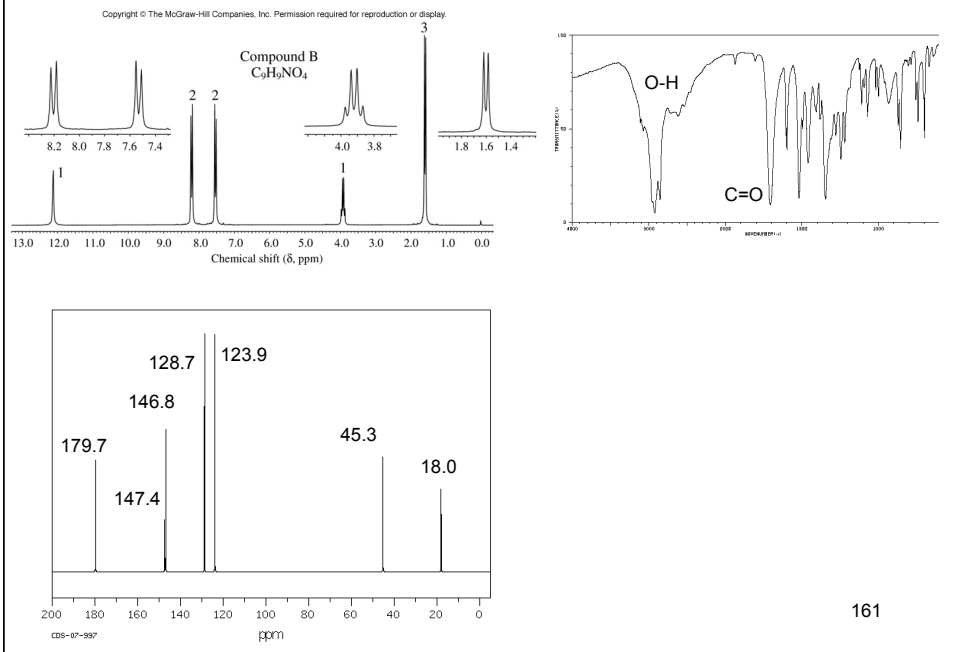
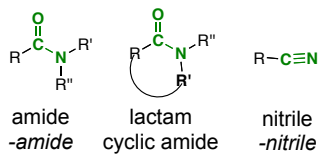
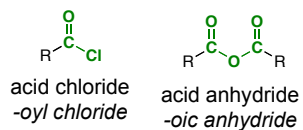
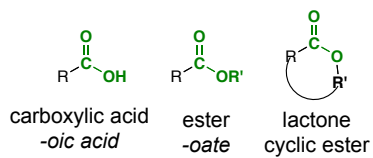


problem 18.33b



Chapter 19: Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution

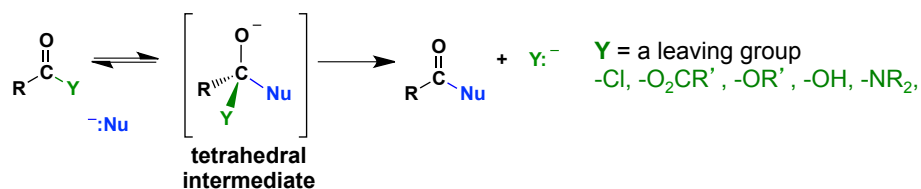
19.1: Nomenclature of Carboxylic Acid Derivatives (please read)



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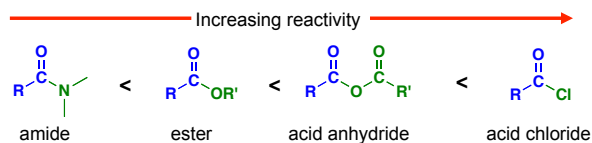
19.3: Nucleophilic Acyl Substitution Mechanisms

The general mechanism of nucleophilic acyl substitution occurs in two stages. The first is addition of the nucleophile (Nu) to the carbonyl carbon to form a *tetrahedral intermediate*. The second stage is collapse of the tetrahedral intermediate to reform the carbonyl with expulsion of a leaving group (Y). There is overall substitution of the leaving group (Y) of the acid derivative with the nucleophile (Nu).

