

By Jalal Hasan Mohammed



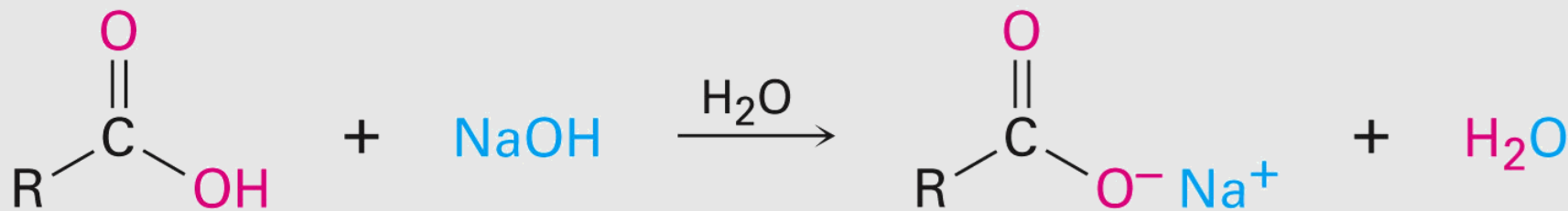
Carboxylic Acids and Nitriles



Dissociation of Carboxylic Acids



- Carboxylic acids are proton donors toward weak and strong bases, producing metal carboxylate salts, $\text{RCO}_2^- + \text{M}^+$
- Carboxylic acids with more than six carbons are only slightly soluble in water, but their conjugate base salts are water-soluble



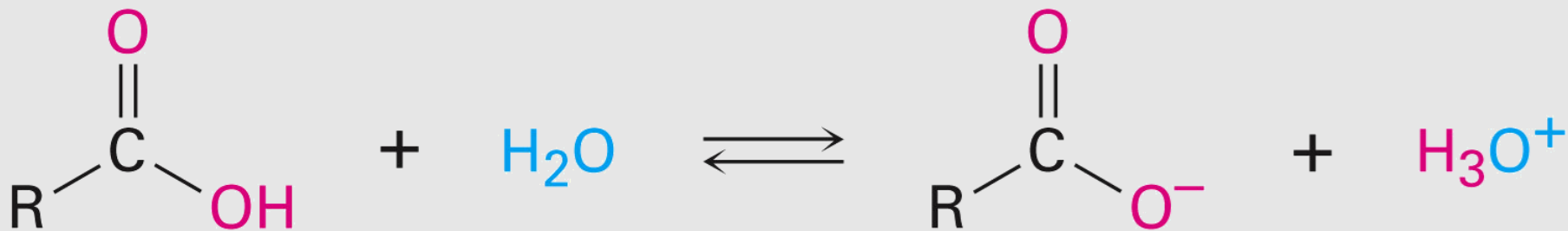
**A carboxylic acid
(water-insoluble)**

**A carboxylic acid salt
(water-soluble)**

Acidity Constant and pK_a



- Carboxylic acids transfer a proton to water to give H_3O^+ and carboxylate anions, RCO_2^- , but H_3O^+ is a much stronger acid
- The acidity constant, K_a , is about 10^{-5} for a typical carboxylic acid ($pK_a \sim 5$)



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

Substituent Effects on Acidity



- Electronegative substituents promote formation of the carboxylate ion

Table 20.3 Acidity of Some Carboxylic Acids

Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	<p>Stronger acid</p> <p>Weaker acid</p>
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C=CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	
CH_3CH_2OH (ethanol)	(1.00×10^{-16})	(16.00)	

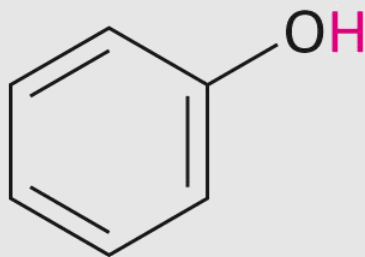
Inductive Effects on Acidity



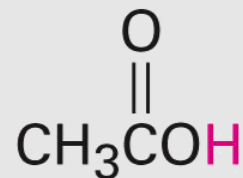
- Fluoroacetic, chloroacetic, bromoacetic, and iodoacetic acids are stronger acids than acetic acid
- Multiple electronegative substituents have synergistic effects on acidity



$$\text{p}K_a = 16$$



$$\text{p}K_a = 9.89$$



$$\text{p}K_a = 4.76$$



$$\text{p}K_a = -7$$

Acidity

Biological Acids and the Henderson-Hasselbalch Equation



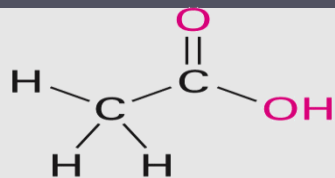
- If pK_a of given acid and the pH of the medium are known, % of dissociated and undissociated forms can be calculated using the Henderson-Hasselbalch eqn

