Chapter 25. Polymers

What we will learn:

- Properties of polymers
- Synthetic organic polymers
- Proteins
- Nucleic acids
- Review of current biochemical problems

Polymer

A molecular compound having a high molar mass and made up of many repeating units

Natural polymers

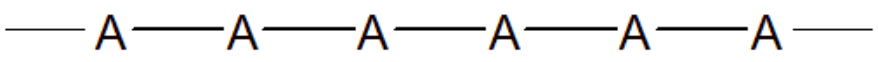
Proteins, nucleic acids, cellulose, rubber, ...

Synthetic polymers

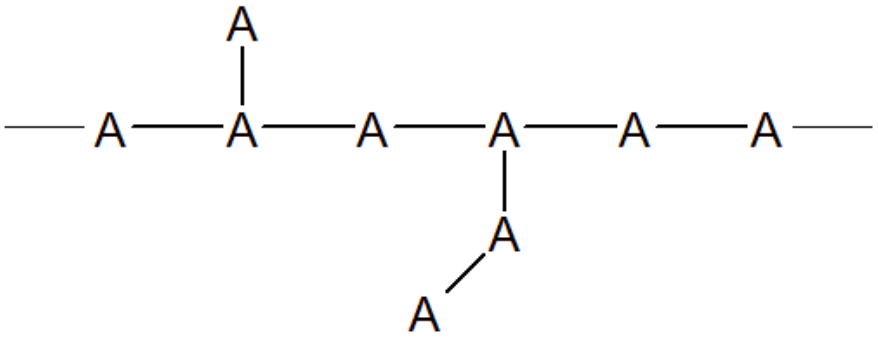
Polyethylene, PVC(polyvinyl chloride), Teflon, Plexiglas, Polystyren, ...

