UNIT 3 VITAMINS

Structure

3.1 INTRODUCTION

You have already learnt about the structure and properties of carbohydrates, lipids and proteins in the earlier two Units of this Course. Now, in this unit we shall focus on vitamins. Vitamins are another group of extremely important nutrients. These are the organic chemicals, other than essential amino acids and fatty acids, that must be supplied to the body in small amounts to maintain health. Being a student of dietetics, it is absolutely important for you to have a comprehensive knowledge about these substances – their nature, structure and properties. You may wonder, why? Well, simply because from a nutritional standpoint, the effect of cooking/processing on these substances will be best understood with the knowledge of the structure, properties etc. of these essential substances. In this Unit we will get to know about the structure, nature and properties of vitamins.

Objectives

After studying this unit, you will be able to:

- describe the chemical nature of vitamins,
- classify the different vitamins into classes to which they belong,
- illustrate their chemical structure,
- discuss the physico-chemical properties of vitamins, and
- relate the chemical structure and biochemical function of the water-soluble vitamins and their metabolites and antagonists to their regulatory role in metabolism.

3.2 VITAMINS – INTRODUCTION AND CLASSIFICATION

Vitamins are *organic compounds required in very small amounts by the body for growth, maintenance and sustenance of life.* But, a prolonged absence of these substances from the diet leads to different general and specific disease symptoms about which you may already be aware of and we have also discussed about them in the Advance Nutrition Course in Units 7 and 8. Do look up these units as you read through this unit.

It was in the year 1880 when *Sir Frederick Crowl* and *Hopkins* first reported the necessity of certain accessory food factors besides the well known dietary substances for healthy living. However, it was *Funk,* who in 1912 first observed that diseases such as beriberi, scurvy and pellagra can be prevented by certain components of the food. He proposed the name *vitamine* for these food components considering that they are all amines. Afterwards, when it was realized that all such compounds do not possess nitrogen in their structures, the name was modified to *vitamin.*

The vitamins share a family of characteristics. They neither are catabolized to generate energy nor are they used for structural purposes. Many vitamins are, in fact, used as cofactors for enzymes and are called as *coenzymes* about which you will learn in detail in the next Unit. Two vitamins viz. vitamin A and D are converted to hormones. Vitamin A also functions as a cofactor in the visual cycle. These are a few functions of vitamins highlighted herewith. You will learn more about their role in Unit 9 later in this course.

Vitamins are generally synthesized by plants and found in animals as a result of food intake and also because of synthesis of some of the vitamins by gut microorganisms. All living beings not necessarily need the same number or kind of vitamins as some of these may be produced by the organism concerned. For instance, rat can synthesize vitamin C but a guinea pig or man cannot. We, human beings, in fact can synthesize only two vitamins – vitamin D and niacin.

Let us then learn about the chemistry of these vitamins. We start our discussion by first classifying them.

Classification of Vitamins

Vitamins widely vary from each other from the structural point of view. Conventionally, they are classified on the basis of their solubility in water or fat. Accordingly, they are classified as:

- *Water-soluble vitamins,* which include thiamin (vitamin B_1), riboflavin (vitamin B_2), niacin and nicotinamide (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine and related compounds (vitamin B_6), cyanocobalamin and related compounds (vitamin B_{12}), ascorbic acid (vitamin C), biotin (vitamin H) and folic acid (vitamin M).

- *Fat-soluble vitamins,* which include retinol (vitamin A), cholecalciferol (vitamin D), tocopherols (vitamin E) and phylloquinone and related compounds (vitamin K)

Based on this classification, we shall review the structure and properties of the two classes of vitamins, starting with water soluble vitamins.

3.3 STRUCTURE AND PROPERTIES OF WATER SOLUBLE VITAMINS

This section will focus only on the native structure and physico-chemical properties of some common water soluble vitamins. You will learn about their coenzyme (modified) forms in the next unit and biochemical role in Unit 9 of this Course. Food sources, daily requirements, physiology of digestion, functions, deficiency diseases, assessment procedures, concept of bioavailability etc. of these vitamins are discussed in the Advance Nutrition Course, Unit 8. Hence it is suggested that you go through the appropriate sections on Vitamins in the two courses together.

This will help you get a comprehensive understanding on the topic. Here we begin our discussion on water soluble vitamins by taking up vitamins belonging to the B-group of vitamins. We start with thiamin, the first of the B-complex vitamins.

3.3.1 Thiamin (vitamin B_1)

Thiamin was first isolated in 1926 from rice polishing by *Jansen* and *Donath.* Its empirical formula was established in 1931 by *Windaus* and co-workers and the chemical structure of the compound was elucidated in 1936 by *Williams* and co-workers.

The chemical name for this water soluble vitamin is 3-[(4-amino-2-methyl-5-pyrimidinyl) methyl] - 5-(2-hydroxyethyl)-4-methylthiazolium. Do not get perturbed by this long name. You would not be expected to remember this chemical name for thiamin. However, the chemical name will help you understand the structure of thiamin. Look at the structure of thiamin given in Figure 3.1. As you would have noticed, thiamin possesses one pyrimidine and one thaizole ring that are connected by a methylene bridge (coloured red).

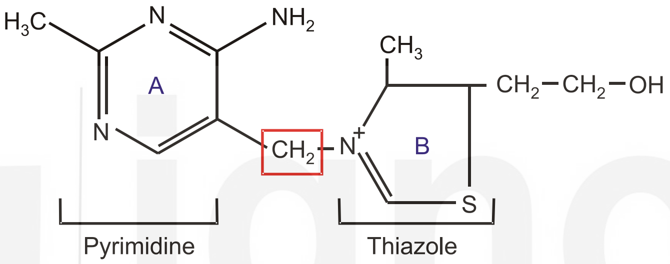

Figure 3.1: Structure of thiamin

Chemically, ring A is called as 2, 5-dimethyl-6-aminopyrimidine and ring B is called as 4-methyl-5-hydroxyethyl thiazole. The thiazole ring bears a primary alcohol side chain that becomes phosphorylated in vivo to give the thiamin phosphate esters that have the cofactor activity. Thiamin occurs in four forms: thiamin, thiamin monophosphate (TMP), thiamin diphosphate (also known as thiamin pyrophosphate, TPP) and thiamin triphosphate (TTP), the later three of which have phosphate molecules attached to the side chain as shown in Figure 3.2, hence called the phosphorylated forms of thiamin. TTP is the most abundant form and constitutes almost 80% of total thiamin. We shall learn more about its activity in Unit 9 subsequently.

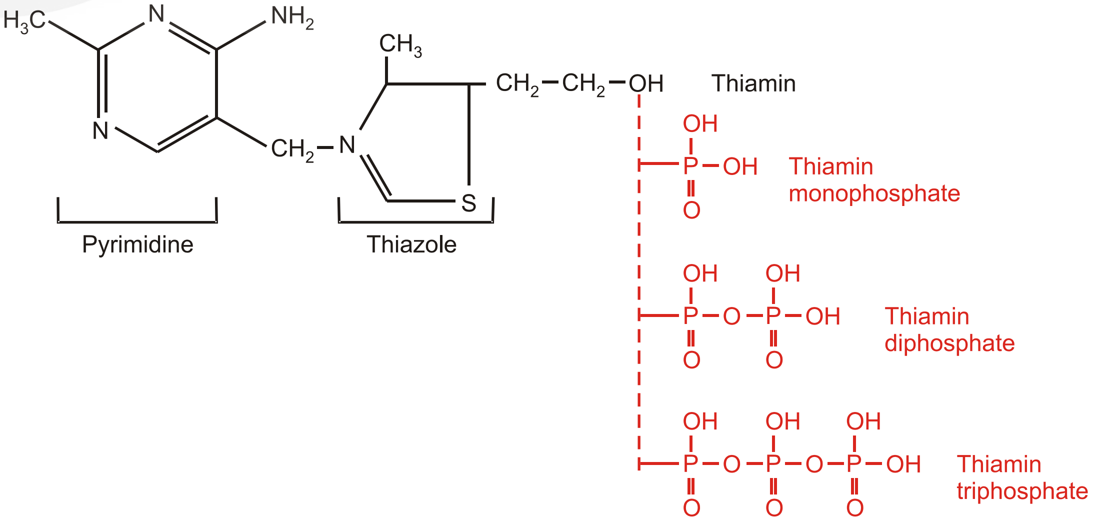

Figure 3.2: Chemical structures of thiamin, thiamin monophosphate, thiamin diphosphate and thiamin triphosphate.

Let us learn about the properties of thiamin next.

Properties

The important physico-chemical properties of thiamin are as follows:

a) Thiamin hydrochloride is a white, needle-shaped crystalline substance.

b) It has a characteristic smell like that of yeast. In fact, the characteristic smell of yeast is due to its content of thiamin. Thiamin has a sulfurours odour and a bitter taste.

c) The compound is readily soluble in water and slightly soluble in alcohol. This property makes it vulnerable, as thiamin in foods is easily lost during washing/soaking and other cooking procedures. Moisture greatly accelerates destruction and thus it is much less stable to heat in fresh foods than in dry foods.

d) It is stable in acid medium at room temperature but destroyed, if heated at 120^{o} C for 30 minutes.

e) Thiamin is readily destroyed by heat in neutral or alkaline medium. It is very sensitive to alkali and can be even destroyed at room temperature in an alkaline medium. This again is an important consideration during cooking procedures. In fact, after you read through the water soluble vitamins, you will realize that this is true in the case of most of the vitamins in this group.

f) The compound is converted to an inactive derivative-thiochrome by controlled oxidation (by the action of potassium ferricyanide in alkaline solution). Thiochrome has a strong fluorescence in UV rays.

g) Thiamin, when dissolved in sodium bisulphate solution at pH 5.0 cleaves into pyrimidine and thiazole. This property is utilized for the chemical estimation of the vitamin.