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

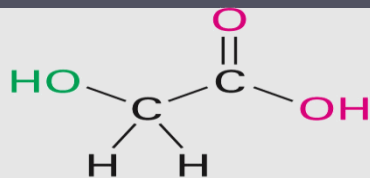
$$\text{pH} = pK_a + \log \frac{[A^-]}{[HA]}$$

Henderson-Hasselbalch equation

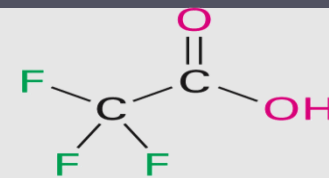
Substituent Effects on Acidity



$pK_a = 4.76$



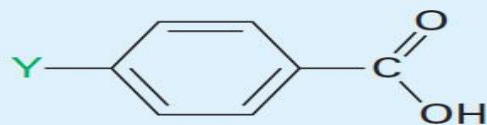
$pK_a = 3.83$




$pK_a = -0.23$



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

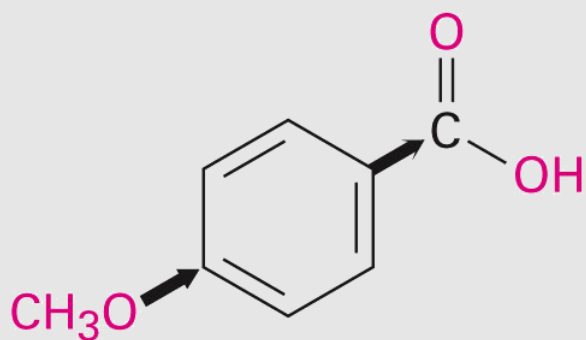


	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid 	-NO ₂	39	3.41	} Deactivating groups
	-CN	28	3.55	
	-CHO	18	3.75	
	-Br	11	3.96	
	-Cl	10	4.0	
	-H	6.46	4.19	
Weaker acid	-CH ₃	4.3	4.34	} Activating groups
	-OCH ₃	3.5	4.46	
	-OH	3.3	4.48	

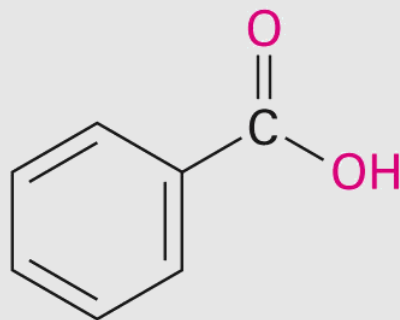
Aromatic Substituent Effects



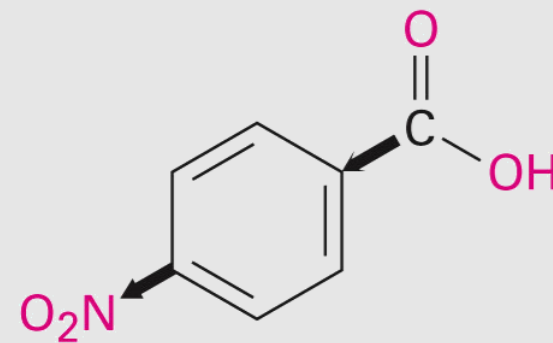
- Electron-withdrawing (EW) groups increase acidity by stabilizing the carboxylate anion. Electron-donating (activating) groups decrease acidity by destabilizing the carboxylate anion
- We can use relative pK_a 's as a calibration for effects on relative free energies of reactions with the same substituents



***p*-Methoxybenzoic acid**
($pK_a = 4.46$)



Benzoic acid
($pK_a = 4.19$)



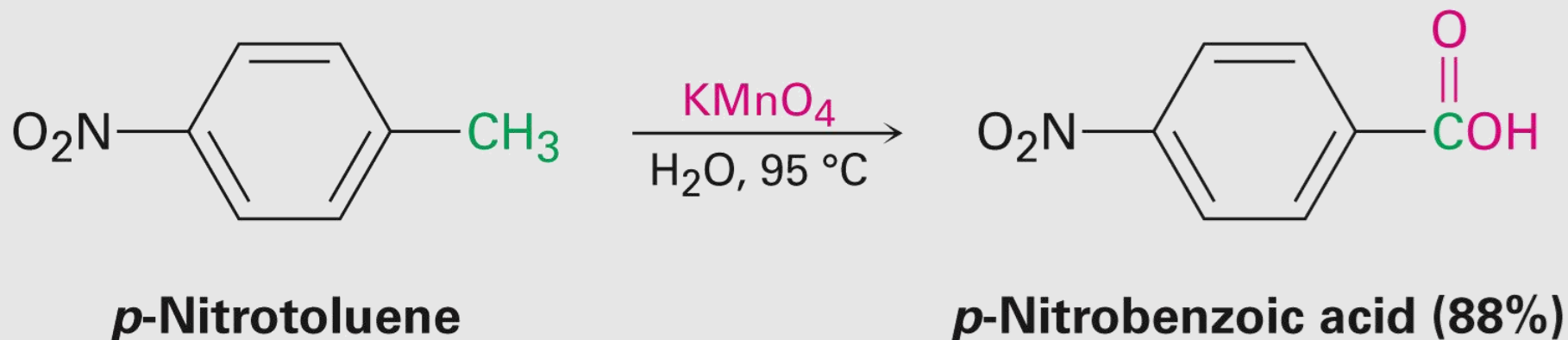
***p*-Nitrobenzoic acid**
($pK_a = 3.41$)