Types of polymer structures

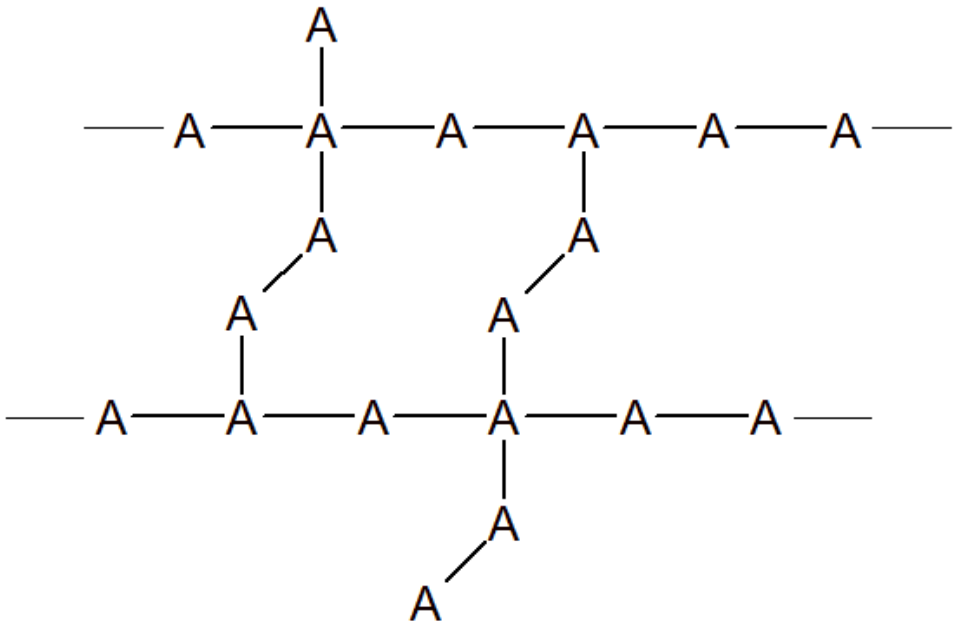
- Homopolymers



Linear



Branched



Cross-linked

Solubility

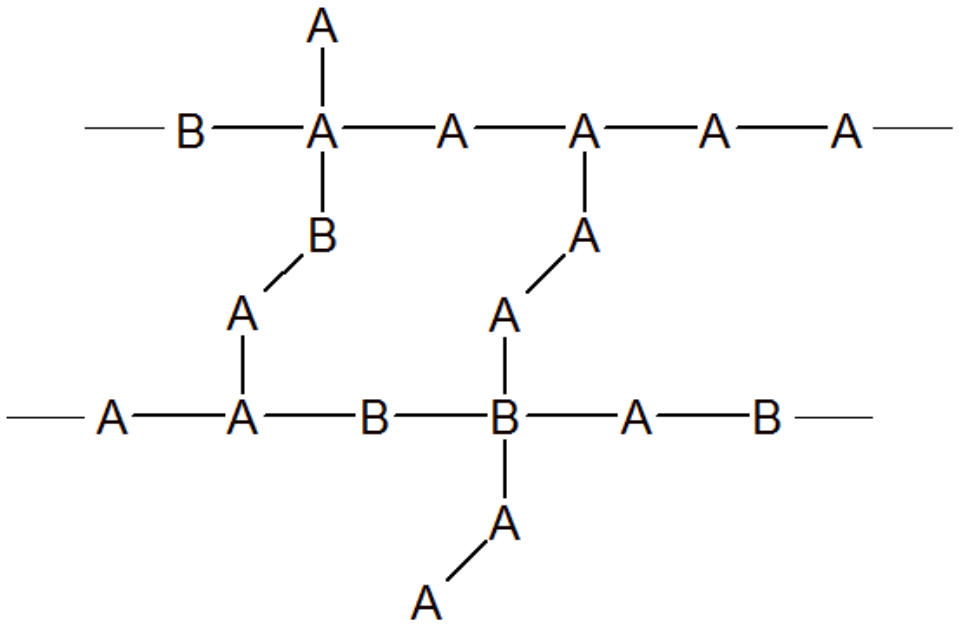
Linear and branched -- usually soluble

Cross-linked -- insoluble (swell)

Elastomer : a lightly cross-linked polymermers, combine properties of 2 polymers

Copolymers

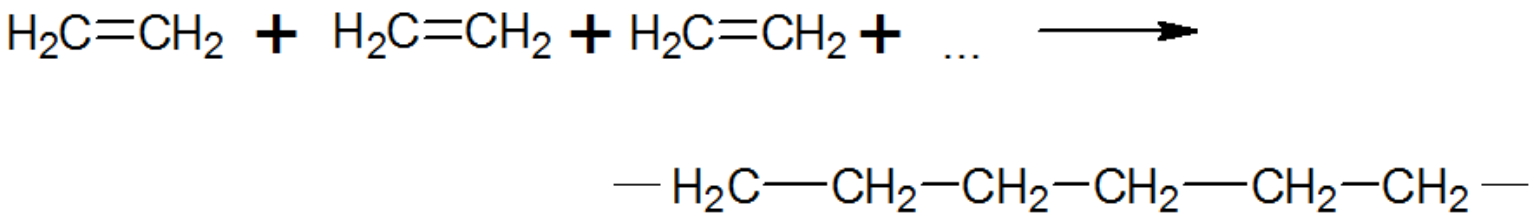
Contain two or more different monomers, combine properties of 2 polymers



Methods of polymerization

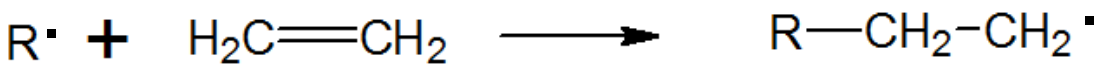
Addition

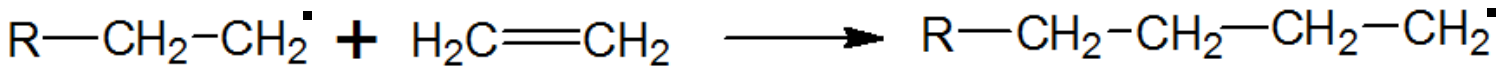
Very common -- works with most alkenes



Requires an initiator (e.g., a catalyst or UV light) to start the “chain” reaction