With this, we move on to the next B-complex vitamin i.e. riboflavin.

3.3.2 Riboflavin (vitamin B_2)

Riboflavin was isolated in a crystalline form from milk by *Kuhn* and co-workers in 1933. Because of this, the early name of the vitamin was *lactoflavin.* It was synthesized by two independent groups of scientists working with *Kuhn* in 1935.

Riboflavin has an isoalloxazine nucleus i.e. a pteridine ring with a benzene ring fused on to it. The side chain is a C5-polyhydroxy group, a derivative of ribitol, a pentahydroxy compound. Riboflavin is chemically known as 6,7-dimethyl-9-D-ribitylisoalloxazine. The structure of riboflavin is given in Figure 3.3. Once again, do not get intimidated by the chemical names of this compound. As a student of dietetics you may not be asked as such to illustrate the structure of these compounds, but surely knowledge of the structure will help you understand the compound and its properties better.

Riboflavin has two major coenzyme derivatives, namely *flavin mononucleotide (FMN)* which is the active component of riboflavin and is formed by the addition of a phosphate group and *flavin adenine dinucleotide (FAD)* which is formed by the combination of FMN with one molecule of adenosine triphosphate (ATP). You will learn more about FMN and FAD in the next unit on enzymes and coenzymes.

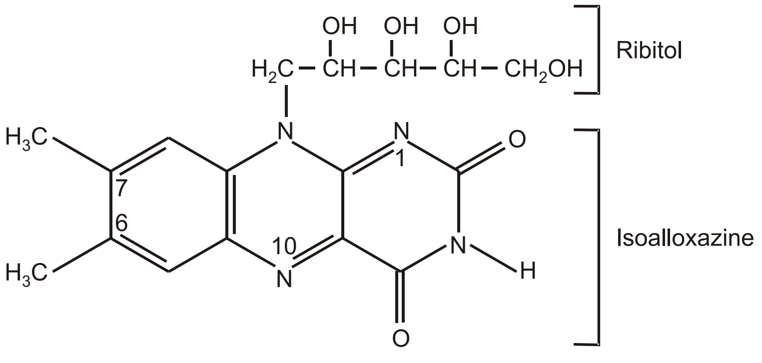

Figure 3.3: Chemical structure of riboflavin

So now let us learn about the properties of riboflavin.

Properties

Some of the important physico-chemical characteristics of riboflavin are as follows:

a) Riboflavin forms needle shaped orange crystals.
b) It is sparingly soluble in water and ethanol but its solubility in water is much less than thiamin.
c) Aqueous solution of vitamin B_2 emits a yellow-green fluorescence. To see this for yourself, empty the contents of a multivitamin capsule into a glass of water. Stir and observe the yellow-green fluorescence. Isn't it amazing.
d) Though the compound is stable to boiling in acid medium, it is readily destroyed by heat in an alkaline medium. This becomes an important consideration during cooking procedure.
e) Riboflavin is sensitive to light and is destroyed if exposed to light for some time. Milk, which is rich in riboflavin, should not be exposed to sunlight for long. So next time when your milk man leaves the milk packet outside, surely you know what to do.
f) Reducing agents such as stannous chloride convert the vitamin to a colourless compound having no fluorescence.
g) When an alkaline solution of riboflavin is exposed to ultra violet rays, it is converted to a compound *lumiflavin* which is soluble in chloroform and has a greenish yellow fluorescence in ultra violet light.
h) When a neutral or acid solution of riboflavin is exposed to ultra violet rays, it is converted to lumichrome which has a slight blue fluorescence in ultra violet light.

The third vitamin in the list is vitamin B_3, i.e. Niacin. Let us get to know the chemistry of this chemical.

3.3.3 Niacin (vitamin B_3)

Though niacin or nicotinic acid has been known to the organic chemists since 1867 and *Funk* isolated it from yeast and rice polishing in order to identify the anti-beriberi vitamin in 1913, it was finally isolated as nicotinamide from liver by *Elvehjem* and his co-workers in 1937. This was actually after the discovery by *Ruffin and Smith* in 1934 that the crude extract of liver was effective against pellagra (you might know that pellagra is the disease condition caused due to the deficiency of niacin in the body).

Niacin or nicotinic acid is pyridine-3-carboxylic acid. It occurs naturally in the body as its amide, *niacinamide* or *nicotinamide.* Amino group substituted into carboxylic acid forms amide group. The chemical structures of niacin forms – nicotinic acid and nicotinamide is presented in Figure 3.4.

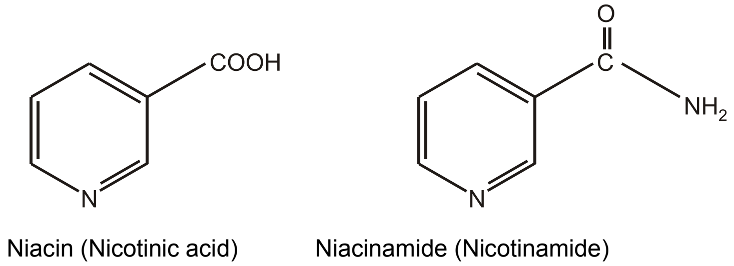

Figure 3.4: Niacin and its derivatives

Niacin is converted into the active forms nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) as shown in Figure 3.4. Both NAD^+ and $NADP^+$ function as cofactors for numerous enzymes about which you will learn in the next Unit and later in Unit 9.

What about the properties of niacin? Read and find out.

Properties

Important physico-chemical properties of niacin and niacinamide are as follows:

a) Niacin is a white crystalline solid.
b) While niacin is sparingly soluble in water, ethanol and glycerol, niacinamide is readily soluble in water.
c) Niacin is fairly heat stable and can withstand a temperature of 120°C for 20 minutes in acid or alkali. It is one of the most stable vitamins.
d) Niacinamide is converted into niacin if heated in strong acid or alkali.

Next, let us get to know about pantothenic acid.

3.3.4 Pantothenic acid (vitamin B_5)

Pantothenic acid, also known as vitamin B_5, is essential to all forms of life. Pure pantothenic acid was first isolated as its calcium salt from yeast by *R. J. Williams* in 1939. Subsequently its synthesis was accomplished by several groups of workers.

The structure of pantothenic acid consists of β-alanine and pantoic acid (dimethyl derivative of butyric acid) joined by a peptide bond (coloured red) as illustrated in Figure 3.5.

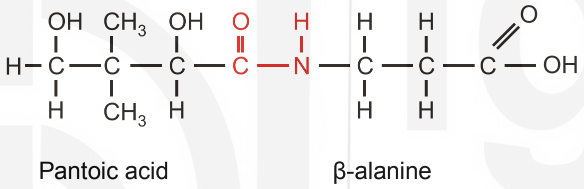

Figure 3.5: Pantothenic acid
(α,γ-dihydroxy-β,β-dimethylbutyryl-β'-alanide)

Pantothenic acid is found throughout living cells in the form of *coenzyme A (CoA)*, a vital coenzyme in numerous chemical reactions. You will get to know about coenzymes in a little while from now in the next Unit. Let us get to learn about the properties of Vitamin B_5 now.

Properties

Important physico-chemical properties of pantothenic acid are as follows:

a) Pantothenic acid is a pale yellow oily liquid that can only be crystallized as its sodium, potassium or calcium salt. These are the forms in which it is generally available.
b) The compound is highly soluble in water.
c) It is stable at 120°C for 30 minutes in neutral medium but is decomposed in acid or alkali solution.
d) It forms esters with alcohols.

The next vitamin in the family of B-group vitamins is pyridoxine. Let us get to know this compound and its related compounds. But first we shall take a break and try to recall what we have learnt so far. Answer the questions in the check your progress exercise 1 and test your understanding of the topic.

Check Your Progress Exercise 1

1) What are vitamins? List a few characteristics which all vitamins possess.

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2) What are the two rings present in the structure of thiamin?

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3) What are the two coenzyme derivatives of riboflavin?

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4) What are two active forms of niacin?

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5) What is an important property of vitamins B_1 and B_2 which is crucial from the point of view of cooking?

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6) Of the vitamins B_1, B_2 and B_3, which is the most stable one?

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7) Name two functional groups (present in the structure) of vitamin B_5.

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8) Name the active form of vitamin B_5 that occurs in our body.

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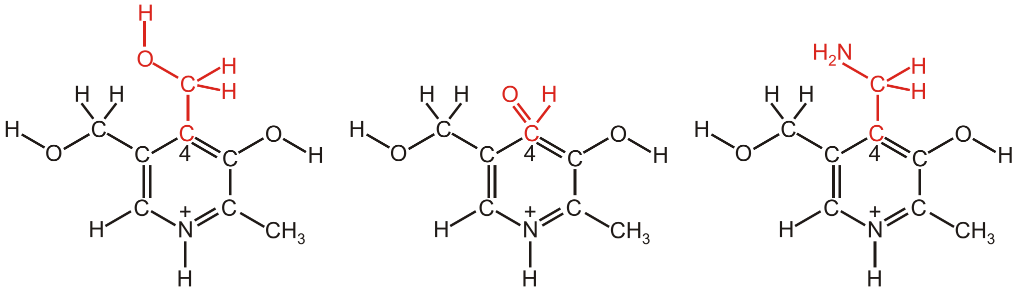
3.3.5 Pyridoxine (Vitamin B_6)

Pyridoxine, one of the B complex vitamins, was isolated in a pure form by five different groups of workers in 1938 and it was synthesized by two groups of workers independently in 1939. It was revealed that vitamin B_6 activity was present in the alcohol derivative of pyridine, called as *pyridoxine* (3-hydroxy-4, 5-dihydroxymethyl-2-methyl pyridine), and also its aldehyde, *pyridoxal* and its amine, *pyridoxamine* as illustrated in Figure 3.6.



