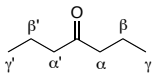
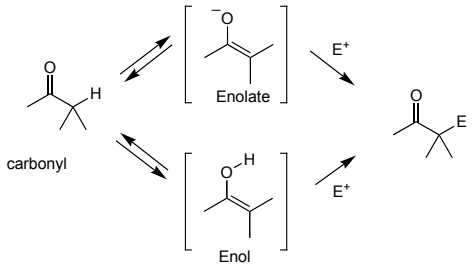
Chapter 22. Carbonyl Alpha-Substitution Reactions

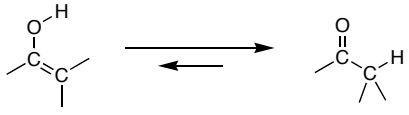




228

Tautomers: isomers, usually related by a proton transfer, that are in equilibrium

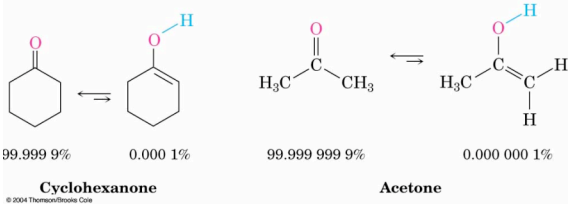
Keto-enol tautomeric equilibrium lies heavily in favor of the keto form.



enol **keto**

C=C	ΔH° = 611 KJ/mol	C=O	ΔH° = 735 KJ/mol
C-O	380	C-C	376
O-H	436	C-H	420

ΔH° = -104 KJ/mol



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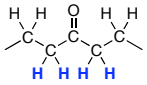
Keto-enol tautomerism is catalyzed by both acid and base

Acid-catalyzed mechanism (Figure 22.1):

Base-catalyzed mechanism (Figure 22.2):

The carbonyl significantly increases the acidity of the α-protons



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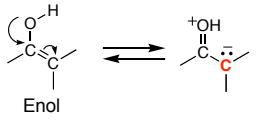
22.2: Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions



nucleophile

General mechanism for acid-catalzyed α-substitution of carbonyls (Figure 22.3)

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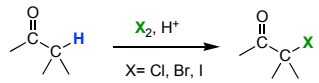
22.3: Alpha Halogenation of Aldehydes and Ketones

an α-proton of aldehydes and ketones can be replaced with a -Cl, -Br, or -I (-X) through the acid-catalyzed reaction with Cl_2 , Br_2 , or I_2 , (X_2) respectively.



Mechanism of the acid-catalyzed α-halogenation (Fig. 22.4)

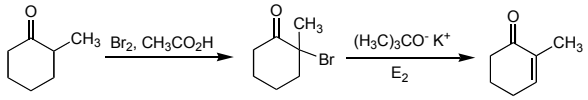
Rate= *k* [ketone/aldehyde] [H^+]

rate dependent on enol formation

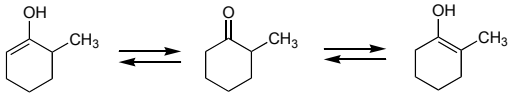
232

α,β-unsaturated ketones and aldehydes:

α -bromination followed by elimination



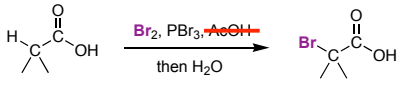
Why is one enol favored over the other?



22.4: Alpha Bromination of Carboxylic Acids:

The Hell–Volhard–Zelinskii (HVZ) Reaction

α-bromination of a carboxylic acid



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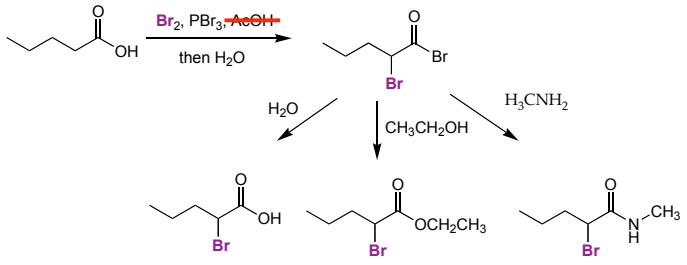
Mechanism (p. 828, please read)