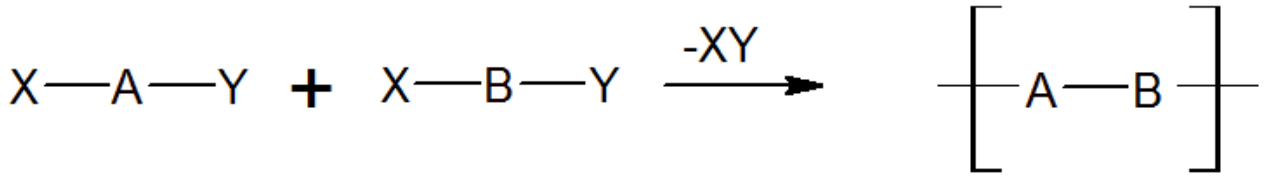
Radical initiation





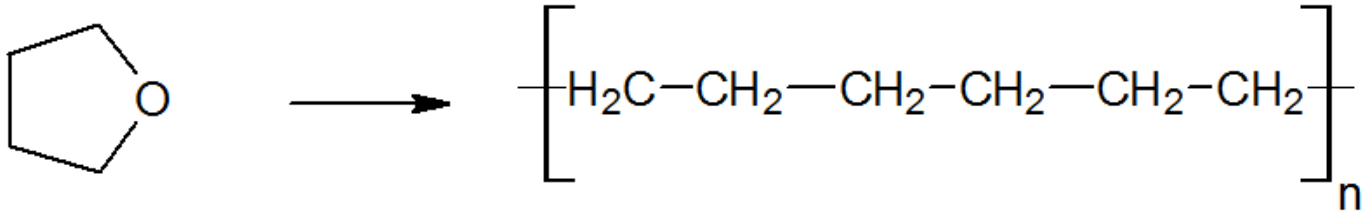
Condensation

Common for polyesters and polyamides a small molecule (e.g., H_2O) by product is formed

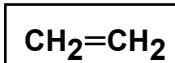
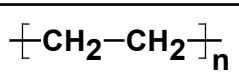
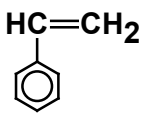
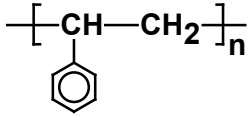
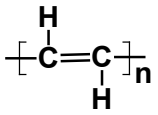
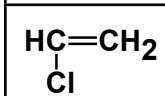
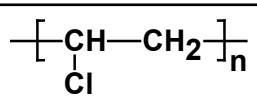
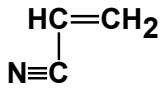
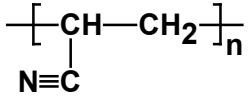
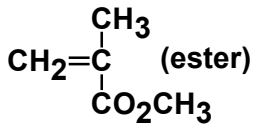
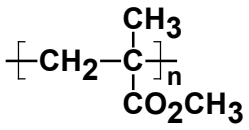
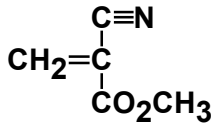
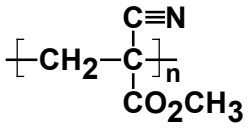


Ring-opening

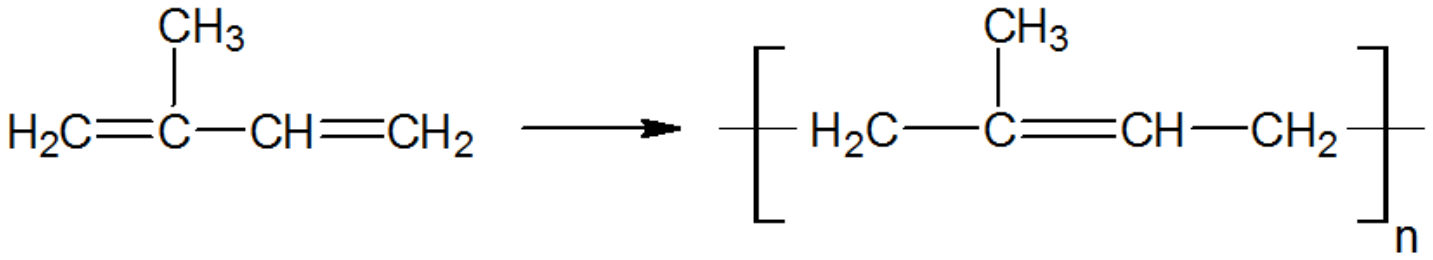
Uncommon except for polyethers and most inorganic polymers, e.g., silicones



