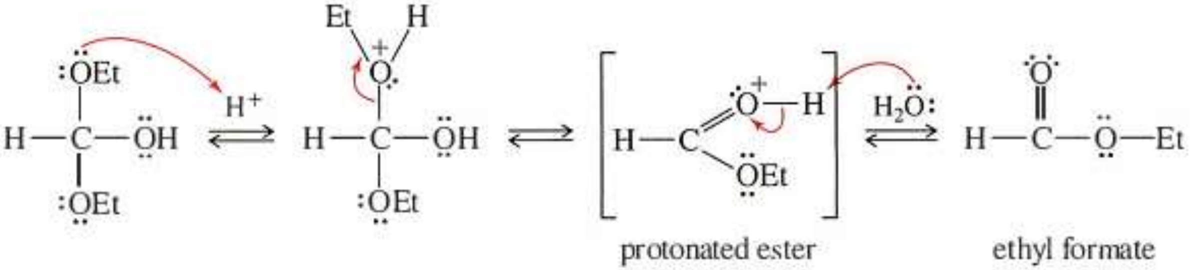


SOLUTION

Ethyl orthoformate resembles an acetal with an extra alkoxy group, so this mechanism should resemble the hydrolysis of an acetal (Section 18-18). There are three equivalent basic sites: the three oxygen atoms. Protonation of one of these sites allows ethanol to leave, giving a resonance-stabilized cation. Attack by water gives an intermediate that resembles a hemiacetal with an extra alkoxy group.



Protonation and loss of a second ethoxyl group gives an intermediate that is simply a protonated ester.



Hydrolysis of ethyl formate follows the reverse path of the Fischer esterification. This part of the mechanism is left to you as an exercise.

Esterification Using Diazomethane

$$R-\overset{\overset{\large O}{\|}}{C}-OH + CH_2N_2 \longrightarrow R-\overset{\overset{\large O}{\|}}{C}-O-CH_3 + N_2\uparrow$$

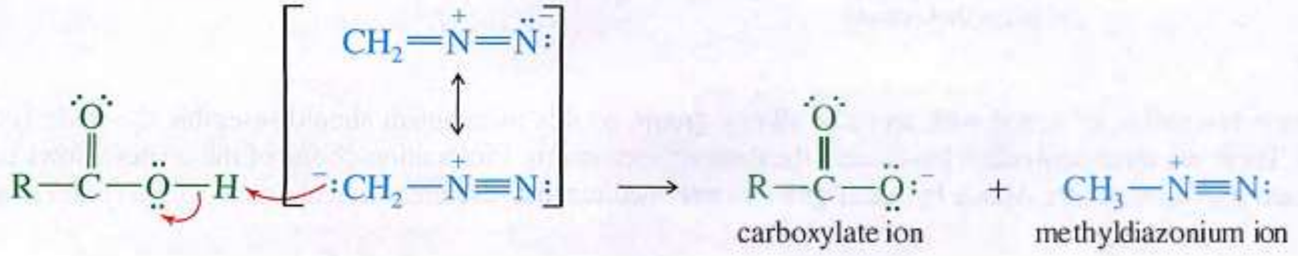
Example

cyclobutanecarboxylic acid

methyl cyclobutanecarboxylate (100%)

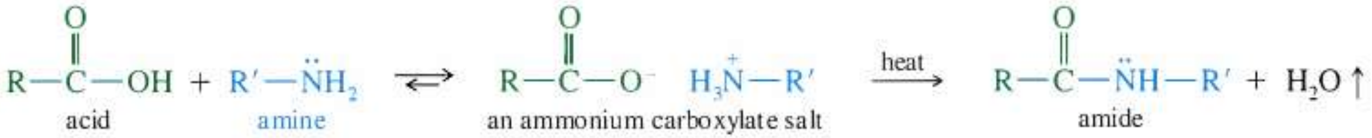
MECHANISM 20-3 Esterification Using Diazomethane

Step 1: Proton transfer, forming a carboxylate ion and a methyldiazonium ion.



