Selected reactions of organic compounds

This lecture is an extract of main ideas from chapters 1-14 + 29, Medical Chemistry II

- Hemiacetals, acetals, aldimines
- Derivatives of acids (esters, anhydrides, amides)
- Dehydrogenations of various substrates
- Oxygenation, hydroxylation, deoxygenation
- Conjugate *vs.* Redox pair
- Transamination of amino acids
- Reactions of citric acid cycle

Mutual reactions of selected compounds

	Acid	**Aldehyde**	**Thiol**	**Alcohol**
Alcohol	ester	hemiacetal	-	ether
Thiol	thioester	thiohemiacetal	sulfide	
Amine	salt[a] / amide[b]	aldimine[c]		
Aldehyde	-	aldol[d]		
Acid	anhydride			

See also
Med. Chem. II
Appendix 1

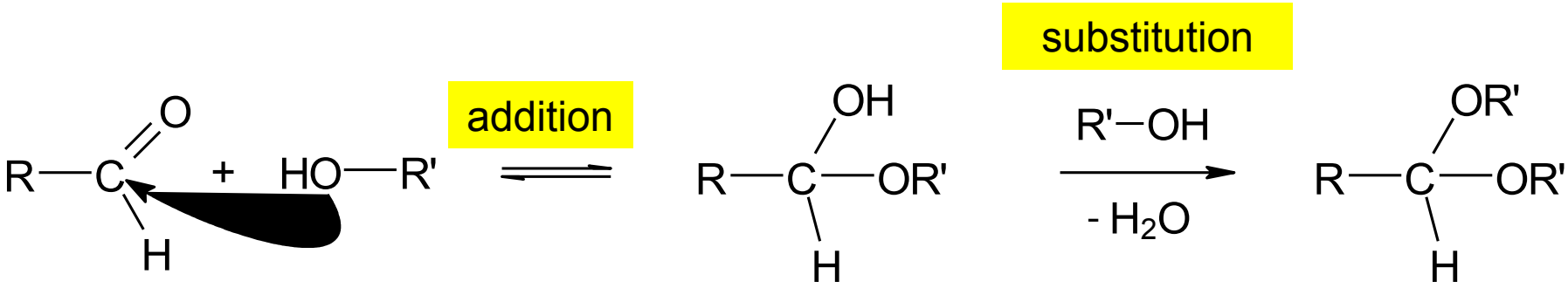
[a]Acid-base reaction.

[b]Condensation (water eliminated).

[c]Called also Schiff base.

[d]Only in strongly alkaline environment.

Hemiacetals and acetals



hemiacetal (unstable)

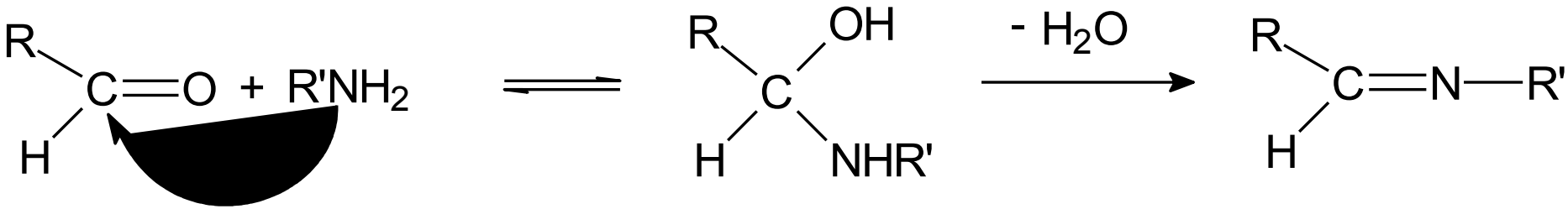
cyclic hemiacetal is stable

acetal

Hemiacetals are made by **addition** of alcohol to carbonyl group.

Acetals are made by **substitution** of the hydroxyl group of hemiacetal by the alkoxyl group (-OR) of alcohol.

Aldimines (Schiff bases) are formed by addition-elimination reaction



unstable intermediate

(aminohemiacetal)

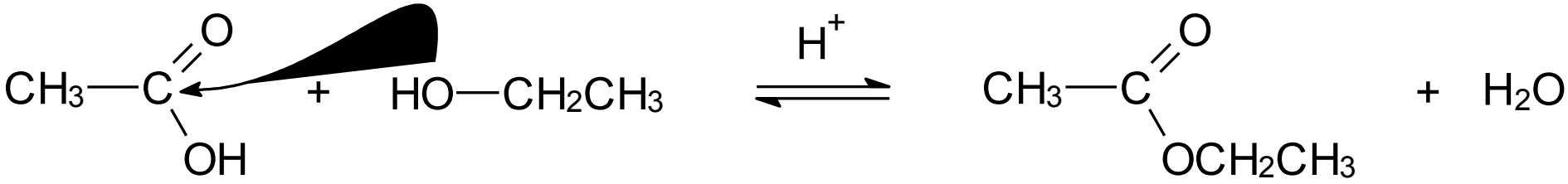
Schiff base

C=NH or C=NR is imino group

Schiff bases in the organism

- Non-enzymatic glycation of proteins (Med. Chem. II, p. 40)
- Transamination of AA – intermediate with pyridoxal phosphate (see later, lecture Amino acids)
- Crosslinks in collagen (Lys ... alLys) (Med. Chem. II, p. 42)
- Linkage of retinal to opsin (biochemistry of vision)

Esters of carboxylic acids are made by condensation reaction with alcohols and water is liberated



acetic acid

ethyl acetate

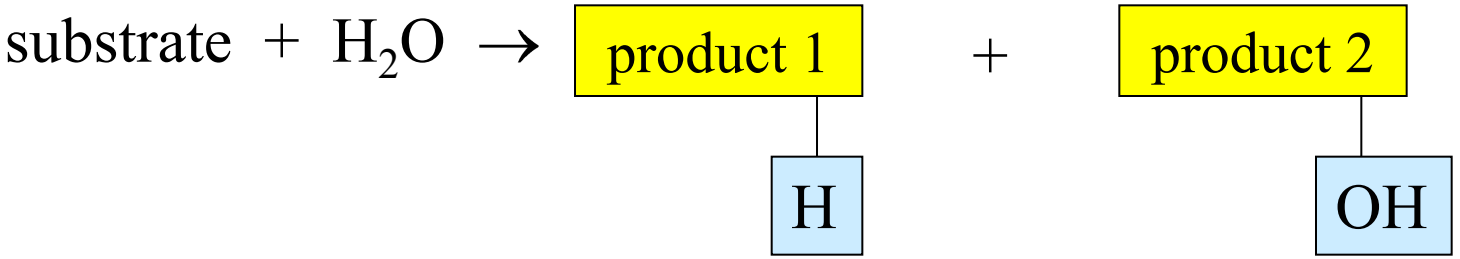
Esterification *in vitro* requires acidic catalysis.

Enzyme esterifications have different mechanism using acyl-CoA.

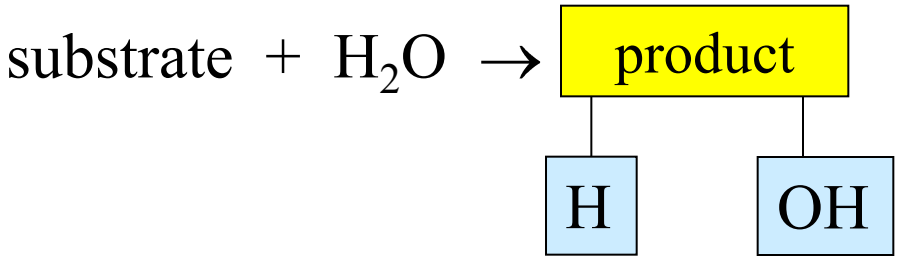
The reverse reaction is the **hydrolysis of ester.**

Distinguish: hydrolysis hydration

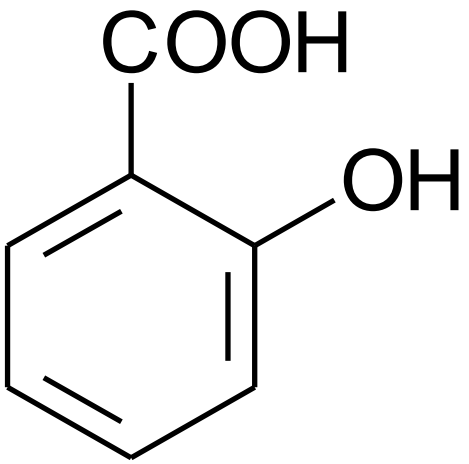
Hydrolysis = decomposition of substrate by the action of water
(typical in esters, amides, peptides, glycosides, anhydrides)



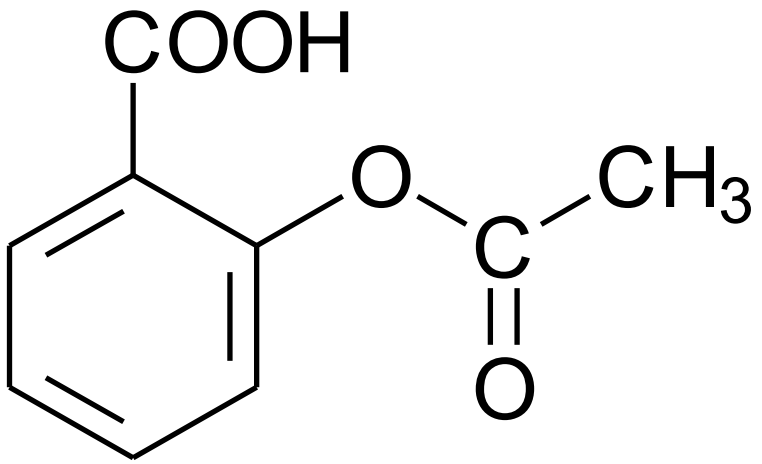
Hydration = addition of water (to unsaturated substrates)



Acetylsalicylic acid has acidic group and ester group



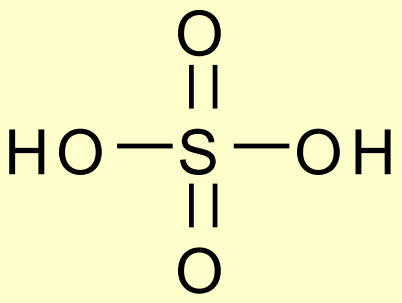
salicylic acid



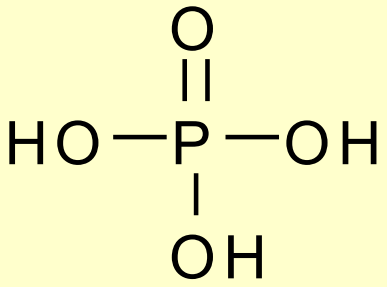
acetylsalicylic acid

Selected inorganic acids

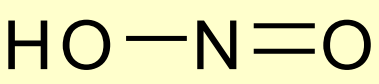
H_2SO_4



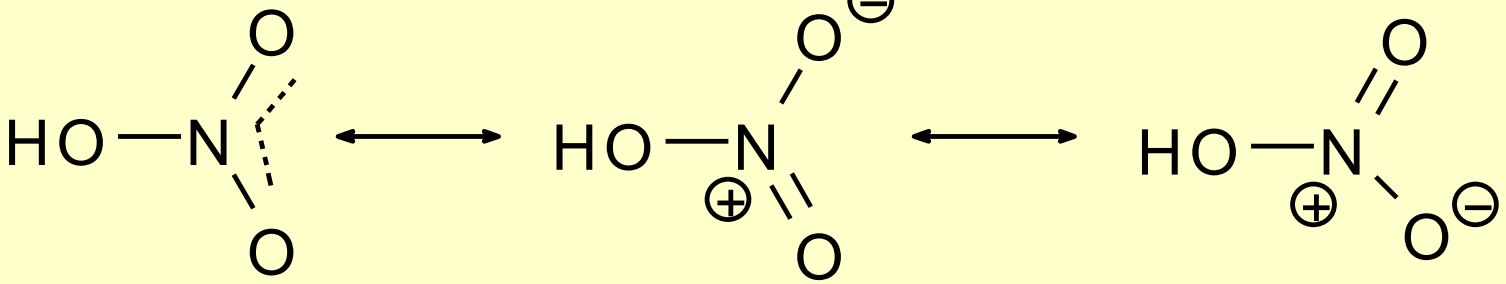
H_3PO_4



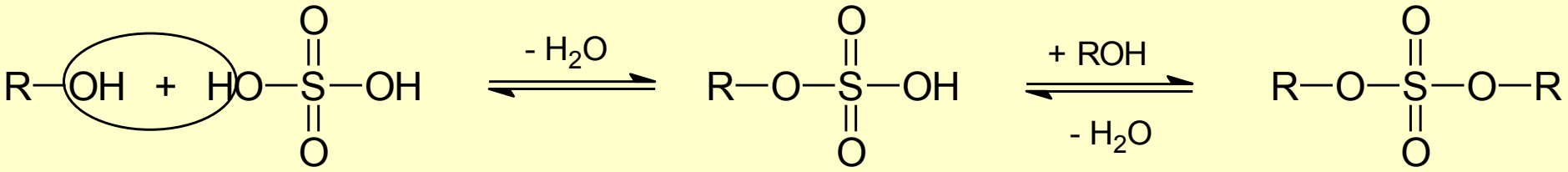
HNO_2



HNO_3



Esters of sulfuric acid

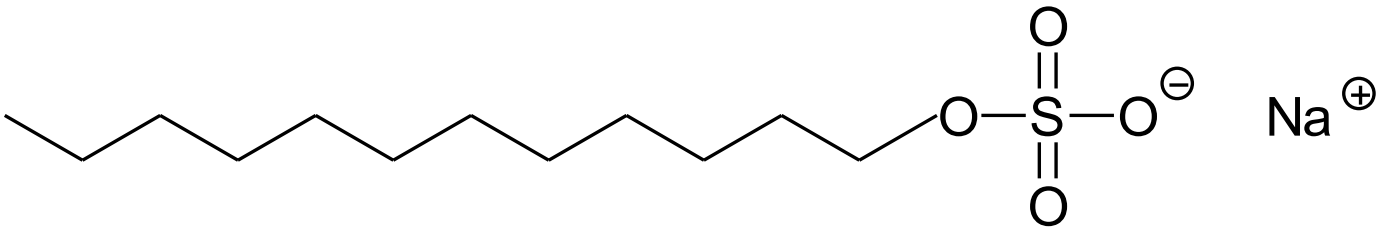


sulfuric acid

alkyl sulfate

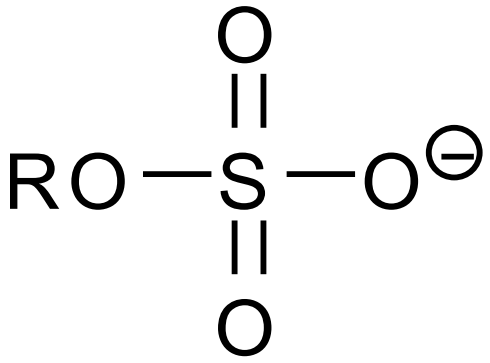
(alkyl sulfuric acid)

dialkyl sulfate

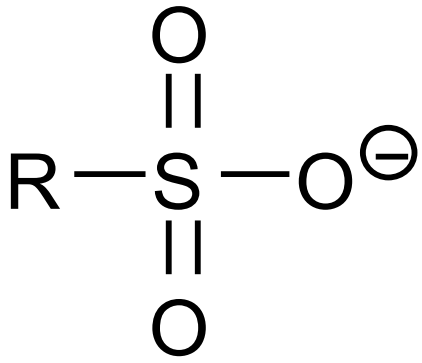


sodium dodecyl sulfate (SDS) is an anionic surfactant

Compare: alkyl sulfate × alkanesulfonate



alkyl sulfate



alkanesulfonate

bond C-O

4 O atoms around S

made by **esterification**

$R\text{-}OH + HO\text{-}SO_2\text{-}OH \rightarrow$

$R\text{-}O\text{-}SO_2\text{-}OH + H_2O$

bond C-S

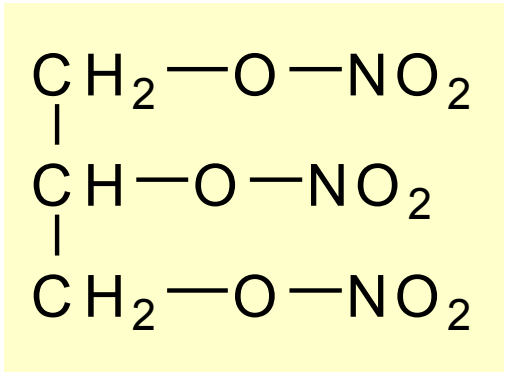
3 O atoms around S

made by **sulfonation**

$R\text{-}H + SO_3 \rightarrow R\text{-}SO_3H$

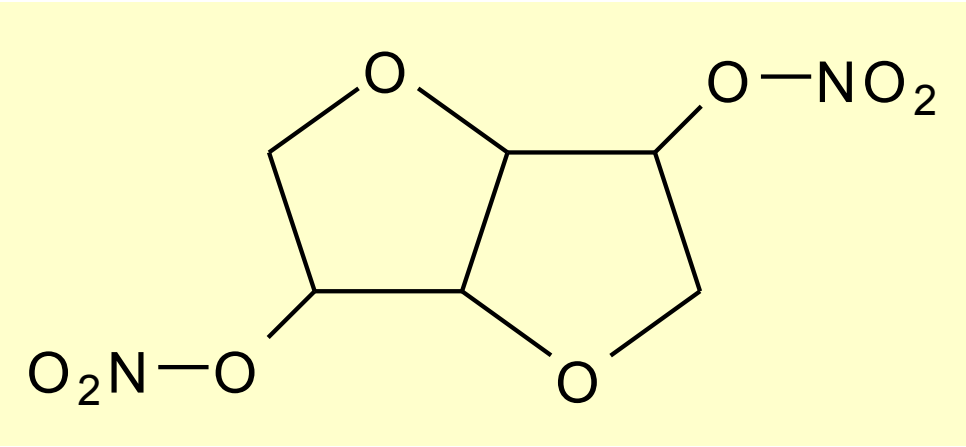
Esters of nitric acid

$$R\text{-}OH + HO\text{-}NO_2 \rightarrow R\text{-}O\text{-}NO_2 + H_2O$$



glycerol trinitrate

(glyceroli trinitras)

