Vitamins, Cofactors, Coenzymes and Prosthetic Groups

EVROPSKÁ UNIE
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Vitamins

exogenic organic compounds essential for certain group of organisms, low daily consumption (compared to e.g. essential amino acids)

Pro-vitamins

vitamin precursors

Cofactors

low-molecular weight compounds required for enzymatic catalysis

Coenzymes

cofactors, carriers of chemical groups

Prosthetic groups

cofactors, non-peptide components of enzymes, involved in catalysis

Vitamins

(for human)

- A – retinol
- B_1 – thiamine
- B_2 – riboflavin
- B_5 – panthotenate
- B_6 – pyridoxine
- B_{12} – cobalamin
- C – ascorbic acid
- D – calciferol
- E – tocoferol
- H or B_7 – biotin
- K – phylloquinon
- PP – niacin

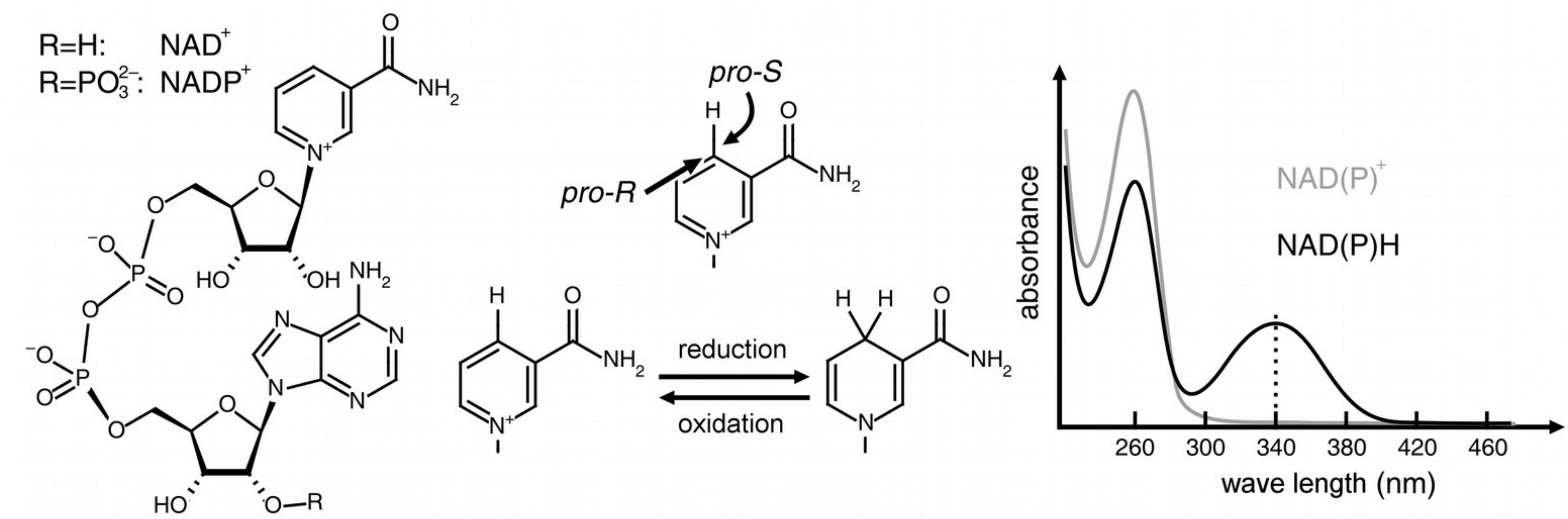
Vitamins, coenzymes, cofactors, prosthetic groups

The terms “vitamins”, “coenzymes”, “cofactors” and “prosthetic groups” are somehow blurred. This is because vitamins were discovered in times when their biochemical function was not clear. Chemists discovered vitamins by analyzing food and by studying biological consequences of their deficiencies. In other words, vitamins were discovered as nutrients with low daily intake, yet important for health. Much later it was found that most (but not all) vitamins are cofactors or their precursors.

Moreover, the terms “coenzymes”, “cofactors” and “prosthetic groups” are also fuzzy. Coenzymes are substrates of enzymatically catalyzed reactions in cell. They can exist in two or multiple forms (e.g. oxidized and reduced). In some reactions they are converted from one form to another (e.g. oxidized) and in other reactions they are converted back (e.g. reduced). The fact that they are recycled in metabolism makes it possible that they are present in relatively low concentrations in a cell. Prosthetic groups are compounds bound to enzymes (covalently or non-covalently) and their change from one form to another and back takes place in a single catalytic cycle. The term cofactors unites coenzymes and prosthetic groups. CAUTION: Some researchers use the term prosthetic group for covalent bound-only prosthetic groups and cofactors for other prosthetic groups.