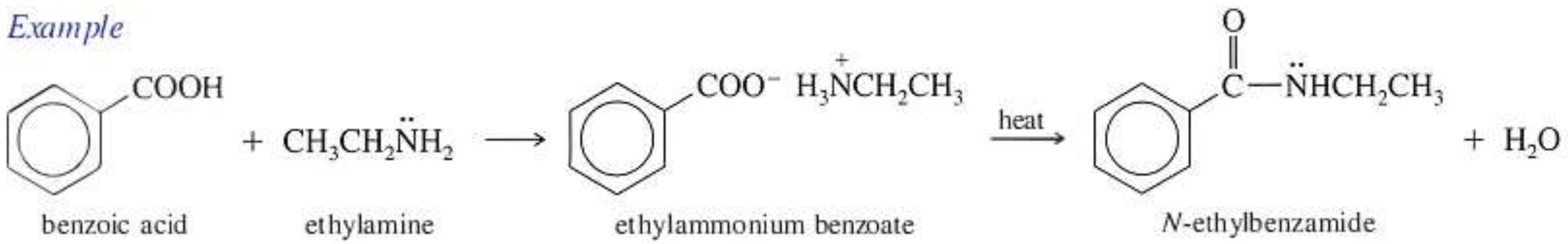
Step 2: Nucleophilic attack on the methyl group displaces nitrogen.

Condensation of Acids with Amines: Direct Synthesis of Amides



$$R-\overset{\overset{\large O}{\|}}{C}-OH + R'-\ddot{N}H_2 \rightleftarrows R-\overset{\overset{\large O}{\|}}{C}-O^- \; H_3\overset{+}{N}-R' \xrightarrow{\text{heat}} R-\overset{\overset{\large O}{\|}}{C}-\ddot{N}H-R' + H_2O\uparrow$$

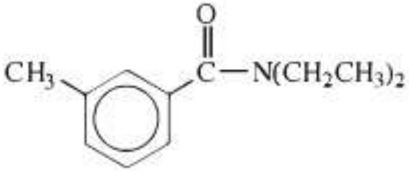
Example



PROBLEM 20-18

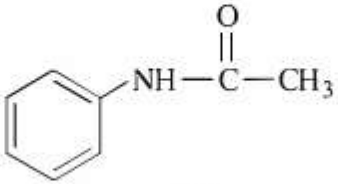
Show how to synthesize the following compounds, using appropriate carboxylic acids and amines.

(a)



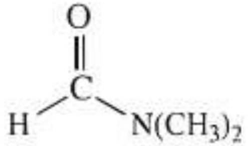
N,N-diethyl-meta-toluamide (DEET insect repellent)

(b)



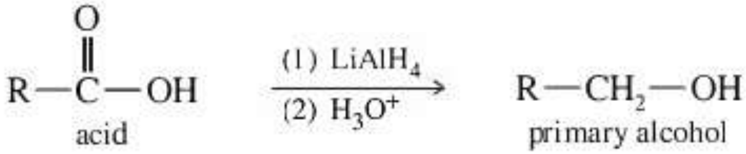
acetanilide

(c)



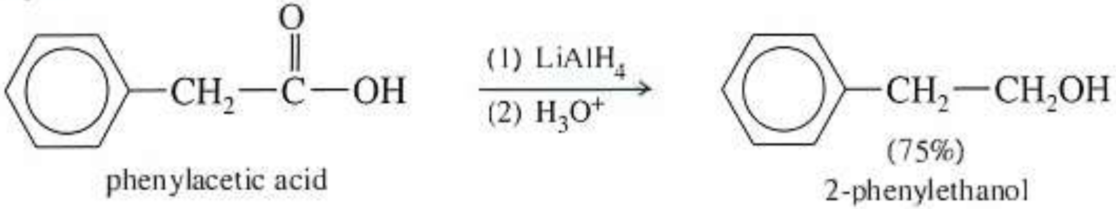
N,N-dimethylformamide (DMF)

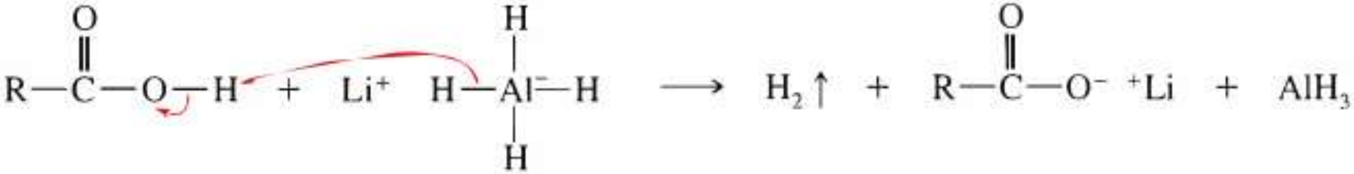
Reduction of Carboxylic Acids



$$R-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[(2)\ H_3O^+]{(1)\ LiAlH_4} R-CH_2-OH$$

