

Vitamins and Coenzymes

Vitamins are compounds that are required in the diet, either because the organism cannot synthesize them, or because the rate of usage by the organism typically exceeds the rate of synthesis of the compound. In nearly all cases, only very small amounts of these compounds are required.

Vitamins are generally classed as either **water-soluble** or **fat-soluble**. The water-soluble vitamins generally act as precursors to coenzymes; the functions of the fat-soluble vitamins are more diverse and less easily categorized.

The water-soluble vitamins are readily excreted in the urine; toxicity as a result of overdose is therefore rare. However, with few exceptions, the water-soluble vitamins are not stored in large amounts, and therefore must be continually supplied in the diet. In contrast, the fat-soluble vitamins are less readily excreted, and are deleterious (and possibly lethal) in high doses. Many of the fat-soluble vitamins are stored; for example, most well nourished individuals have a three-month supply of vitamin D.

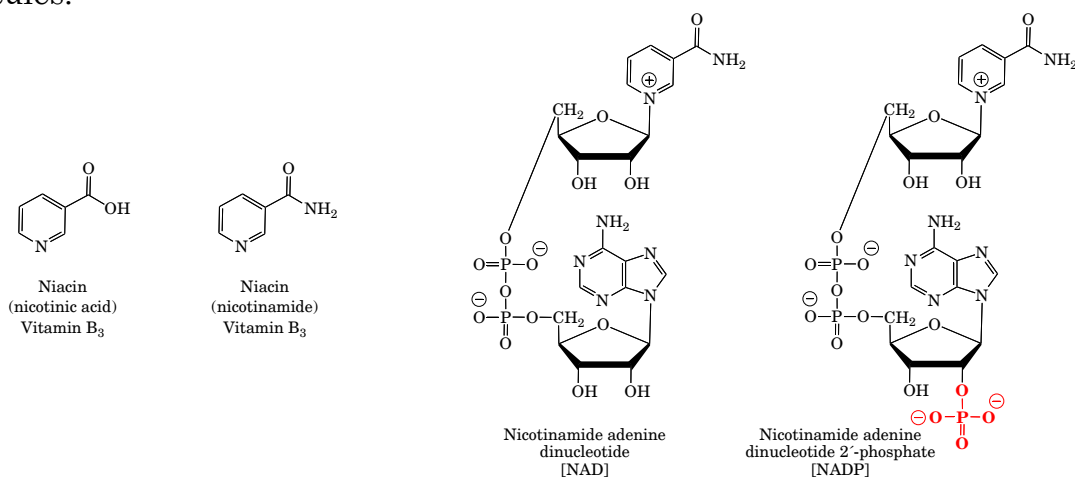
Water soluble vitamins

The water-soluble vitamins include the B complex vitamins (the actual B vitamins, biotin, and folic acid) and vitamin C.

First we will look at three classes of vitamin-derived coenzymes used to carry electrons: the nicotinamide coenzymes, the flavin coenzymes, and ascorbic acid.

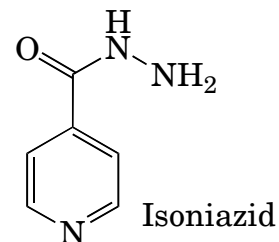
Vitamin B₃ (niacin)

Niacin is the name for both nicotinamide and nicotinic acid, either of which can act as a precursor of nicotinamide coenzymes. Niacin is required for the synthesis of two coenzyme molecules: NAD and NADP. Note the phosphate attached to the 2'-position of the lower ribose ring in NADP, which is the only difference between the molecules.



Humans can synthesize nicotinamide cofactors from tryptophan. However, the process is somewhat inefficient; synthesis of 1 mg of niacin requires about 60 mg of

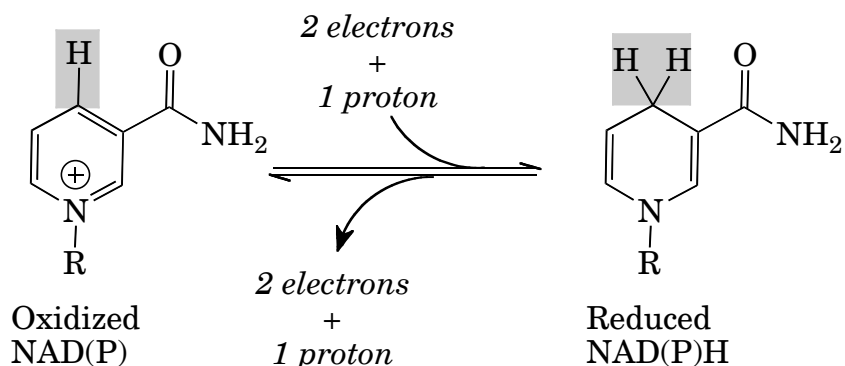
tryptophan. Niacin deficiency therefore is usually the result of a diet deficient in both niacin and tryptophan. However, some diets contain tryptophan or niacin in a biologically unavailable form. In corn, the niacin is poorly absorbed unless the corn is treated with alkali prior to ingestion. In the rural south of the early 20th century, this preparation step was largely ignored; the symptoms of the resulting **pellagra** (niacin-deficiency), such as sun-sensitivity and dementia, led to the pejorative term “red-neck” for individuals from this region of the US. Pellagra is also observed in high sorghum diets (sorghum contains niacin-synthesis inhibitors) or in some individuals taking isoniazid (isoniazid is an antibiotic used to treat tuberculosis, but also inhibits niacin uptake and synthesis).



Nicotinic acid (but not nicotinamide) reduces release of free fatty acids from adipose tissue, probably via binding to a receptor that also binds hydroxycarboxylic acids, and has been used to reduce plasma cholesterol. However, some individuals cannot tolerate the high levels of nicotinic acid required.

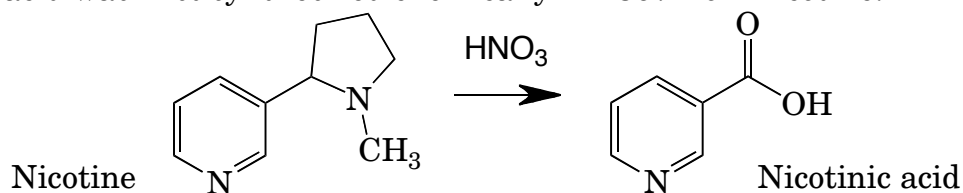
The niacin derived coenzymes NAD and NADP act as **soluble electron carriers** between proteins. NAD and NADP thus act as substrates for enzymes involved in oxidation and reduction reactions. NAD is primarily involved in **catabolic reactions**. NAD accepts electrons during the breakdown of molecules for energy. In contrast, NADPH (the reduced form of NADP) is primarily involved in **biosynthetic reactions**; it donates electrons required for synthesizing new molecules. In most cells, NAD concentration is much higher than that of NADH, while NADPH is actively maintained at levels much higher than those of NADP.

The two possible electronic states for the nicotinamide cofactors are shown below:



The oxidized forms of both nicotinamide coenzymes can **only accept electrons in pairs**. The reduced forms of the coenzymes can **only donate pairs of electrons**. Note the two changes in the ring during the reduction. The addition of the electron pair is accomplished by the addition of a hydride ion to the carbon *para* to the pyridine nitrogen, and results in the loss of the positive charge on the ring.

Nicotinic acid was first synthesized chemically in 1867 from nicotine:



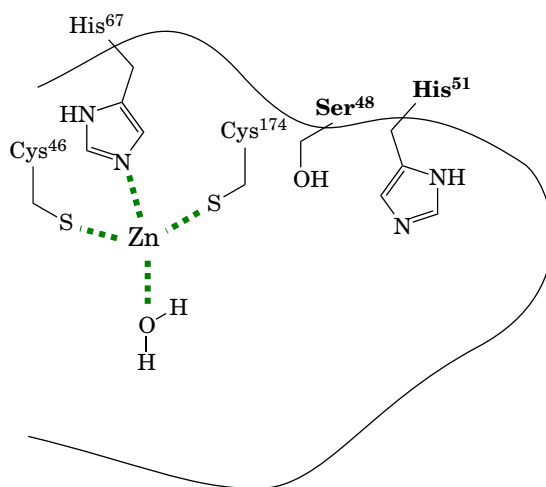
The name “niacin” was introduced to remove the association with nicotine and tobacco.

Alcohol Dehydrogenase

An example of the role of NAD in redox chemistry is provided by the oxidoreductase enzyme **liver alcohol dehydrogenase**. The name of the enzyme includes the tissue of origin and the substrate. The word “dehydrogenase” is an indication of the fact that the enzyme catalyzes an oxidation-reduction reaction. (“Dehydrogenase” means “catalyzes hydrogen removal”.)

Alcohol dehydrogenase can catalyze the oxidation of several different alcohols. In each case it uses NAD as the electron acceptor. The active site is thus moderately non-specific for the alcohol, although it is quite specific for NAD compared to NADP.