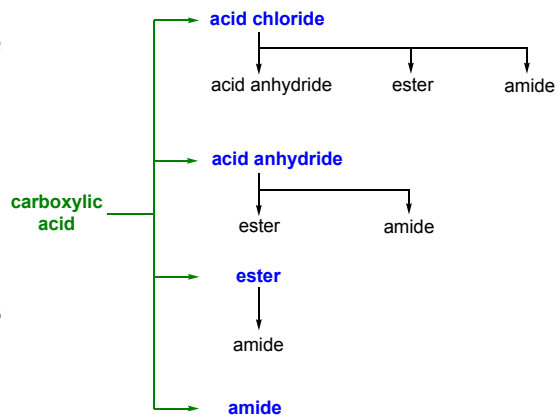


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19.2: Structure and Reactivity of Carboxylic Acid Derivatives

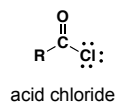
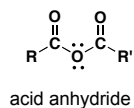
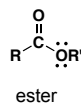
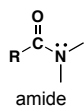


All acyl derivatives can be prepared directly from the carboxylic acid. Less reactive acyl derivative (amides and esters) are more readily prepared from more reactive acyl derivatives (acid chlorides and anhydrides)



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The reactivity of the acid derivative is related to its resonance stabilization. The C-N bond of amides is significantly stabilized through resonance and is consequently the least reactive acid derivative. The C-Cl bond of acid chlorides is the least stabilized by resonance and is the most reactive acid derivative.

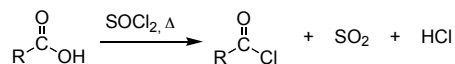


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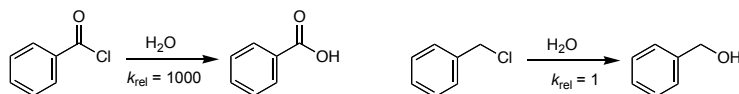
19.4: Nucleophilic Acyl Substitution in Acyl Chlorides

Preparation of acid chlorides from carboxylic acids:

Reagent: **SOCl₂** (thionyl chloride)



Acid chlorides are much more reactive toward nucleophiles than alkyl chlorides



Nucleophilic acyl substitution reactions of acid halides (Table 19.1)

1. *Anhydride formation (Ch. 19.4):* Acid chlorides react with carboxylic acids to give acid anhydrides

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2. *Ester formation* (Ch. 15.8): Acid chlorides react with alcohols to give esters. Reactivity: 1° alcohols react faster than 2° alcohols, which react much faster than 3° alcohols

3. *Amide formation* (Ch. 19.4): Acid chlorides react with ammonia, 1° or 2° amines affords amides.

4. *Hydrolysis* (Ch. 19.4): Acid chlorides react with water to afford carboxylic acids

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19.5: Nucleophilic Acyl Substitution in Acid Anhydrides

Anhydrides are prepared from acid chlorides and a carboxylic acid

Reactions of acid anhydrides (Table 19.2): Acid anhydrides are slightly less reactive than acid chlorides; however, the overall reactions are nearly identical and they are often used interchangeably.

1. *Ester formation* (Ch. 15.8):

2. *Amide Formation* (Ch. 19.14):

3. *Hydrolysis to give carboxylic acids* (Ch. 19.5):

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19.6: Physical Properties and Sources of Esters (please read)

19.7: Reactions of Esters: A Preview.

Preparation of esters (Table 19.3, p. 782)

1. Fischer esterification (Ch. 15.8 & 18.14)

2. Reaction of acid chlorides or acid anhydrides with alcohols (Ch. 15.8, 19.4 & 19.5)

3. Baeyer-Villiger oxidation of ketones (p. 732)

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Nucleophilic acyl substitution reactions of esters (Table 19.4):

Esters are less reactive toward nucleophilic acyl substitution than acid chlorides or acid anhydrides.

1. *Amide formation* (Ch. 19.11): Esters react with ammonia, 1° and 2° amines to give amides

2. *Hydrolysis* (Ch. 19.9-19.10): Esters can be hydrolyzed to carboxylic acids and an alcohol with aqueous base or acid-catalysis.

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19.8: Acid-catalyzed Ester Hydrolysis. Reverse of the Fischer esterification reaction. (Mechanism 19.2, p. 784-5)

Protonation of the ester carbonyl accelerates nucleophilic addition of water to the carbonyl carbon giving the tetrahedral intermediate. Protonation of the -OR' group then accelerates the expulsion of HOR'.
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19.9: Ester Hydrolysis in Base: Saponification
Mechanism of the base-promoted hydrolysis (Mechanism 19.3, p. 789)

Why is the saponification of esters not base-catalyzed?

