CHEM 529

Enzyme and Coenzyme Mechanisms

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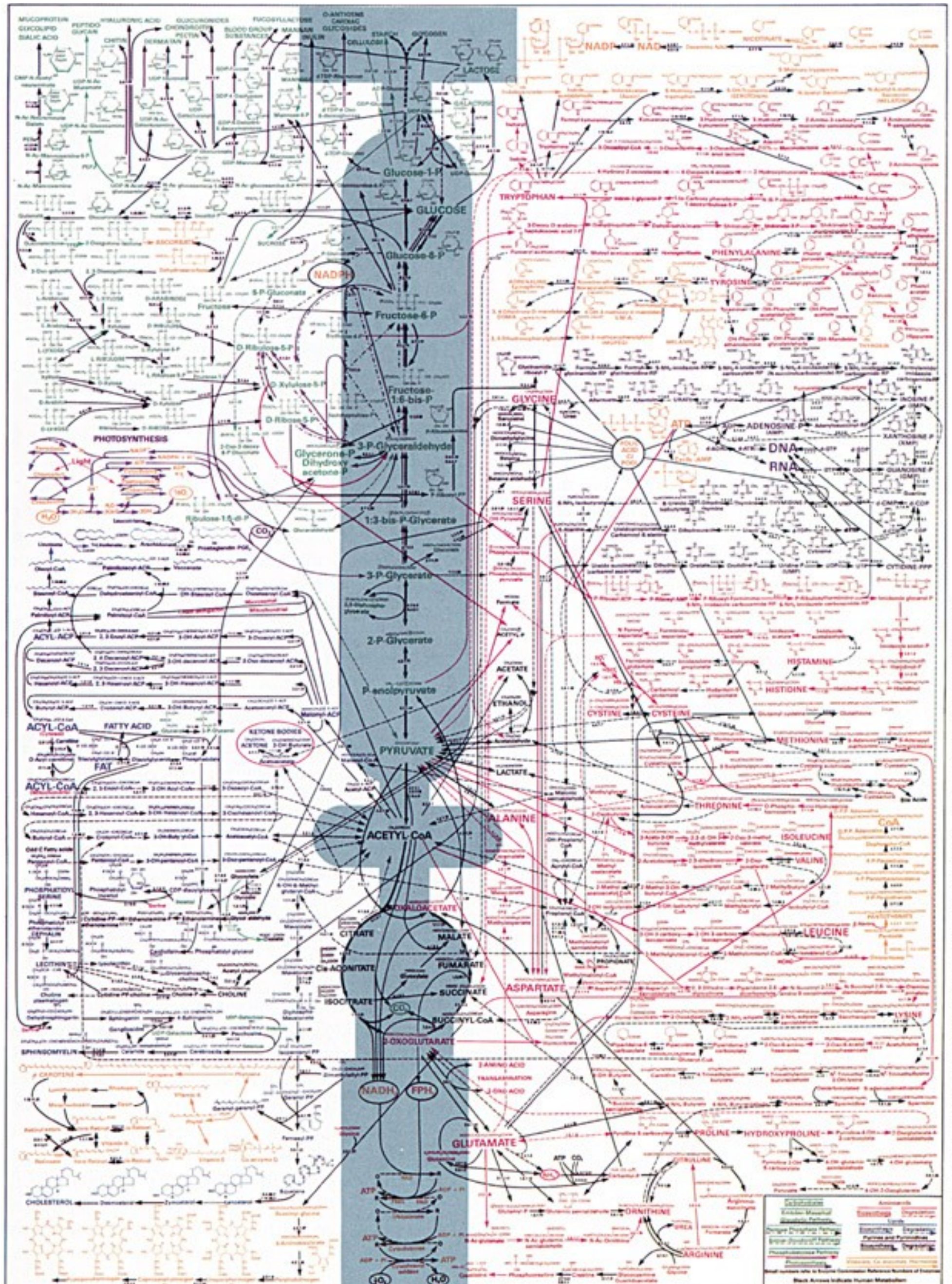
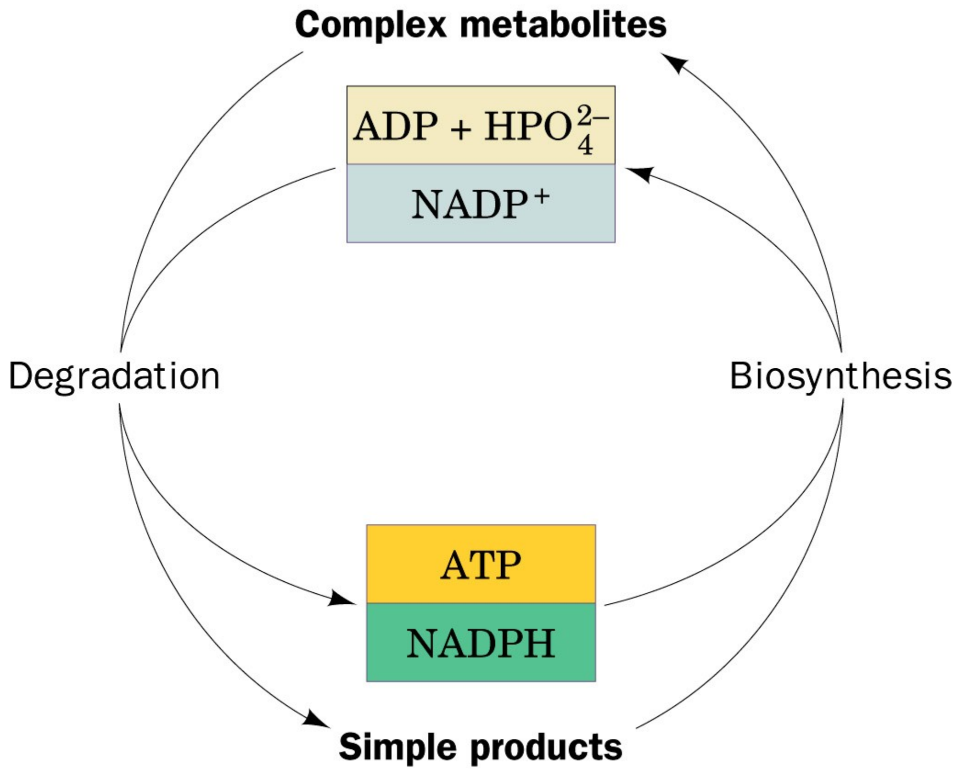
Fall 2014