α-bromo carboxylic acids, esters, and amides



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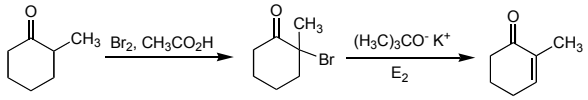
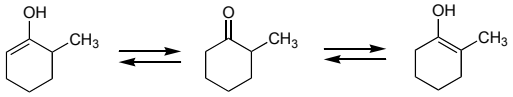
α,β-unsaturated ketones and aldehydes:
α -bromination followed by elimination

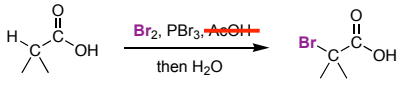


Why is one enol favored over the other?



22.4: Alpha Bromination of Carboxylic Acids:
The Hell–Volhard–Zelinskii (HVZ) Reaction

α-bromination of a carboxylic acid



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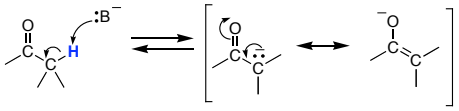
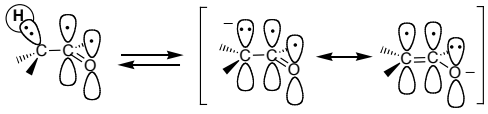
22.5: Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

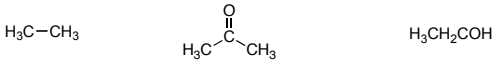
Base induced enolate formation



Enolate anion

The negative charge of the enolate ion (the conjugate base of the aldehyde or ketone) is stabilized by delocalization onto the oxygen





ethane	acetone	ethanol
pK_a= 60	pK_a= 19	pK_a= 16

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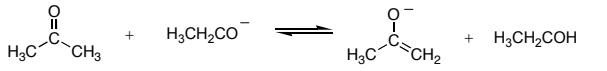
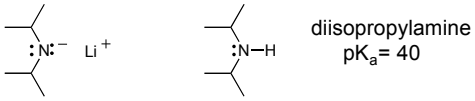
Base induced enolate formation



acetone	ethoxide	enolate	ethanol
pK_a= 19			pK_a= 16
(weaker acid)	(weaker base)	(stronger base)	(stronger acid)

Lithium diisopropylamide (LDA): a very strong base



diisopropylamine
pK_a= 40

LDA is used to generate enolate ions from carbonyl by abstraction of α-protons

pK_a= 19			pK_a= 40
(stronger acid)	(stronger base)	(weaker base)	(weaker acid)

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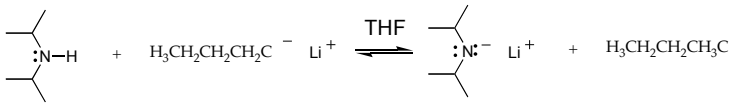
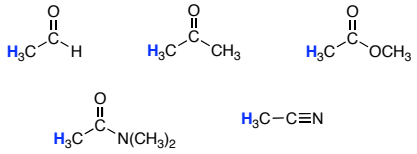


pK_a= 40 pK_a= 60

α-deprotonation of a carbonyl compound by LDA occurs rapidly in THF at -78° C.

Typical pK_a's of carbonyl compounds (α-protons):

aldehydes	17
ketones	19
esters	25
amides	30
nitriles	25



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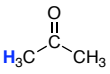
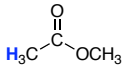
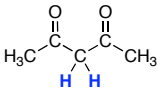
Acidity of 1,3-dicarbonyl compounds