NAD$^+$

$\varepsilon_{NAD(P)H,340} = 6{,}22.10^3$ l/mol/cm

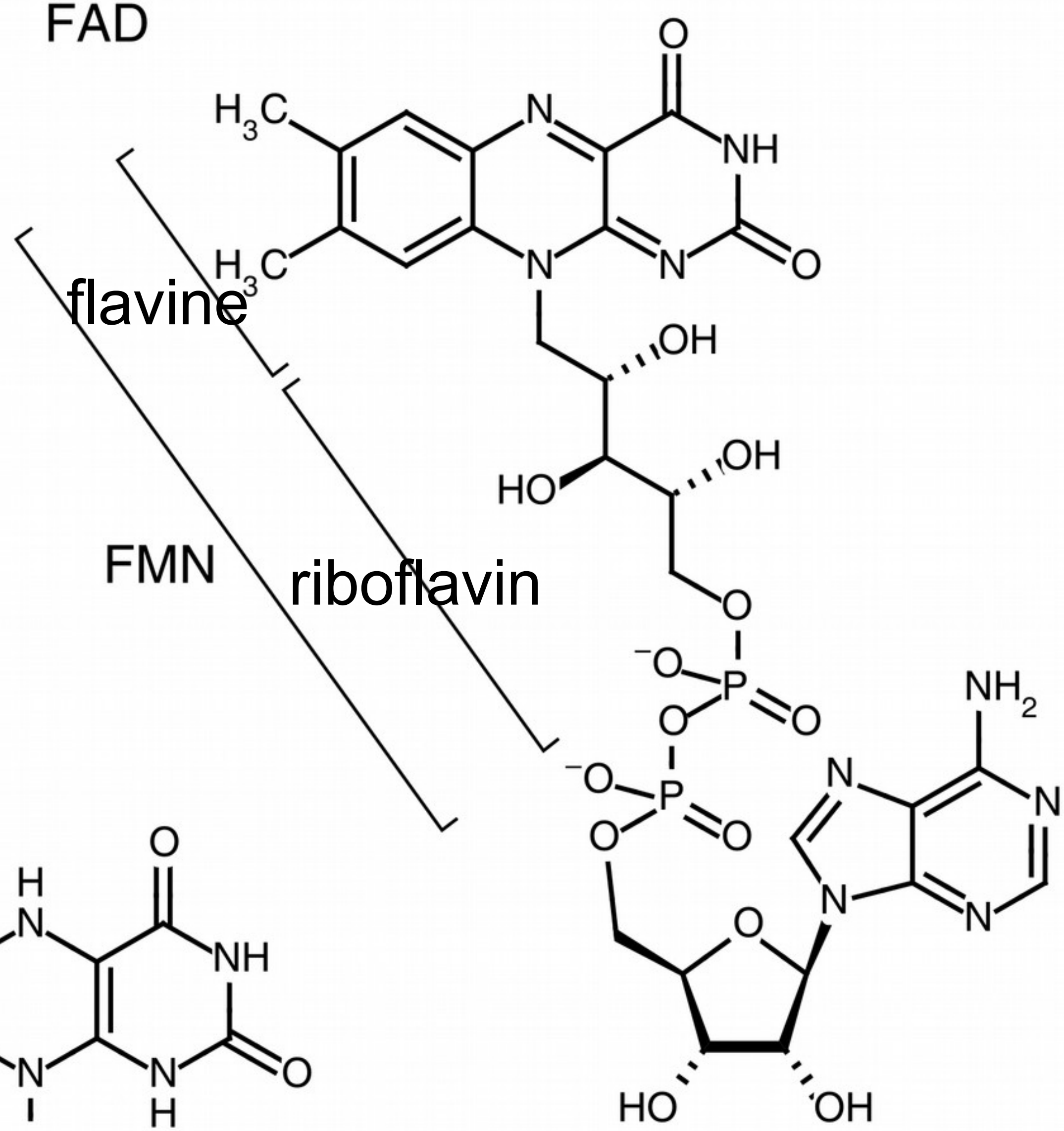


Nicotinamide (niacin, vitamin PP)

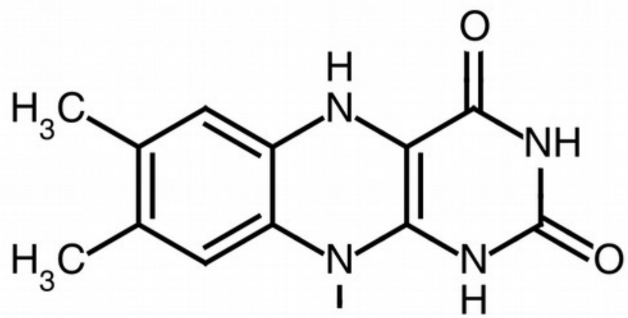
NAD$^+$ or NADP$^+$ are typical coenzymes of oxidoreductases (interestingly, it can be a prosthetic group of a hydrolase – *S*-adenosylhomocystein hydrolase). Niacin is its precursor. Most enzymes are NAD$^+$ or NADP$^+$ specific and these coenzymes play different roles in metabolism. Interesting feature of NADH or NADPH is its absorbance maximum at 340 nm. Thanks to this it is possible to measure rates of enzymatic reactions using these coenzymes. This is important in clinical diagnostics.

FAD/FMN

FAD



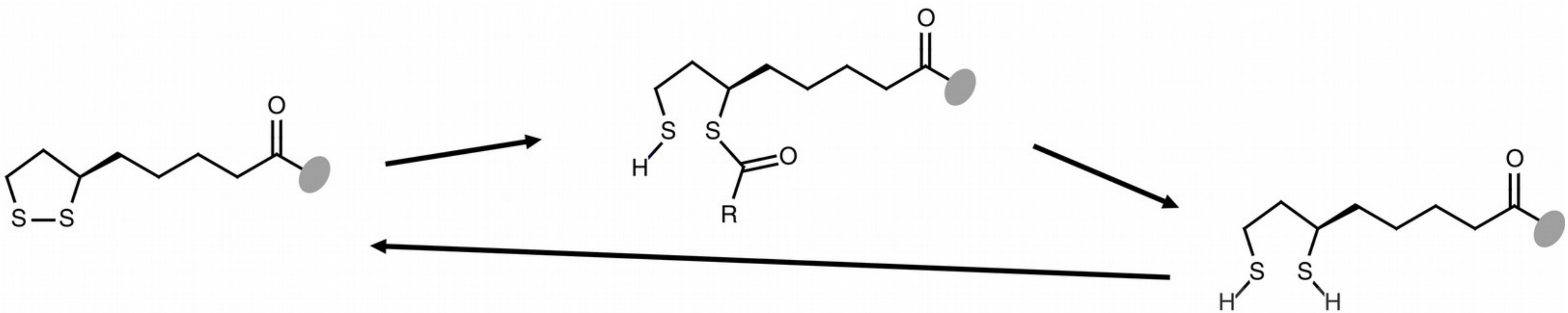
$FADH_2$



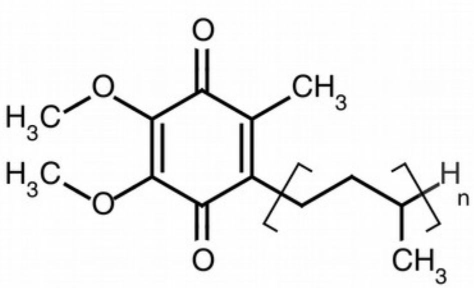
Riboflavin – vitamin B_2

FAD is a typical prosthetic group of oxidoreductases. Riboflavin (vitamin B_2) is its precursor. It can exist in oxidized and reduced form or in other forms (some enzymes use FAD in more complicated reactions). Similarly to NAD^+ and $NADP^+$ it is possible to distinguish spectrophotometrically between oxidized and reduced forms, but it is not (so much) useful as for $NAD(P)^+$ because FAD is a prosthetic group.