Acidity

Preparing Carboxylic Acids



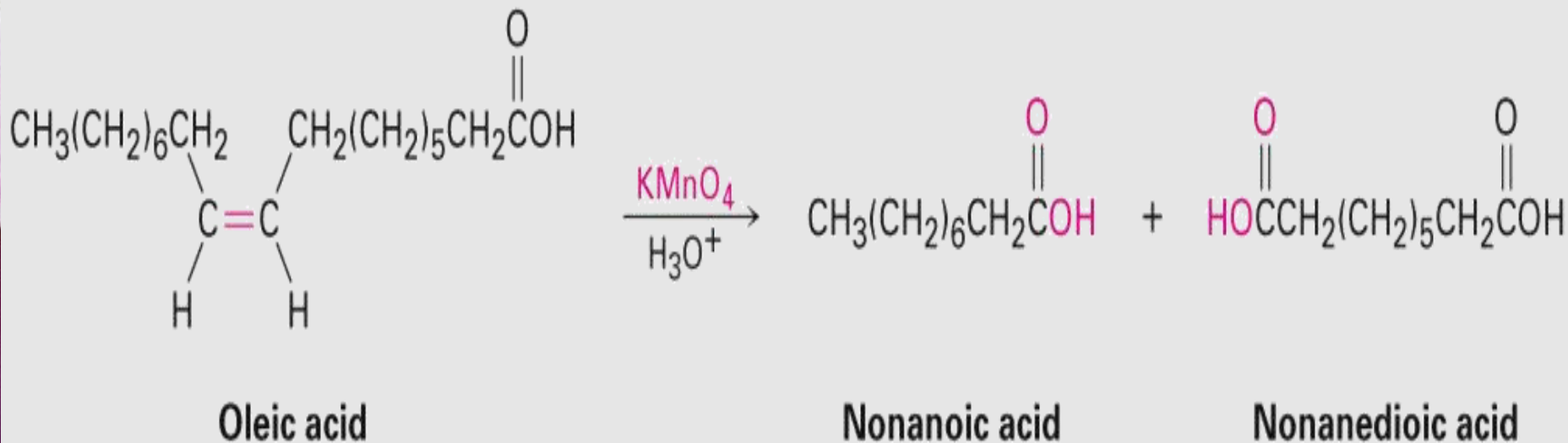
- Oxidation of a substituted alkylbenzene with KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ gives a substituted benzoic acid (see Section 16.9)
- 1° and 2° alkyl groups can be oxidized, but tertiary groups are not



From Alkenes



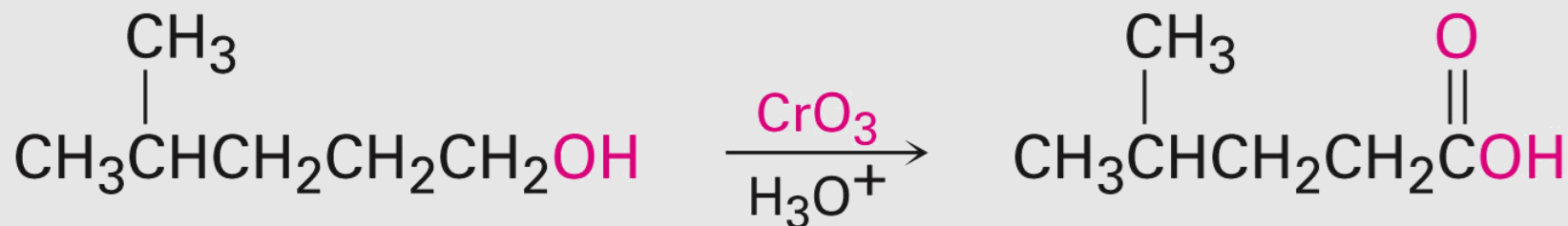
- Oxidative cleavage of an alkene with KMnO_4 gives a carboxylic acid if the alkene has at least one vinylic hydrogen (see Section 7.9)