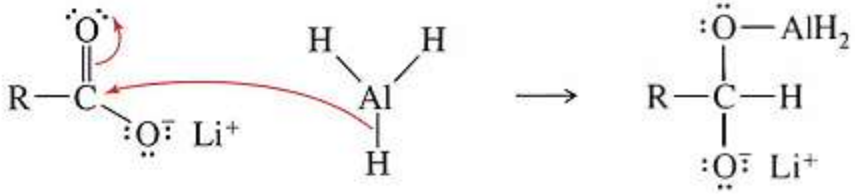
Example



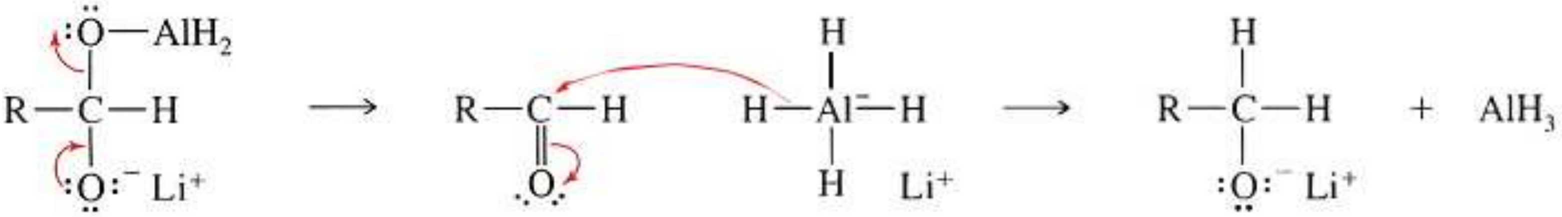


$$R-\overset{O}{\overset{\|}{C}}-O-H + Li^+ \quad H-\overset{H}{\underset{H}{Al^-}}-H \longrightarrow H_2\uparrow + R-\overset{O}{\overset{\|}{C}}-O^- \ {}^+Li + AlH_3$$

Several paths are possible for the rest of the mechanism. In one likely path, AlH_3 adds to the carbonyl group of the lithium carboxylate salt.

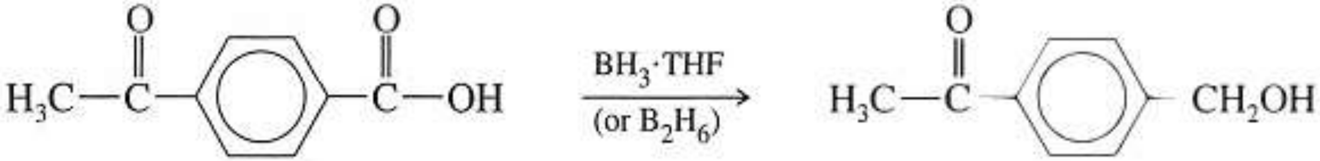


Elimination gives an aldehyde, which is quickly reduced to a lithium alkoxide.



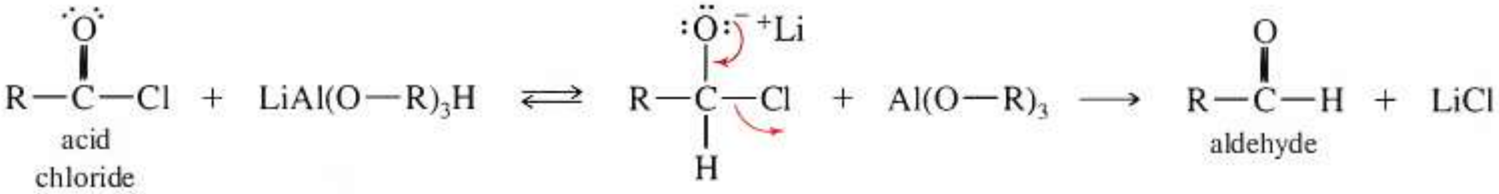
Water added in the second step protonates the alkoxide to the primary alcohol.

