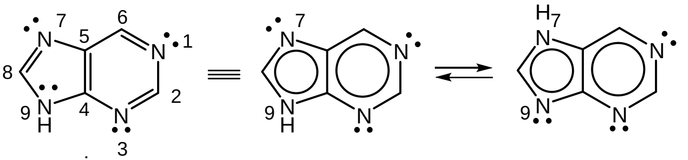
№ 39. BICYCLIC HETEROCYCLIC COMPOUNDS – PURINE, PTERIDINE, AND THEIR DERIVATIVES.

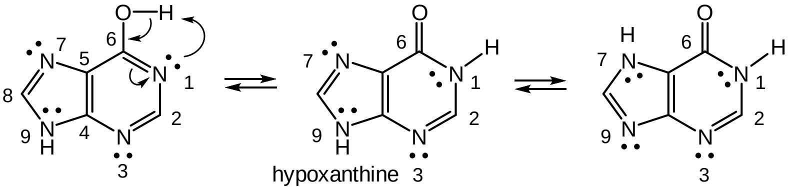
Purine is a heterocyclic aromatic organic compound, consisting of a pyrimidine ring fused to an imidazole ring. Therefore purine is a tetraaza heterocycle. A fused ring has two adjacent atoms that are common for two rings and they share the bonds between these atoms. Purines, including substituted purines and their tautomers are the most widely distributed kind of nitrogen-containing heterocycle in nature.



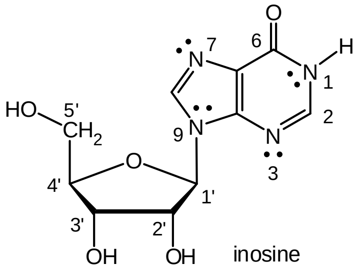
purine

Purine is very stable aromatic system with 10π electrons, like naphthalene. The molecule is planar. All nitrogen atoms are sp^2 hybridized. One N is pyrrole-like, supplying lone electron pair to the π system, the other three nitrogen atoms are pyridine-like, providing one π electron each. These three nitrogen atoms determine the basic character of purine because they have lone pairs unengaged in conjugation and available to a proton. Tautomerism is possible in the imidazole ring, therefore the two connected with arrows structures are undistinguishable. The position N(9) is the point of attachment in most important natural purine derivatives.

Purine derivatives.


hypoxanthine
purine-6(9*H*)-one, most stable form

Hypoxanthine is a naturally occurring purine derivative (purin-6-one, known also as 6-hydroxypurine). It is occasionally found as a constituent of nucleic acids where it is present in the anticodon of tRNA in the form of inosine. Hypoxanthine is a necessary additive in certain cell, bacteria, and parasite cultures as a substrate and nitrogen source. Several tautomeric structures can be drawn for hypoxanthine. The most stable are those with lactam unit, the keto forms. Inosine is N(9) substituted hypoxanthine with β-D-ribose, via beta-glycosidic linkage. Hypoxanthine is oxidized to xanthine.

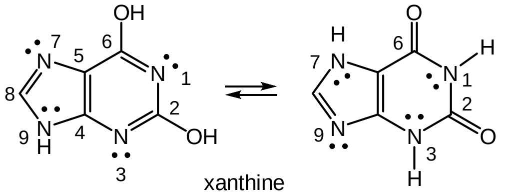

inosine

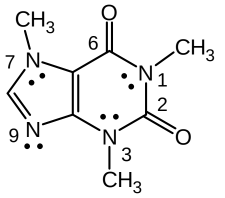
Xanthine (2,6-dihydroxypurine) is a product of purine catabolism (degradation). Its diketo form is the stable one.

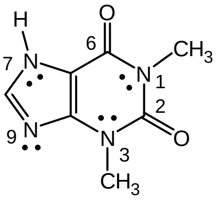
- ☐ It is created from guanine (2-NH_2) by guanine deaminase.
- ☐ It is created from hypoxanthine by xanthine oxidoreductase.

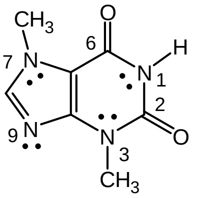
Xanthine is subsequently converted to uric acid. Several mild stimulants are derived from xanthine, including caffeine and theobromine.