Pyridoxine Pyridoxal Pyridoxamine

Figure 3.6: Structure of pyridoxine and related compounds

As can be seen in Figure 3.6, pyridoxine contains a pyridine nucleus, two primary alcoholic groups and one phenolic hydroxyl group. By replacing the $-CH_2OH$ group on position 4 of the pyridoxine molecule with $-CH_2NH_2$ and –CHO respectively, two related compounds, pyridoxamine and pyridoxal can be formed as shown in Figure 3.6 which also have vitamin activity. These three compounds are interchangeable. The biologically active form or the so called coenzyme of pyridoxine is *pyridoxal phosphate.* This coenzyme is remarkably versatile, being involved in transaminations, decarboxylations, racemizations and numerous modifications of amino acid side chains. You shall learn more about it later in the next Unit on enzymes and coenzymes.

The properties of pyridoxine and its related compounds are discussed next.

Properties

Pyridoxine has the following physico-chemical characteristics:

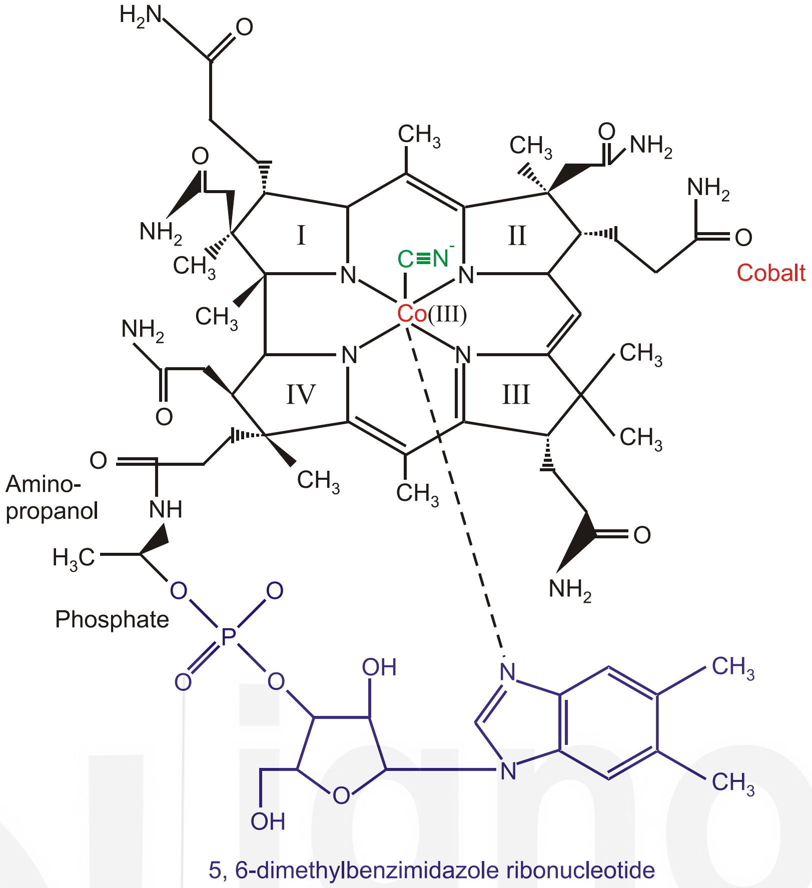
a) It forms white, odourless crystals.
b) The compound is readily soluble in water.
c) When a neutral or alkaline solution of pyridoxine is autoclaved at 120^oC for 30 minutes, partial destruction of the vitamin occurs.
d) When the alkaline solution of pyridoxine is exposed to light, it is slowly destroyed.
e) Pyridoxine produces a coloured complex by reacting with 2,6-dichloroquinone chlorimide.
f) It forms salts with mineral acids and gives a violet colour with $FeCl_3$.

3.3.6 Cyanocobalamin and Related Compounds (vitamin B_{12})

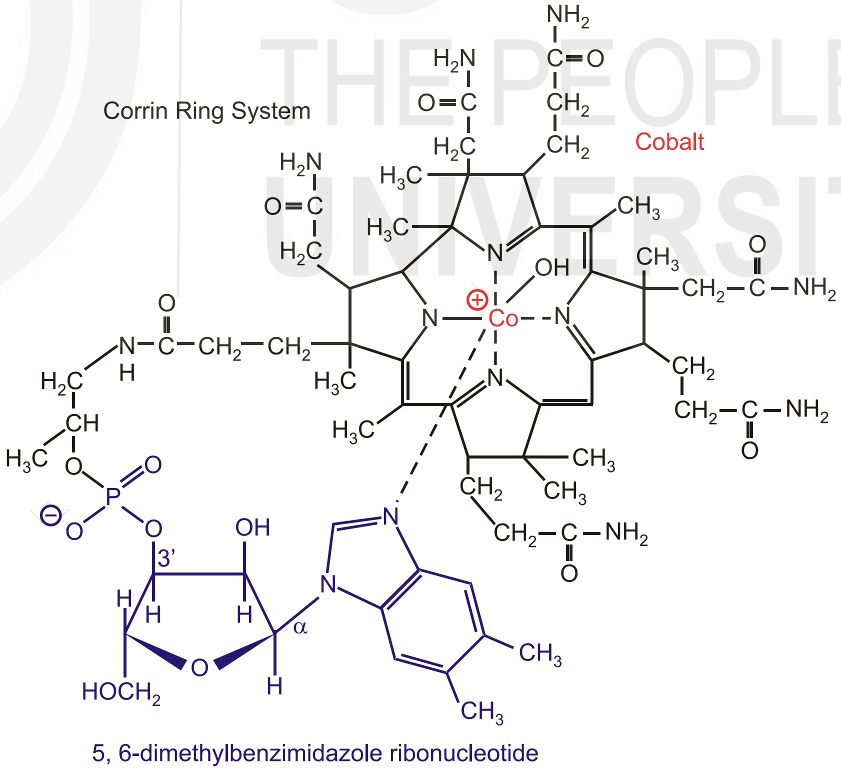
You might have heard of pernicious anaemia. Yes, it is a type of anaemia (low red blood cell count) caused by the body's inability to absorb vitamin B_{12}. Since *Minor* and *Murphy* discovered in 1926 that liver extract can cure pernicious anaemia, many attempts were undertaken over a period of 20 years to isolate the active principle from liver. Ultimately the isolation of crystalline vitamin was achieved by *Smith* and *Parker*, as well as, *Rickes* and co-workers, independently, in 1948.

The chemical structure of cyanocobalamin was determined by *Dorothy Crowfoot Hodgkin.* Structure of cyanocobalamin is relatively large and complex in comparison to other vitamins as can be seen in Figure 3.7 (a). The central portion of the molecule consists of 4 reduced and substituted pyrrole rings (numbered I to IV) surrounding a cobalt (Co) atom. This central structure is known as *corrin* ring system. Below the system, there is a 5,6-dimethyl benzimidazole riboside that is connected at one end to the central cobalt atom and at the other end to the ribose moiety. The ribose moiety is connected to ring IV of the tetrapyrrole nucleus through phosphate and aminopropanol. Cyanide is attached to the cobalt atom and thus the name cyanocobalamin. The structure of cyanocobalamin is presented below in Figure 3.7.

Do not get bogged down with this complex structure. It is meant more for your understanding rather than for reproduction.



(a) Cyanocobalamin



(b) Cobalamin (vitamin B_{12})

Figure 3.7: Structure of vitamin B_{12}

Removal of cyanide results in the formation of 'cobalamin', as illustrated in Figure 3.7 (b). When the cyanide is substituted by other groups, different other derivatives result. For example, when methyl substitutes cyanide, methylcobalamin results.

Let us now move on to the properties of cyanocobalamin.

Properties

The physico-chemical properties of cyanocobalamin are as follows:

a) The vitamin can be obtained in a crystalline form.
b) It is freely soluble in water.
c) Crystalline vitamin B_{12} is stable to heating at 100°C for fairly long periods. Cyanocobalamin solution, when autoclaved, is converted partly to hydroxocobalamin. As this compound is heat labile, it is destroyed if heated at 120°C for 30 minutes.
d) The compound is resistant to boiling in neutral or acid medium but readily destroyed in alkali.
e) On exposure to sunlight, the aqueous solution of vitamin B_{12} leads to destruction of the vitamin.
f) Vitamin C, when added to a solution of vitamin B_{12}, results in the reduction and subsequent destruction of the vitamin.