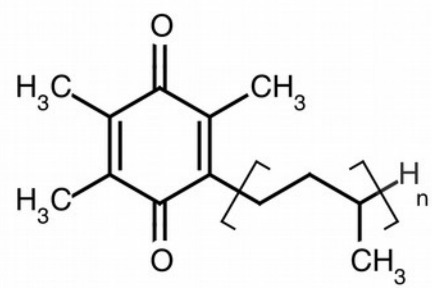
lipoic acid



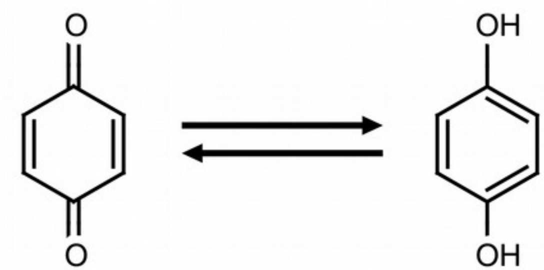
quinons



ubiquinon

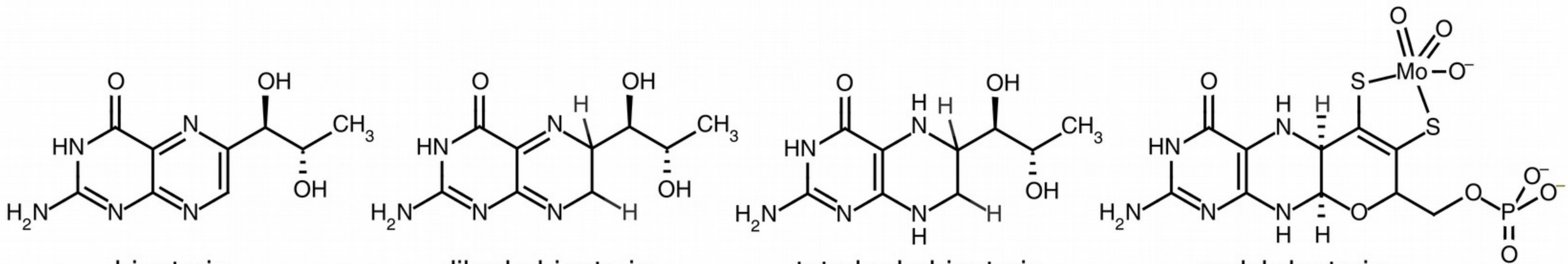


plastoquinon



Pyruvate dehydrogenase complex and 2-oxoglutarate dehydrogenase complex use a specific prosthetic group called lipoic acid. It is bound by amidic bond to Lys side chains. It can exist in oxidized, reduced and acylated reduced form (with acetyl or succinyl as the acyl). Ubiqinon and plastoquinon are quinonic coenzymes. They are highly non-polar. Unlike usual coenzymes, which are dissolved and diffuse in the 3D space of the cell, quninones are dissolved and diffuse in the 2D space of the membrane of mitochondria or thylakoid, respectively.

pterins



biopterin dihydrobiopterin tetrahydrobiopterin molybdopterin

$$Phe + O_2 + THB \rightarrow Tyr + H_2O + DHB$$

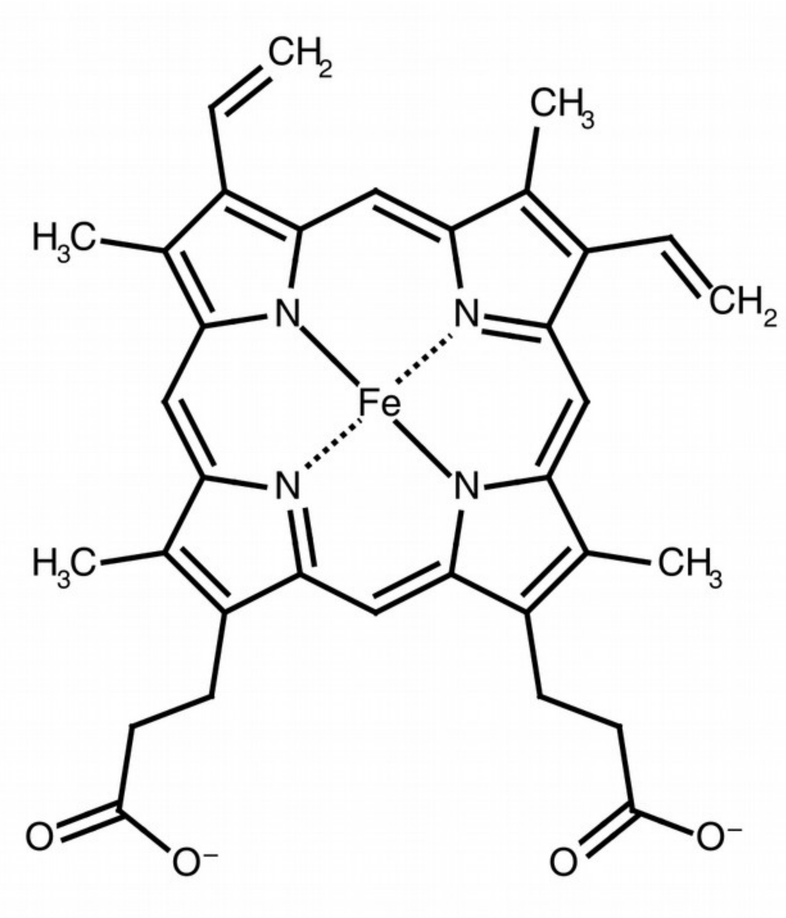
Pterins are interesting cofactors of oxidoreductases. (Di/tetrahydro)biopterin is a coenzyme of phenylalanine hydroxylase. This enzyme is famous for its inborn deficiency causing phenylketonuria. THB has been approved to treat this disease. Molybdopterin is a prosthetic group of xanthine oxidase. It is an interesting example of molybden-containing compound and enzyme in human body.

heme

binding to a protein - non-covalent/coordination-covalent
- covalent (addition of SH to vinyls)

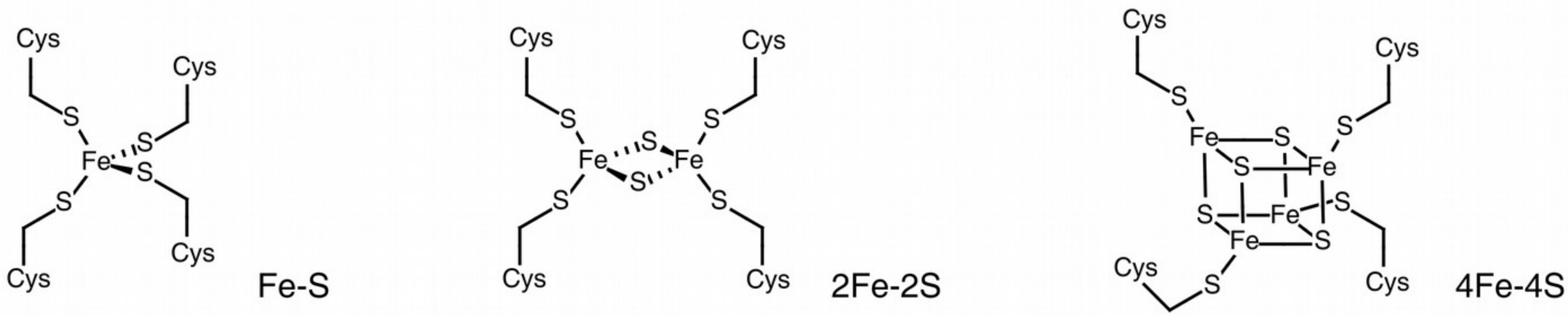
role in proteins
- transport of oxygen
- electron traffic
- catalysis

cytochromes



Heme is famous for its role in hemoglobin. Hemoglobin is an oxygen-binding protein, not enzyme. Heme plays important role in many enzymes, mostly oxidoreductases. Iron can exist in II or III oxidation states. It can also exist in high-spin states. Furthermore, it can bind many ligands by coordination covalent bond.