N-Methyl xanthine derivatives. Alkaloids in coffee (**caffeine**), tea (**caffeine and theophylline**), cacao beans (**theobromine**) are N-methyl xanthine derivatives. These alkaloids are psychoactive substances.


xanthine
(purine-2,6-dione)


caffeine
(1,3,7-trimethylpurine-2,6-dione)


theophylline
(1,3,-dimethylpurine-2,6-dione)

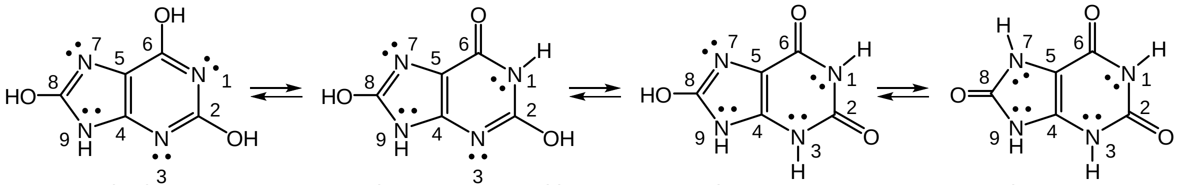

theobromine
(3,7-dimethylpurine-2,6-dione)

These alkaloids have common physiological action:

- central nervous system stimulatory effect;
- relaxing smooth muscle;
- increasing heart muscle contractility and efficiency;
- increasing heart rate;
- increasing blood pressure;
- increasing renal blood flow (they nave diuretic effect);
- some anti-inflammatory effects.

Caffeine is widely consumed in the world in coffee as mild stimulant. It is an ergogenic, i.e. increasing a person's capability for mental or physical labor.

Uric acid. In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine metabolism. Uric acid is excreted in urine.



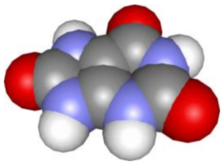
lactim

lactam I, more stable
dibasic acid

lactam II
monobasic acid

lactam III
keto form

Uric acid can be considered aromatic system with 10π electrons regardless of the fact that the mono- and diketo forms are the preferred tautomers. The more stable form is a diprotic acid due to possibility for deprotonation of two hydroxyl groups with phenolic character. Uric acid is a diprotic acid with pK_{a1}=5.4 and pK_{a2}=10.3. In strong alkali at high pH it forms the dually charged full urate anion, but at biological pH or in the presence of carbonic acid or carbonate ions it forms the singly charged hydrogen or acid urate ion by deprotonation at C(2) which is proven by X-ray analysis of crystals from gout deposit. The reason for acid salt formation is that uric acid pK_{a2} is greater than the pK_{a1} of carbonic acid. Since uric acid second ionization is so weak, the full urate salts tend to hydrolyze back to hydrogen urate salts and free base at pH values around neutral.

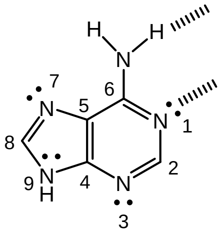


Uric acid keto form

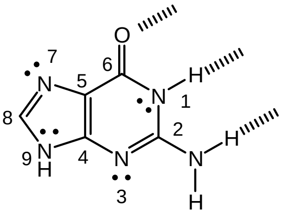
The normal urates are soluble in water, whereas the acid urates are insoluble; lithium acid urate is most soluble. This solubility difference is associated with gout where formation of sodium urate is more rapid than its rate of elimination and salt crystals precipitate in joints. Gout is a medical condition that usually presents with recurrent attacks of acute inflammatory arthritis (red, tender, hot, swollen joint). It is caused by elevated levels of uric acid in the blood that crystallizes and deposits in joints, tendons, and surrounding tissues. Hyperuricemia (abnormally high blood level of uric acid) is the underlying cause of gout. This can occur for a number of reasons including dietary, genetic, or underexcretion of urate Regardless of the serum concentration of uric acid, precipitation of uric acid is enhanced when the blood pH is low (acidosis). A similar pH-sensitive effect occurs in urine, leading to kidney stones containing uric acid.