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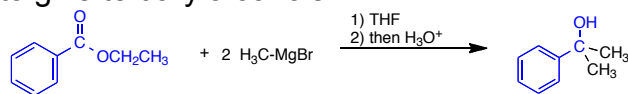
19.10: Reaction of Esters with Ammonia and Amines.

Esters react with ammonia, 1°, and 2° amines to give amides.

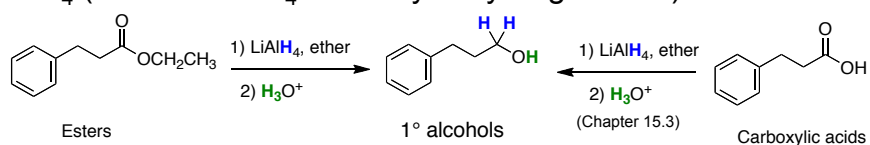
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19.11: Reaction of Esters with Grignard and Organolithium Reagents and Lithium Aluminum Hydride

Esters react with two equivalents of an organolithium or Grignard reagent to give tertiary alcohols.

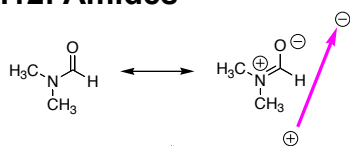


Esters (and carboxylic acids) are reduced to 1° alcohols with LiAlH₄ (but not NaBH₄ or catalytic hydrogenation).



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19.12: Amides



amide bond has a large dipole moment ~ 3.5 Debye

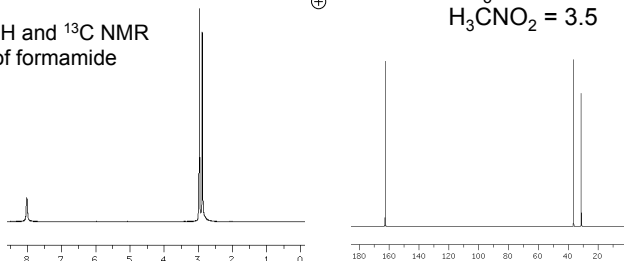
$\text{H}_2\text{O} = 1.85 \text{ D}$

$\text{NH}_3 = 1.5 \text{ D}$

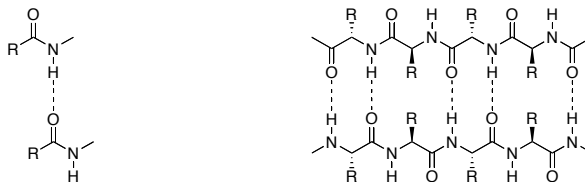
$\text{H}_3\text{CNO}_2 = 3.5$



^1H and ^{13}C NMR of formamide

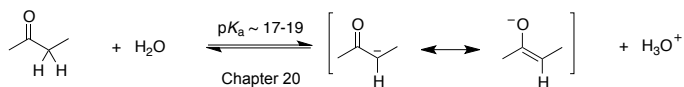
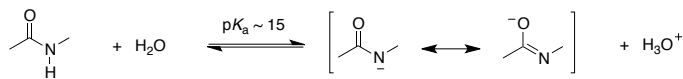
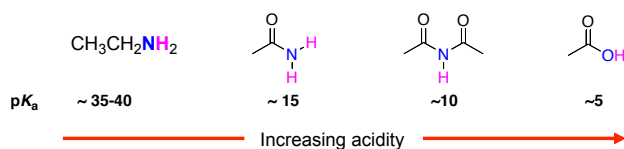


The N-H bond of an amide is a good hydrogen bond donor and the C=O is a good hydrogen bond acceptor.



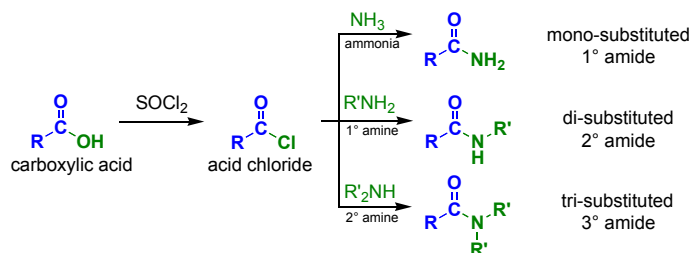
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Acidity of Amides: The resulting negative charge from deprotonation of an amide N-H is stabilized by the carbonyl



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Synthesis of Amides: Amides are most commonly prepared from the reactions of ammonia, 1° or 2° amines with acids chlorides, acid anhydrides or esters. This is a nucleophilic acyl substitution reaction.