FeS proteins



Glutathione

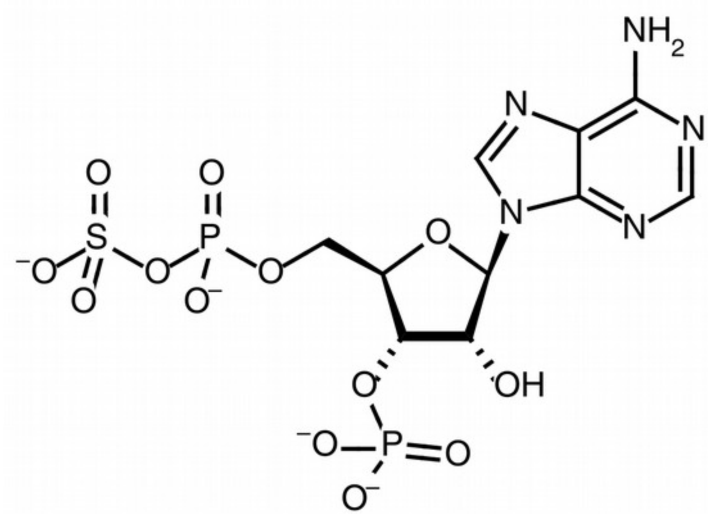
γ-Gly-Cys-Gly

Iron in iron-sulfur clusters of FeS protein can exist in II or III states. These clusters can act as a kind of “electric wiring” in proteins and enzymes. 4Fe-4S can be also play other roles than electron transport, for example in aconitase.
Glutathione is a peptidic coenzyme. The reduced form is a tripeptide. The oxidized form is its disulfide-linked dimer. It participates in many spontaneous reactions with oxidative species. It can be reduced by glutathione reductase using NADPH.

ATP
- transfer of phosphate
- can work as a cofactor

Activated monosaccharides, phospholipid heads etc.

PAPS – 3'-phosphoadenosine-5'-phosphosulphate

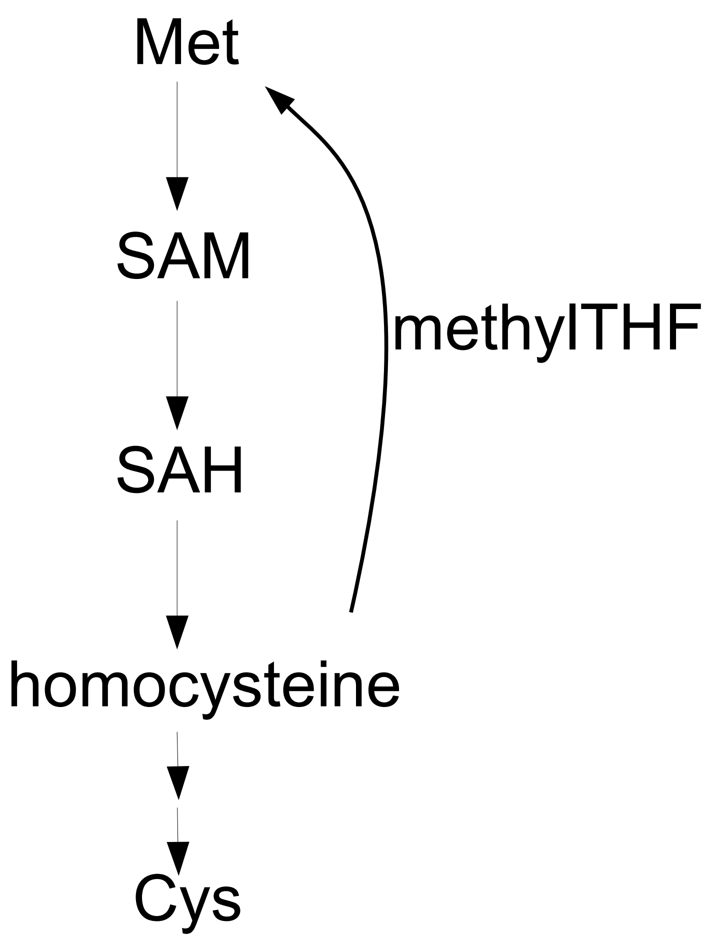


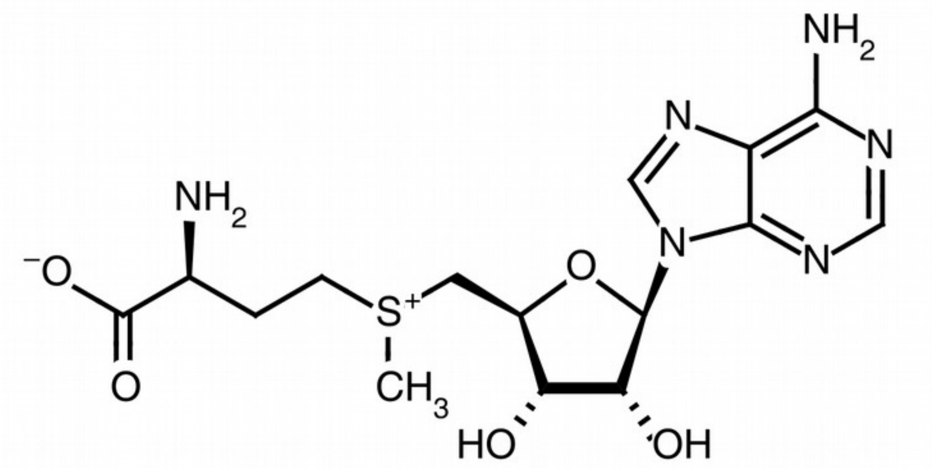
ATP is source of energy (in reactions catalysed by hydrolases and ligases) and source of phosphate (in reactions catalysed by transferases). Phosphotransferases are called kinases.