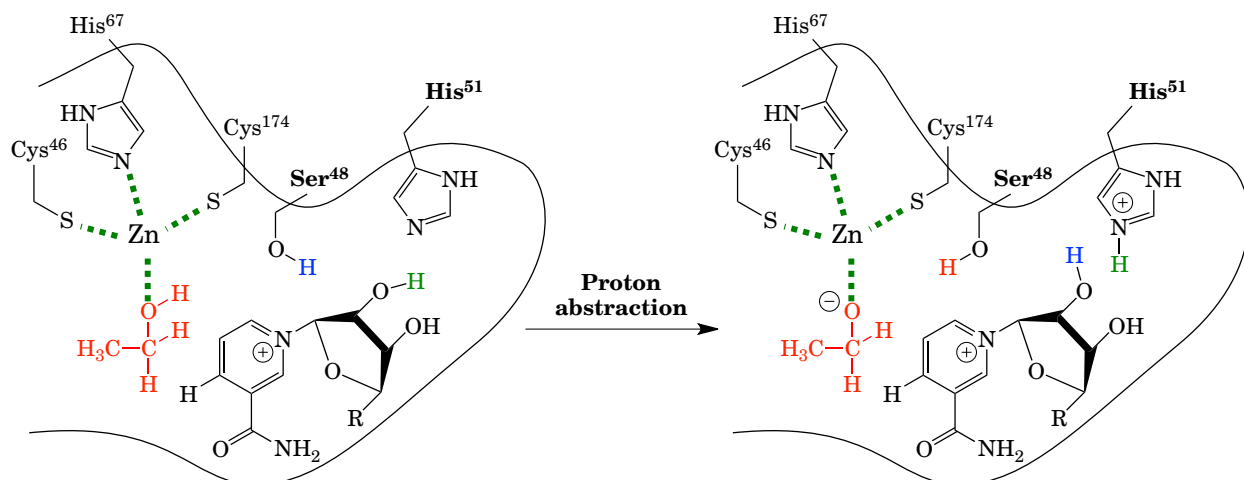
In the absence of substrate, the alcohol dehydrogenase active site is occupied by water molecules. Note the zinc ion, a metal ion cofactor that is required for catalytic activity (alcohol dehydrogenase actually binds two zinc ions, but the other is thought to have an exclusively structural role). The zinc is bound to three enzyme side-chains (two cysteine residues and a histidine residue).



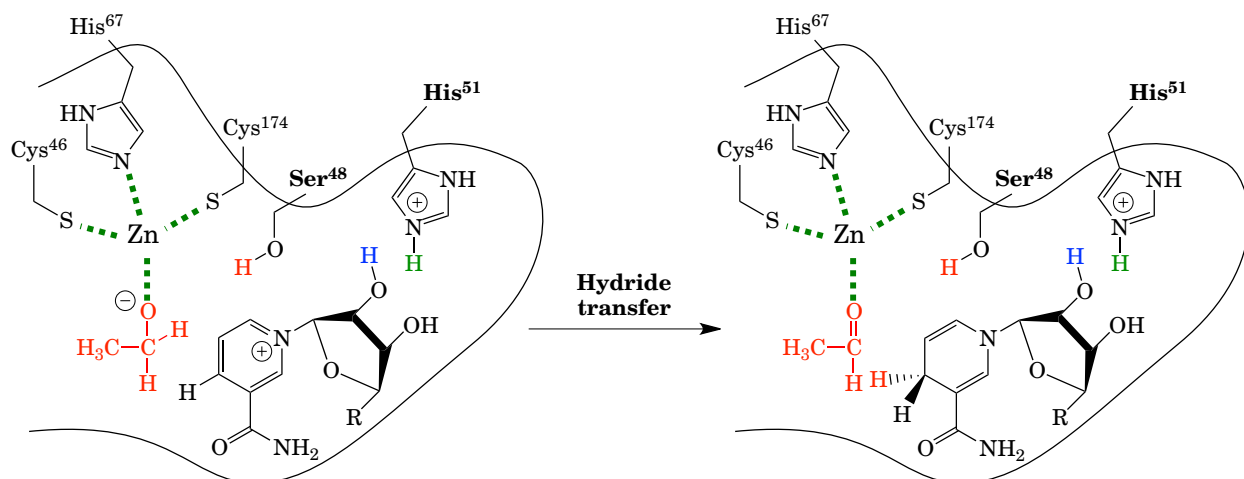
Binding of substrate causes a conformational change that excludes water from the active site, and that positions the substrates in preparation for catalysis. When the substrate binds, the zinc ion coordinates (*i.e.* binds) to the alcohol oxygen. This bond between the zinc ion and the substrate assists in stabilizing the negative charge that will develop on the substrate oxygen (to put this in familiar terms, in the

enzyme active site, the alcohol hydroxyl group pK_a decreases from ~ 18 to ~ 6.4 .

The His⁵¹ indirectly removes a proton from the alcohol. This process involves a chain of proton removals: the histidine removes a proton from the NAD ribose; the NAD ribose removes a proton from Ser⁴⁸, and Ser⁴⁸ removes a proton from the substrate alcohol. (The proton abstraction by the His⁵¹ is possible because, in the substrate-occupied active site, the pK_a of His⁵¹ increases considerably.)



The NAD can then accept a hydride (H^-) from the substrate, to produce NADH and the aldehyde form of the substrate.

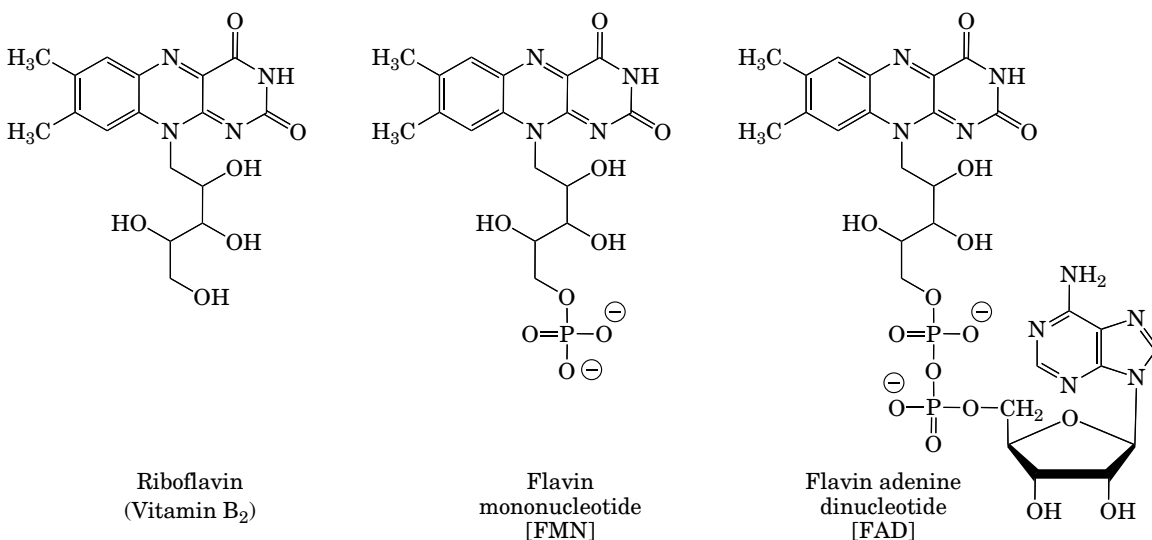


The last step in the catalytic process is the release of the products (acetaldehyde and NADH), which regenerates the original enzyme. The release of the substrates allows the deprotonation of His⁵¹, and resets the enzyme for the next catalytic cycle.

The mechanism of alcohol dehydrogenase thus includes transition state stabilization (the stabilization of the negative charge on the substrate oxygen in particular), as well as acid-base catalysis. It also illustrates the marked changes in pK_a values that can occur in specific environments.

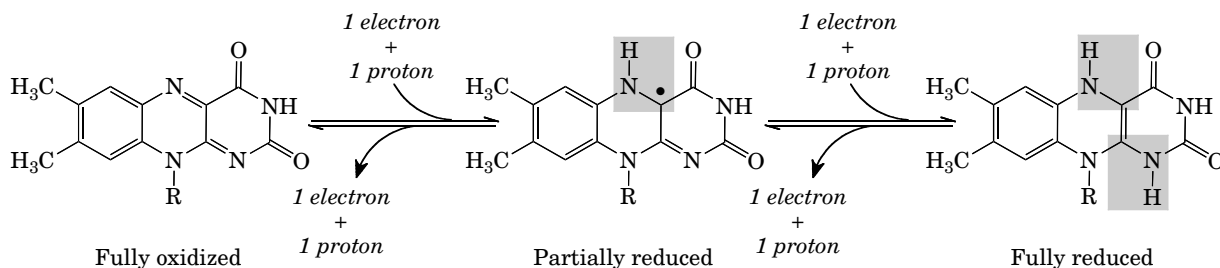
Vitamin B₂ (riboflavin)

Riboflavin is the precursor to the flavin coenzymes FMN and FAD. Flavins are yellow in color and are light sensitive (flavins in food left out in the sun degrade fairly rapidly). Riboflavin deficiency is so rare that it has no name. Note that FMN is not really a nucleotide, and FAD is not a dinucleotide. These names are historical, and were assigned before the structures of the molecules were determined.