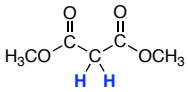
ketone
pK_a= 19



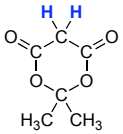
ester
pK_a= 25



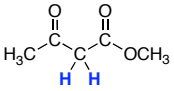
1,3-diketone
pK_a= 9



1,3-diester
pK_a= 13



Meldrum's acid
pK_a= 5

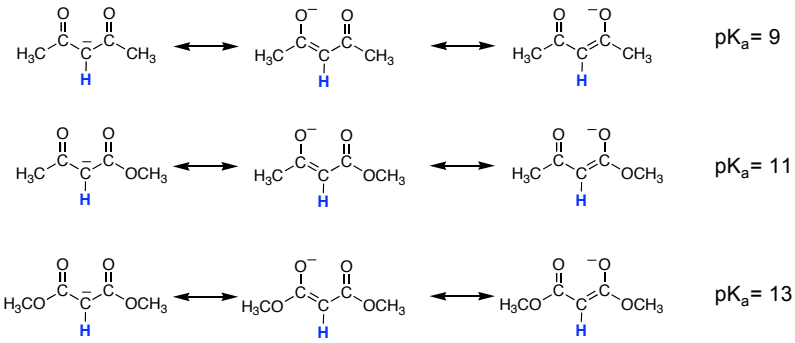


1,3-keto ester
pK_a= 11

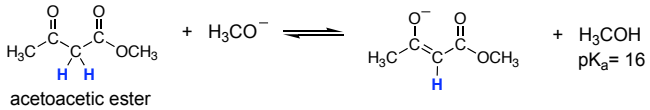
Why is Meldrum's acid more acidic than other dicarbonyl compounds?

239

Delocalization of the negative charge over two carbonyl groups dramatically increases the acidity of the α-protons



Enolate formation for a 1,3-dicarbonyl is very favorable



acetoacetic ester
pK_a= 11

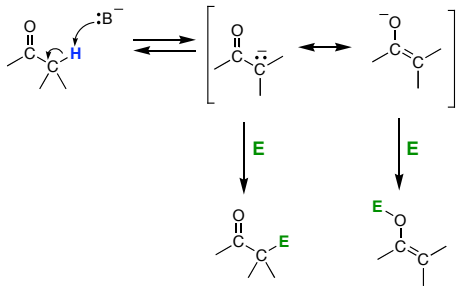
240

22.6: Reactivity of enolate ions

By treating carbonyl compounds with a strong base such as LDA, quantitative α-deprotonation occurs to give an enolate ion.

Enolate ions are much more reactive toward electrophiles than enols.

Enolates can react with electrophiles at two potential sites



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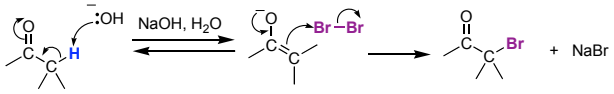
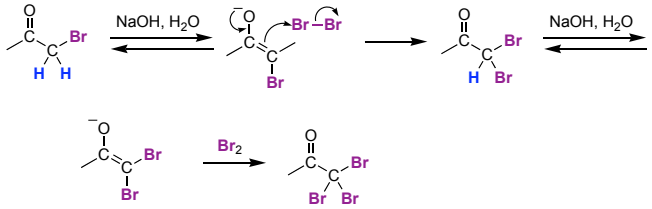
22.7 Halogenation of Enolate Ions: The Haloform Reaction

Carbonyls undergo α-halogenation through base promoted enolate formation



Base promoted α-halogenation carbonyls is difficult to control because the product is more acidic than the starting material; mono-, di- and tri-halogenated products are often produced



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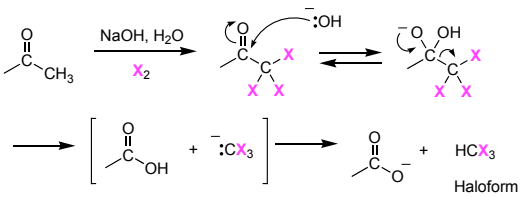
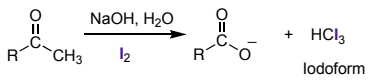
Haloform reaction:



Iodoform reaction: chemical tests for a methyl ketone



Iodoform: bright yellow precipitate

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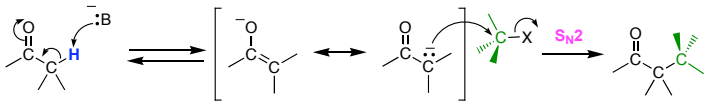
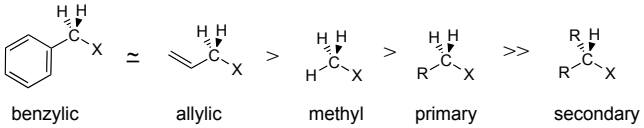
22.8 Alkylation of Enolate Ions

Enolates react with alkyl halides (and tosylates) to form a new C-C bond (alkylation reaction)



Reactivity of alkyl halides toward S_N2 alkylation:



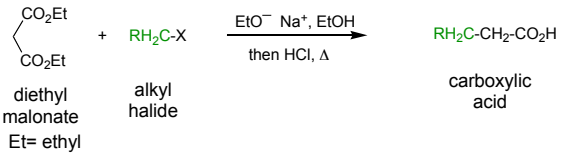
benzylic allylic methyl primary secondary

tosylate ≃ -I > -Br > -Cl

Tertiary, vinyl and aryl halides and tosylates do <u>not</u> participate in S_N2 reactions

Malonic Ester Synthesis

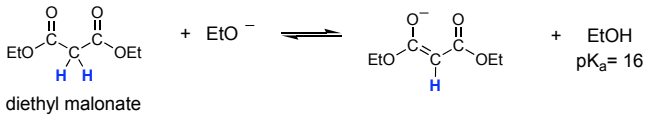
overall reaction



diethyl malonate
Et= ethyl

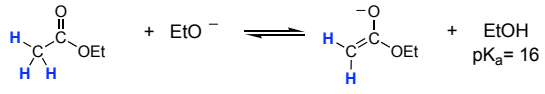
alkyl halide

carboxylic acid



diethyl malonate
pK_a= 13

pK_a= 16

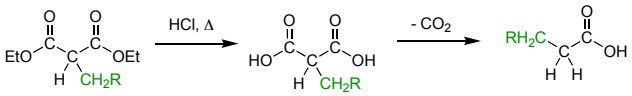


ethyl acetate
pK_a= 25

pK_a= 16

A malonic ester can undergo one or two alkylations to give an α-substituted or α-disubstituted malonic ester

Decarboxylation: Treatment of a malonic ester with acid and heat results in hydrolysis to the malonic acid (β-di-acid). An acid group that is β to a carbonyl will lose CO_2 upon heating.



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Mechanism of decarboxylation:

β-dicarboxylic acid (malonic acid synthesis)

β-keto carboxylic acid (acetoacetic ester synthesis)

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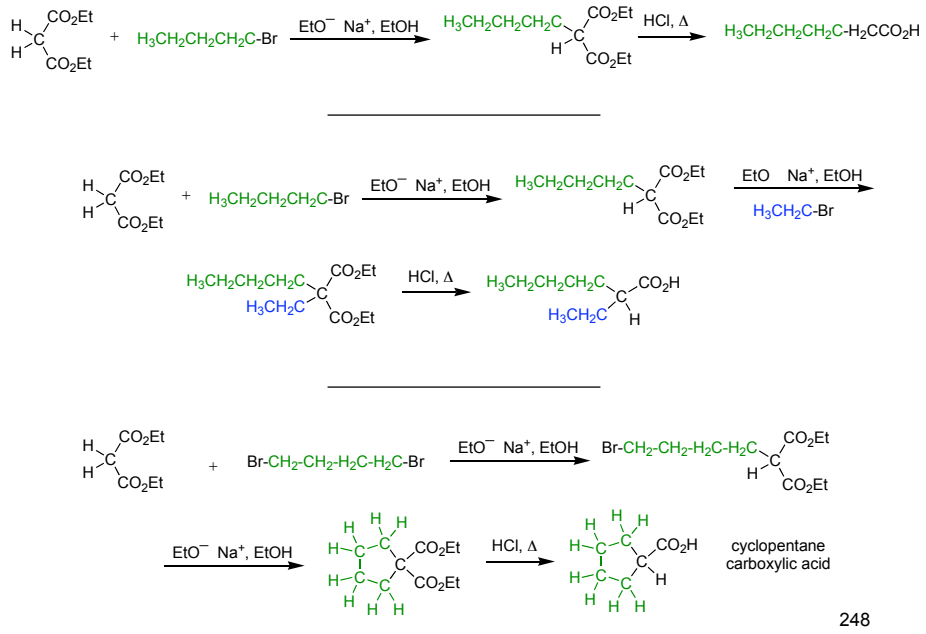