3.3.7 Biotin (vitamin H)

It was revealed that egg yolk could prevent dermatitis and emaciation in rats that were kept on raw egg white as the main protein source. The factor of the egg yolk was called as *anti egg white injury factor. Szent Gyorgyi,* in 1931, first recognized it as a vitamin and named the factor as *vitamin H.* The vitamin was subsequently isolated in 1939 by *Gyorgyi, Kuhn and Lederer.* In 1942, *Melville* and co-workers isolated the vitamin from milk and named it as *Biotin.* It was first synthesized in 1943. The structure of the vitamin was established as hexahydro-2-oxo-1-thieno-3, 4-imidazole-4-valeric acid. Its structure is presented in Figure 3.8.

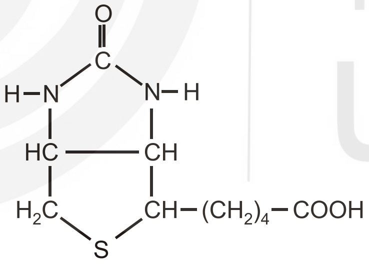


Figure 3.8: Structure of biotin

What are its properties? Let's read and find out.

Properties

Important physico-chemical properties of biotin include the following:

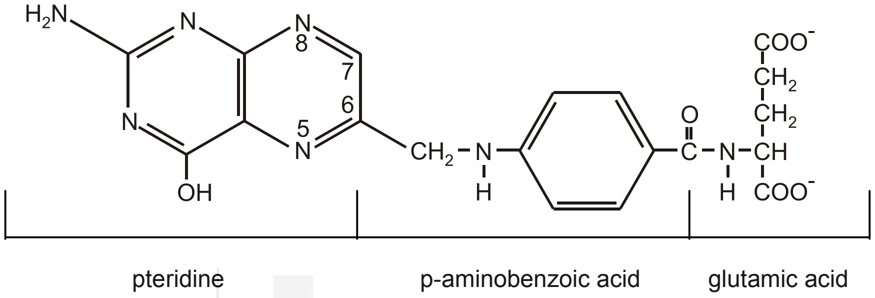
a) It forms colourless, needle shaped crystals.
b) The vitamin is sparingly soluble in cold water but highly soluble in hot water. The compound is sparingly soluble in alcohol.
c) Biotin forms salts with alkali hydroxides such as NaOH.
d) The compound is photostable.
e) Biotin is destroyed in acid solution.

Finally, let us get to know about folic acid, the last of the vitamin from the B-Complex family.

3.3.8 Folic acid and Related Compounds (vitamin M)

Folic acid is a water soluble B-vitamin that helps build healthy cells. Along with iron, this vitamin is crucial during pregnancy as you may already know. Folic acid was isolated in a crystalline form from liver by *Pifiner* and co-workers in 1947 for the first time.

The vitamin that is also called as *folacin* or pteroylglutamic acid consists of a pteridine ring attached to a p-aminobenzoic acid and conjugated with one molecule of glutamic acid as presented in Figure 3.9. The molecule varies in structure by reduction of the pteridine moiety to dihydro folic acid (DHF) and tetrahydro folic acid (THF).



positions 7 & 8 carry hydrogens in dihydrofolate (DHF)
positions 5-8 carry hydrogens in tetrahydrofolate (THF)

Figure 3.9: Structure of folate

There are at least three chemically related and nutritionally important compounds belonging to folic acid group that occur naturally. They only differ in the number of glutamic acid residues attached to the pteridine-aminobenzoic acid complex. Moreover, two reduced forms of folic acid, namely 7, 8-dihydrofolic acid (DHF) and 5, 6, 7, 8-tetrahydrofolic acid (THF) may be present in the tissues as discussed earlier. Let us now move on to the important properties of folic acid.

Properties

Folic acid has the following important physico-chemical properties:

a) It is a yellow, spear-shaped crystalline substance.
b) The compound is sparingly soluble in water.
c) It is stable in acid solution but when heated in alkali, it is readily destroyed.
d) The vitamin can withstand a temperature of 120^{o}C for 30 minutes at neutral pH but at pH 1.0, folic acid loses about 70-100% of its activity when autoclaved at 120^{o}C for 30 minutes.
e) Riboflavin accelerates the photo-oxidation of folic acid.

With folic acid, we come to an end of our study of the B-complex vitamins. Let us now look at the other water soluble vitamin i.e. vitamin C.

3.3.9 Ascorbic Acid (vitamin C)

Although the antiscorbutic (preventing the disease scurvy) effects of citrus fruits was known for a long time, the first important step towards its isolation was the discovery of *Holst and Frolich* in 1907. They reported that guinea pigs, like man and monkey, were also susceptible to scurvy. The isolation of vitamin C was carried out by *Zilva* during 1917-1927.

In 1928, while working in *Hopkin's* laboratory *Szent Gyorgyi* isolated ascorbic acid from adrenal glands, oranges, as well as, from cabbage but he failed to recognize it as a vitamin. He called it as *hexuronic acid.* Afterwards, in 1932 *Glen King* isolated the vitamin in a crystalline form from lemon juice and identified it with *Szent Gyorgyi's* acid. Within a few months of this the chemical structure of the vitamin was elucidated by *Haworth* and *Hirst* and its synthesis was also accomplished. In 1933, vitamin C was named as *Ascorbic acid.*

Ascorbic acid exists as L-ascorbic acid. Surely, by now you know the significance of L (as already been explained in Unit 1 of this Course). L-ascorbic acid is a hexose sugar. In fact, ascorbic acid is a derivative of carbohydrate. It is closely related to the monosaccharide sugars in its structure as highlighted in Figure 3.10. It is the most unstable of all vitamins and is readily oxidized to L-dehydroascorbic acid (DHA). DHA possesses the same vitamin activity as the L-ascorbic acid.

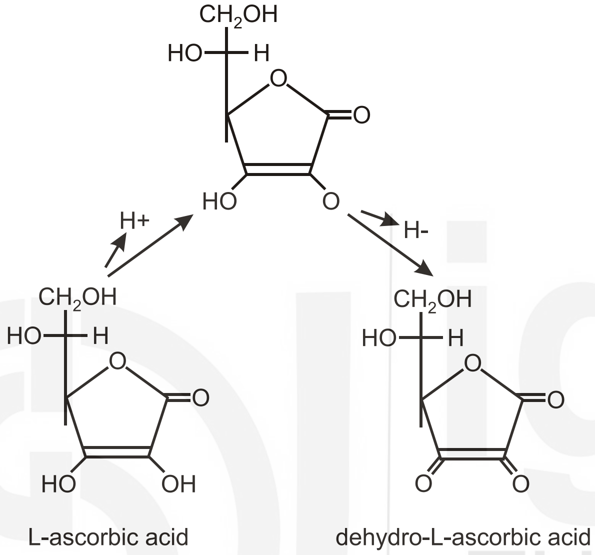


Figure 3.10: Structures of different forms of ascorbic acid

Ascorbic acid has many vital functions to play. Let us read and find out.

Properties

Ascorbic acid possesses following important physico-chemical properties:

a) It is a white crystalline substance.
b) It is freely soluble in water.
c) Solution of the vitamin tastes sour.
d) In dry condition it is stable in air and light.
e) It is fairly stable in cold acid solution.
f) In an aqueous medium, particularly alkaline, it is easily oxidized on exposure to heat, light and traces of metals such as copper or silver.
g) It is easily destroyed during cooking.
h) The compound is a powerful reducing agent and can reduce fehling's solution. This is due to the presence of enol group (carbons 2 and 3) in its structure. (You have already learnt about the enol group in the carbohydrate Unit 1).
i) Vitamin C also reduces 2, 6-dichlorophenolindophenol to a colourless leuco compound. This reaction is very commonly utilized for chemical estimation of the vitamin.
j) Both the reduced form (L-ascorbic acid) and the oxidized form (L-dehydroascorbic acid) are biologically active.

Check Your Progress Exercise 2

1) What are the two related compounds of pyridoxine? How are these different from pyridoxine?

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2) Write down the name of the vitamin that contains a metal in the structure.

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3) What is a Corrin ring system?

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4) Name a few compounds or conditions which can cause the destruction of vitamin B_{12} .

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5) Write down the structure of nicotinamide and L-ascorbic acid.

6) Give any four important physico-chemical properties of Vitamin C.

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The unit so far focussed on the structure and physico-chemical properties of water-soluble vitamins. Next, a detailed discussion on fat soluble vitamins follows.

3.4 STRUCTURE AND PROPERTIES OF FAT SOLUBLE VITAMINS

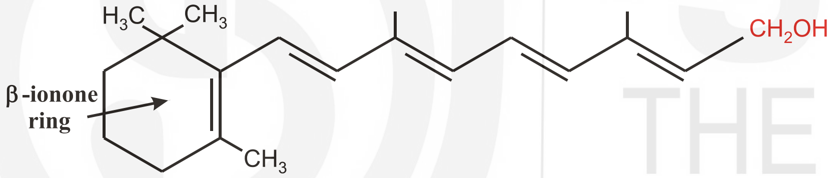
After going through this section, you will be able to understand the structural and physico-chemical aspects of fat soluble vitamins, namely vitamin A, D, E and K. Biochemical roles of these vitamins will be discussed in Unit 9 of this Course and their food sources, daily requirements, deficiency diseases, assessment procedures, etc. will be discussed in the Advance Nutrition Course, as informed earlier. Here, we begin our study of fat soluble vitamins with a general note i.e. all fat soluble vitamins have common features about their structure. They all contain an aromatic ring structure with an aliphatic side chain, one or more double bonds either in the ring or in the side chain and a functional group such as aldehyde, ketone, methyl or hydroxyl group. Let us take each vitamin one by one and understand its structure. We begin with vitamin A.