From Alcohols

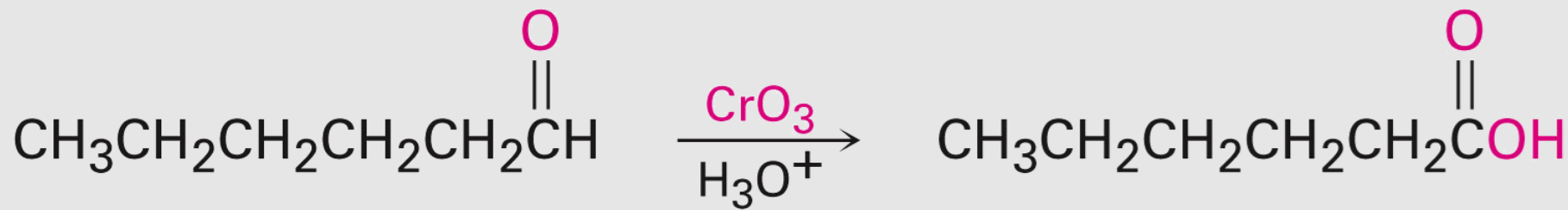


- Oxidation of a primary alcohol or an aldehyde with CrO_3 in aqueous acid



4-Methyl-1-pentanol

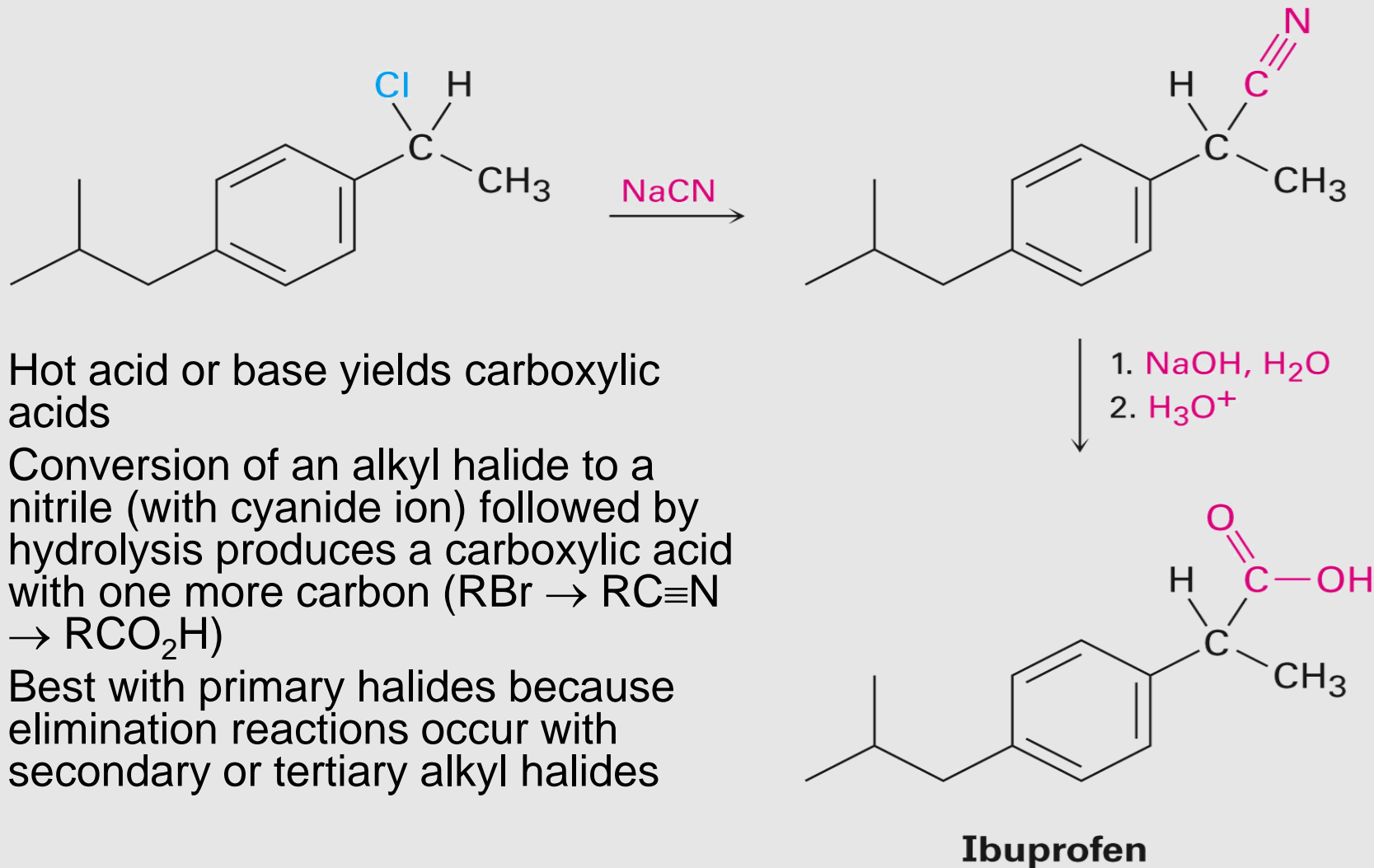
4-Methylpentanoic acid



Hexanal

Hexanoic acid

Hydrolysis of Nitriles

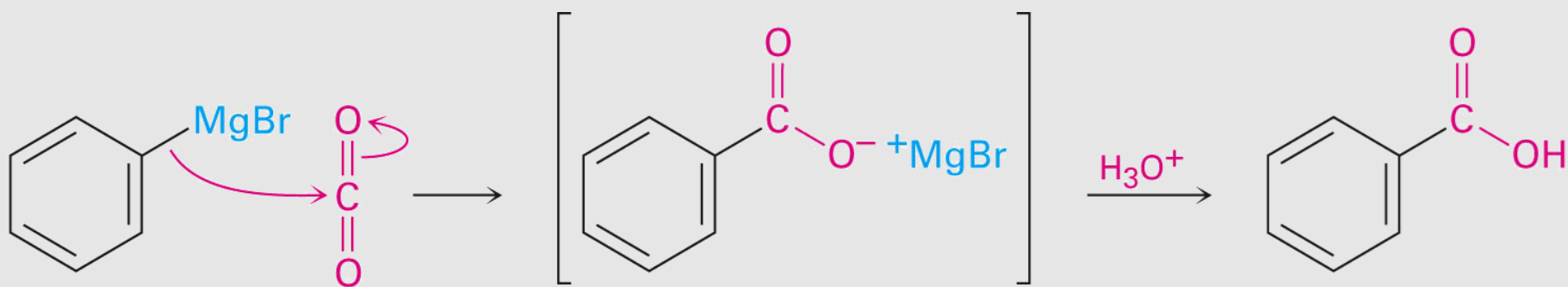


- Hot acid or base yields carboxylic acids
- Conversion of an alkyl halide to a nitrile (with cyanide ion) followed by hydrolysis produces a carboxylic acid with one more carbon ($RBr \rightarrow RC\equiv N \rightarrow RCO_2H$)
- Best with primary halides because elimination reactions occur with secondary or tertiary alkyl halides

Carboxylation of Grignard Reagents



- Grignard reagents react with dry CO_2 to yield a metal carboxylate
- Limited to alkyl halides that can form Grignard reagents
- The organomagnesium halide adds to $\text{C}=\text{O}$ of carbon dioxide
- Protonation by addition of aqueous HCl in a separate step gives the free carboxylic acid