Some complex molecules, such as saccharides or phospholipids are synthesized from building blocks such as CDP or UDP (e.g. UDP-glucose).

PAPS is a coenzyme of sulfotransferases. It can be used in synthesis of sulfated carbohydrates such as heparins.

SAM (*S*-adenosylmethionine, AdoMet)





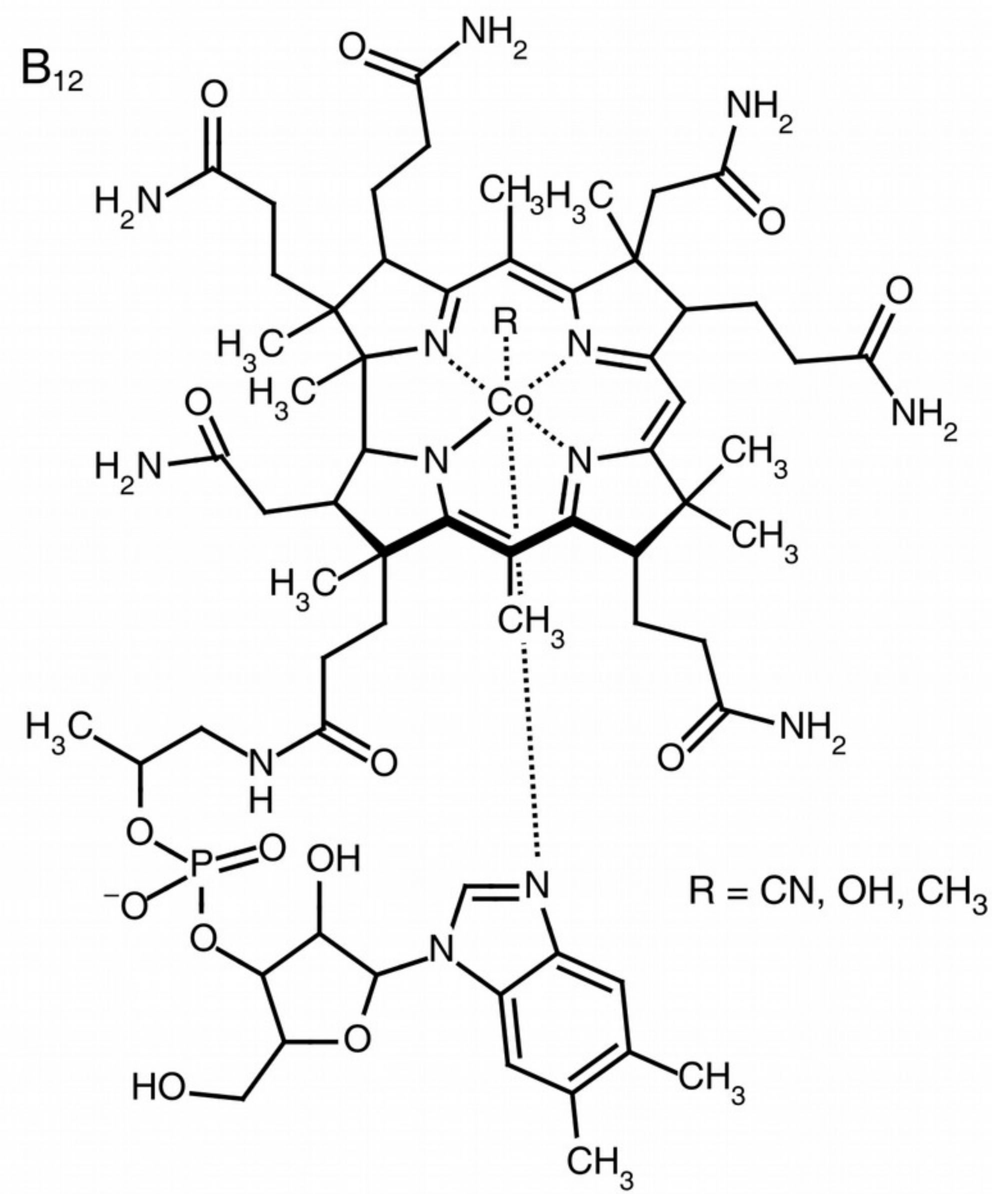
The methylating agent in cells is *S*-adenosinemethionine (SAM or AdoMet). It is an intermediate of methionine metabolism. Some proteins, DNA or folates (see later) can be methylated.

Cobalamin (B_{12})

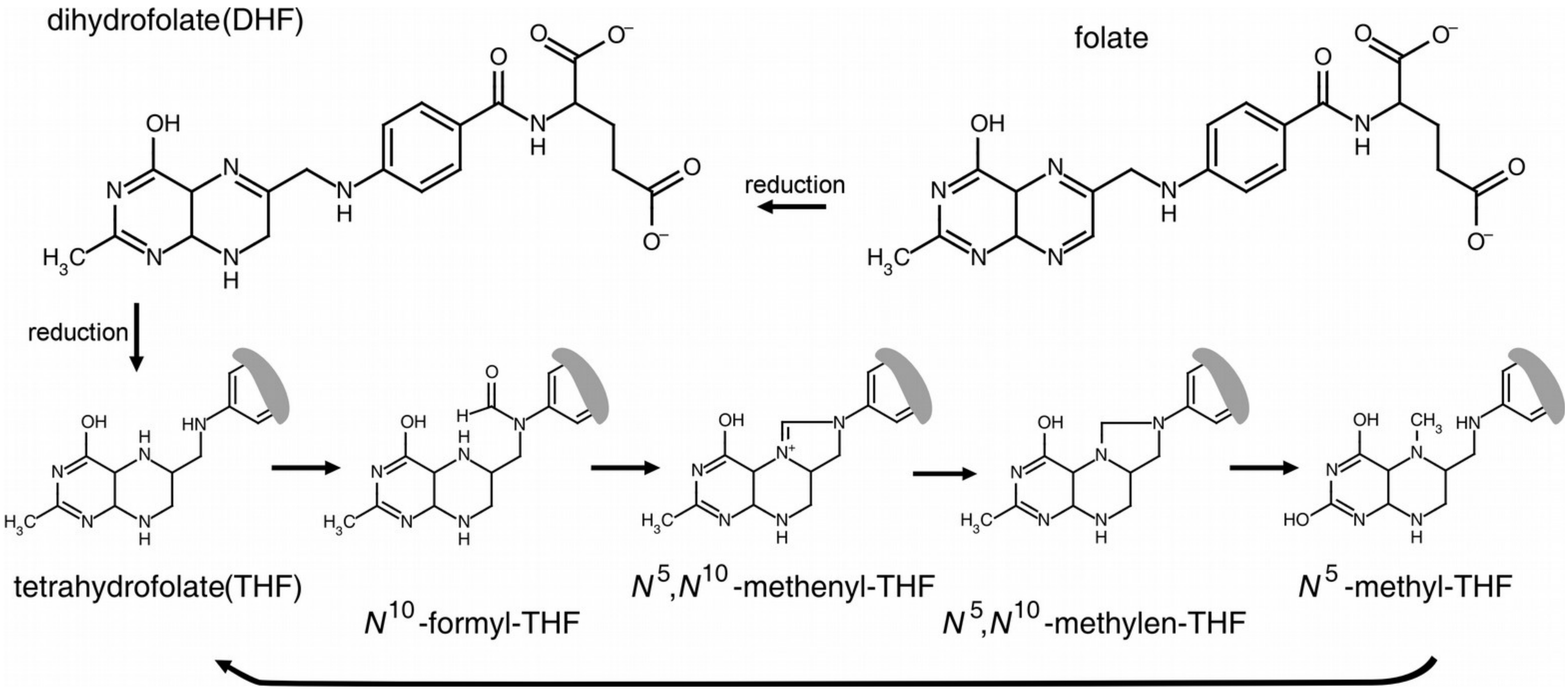
transfer of methyl group
(methylmalonate-CoA → succinate-CoA)
NDP → dNDP
others