3.4.1 Vitamin A (Retinol and Related Compounds)

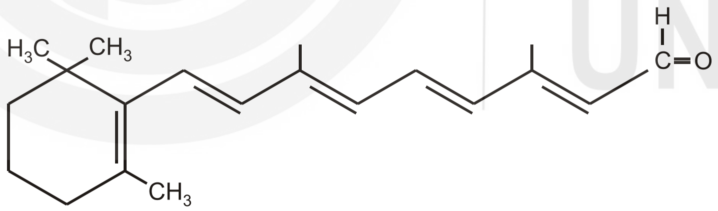
Hopkins, in his studies conducted between 1906 and 1912, observed that rats fed on a diet of casein, starch, sugar, lard and inorganic salts failed to grow and finally died. It was also observed that the rats could survive when a small amount of milk was added in their daily diet. With this finding, an *accessory food factor* in milk was established. In 1913, two groups of workers isolated the factor from butter, egg yolk and cod liver oil and reported that the factor was fat soluble. *McCollum* and *Davis* in 1915 proposed the name 'fat-soluble A' for the factor. *Rosenheim* and *Drummond* first indicated the relationship of vitamin A to the plant pigment carotene in 1920. Subsequently, *Moore* in 1957 conclusively proved that carotene is the precursor of vitamin A.

The term "Vitamin A" is commonly used for those retinoids which exhibit the biological activity of retinol. The term retinoid is used to describe several related molecules – principally retinol, retinal, retinoic acid and retinyl palmitate, as well as, their numerous synthetic analogs. What are these retinoids? Let us get to know them.

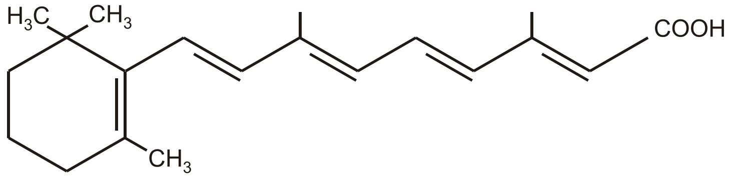
Well, it is clear that Vitamin A is the collective name for a group of fat-soluble vitamins. There are two compounds possessing the activities of vitamin A. Can you name them? Yes, these are *retinol* (vitamin A_1) and *3-dehydroretinol* (vitamin A_2). Retinol or vitamin A_1 is the main useable form of vitamin A in foods, often called *preformed vitamin A* as it is the active form in the body. Look at the structure of retinol given in Figure 3.11(a). You can see that it consists of a hydrocarbon chain with a β-ionone ring at one end and an alcohol group (in red colour) at the other. Retinol is chemically a "pale yellow crystalline solid". The solid and its metabolites exist in nature as various isomers. The isomers of retinal are presented in Figure 3.11 (e).



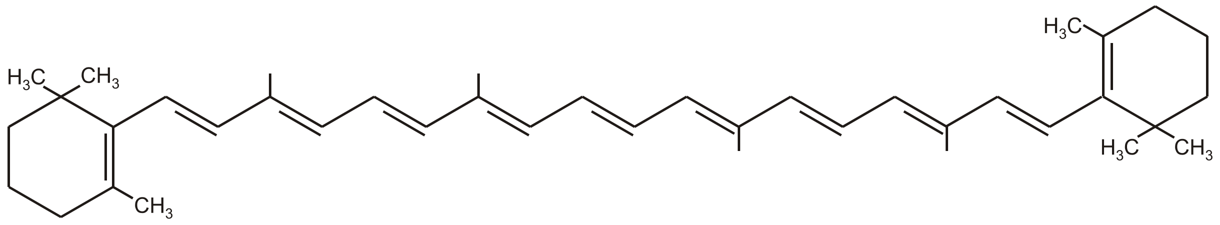
(a) Retinol



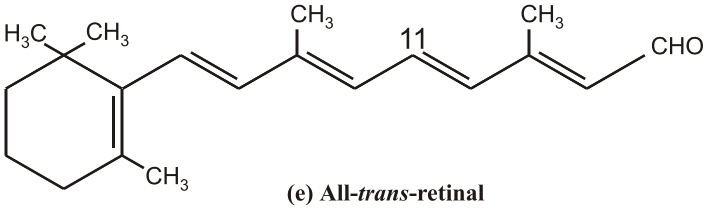
(b) Retinal (retinaldehyde)



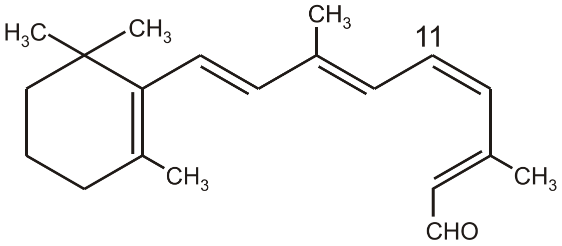
(c) Retinoic Acid



(d) β-carotene



(e) **All-*trans*-retinal**



(f) **11-*cis*-retinal**

Figure 3.11: Structure of retinol, retinal, retinoic acid, β-carotene and isomers of retinal

The 3-dehydroretinol or vitamin A_2 which occurs only in the liver of some Indian fish is of little nutritional importance. Moreover, it has only half the biological activity of retinol. It differs structurally from retinol by possessing an additional double bond between carbon 3 and 4 of the β-ionone ring.

Retinol (an alcohol) can only be found in animal sources. It is the immediate precursor to two important active forms – *retinal* and *retinoic acid*. The terminal alcohol group (–OH) of retinol can be oxidized in the body to form an *aldehyde* (CHO)*, retinal* or an acid (COOH), *retinoic acid* as can be seen in Figure 3.11 (b, c). *Retinal (11-cis-retinal)*, plays a critical role in vision and *retinoic acid*, serves as an intracellular messenger that affects transcription of a number of genes. You will learn more about these functions in the Advance Nutrition Course, Unit 7. The primary storage forms of retinol in the body are retinyl esters, the most common of which is *retinyl palmitate.*

Vitamin A does not occur in plants, but many plants contain *carotenoids* such as *beta-carotene* that can be converted to vitamin A within the intestines and other tissues. Beta carotene, a hydrocarbon, is one of a family of dark pigments called provitamin A carotenoids. The most important of carotenes, Beta Carotene (β-carotene) {refer to Figure 3.11(d)} which is widely distributed in plants can be split in the middle of its long hydrocarbon chain in the body to yield two molecules of retinol. It is the only carotenoid having a structural similarity with retinol in both halves of the molecule. Other carotenoids such as α-carotene, γ-carotene, cryptoxanthine, etc. on cleavage yield only one molecule of retinol.

Having understood the structure of vitamin A, let us have a look at its properties.

Properties

Physico-chemical properties of vitamin A are as follows:

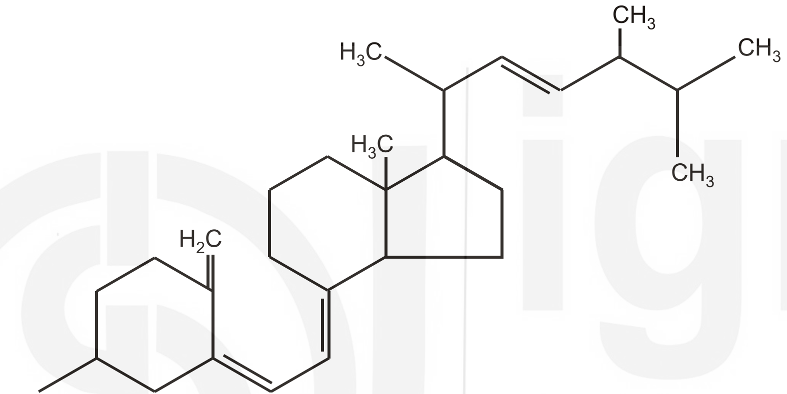
a) Retinol is a pale yellow, almost colourless liquid.
b) It is soluble in fats and fat solvents but not in water.
c) Vitamin A can withstand the ordinary cooking temperature (100^{o}C) for a short period in absence of oxygen.
d) Fats containing retinol become rancid on oxidation which destroys the vitamin.
e) Retinol, on exposure to sunlight, gets destroyed.
f) Oxidation and subsequent destruction of retinol is prevented in the presence of vitamin E.

Next, we move on to the study of vitamin D.

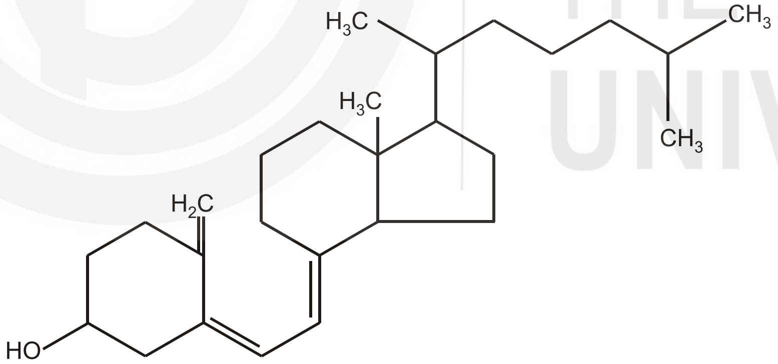
3.4.2 Vitamin D (Cholecalciferol and Related Compounds)

Nutritional value of cod liver oil was recognized by *Hughes Bennett* and it was used by *Trousseau* in the treatment of rickets. But, *Mellanby* in 1918, for the first time observed that rickets was responding to a fat-soluble vitamin present in cod liver oil. The vitamin was subsequently synthesized in 1931.

