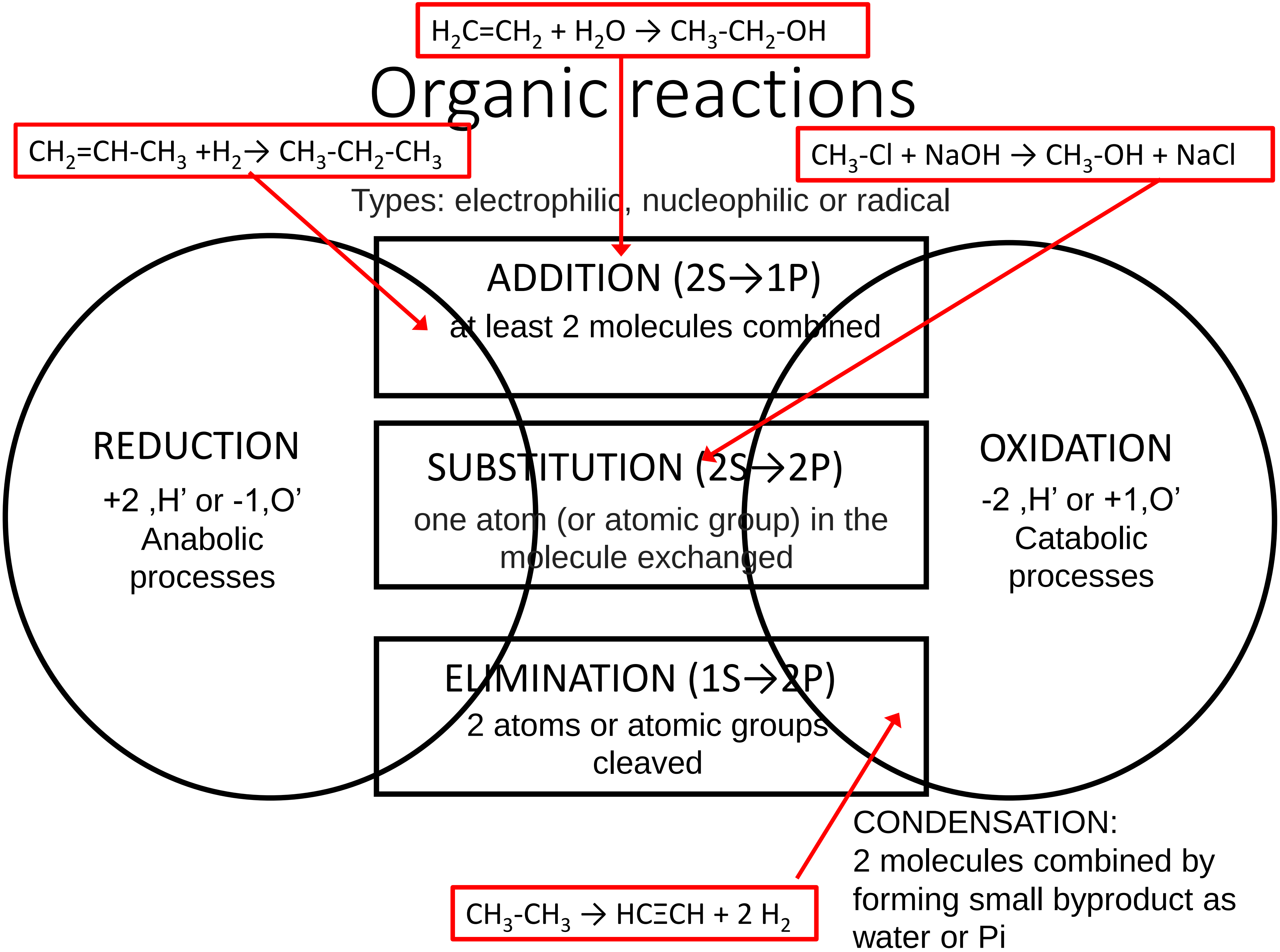
Organic molecules, structure and function

From the Chemistry Exam to the Final Exam in Biochemistry

Dr. Lengyel Anna

Organic reactions



$H_2C=CH_2 + H_2O \rightarrow CH_3\text{-}CH_2\text{-}OH$

$CH_2=CH\text{-}CH_3 + H_2 \rightarrow CH_3\text{-}CH_2\text{-}CH_3$

$CH_3\text{-}Cl + NaOH \rightarrow CH_3\text{-}OH + NaCl$

Types: electrophilic, nucleophilic or radical

ADDITION (2S→1P)

at least 2 molecules combined

SUBSTITUTION (2S→2P)

one atom (or atomic group) in the molecule exchanged

ELIMINATION (1S→2P)

2 atoms or atomic groups cleaved

REDUCTION

+2 ,H’ or -1,O’

Anabolic processes

OXIDATION

-2 ,H’ or +1,O’

Catabolic processes

CONDENSATION:

2 molecules combined by forming small byproduct as water or Pi

$CH_3\text{-}CH_3 \rightarrow HC\equiv CH + 2\ H_2$

Organic molecules

Alkanes: saturated aliphatic hydrocarbons C_nH_{2n+2}

- Substitution – e.g. with halogens $CH_4 + Cl_2 \rightarrow CH_3\text{-}Cl + HCl$
- Combustion – e.g. $C_3H_8 + 5\ O_2 \rightarrow 3\ CO_2 + 4\ H_2O$

Cycloalkanes: saturated hydrocarbons with at least one ring C_nH_{2n}

- Same behavior as alkanes, but addition is also possible e.g. with halogens

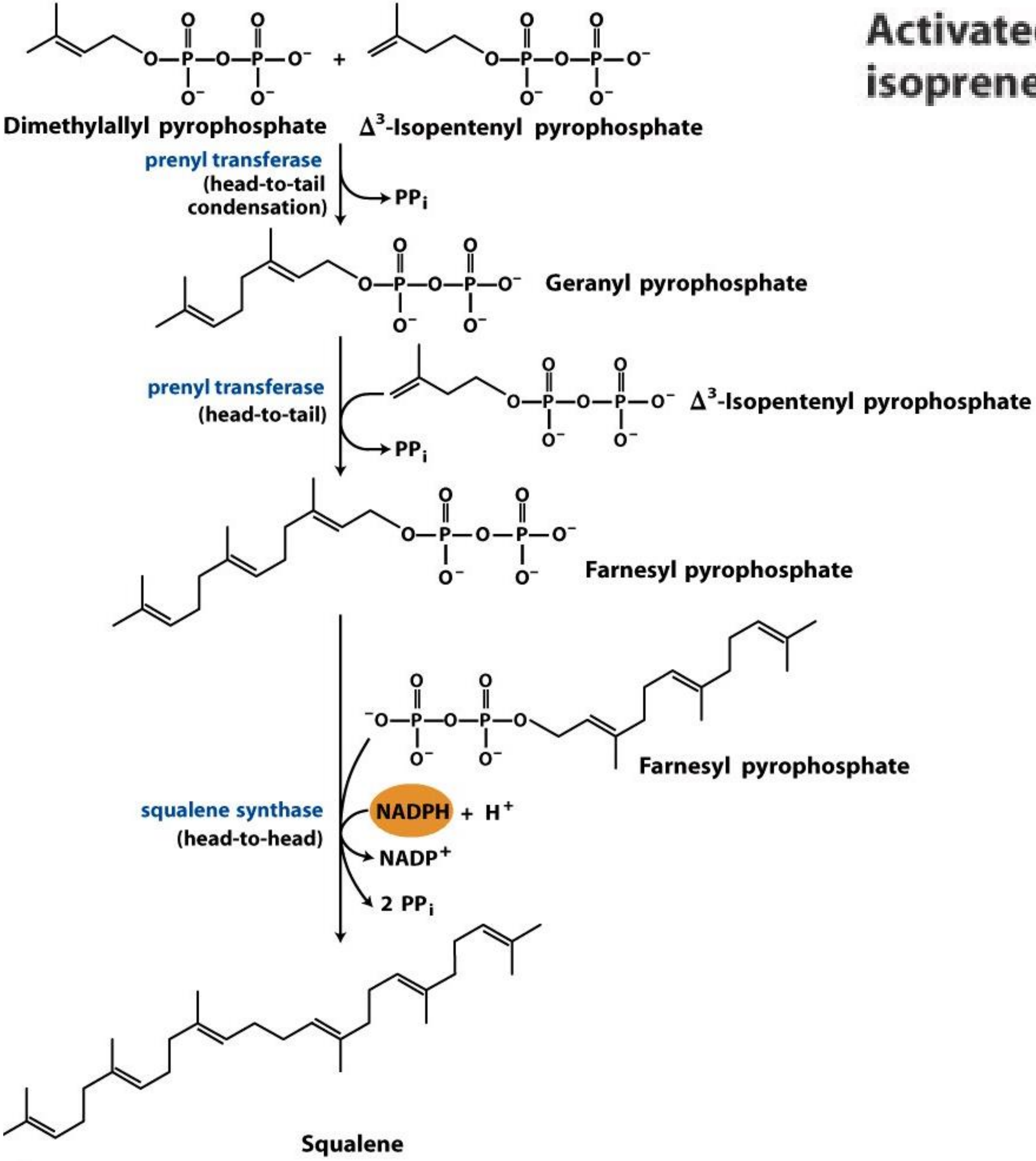
Alkenes, alkynes: unsaturated hydrocarbons containing C-C double bond C_nH_{2n} or C-C triple bond C_nH_{2n-2}

- Electrophilic addition (saturation) with hydrogen, water, hydrogen halides or halogens
- Oxidation with peroxide to epoxides, with permanganate to vicinal diols

Types: polyenes with cumulative, conjugated or isolated double bonds

Polymerization e.g. polyethylene or polymethyl methacrylate

Activated isoprenes



Dimethylallyl pyrophosphate + Δ^3-Isopentenyl pyrophosphate

prenyl transferase (head-to-tail condensation)

PP_i

Geranyl pyrophosphate

prenyl transferase (head-to-tail)

Δ^3-Isopentenyl pyrophosphate

PP_i

Farnesyl pyrophosphate

squalene synthase (head-to-head)