Phenylmagnesium
bromide

Benzoic acid

Reactions of Carboxylic Acids: An Overview

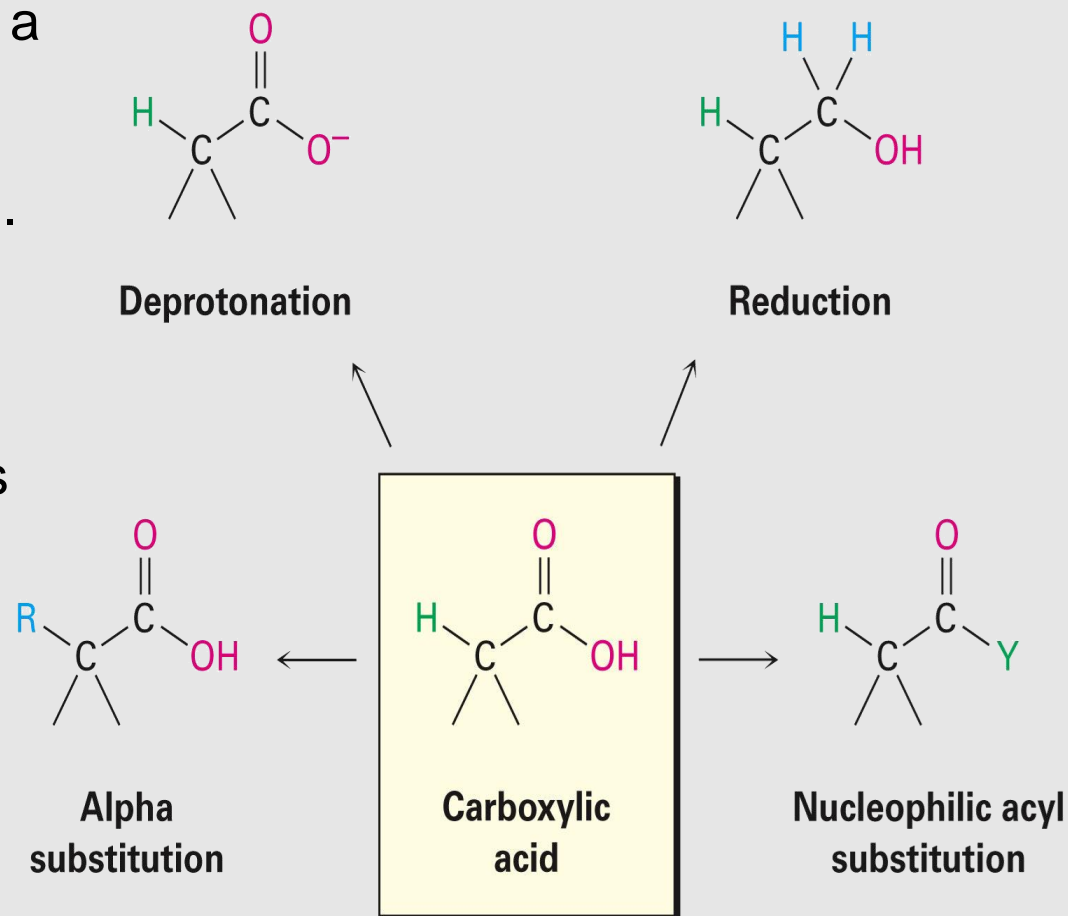


Review

- CA can transfer a proton to a base (produces good nucleophile).
- CA can be reduced by LAH.

Chapters 21, 22

- Nucleophile can add to carbonyl carbon of CA.
- In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones



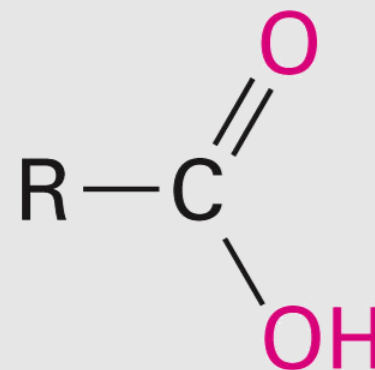
Chemistry of Nitriles



- Nitriles and carboxylic acids both have a carbon atom with three bonds to an electronegative atom, and contain a π bond
- Both are electrophiles



**A nitrile—three
bonds to nitrogen**

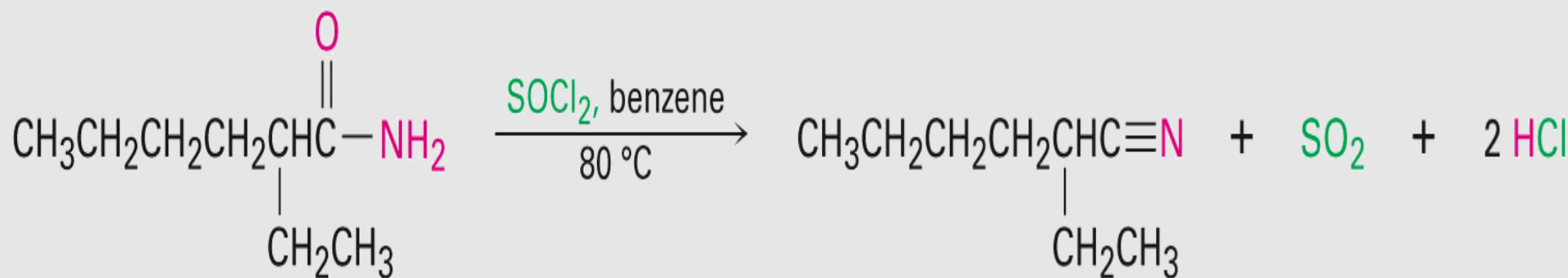


**An acid—three
bonds to two oxygens**

Preparation of Nitriles by Dehydration



- Reaction of primary amides RCONH_2 with SOCl_2 or POCl_3 (or other dehydrating agents)
- Not limited by steric hindrance or side reactions (as is the reaction of alkyl halides with NaCN)