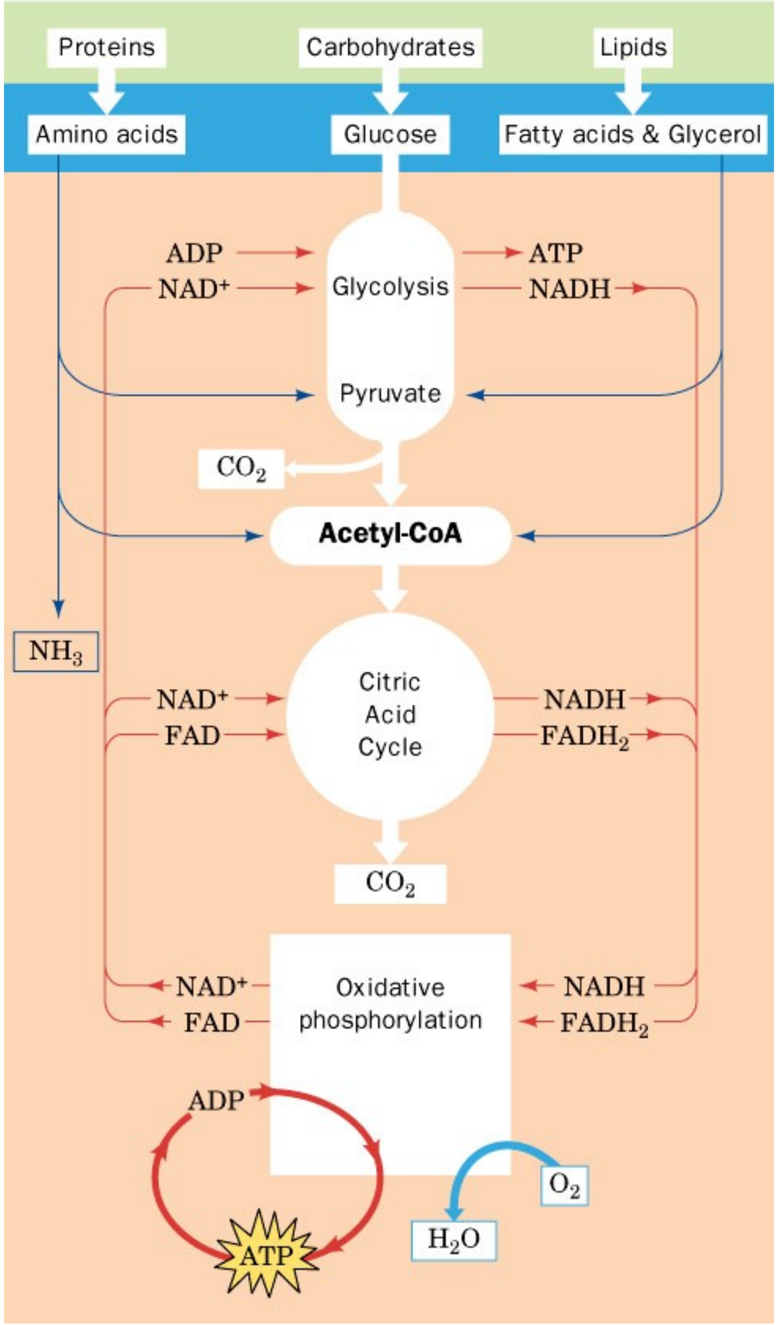


Designed by Donald Nicholson. Published by BDH, Ltd., Poole 2, Dorset, England

Map of the major metabolic pathways in a typical cell



ATP and NADPH are sources of free energy for biosynthetic reactions



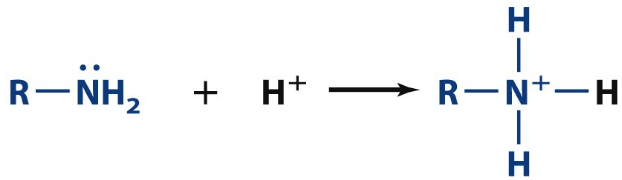
Overview of human catabolism

Review of biologically-important functional groups and their properties

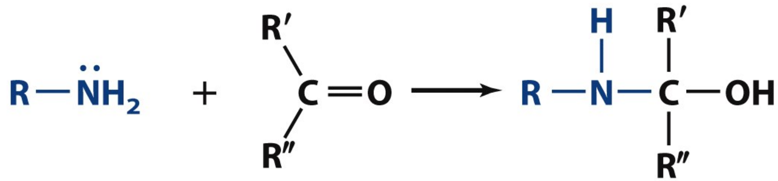
blackboard discussion

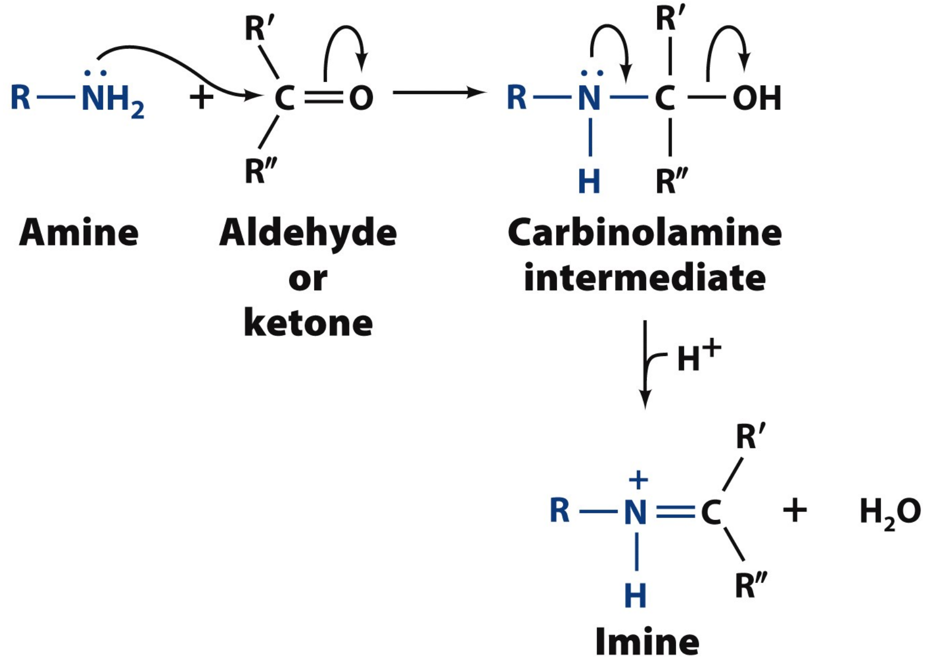
Imine formation

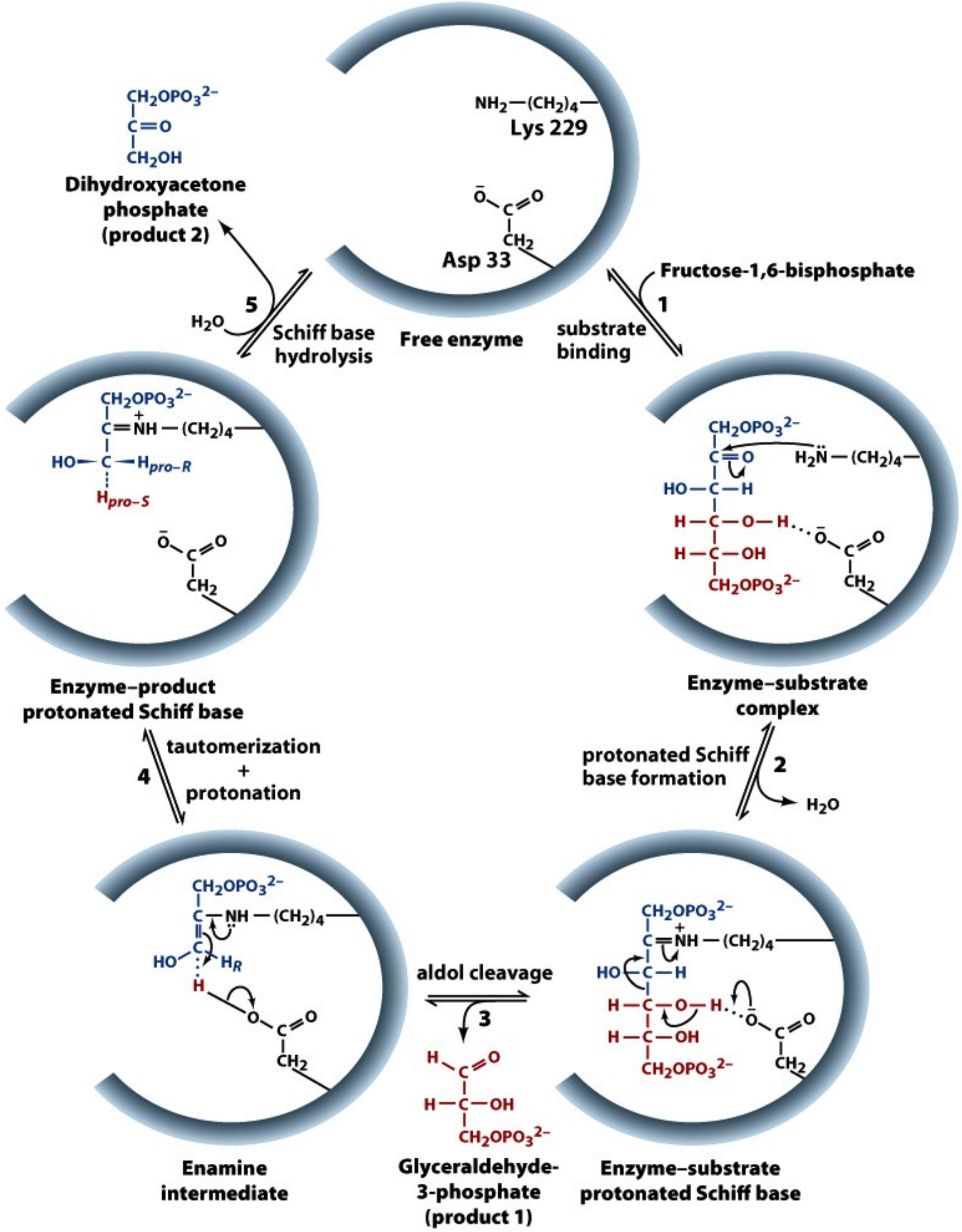
Basic reaction of an amine



Nucleophilic reaction of an amine

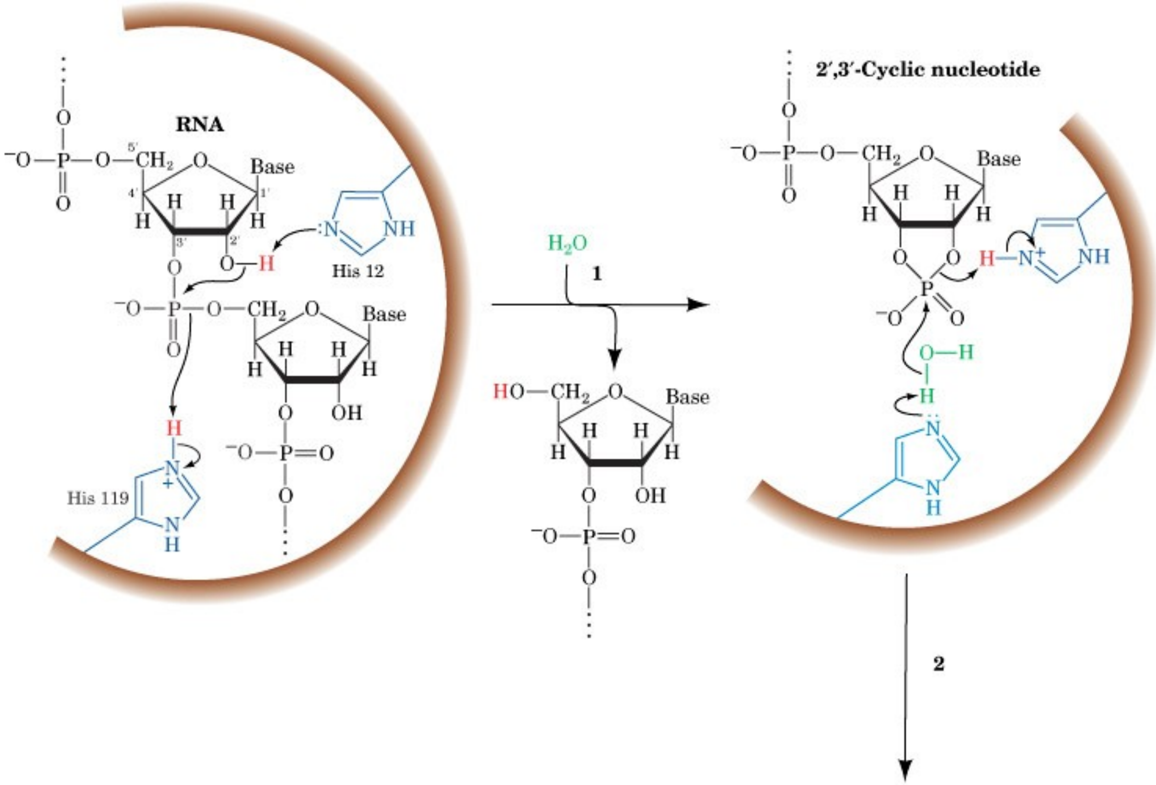