Farnesyl pyrophosphate

NADPH + H^+

$NADP^+$

2 PP_i

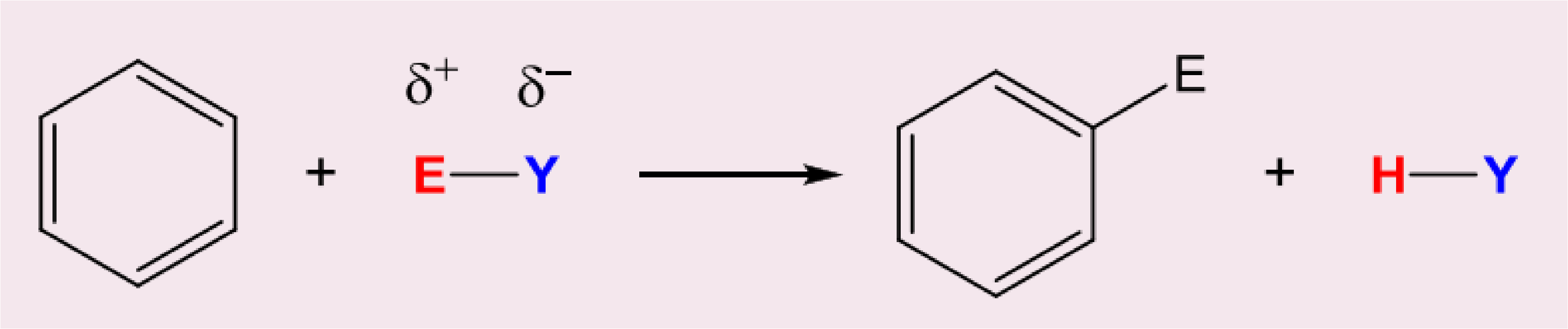
Squalene

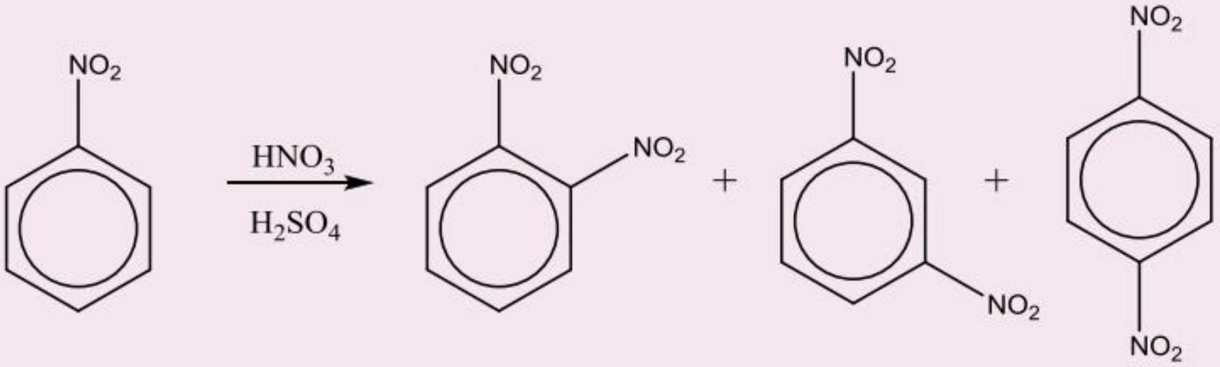
Organic molecules

Aromatic hydrocarbons: have planar ring with completely conjugated double bond system, the number of π electrons equal 4n+2 (n=0, 1, 2,…) following Hückel's rule

- Only electrophilic substitution is possible with catalysts

E.g. bromation (halogenation), nitration, sulphonation, alkylation, acylation





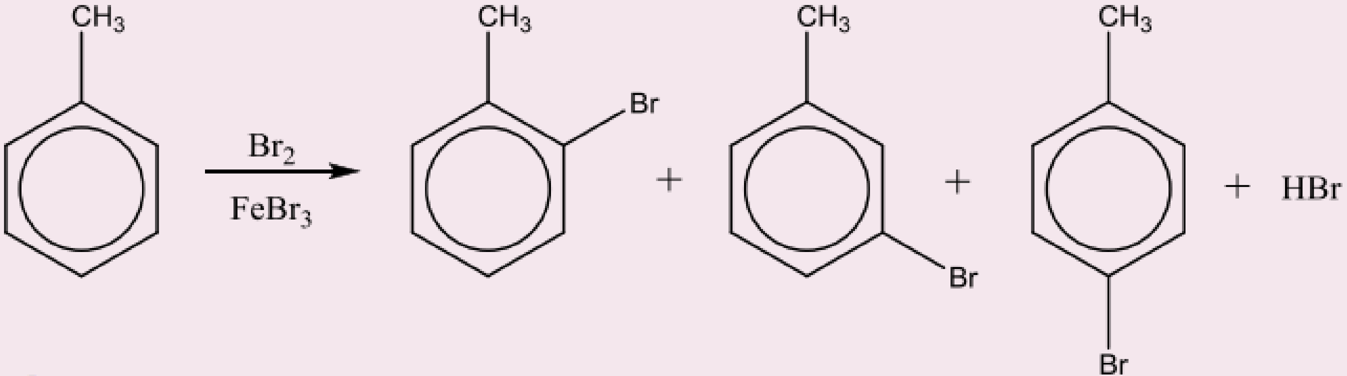
nitrobenzene

ortho- dinitrobenzene — 6 %

meta- — **93 %**

para- — 1 %

Nitro group: meta director



toluene

Methyl-group:

o- , p- director

(also amino groups)

ortho- bromotoluene — **40 %**

meta- — (in traces)

para- — **60 %**

Organic molecules

Hydroxy compounds

- **Alcohols:** hydroxy-derivatives of the hydrocarbons, the group is connected to a carbon with 4 single bonds
- **Enols:** the OH-group is connected to a carbon atom with a double bond (C=C)
- **Phenols:** the OH-group is connected directly to carbon which is part of an aromatic ring
- **Aromatic alcohols:** the OH-group is connected to a carbon with 4 single bonds but the molecule contains an aromatic ring as functional group

Organic molecules

Alcohols:

Primary – secondary – tertiary alcohols

Monovalent – Divalent (Diol) – Trivalent (Triol) - Polyol

Typical reactions:

Oxidation

ALCOHOL	Primary	Secondary	Tertiary
Mild oxidation	aldehyde	ketone	no reaction
Strong oxidation	carboxylic acid	no reaction	-

Elimination – with strong acids to form alkenes (Zaitsev’s rule: the most substituted double bond/product is favored; H is removed from the C which had originally less H)

Nucleophilic substitution e.g. with HCl

Ether formation R-O-R’

Organic molecules

<u>Thiols (mercaptans)</u>: R-SH (Sulfhydryl-group)

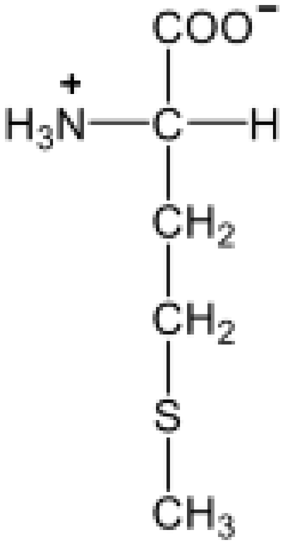
Similar to alcohols - Mild oxidation to disulfides

- Strong oxidation to sulfonic acids

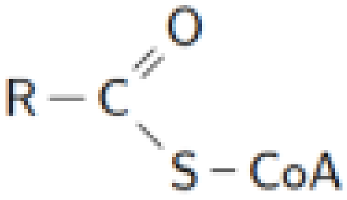
$$CH_3CH_2{-}SO_3H \xleftarrow[(HNO_3,\ H_2O_2)]{\text{Oxidation}} CH_3CH_2{-}SH \xrightarrow[(O_2,\ I_2)]{\text{Oxidation}} CH_3CH_2{-}S{-}S{-}CH_2CH_3$$

ethanesulfonic acid ethanethiol diethyl disulfide

Thioether e.g.



Thioester e.g.



Organic molecules

Oxo compounds

- **Aldehydes:** RCHO, formyl group CHO
- **Ketones:** RCOR’, carbonyl group C=O

Symmetric, asymmetric, aliphatic, aromatic, aralkylketones, endocyclic-exocyclic ketones

Reactions:

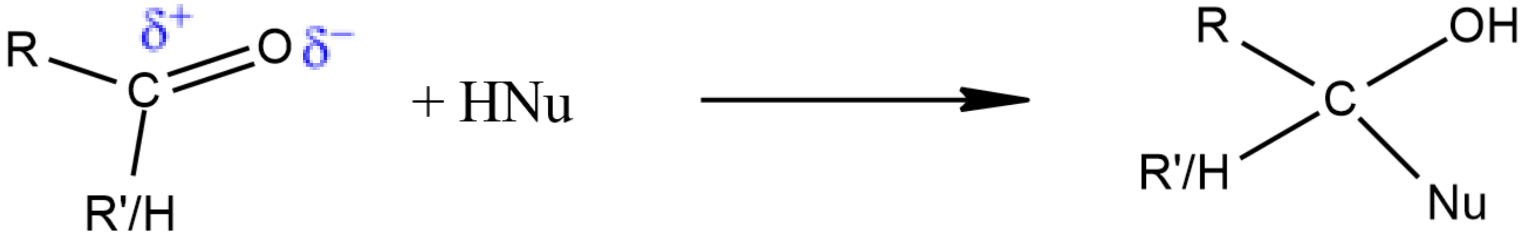
Oxidation: aldehydes to carboxylic acids, ketones Ø

Reduktion: aldehydes to primary alcohols, ketones to secondary alcohols

Nucleophilic addition with water, alcohols, amines

Organic molecules

Nucleophilic addition with water, alcohol, amine

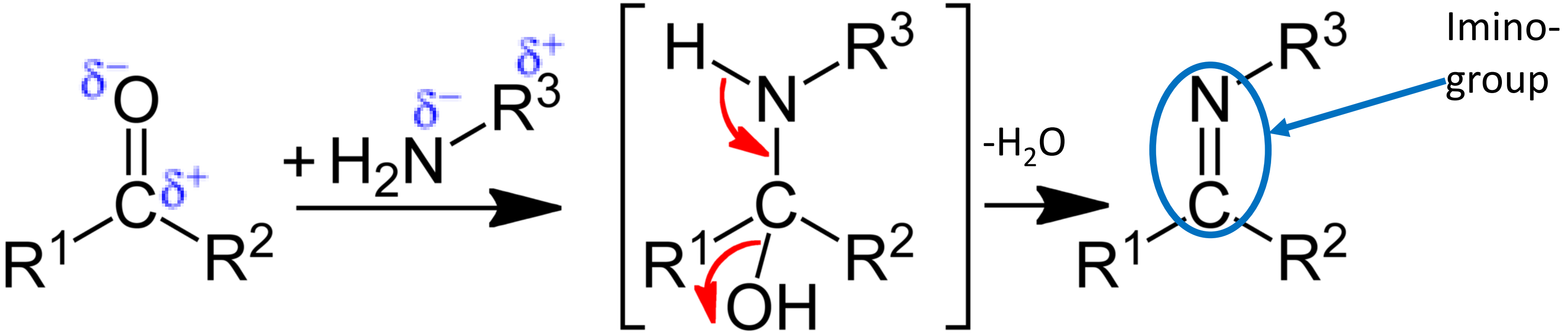


HNu= H-OH → unstable hydrate

HNu= R-OH → hemiacetal/hemiketal

+ Substitution with a 2nd alcohol → Acetal/Ketal +H_2O

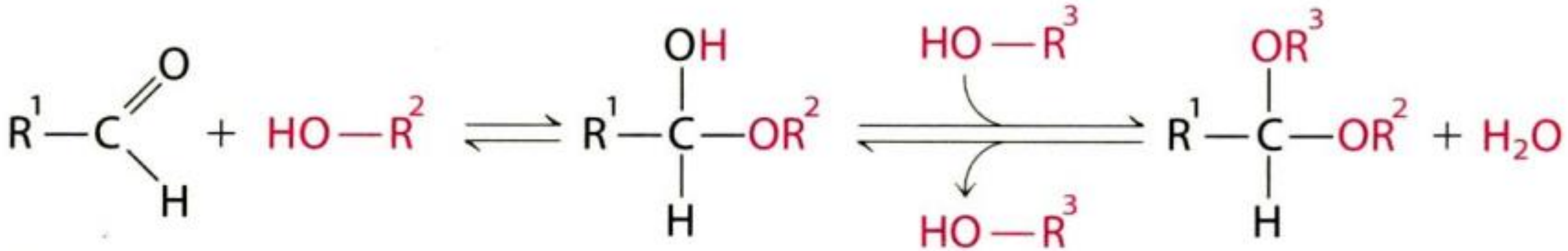
HNu= R-NH_2 → (unstable intermediate) Schiff base (=imine)