Purine bases. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are long polymers of nucleotides. The DNA, RNA skeleton is made of sugars and phosphate groups. Attached to each sugar is one of four bases. Some are pyrimidine bases, and some – purine bases. The purine bases are **adenine** and **guanine**. A nucleotide is nucleoside connected to phosphate group. Nucleoside is built of a nucleobase bound to a ribose or deoxyribose sugar via a beta-glycosidic linkage. Nucleotides are molecules that, when joined together, make up the structural units of RNA and DNA. From the description of pyrimidine bases is already known that uracil base pairs with adenine. Therefore adenine must have the ability to form two hydrogen bonds. Cytosine base pairs with guanine, consequently guanine must possess three suitable places to form three hydrogen bonds. The atom attached to the sugar is N(9) of the purine skeleton.

Adenine. Adenine (6-aminopurine) is a purine derivative with a variety of roles in biochemistry including cellular respiration, in the form of both the energy-rich adenosine triphosphate (ATP, a nucleotide) and the cofactors nicotinamide adenine dinucleotide (NAD, as a nucleotide) and flavin adenine dinucleotide (FAD). Adenine plays important role in protein synthesis and as a chemical component of DNA and RNA. In their structure, the amino group and the adjacent nitrogen are engaged in hydrogen bonding (dashed lines).



Adenine (A)
6-aminopurine
in RNA and DNA

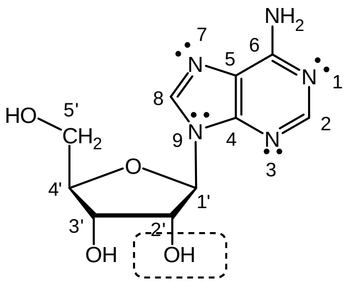


Guanine (G)
2-amino-6-hydroxypurine
in RNA and DNA

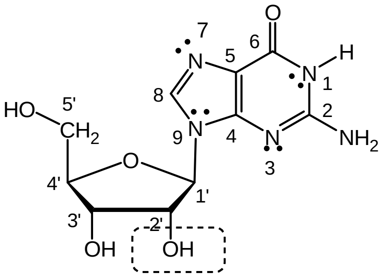
Guanine. Guanine (2-amino-6-hydroxypurine) has two tautomeric forms. Major is the keto form, the 6-OH (lactim, or enol) form has no biochemical relevance in regard to DNA, RNA. The amino and the keto groups, along with the nitrogen between them are engaged in three hydrogen bonds (dashed lines) in nucleic acids. Both adenine and guanine are planar, aromatic systems. This planarity has its role, along with the flat cytosine, uracil and thymine in the structure of DNA and RNA.

Adenine and guanine bonded at N(9) to ribose or 2-deoxyribose give the four possible nucleosides from purine bases: **adenosine**, **deoxyadenosine**, **guanosine**, and **deoxyguanosine**.

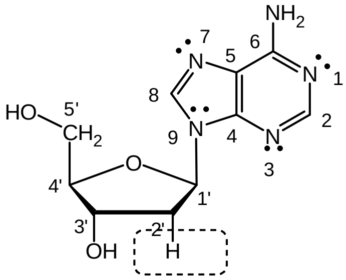
Adenosine plays an important role in biochemical processes, such as energy transfer − as in the nucleotides adenosine triphosphate (ATP) and adenosine diphosphate (ADP) − as well as in signal transduction as cyclic adenosine monophosphate, cAMP. Adenosine has an inhibitory effect in the central nervous system (CNS); it promotes sleepiness. Caffeine's stimulatory effects, on the other hand, are primarily due to its inhibition of adenosine by binding to the same receptors, and therefore blocking adenosine receptors in the CNS. This reduction in adenosine activity leads to increased activity of the neurotransmitters dopamine and glutamate.