FMN and FAD are non-covalently attached to their enzymes, but generally do not dissociate. These compounds therefore nearly always function as **prosthetic** groups, and act as storage locations for electrons within proteins.

The isoalloxazine ring can accept or transfer electrons one at a time, although they can carry up to two electrons. This ability to accept either one or two electrons is often of critical importance for biological reactions. The structures below show the different electronic states observed for both flavin coenzymes.



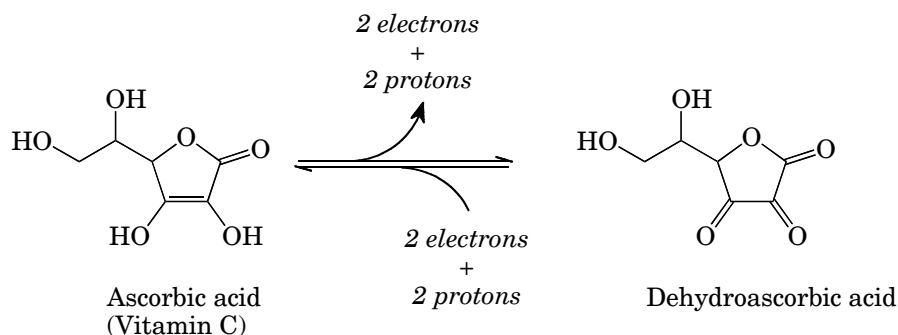
The “partially reduced” form contains a radical (note that the carbon with the “•” has only three actual bonds). This form of the compound (technically known as the **semiquinone** form of the isoalloxazine ring) is actually fairly stable. It is the relative stability of this state which allows flavin-containing enzymes the flexibility of transferring electrons either one or two at a time.

The **flavin and nicotinamide coenzymes are critically important electron carriers** for a wide variety of biological processes. Both types of coenzymes are used

by a number of enzymes. The nicotinamide coenzymes are used for carrying pairs of electrons **between** proteins, while the flavins primarily function as temporary storage for electrons **within** proteins.

Vitamin C (ascorbic acid)

Most animals can synthesize vitamin C from glucose, but primates (and guinea pigs) are an exception. Vitamin C acts as a reducing agent (as shown below), and is important in maintaining some metal cofactors in reduced state. It is required for proline and lysine hydroxylation (in collagen synthesis), for *dopamine β -hydroxylase* (an enzyme essential for norepinephrine and epinephrine synthesis), for bile acid synthesis, and for tyrosine degradation. It also assists in iron absorption and is a general antioxidant.



Some vitamin C is stored, especially in the adrenal. These stores can last for 3 to 4 months before symptoms of scurvy begin to appear.

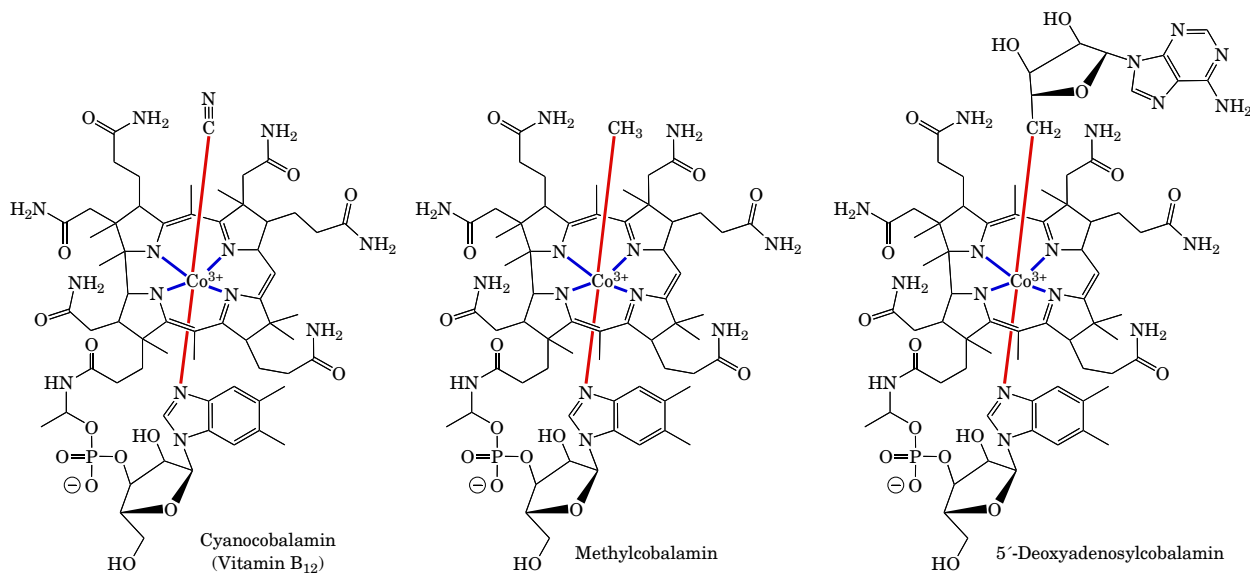
Vitamin B₁₂ (cobalamin)

Vitamin B₁₂ is a complex compound that is converted into several coenzymes.⁴ It is used for shifting of hydrogen between carbon atoms, usually in conjunction with a shift of some other group (*e.g.*, NH₂, or CH₃); Vitamin B₁₂ can also act as a methyl group carrier, accepting the carbon from tetrahydrofolate derivatives. In humans, vitamin B₁₂ has only two known functions: 1) in the methionine synthase reaction, vitamin B₁₂ accepts a methyl group from methyl-THF and donate it to homocysteine to form methionine and 2) vitamin B₁₂ is a coenzyme for methylmalonyl-CoA mutase, which catalyzes the rearrangement of methylmalonyl-CoA (from odd chain fatty acid metabolism and some amino acids) to succinyl-CoA. The structures below include the structure of the actual vitamin and of the two major coenzyme forms found in humans. (The cyanide group in cyanocobalamin is not necessarily present, and is typically an artifact of purification.) 5'-Deoxyadenosyl cobalamin is the coenzyme required by **methylmalonyl-CoA mutase**, while methylcobalamin acts as the methyl-group donor during the **methionine synthase** reaction.

Vitamin B₁₂ is not made in plants; it is only synthesized by microorganisms. Strict vegetarians occasionally have difficulty obtaining enough vitamin B₁₂, although the dietary requirements for vitamin B₁₂ are very low (the RDA is 6 μ g/day). Deficiency

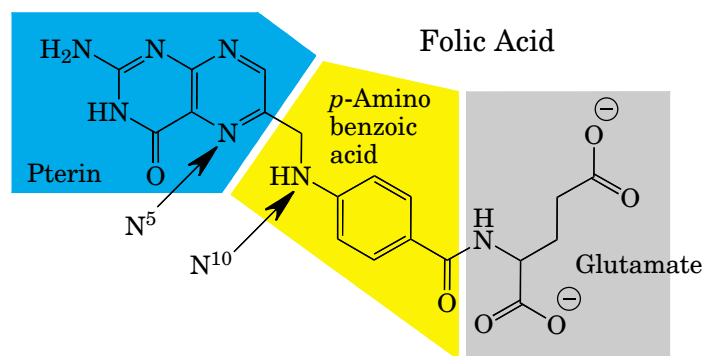
⁴ Note that the corrin ring of vitamin B₁₂ is similar, but not identical, to the porphyrin ring found in heme-containing proteins. Vitamin B₁₂ is **not** used as a source of heme.

in vitamin B₁₂ results in a potentially lethal condition called **pernicious anemia**. In addition to a dietary deficiency in the vitamin, vitamin B₁₂ deficiency may be caused by a lack of intrinsic factor, a glycoprotein required for absorption of the vitamin. Vitamin B₁₂ is deficiently also observed as a result of impaired absorption in patients who have undergone bariatric surgery, and as a consequence of aging.