Question

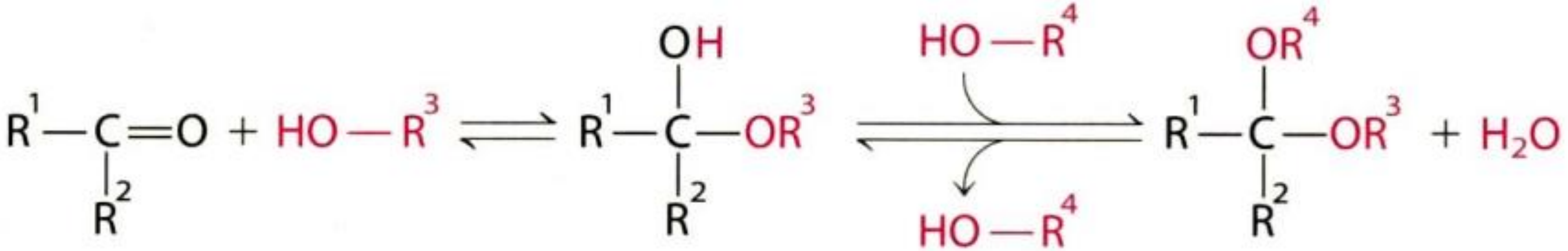
A glycoside is the carbohydrate form of an

a. ether
b. acetal
c. aglycone
d. alcohol



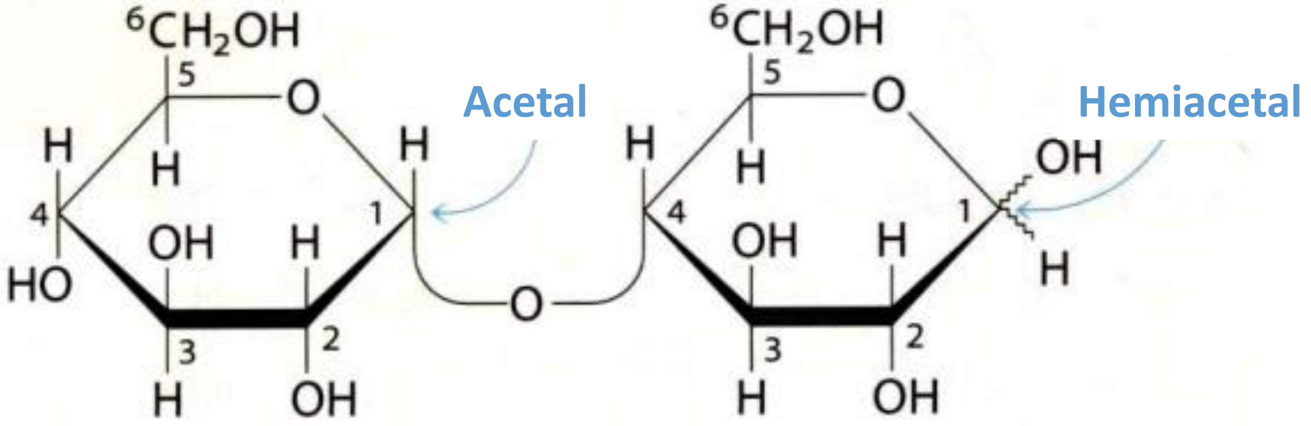
$$R^1-\overset{\displaystyle O}{\overset{\|}{C}}-H + HO-R^2 \rightleftharpoons R^1-\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}}-OR^2 \underset{HO-R^3}{\overset{HO-R^3}{\rightleftharpoons}} R^1-\overset{\displaystyle OR^3}{\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}}-OR^2 + H_2O$$

Aldehyde **Alcohol** **Hemiacetal** **Acetal**



$$R^1-\underset{\underset{\displaystyle R^2}{|}}{C}=O + HO-R^3 \rightleftharpoons R^1-\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle R^2}{|}}{C}}}-OR^3 \underset{HO-R^4}{\overset{HO-R^4}{\rightleftharpoons}} R^1-\overset{\displaystyle OR^4}{\overset{|}{\underset{\underset{\displaystyle R^2}{|}}{C}}}-OR^3 + H_2O$$

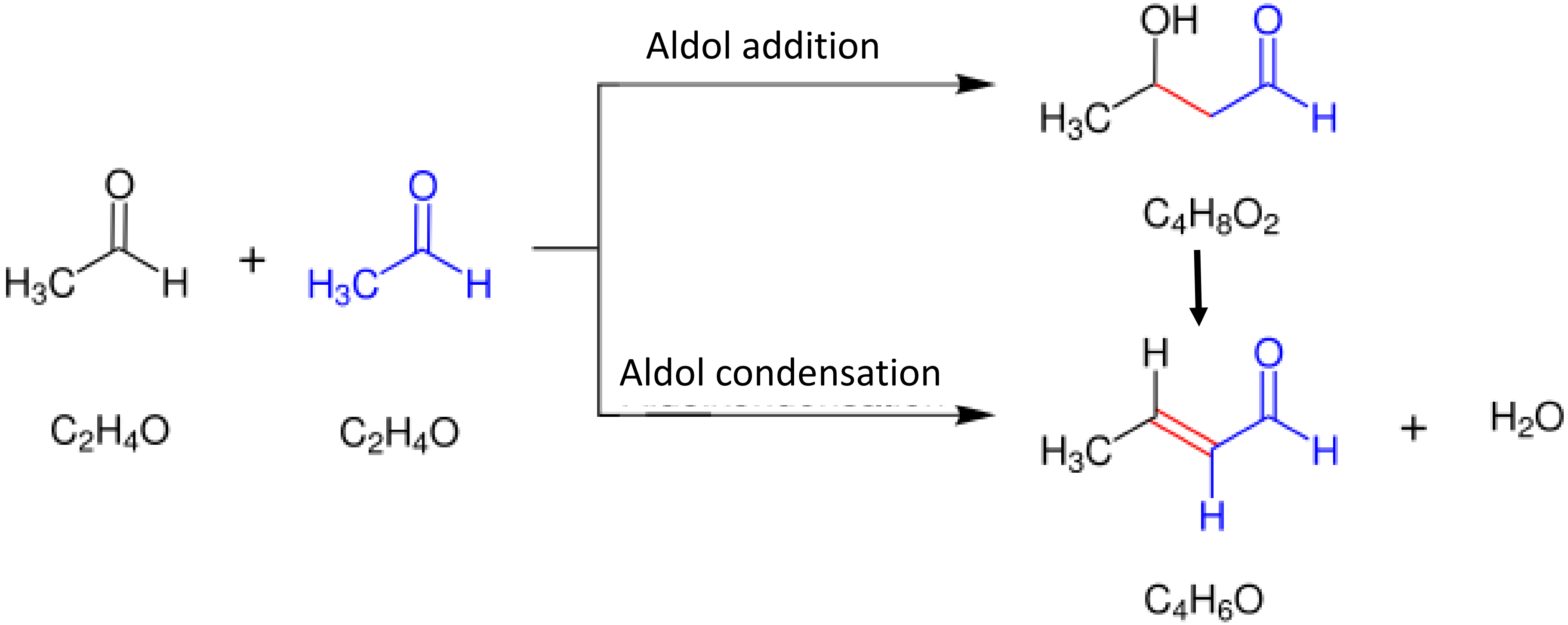
Ketone **Alcohol** **Hemiketal** **Ketal**



Maltose
α-D-Glucopyranosyl-(1→4)-D-glucopyranose

Aldol reaction

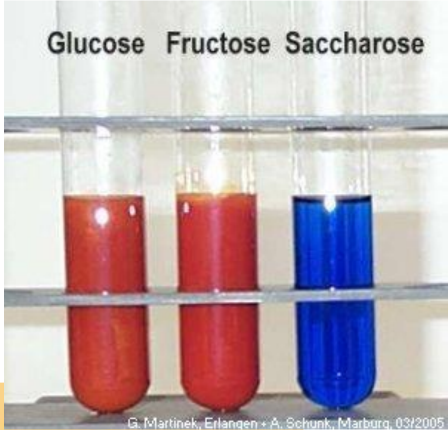
Aldol dimerization or aldol addition: in a basic solution a deprotonated aldehyde serves as a nucleophile and attacks an other aldehyde as an electrophile



Aldol addition

Aldol condensation

Fehling’s test

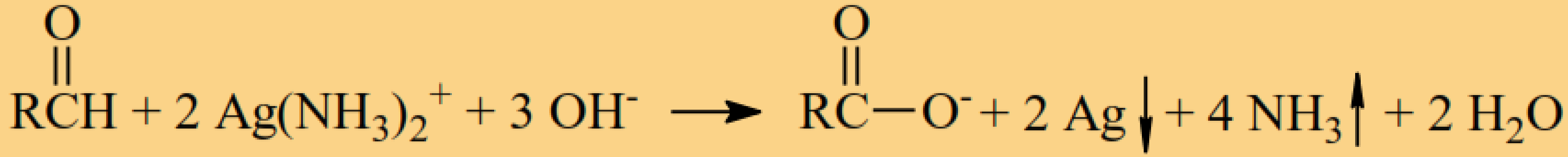


G. Martinek, Erlangen + A. Schunk, Marburg, 03/2005

$$2\,Cu^{2+} + R\text{—}CHO + 5\,OH^- = Cu_2O + RCOO^- + 3\,H_2O$$

aldehyde **carboxylic acid**

Tollens’s silver mirror test

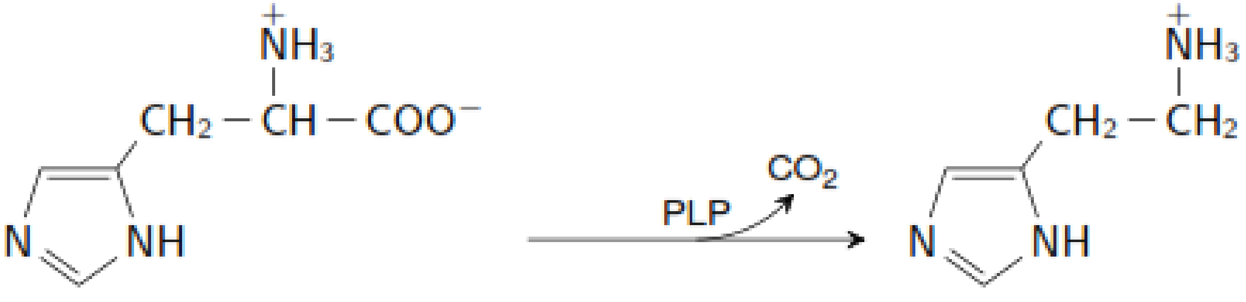


$$\overset{\overset{\displaystyle O}{\|}}{RCH} + 2\,Ag(NH_3)_2^+ + 3\,OH^- \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}\text{—}O^- + 2\,Ag\downarrow + 4\,NH_3\uparrow + 2\,H_2O$$

aldehyde **carboxylic acid**

Organic molecules – carboxylic acids

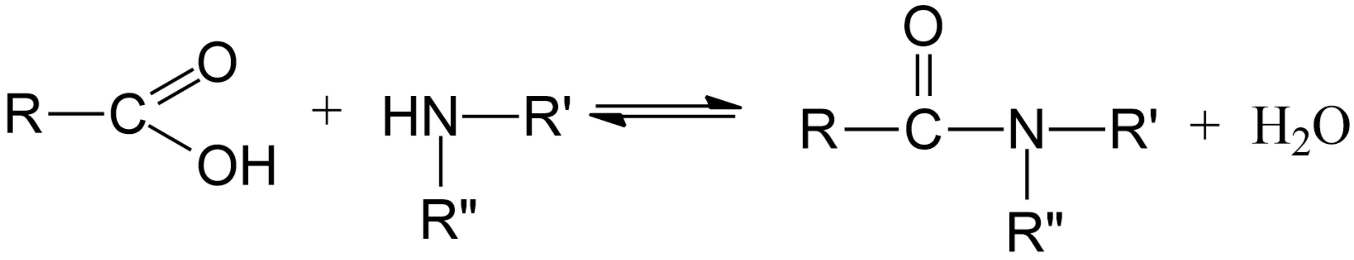
- R-COOH, carboxyl group
- Acidic dissociation, salt formation
- Decarboxylation