$$R{-}CH_2{-}O^- \, Li^+ + H_2O \longrightarrow R{-}CH_2{-}OH + LiOH$$



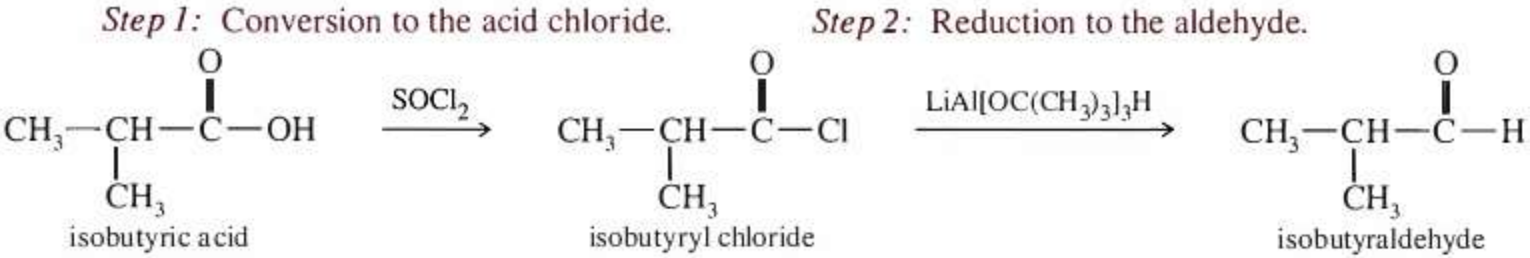
(80%)

Reduction to Aldehydes



$$R-\overset{O}{\overset{\|}{C}}-Cl + LiAl(O-R)_3H \rightleftharpoons R-\overset{:\ddot{O}:^- \ {}^+Li}{\overset{|}{\underset{\underset{H}{|}}{C}}}-Cl + Al(O-R)_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}-H + LiCl$$

Example

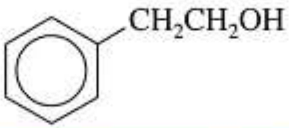


$$CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{\|}{C}}-OH \xrightarrow{SOCl_2} CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow{LiAl[OC(CH_3)_3]_3H} CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{O}{\overset{\|}{C}}-H$$

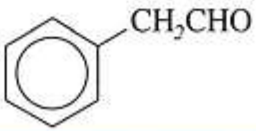
PROBLEM 20-19

Show how you would synthesize the following compounds from the appropriate carboxylic acids or acid derivatives.

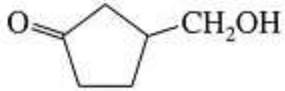
(a)



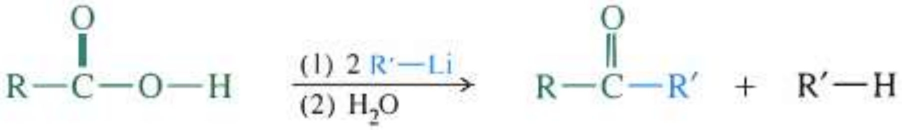
(b)



(c)

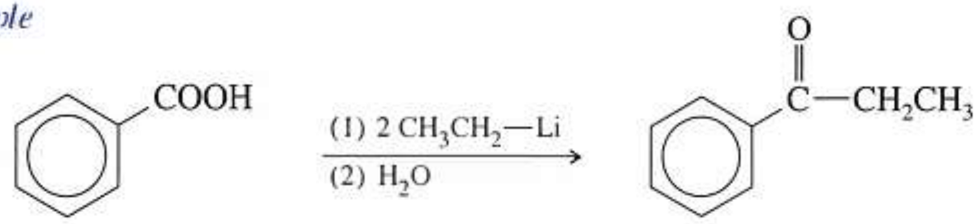


Alkylation of Carboxylic Acids to Form Ketones



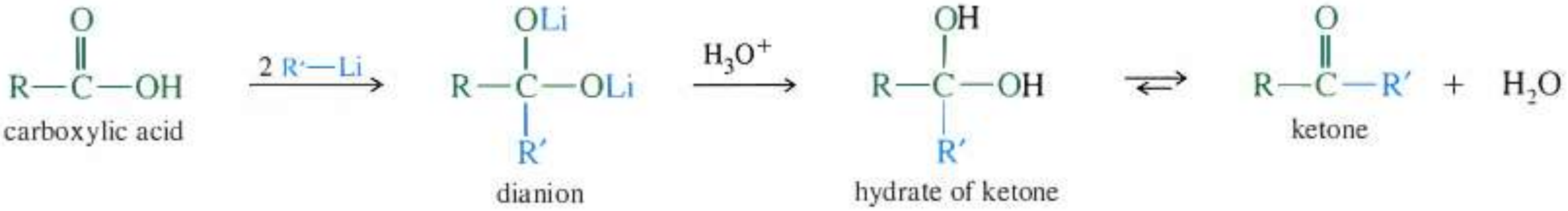
$$R-\overset{O}{\overset{\|}{C}}-O-H \xrightarrow[\text{(2) } H_2O]{\text{(1) 2 } R'-Li} R-\overset{O}{\overset{\|}{C}}-R' + R'-H$$

Example



benzoic acid

propiophenone



carboxylic acid

dianion

hydrate of ketone

ketone

PROBLEM 20-20

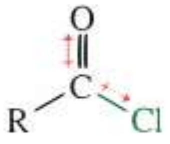
Propose a mechanism for conversion of the dianion to the ketone under mildly acidic conditions.