The most complicated vitamin with lowest daily income is B_{12}. It plays important role in conversion of maleinate to succinate in degradation of fatty acids with odd number of atoms. It also participates in methionine biosynthesis. It is highly non-polar. Therefore it cannot circulate in body in a bare form and must be bound to one three of protein carriers.

carriers:
- haptocorrin
- intrinsic factor
- transcobalamin



folic acid



purine biosynthesis
uracyl → thymine
Gly → Ser,Thr
vitamin of B-group – folacin

Folates participate in many reactions as carriers of single-carbon moieties such as methyl, methylene or formyl. Its derivative methothrexate inhibits some of folate metabolism reactions. It is used as anticancer and immunosuppressive drug.

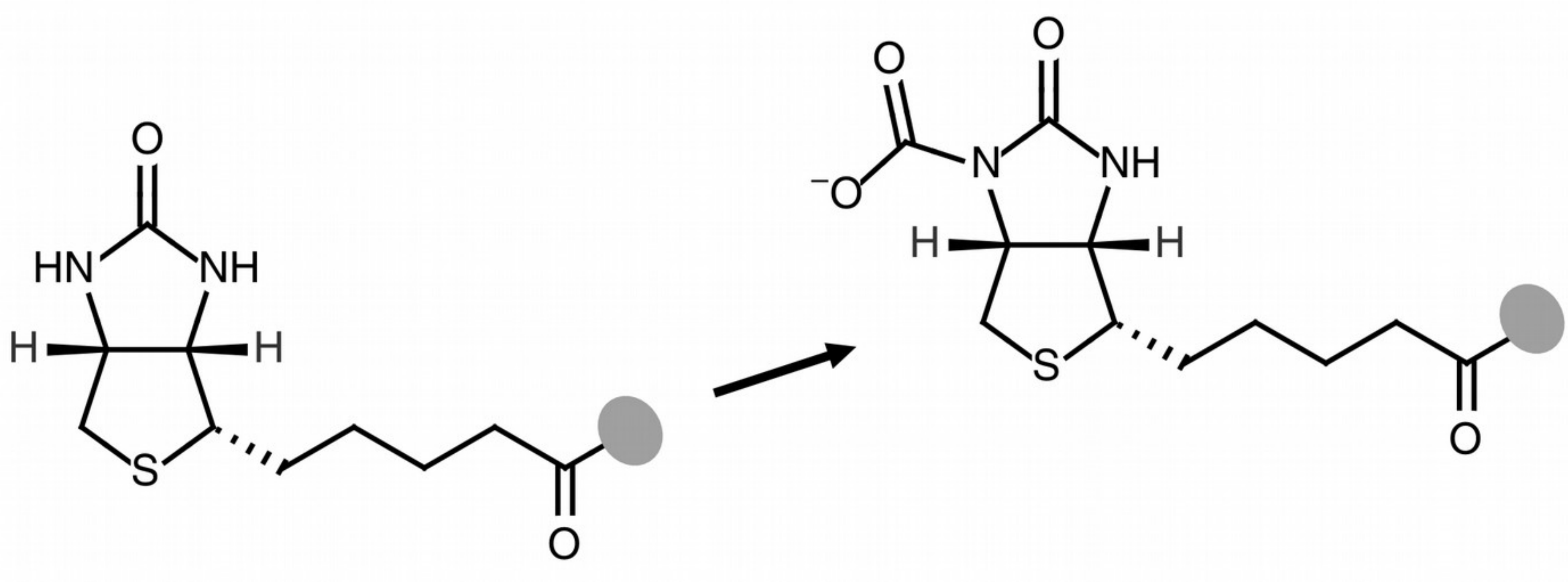
Biotin (vitamin H, B_7)

transfer of CO_2

$HCO_3^- + ATP \rightarrow HCO_3\text{-}P$

$HCO_3\text{-}P$ + biotin-BC →
carboxylated biotin-BCCP

Biotin caries a carboxylic group. It is a prosthetic group bound to the enzyme (or biotin carboxyl carrier protein, BCCP) covalently by amidic bond to Lys side chain. There are two proteins with extreme affinity to biotin – avidin from eggs and bacterial streptavidin. These proteins are often used in molecular biology research for affinity techniques.

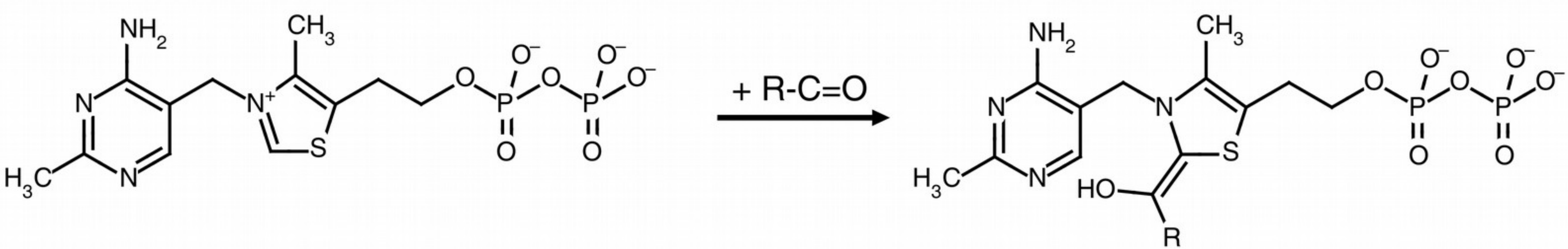


thiamine diphosphate (TPP, thiamine pyrophosphate)