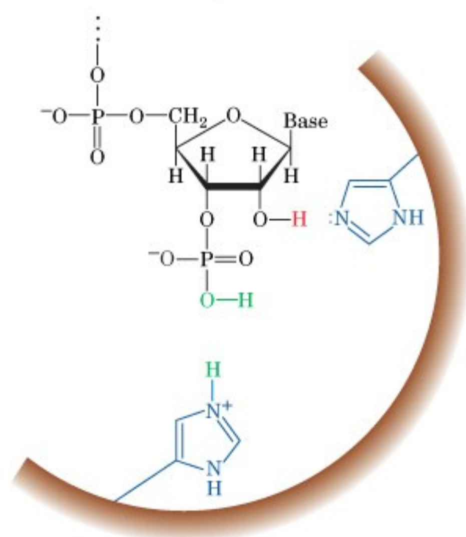




Proposed mechanism of rabbit muscle aldolase: Imine (Schiff base) intermediate

Mechanism of RNase A

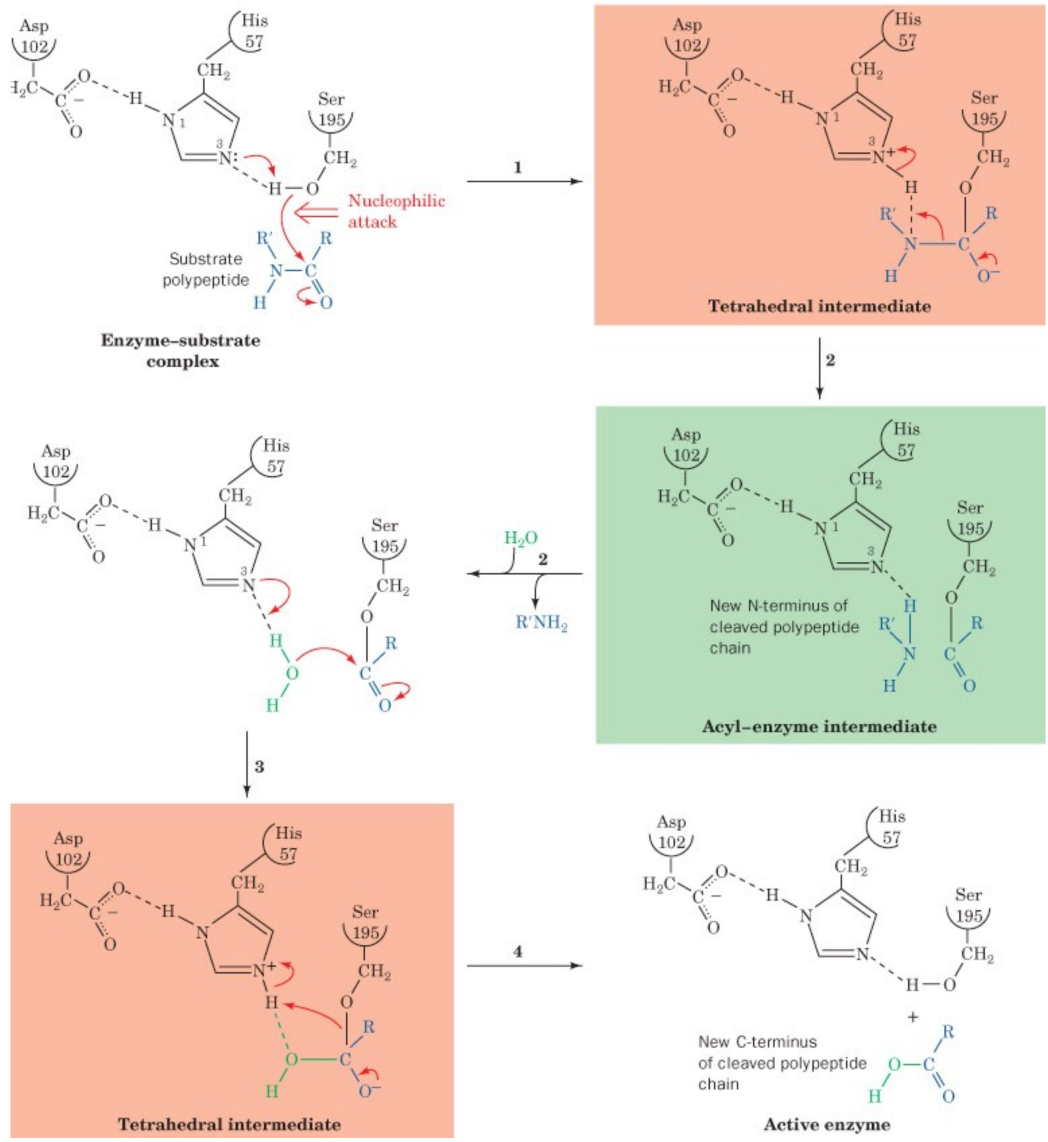




The bovine pancreatic RNase A catalyzed hydrolysis of RNA is a two-step process with the intermediate formation of a 2′,3′-cyclic nucleotide.

two histidines serve as proton donor and acceptor; an acid-base catalytic mechanism

Catalytic mechanism of serine proteases



Free energies of hydrolysis of some biologically-important compounds

Standard free energies of hydrolysis of common functional groups in biochemistry

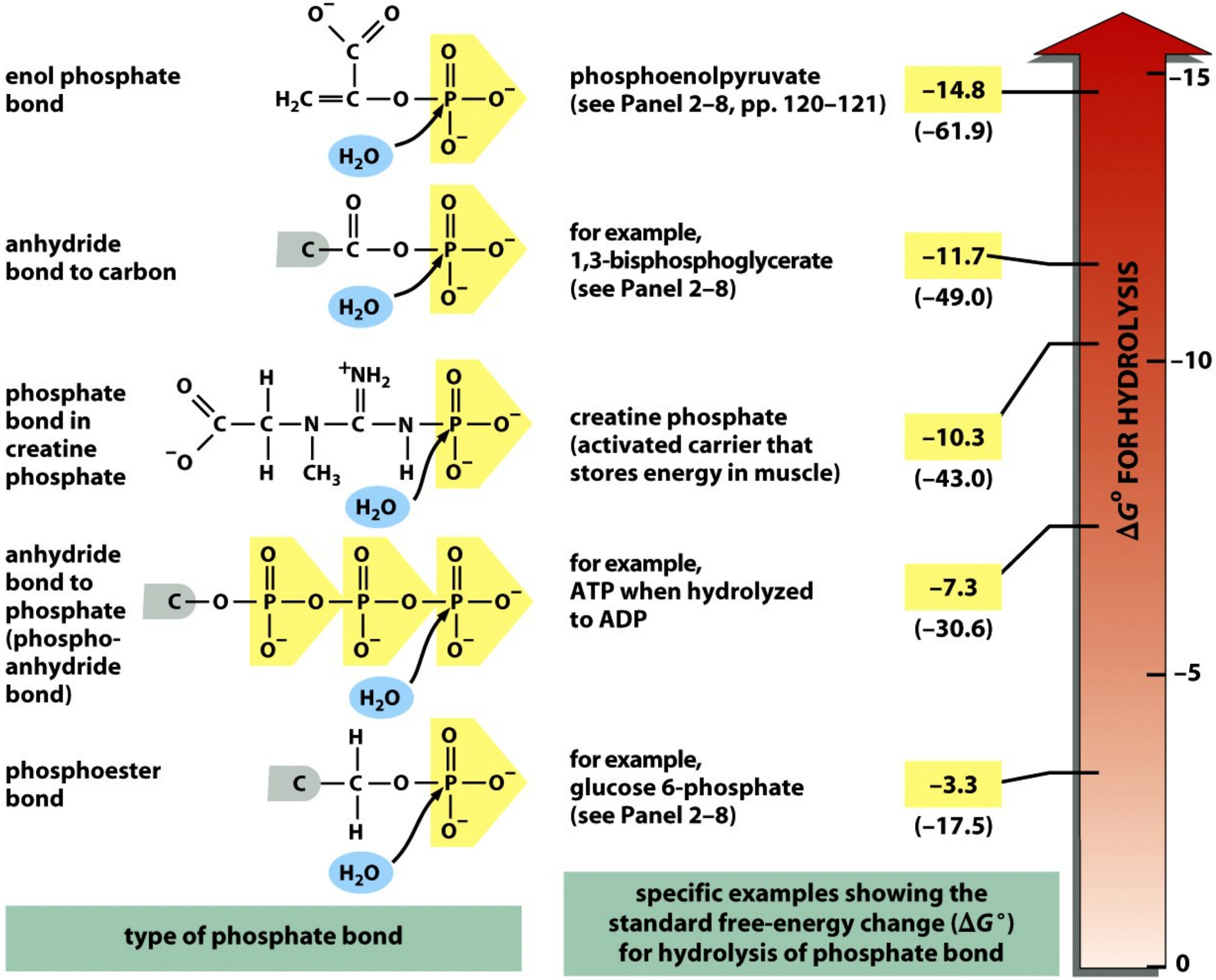
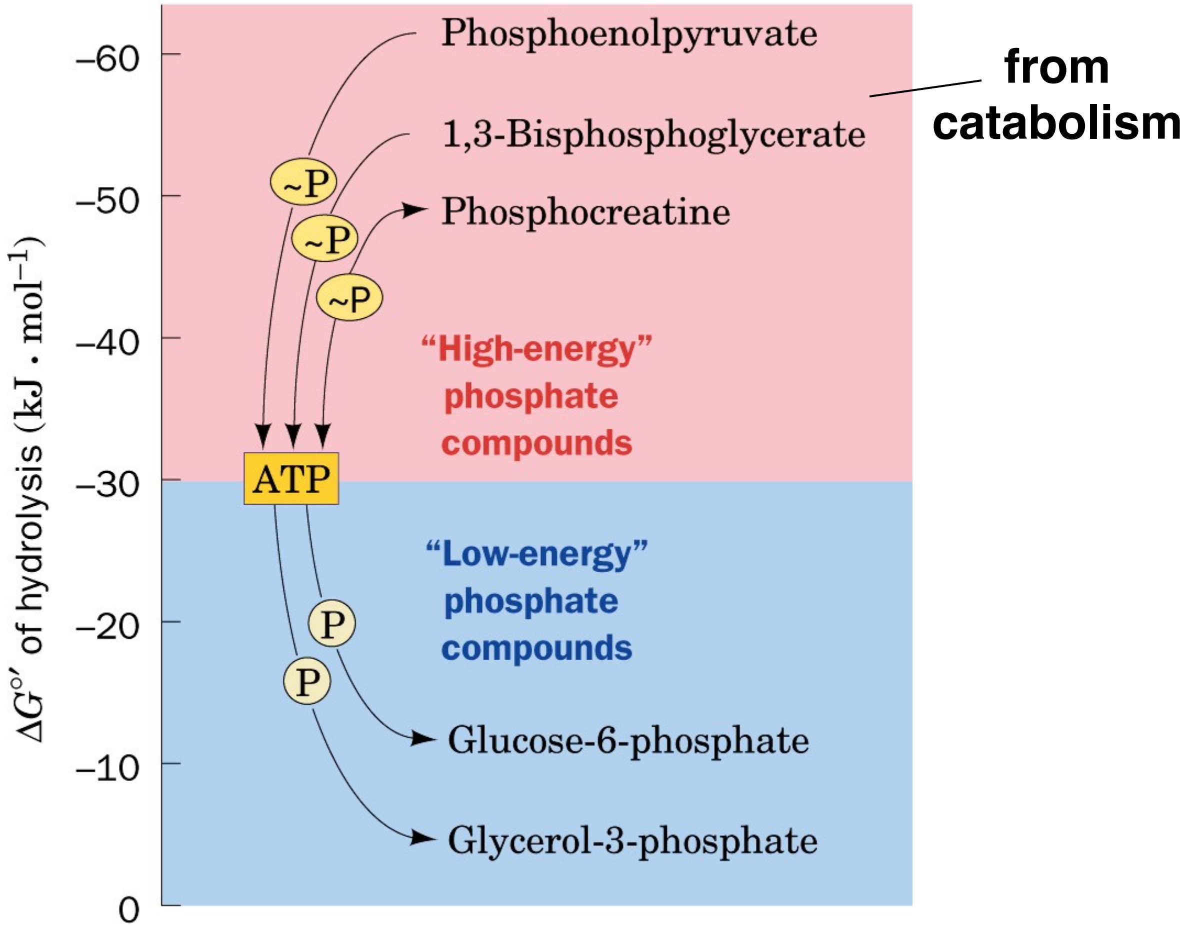


Figure 2-74 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Standard free energies of hydrolysis of some phosphate-containing compounds of biological interest

Compound	ΔG (kJ · mol^{-1})
Phosphoenolpyruvate	−61.9
1,3-Bisphosphoglycerate	−49.4
Acetyl phosphate	−43.1
Phosphocreatine	−43.1
PP_i	−33.5
ATP (→ AMP + PP_i)	**−32.2**
ATP (→ ADP + P_i)	**−30.5**
Glucose-1-phosphate	−20.9
Fructose-6-phosphate	−13.8
Glucose-6-phosphate	−13.8
Glycerol-3-phosphate	−9.2

Source: Jencks, W.P., *in* Fasman, G.D. (Ed.), *Handbook of Biochemistry and Molecular Biology* (3rd ed.), *Physical and Chemical Data,* Vol. I, *pp.* 296–304, CRC Press (1976).



The flow of phosphoryl groups from high-energy phosphate donors, via the ATP–ADP system, to low-energy phosphate acceptors (note the central role of ATP as energy currency).

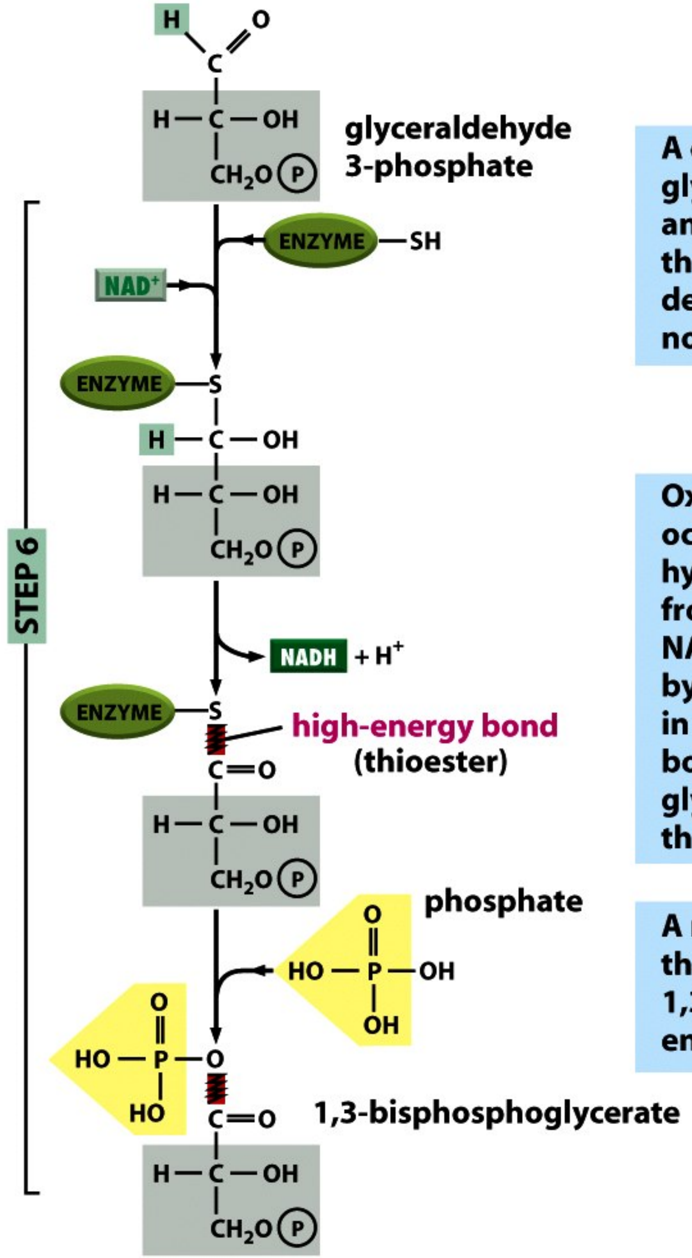


Figure 2-72a part 1 of 2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

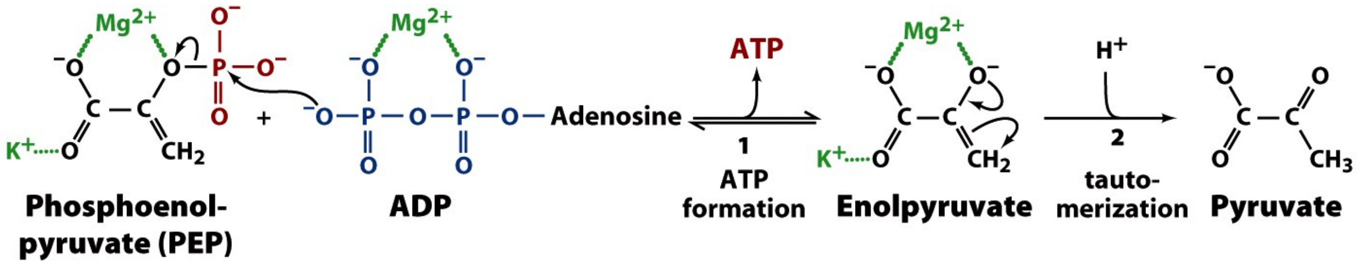
A covalent bond is formed between glyceraldehyde 3-phosphate (the substrate) and the –SH group of a cysteine side chain of the enzyme glyceraldehyde 3-phosphate dehydrogenase, which also binds noncovalently to NAD^+.

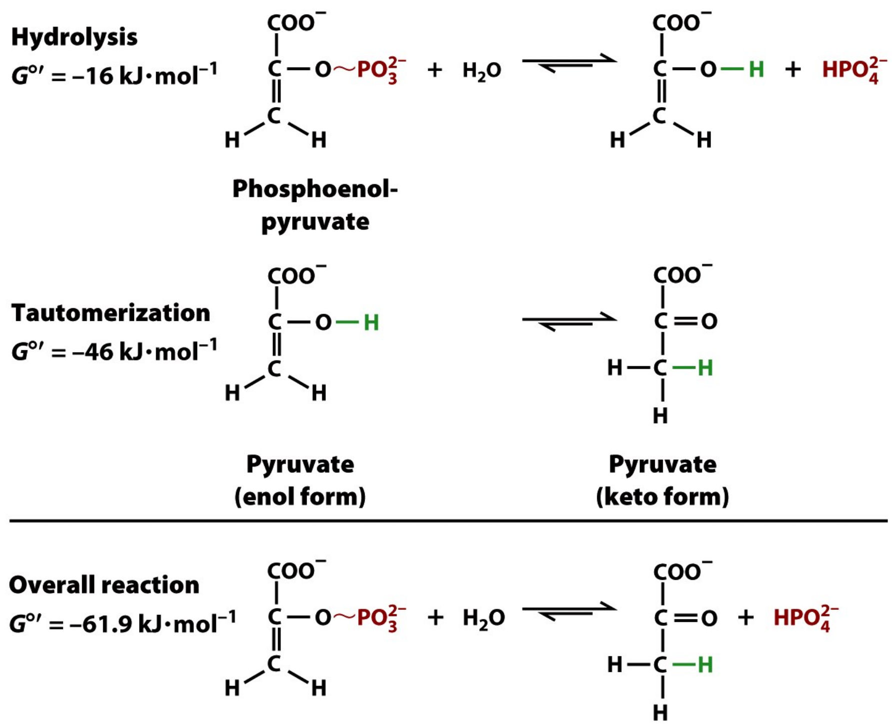
Oxidation of glyceraldehyde 3-phosphate occurs, as two electrons plus a proton (a hydride ion, see Figure 2–60) are transferred from glyceraldehyde 3-phosphate to the bound NAD^+, forming NADH. Part of the energy released by the oxidation of the aldehyde is thus stored in NADH, and part goes into converting the bond between the enzyme and its substrate glyceraldehyde 3-phosphate into a high-energy thioester bond.

A molecule of inorganic phosphate displaces the high-energy bond to the enzyme to create 1,3-bisphosphoglycerate which contains a high-energy acyl-anhydride bond.