Folic acid

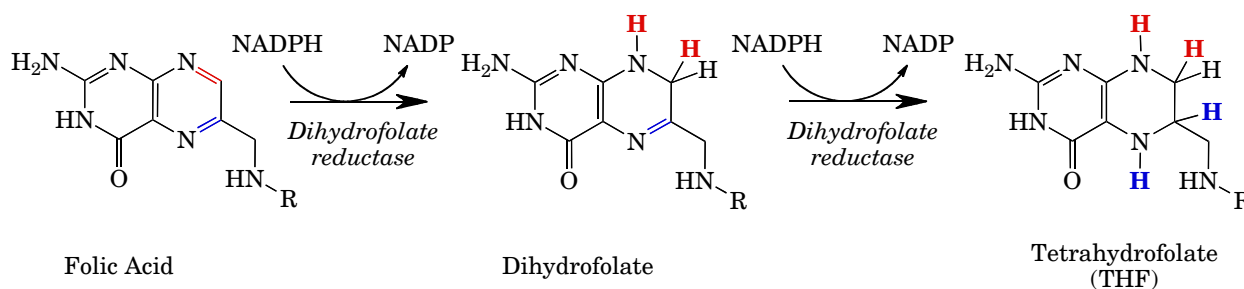
Folic acid is comprised of a pterin ring linked to *p*-aminobenzoic acid (PABA) that is in turn linked to glutamic acid. Humans require folate in the diet because they cannot synthesize PABA (the sunscreen compound) and cannot create the link to the glutamate. The structure of folic acid is shown below (the shaded regions indicate the different components within the structure):



The physiologically active form of folate has several glutamate residues (usually 5 in humans, and 7 in plants; although the absorbed form contains a single glutamate due to removal of the others by peptidases in the intestines).

Folate must be converted to the active coenzyme, **tetrahydrofolate**, by two

successive redox reactions catalyzed by **dihydrofolate reductase**.



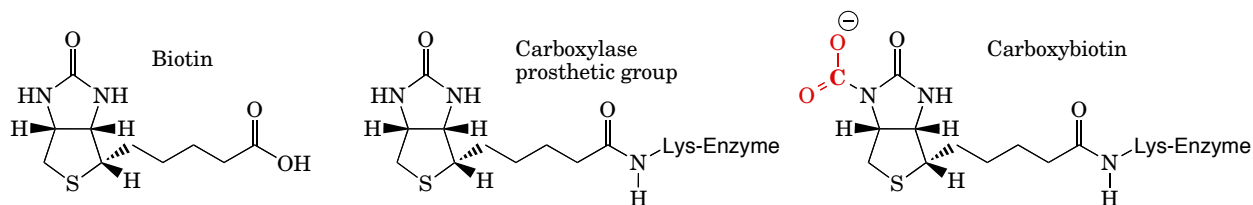
Tetrahydrofolate acts as a single carbon carrier. The carbon can be present in most of the possible oxidation states for carbon with the exception of carbonate. The carbon unit is attached to the tetrahydrofolate molecule at either the N⁵-position or the N¹⁰-position, or by forming a bridge between the N⁵ and N¹⁰-positions.

Tetrahydrofolate is required for a number of biosynthetic enzymes. During thymidine synthesis (in the conversion of dUMP to dTMP catalyzed by thymidylate synthase), tetrahydrofolate is converted to dihydrofolate; the dihydrofolate must be reduced to tetrahydrofolate to restore the active cofactor. Because thymidine is required to synthesize DNA, and because dividing cells must synthesize DNA, inhibition of dihydrofolate reductase (*e.g.*, by methotrexate) prevents cell division.

Because of its importance to growing cells, folate is required to prevent some types of birth defects. In adults, folate deficiency causes **megaloblastic anemia**. Folic acid is the source of the methyl group donated by methylcobalamin in the *methionine synthase* reaction, and therefore folic acid deficiency shares some symptoms with vitamin B₁₂ deficiency.

Biotin

Some, although not all, animal carboxylase enzymes (enzymes that add CO₂ to substrates) require the water-soluble vitamin biotin. Biotin is covalently attached to the enzyme by an amide link to a lysine side chain.



An ATP-dependent process covalently links CO₂ (using HCO₃⁻ as the actual substrate) to one of the biotin nitrogens; the carboxybiotin then acts as a carboxylate donor for the substrate.

Animals have four biotin dependent enzyme complexes:

- 1) **Pyruvate carboxylase**, the first step in of the gluconeogenic pathway from pyruvate, and an important source of oxaloacetate for the TCA cycle.
- 2) **Acetyl-CoA carboxylase**, the control step for fatty acid synthesis (this

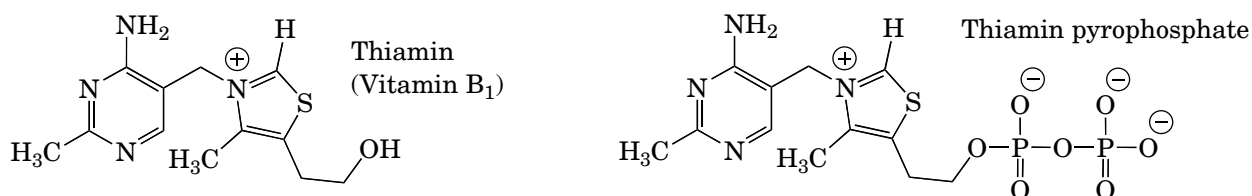
enzyme converts acetyl-CoA to malonyl-CoA).

- 3) **Propionyl-CoA carboxylase**, which produces methylmalonyl-CoA, the first step in the conversion of propionyl CoA (generated from odd-chain fatty acid and some amino acid oxidation) to succinyl-CoA, which can enter the TCA cycle.
- 4) **β -Methylcrotonyl-CoA carboxylase**, an enzyme required for oxidation of leucine and some isoprene derivatives.

Biotin deficiency is sometimes found in consumers of raw chicken eggs, because raw eggs contain a protein called avidin that binds biotin with very high affinity and prevents its absorption (avidin is denatured by the cooking process, so cooked egg consumption is not linked to biotin deficiency).

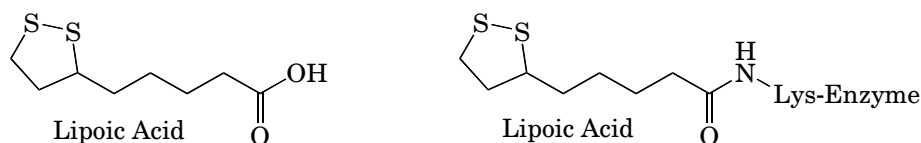
Vitamin B₁ (thiamin)

The vitamin thiamin is converted to the coenzyme thiamin pyrophosphate in an ATP-dependent reaction. Thiamin pyrophosphate is a coenzyme required for certain types of oxidative decarboxylation reactions, including the reactions catalyzed by the pyruvate dehydrogenase complex (see below) and related enzymes. Deficiency in thiamin causes **beriberi**, a disorder due to impaired energy metabolism, especially in the muscles and brain.



Lipoic acid

Lipoic acid forms an amide link to a specific lysine residue of certain enzymes. The lipoamide prosthetic group acts as an acyl carrier. Lipoic acid may not be a vitamin; no dietary deficiency has ever been observed, and some evidence suggests that humans can synthesize lipoic acid.

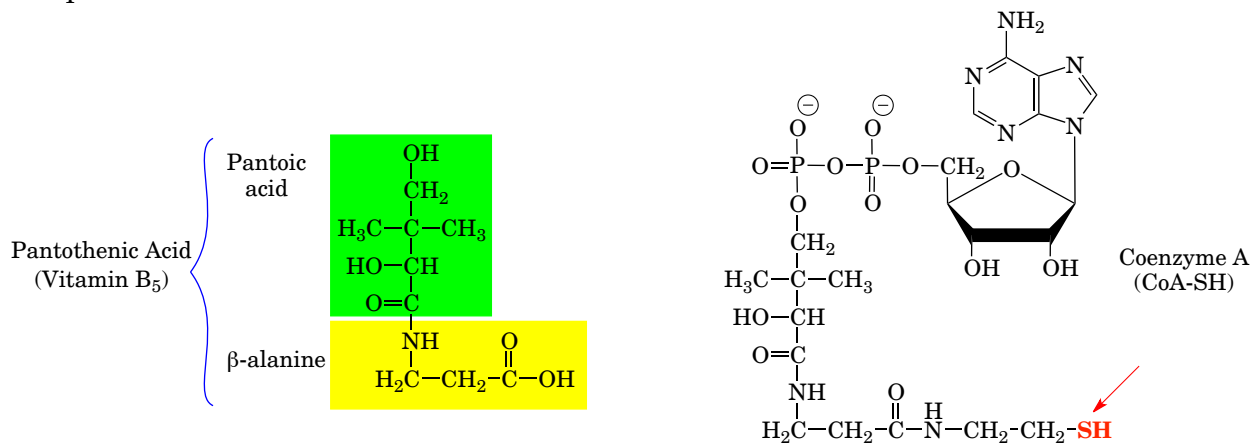


Vitamin B₅ (pantothenic acid)

Pantothenic acid is the precursor of Coenzyme A and of the prosthetic group of the Acyl Carrier Protein domain in fatty acid synthase. The active form of the cofactor is produced by formation of a peptide bond to cysteine followed by decarboxylation of the cysteine residue, and then by conjugation to the remainder of the coenzyme.