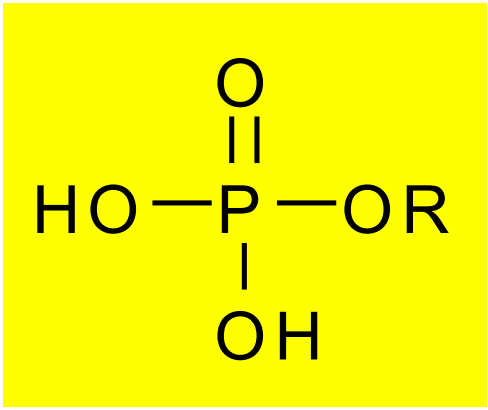


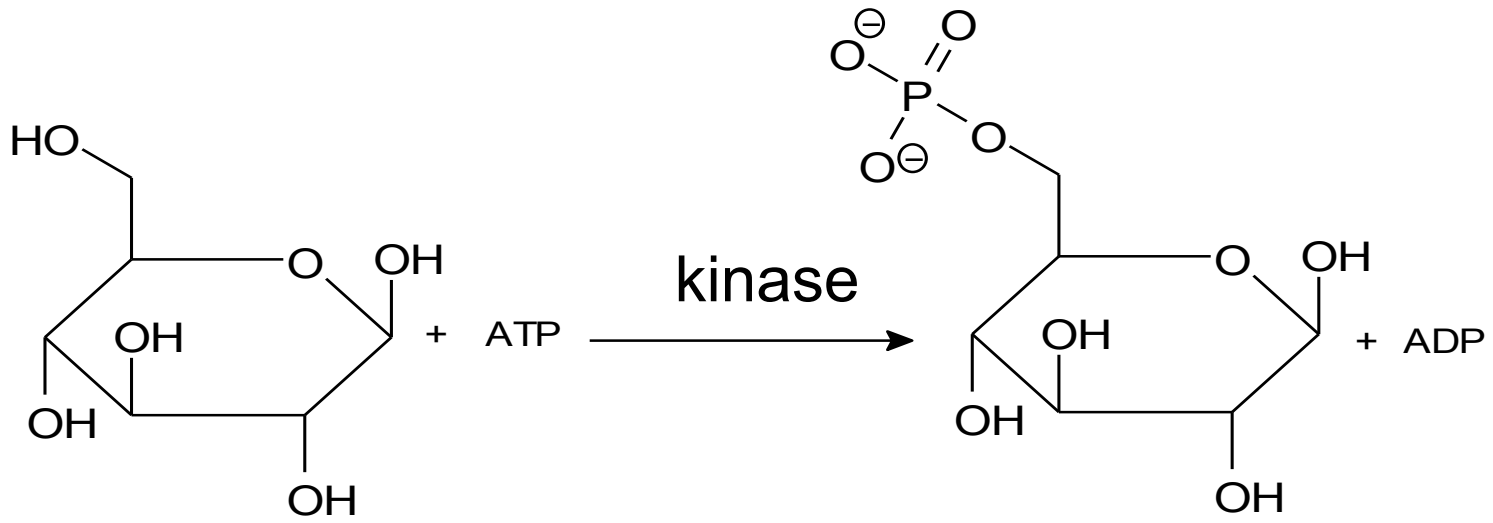
isosorbide dinitrate

(isosorbidi dinitras)

both exhibit vasodilatation effect

Monoesters of phosphoric acid

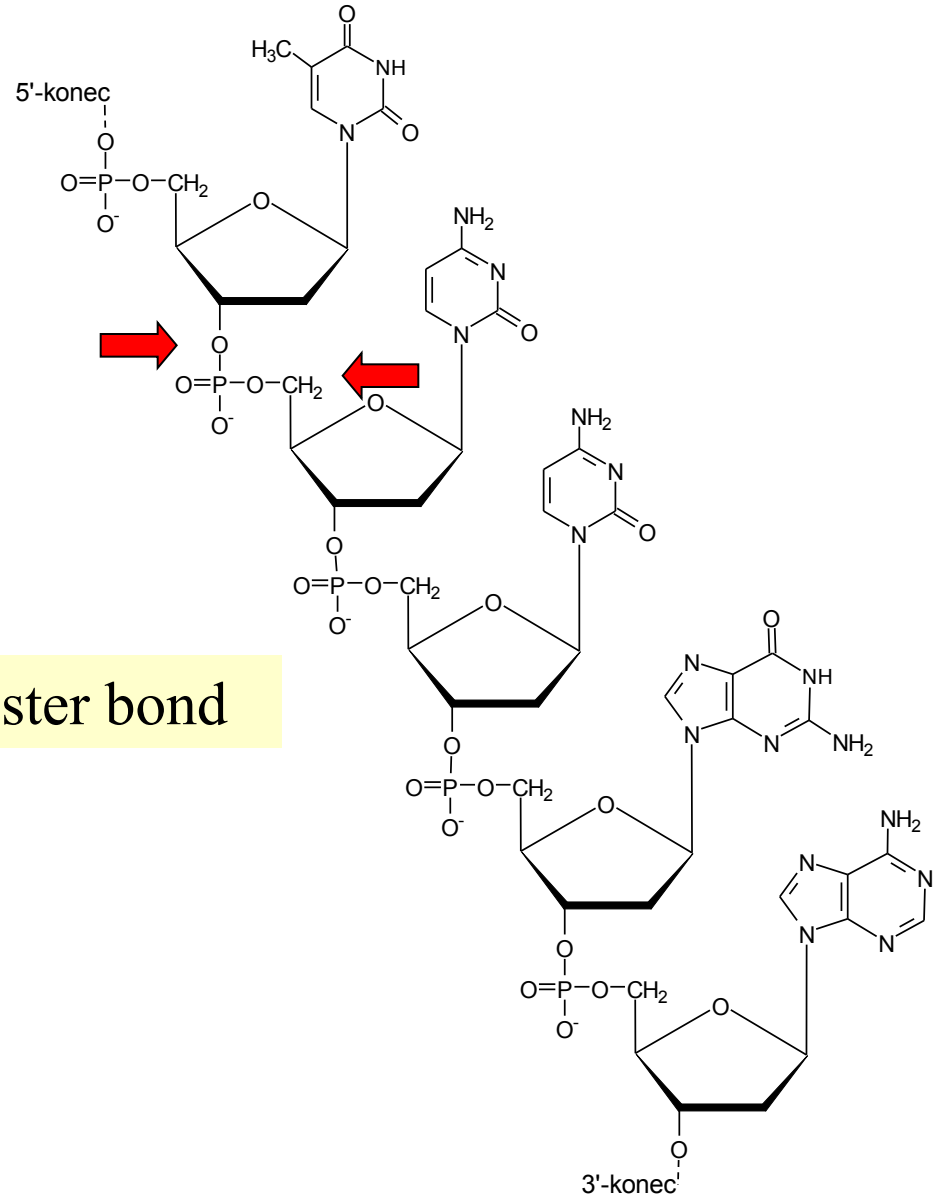




glucose

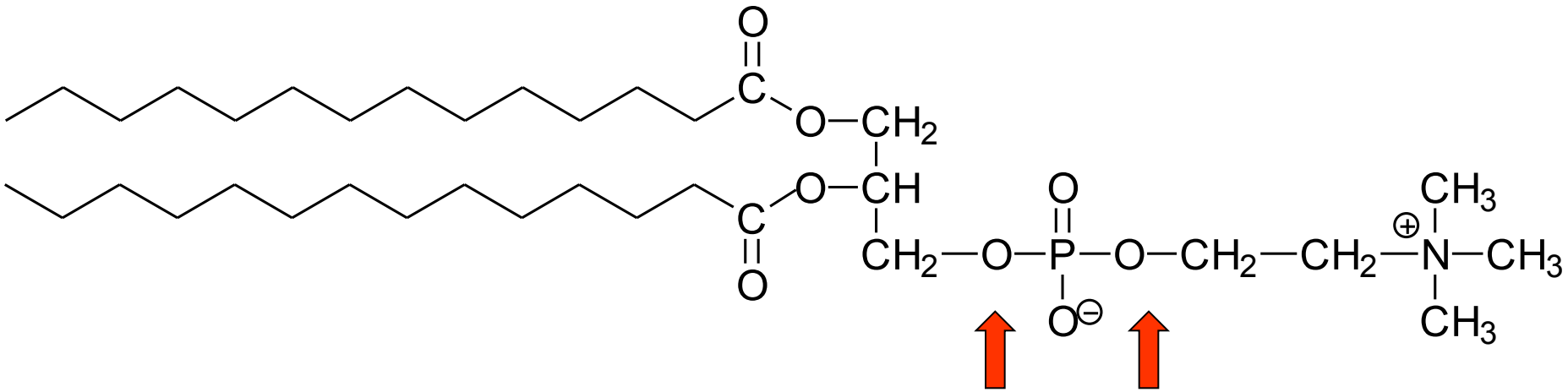
glucose 6-phosphate

Diesters of phosphoric acid are linkage elements in nucleic acids

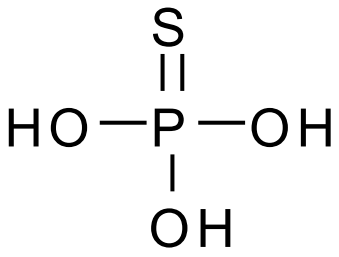


3’,5’-phosphodiester bond

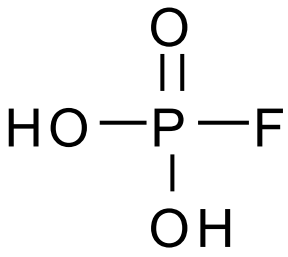
Diesters of phosphoric acid are linkage moieties in phospholipids



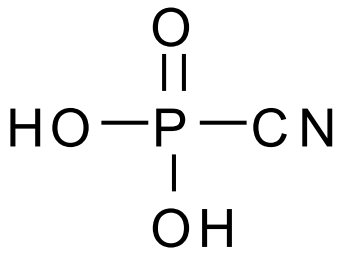
Organophosphates



thiophosphoric acid

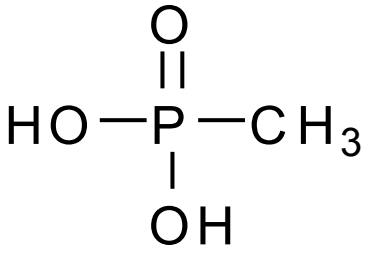


fluorophosphoric acid

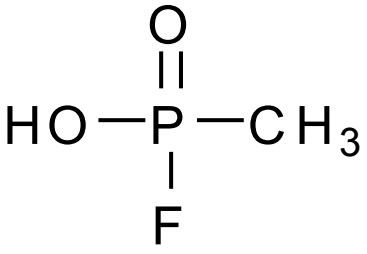


cyanophosphoric acid

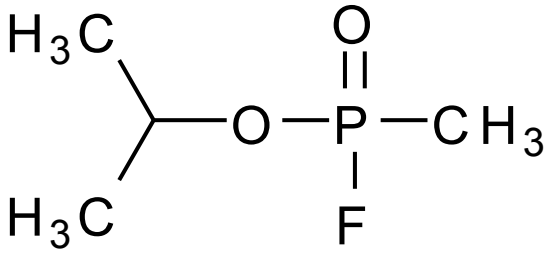
Compare: sulfonic ac. (C-S) × phosphonic ac. (C-P)



methylphosphonic acid

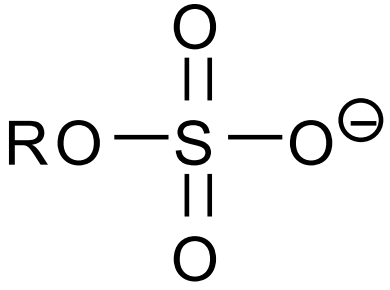


methylfluorophosphonic acid

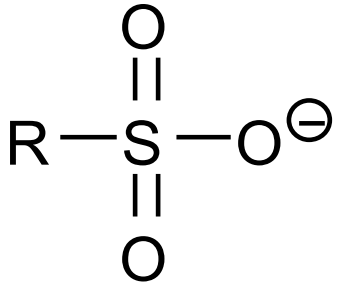


sarin

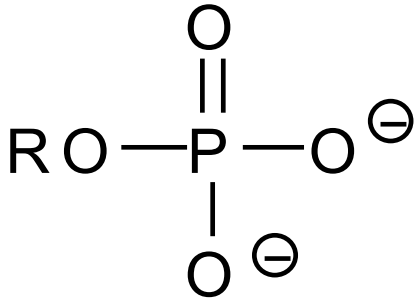
Compare the structures



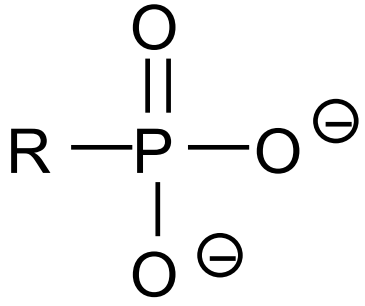
alkyl sulfate



alkanesulfonate

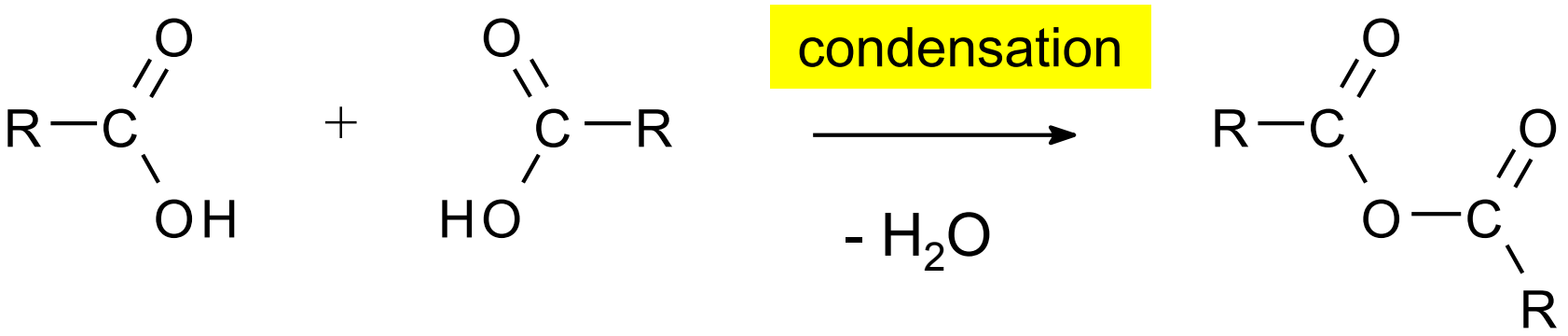


alkyl phosphate

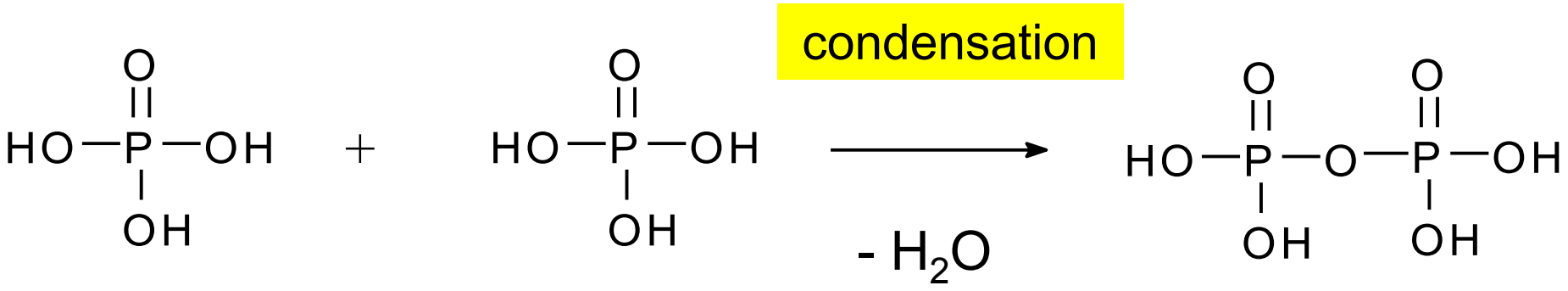


alkanephosphonate

Carboxylic acid anhydride



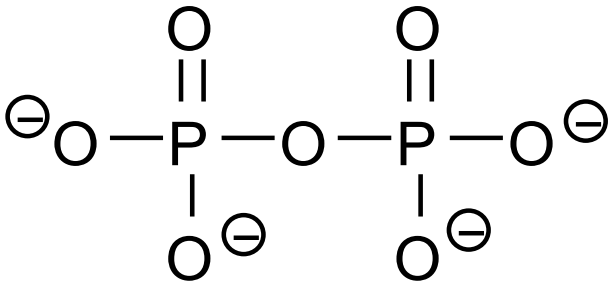
Phosphoric acid anhydride is diphosphoric acid (diphosphate)*



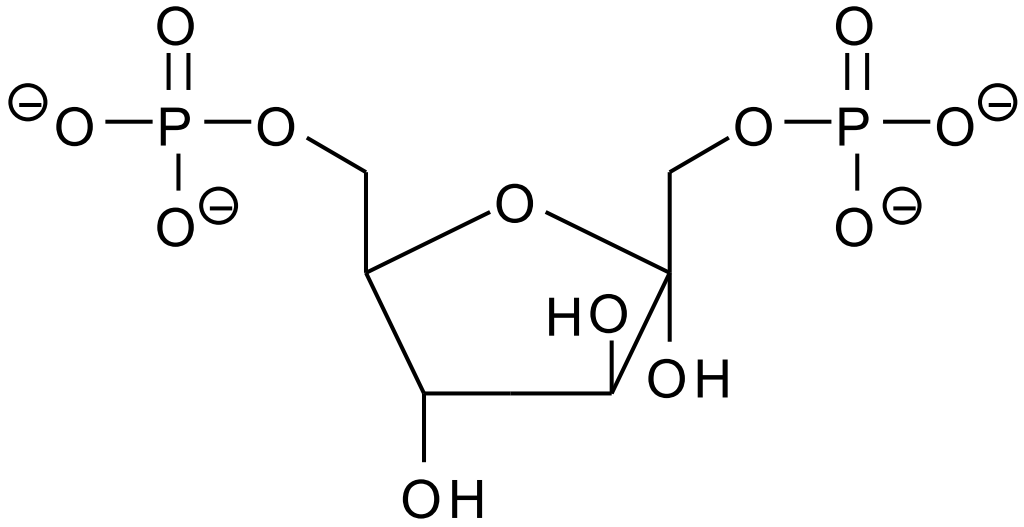
occurs in ATP, ADP, NAD^+, FAD

* Historical term is „pyrophosphate“ (e.g. Harper’s Biochemistry)