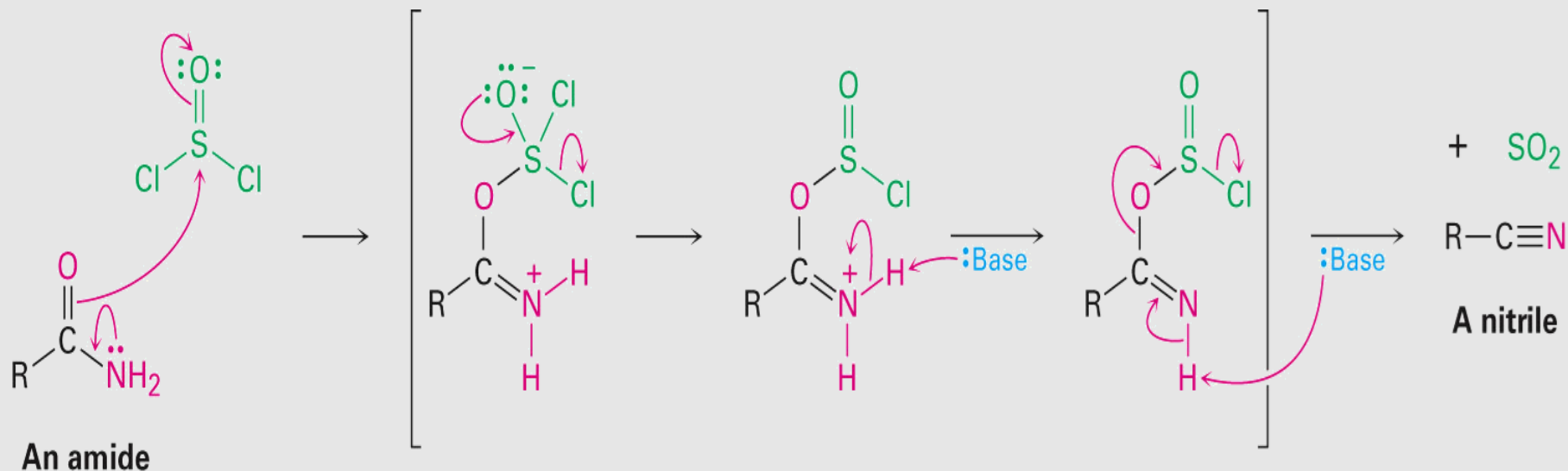
2-Ethylhexanamide

2-Ethylhexanenitrile (94%)

Mechanism of Dehydration of Amides



- Nucleophilic amide oxygen atom attacks SOCl_2 followed by deprotonation and elimination

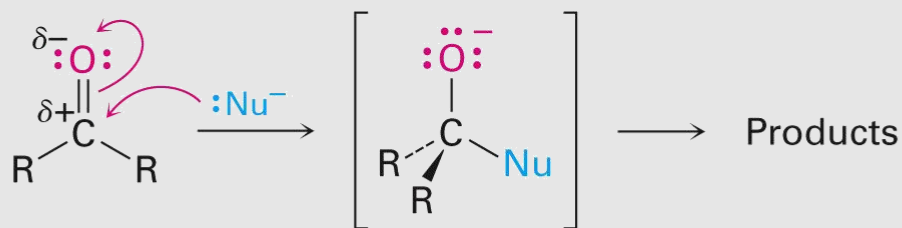


Reactions of Nitriles

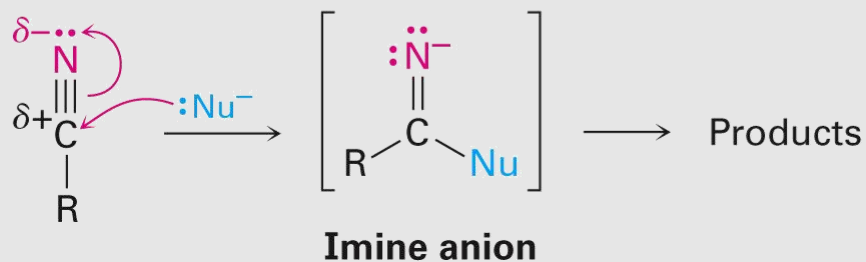
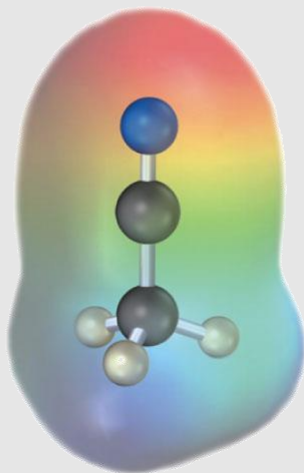


- $\text{RC}\equiv\text{N}$ is strongly polarized and with an electrophilic carbon atom
- Attacked by nucleophiles to yield sp^2 -hybridized imine anions