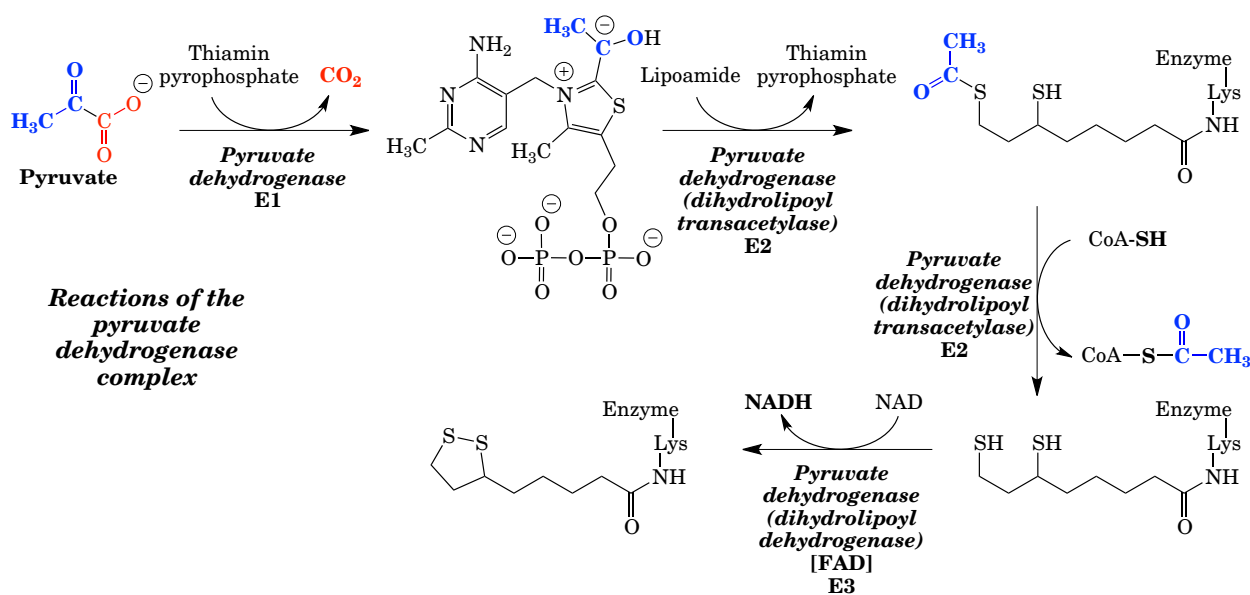
The coenzymes produced from pantothenic acid act as carriers of acyl chains in a variety of metabolic reactions, including those in portions of the TCA cycle, in fatty

acid oxidation, and in fatty acid synthesis among many others. Coenzyme A (usually abbreviated CoA) has a free sulfhydryl group (note the arrow in the drawing below). The sulfhydryl group is used to carry the carbon compounds; the remainder of the molecule acts as a “handle”. In other words, the remainder of coenzyme A provides a structure that the enzyme can bind and orient when catalyzing reactions involving the attached carbon unit. Free CoA is often termed CoA-SH to indicate free sulfhydryl group, and to remind the reader of the attachment site for the carbon compounds.



Pantothenic acid is readily available in most foods; deficiency in this vitamin is rare except in individuals with extremely poor diets (such as concentration and prisoner-of-war camp inmates).

An **example** of the function of several coenzymes is provided by the pyruvate dehydrogenase reaction. Pyruvate dehydrogenase is very large multienzyme complex (the complex contains 60 polypeptides in bacteria, and over 130 polypeptides in humans). Pyruvate dehydrogenase requires five coenzymes: thiamin pyrophosphate, lipoamide, FAD, NAD, and CoA.



The reactions catalyzed by the pyruvate dehydrogenase complex are:

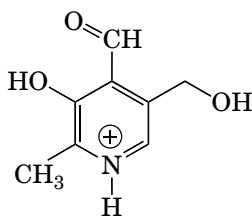
1. Addition of the ketoacid (pyruvate) to thiamin pyrophosphate at the position next to the N^+ (carbanion addition) to form a hydroxyethyl product, with release of the carboxylate as CO_2 .
2. Reaction of lipoamide with the hydroxy ethyl product to re-form free thiamin pyrophosphate and acetyl lipoamide.
3. Reaction of acetyl lipoamide with CoA-SH to form acetyl-CoA and dihydrolipoamide.
4. Reduction of FAD by the dihydrolipoamide.
5. Reduction of NAD^+ by the $FADH_2$ to NADH.

The net reaction is the formation of acetyl-CoA and CO_2 , with NADH formed to conserve the electrons released during pyruvate oxidation to allow their use for other processes.

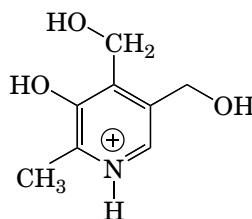
The reaction catalyzed by pyruvate dehydrogenase is required for entry of pyruvate into the tricarboxylic acid (TCA) cycle. In addition, at least two closely related enzyme complexes, α -ketoglutarate dehydrogenase (an enzyme in the TCA cycle) and branched-chain α -ketoacid dehydrogenase (an enzyme required for leucine, isoleucine, and valine breakdown), are found in humans.

Vitamin B₆ (pyridoxine, pyridoxal, pyridoxamine)

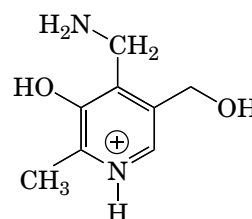
Three forms of vitamin B₆ can be absorbed from the diet:



Pyridoxal

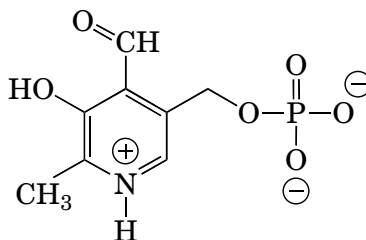


Pyridoxine



Pyridoxamine

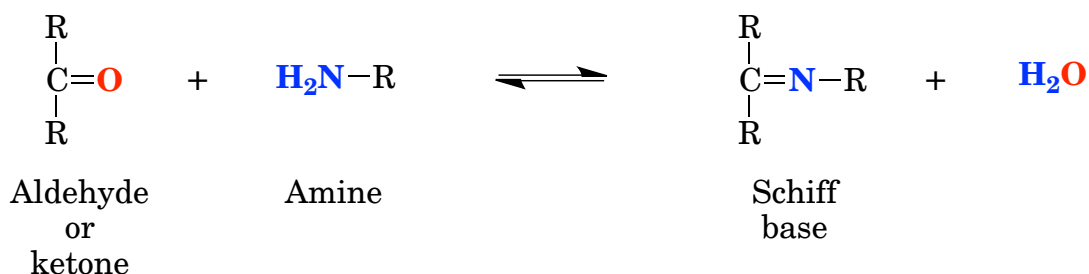
The primary cofactor form is pyridoxal phosphate:



Pyridoxal phosphate

Pyridoxal phosphate is another prosthetic group. It forms a reversible covalent association with enzymes; it is typically present as a Schiff base with a lysine ϵ -amino group in the resting state. Pyridoxal phosphate is used in a wide variety of

reactions; it is especially important in reactions involving amino acids, because the aldehyde forms a Schiff base with the α -amino group, allowing stabilization of intermediates for many types of reactions.

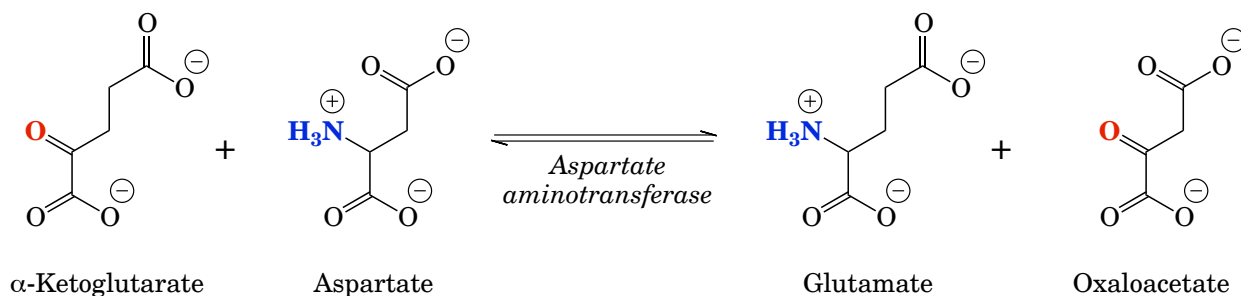


Schiff base formation (shown above) is a readily reversible process in aqueous solution: carbon-oxygen double bonds can exchange with carbon-nitrogen double bonds. (Note that carbon-nitrogen *single* bonds do not allow this process, and therefore are in some respects more stable than carbon-nitrogen double bonds, at least in aqueous environments.)

Pyridoxal phosphate is also a cofactor for **glycogen phosphorylase** (it forms a Schiff base with a lysine from the enzyme); about 75% of the pyridoxal phosphate in the body is part of phosphorylase. Glycogen phosphorylase is responsible for degradation of glycogen; we will discuss this reaction later in this course. Deficiency in pyridoxal is fairly rare; it is either associated with other B vitamin deficiencies, with isoniazid treatment, with alcoholism, or with oral contraceptive use combined with inadequate diet (although in these cases, it is usually the breast-fed infant that suffers).

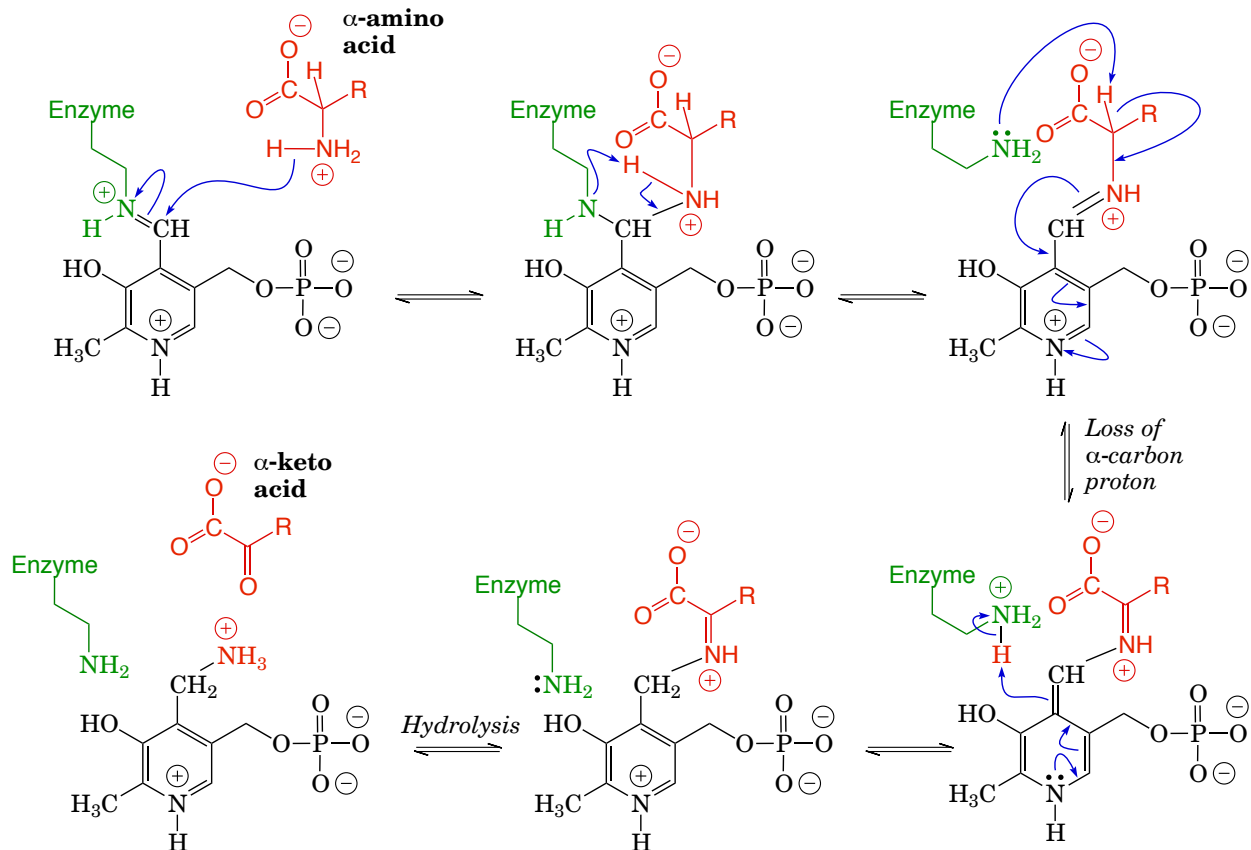
Examples of pyridoxal phosphate-dependent enzymes are provided by **aspartate aminotransferase** and **serine hydroxymethyltransferase**. Aspartate aminotransferase is a member of a class of enzymes that allow exchange of amino groups from one compound to another. Serine hydroxymethyltransferase is involved in amino acid metabolism, and is the major carbon source for tetrahydrofolate-dependent carbon-donation reactions.

First, we will look at the aminotransferase mechanism. All aminotransferases transfer amine groups (as the name implies) from one carbon compound to another. The substrates and products are an amino acid and an α -ketoacid, with the only difference being which carbon chain contains the amine.



In the absence of substrate, the aminotransferase pyridoxal phosphate is bound to the enzyme via a Schiff base linkage to the ϵ -amino group of a lysine residue.

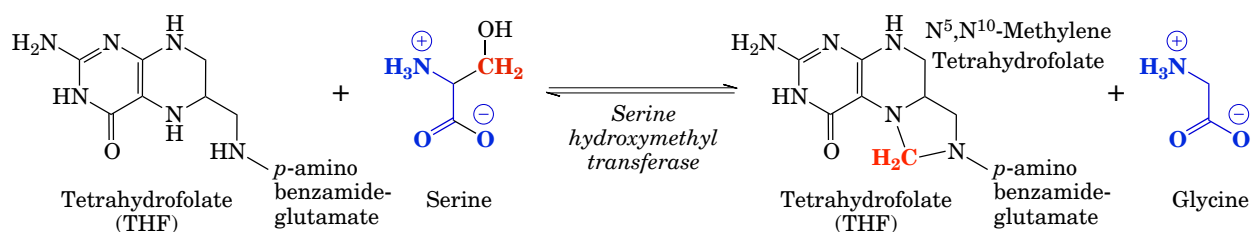
The reaction begins with the binding of an α -amino acid. An exchange process allows the α -amino acid to form a Schiff base with the pyridoxal phosphate, displacing the lysine ϵ -amino group (shown as a two step process in the diagram). The Schiff base then rearranges, with loss of the hydrogen attached to the α -carbon; the α -carbon is now present as a Schiff base. This can then hydrolyze to release the α -ketoacid. Note, however, that the “pyridoxal” phosphate now has an amine; the enzyme must then bind another α -ketoacid and reverse the process to complete the catalytic cycle. The pyridoxal phosphate therefore acts as both a mechanism for enhancing the reaction by altering the chemistry at the α -carbon, and as a temporary storage location for the amine group.



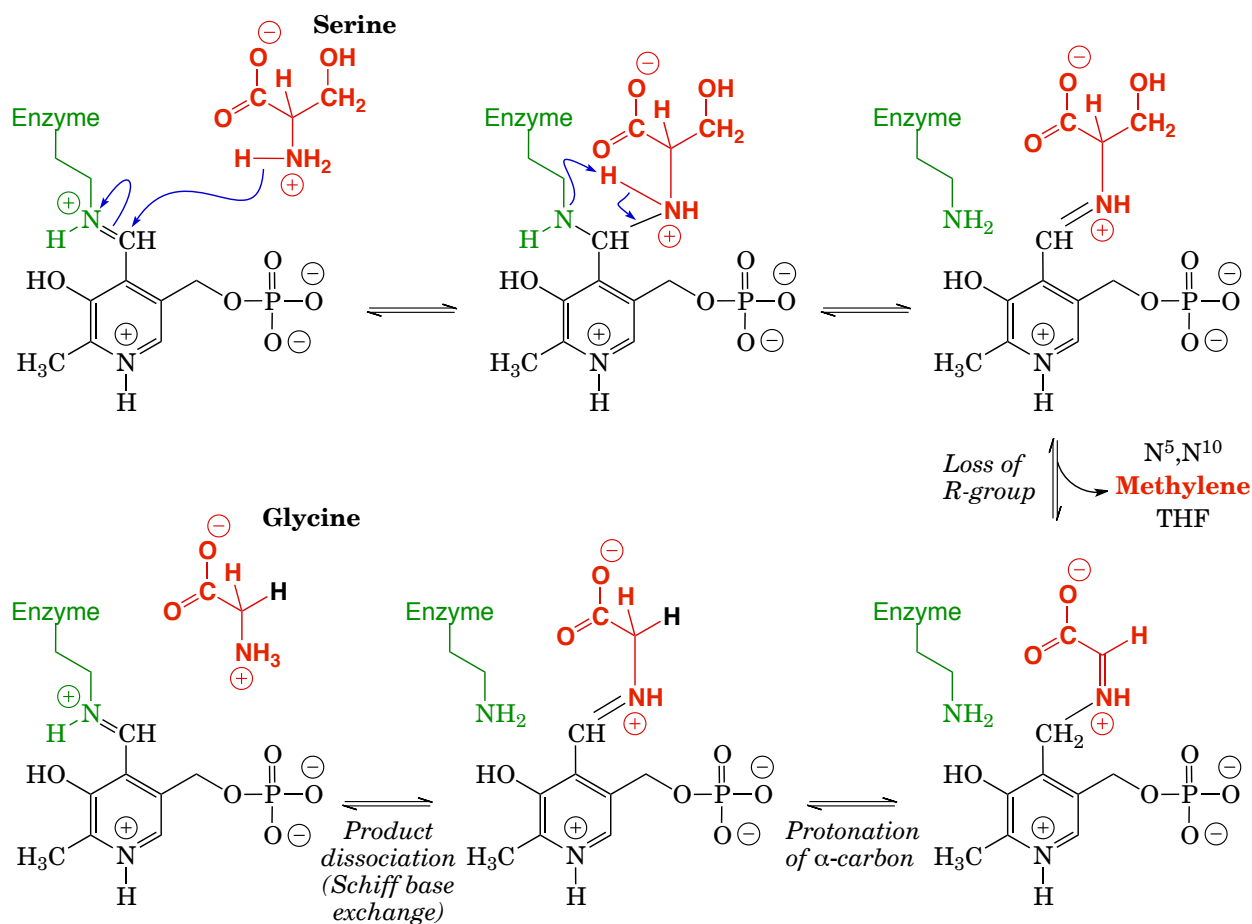
Serine hydroxymethyltransferase catalyzes a different reaction (below). Although it exhibits very little sequence similarity with aspartate aminotransferase, and limited similarity in the reaction it catalyzes, the two enzymes have a similar overall three-dimensional structures.