Compare: diphosphate × bisphosphate

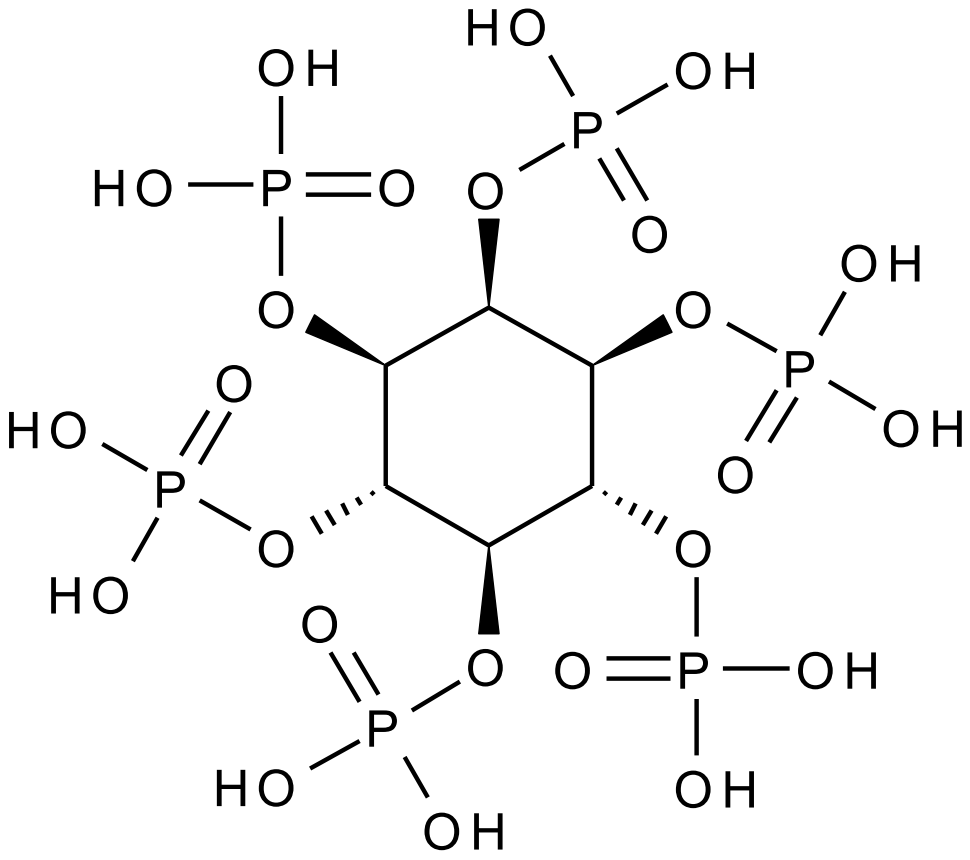


diphosphate
(anhydride)

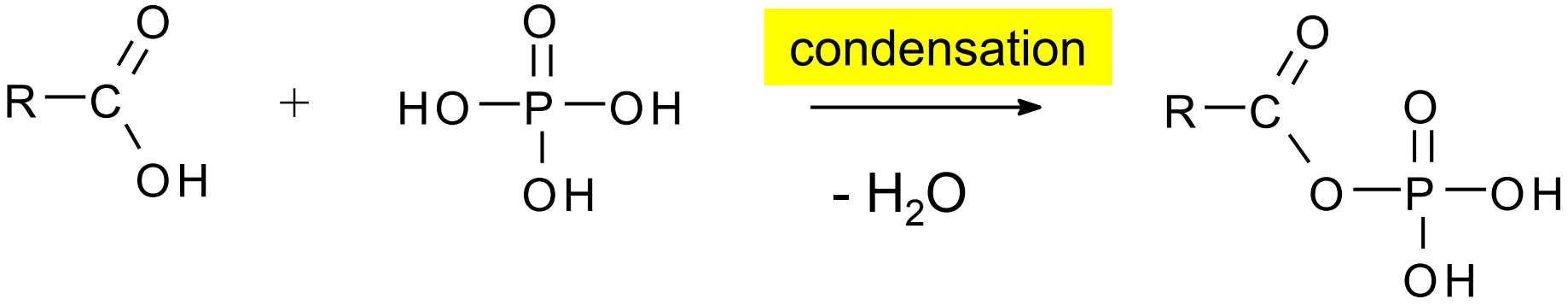


fructose 1,6-bisphosphate
(double ester)

Hexakisphosphate of inositol is phytic acid



Mixed anhydride of carboxylic acid and phosphoric acid is acyl phosphate

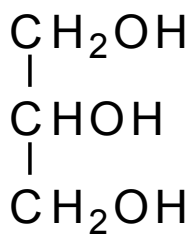


acyl phosphate

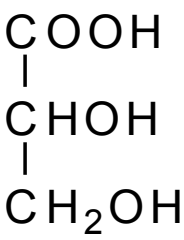
Acyl phosphates are macroergic compounds

- 3-phosphoglyceroyl phosphate (1,3-bisphosphoglycerate)
- carbamoyl phosphate

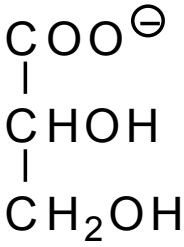
1,3-Bisphosphoglycerate



glycerol

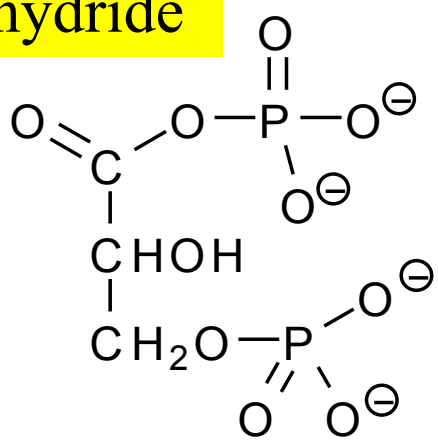


glyceric acid



glycerate

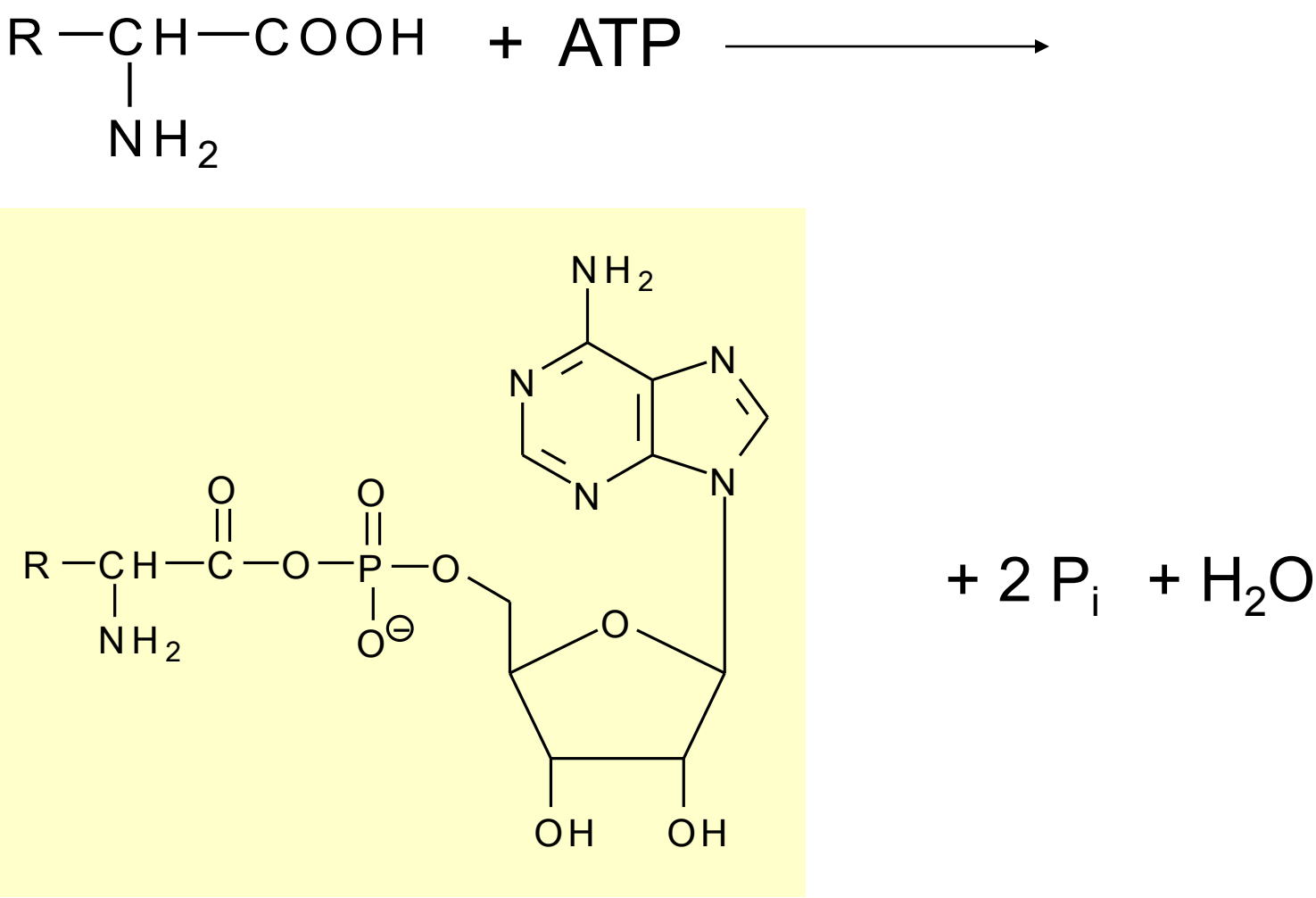
anhydride



ester

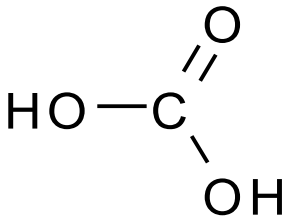
1,3-bisphosphoglycerate

Activation of amino acid by ATP in proteosynthesis

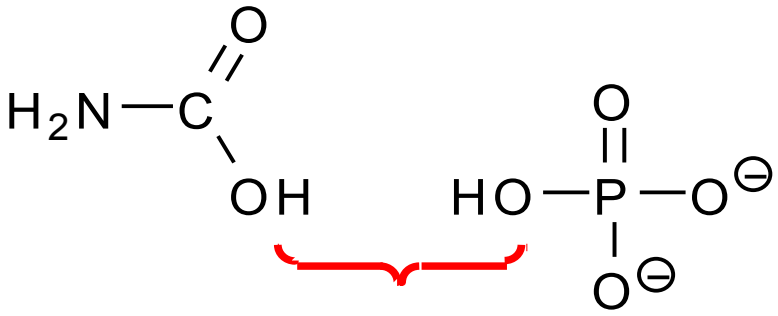


aminoacyl-AMP (mixed anhydride)

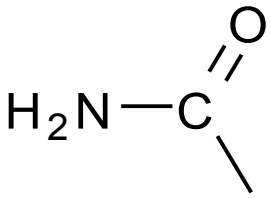
Carbamoyl phosphate



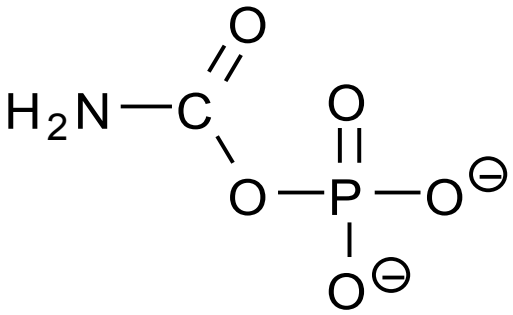
carbonic acid H_2CO_3



carbamic acid phosphate



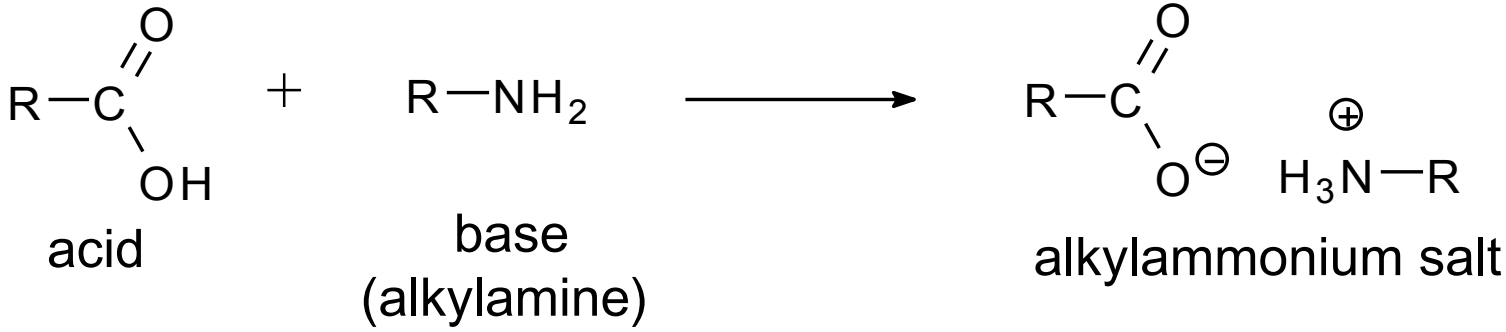
carbamoyl
(acyl of carbamic ac.)



carbamoyl phosphate

Amines and acids can react in two ways

Low temperature: acid-base reaction

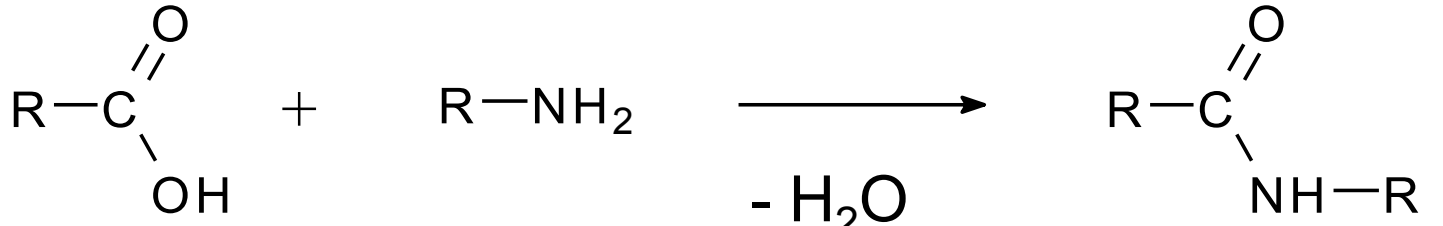


acid

base (alkylamine)

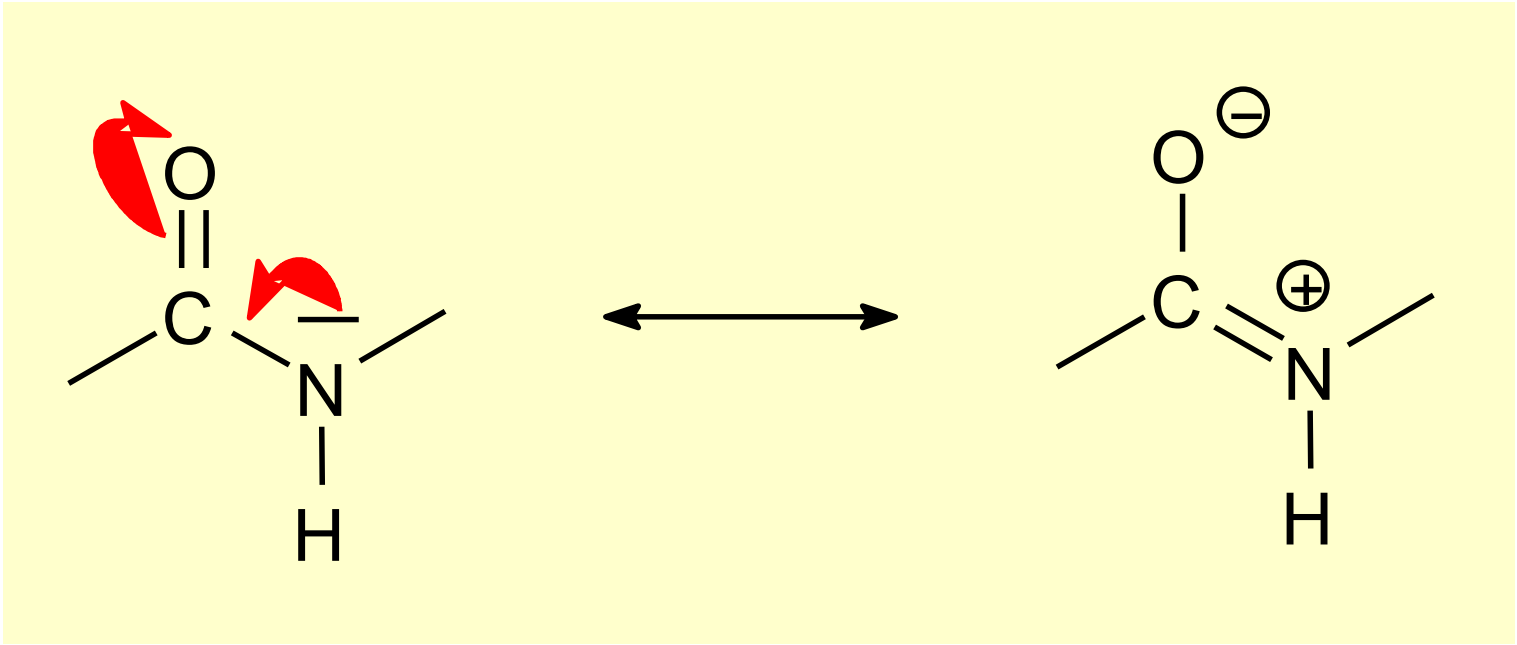
alkylammonium salt

High temperature: condensation



N-alkylamide

Amides are polar non-electrolytes

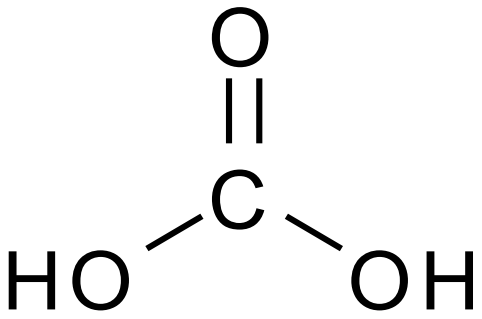


Free el. pair on nitrogen is in conjugation with double bond

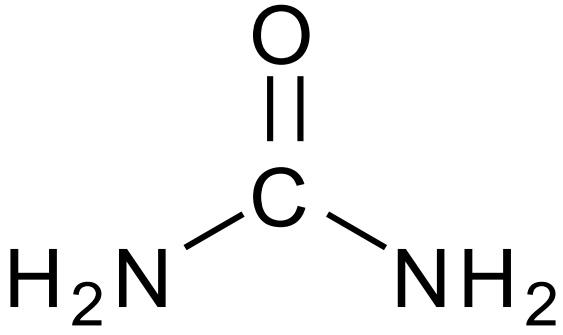
Compare properties

Feature	Amines	Amides
General formula	$R\text{-}NH_2$	$R\text{-}CO\text{-}NH_2$
El. pair on nitrogen	free and available	conjugated with C=O
Basic properties	yes	no
Salt formation	yes	no
In water behaves as	weak electrolyte	non-electrolyte
Polar compound	yes	yes
pH of aqueous solution	basic	neutral