Vitamin D encompasses a group of sterols, of which only two have significant nutritional importance. These are *ergocalciferol* or activated ergosterol or *vitamin D_2* and *cholecalciferol* or activated 7-dehydrocholesterol or *vitamin D_3*. Figure 3.12 illustrates the structures of vitamin D_2 and D_3. Both these compounds have identical biological activities in man. You may recall reading earlier in Unit 2, sub-section 2.3.4 that plants contain ergosterol, which is an unsaturated compound containing an extra methyl group in its side chain (refer to Figure 3.12). 7-dehydrocholesterol is found in animals and humans. Cholecalciferol, in fact, is a type of steroid hormone made in the skin from cholesterol when the skin is in direct sunlight. Let us learn about this now.



Vitamin D_2



Vitamin D_3

Figure 3.12: Structures of vitamin D compounds

Ultra violet (UV) irradiation cleaves B ring of both the compounds (ergosterol, 7–dehydrocholesterol) with the formation of ergocalciferol (vitamin D_2) in plants (by UV irradiation of ergosterol) and cholecalciferol (vitamin D_3) in animals. In the skin, 7–dehydrocholesterol is converted to cholecalciferol (vitamin D_3) following UV irradiation. The Figure 3.13 shows the formation of vitamin D_3 from its precursor, 7–dehydrocholesterol.

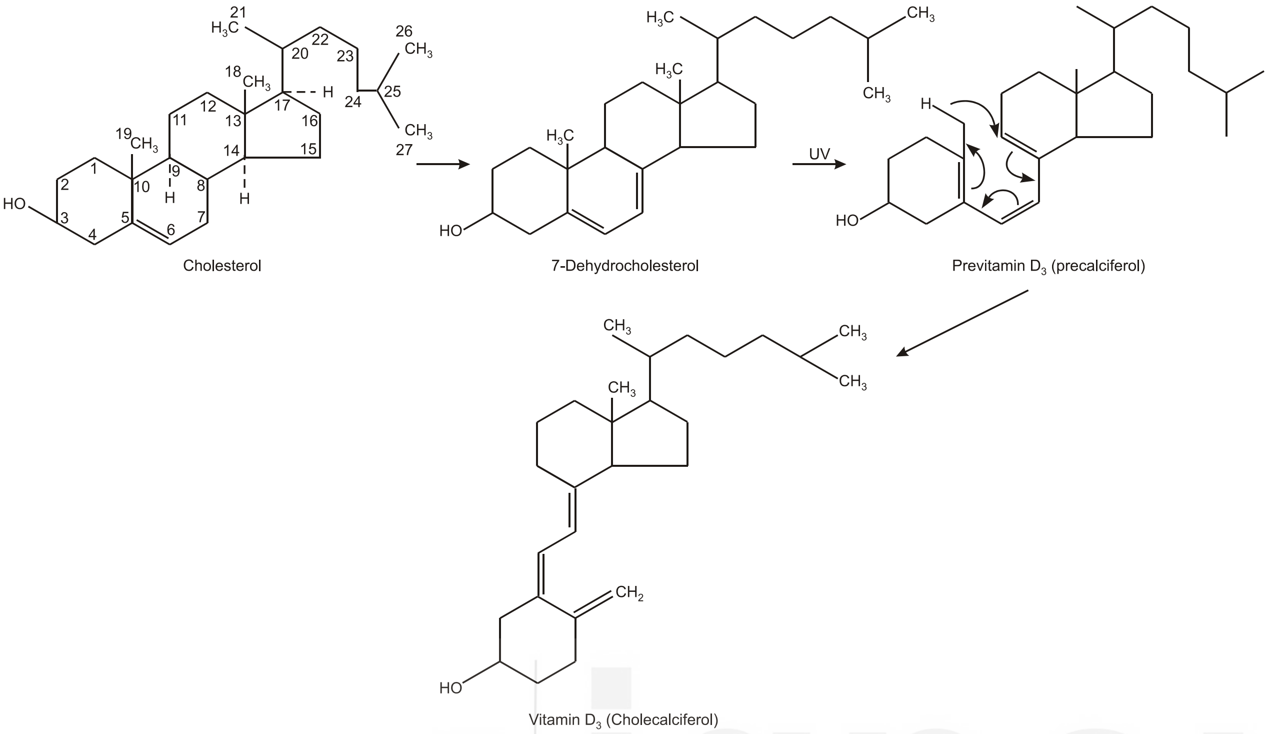
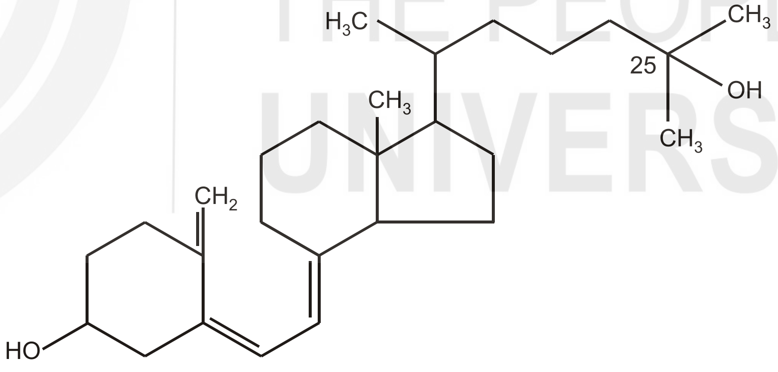
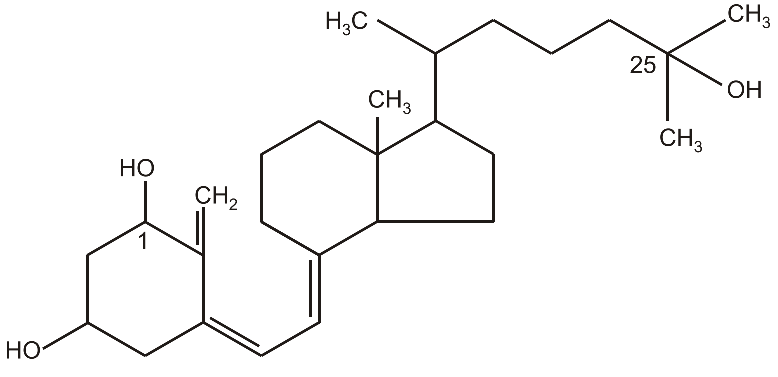


Figure 3.13: Steps in the formation of vitamin D_3 in skin

The liver and other tissues metabolize vitamin D to 25-hydroxy vitamin D (25OH)D, the principal circulating form of vitamin D. 25(OH)D is then further metabolized to 1, 25-dihydroxy vitamin D_3 (1,25$(OH)_2$D) principally in the kidney. 1, 25$(OH)_2$ D is the principal hormonal form of vitamin D, responsible for most of its biologic actions. Figure 3.14 gives the structure of 25-hydroxyvitamin D_3 and 1, 25-dihydroxyvitamin D.



25-hydroxyvitamin D_3



1, 25-dihydroxyvitamin D_3

Figure 3.14: Structure of principal vitamin D_3 forms

Properties

The physico-chemical properties of vitamin D are as follows:

a) Both vitamin D_2 and D_3 are soluble in fats and fat solvents.
b) They are not destroyed in presence of acid or alkali.
c) Both the compounds can withstand the normal cooking temperature (100^oC) and preserving processes.
d) They are fairly stable to oxidation.
e) In general, vitamin D is more stable than vitamin A.

Here, let us take a break and recapitulate what we have learnt so far about fat-soluble vitamins.

Check Your Progress Exercise 3

1) Write down the chemical name of vitamin A. What factors lead to its destruction?

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2) What are the two active forms of vitamin A? What is their physiological role in the body?

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3) Name the compound that is structurally similar to retinol and can be easily converted to vitamin A.

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4) Name the commonest form of vitamin D? How does its structure differ from other members of the group?

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5) Indicate the steps involved in the formation of vitamin D_3.

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6) List any two properties of vitamin D to indicate that it is much more stable vitamin than vitamin A.

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Now, let us study about the remaining two fat-soluble vitamins.

3.4.3 Vitamin E (Tocopherols)

Vitamin E is an essential fat-soluble vitamin that functions, at least in part, as a lipid-soluble antioxidant. Presence of vitamin E was first revealed by *Evans* and *Bishop* in 1923. They observed that rats fed on a diet of corn starch, lard, casein, butter and yeast failed to reproduce. They also noticed that this was corrected by vegetable oil supplementation. The vitamin was isolated in 1936 by *Evans* and co-workers from wheat germ oil and was named as *tocopherol.* Subsequently, synthesis of the vitamin was accomplished by two independent groups of workers in 1938.