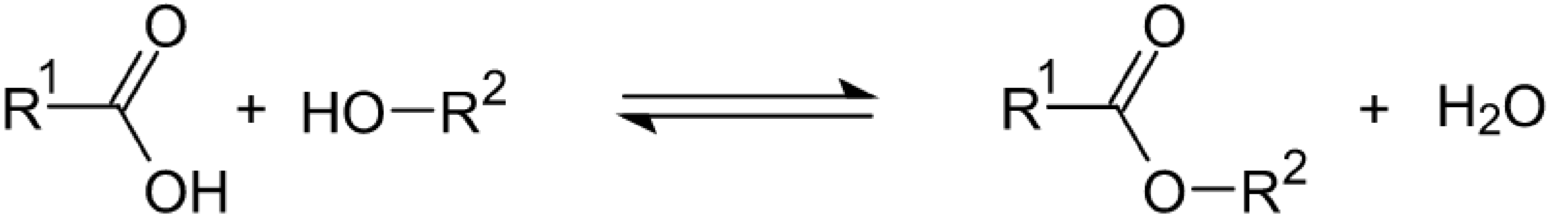


Histidine

Histamine

- Reduktion
- Nucleophilic substitution – amide or ester formation

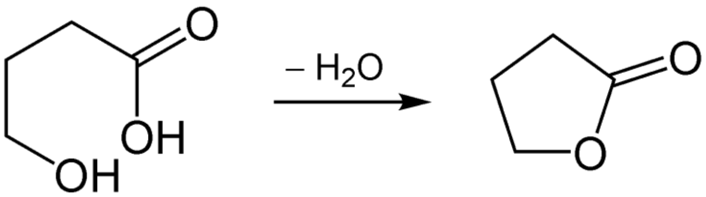


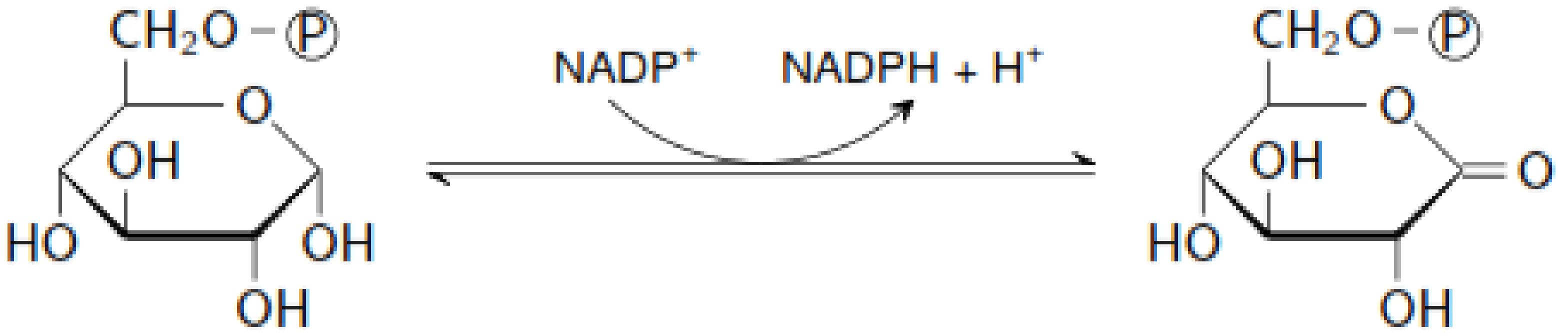


Organic molecules – carboxylic acids

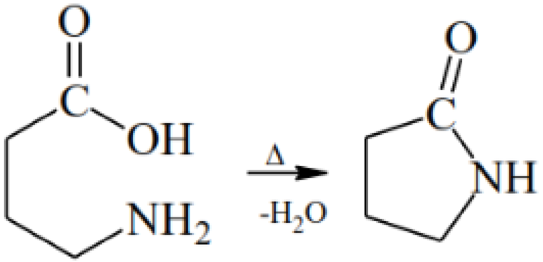
Special intramolecular reactions:

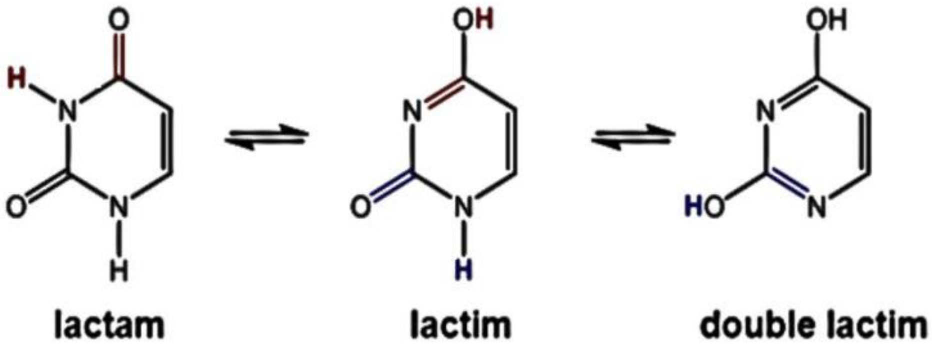
- Lactone formation (cyclic ester)

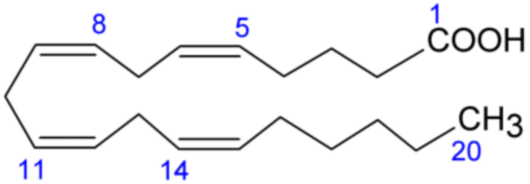




- Lactam formation (cyclic amide)





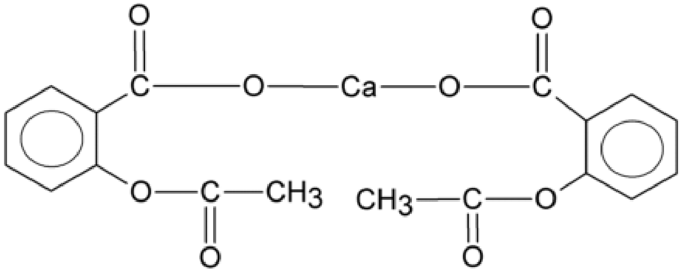


Phospholipids

Steroids

Steroids inhibit: Prostaglandins
Tromboxans
Leukotriens

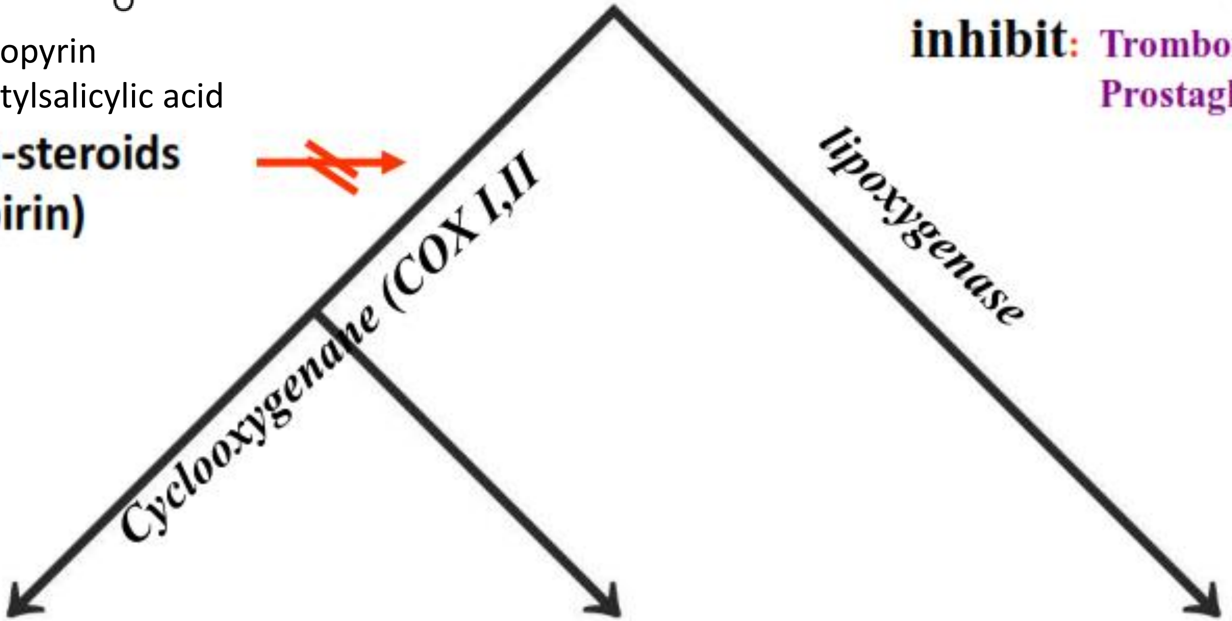
Arachidonate (20:4)



Kalmopyrin
Ca-salt of acetylsalicylic acid

Non-steroids (aspirin)

Non-steroids (aspirin) inhibit: Tromboxans
Prostaglandins



Prostaglandins **Thromboxanes** **Leukotrienes**

Organic molecules

<u>**Amines:**</u> derivatives of ammonia

- primary amine $R\text{-}NH_2$, primary amino group $–NH_2$
- secondary amine R-NH-R, secondary amino group –NHR
- tertiary amine NR_3, tertiary amino group $–NR_2$
- quaternary ammonium salts NR_4^+, quaternary ammonium group $–NR_3^+$