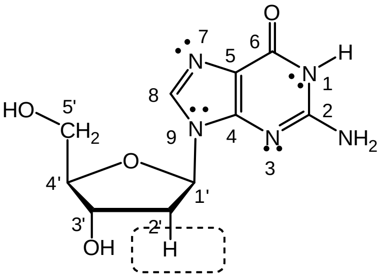
Adenosine



Guanosine



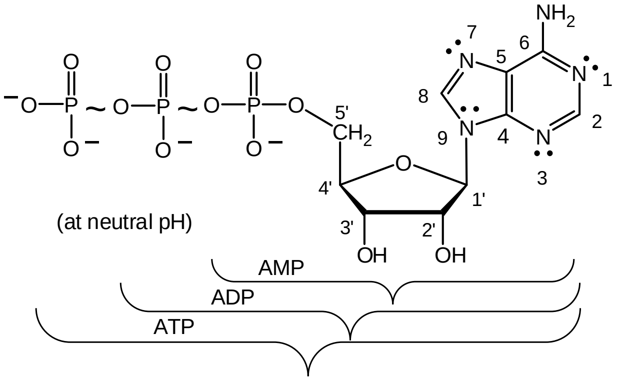
Deoxyadenosine



Deoxyguanosine

Guanosine is a nucleoside comprising guanine attached to a ribose (ribofuranose) ring via a β-N(9)-glycosidic bond. Guanosine can be phosphorylated to become GMP (guanosine monophosphate), cGMP (cyclic guanosine monophosphate), GDP (guanosine diphosphate) and GTP (guanosine triphosphate). These compounds are nucleotides. Nucleotides are phosphoric acid esters of nucleosides.

Adenosine-5'-triphosphate (ATP) is a multifunctional nucleotide used in cells as a coenzyme. It is often called the "molecular unit of currency" of intracellular energy transfer. ATP transports chemical energy within cells for metabolism. It is produced by phosphorylation and cellular respiration. ATP is produced by the enzyme ATP synthase from inorganic phosphate and adenosine diphosphate (ADP) or adenosine monophosphate (AMP). ATP is used by enzymes and structural proteins in many cellular processes, including biosynthetic reactions, motility, and cell division. Metabolic processes that use ATP as an energy source convert it back into its precursors. ATP is continuously recycled in organisms, with the human body turning over its own weight in ATP each day. One molecule of ATP contains three phosphate groups. They are connected by bonds that resemble the bond in carboxylic acid anhydrides (RCO-O-COR). In neutral solution, ATP is ionized and exists mostly as ATP^{4-}, with a small proportion of ATP^{3-}. The hydrolysable bonds are indicated in the structure with ~ line. Their hydrolysis releases great amount of energy.

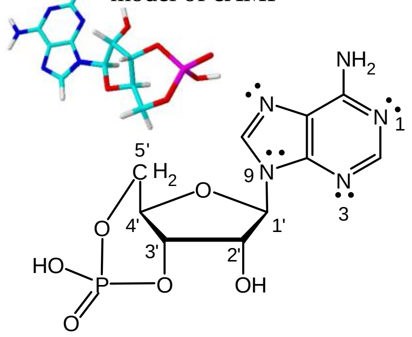


ATP is an unstable molecule in unbuffered water, which hydrolyses to ADP and phosphate. This is so because the strength of the bonds between the phosphate residues in ATP are less than the strength of the "hydration" bonds between its products and water. A system that is far from equilibrium contains Gibbs free energy, and is capable of doing work. Living cells maintain the ratio of ATP to ADP at a point ten orders of magnitude from equilibrium, with ATP concentrations a thousandfold higher than the concentration of ADP. This displacement from equilibrium means that the hydrolysis of ATP in the cell releases a great amount of energy.

$$\mathrm{ATP} + \mathrm{H_2O} \longrightarrow \mathrm{ADP} + \mathrm{P_i} \quad \Delta G = -30.5\ \mathrm{kJ.mol^{-1}}$$