PROBLEM 20-21

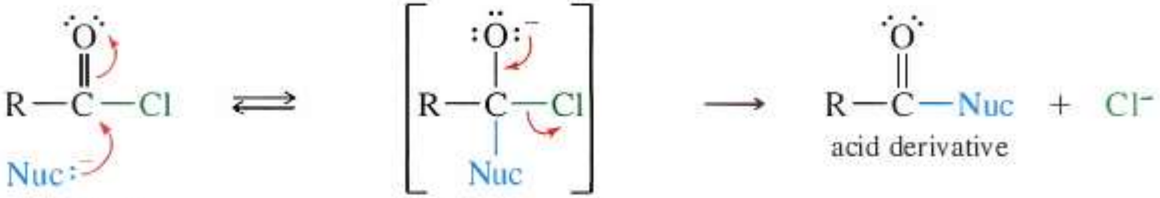
Show how the following ketones might be synthesized from the indicated acids, using any necessary reagents.

(a) propiophenone from propionic acid (two ways, using alkylation of the acid and using Friedel–Crafts acylation)

(b) methyl cyclohexyl ketone from cyclohexanecarboxylic acid



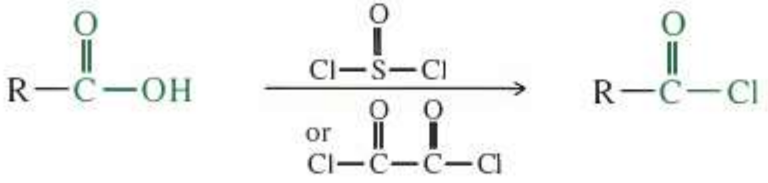
an acid chloride (acyl chloride)



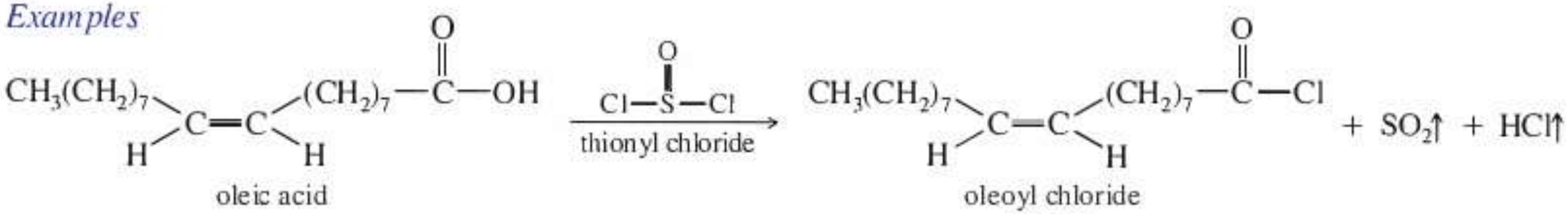
acid chloride

tetrahedral intermediate

acid derivative



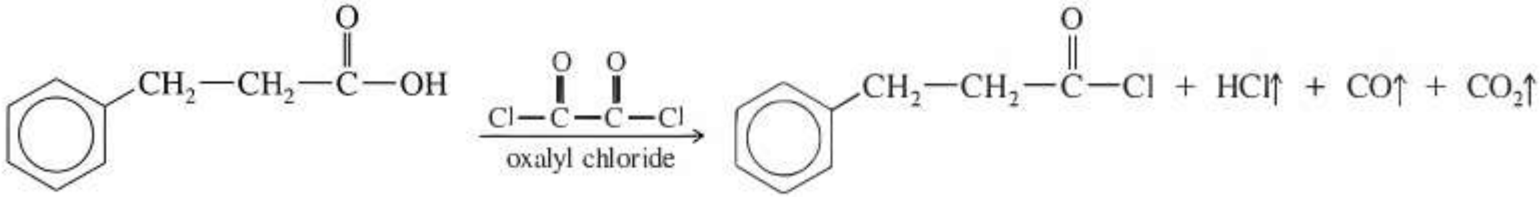
Examples



oleic acid

thionyl chloride

oleoyl chloride (95%)



oxalyl chloride

3-phenylpropanoic acid

3-phenylpropanoyl chloride (95%)