Urea is diamide of carbonic acid

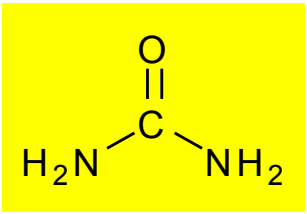


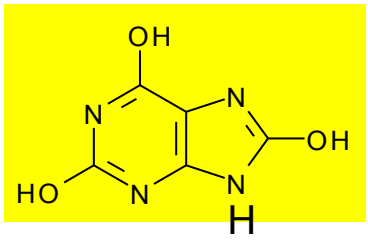
carbonic acid



urea

Compare

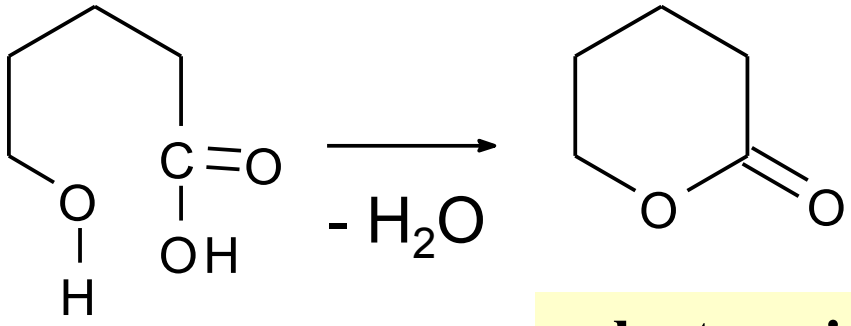




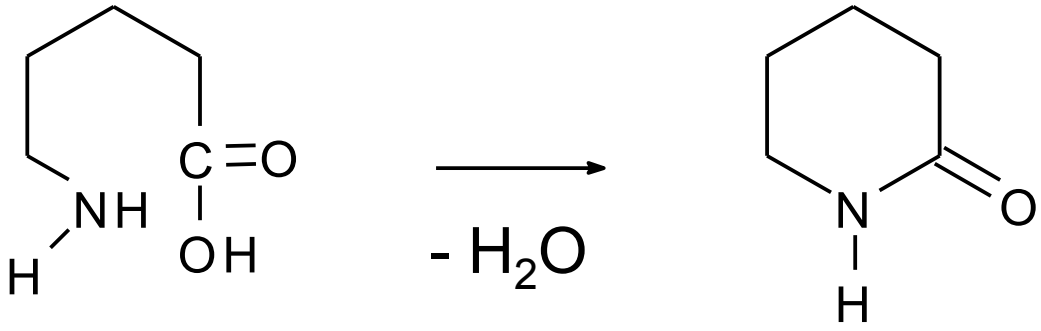
Feature	Urea	Uric acid
Chemical name	carbonic ac. diamide	2,6,8-trihydroxypurine
Latin name	urea	acidum uricum
In water	non-electrolyte	weak diprotic acid
Solubility in water	excelent	poor*
Aqueous solution is	neutral	weakly acidic
Reducing property	no	yes ⇒ antioxidant
Salt formation	no	yes (two types)
Catabolite of	amino acids	adenine and guanine

* Depends on pH, in acidic pH precipitates from solution !!!!

Lactone *versus* Lactam

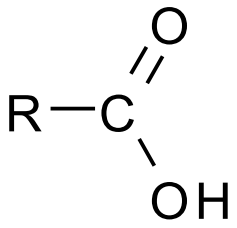


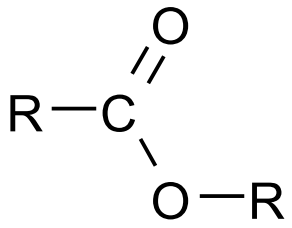
lactone is cyclic ester

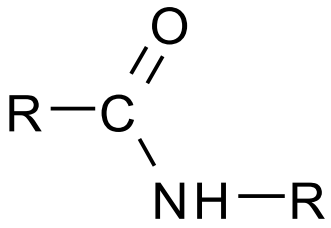


lactam is cyclic amide

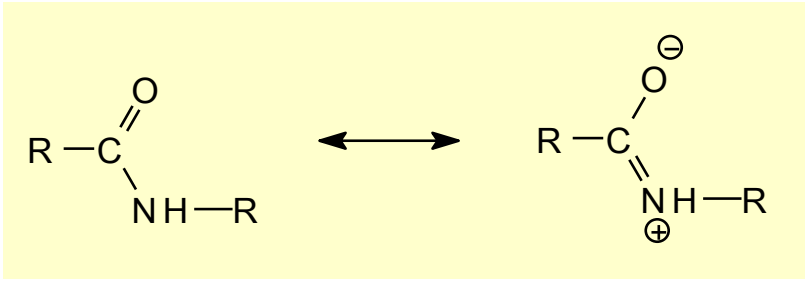
Compare properties







Carboxylic acid	Ester	Amide
weak electrolyte	non-electrolyte	non-electrolyte
polar	**non-polar**	**polar**
soluble in H_2O	insoluble in H_2O	soluble in H_2O

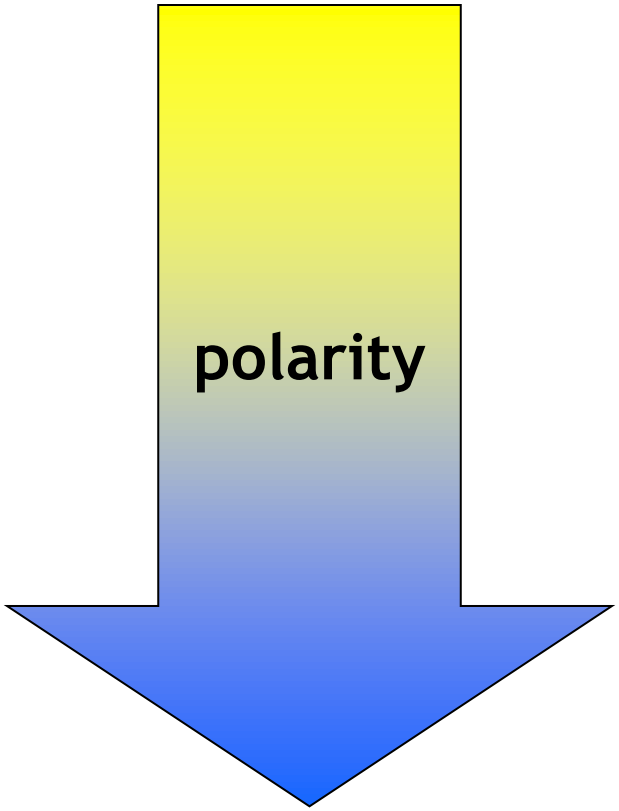


Polarity of organic compounds

(see Medical Chemistry II, chapter 4)

non-polar compounds

- hydrocarbons
- halogen derivatives
- ethers
- esters
- ketones
- amines
- amides
- alcohols
- carboxylic acids



Dehydrogenations of various substrates

Substrate	Product
alkane	alkene
primary alcohol	aldehyde
secondary alcohol	ketone
endiol	diketone
aldehyde hydrate	carboxylic acid
hemiacetal / cyclic hemiacetal	ester / lactone
hydroxy acid	oxo acid
p-diphenol	*p*-quinone
thiol	disulfide
amino acid	imino acid

see Med. Chem. II Appendix 3

Dehydrogenations in enzyme reactions

- Substrate loses **2 H** atoms from typical groups:

  primary alcohol group -CH_2-OH (e.g. ethanol, cholin)

  secondary alcohol group >CH-OH (lactate, malate)

  endiol group HO-(R)C=C(R)-OH (vitamin C)

  secondary amine group >CH-NH_2 (amino acid)

  saturated hydrocarbon group -CH_2-CH_2- (fumarate, acyl-CoA)
- Product acquires a **double bond** (C=O, C=NH, CH=CH)
- 2 H atoms are transferred to cofactor

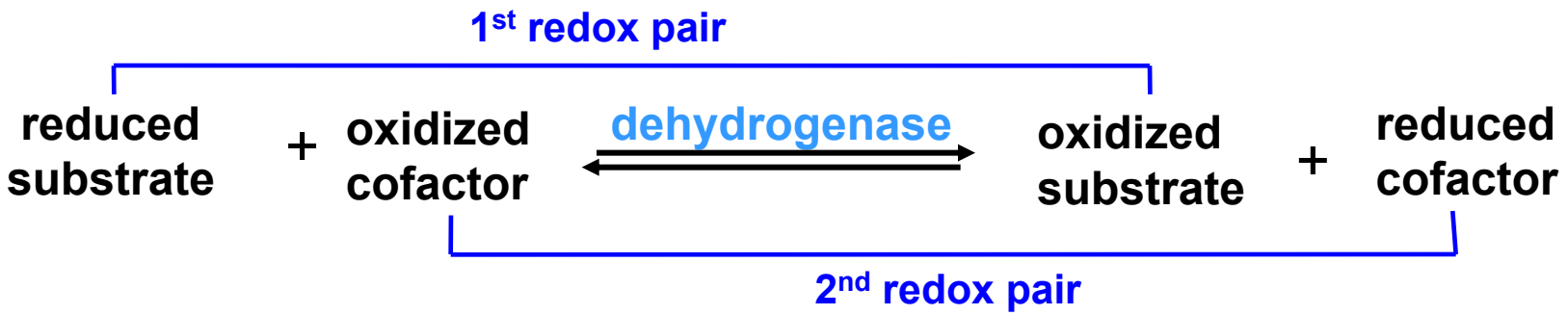
Enzyme dehydrogenations require the cooperation of three components

enzyme + **substrate** + **cofactor**

(lactate dehydrogenase) **(lactate)** **(NAD$^+$)**

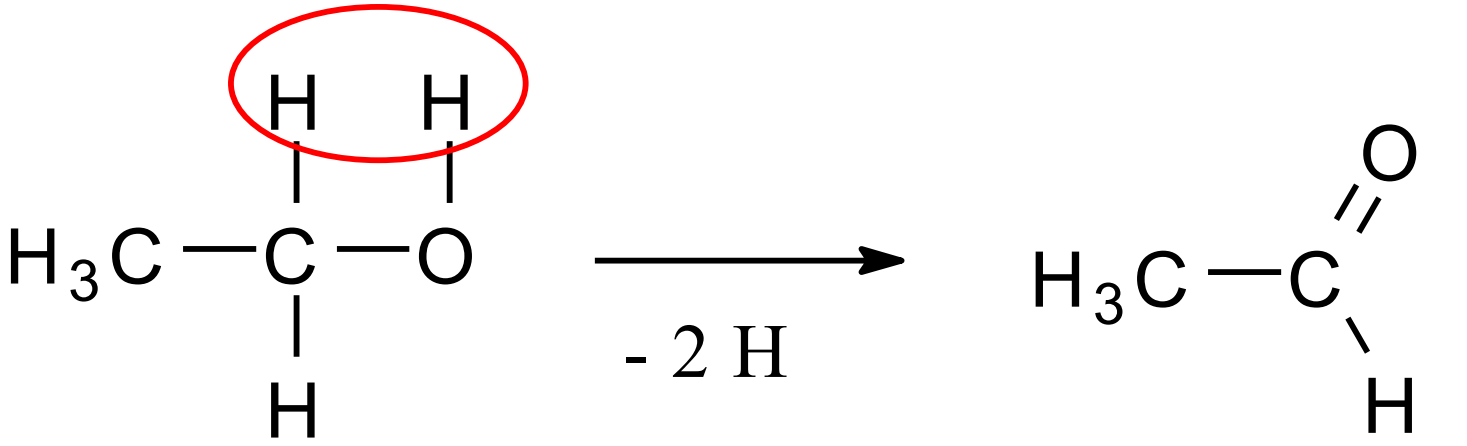
suffix *-ase*

vitamin B derivative



Dehydrogenation of ethanol

(simplified scheme = redox pair)

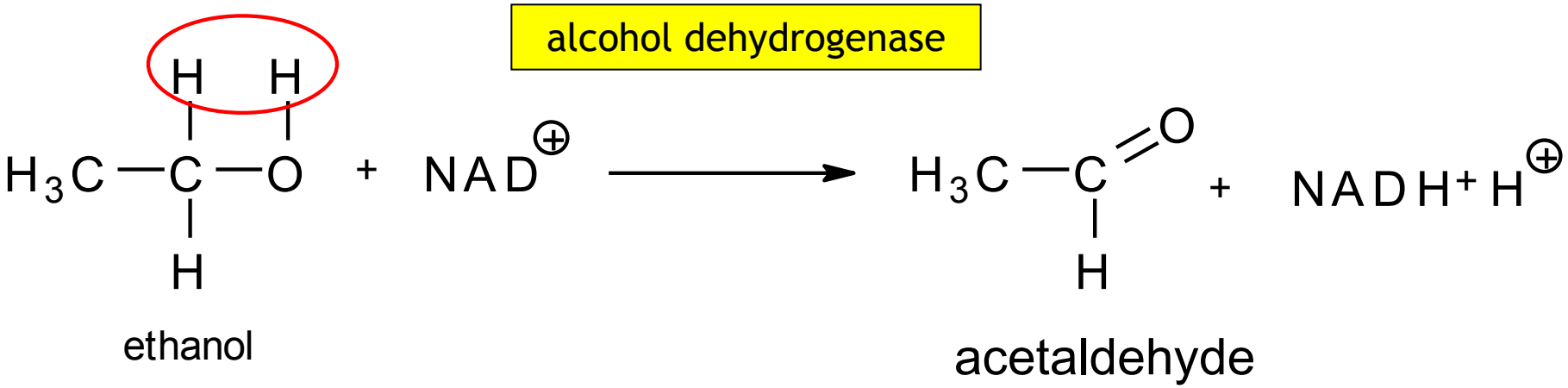


ethanol

acetaldehyde

Dehydrogenation of ethanol

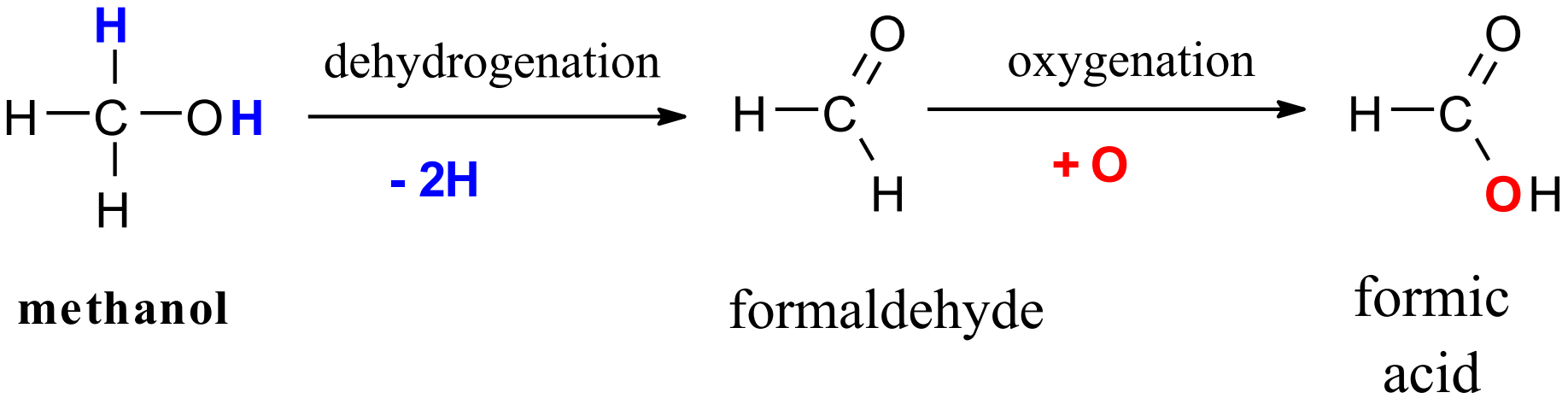
(complete reaction with cofactor, two redox pairs)



NAD^+ = nicotinamide adenine dinucleotide

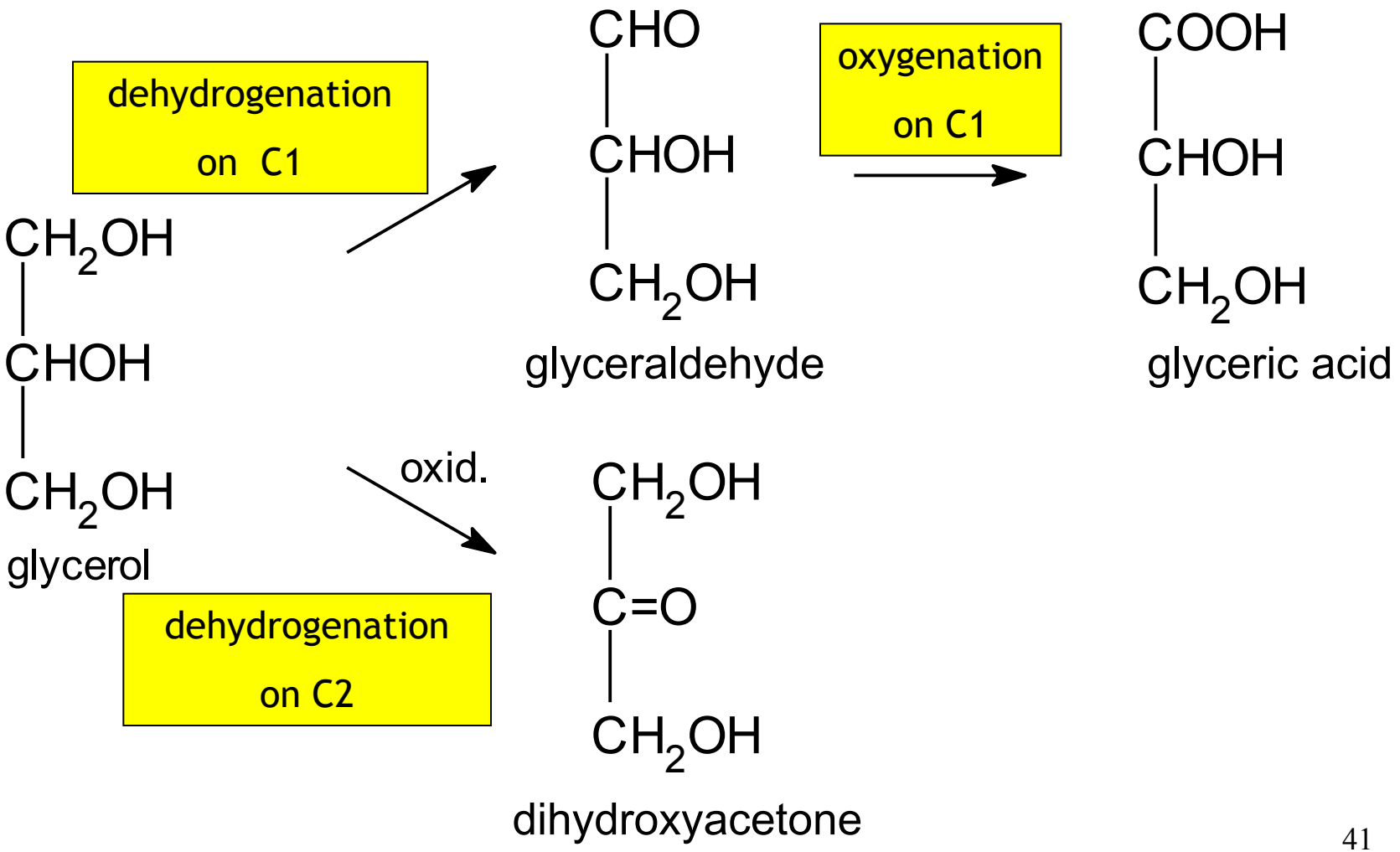
Oxidation of methanol

(simplified scheme)