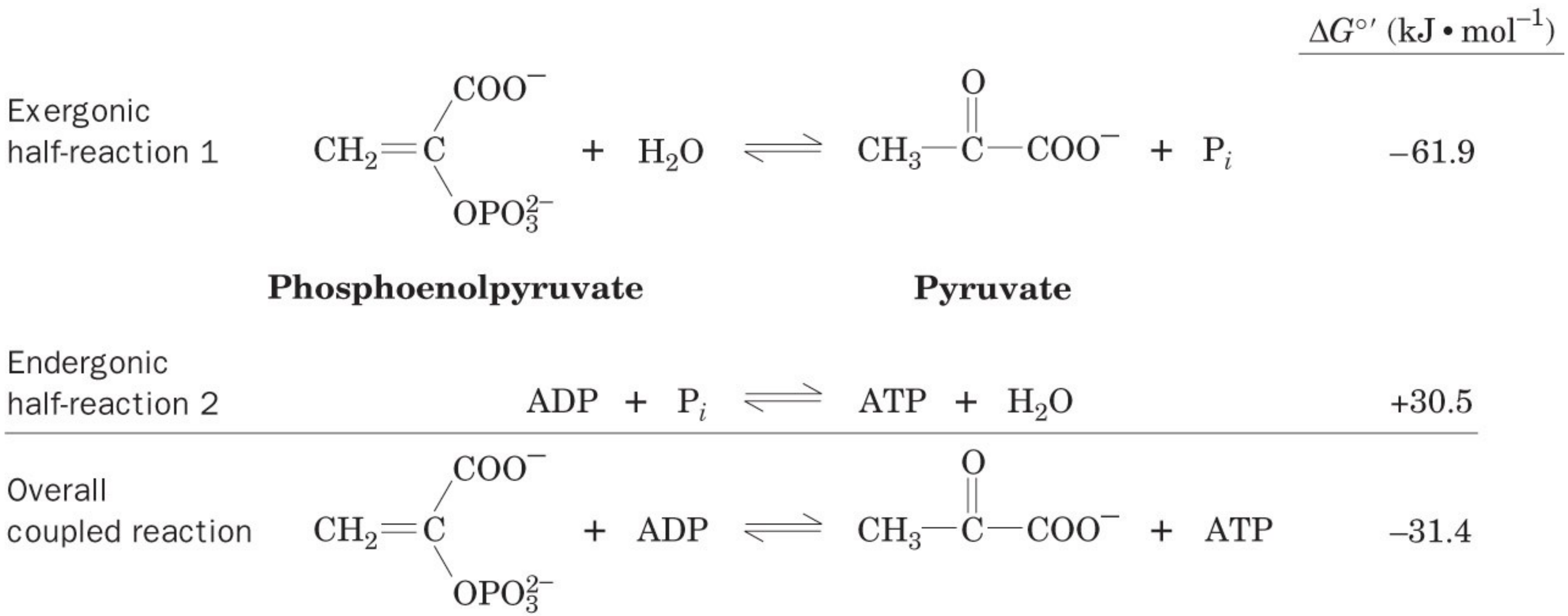
Generation of a high-energy phosphate in glycolysis

Explanation of the very negative change in standard free energy associated with the pyruvate kinase reaction

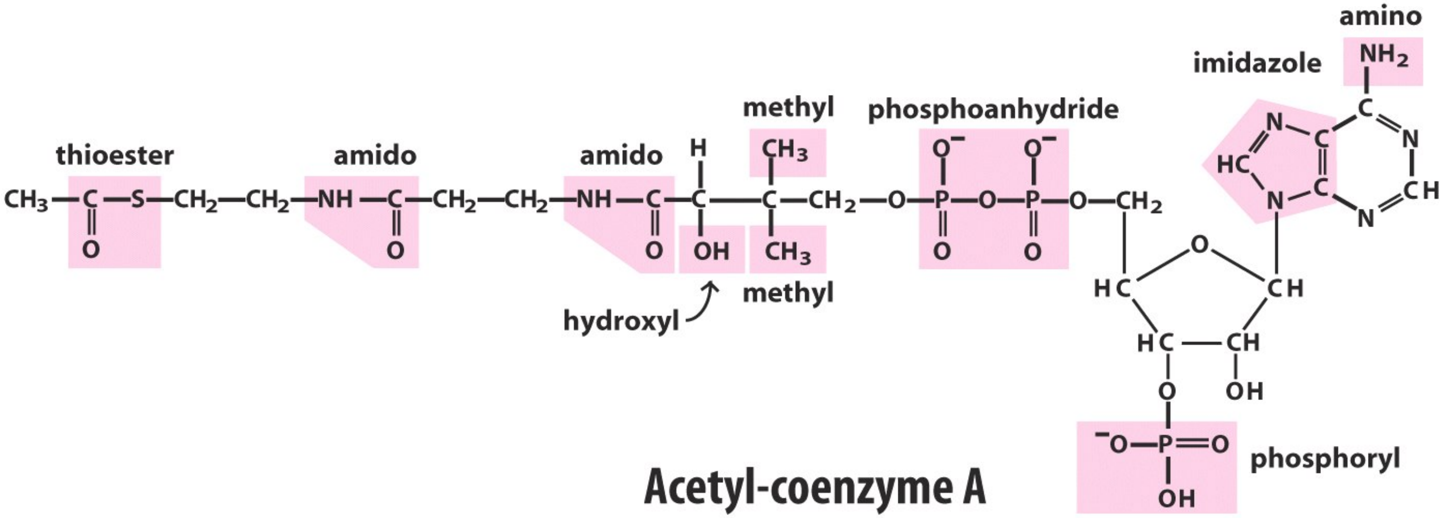




Coupled reactions involving ATP synthesis: The pyruvate kinase-catalyzed phosphorylation of ADP by phosphoenolpyruvate (PEP) to form ATP and pyruvate (the second substrate-level phosphorylation reaction of glycolysis)



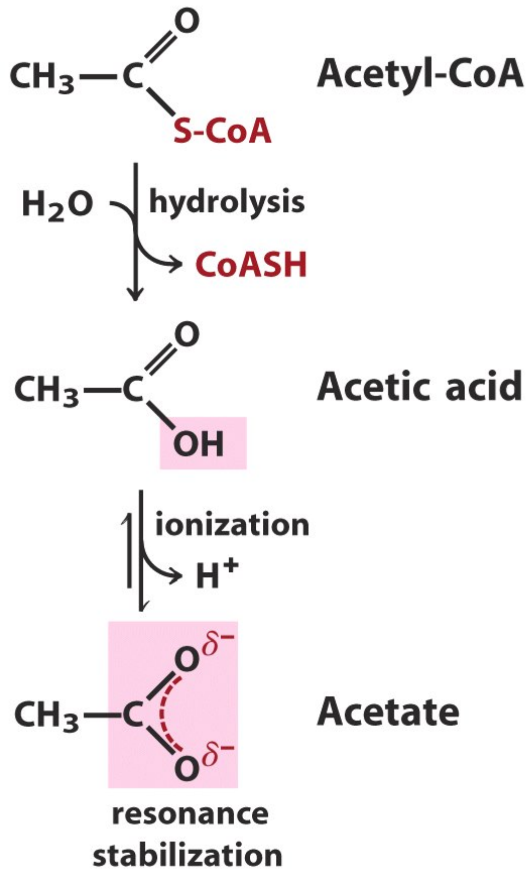
Acetyl CoA: A biological thioester



Acetyl-coenzyme A

Coenzyme A = CoASH

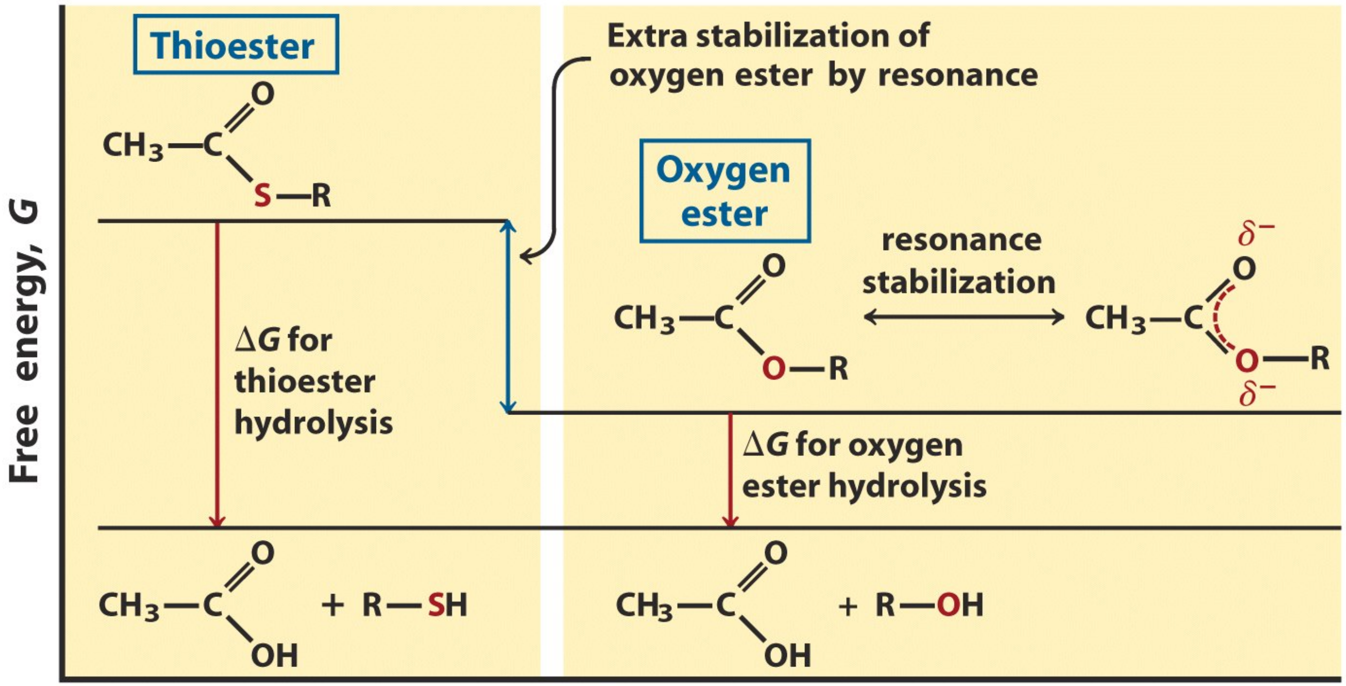
Acetyl CoA hydrolysis



$$\text{Acetyl-CoA} + H_2O \longrightarrow \text{acetate}^- + \text{CoA} + H^+$$

$$\Delta G'^\circ = -31.4 \text{ kJ/mol}$$

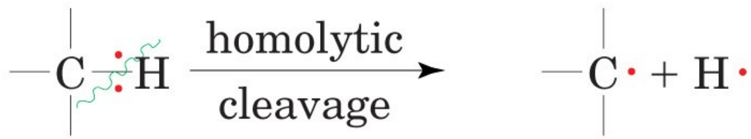
Explanation of the energetics of acetyl CoA hydrolysis



Some fundamental chemical mechanisms

Modes of C—H bond breaking

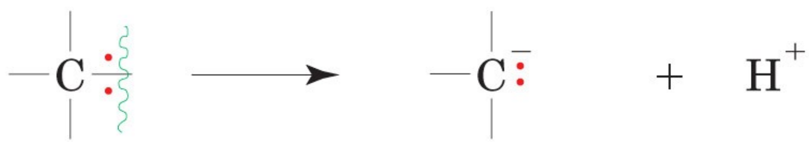
Homolytic:



Radicals

Heterolytic:

(i)



Carbanion **Proton**

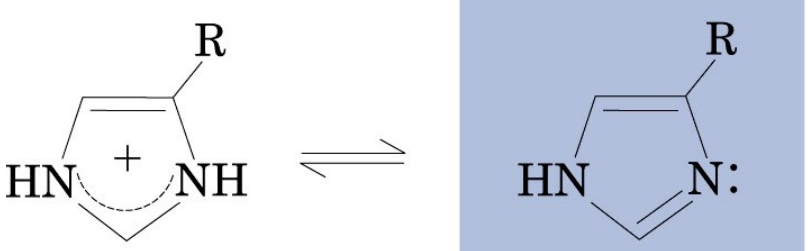
(ii)

Carbocation **Hydride ion**

Biologically-important nucleophilic groups

(a) **Nucleophiles**

		Nucleophilic form		
$R\ddot{O}H$	$\rightleftharpoons$	$R\ddot{O}:^-$	$+\ H^+$	**Hydroxyl group**
$R\ddot{S}H$	$\rightleftharpoons$	$R\ddot{S}:^-$	$+\ H^+$	**Sulfhydryl group**
RNH_3^+	$\rightleftharpoons$	$R\ddot{N}H_2$	$+\ H^+$	**Amino group**



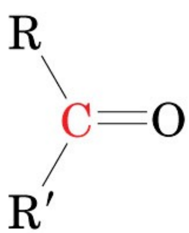
$+\ H^+$ **Imidazole group**

Biologically-important electrophilic groups

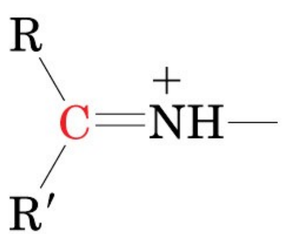
(b) **Electrophiles**

H^{+} **Protons**

M^{n+} **Metal ions**

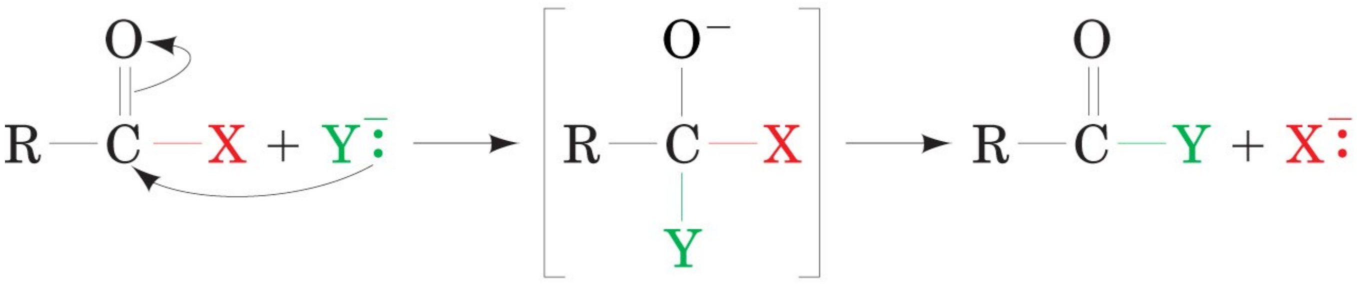


Carbonyl carbon atom



Cationic imine (Schiff base)

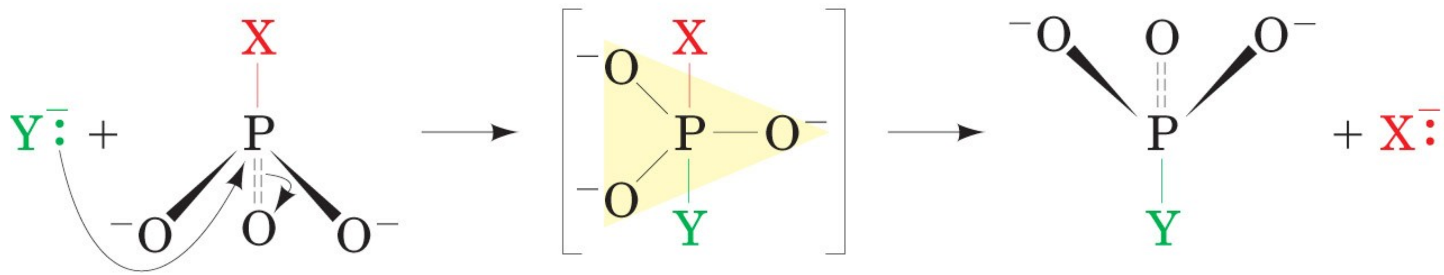
Metabolic group-transfer reactions:
Acyl group transfer



Tetrahedral intermediate

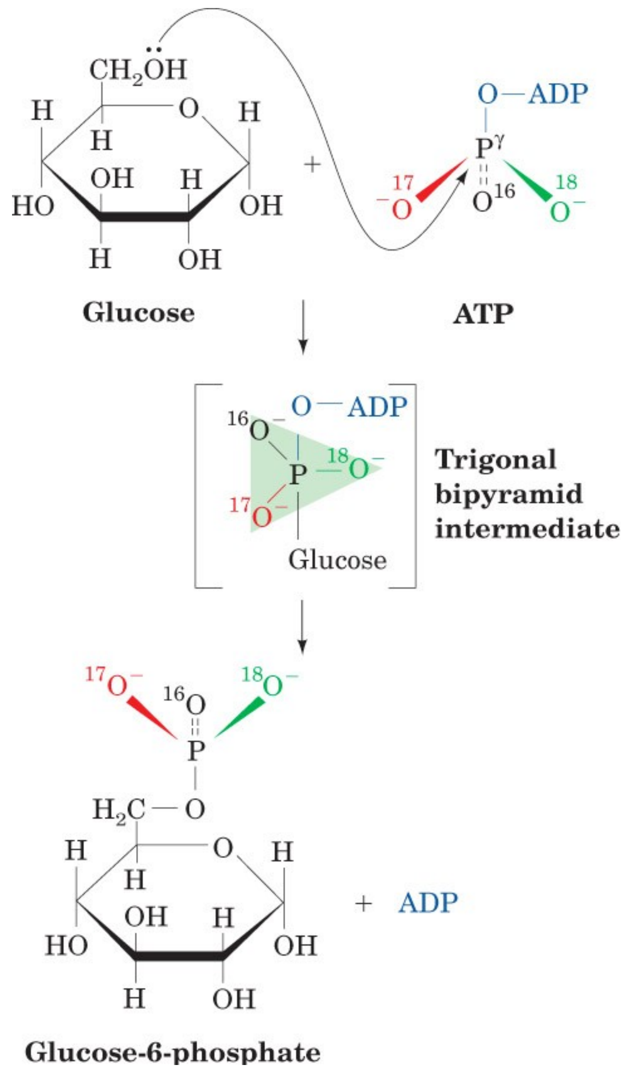
Metabolic group-transfer reactions:

Phosphoryl group transfer



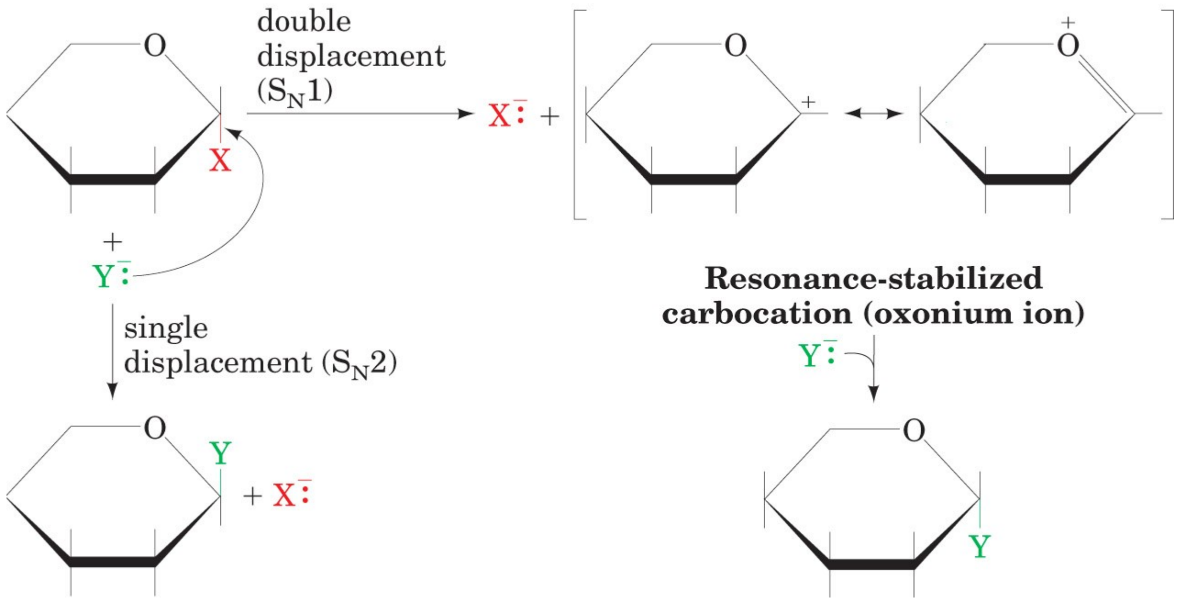
Trigonal bipyramid intermediate

A phosphoryl group transfer reaction: Hexokinase



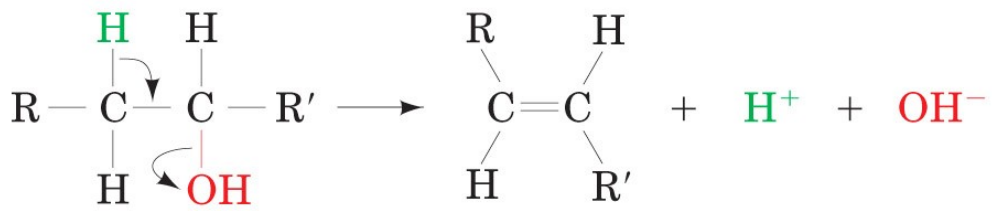
Metabolic group-transfer reactions:

Glycosyl group transfer

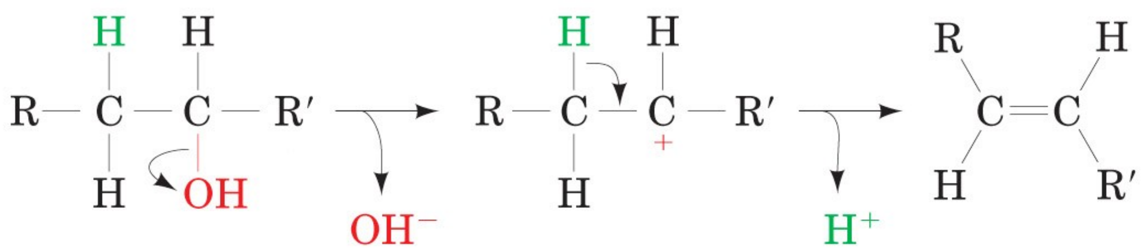


Elimination reaction mechanisms using dehydration as an example

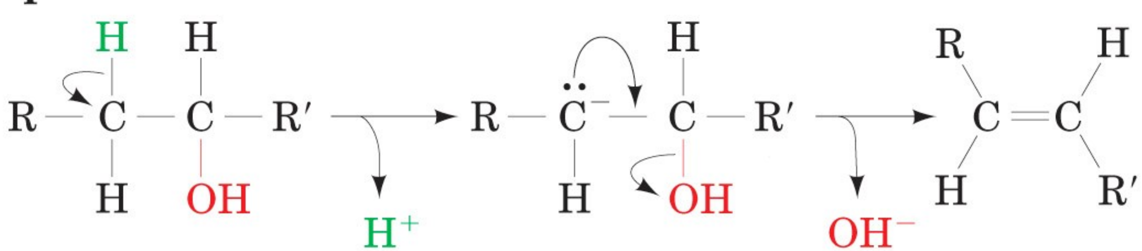
Concerted

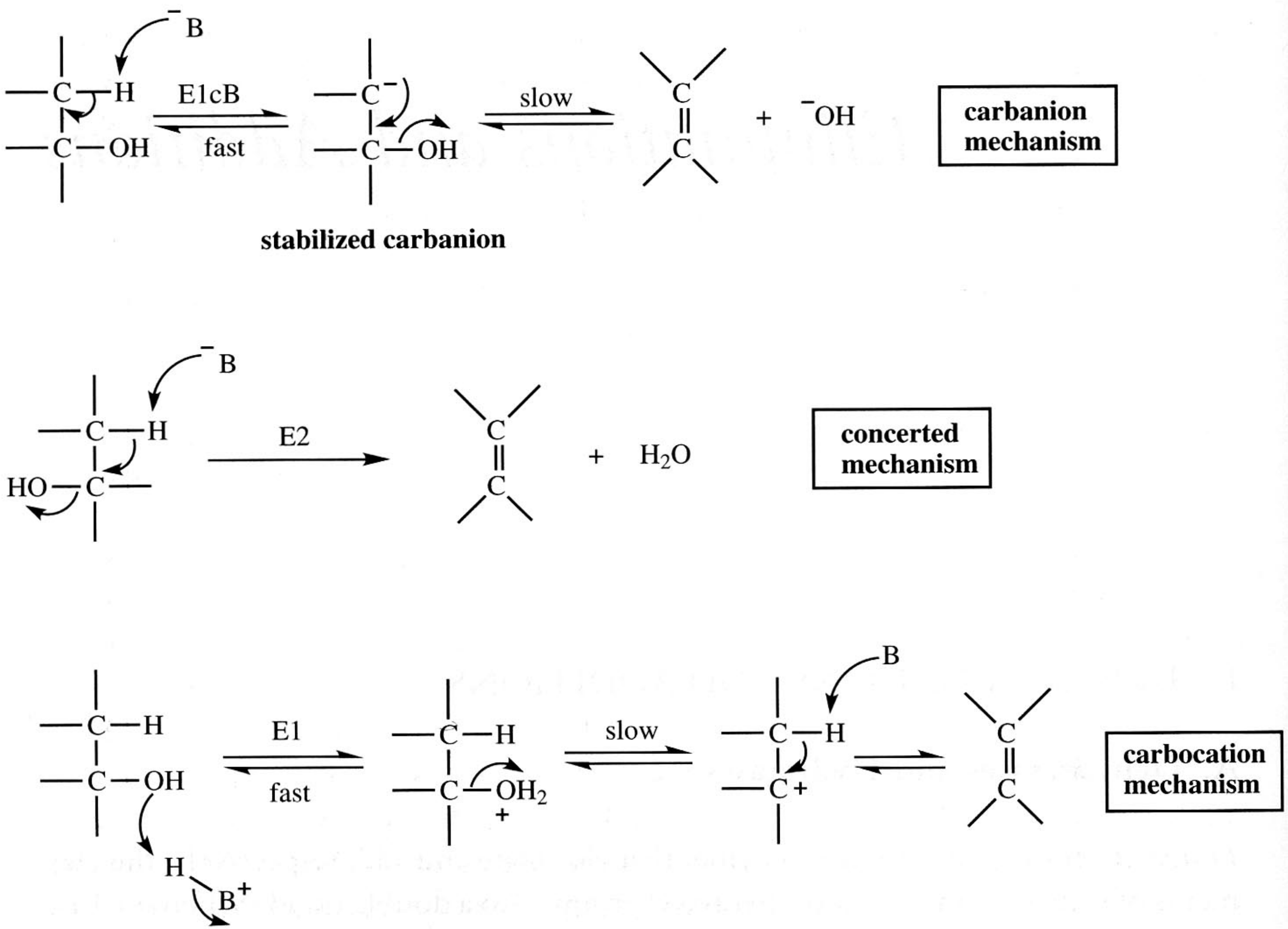


Stepwise via a carbocation



Stepwise via a carbanion

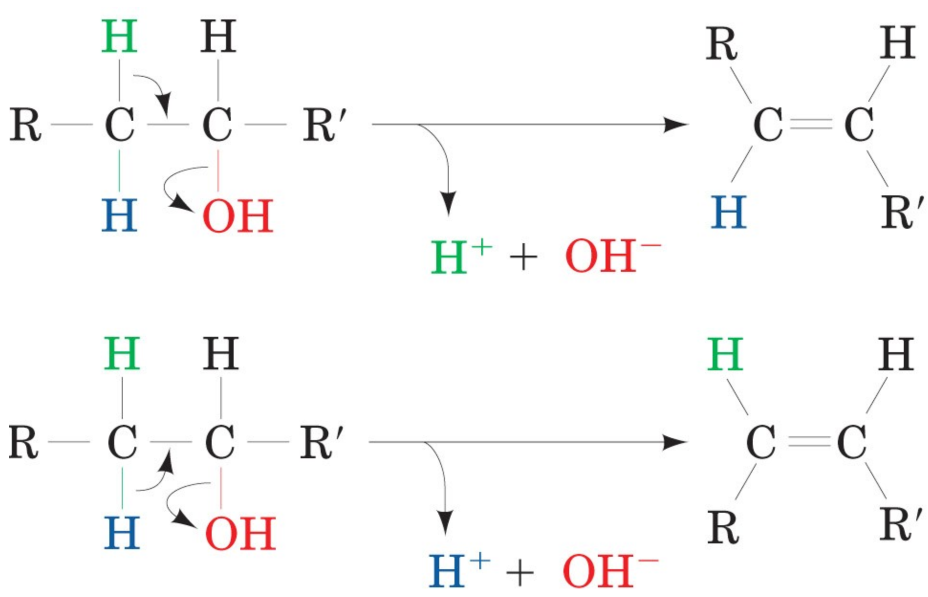




SCHEME 10.2 Three general mechanisms for dehydration.