Common addition polymers

	ethylene		polyethylene
	styrene		polystyrene
	acetylene		poly(acetylene)
	vinyl chloride		poly(vinyl chloride) PVC
	tetrafluoroethene		Teflon
	cyanoethene		Orlon
	methyl methacrylate		Plexiglas (Lucite)
	methyl cyanoacrylate		Super glue

Addition polymerization of dienes

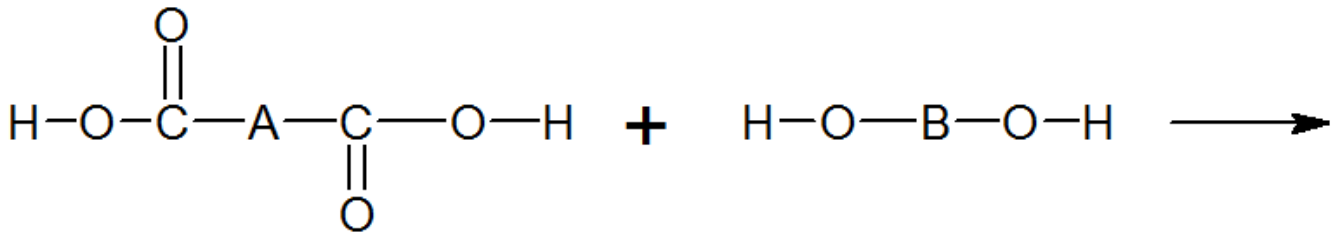


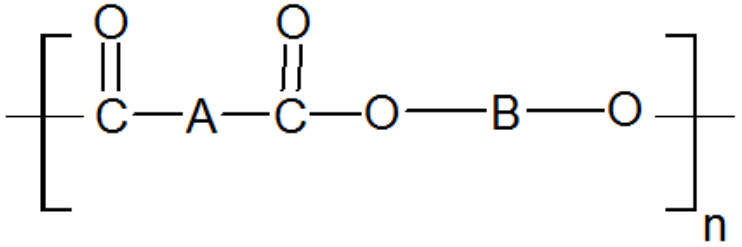
isoprene
(2-methyl-1,3-butadien)