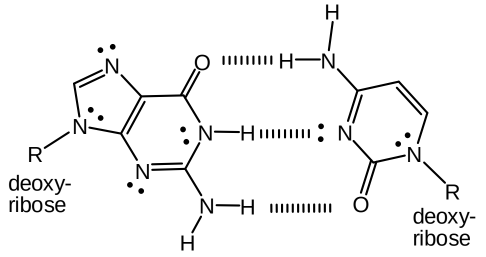
$$\mathrm{ATP} + \mathrm{H_2O} \longrightarrow \mathrm{AMP} + \mathrm{PP_i} \quad \Delta G = -45.6\ \mathrm{kJ.mol^{-1}}$$

tubular molecular model of cAMP

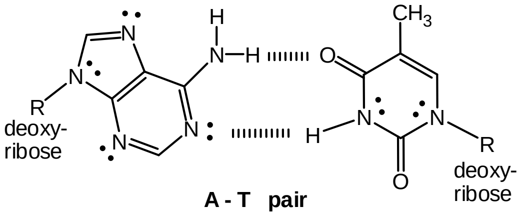


Cyclic adenosine monophosphate (**cAMP**, cyclic AMP or 3'-5'-cyclic adenosine monophosphate) is a secondary messenger important in many biological processes. cAMP is derived from adenosine triphosphate (ATP) and used for intracellular signal transduction. cAMP is used for intracellular signal transferring such as the effects of hormones like glucagon and adrenaline, which cannot pass through the cell membrane. cAMP is involved in the activation of enzymes and regulates the effects of adrenaline and glucagon. It also regulates the passage of Ca^{2+} through ion channels.

Base pairing. In molecular biology and genetics, two nucleotides on opposite complementary DNA or RNA strands that are connected via hydrogen bonds are called a **base pair** or Watson-Crick DNA base pair. Two chains of DNA or RNA are held together by multitude of hydrogen bonds between purine and corresponding pyrimidine base. Before the discovery of DNA structure, there was biochemical evidence that the amount (moles) of cytosine equals the amount of guanine, and that of thymine equals adenine. The sugar-phosphate backbone of the chains runs in antiparallel direction. That is, the C(3') deoxyribose end of the chain faces the C(5') end of the second chain. **Guanine binds to cytosine** (**C-G**) through three hydrogen bonds. In cytosine, the NH_2 group acts as the hydrogen donor and the C(2) carbonyl and the N(3) nitrogen as the hydrogen-bond acceptors. Guanine has a C=O group at C(6) that acts as the hydrogen bond acceptor, whereas the group at N(1) and the amino group at C(2) act as the hydrogen donors. Such fitting arrangement of donor and acceptor sites is called, complementarity of donor-acceptor of H-bonds in cytosine and guanine. The complementarity assures tight fit of the planar bases facing each other.



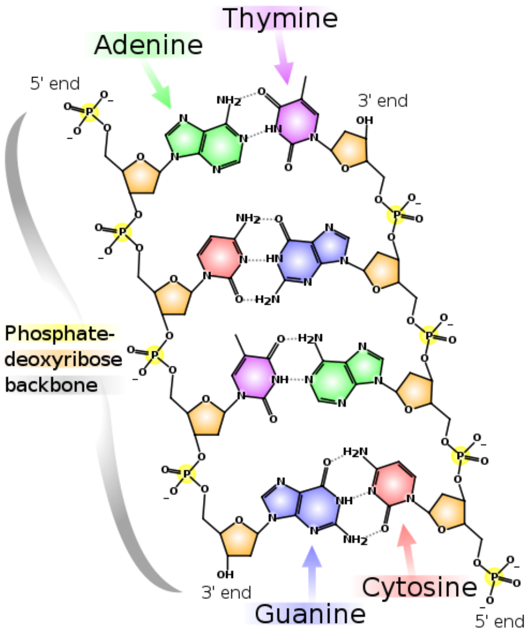
G - C pair



A - T pair

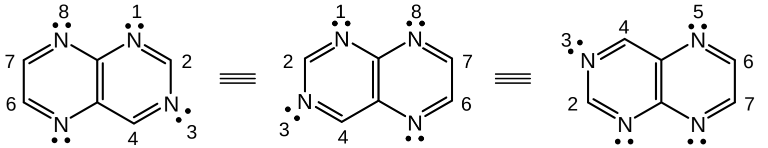
Adenine binds thymine (**A-T**) to form a base pair using two hydrogen bonds (dashed lines). Both types of base pairs are located inside the DNA double helix structure in parallel planes. Between them exists also stabilizing interaction of their aromatic systems. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature. A complementary strand of the DNA sequence 5' AGTCATG 3' is
3' TCAGTAC 5'

As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. The reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.