R = aliphatic or aromatic amines

Alkylation with alkyl halogenides

Acylation to amides with esters, anhydrides or acyl halides

Organic molecules

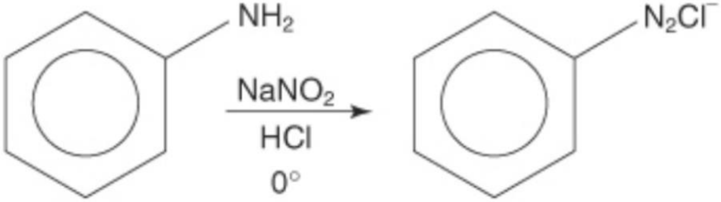
Reaction with nitrous acid:

With primary amines: an alcohol and nitrogen gas are formed

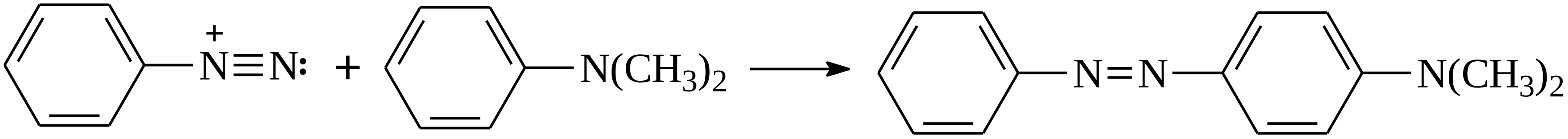
With secondary amines: nitrosoamines are formed, tertiary Ø

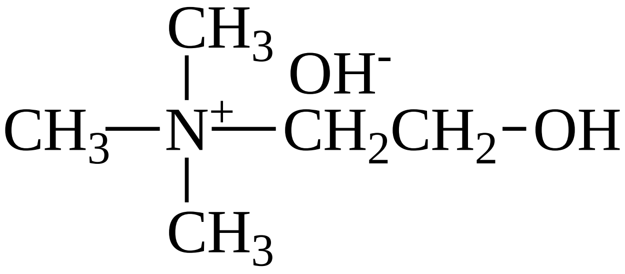
$$CH_3-NH-CH_3 \xrightarrow[HCl]{NaNO_2} (CH_3)_2-N-N=O$$

With primary aromatic amines: aryldiazonium salts are formed (Diazotation)

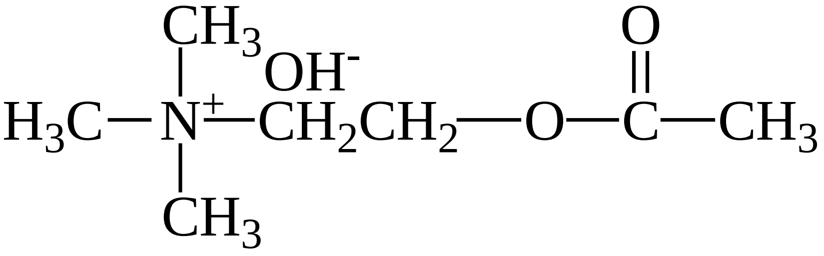


Aryldiazonium ions react with aromatic rings to form azodies (diazo coupling)

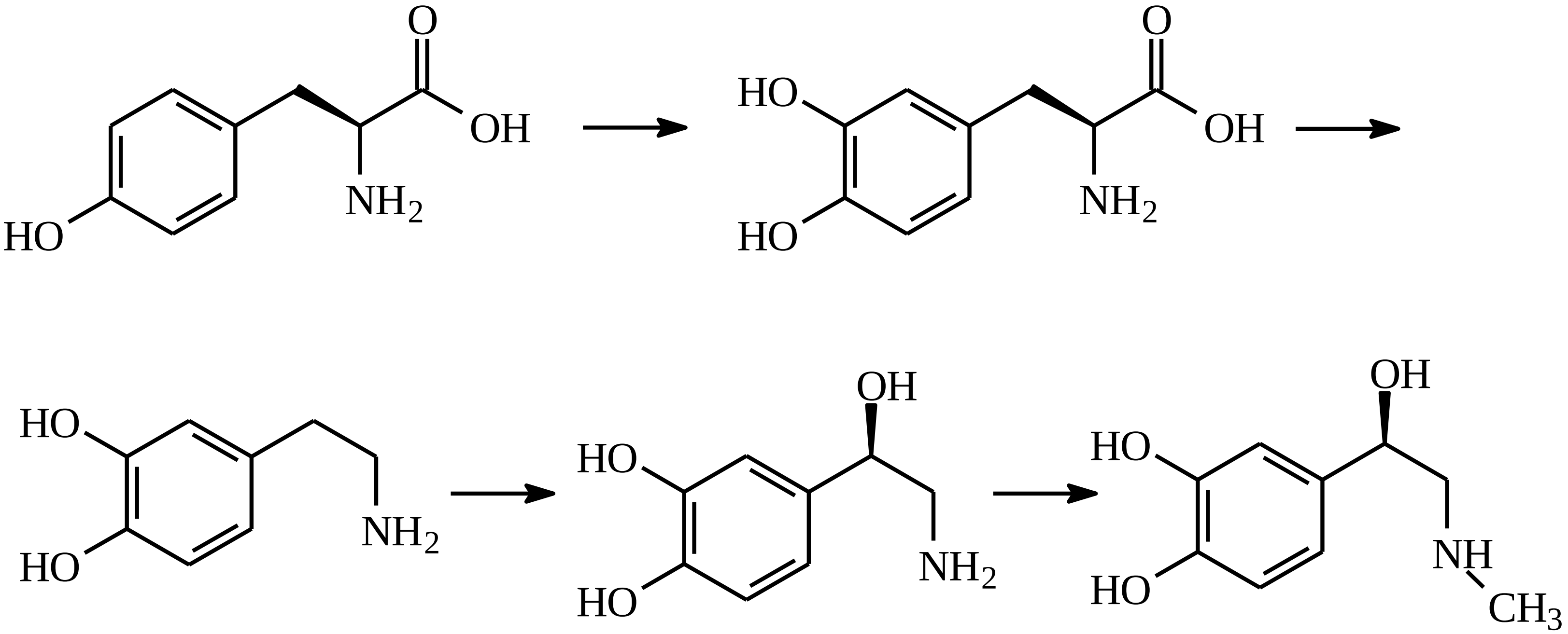


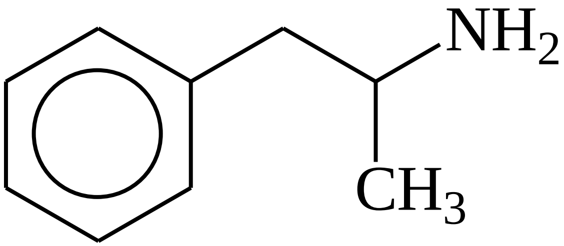


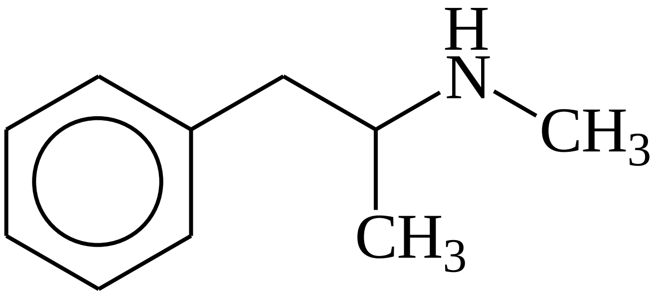
$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{N^+}}-CH_2CH_2-OH \quad OH^-$$



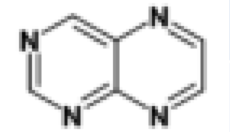
$$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{N^+}}-CH_2CH_2-O-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 \quad OH^-$$







<u>**Heterocyclic compounds:**</u> cyclic chemicals with ring system containing at least 2 different elements, mostly O, S, and N beside C atoms.

NAME	STRUCTURE	PROPERTIES	IMPORTANT PART OF…
Pyrrole		Aromatic, weak acid, planar 5 ring	Porphynes, porphyrins, hemoglobin, B12, bilirubin, cytochromes
Pyrrolidine		Saturated, weak base	Nicotine, proline, hydroxyproline
		Pyrrole+benzene ring, aromatic weak acid	Tryptophan, skatole, serotonin, tryptamine
		Aromatic, weak base, planar 6 ring	Nicotine, B6, B3, nicotinic acid, NAD$^+$
Pyrimidine		Aromatic, weak base	B1, bases in DNA/RNA (C,T,U), barbiturates
		Aromatic, amphoteric planar 5 ring	Histidine, histamine
Purine		Pyrimidine+imidazole, aromatic, amphoteric	Bases in DNA/RNA(A,G) uric acid, caffeine
		Aromatic, weak base	B2, folic acid,

ISOMERS

Racemic mixture:
equal amounts of left- and right-handed enantiomers of a chiral molecule

CONSTITUTIONAL ISOMERS (Structural isomers)

- Different order of atoms
- Different structural formula
- Usually NOT interconvertible

(Except: cyclic-open form of sugars, rearrangement of vinyl-alcohol to acetaldehyde)

- Different chemical/physical properties

Functional (group) isomers

Chain isomers

Position (Substitutional) isomers

Valence isomers

Tautomers (oxo-enol isomers)

STEREOISOMERS

Same structure, different spatial arrangement

CONFORMATIONAL ISOMERS

- Different spatial arrangement due to rotation around σ bond
- In cyclic molecules partial rotation, substituents in equatorial position more stable
- ALL cases interconvertible
- Always a mixture of different isomers

Eclipsed vs Staggered

Chair vs Boat

CONFIGURATIONAL ISOMERS

GEOMETRICAL ISOMERS

- Specific reference plane in the molecular structure determined by a double bond or a ring
- NOT interconvertible
- Different chemical/physical properties

Cis (E) Trans (Z)

OPTICAL ISOMERS

1 or more chiral C atoms

ENANTIOMERS

- 1 or more chiral C atoms, and for ALL of them they can be mirrored
- Non-identical mirror images
- NOT interconvertible
- Same chemical/physical properties, only different in polarized light

DIASTEREOMERS

- 1 or more chiral C atoms, BUT mirroring is NOT possible for all of them only for 1 or 2
- Same chemical properties, different physical properties due to different crystal structure
- Epimers are diastereomers with several chiral C atoms but only 1 is different

CONSTITUTION:
connection order of atoms

CONFORMATION:
spatial arrangement of a molecule

CONFIGURATION:
spatial orientation of the different atoms/functional groups attached to the same one atom

Question

Which of the following physical properties differ for each of a pair of enantiomers?

a. solubility in ethanol

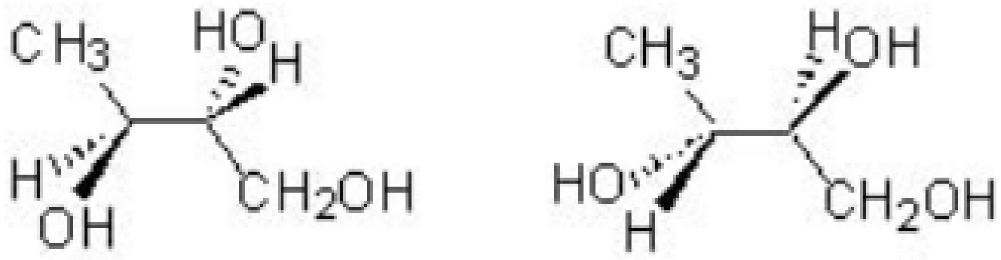
b. direction of rotation of plane-polarized light

c. boiling point and melting point

d. index of refraction

Question

Determine the relationship between the two molecules shown.