Carbonyl compound



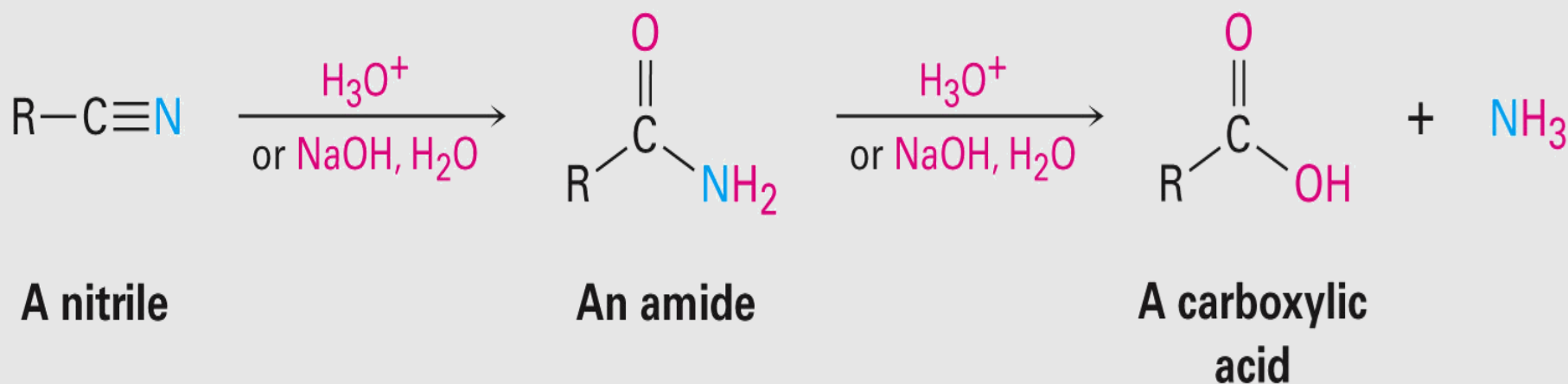
Nitrile



Hydrolysis: Conversion of Nitriles into Carboxylic Acids



- Hydrolyzed in with acid or base catalysis to a carboxylic acid and ammonia



Mechanism of Hydrolysis of Nitriles

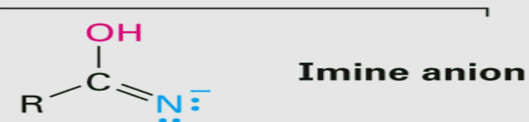
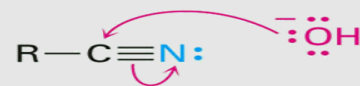


- Nucleophilic addition of hydroxide to $C\equiv N$ bond
- Protonation gives a hydroxy imine, which tautomerizes to an amide
- A second hydroxide adds to the amide carbonyl group and loss of a proton gives a dianion
- Expulsion of NH_2^- gives the carboxylate

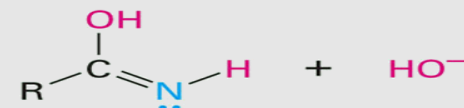




1 Nucleophilic addition of hydroxide ion to the CN triple bond gives an imine anion addition product.



2 Protonation of the imine anion by water yields a hydroxyimine and regenerates the base catalyst.



3 Tautomerization of the hydroxyimine yields an amide in a reaction analogous to the tautomerization of an enol to give a ketone.



4 Further hydrolysis of the amide gives the anion of a carboxylic acid by a mechanism we'll discuss in Section 21.7.



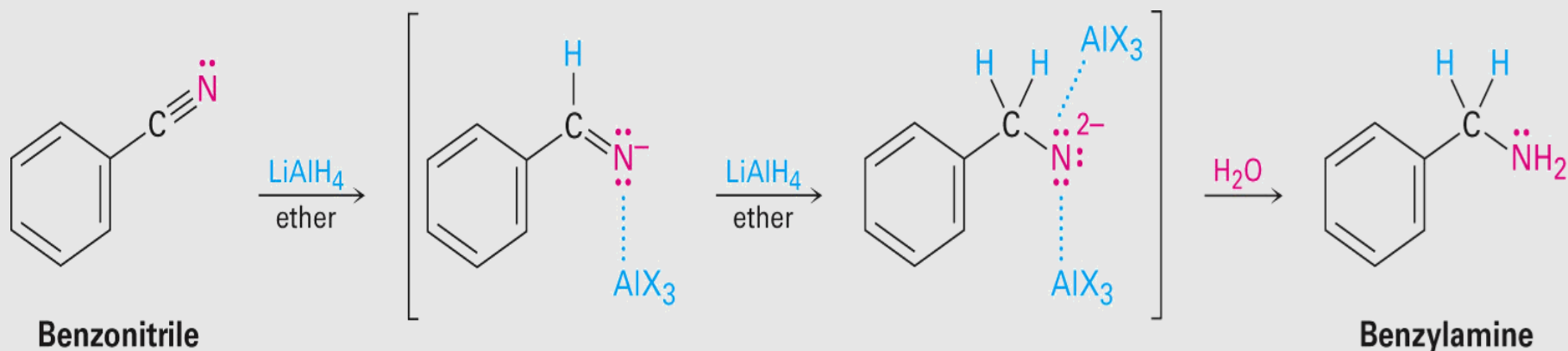
Carboxylate ion

Reduction: Conversion of Nitriles into Amines



Reduction of a nitrile with LiAlH_4 gives a primary amine

- Nucleophilic addition of hydride ion to the polar $\text{C}\equiv\text{N}$ bond, yielding an imine anion
- The $\text{C}=\text{N}$ bond undergoes a second nucleophilic addition of hydride to give a *dianion*, which is protonated by water



Reaction of Nitriles with Organometallic Reagents



- Grignard reagents add to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone