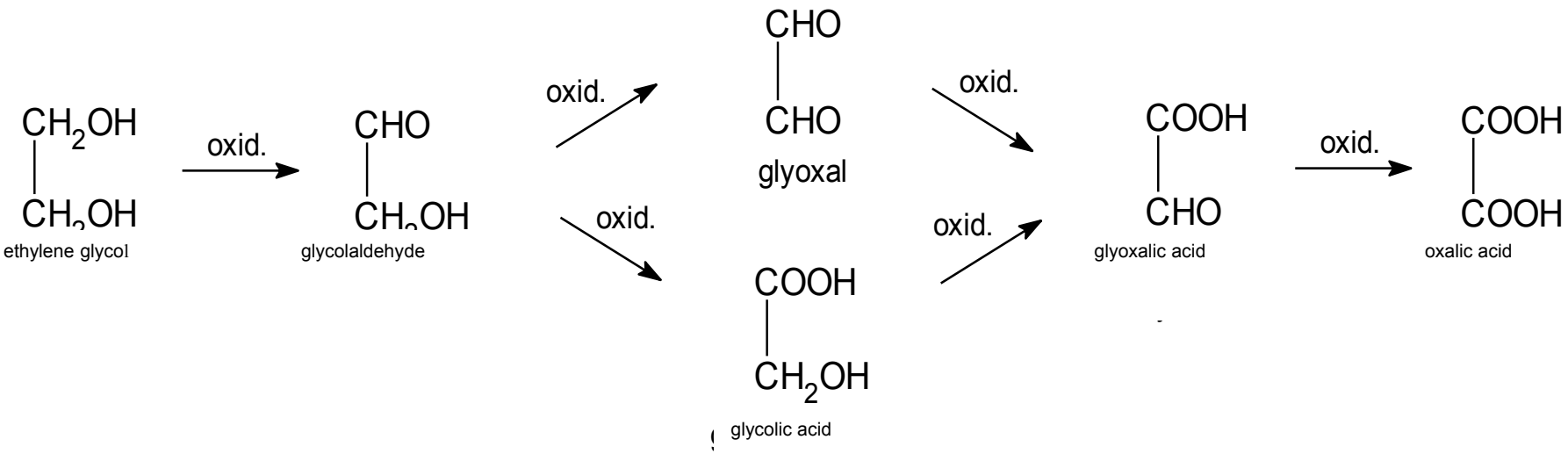


methanol formaldehyde formic acid

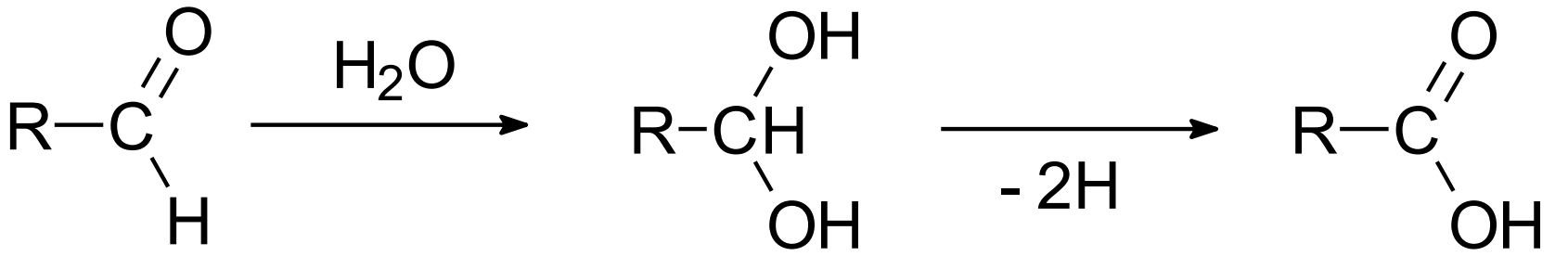
Two ways of glycerol oxidation



Oxidation of ethylene glycol proceeds stepwise with a number of intermediates



Dehydrogenation of aldehyde hydrate



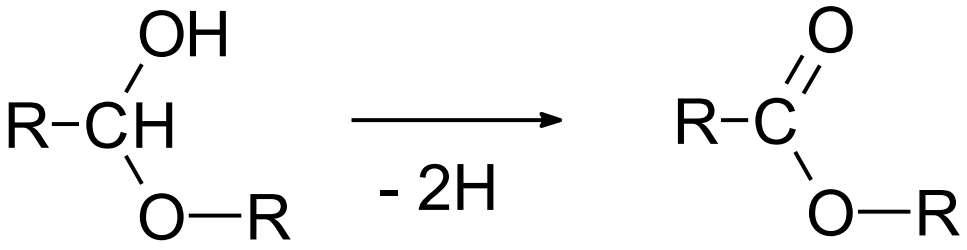
aldehyde

aldehyde hydrate

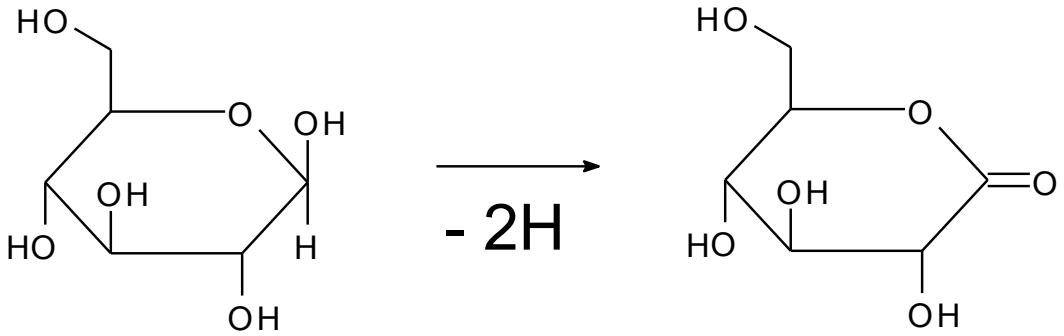
carboxylic acid

unstable intermediate

Dehydrogenation of hemiacetal

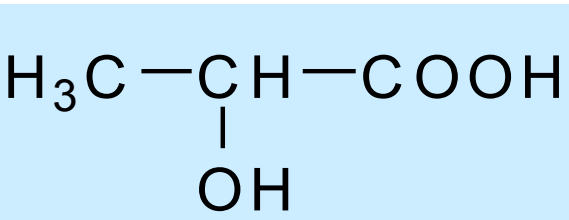


hemioacetal ester

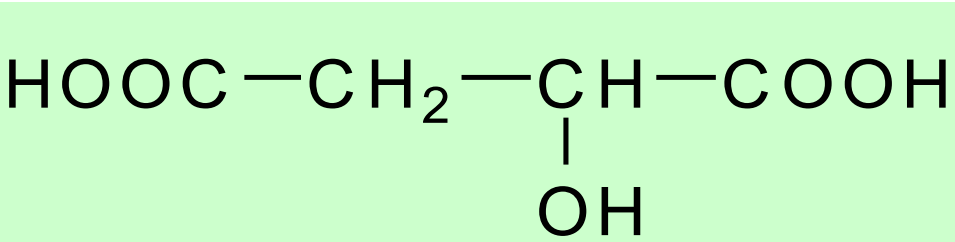


cyclic hemiacetal (glucopyranose) gluconolactone

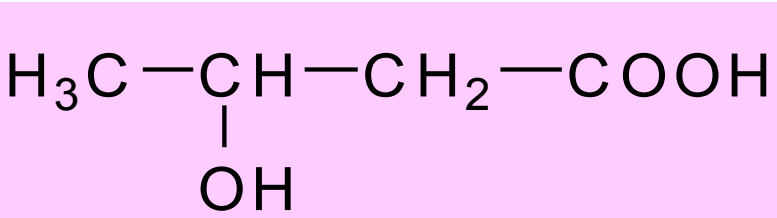
Hydroxy acids as dehydrogenation substrates



lactic acid (lactate)
acidum lacticum

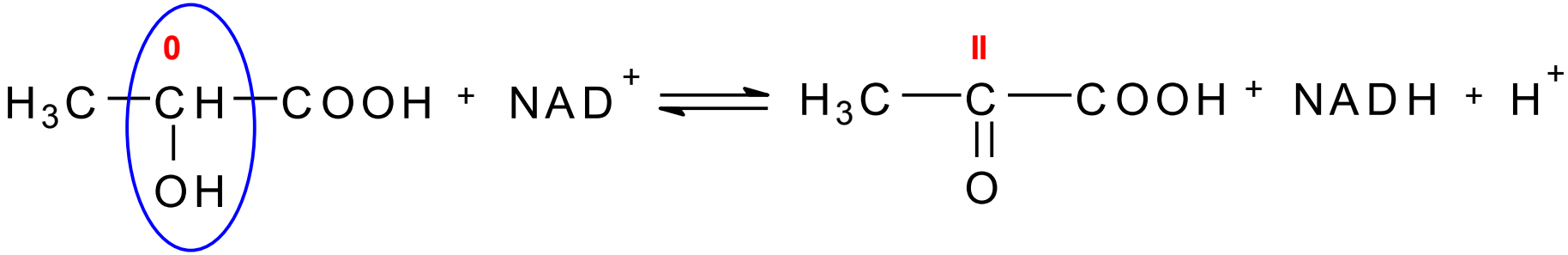


malic acid (malate)
acidum malicum



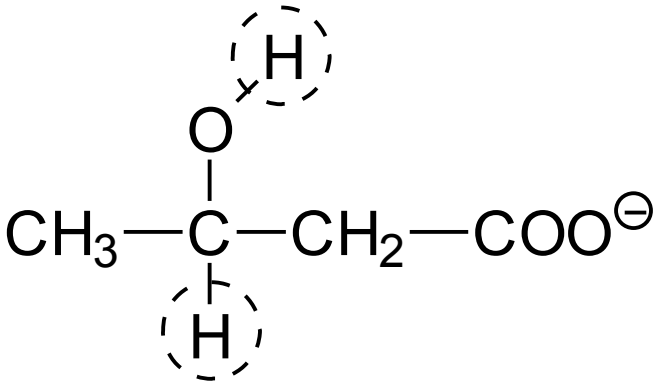
β-hydroxybutyric acid
β-hydroxybutyrate

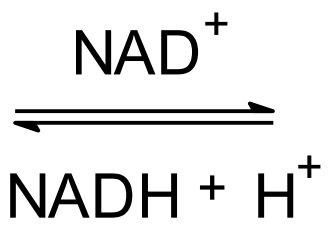
Dehydrogenation of lactic acid (lactate)

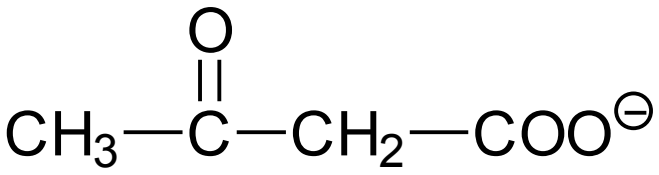


lactate pyruvate

Other examples



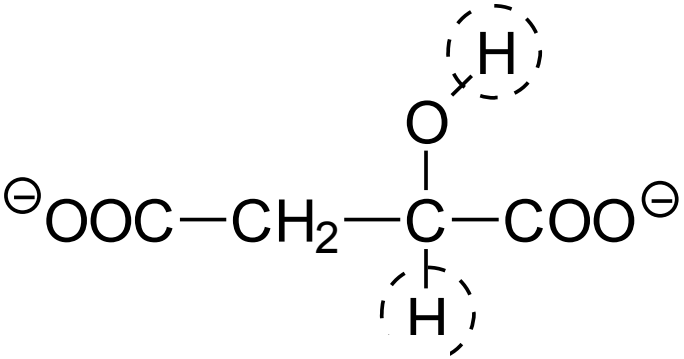


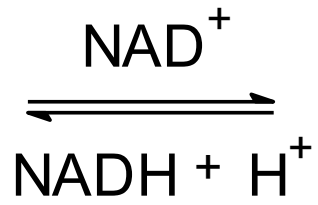


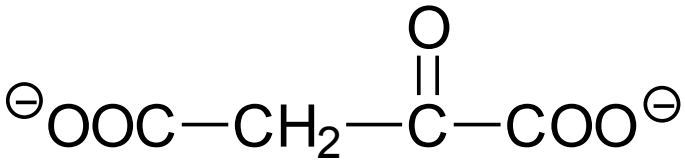
Beta-hydroxybutyrate

Ketone bodies

acetoacetate







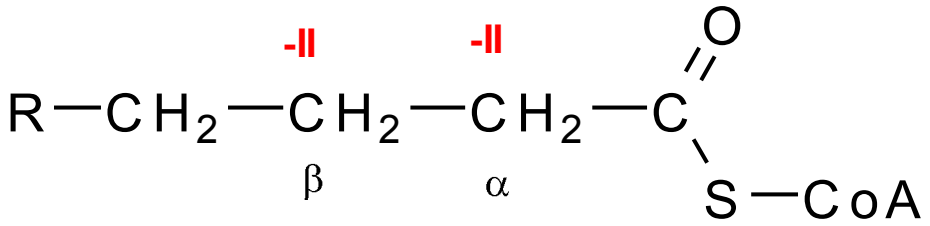
malate

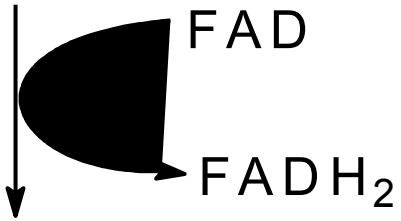
CAC reaction

oxaloacetate

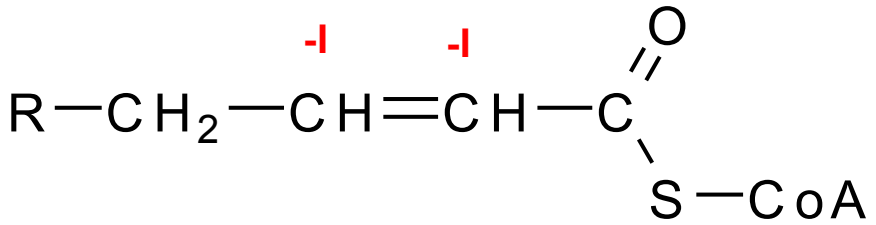
α,β-Dehydrogenation of acyl (catabolism of fatty acids)

saturated acyl-CoA





α,β-unsaturated acyl-CoA



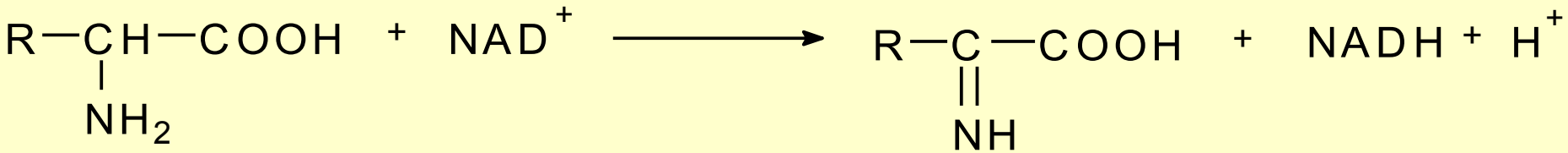
Dehydrogenation of amino compounds

$$R\text{-}CH_2\text{-}NH_2 + FMN \rightarrow R\text{-}CH{=}NH + FMNH_2$$

amine imine

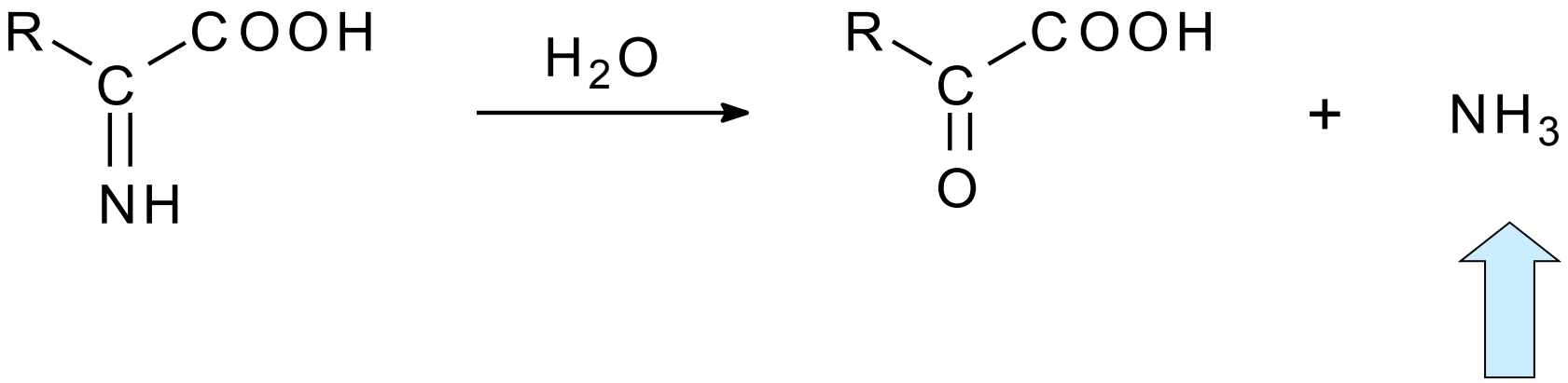
imino group

>C=NH

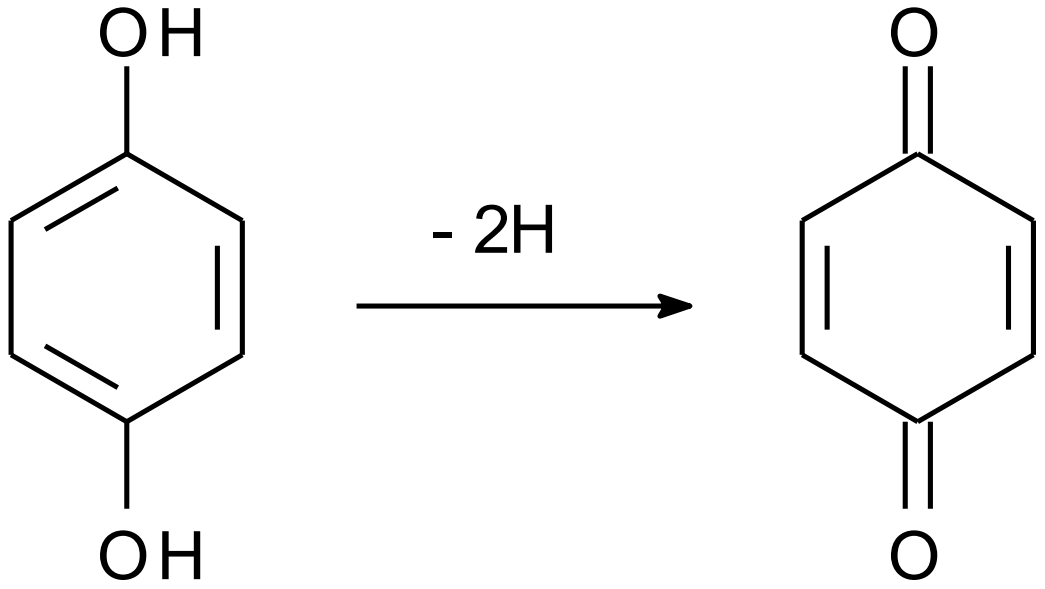


2-amino acid 2-imino acid

The hydrolysis of imino acid gives oxo acid and free (toxic) ammonia



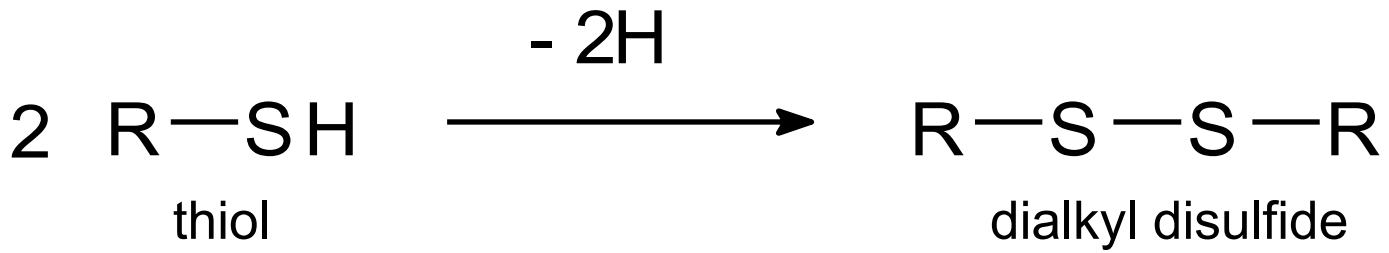
Dehydrogenation of diphenol

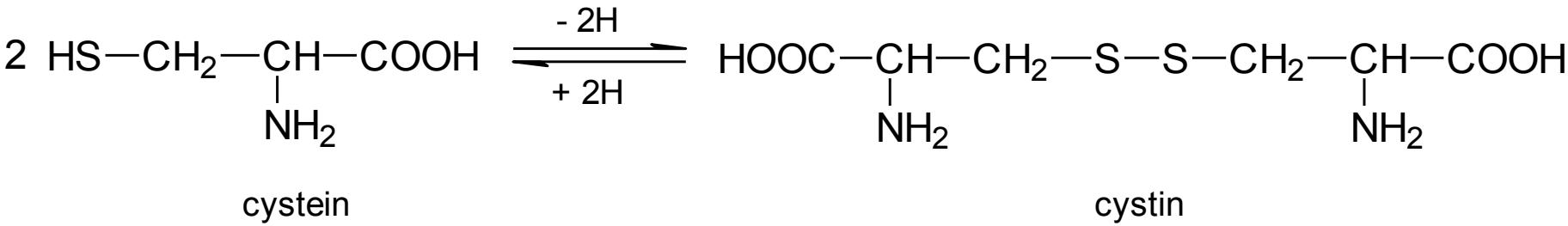


benzene-1,4-diol (hydroquinone)
(aromatic ring)

p-benzoquinone
(not aromatic)

Dehydrogenation of -SH substrates proceeds with two molecules (mild oxidation)*



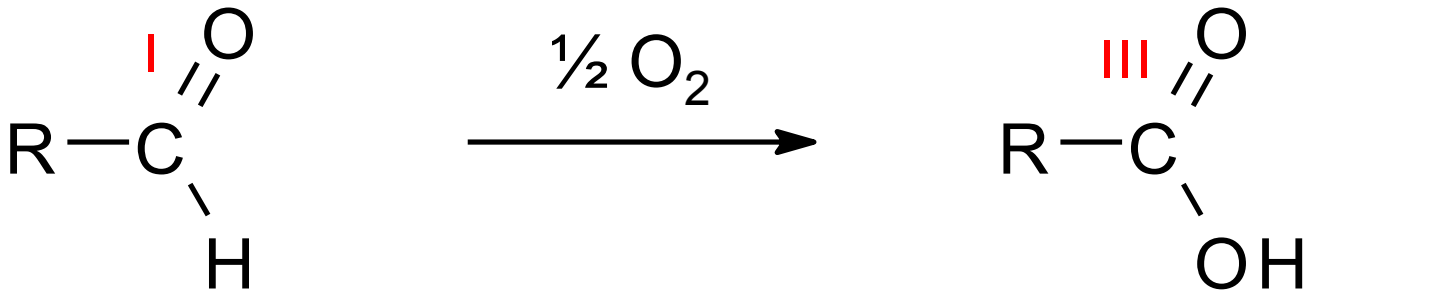


disulfide bridges in proteins

* Strong oxidation occurs with one molecule to give sulfonic acid.

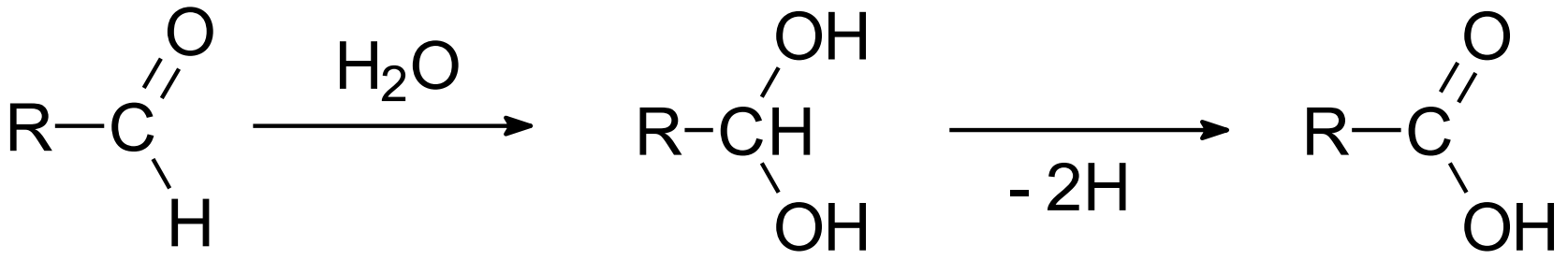
Oxygenation of aldehyde

Direct:



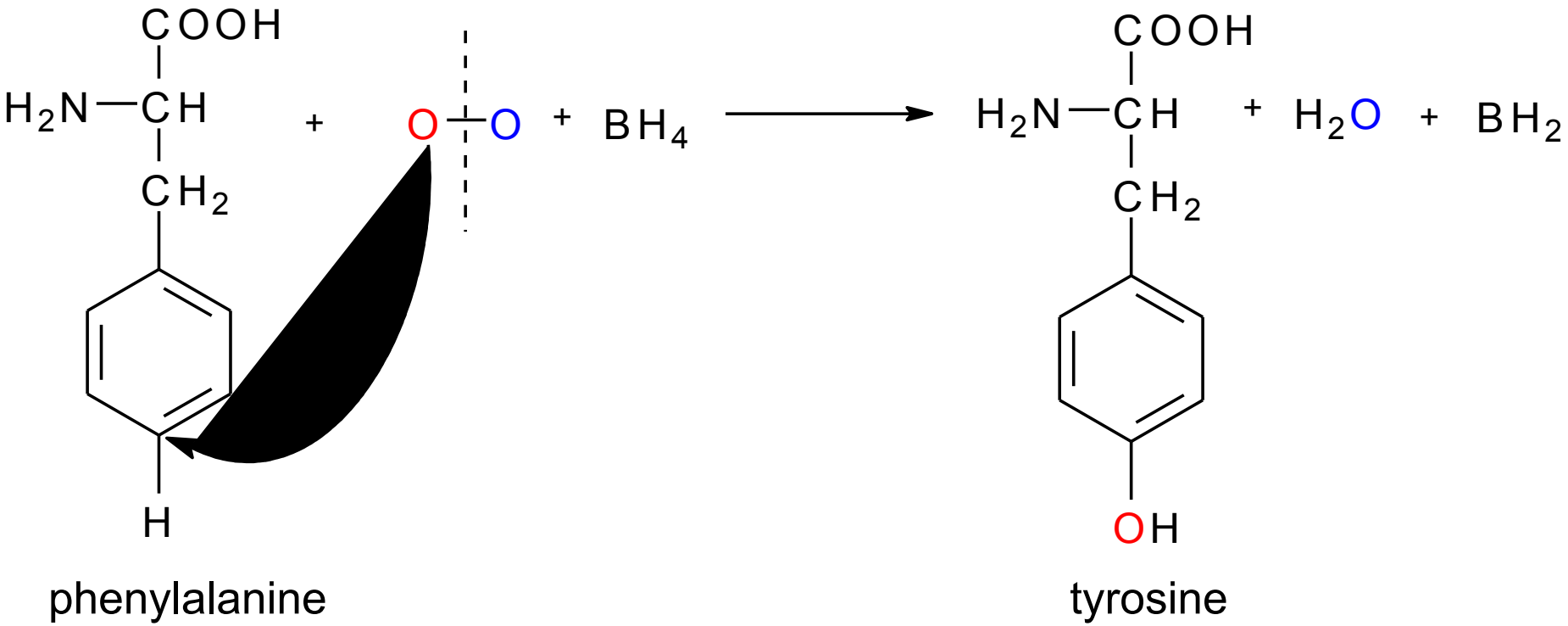
aldehyde carboxylic acid

Indirect:



aldehyde aldehyde hydrate carboxylic acid

Hydroxylation of phenylalanine



phenylalanine

tyrosine

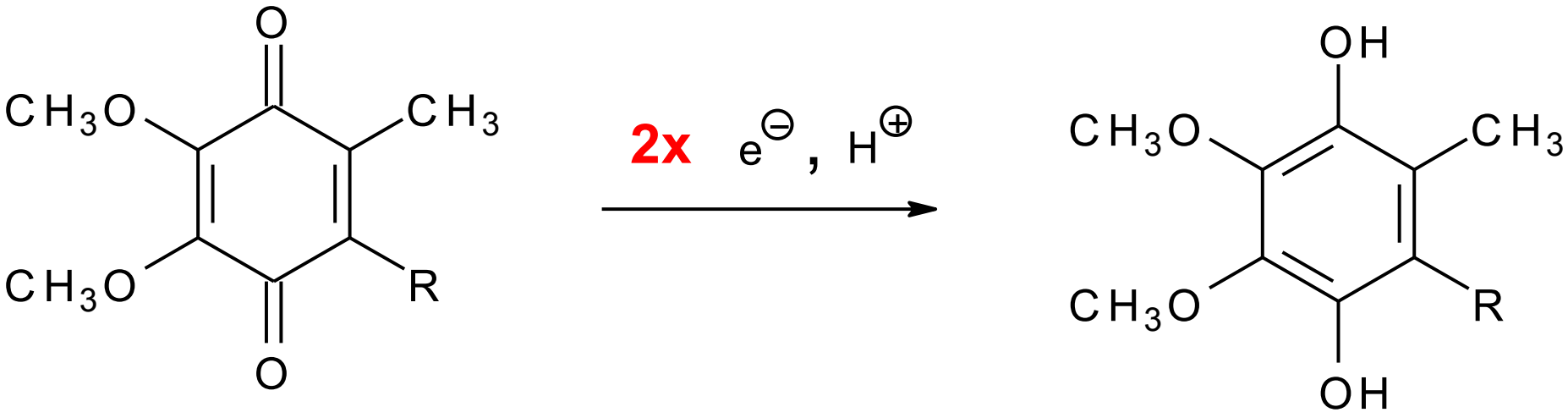
tetrahydrobiopterine (BH_4) is a donor of 2H to make water from the second oxygen atom

Biochemical hydrogenations

- Substrate gains 2 H
- Mainly from NADPH + H^+
- Reduction syntheses (FA, cholesterol)

$$-CH=CH- + NADPH+H^+ \rightarrow -CH_2-CH_2- + NADP^+$$

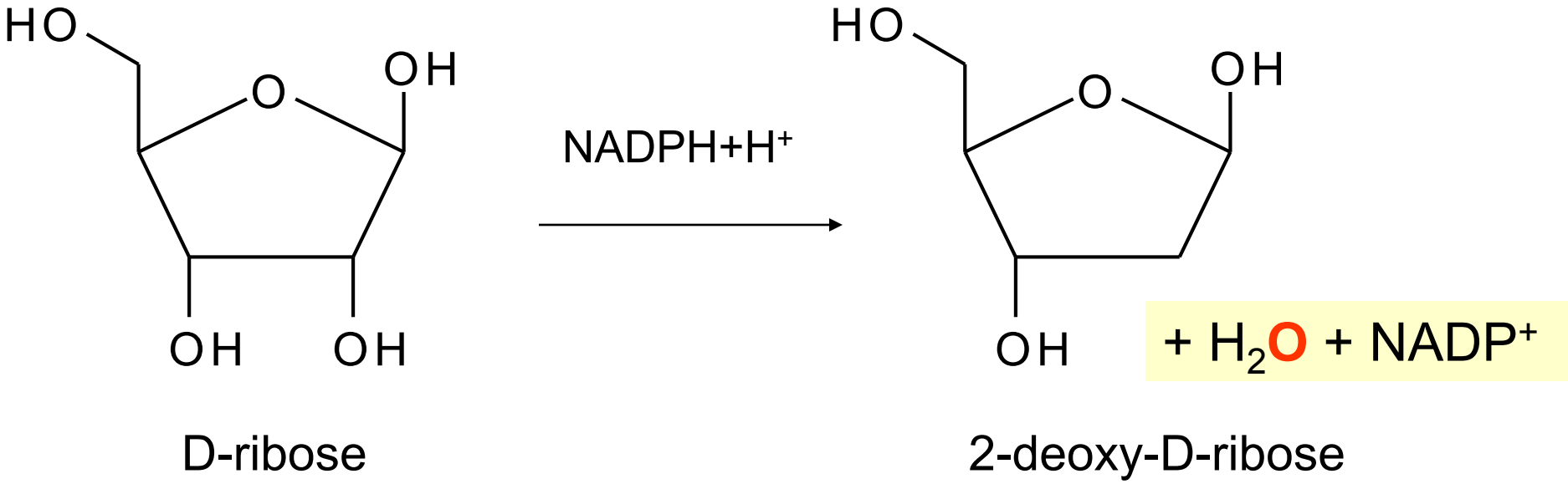
Hydrogenation of ubiquinone



ubiquinone

ubiquinol

Deoxygenation is quite rare reaction



Redox *versus* Conjugate pair

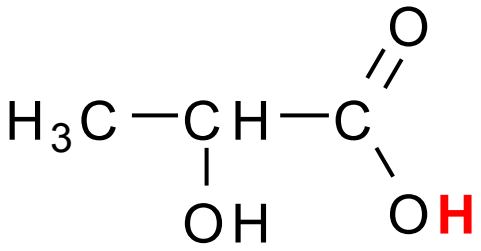
Distinguish:

A donor of H^+	=	acid
A donor of H	=	reductant

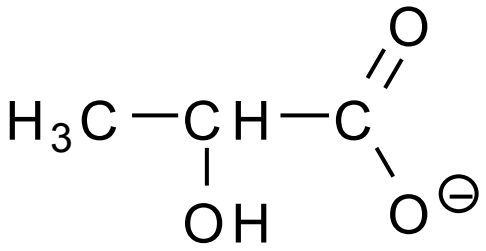
An acceptor of H^+	=	base
An acceptor of H	=	oxidant

Example 1

Conjugate pair

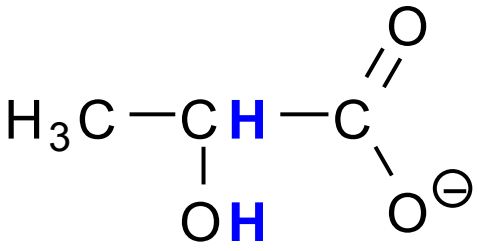


lactic acid

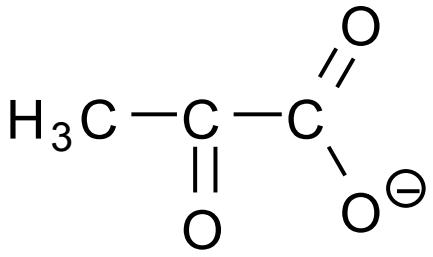


lactate (conjugate base)