a. constitutional isomers

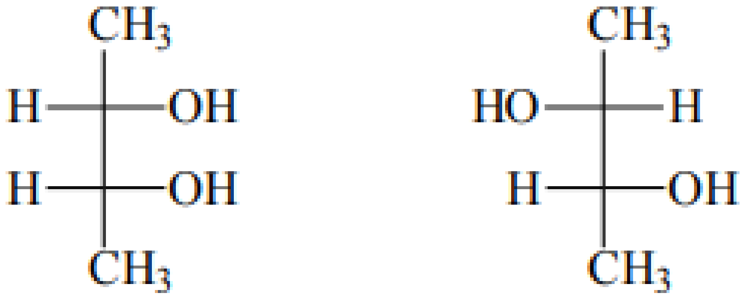
b. enantiomers

c. diastereomers

d. identical molecules

Question

The relationship between the following two structures is:



(A) enantiomers

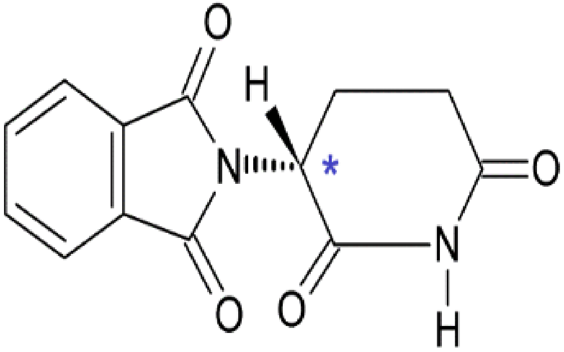
(B) diastereomers

(C) structural isomers

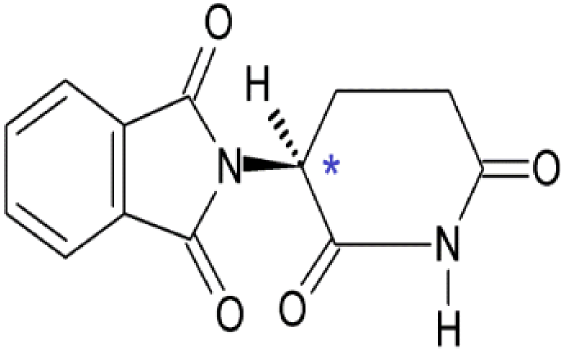
(D) identical

(E) none of the above

The Contergan scandal



R(+)-thalidomide = R(+) Contergan

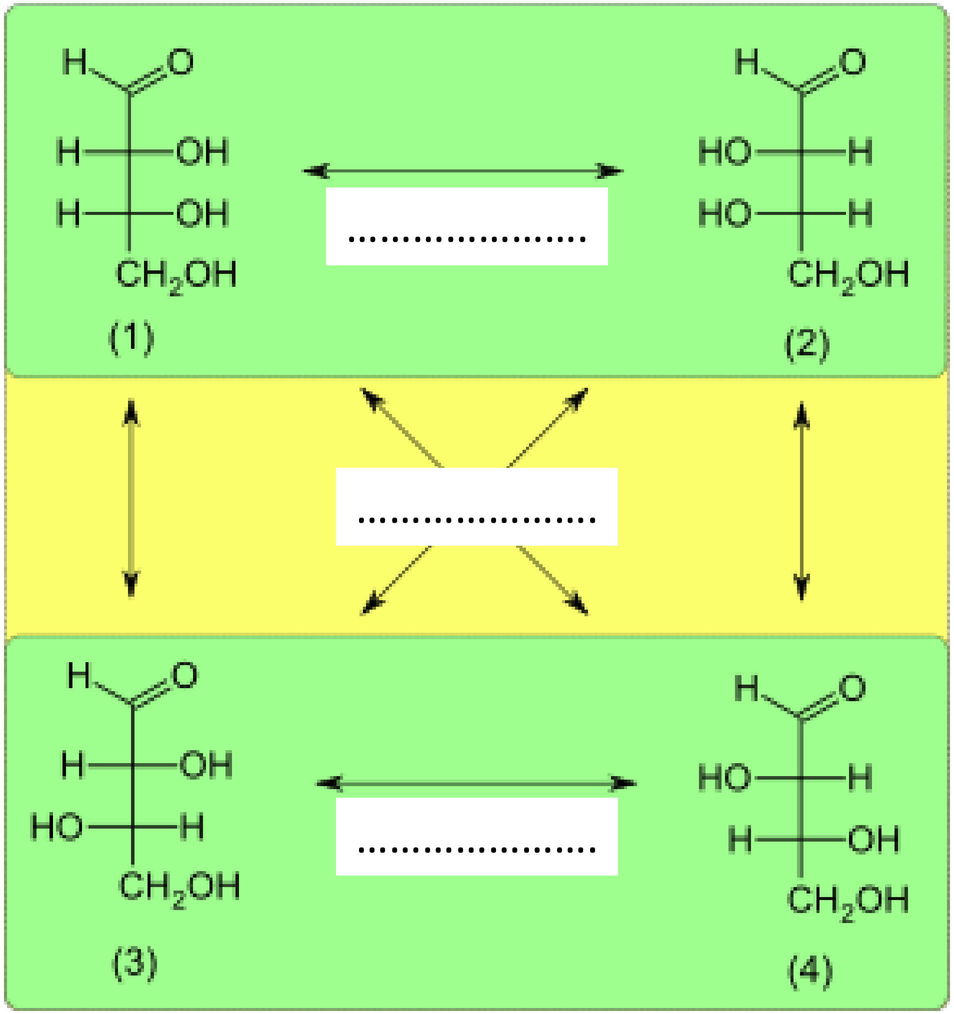


S(-)-thalidomide = S(-) Contergan

Thalidomide is a good tranquilizer and sleep aid. It was first marketed in 1957 in West Germany under the trade name Contergan. Primarily prescribed as a sedative or hypnotic, later it was used to treat nausea and to alleviate morning sickness in pregnant women. Shortly after the drug was sold thousands of infants were born with phocomelia (malformation of the limbs).Thalidomide is provided as a racemic mixture of two enantiomers: R(+)-thalidomide is the bioactive form of the molecule, S(-)-thalidomide causes the severe (teratogenic) side effects. Though the enantiomers could be separated, this couldn’t solve the problem, because the body converts each enantiomer into the other through mechanisms that are not well understood, so the teratogenic compound remains always present. In 1961 it was taken off the market due to massive pressure from the press and public.

Today, thalidomide is used mainly as a treatment of certain cancers (multiple myeloma) and of a complication of leprosy.

Question

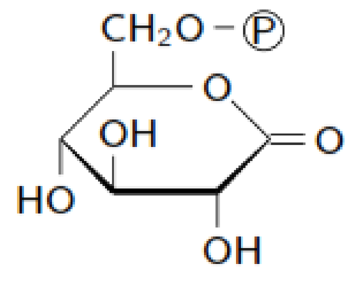
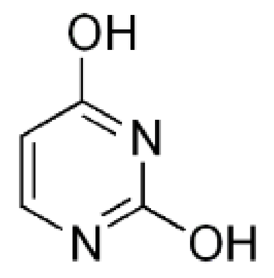
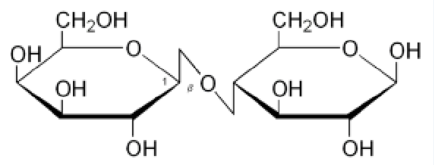
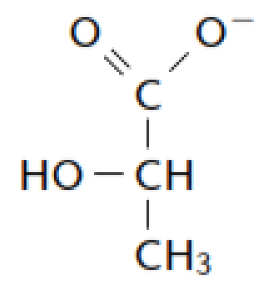
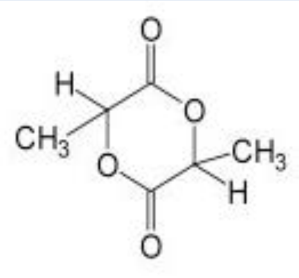
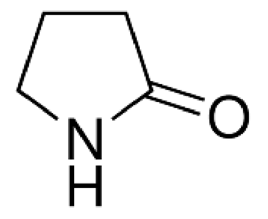

H
O
H
OH
H
OH
CH₂OH
(1)
....
H
O
HO
H
HO
H
CH₂OH
(2)
....
H
O
H
OH
HO
H
CH₂OH
(3)
....
H
O
HO
H
H
OH
CH₂OH
(4)

Form pairs!

Tautomer of Lactam with –N=C–OH group

Sugar in milk

Cyclic intramolecular ester

	A	B	C	D	E
1	LACTASE		LACTAM		LACTID
2			Enzyme	LACTONE	
3	LACTATE	LACTOSE		LACTIM	

Cyclic intramolecular amide

Salt of lactic acid

Cyclic intramolecular diester

Milk sugar cleaving enzyme

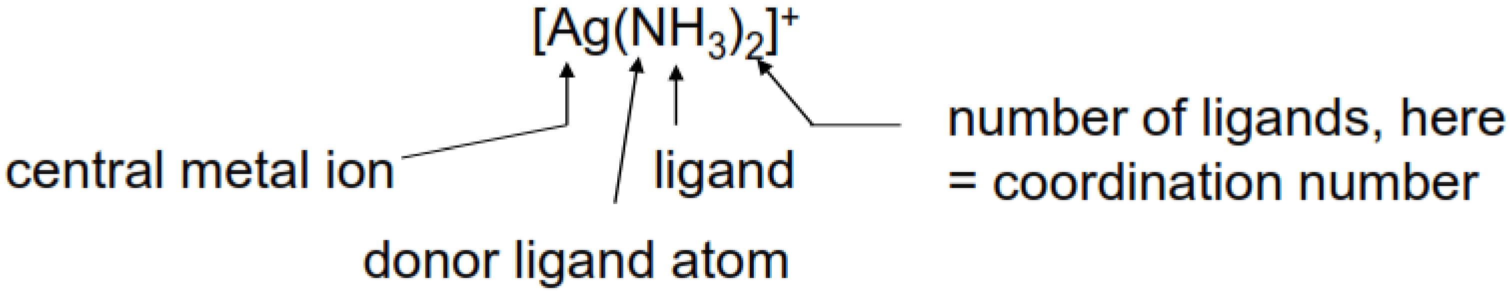
Complexes

Definition: Compounds in which a metal atom or ion is surrounded by a number of oppositely (negatively) charged ions or by neutral molecules (called ligands).

Each ligand possesses lone electron pairs (Lewis base) available for donation to vacant orbitals of the metal atom or ion (Lewis acid).

Coordination number: the number of ligand donor atoms or coordinative bonds.

Chelating agents: ligands forming at least 2 coordinative bonds with the same central metal.