natural rubber

Common condensation polymers

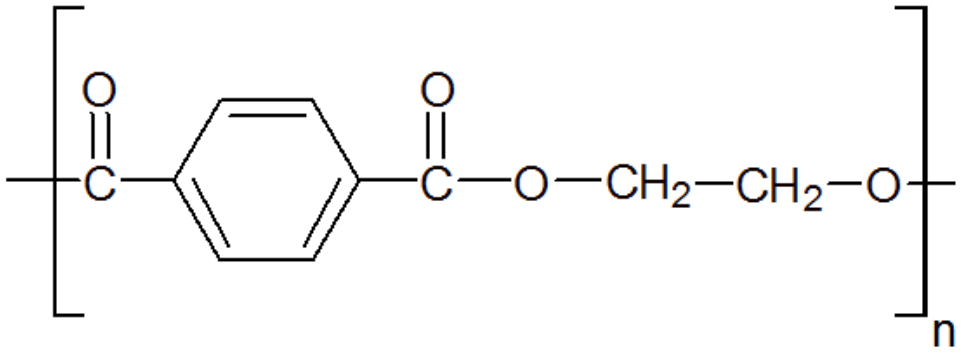
Polyesters





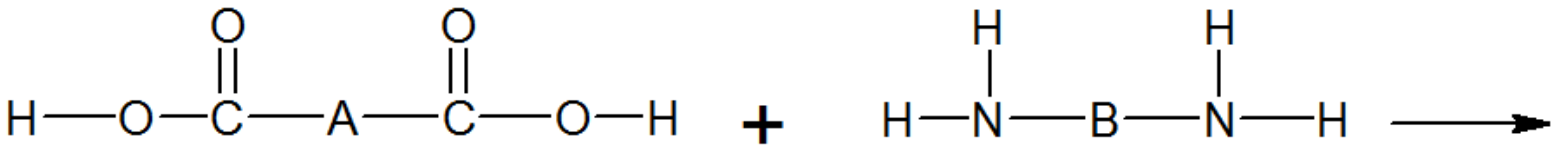
A = 

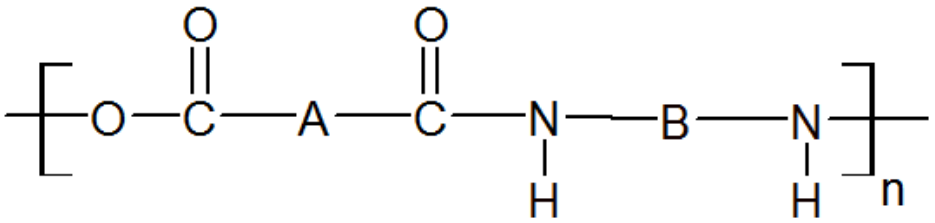
B = $-CH_2-CH_2-$



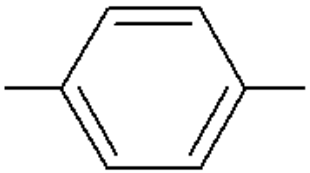
Polyamides

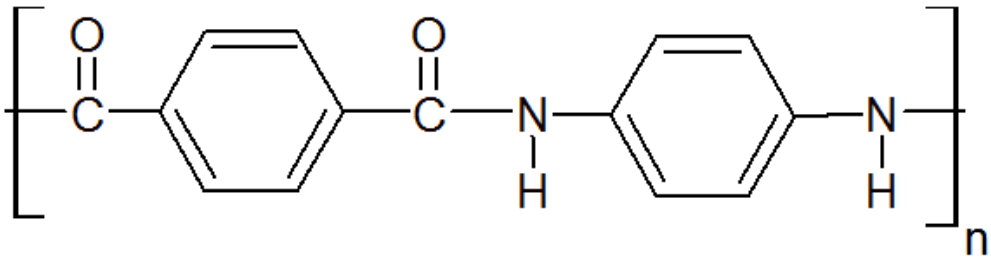
(nylons)





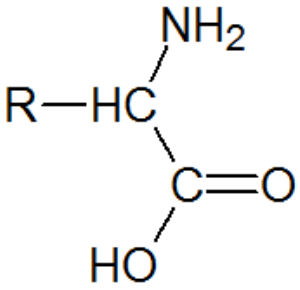
A = B =

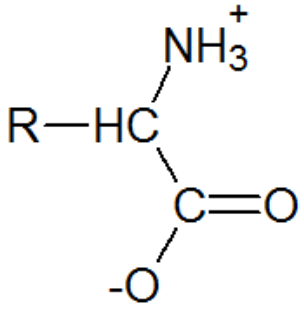


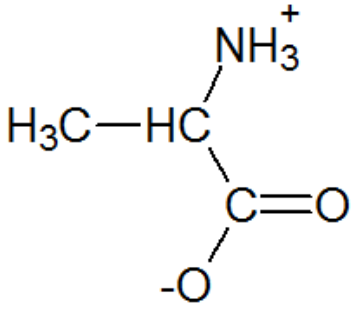


Proteins

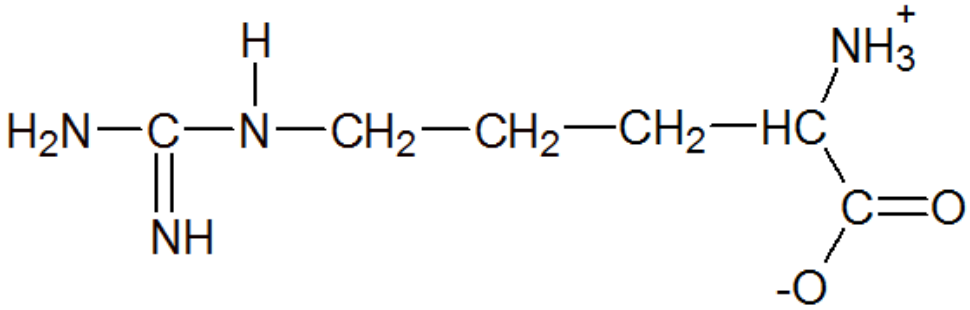
- Biological condensation polymers
- Monomers are 20 amino acids (different R groups)