Vitamin E refers to a group of compounds known as tocopherols which are the derivatives of a parent compound called as *'tocol'*. Four tocopherols namely α, β, γ and δ-tocopherols have been isolated. They differ from each other in the number and position of methyl groups attached to the aromatic nucleus. While β and γ-tocopherols have two methyl groups, α and δ-tocopherols have three and one methyl groups, respectively. All of these compounds possess comparable physiological properties, although α-tocopherol which is synthesized commercially is most potent. Some tocopherols are derivatives of tocotrienol, which has three double bonds in the aliphatic side chain. Structure of α-tocopherol is shown in Figure 3.15:

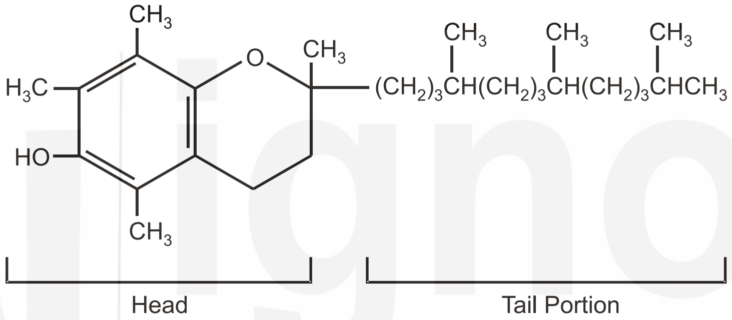


Figure 3.15: α-tocopherol

The tocopherols basically consist of a "ring" portion called a chromane "head" or "ring" and a "tail" portion called a "phytyl" group. A chromane head has two rings which are essentially naphthalene with one carbon atom substituted with an oxygen atom, thus a cyclic ether and a pyhtyl group consists of a saturated 16-carbon isoprenoid. Isoprene is *a branched chain unsaturated hydrocarbon of five carbon atoms*. The tocotrienols are essentially identical to the tocopherols, except that they have three double bonds in the tail at 3', 7' and 11'. This can "loosely" be called an unsaturated phytyl group or isoprenoid.

Next, let us get to know about the properties of tocopherols.

Properties

Physico-chemical properties of vitamin E are as follows:

a) Tocopherols are yellow, oily liquids.
b) They are freely soluble in fat solvents.
c) The compounds are remarkably stable to heat. They can even withstand a temperature above 100°C.
d) Activity of vitamin E is destroyed in presence of oxidizing agents.
e) In alkaline medium, tocopherols are destroyed.
f) They are, however, stable to acidic medium.
g) When exposed to ultra violet light, the vitamin is destroyed.
h) All these compounds exhibit strong antioxidant properties.

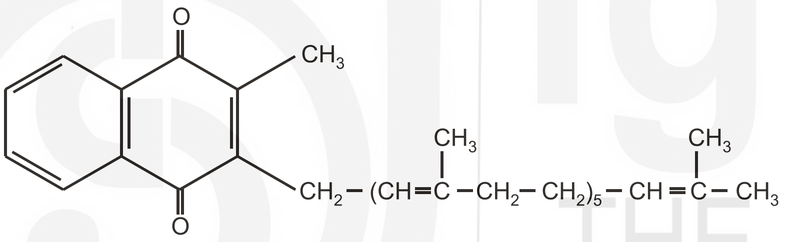
Finally, let us learn about vitamin K.

3.4.4 Vitamin K

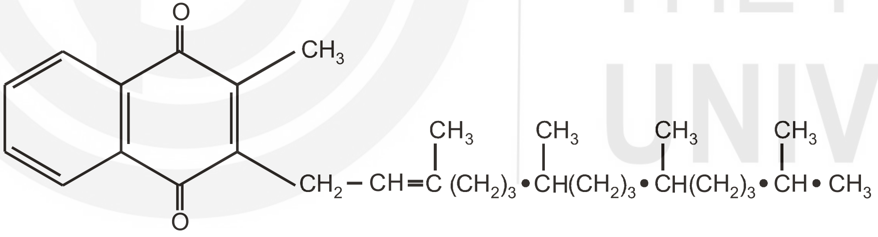
Vitamin K, as you may already know, is a fat-soluble vitamin that plays an important role in blood clotting. It was first observed in 1934 by *Dam* and *Schonheyder* that bleeding in chickens that was unrelated to vitamin C deficiency could be prevented by alfalfa or decayed fish meal effectively. It was possible to extract the active principle with ether and named as vitamin K by *Dam* in 1935. *Dam, Karrer* and co-workers isolated pure vitamin K_1 in 1939 and in the same year, *Doisy* and co-workers isolated pure vitamin K_2. Immediately after this, synthesis of the vitamin was accomplished by three different groups of workers.

Several compounds having vitamin K activity are known. These are basically derivatives of *napthoquinone.* The best known being *vitamins K_1 (phylloquinone or phytalmenaquinone), K_2 (menaquinone or multiprenyl menaquinone)* and *K_3 (menadione)*.

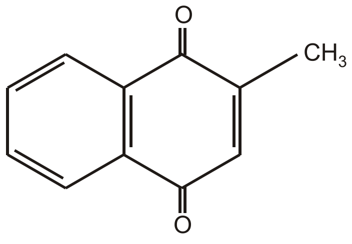
Vitamin K_1 or 2-methyl-3-phytyl-1,4-napthoquinone occurs naturally in plant foods, vitamin K_2 or 2-methyl-3-difarnesyl-1,4-napthoquinone is synthesized by bacteria and vitamin K_3, popularly called as menadione, is 2-methyl-1,4-napthoquinone which is a synthetic compound. While vitamin K_1 possesses a phytyl chain in position 3 of the aromatic nucleus, K_2 possesses a difarnesyl residue instead. Vitamin K_3 does not have any hydrocarbon chain attached to the aromatic nucleus. Among these three compounds, *menadione is the most potent*. Structures of vitamin K_1, K_2 and K_3 are presented here. Looking at Figure 3.16, you would have realized that the three structures differ only in side chain.



Vitamin K_1



Vitamin K_2
("n" can be 6, 7 or 9 isoprenoid groups)



Vitamin K_3

Figure 3.16: Structures of vitamin K and its forms

Properties

Physico-chemical properties of vitamin K are as follows.

a) Vitamin K_1 is yellow oil, whereas, vitamin K_2 is a yellow crystalline solid.
b) The natural vitamins K are only soluble in fat solvents.
c) Vitamin K_3 is slightly soluble in water for not having the long hydrocarbon chain.
d) Both vitamin K_1 and K_2 are alkali sensitive.
e) These compounds are also sensitive to light.
f) Both vitamin K_1 and K_2 are fairly stable to heat treatment.

After studying the structures of the fat soluble vitamins, you must have understood now that the chromane ring structure forms the basis for all fat soluble vitamins. Vitamin A consists of the β-ionione ring. The side chain consists of two isoprene units, four double bonds and one alcoholic group. Vitamin D consists of a sterane ring with differing side chain structures. Vitamin E has a chromane ring with an isoprenoid side chain and vitamin K, a quinine ring with isoprenoid side chain. These aspects of chemistry account for their biological potency and activity, about which you will learn in the Advance Nutrition Course.

Check Your Progress Exercise 4

1) How many types of tocopherols are commonly found in nature? Out of these which one is most potent as a vitamin?

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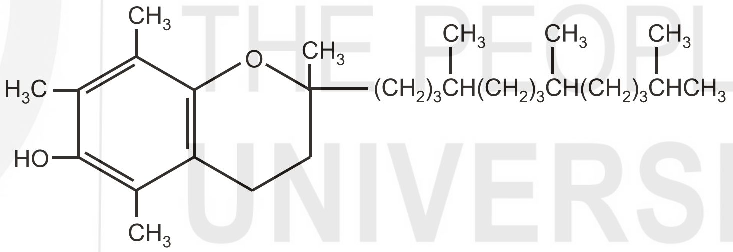
2) Name the structure. Indicate the 'head' and 'tail' portion (giving their name) in the following structure:



3) Which compounds/conditions lead to the destruction of vitamin E?

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4) Which member of the vitamin K group is synthesized by bacteria? What is its chemical name? How is it structurally different from rest of the members?

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5) What is menadione? Is it available in the nature?

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6) Compare and contrast any wo physico-chemical properties of vitamin K_1 and K_2.

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3.5 LET US SUM UP

In this unit we learnt the chemistry of a very important group of nutrients, vitamins. Besides learning the structure and physico-chemical properties of these substances, you also had an idea on what basis vitamins are classified and also a brief history of their discovery.

All the important vitamins namely, Vitamins B_1, B_2, niacin, pantothenic acid, B_6, B_{12}, C, biotin and folic acid from the water soluble group and vitamins A, D, E and K from the fat soluble group were covered in the unit.

You not only visualized the structures of different vitamins but also got an idea how the structure of different members of same vitamin group differs. This difference sometimes results in difference in the activity of the vitamin. By learning the physico-chemical properties of the vitamins, you not only had an idea about the stability of the particular vitamin against different environmental factors but you could also compare the vulnerability of the substance in comparison to other vitamins.

This unit actually acted as a foundation for further studies on vitamins, such as their biochemical role, assessment, deficiency and excess, food sources and daily requirements, etc. that you will learn in different units of the appropriate sections.

3.6 GLOSSARY

Alfalfa	:	a perennial hay crop of the highest quality.
Autoclaved	:	heating in an instrument called as autoclave in which the boiling point of water can be elevated by increasing pressure more than atmospheric pressure.
Beri-beri	:	disease occurs due to vitamin B_1 deficiency.
Casein	:	the main protein of milk.
Coenzyme	:	a molecule that binds to an enzyme and is essential for its activity, but is not permanently altered by the reaction. Many coenzymes are derived from vitamins.
Emaciation	:	abnormal thinning
Fat solvents	:	solvents in which fats are soluble e.g. methanol, chloroform, acetone, etc.
Fehling's solution	:	alkaline copper sulphate reagent.
Isoprene	:	a branched chain unsaturated hydrocarbon of five carbon atoms.
Lard	:	the semisolid oil of hog's (full grown pig) fat.
Pellagra	:	disease occurs due to niacin deficiency.
Pernicious anaemia	:	a type of anaemia i.e. low red blood cell count caused by the body's inability to absorb vitamin B_{12}.
Photo-oxidation	:	oxidation due to exposure to light.
Scurvy	:	disease occurs due to vitamin C deficiency.
Vitamins	:	the organic compounds required in very small amounts by the body for growth, maintenance and sustenance of life.