Redox pair



lactate

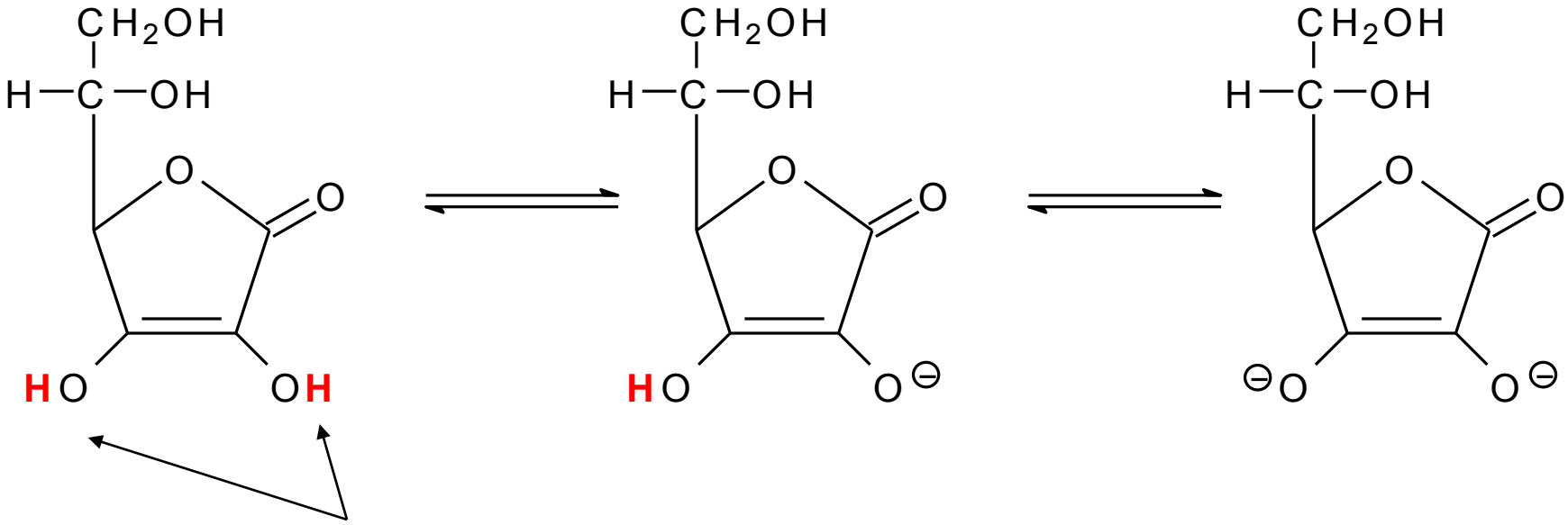


pyruvate

Example 2

L-Ascorbic acid is a weak diprotic acid

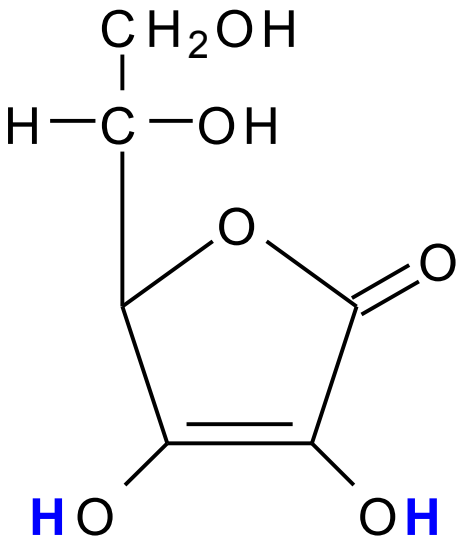
$pK_{A1} = 4.2$ $pK_{A2} = 11.6$



two enol hydroxyls

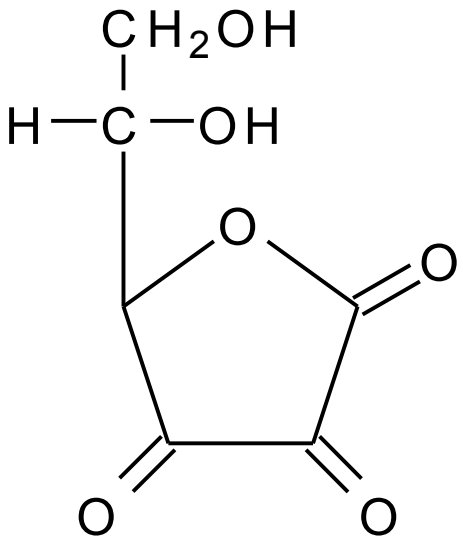
Two conjugate pairs:
Ascorbic acid / hydrogen ascorbate
Hydrogen ascorbate / ascorbate

L-Ascorbic acid has reducing properties (antioxidant)



ascorbic acid

(reduced form)



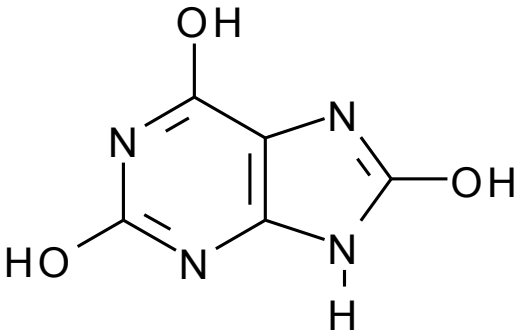
dehydroascorbic acid

(oxidized form)

Example 3

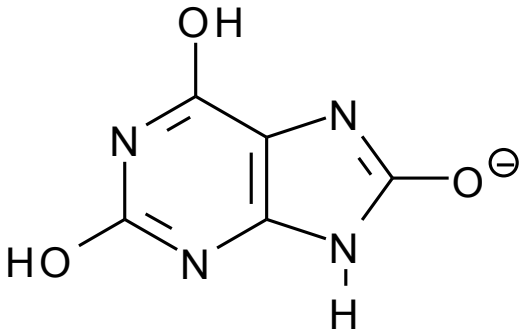
Uric acid (lactim) is a weak diprotic acid

$pK_{A1} = 5.4$ $pK_{A2} = 10.3$

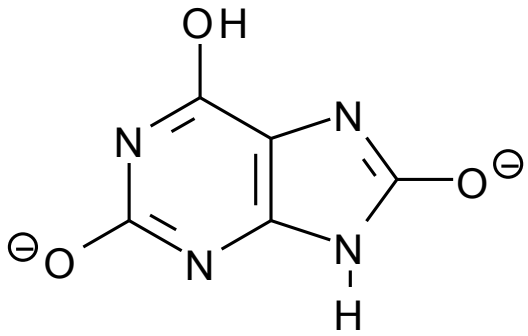


uric acid

2,6,8-trihydroxypurine

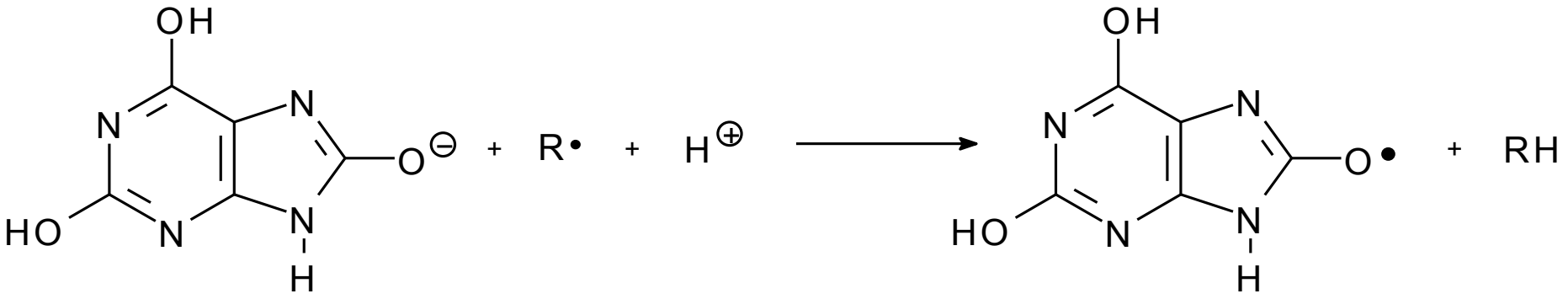


hydrogen urate



urate

Uric acid has reducing properties (physiological antioxidant)



hydrogen urate anion
(reduced form)

hydrogen urate radical
relatively stable
(oxidized form)

↓

various products

Hydrogen urate anion affords one electron

R· is oxygen radical like ·OH, superoxide.

Transaminations of amino acids

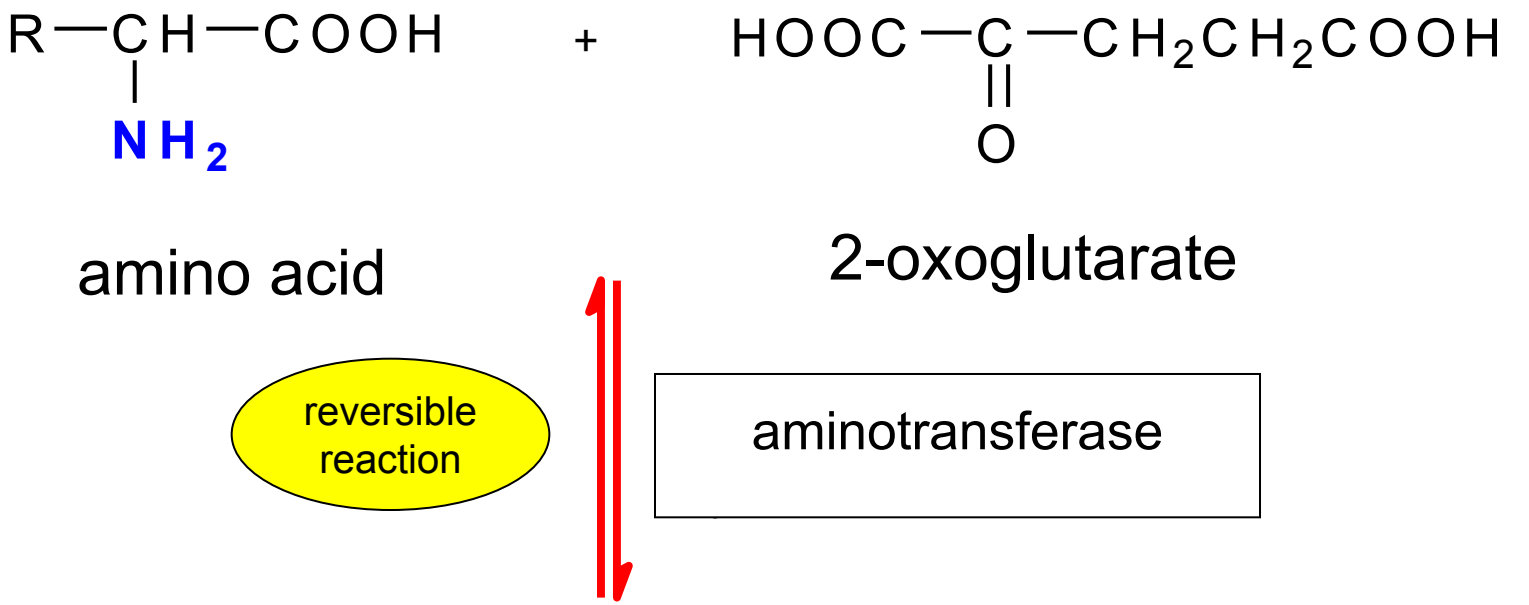
Catabolic pathway of nitrogen (in blue colour)

- nitrogen input → dietary **proteins** → **AA** (stomach, intestine)
- **transamination** of AA in cells → **glutamate**
- dehydrogenation + deamination of glutamate → **NH_3**
- detoxication of ammonia (liver) → **urea** → nitrogen output

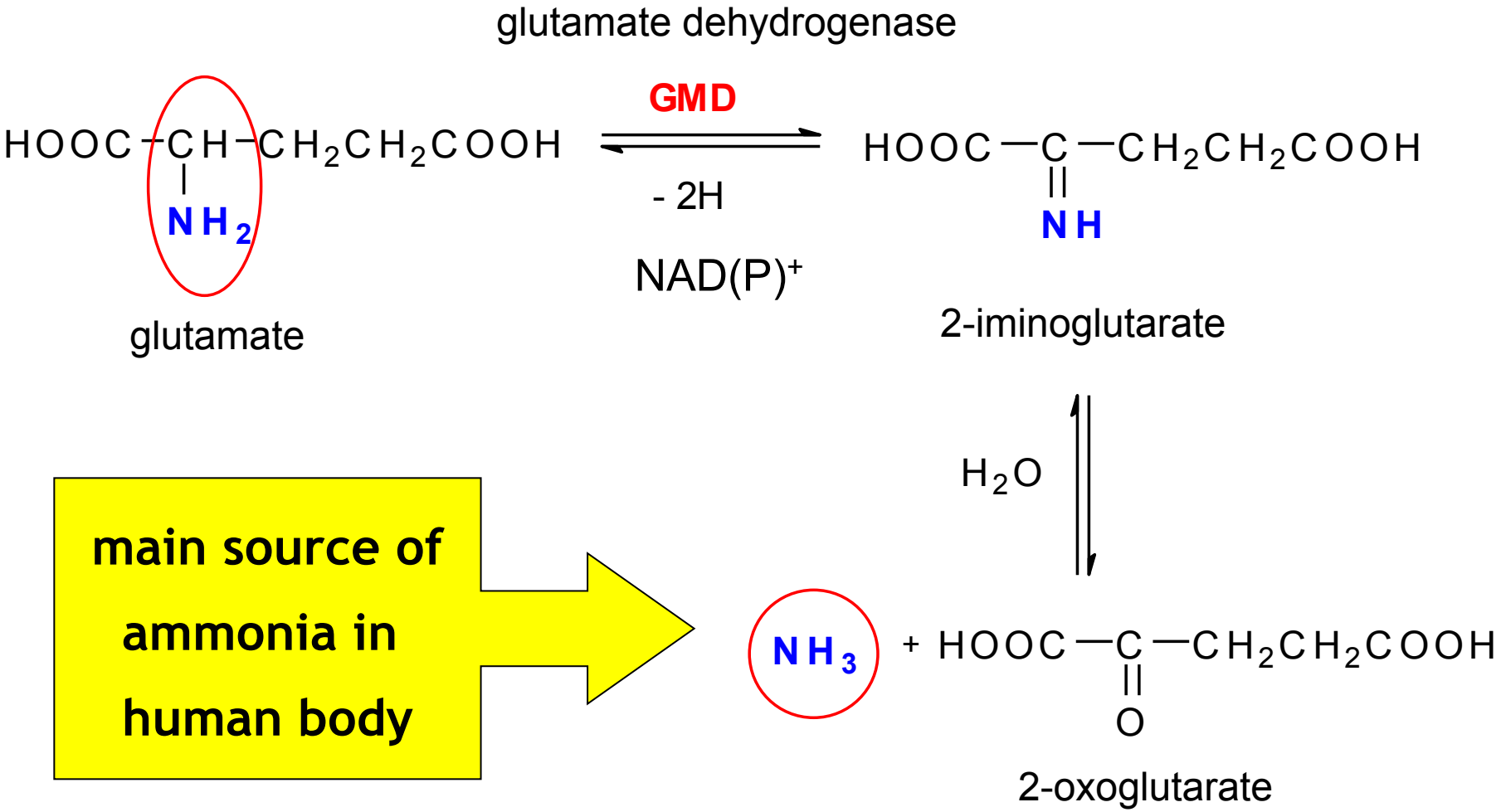
Transamination

- amino group is transferred from AA to 2-oxoglutarate
- enzyme: aminotransferase
- cofactor: pyridoxal phosphate
- amino acid gives the corresponding oxo acid
- the second product is glutamate