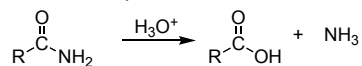


When an acid chloride or anhydride is used, a mole of acid (HCl or carboxylic acid) is produced. Since amines are bases, a second equivalent (or an equivalent of another base such as hydroxide or bicarbonate) is required to neutralize the acid

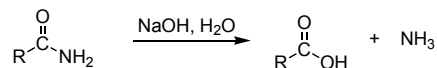
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19.13: Hydrolysis of Amides. Amides are hydrolyzed to the carboxylic acids and amines.

Acid-promoted mechanism (Mechanism 19.4, p. 797)

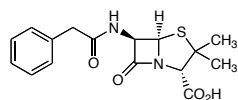


Base-promoted mechanism (Mechanism 19.5, p. 799)

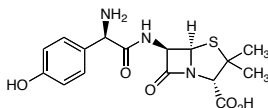


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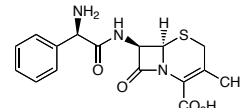
19.16: Lactams. (please read) cyclic amides – β -lactams (4-membered ring lactams) are important anti-bacterial agents.



Penicillin G



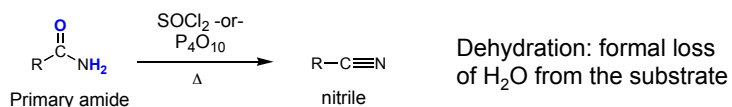
Amoxicillin



Cephalexin

19.17: Preparation of Nitriles (Table 19.6, page 802)

1. Reaction of cyanide ion with 1° and 2° alkyl halides – this is an S_N2 reaction. (Ch. 8.1 & 8.10)
2. Cyanohydrins – reaction of cyanide ion with ketones and aldehydes. (Ch. 17.7)
3. Dehydration of primary amides with SOCl_2 (or P_4O_{10})



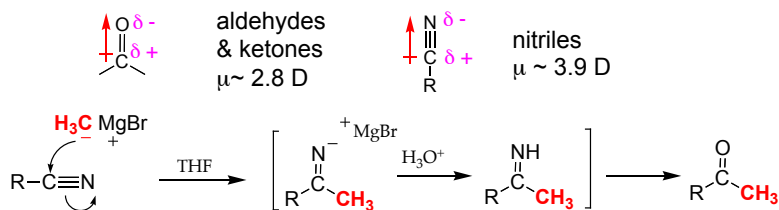
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19.16: Hydrolysis of Nitriles. Nitriles are hydrolyzed in either aqueous acid or aqueous base to carboxylic acids. The corresponding primary amide is an intermediate in the reaction. Base-promoted mechanism (Mechanism. 19.6, p. 804)

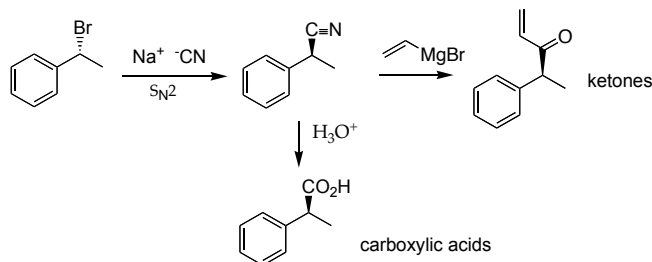
Acid-promoted hydrolysis:

180

19.19: Addition of Grignard Reagents to Nitriles. One equiv. of a Grignard Reagent will add to a nitrile. After aqueous acid work-up, the product is a ketone.



Must consider functional group compatibility; there is wide flexibility in the choice of Grignard reagents.