$[Ag(NH_3)_2]^+$

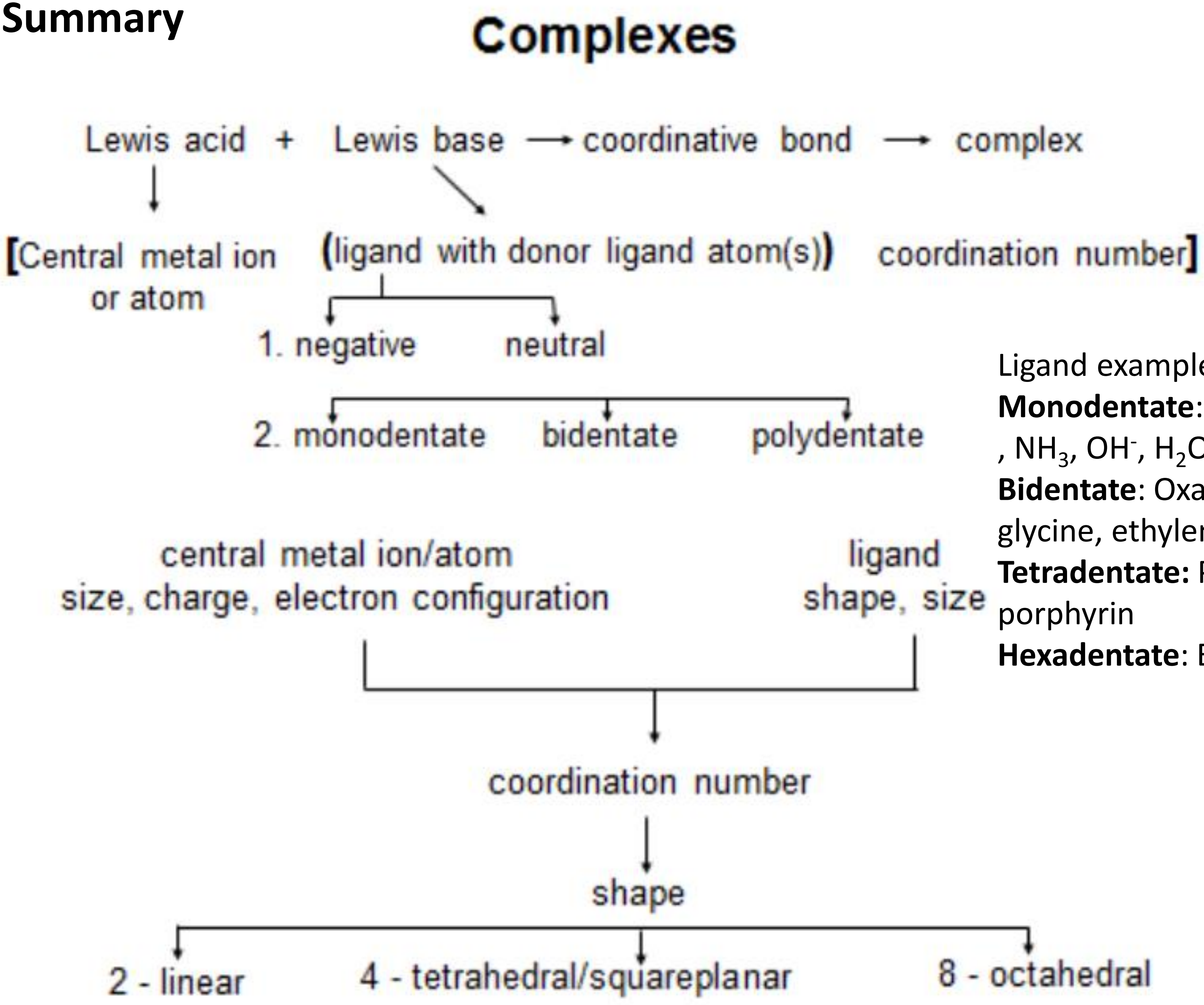
central metal ion

ligand

number of ligands, here = coordination number

donor ligand atom

Summary



Complexes

Lewis acid + Lewis base → coordinative bond → complex

[Central metal ion or atom (ligand with donor ligand atom(s)) coordination number]

1. negative, neutral

2. monodentate, bidentate, polydentate

central metal ion/atom
size, charge, electron configuration

ligand
shape, size

coordination number

shape

2 - linear
4 - tetrahedral/squareplanar
8 - octahedral

Ligand example:

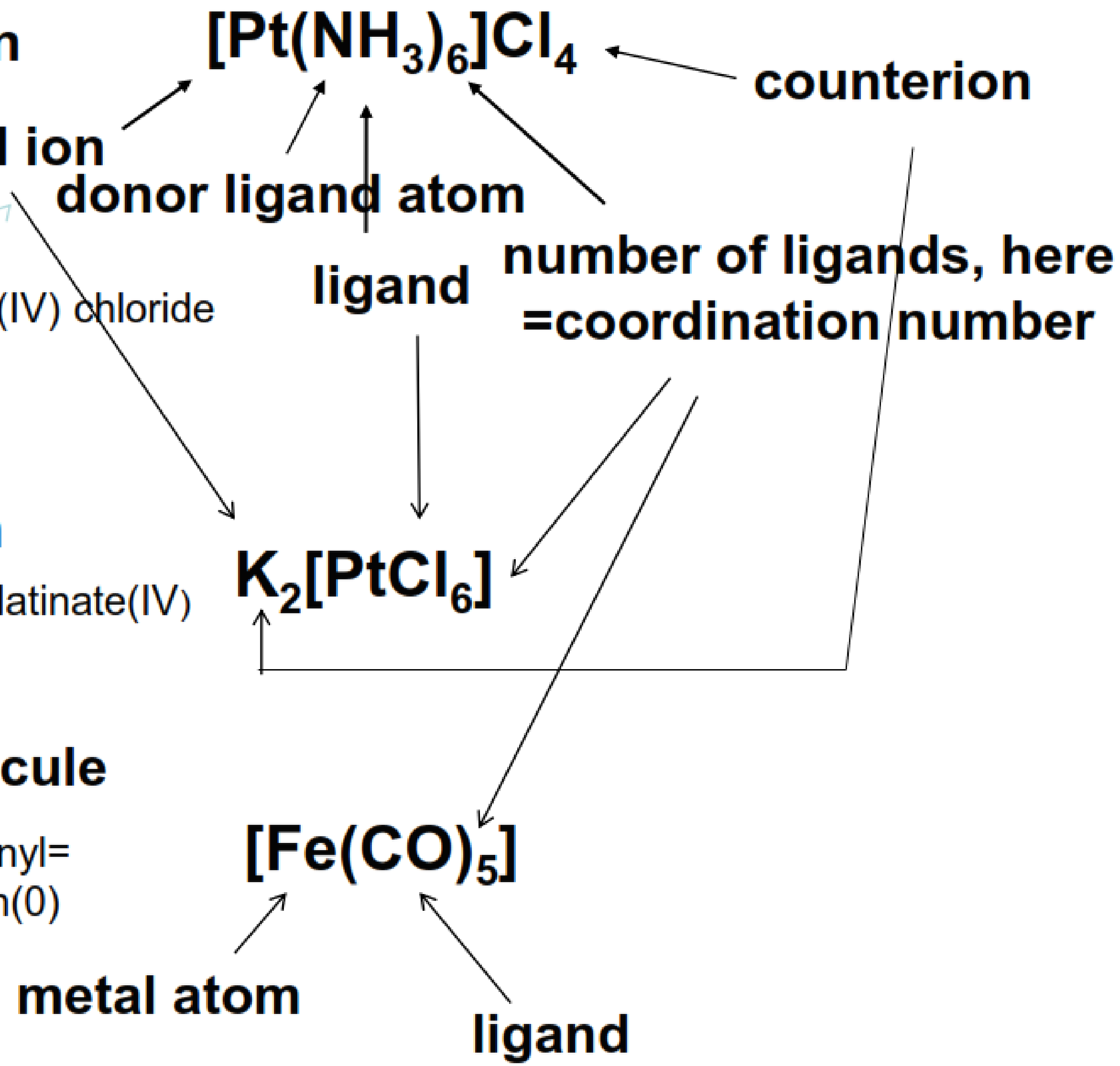
Monodentate: CO, Cl^-, CN^-, NH_3, OH^-, H_2O

Bidentate: Oxalate, glycine, ethylenediamine

Tetradentate: Porphine, porphyrin

Hexadentate: $EDTA^{4-}$

Complexes



1. complex cation

$[Pt(NH_3)_6]Cl_4$

counterion

central metal ion

donor ligand atom

ligand

number of ligands, here =coordination number

Hexaammineplatinum(IV) chloride

2. complex anion

Potassium hexachloroplatinate(IV)

$K_2[PtCl_6]$

3. complex molecule

Iron(0)pentacarbonyl=
Pentacarbonyliron(0)

$[Fe(CO)_5]$

central metal atom

ligand

Question

Which of the following is true?

A. Hemoglobin is involved in transporting oxygen

B .Myoglobin is involved in oxygen storage

C. Compared to oxygen, carbon monoxide has a higher affinity for hemoglobin

D. A, B and C

E. A and C

Question

What contains 2 alpha chains and 2 beta chains that assume a quaternary higher order conformation?

A. Maternal hemoglobin
B. Myoglobin
C. Immunoglobulin
D. Fetal hemoglobin

Question

What consists of 2 alpha chains and 2 gamma chains?

A. Maternal hemoglobin
B. Myoglobin
C. Immunoglobulin
D. Fetal hemoglobin

Question

What has the highest affinity for oxygen?

A. Maternal hemoglobin without 2,3-bisphosphoglycerate
B. Myoglobin
C. Maternal hemoglobin with 2,3-bisphosphoglycerate
D. Fetal hemoglobin with 2,3- bisphosphoglycerate

Question

When binding with oxygen, what type of binding curve does hemoglobin have?

A. Linear
B. Sigmoidal
C. Hyperbolic
D. It has none

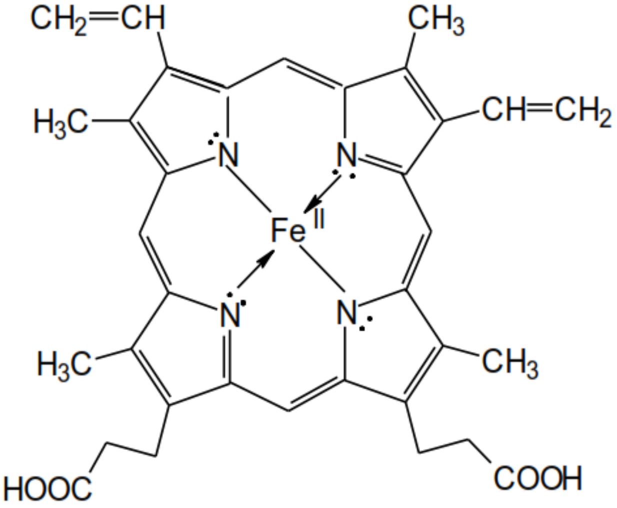
Question

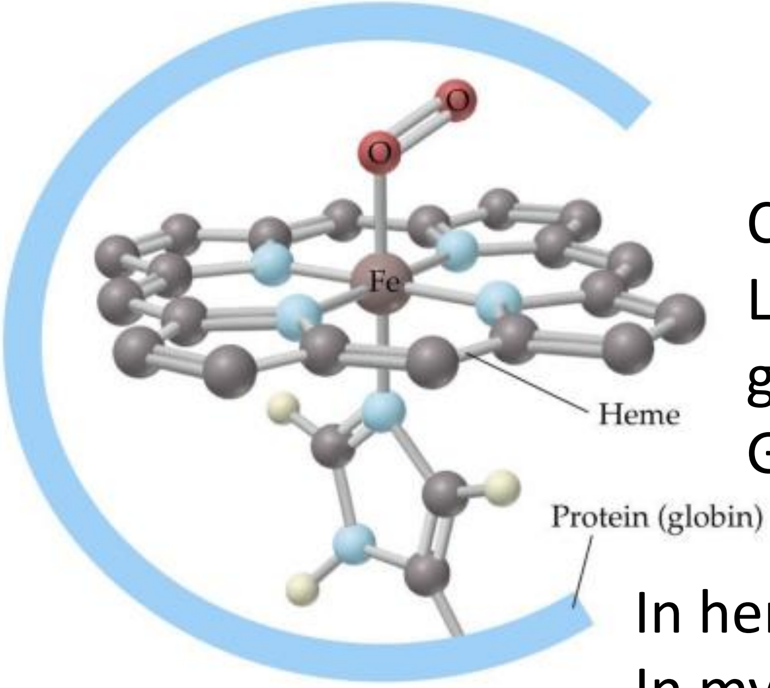
When binding with oxygen, what type of binding curve does myoglobin have?