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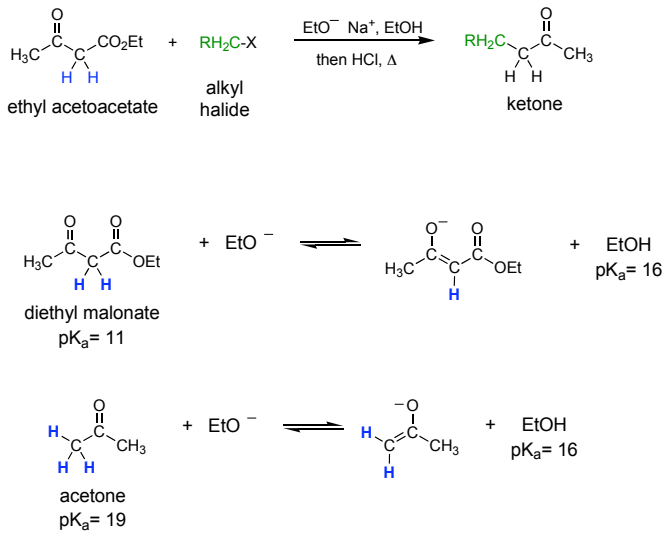
Acetoacetic ester synthesis



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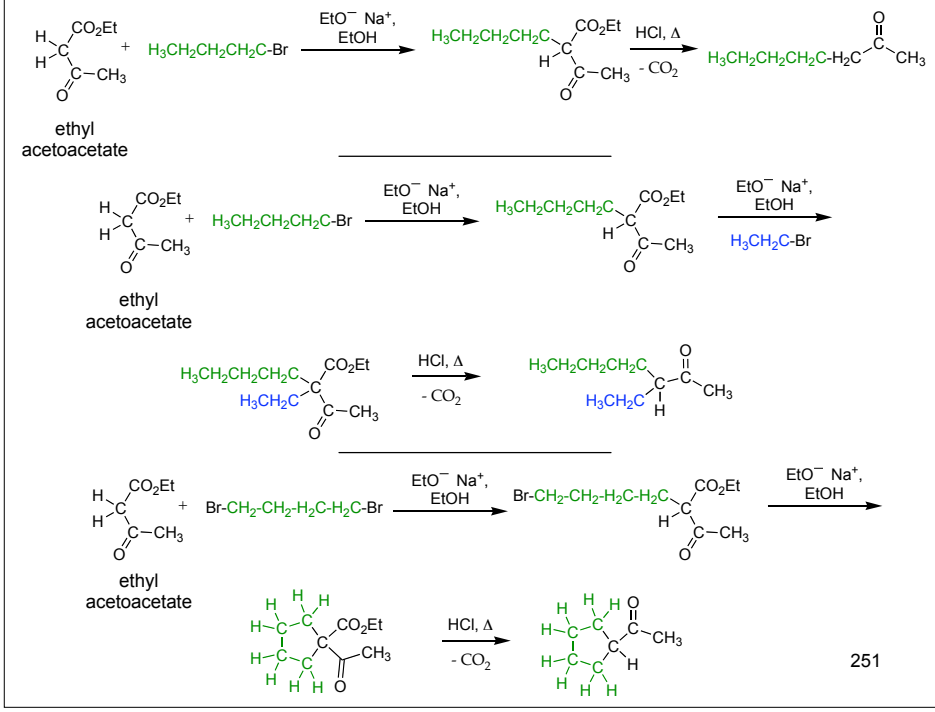
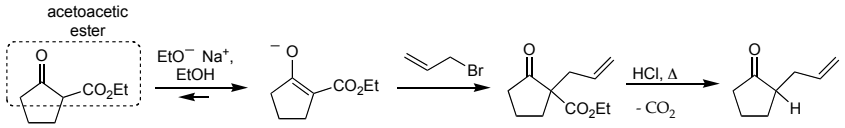
An acetoacetic ester can undergo one or two alkylations to give an α-substituted or α-disubstituted acetoacetic ester

Decarboxylation: Treatment of the acetoacetic ester with acid and heat results in hydrolysis to the acetoacetic acid (β-keto acid), which undegoes decarboxylation

250

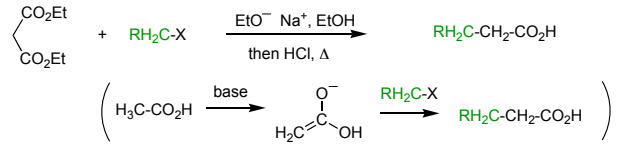


251

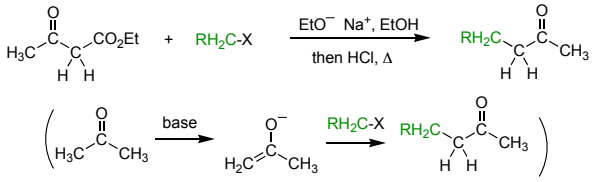


Summary:

Malonic ester synthesis: equivalent to the alkylation of a carboxylic (acetic) acid enolate



Acetoacetic ester synthesis: equivalent to the alkylation of an acetone enolate



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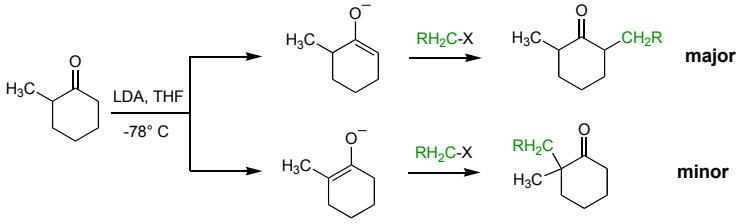
Direct alkylation of ketones, esters and nitriles

α-Deprotonation of ketones, esters and nitriles can be accomplished with a strong bases such as lithium diisopropylamide (LDA) in an aprotic solvent such as THF. The resulting enolate is then reacted with alkyl halides to give the α-substitution product.



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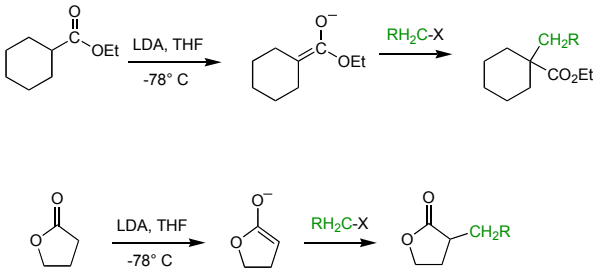
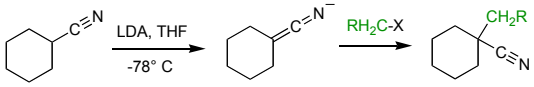
Ester enolate



Nitrile enolate



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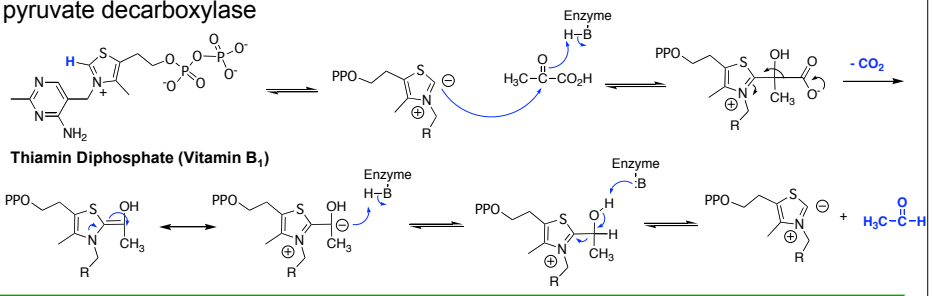
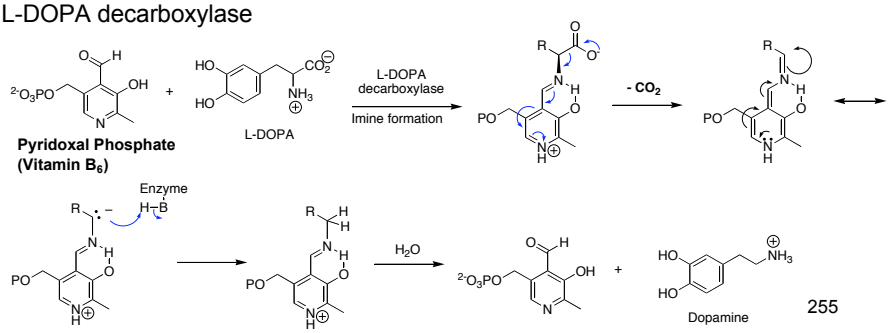
Biological decarboxylation reactions:

pyruvate decarboxylase



Thiamin Diphosphate (Vitamin B_1)

L-DOPA decarboxylase



Pyridoxal Phosphate (Vitamin B_6)

L-DOPA

Dopamine

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