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19.20: Spectroscopic Analysis of Carboxylic Acid Derivatives

IR: typical C=O stretching frequencies for:

carboxylic acid:	1710 cm^{-1}
ester:	1735 cm^{-1}
amide:	1690 cm^{-1}
aldehyde:	1730 cm^{-1}
ketone:	1715 cm^{-1}
acid chlorides:	1800 cm^{-1}
anhydrides:	1750 and 1815 cm^{-1}

Conjugation (C=C π -bond or an aromatic ring) moves the C=O absorption to lower energy (right) by $\sim 15 \text{ cm}^{-1}$

aliphatic ester 1735 cm^{-1}	conjugated ester 1725 cm^{-1}	aromatic ester 1725 cm^{-1}
aliphatic amide 1690 cm^{-1}	conjugated amide 1675 cm^{-1}	aromatic amide 1675 cm^{-1}

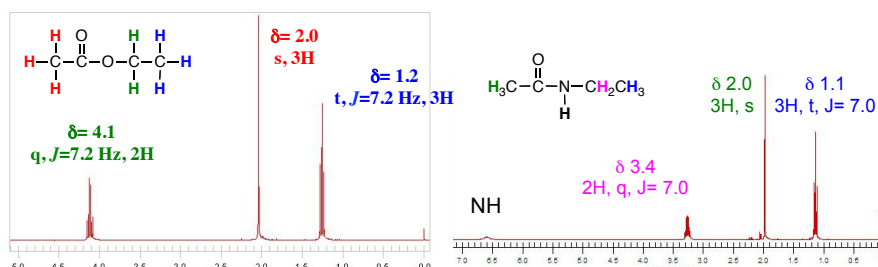
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^1H NMR:

Protons on the α -carbon (next to the $\text{C}=\text{O}$) of esters and amides have a typical chemical shift range of δ 2.0 - 2.5 ppm.

Protons on the carbon attached to the ester oxygen atom have a typical chemical shift range of δ 3.5 - 4.5 ppm.

The chemical shift of an amide N-H proton is typically between δ 5-8 ppm. It is broad and often not observed.

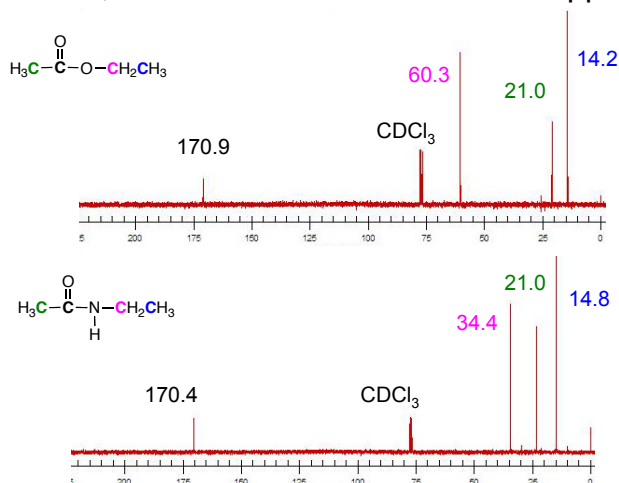


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^{13}C NMR: very useful for determining the presence and nature of carbonyl groups. The typical chemical shift range for $\text{C}=\text{O}$ carbon is δ 160 - 220 ppm.

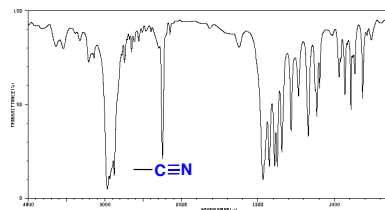
Aldehydes and ketones: δ 190 - 220 ppm

Carboxylic acids, esters and amides: δ 160 - 185 ppm

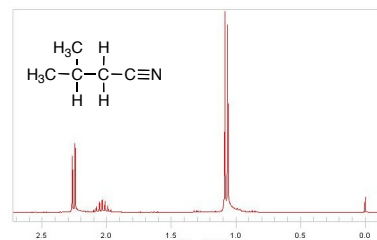


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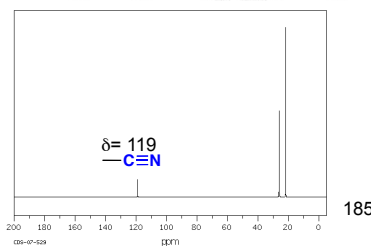
Nitriles have a sharp IR absorption near 2250 cm^{-1} for alkyl nitriles and 2230 cm^{-1} for aromatic and conjugated nitriles (highly diagnostic)



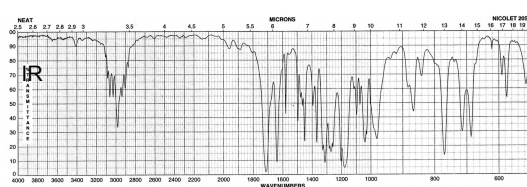
The nitrile functional group is invisible in the ^1H NMR. The effect of a nitrile on the chemical shift of the protons on the α -carbon is similar to that of a ketone.