thiamine = vitamin B_1

pyruvate dehydrogenase
2-oxoglutarate dehydrogenase
pyruvate decarboxylase

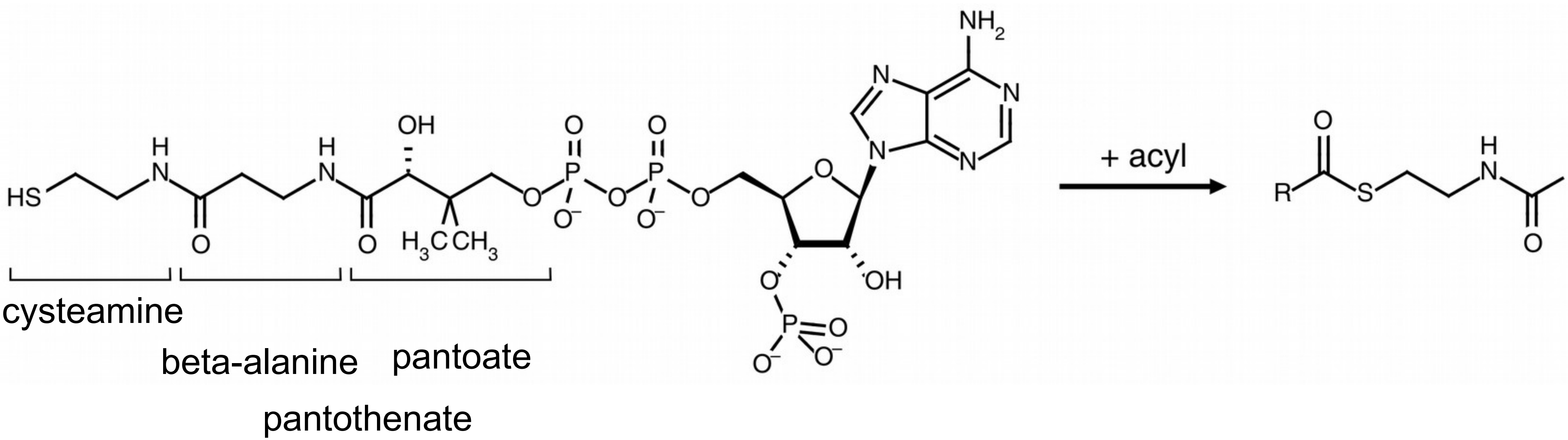
$$TPP + R\text{-}CO\text{-}COO^{-} \rightarrow TPP\text{-}C(OH)R + CO_2$$



TPP participates in decarboxylation of pyruvate or 2-oxoglutarate in pyruvate or 2-oxoglutarate dehydrogenase complexes, pyruvate decarboxylase and other enzymes.

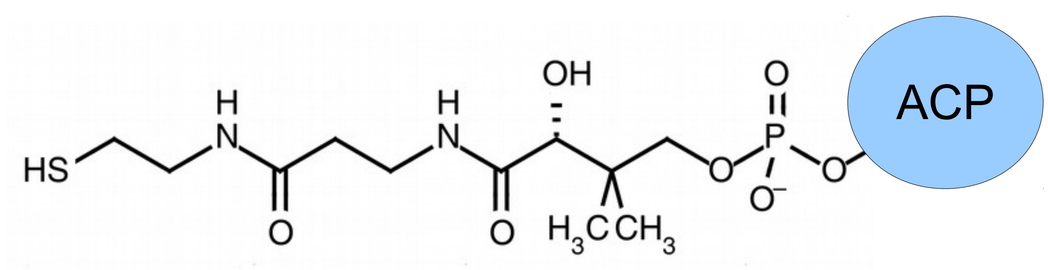
Coenzyme A

pantothenate = vitamin B_5



Coenzyme A is a carrier of acyl groups. It is composed of ADP (its 3'-phosphate), pantioc acid, β-alanine (pantoic acid and β-alanine form pathothenic acid) and cysteamine. Cysteamin and β-alanine are decarboxylation products of Cys and Asp.