A. Linear
B. Sigmoidal
C. Hyperbolic
D. It has none

Hemoglobin, myoglobin

Porphyrin is a planar, natural chelator, tetradentate ligand in globins, associated with Fe^{2+} called heme.





Coordination number: 6
Ligands: planar tetradentate porphyrin, globin protein (His), and oxygen molecule
Geometry: octahedral

In hemoglobin: 4 globin chains, 4 heme, 4 O_2
In myoglobin: 1 globin chains, 1 heme, 1 O_2

Question

Which of the following statements describes the oxygen binding curve of hemoglobin?

A. Each of the four oxygens bind with equal facility

B. The binding of the first oxygen molecule enhances the binding of the other three oxygen molecules

C. The binding of the first oxygen molecule makes the binding of the other three oxygen molecules more difficult

D. The binding of the first oxygen molecule has no effect on the binding of the remaining three oxygen molecules

E. Each successive oxygen bound makes the remaining sites less likely to bind oxygen

Question

Under which of the following conditions will hemoglobin bind less oxygen?

A. The pH increases from 7.0 to 7.2

B. The oxygen pressure increases from 500 mm to 1000 mm

C. The concentration of carbon dioxide increases

D. The 2,3-BPG is removed

E. None of the above

Question

Which of the following is in red muscle and consists of a single polypeptide with a prosthetic heme group?

A. Maternal hemoglobin
B. Myoglobin
C. Immunoglobulin
D. Fetal hemoglobin

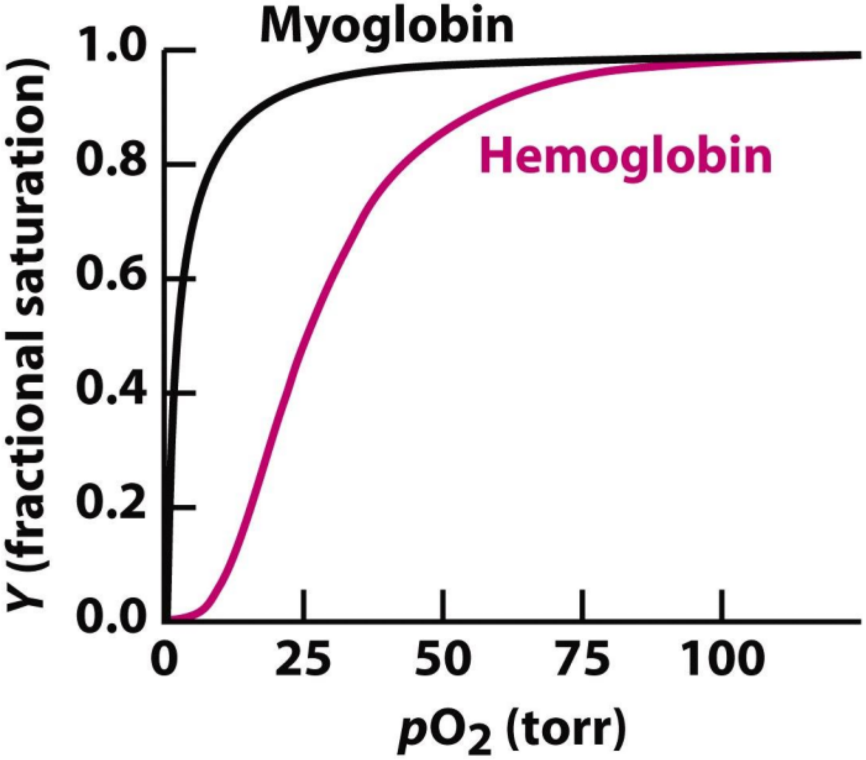
Hemoglobin, myoglobin

Hemoglobin transports the blood gases in erythrocytes.

Myoglobin transports and stores oxygen in myocytes.

The oxygen binding sites are very similar in structure, but the oxygen affinities are different.

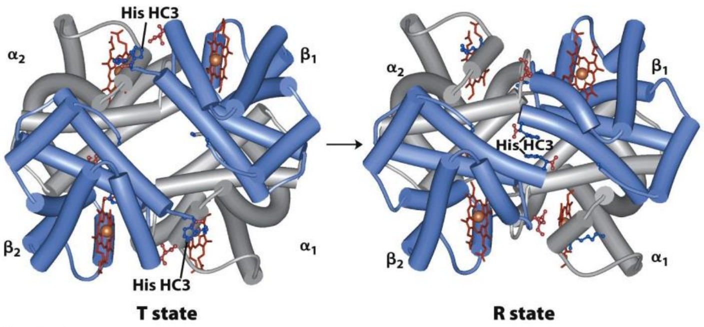
Partially because of the cooperative oxygen binding, partially because of the adjusting effect of 2,3BPG as heterotropic allosteric modulator.



Even in different developmental periods, the hemoglobin subunits are different and so the affinity for oxygen.

Adult: $\alpha_2\beta_2$, fetal: $\alpha_2\gamma_2$, embryonal: $\alpha_2\varepsilon_2$

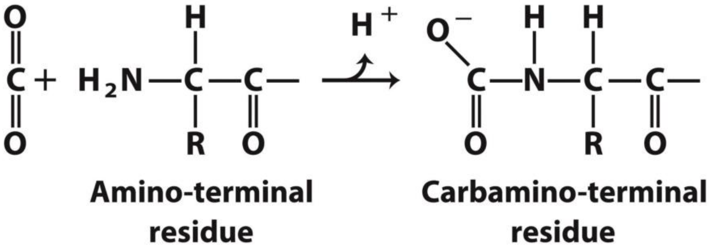
Hemoglobin binds oxygen by a **cooperative mechanism:** binding of the first O_2 molecule initiates allosteric rearrangements and this increases the affinity of the still free heme groups towards O_2.



O_2 binding triggers a transformation from **T-state to R-state**.

So oxygen is a **homotropic allosteric activator** of hemoglobin**.**

CO_2 binds hemoglobin as a carbamate-group and stabilizes the T-state.



$$O{=}C{=}O + H_2N{-}\overset{H}{\underset{R}{C}}{-}\underset{O}{\overset{\|}{C}}{-} \xrightarrow{H^+} {}^{-}O{-}\underset{O}{\overset{\|}{C}}{-}\overset{H}{N}{-}\overset{H}{\underset{R}{C}}{-}\underset{O}{\overset{\|}{C}}{-}$$

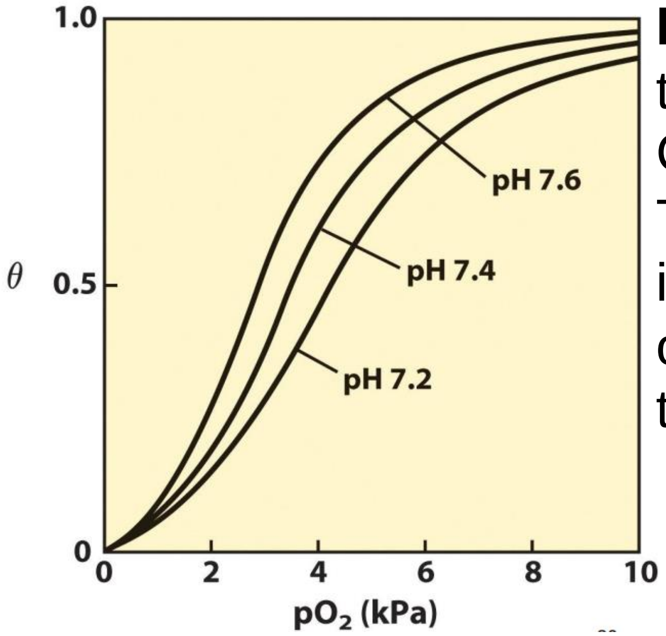
Heterotropic allosteric modulator is 2,3BPG. It binds to the T-state of hemoglobin (deoxyhemoglobin) and stabilizes it so it can not transform to the oxygen-affiner R-state. When 2,3-BPG is bound Hb can release O_2 at lower partial pressure. 2,3BPG is produced by the Luebering-Rapoport shunt (pathway coupled to glycolysis) from 1,3-BPG by the enzyme BPG mutase.

An increase in the 2,3-BPG concentration can be observed in the height adjustment: as the O_2-saturation in blood decreases, the O_2 release become more difficult, but the organs would need the same supply, so the body should solve this problem. With producing more 2,3BPG the O_2 affinity decreases, so the peripheral tissues can get the necessary supply.

Question

What phenomenon occurs when decreased pH causes hemoglobin to release oxygen into tissues?

A. Allosteric effect
B. ELISA
C. Bohr shift
D. Western blotting
E. B and D



Bohr effect describes how the affinity of hemoglobin towards O_2 decreases when the pH decreases or the CO_2 concentration increases.

Together with the cooperative binding of O_2 and the influence of 2,3-BPG, this property ensures the optimal functioning of hemoglobin as an oxygen transporter.

The oxygen binding curve is **shifted to the right** on the horizontal axis by:

- temperature increase
- decrease in pH
- increase in the concentration of 2,3-BPG in the erythrocytes
- increase the concentration of CO_2

The shift to the right causes hemoglobin to release oxygen more easily.

E.g. a working muscle consumes a lot of O_2 for contraction. Since it converts the energy partially into heat, the temperature rises in the working muscles. It also releases lactic acid so the pH drops. As a result of the increased metabolism, more CO_2 is produced: due to the local effects, the muscles can extract more O_2 from the blood.

The oxygen binding curve is **shifted to the left** on the horizontal axis by:

- temperature decrease
- increase in pH
- decrease in the concentration of 2,3-BPG in the erythrocytes
- decrease in the concentration of CO_2

The left shift causes hemoglobin to bind oxygen more strongly.

E.g. in cardiac surgery hypothermia of the patient is necessary to maximally saturate his blood with oxygen.

Question

When will hemoglobin have the highest affinity for oxygen?

A. When pH is low
B. When carbon monoxide levels are high
C. At high elevations
D. When 2,3-bisphosphoglycerate levels are low

Thank you for your attention!