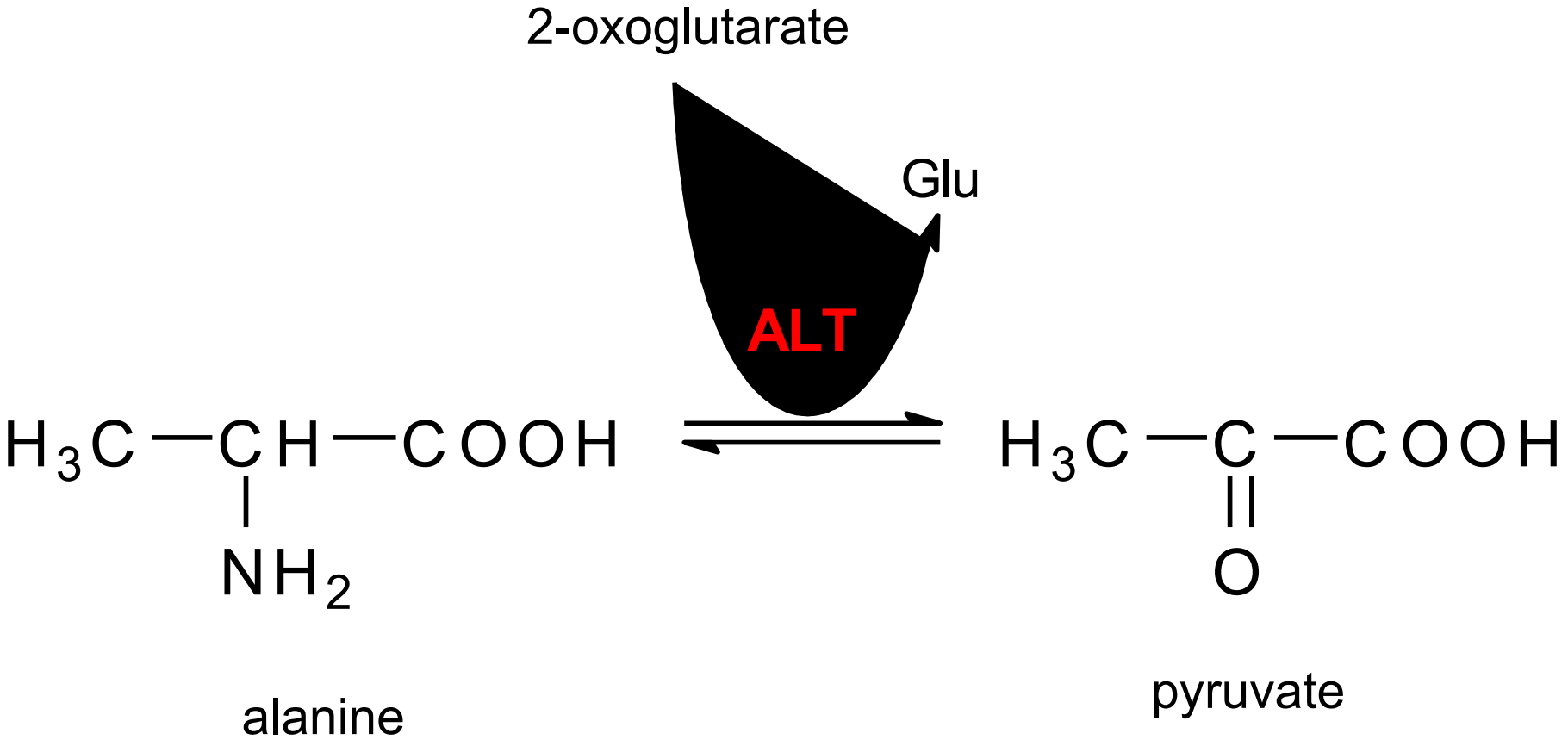
General scheme of transamination



Dehydrogenation deamination of glutamate

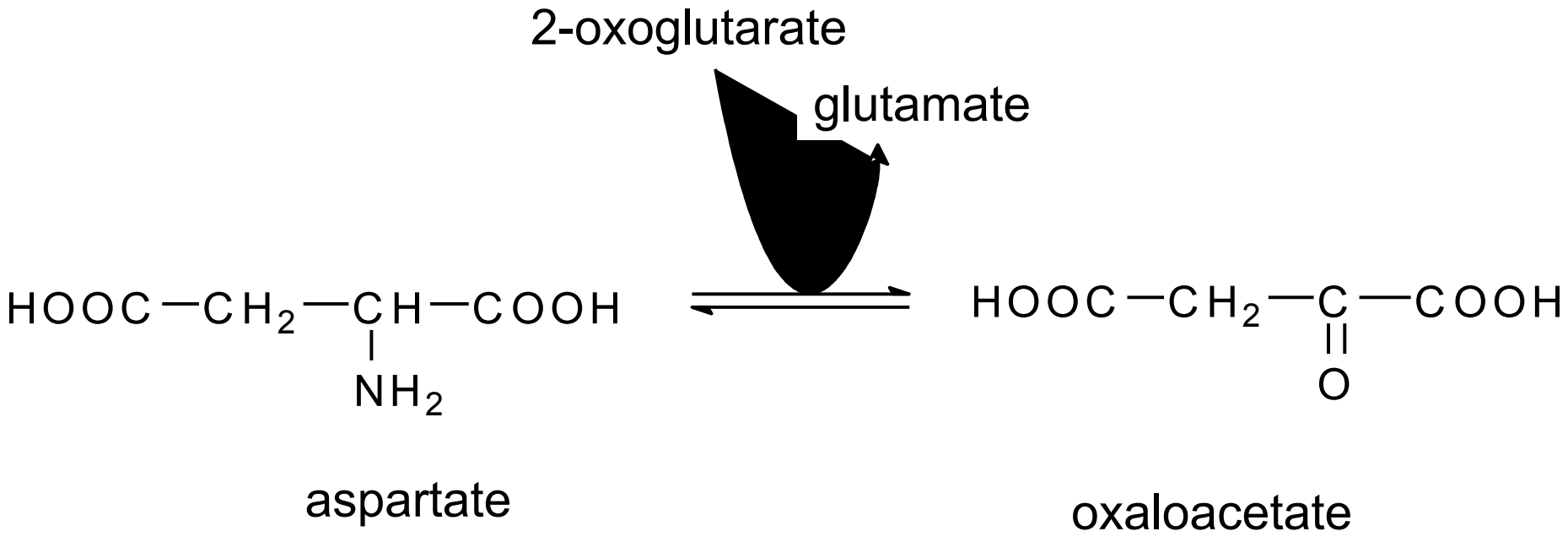


Transamination of alanine



ALT = alanine aminotransferase

Transamination of aspartate



Remember

pyruvate / lactate = redox pair

pyruvate / alanine = transamination pair

oxaloacetate / malate = redox pair

oxaloacetate / aspartate = transamination pair

Reactions of citric acid cycle

How is CO_2 made from acetyl-CoA?

Citric acid cycle

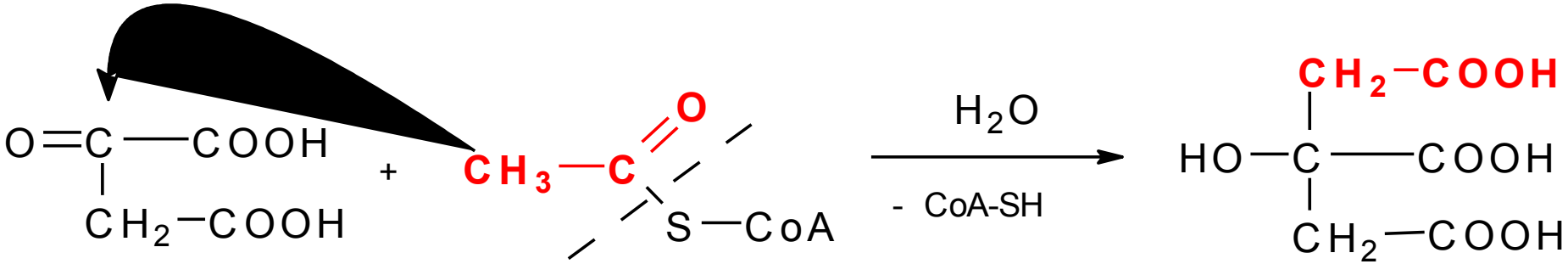
- Initial substrate: acetyl-CoA
- Three types of products:

  2× CO_2 → eliminated from body by lungs

  4× reduced cofactors → reoxidized in respiratory chain

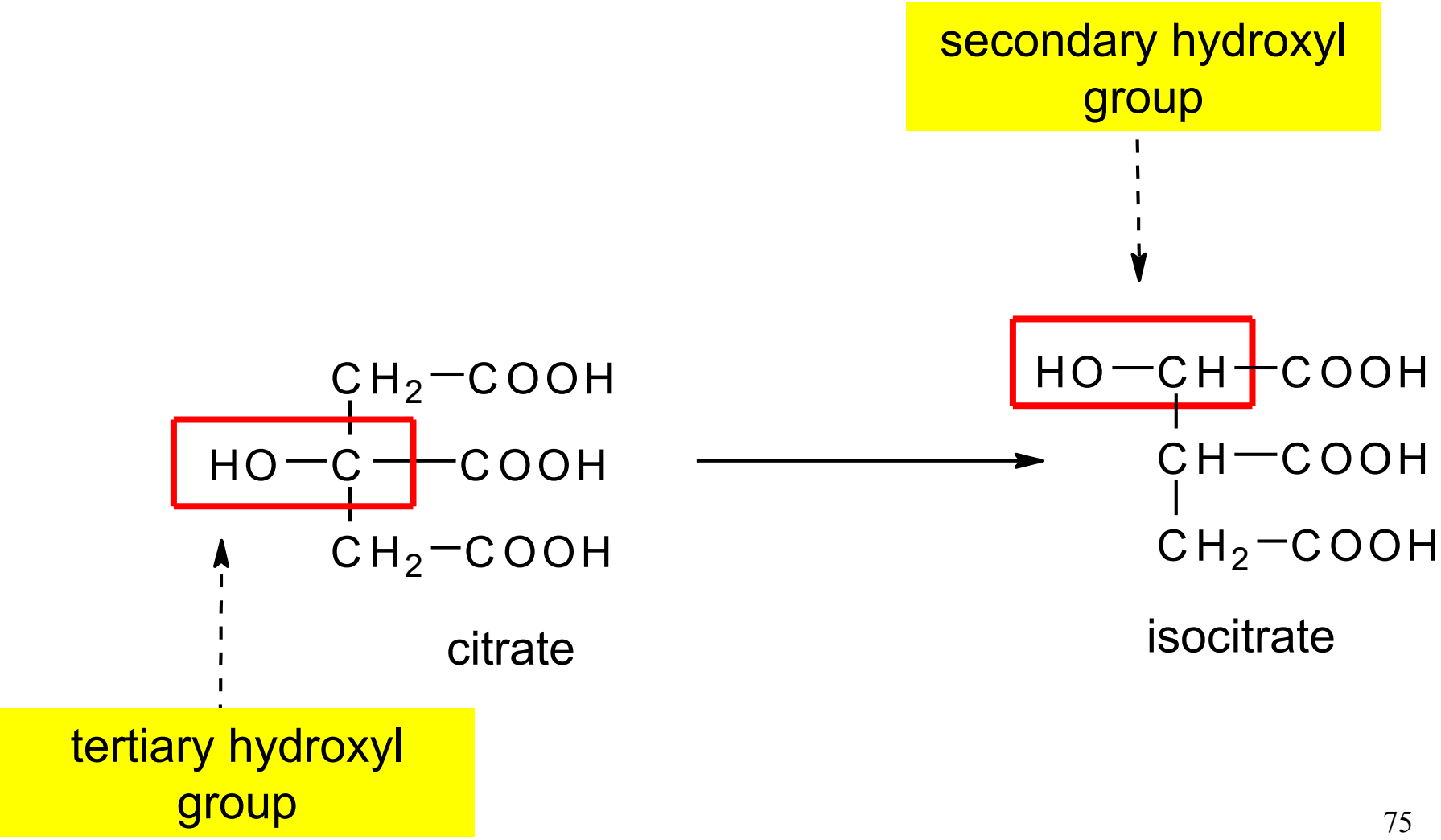
  1× GTP → substrate-level phosphorylation

Condensation of oxaloacetate with acetyl-CoA

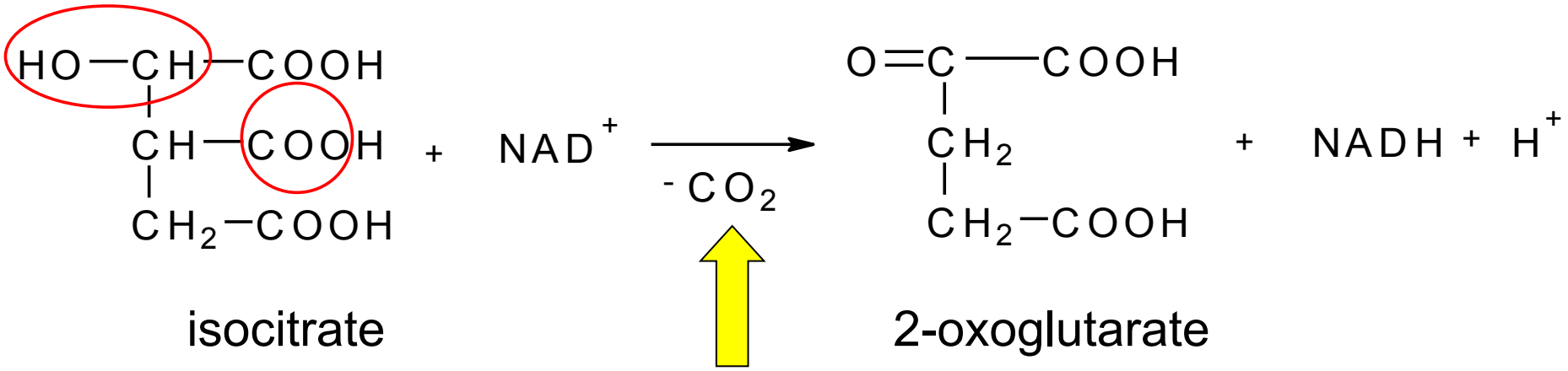


oxaloacetate acetyl-CoA citrate

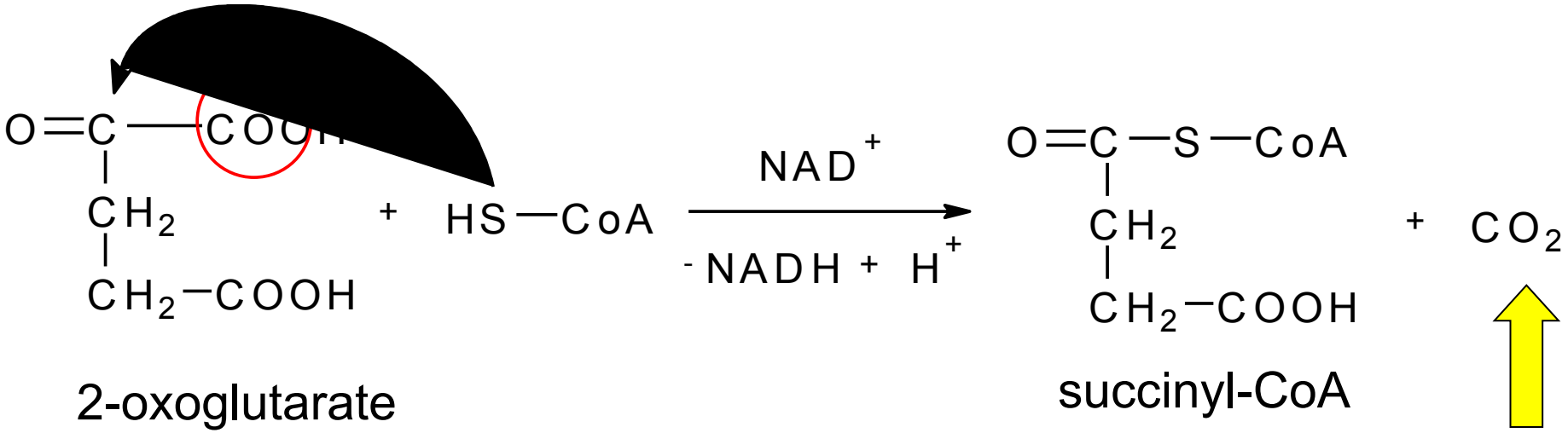
Isomeration of citrate to isocitrate



Decarboxylation and dehydrogenation of isocitrate



Decarboxylation and dehydrogenation of 2-oxoglutarate

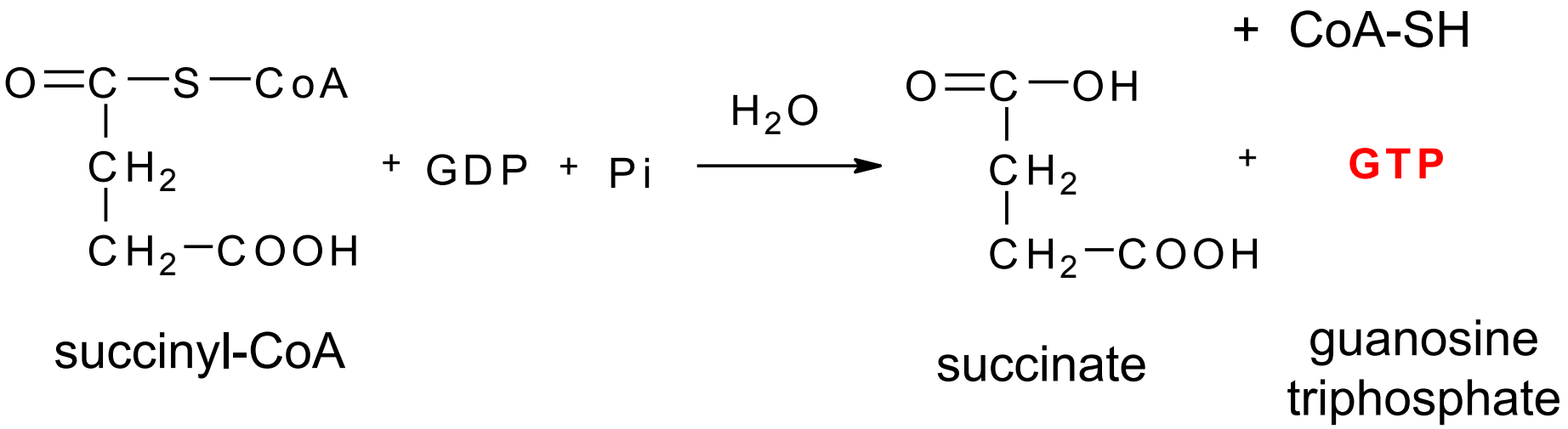


2-oxoglutarate

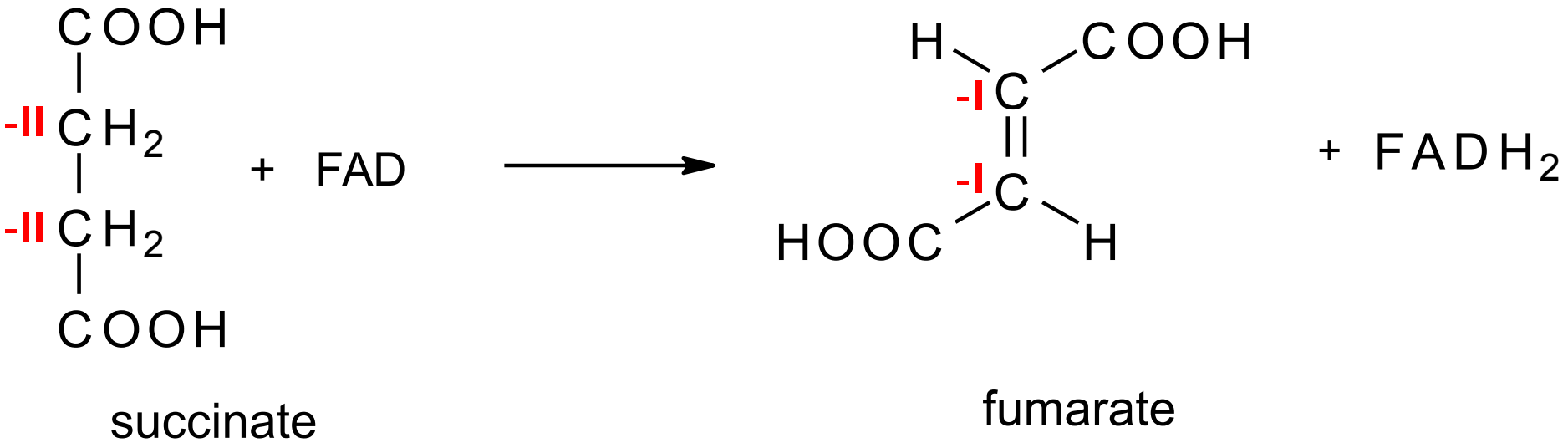
succinyl-CoA thioester

macroergic intermediate

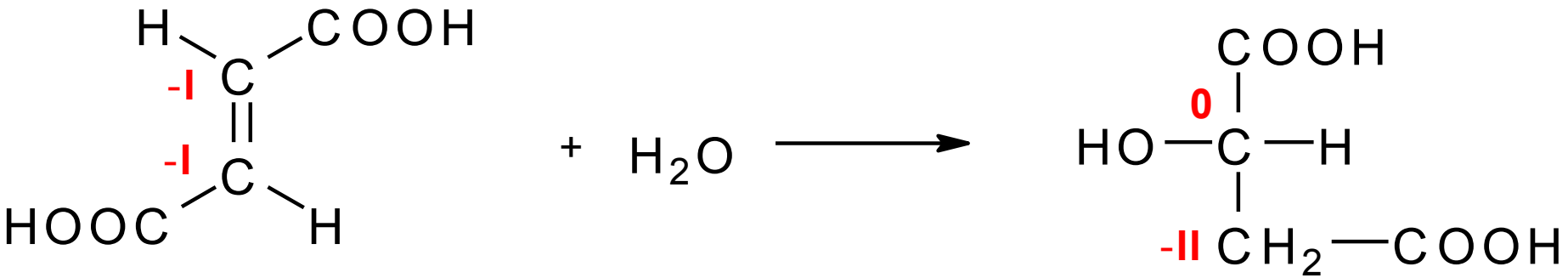
Substrate phosphorylation gives GTP



Dehydrogenation of succinate



Hydration of fumarate



fumarate

L-malate

$\Sigma = -II$

$\Sigma = -II$

Hydration is not a redox reaction

Dehydrogenation of L-malate