Elimination reaction mechanisms using dehydration as an example

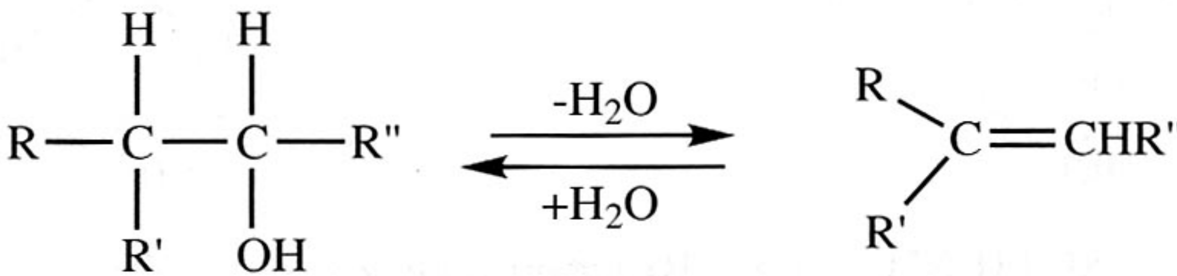
Reaction stereochemistry



trans (anti)

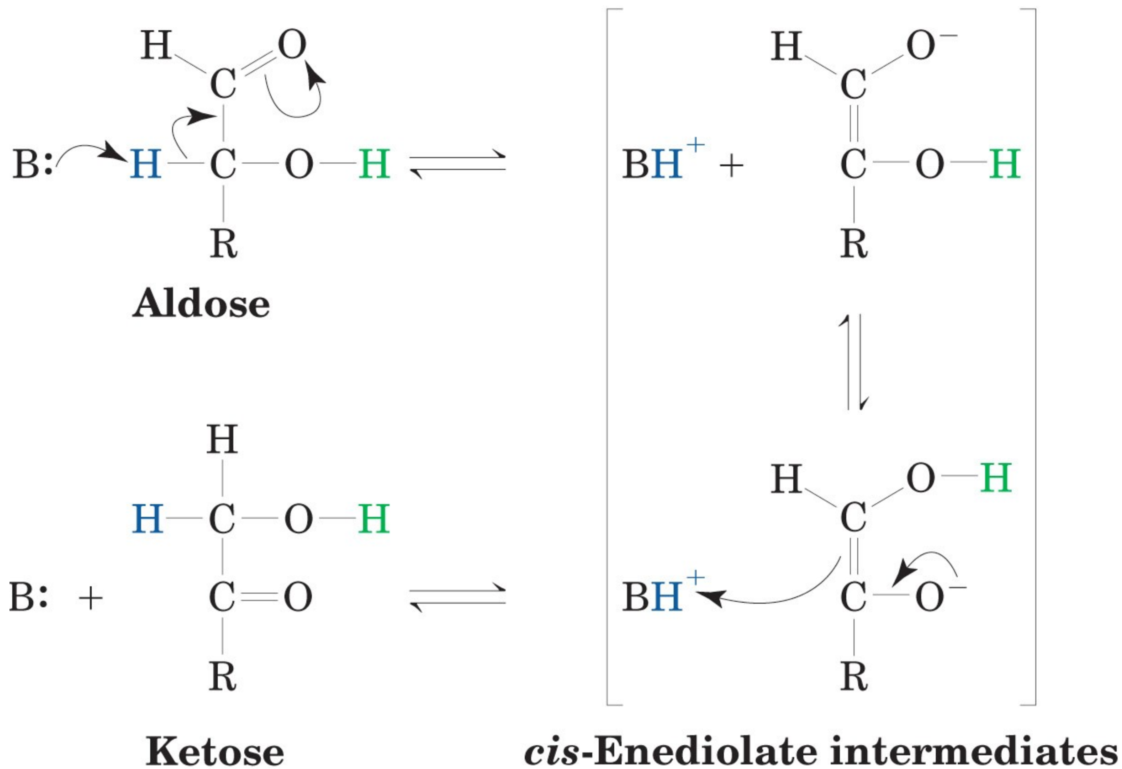
cis (syn)

Example of an enzyme-catalyzed elimination reaction

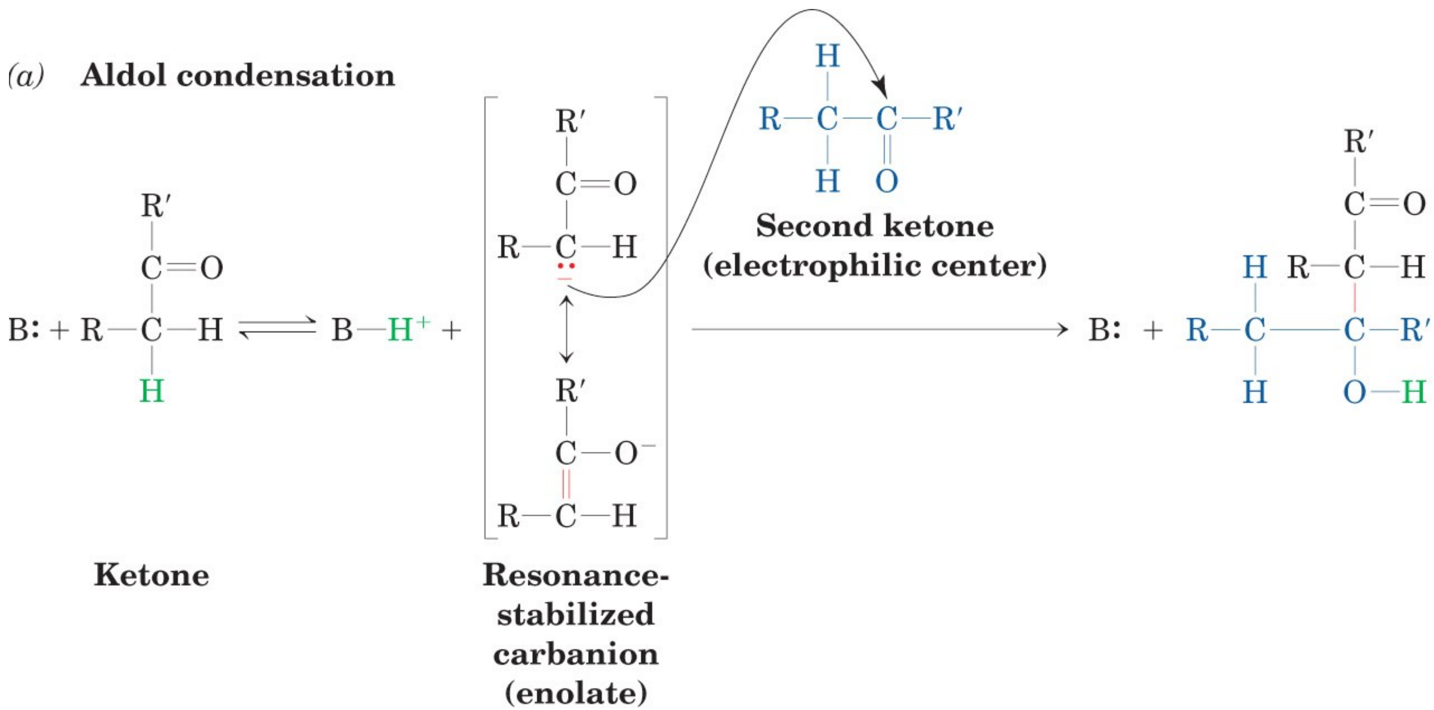


SCHEME 10.1 Reactions catalyzed by dehydratases and hydratases.

Mechanism of aldose-ketose isomerization

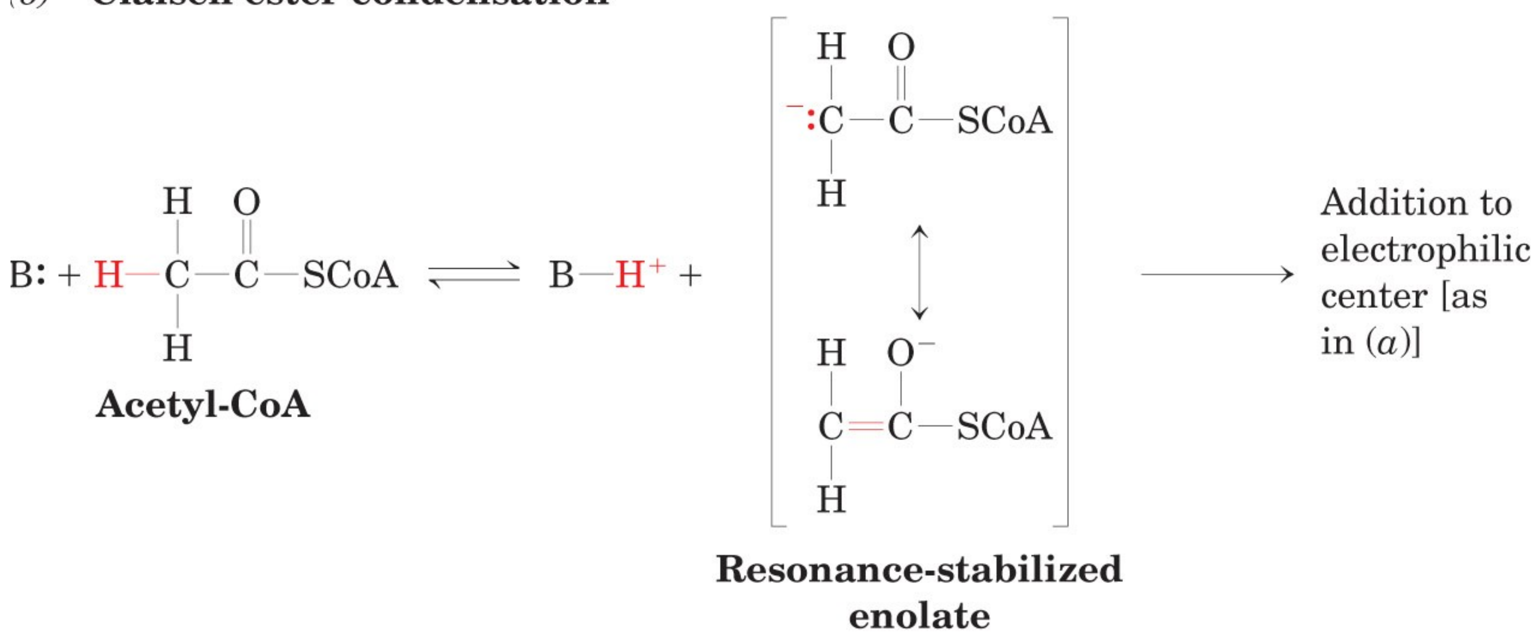


C—C bond formation and cleavage reactions: Aldol condensation



C—C bond formation and cleavage reactions: Claisen condensation (ester)

(b) **Claisen ester condensation**



C—C bond formation and cleavage reactions: Decarboxylation of a β-keto acid