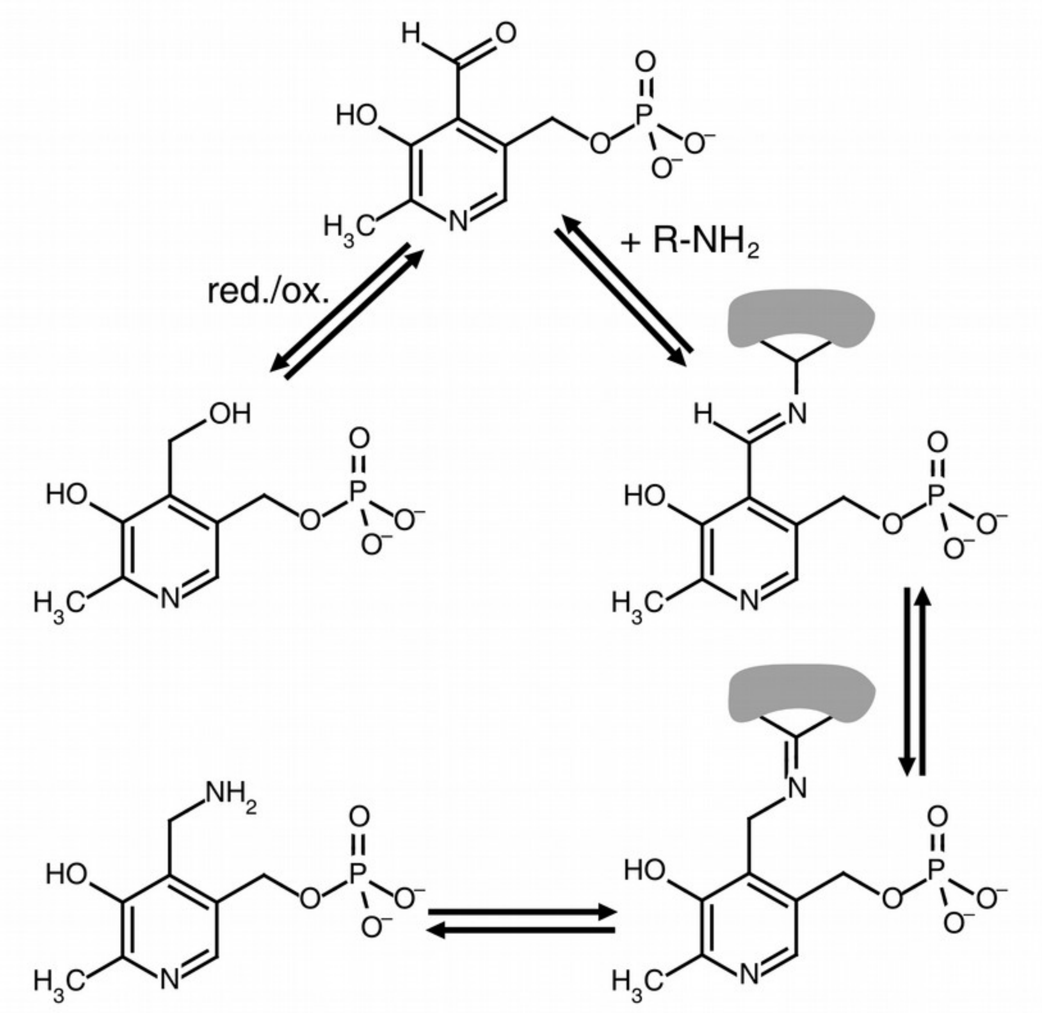
acyl carrier protein



pyridoxalphosphate

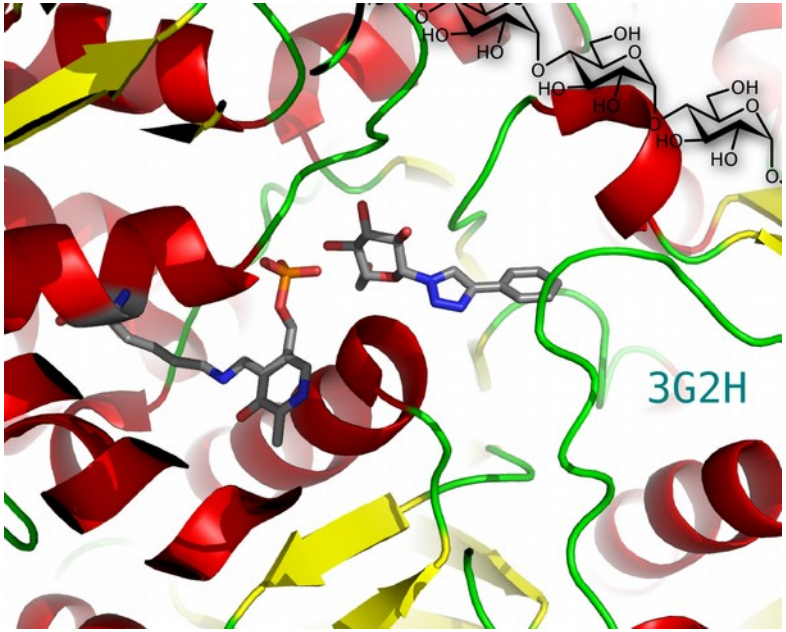
pyridoxal/ol/amin = vitamin B_6

Pyridoxalphosphate is very versatile prosthetic group. It is usually bound noncovalently, but some enzymes in the resting state bind it covalently via a Shiff base to a Lys sidechain. It can participate in transamination reaction depicted here. First, the amino acid (e.g. Ala) binds, double bonds are rearranged and oxoacid (pyruvate) is released. Next, the whole procedure repeats in the opposite direction and with a different amino/oxoacid. Usually, 2-oxoglutarate binds and Glu is produced.

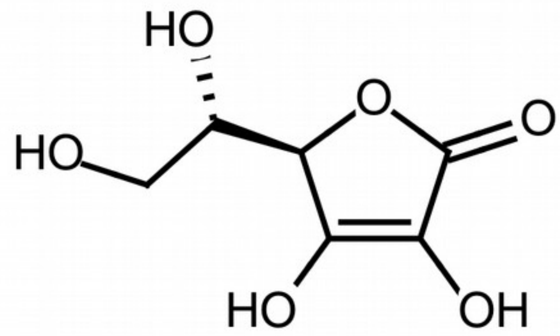


pyridoxalphosphate

PLP participates in many other reactions (mostly) of amino acid metabolism:
- transamination
- decarboxylation
- racemisation
- deamination (Ser → pyruvate)
- amino acid transport through a membrane
- nicotinic acid biosynthesis
- phosphorylase



Ascorbic acid



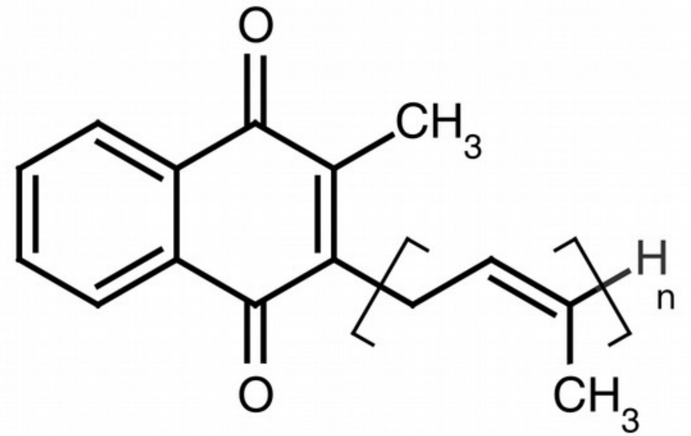
Vitamin C (vit. for humans)

reducing agent:
dopamin + ascorbate + O_2
→ norepinephrin
+ dehydroascorbate

cofactor:
hydroxylation of collagen

antioxidant

Phylloquinones (vit. K)



Glu → γ-carboxy-Glu
blood coagulation

Antivitamin: warfarin

Retinol/retinal (vitamin A)
- biochemistry of vision
- signaling molecule

Tocopherols (vitamin E)
- antioxidants

Calciferol (vitamin D)
- hormonal function in calcium metabolism

As mentioned at the beginning, at the time of vitamin discovery there was little information about their biochemical function. As found later, most vitamins are precursors cofactors and cofactors, but not all. Vitamins A, C, D, E and K do not fall into the group of cofactor vitamins. Vitamin A is a part of rhodopsin – light-sensing G protein-coupled receptor (GPCR). It is also important hormone in tissue development. Vitamin C is reducing agent in norepinephrine biosynthesis. In hydroxylation of collagen it keeps iron ion in 2+ state. Vitamin D plays hormonal role in calcium metabolism. Vitamins E are antioxidants. Vitamins K is involved in carboxylation of glutamyl residues in key blood coagulation factors. It is therefore important for blood coagulation. Vitamin K analogues – warfarins – are used to treat thrombosis.