3.7 ANSWERS TO CHECK YOUR PROGRESS EXERCISES

Check Your Progress Exercise 1

1) Vitamins are organic compounds required in very small amounts by the body for growth, maintenance and sustenance of life. They neither are catabolized to generate energy nor are they used for structural purposes. They are used as cofactors for enzymes and are called as coenzymes.

2) Pyrimidine and thiazole ring, are the two rings present in the structure of thiamin.

3) Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD) are the two coenzyme derivatives of riboflavin.

4) Nicotinamide adenine dinucleotide (NAD^+) and Nicotinamide adenine dinucleotide phosphate (NADP) are the two active forms of Niacin.

5) Both the vitamins are readily soluble in water. This property makes them vulnerable, as they are easily lost during washing/ soaking and other cooking procedures.

6) Vitamin B_3 is the most stable vitamin.

7) Pantoic acid and β-alanine are two functional groups of vitamin B_5.

8) Coenzyme A (CoA) is the active form of vitamin B_5 that occurs in our body.

Check Your Progress Exercise 2

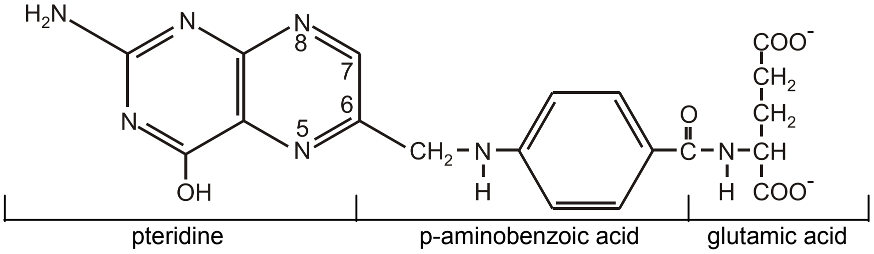
1) The two related compounds of pyridoxine are pyridoxal and pyridoxamine. Pyridoxine contains a pyridine nucleus, two alcoholic groups and one phenolic hyhdroxyl group. While pyridoxal is formed by replacing $–CH_2OH$ group with $–CHO$ and pyridoxamine by $–CH_2NH_2$.

2) Vitamin B_{12} (Cyanocobalamin) is the vitamin that contains a metal in the structure.

3) The central portion of the cyanocobalamin molecule consisting of 4 reduced and substituted pyrrole rings (numbered I to IV) surrounding a cobalt (Co) atom. This is referred to as a corrin ring system.

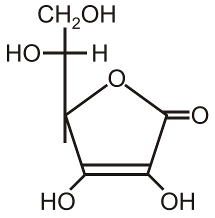
4) Vitamin B_{12} can be destroyed:
   - when heated at 120°C for 30 minutes
   - in alkali
   - on exposure to sunlight, and
   - by the addition of vitamin C to a solution of vitamin B_{12}.

5) The structure of nicotinamide is as follows:



positions 7 & 8 carry hydrogens in dihydrofolate (DHF)
positions 5-8 carry hydrogens in tetrahydrofolate (THF)

The structure of L-ascorbic acid is as follows:



6) Properties of vitamin C include:
   - It is fairly stable in cold acid solution.
   - In an aqueous medium, particularly alkaline, it is easily oxidized on exposure to heat, light and traces of metals such copper or silver.
   - It is easily destroyed during cooking.
   - It is a powerful reducing agent.

Check Your Progress Exercise 3

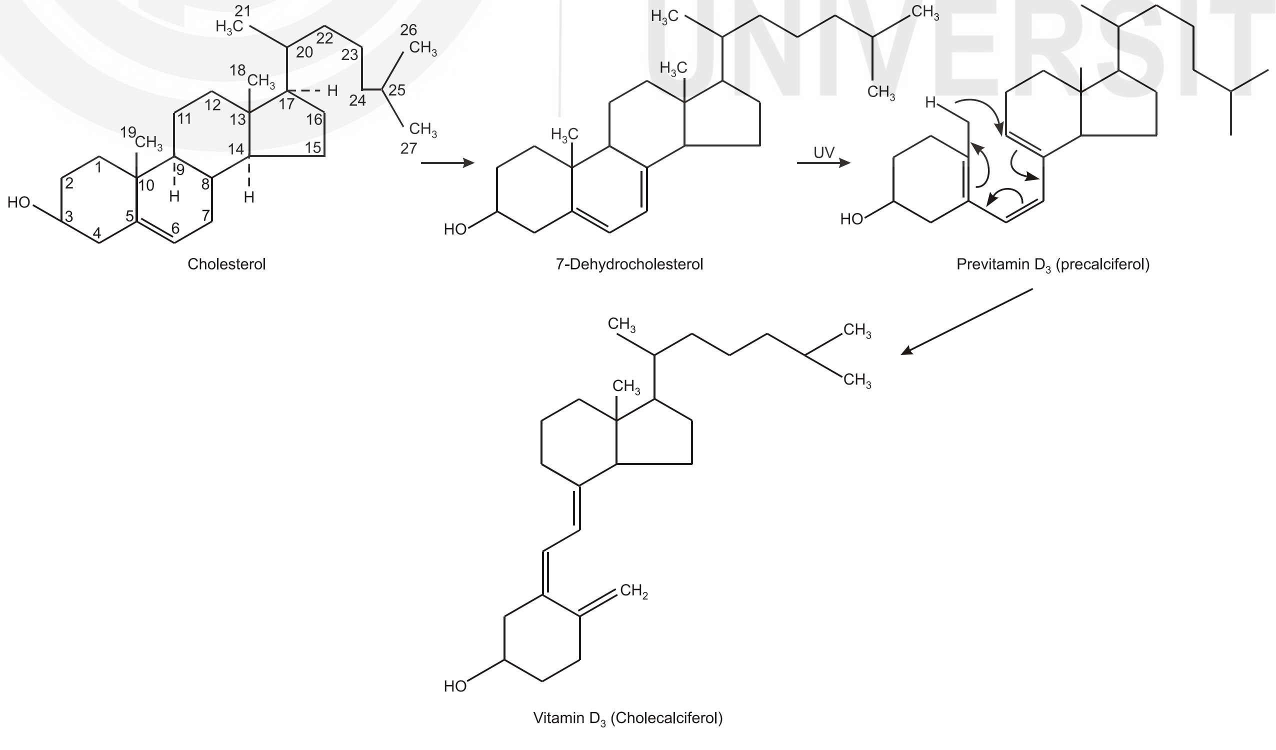
1) Retinol is the chemical name of vitamin A. Oxidation and exposure to sunlight can cause its destruction.

2) Retinol and retinoic acid are the two active forms of vitamin A. Retinal plays a critical role in vision while retinoic acid serves as an intracellular messenger that affects transcription of a number of genes.

3) β-carotene is structurally similar to retinol and can be easily converted to vitamin A.

4) 7-dehydrocholesterol is the commonest form of vitamin D. The other vitamin D compound is ergocalciferol, which is different from 7-dehydrocholesterol in that, it is an unsaturated compound containing an extra methyl group in its side chain.

5) The steps involved in the formation of vitamin D_3 are:

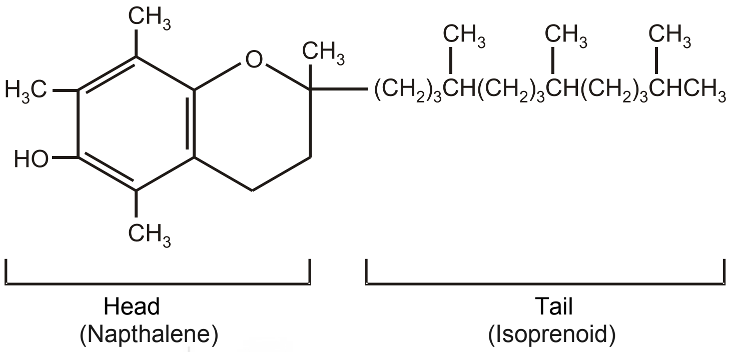


6) Vitamin D is much more stable than vitamin A, as:
   - It can withstand the normal cooking temperatures and preserving processes.
   - It is fairly stable to oxidation.

Check Your Progress Exercise 4

1) Four tocopherols have been isolated – α, β, γ and δ. The most potent of these is the α-tocopherol.

2) The structure is α–tocopherol.



3) Oxidizing agents, alkaline medium and UV light lead to the destruction of vitamin E.

4) Vitamin K_2 or 2-methyl-4-difarnesyl-1, 4- naphthoquinone is synthesized by bacteria while vitamin K_1 possesses a phytylquinone chain in position 3 of the aromatic nucleus, K_2 possesses a difarnesyl residue instead and vitamin K_3 does not have any hydrocarbon chain attached to the aromatic nucleus.

5) Menadione is vitamin K_3 (2-methyl-1, 4-napthoquinone). No, it is not found in nature – it is a synthetic compound.

6) Vitamin K_1 is yellow oil whereas vitamin K_2 is a yellow crystalline solid. Both compounds are light and alkali-sensitive and are fairly stable to heat treatment.