Pteridine and its derivatives.

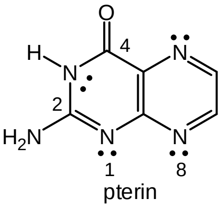
Pteridine is an aromatic tetraaza heterocycle comprising fused pyrimidine and pyrazine rings. All nitrogen atoms are basic of pyridine type.

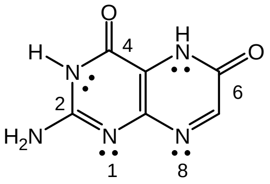

nomenclature pteridine most often used

Pteridine structure can be drawn in several equivalent way, with the right structure usually used. The pteridine ring system is found in various natural products, e.g. pterins, xanthopterin, folic acid.

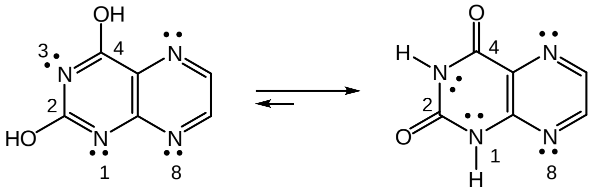
Pterins, as a group, are compounds that are derivatives of 2-amino-4-oxopteridine, with additional functional groups attached to the pyrazine ring. They were discovered in the pigments of butterfly wings. Pterins are usually associated with coloration in the biological world. Pterins also function as cofactors in enzyme catalysis.

Xanthopterin is a yellow, crystalline solid that occurs mainly in the wings of butterflies and is found in the urine of mammals. Small microorganisms convert it into folic acid.

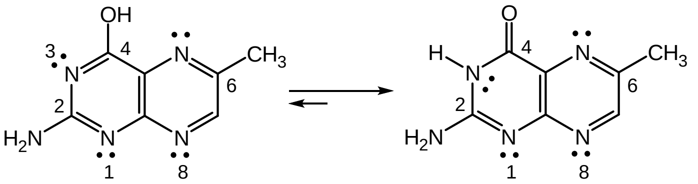

pterin


xanthopterin

Pteridine-2,4-dione (2,4-dihydroxypteridine) is portion of riboflavin structure. Riboflavin is vitamin B_2. It is an easily absorbed micronutrient with a key role in maintaining health in humans, segment of flavin adenine dinucleotide (FAD). As such, vitamin B_2 is required for a wide variety of cellular processes. It plays a key role in energy metabolism, and for the metabolism of fats, ketone bodies, carbohydrates, and proteins.



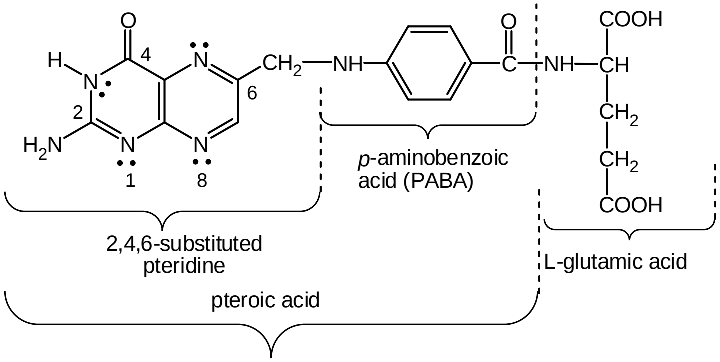
pteridine-2,4-dione



2-amino-6-methylpteridin-4-one

One of the pterins is 2-amino-6-methylpteridin-4-one. It is part of **folic acid**. The term folate is used in general to compounds related to folic acid.

folic acid



Vitamin B_9 (folic acid and folate inclusive) is essential to numerous bodily functions. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in biological reactions involving folate. It is especially important during periods of rapid cell division and growth. Both children and adults require folic acid to produce healthy red blood cells and prevent anemia.