The first part of the reaction mechanism, the binding of the serine substrate, is essentially identical to that seen for aspartate aminotransferase. However, the

bound substrate then undergoes loss of the R-group, rather than loss of the hydrogen attached to the α -carbon. The Schiff base then rearranges to allow the dissociation of glycine, and regeneration of the enzyme.



The R-group (a carbon at an oxidation state equivalent to formaldehyde) removed from the serine does not dissociate from the enzyme, but is instead attached to tetrahydrofolate (this fairly complex process is not explicitly shown in the reaction mechanism scheme below). The reaction is reversible; glycine and N^5,N^{10} -methylene tetrahydrofolate can be used to synthesize serine, although the forward direction is more common physiologically.



The aminotransferase and serine hydroxymethyltransferase reactions shown above

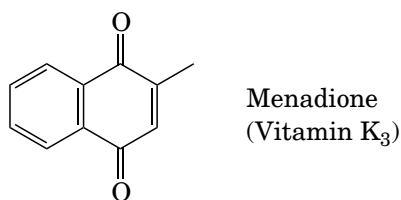
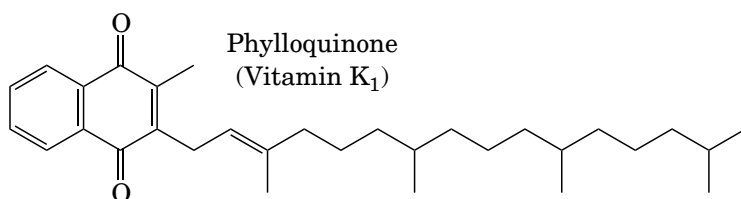
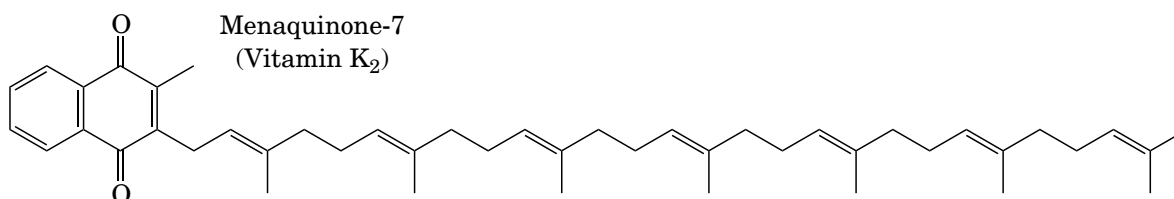
are useful examples of the versatility of the pyridoxal phosphate-dependent enzymes. Nearly all enzymes that catalyze reactions involving chemical alterations to an amino acid α -carbon use pyridoxal phosphate. The Schiff base formation alters the chemistry at this carbon, and allows modification of any of the four substituents of this carbon.

Fat soluble vitamins

The fat-soluble vitamins have a variety of roles. Vitamin K is the only one that acts as a classical coenzyme, although retinal, a derivative of vitamin A, is a prosthetic group for rhodopsin and related proteins, which are G-protein coupled receptor family proteins that act as photon receptors in the retina.

Vitamin K

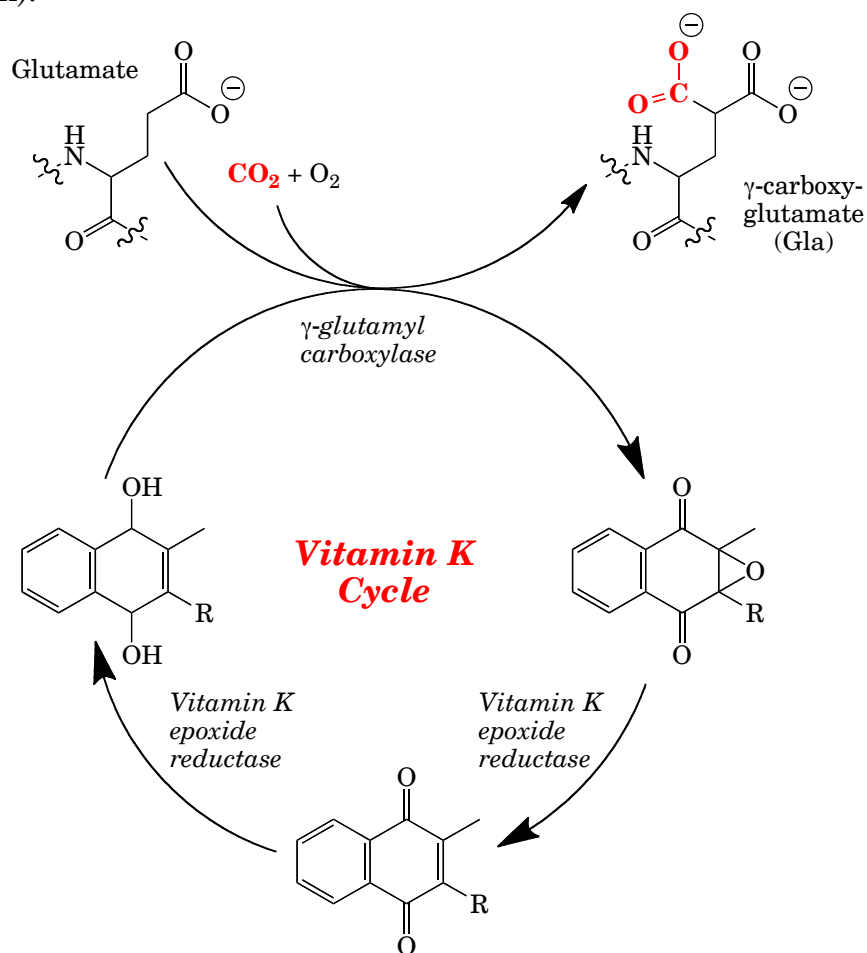
Vitamin K was awarded the letter K due to its role in coagulation processes (the German word for coagulation starts with a K). Menadione is a synthetic compound that can be converted into the active forms of Vitamin K. It can be absorbed readily, but has been found to be toxic and is rarely used in supplements; the other forms require fat absorption mechanisms. Menaquinone is a bacterial product, and can be produced in humans from menadione (the "7" refers to the number of isoprene units; humans use 6, 7, or 9 isoprene chains). Phylloquinone is a plant version of the vitamin, which is used by plants in photosynthesis; the role of phylloquinone in plants is totally unrelated to the function of vitamin K in humans.



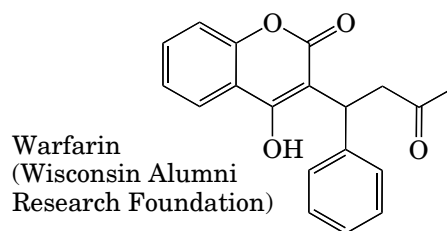
Vitamin K is required as an enzyme cofactor in the synthesis of γ -carboxyglutamic acid. γ -Carboxyglutamic acid is formed as a post-translational modification required for some proteins. This unusual amino acid residue is important for the function of

a number of proteins, the most notable being some of the clotting factors.

The synthesis of γ -carboxyglutamate from glutamate residues is a cycle (see figure below). The reduced form of vitamin K acts as coenzyme for the carboxylase that produces the modified glutamate side-chain (note that this carboxylase does not require biotin).