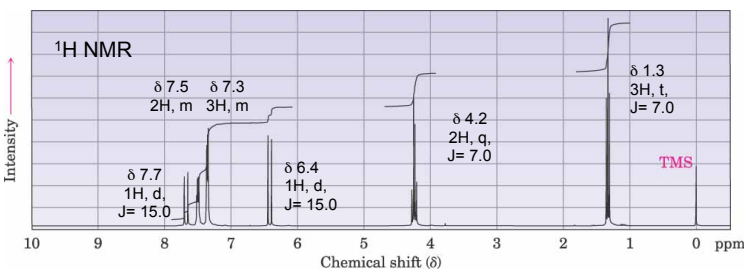
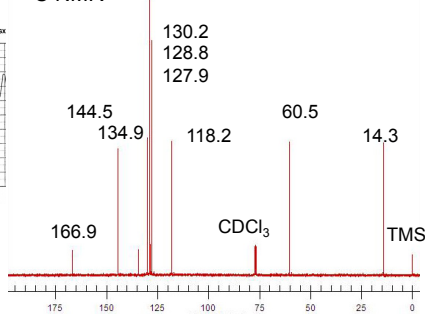
The chemical shift of the nitrile carbon in the ^{13}C spectrum is in the range of $\sim 115\text{--}130$ (significant overlap with the aromatic region).



$\text{C}_{11}\text{H}_{12}\text{O}_2$

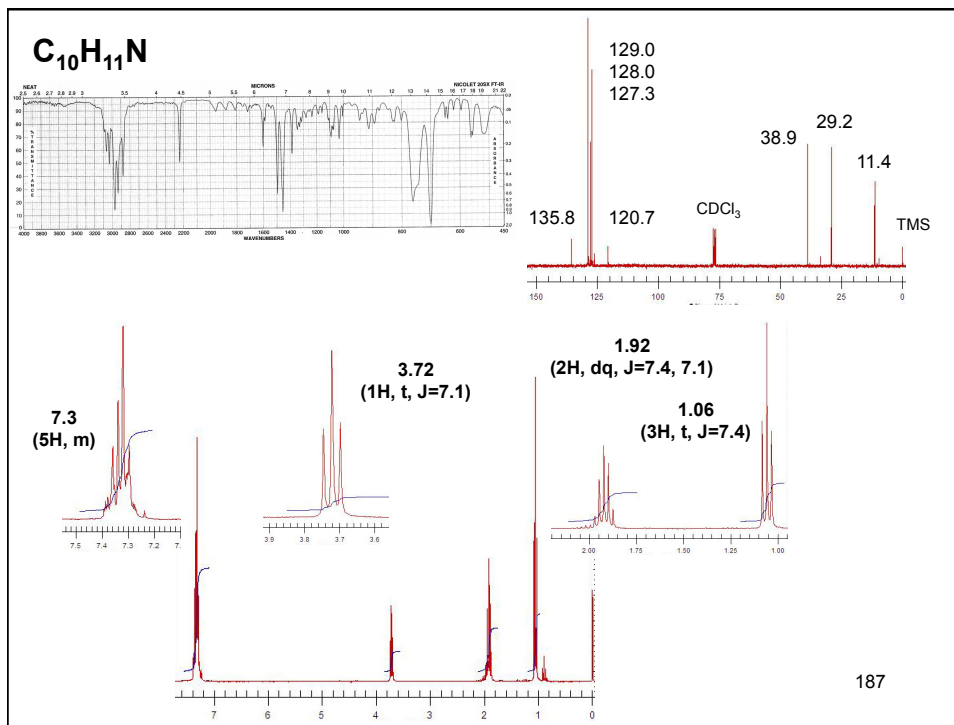


^{13}C NMR

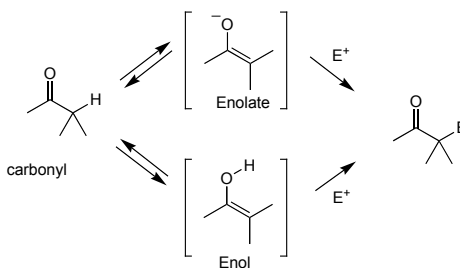


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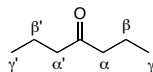
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Chapter 20: Enols and Enolates



20.1: Enol Content and Enolization



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