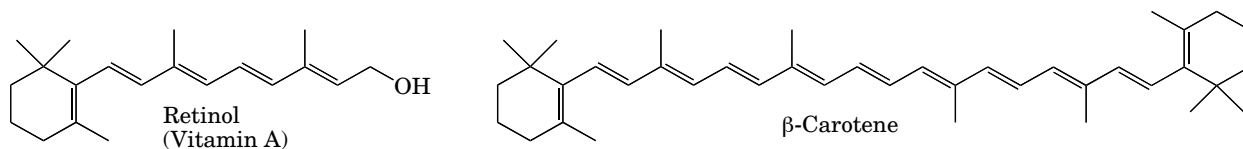
Formation of the active hydroquinone form of vitamin K, and regeneration of the quinone are both catalyzed by **vitamin K epoxide reductase (VKOR)**. Vitamin K epoxide reductase is inhibited by warfarin, a compound developed by the Wisconsin Alumni Research Foundation. Indirect inhibition of γ -carboxyglutamate formation is the basis of the anticoagulant action of warfarin, which is used in small doses as an anticoagulant in stroke patients, and in higher doses as a rodent poison. Variation in response to warfarin is observed in rats and in humans; this variation is probably due to differences both in amount and in structure of vitamin K epoxide reductase, and/or to differences in dietary levels of vitamin K.



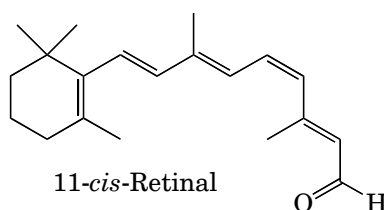
The remaining fat-soluble vitamins play important roles in humans, but do not act as classical coenzymes or coenzyme-precursors.

Vitamin A

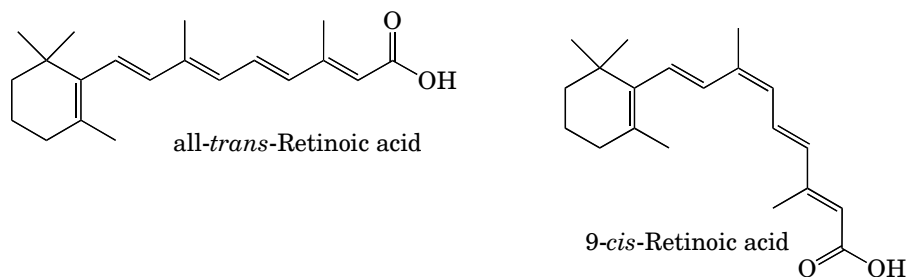
Retinol is vitamin A, although most animals can convert the plant terpene β -carotene into retinol. Retinol is toxic at higher levels; in contrast, β -carotene does not appear to be toxic to most animals.



Vitamin A has a few known major functions: 1) Retinol acts as the precursor of the visual pigment 11-*cis*-retinal. Light absorption converts the 11-*cis*-retinal present as a prosthetic group in the protein rhodopsin to all *trans*-retinal; this is the first step in detecting the presence of light.



2) Retinol can be converted (irreversibly) to retinoic acid. All *trans*-retinoic acid and 9-*cis*-retinoic acid are ligands for nuclear receptors, and are important in regulation of the cell growth and differentiation processes involved in the growth and development of animals.



3) Retinoic acid may have a role in glycoprotein biosynthesis.

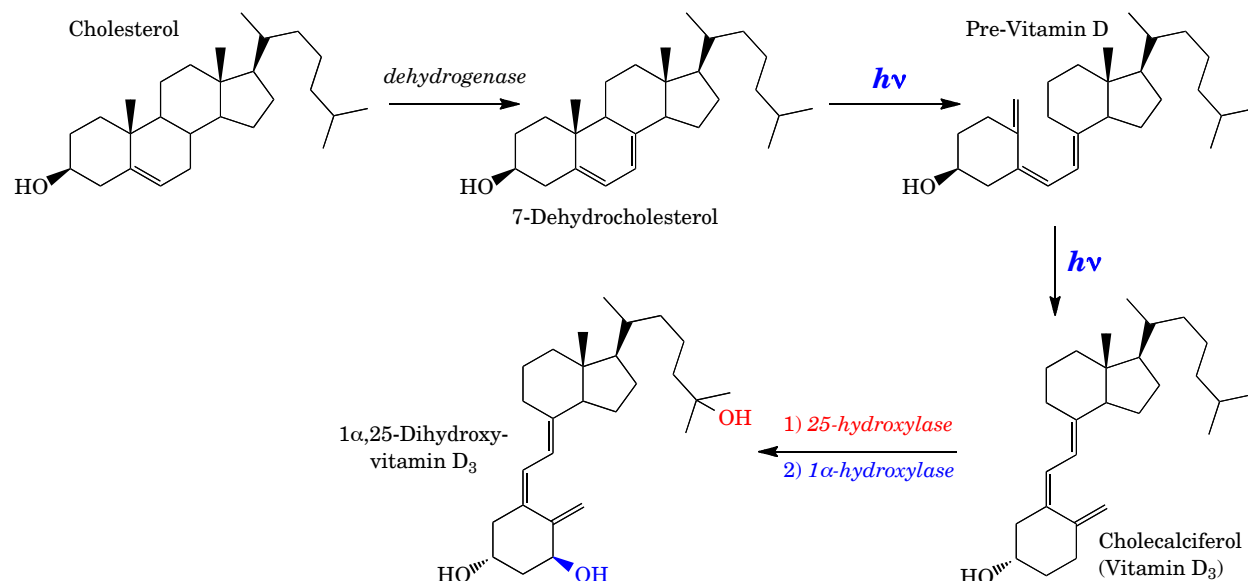
Retinol has a specific serum carrier protein, synthesized in the liver, and both retinol and retinoic acid have specific cytosolic carrier proteins. The main function of retinol may be to act as a precursor of retinal and retinoic acid, but retinol function is incompletely understood.

Retinol is “sticky”, in that it tends to bind to glass and plastic, and is light sensitive. Patients dependent on intravenous nutrition may be somewhat retinol deficient due

to losses of the retinol bound to the IV tubing or to photo-inactivation of the compound. β -carotene and retinoids are antioxidants, and may play important roles in scavenging free radicals released during metabolism.

Vitamin D

Humans can synthesize vitamin D; it is a vitamin only in humans not exposed to sunshine.

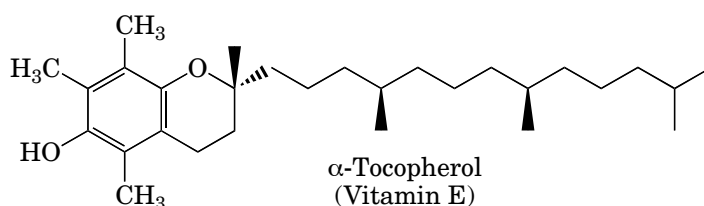


The current working hypothesis for vitamin D action suggests that vitamin D must be converted to the active form, 1 α ,25-dihydroxyvitamin D, by two sequential hydroxylations. The 1 α ,25-dihydroxyvitamin D acts as a hormone, and has a specific nuclear receptor. Other derivatives of vitamin D may have biological functions, but, if so, these functions are much less well understood.

Deficiency in vitamin D causes Rickets (in children) and osteomalacia (in adults) due to inability to absorb calcium. Overdoses of vitamin D result in hypercalcemia and abnormalities of calcium metabolism that are debilitating but rarely, if ever lethal.

Vitamin E

α -Tocopherol is the most biologically active form of vitamin E. Vitamin E is an important antioxidant; it acts as a radical scavenger. It has no other known physiological function. It is likely that the current RDA is too low for full benefit from its antioxidant effects.



Summary

Vitamins are compounds that are required in relatively small amounts but that cannot be synthesized in quantities large enough to meet the normal needs of the organism.

Many vitamins, and especially the water-soluble vitamins, act as precursors for the production of coenzymes. Coenzymes allow a much larger number of reaction mechanisms than would be possible for enzymes composed only of the standard amino acids. Many of the coenzymes act as temporary storage locations for electrons or small molecules, and as “handles” that allow proper positioning of the covalently bound substrate during the reaction.

Vitamin-derived coenzymes are involved in a number of oxidation and reduction reactions. This is especially notable for the flavin-derived prosthetic groups FMN and FAD, and the nicotinamide-derived coenzymes NAD and NADP. Many of these enzymes catalyze physiologically reversible reactions. Due to the metabolic importance of these compounds, all biochemists need to understand the chemistry of the flavin and nicotinamide coenzymes.

Folic acid, cobalamin, and biotin are all used for holding single carbon units. Biotin is a prosthetic group that is covalently attached to the enzyme. Tetrahydrofolate-derivatives and cobalamin derivatives are used as freely diffusing carbon carriers.

Thiamin pyrophosphate and lipoic acid are used to covalently bind small molecules (of two or more carbons). Coenzyme A is a soluble carbon carrier; it carries molecules units ranging in size from two to about 24 carbons.

Pyridoxal phosphate is used as a prosthetic group by glycogen phosphorylase and by most of the enzymes involved in altering the α -carbon of amino acids.

Vitamin K (and perhaps retinal) are the only fat-soluble vitamins that act as coenzymes. The other fat-soluble vitamins have non-enzymatic roles.