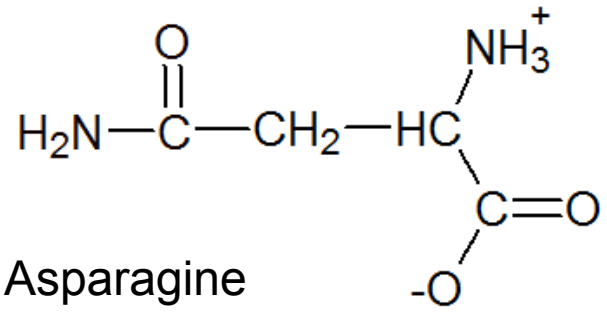




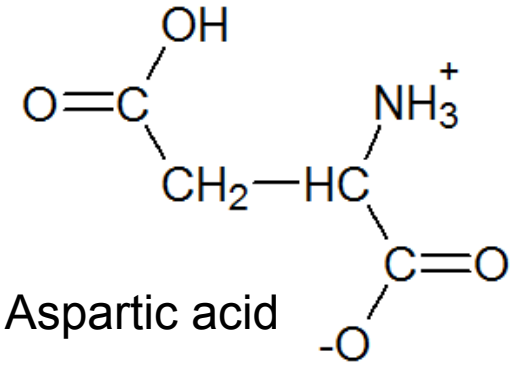
Alanine



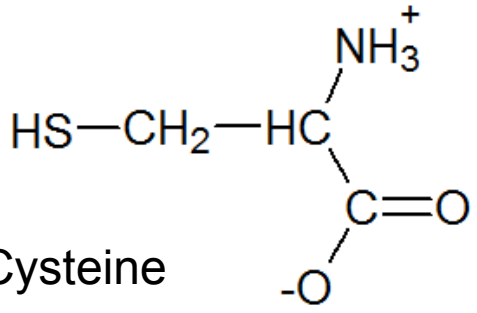
Arginine



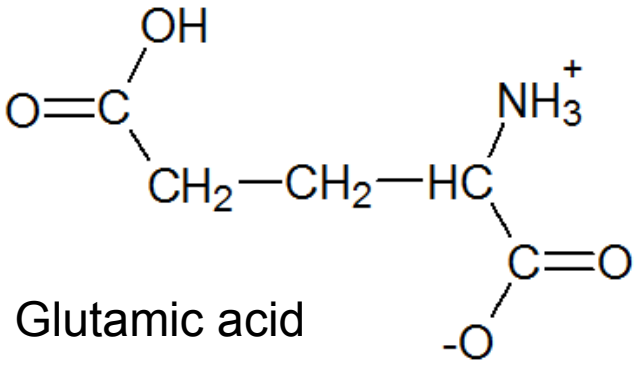
Asparagine



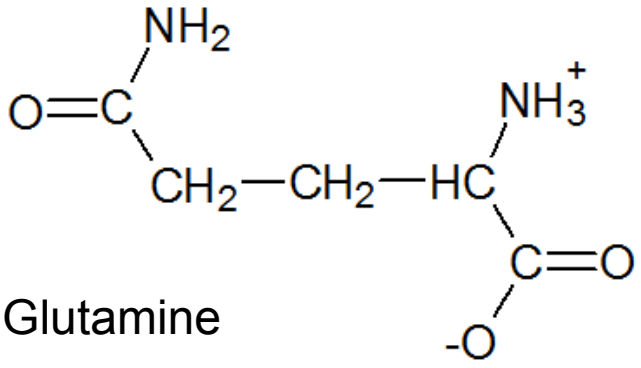
Aspartic acid



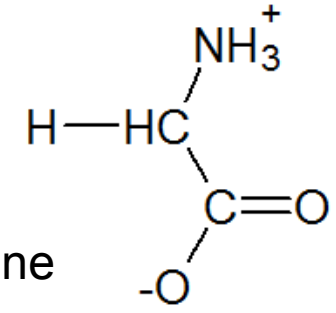
Cysteine



Glutamic acid



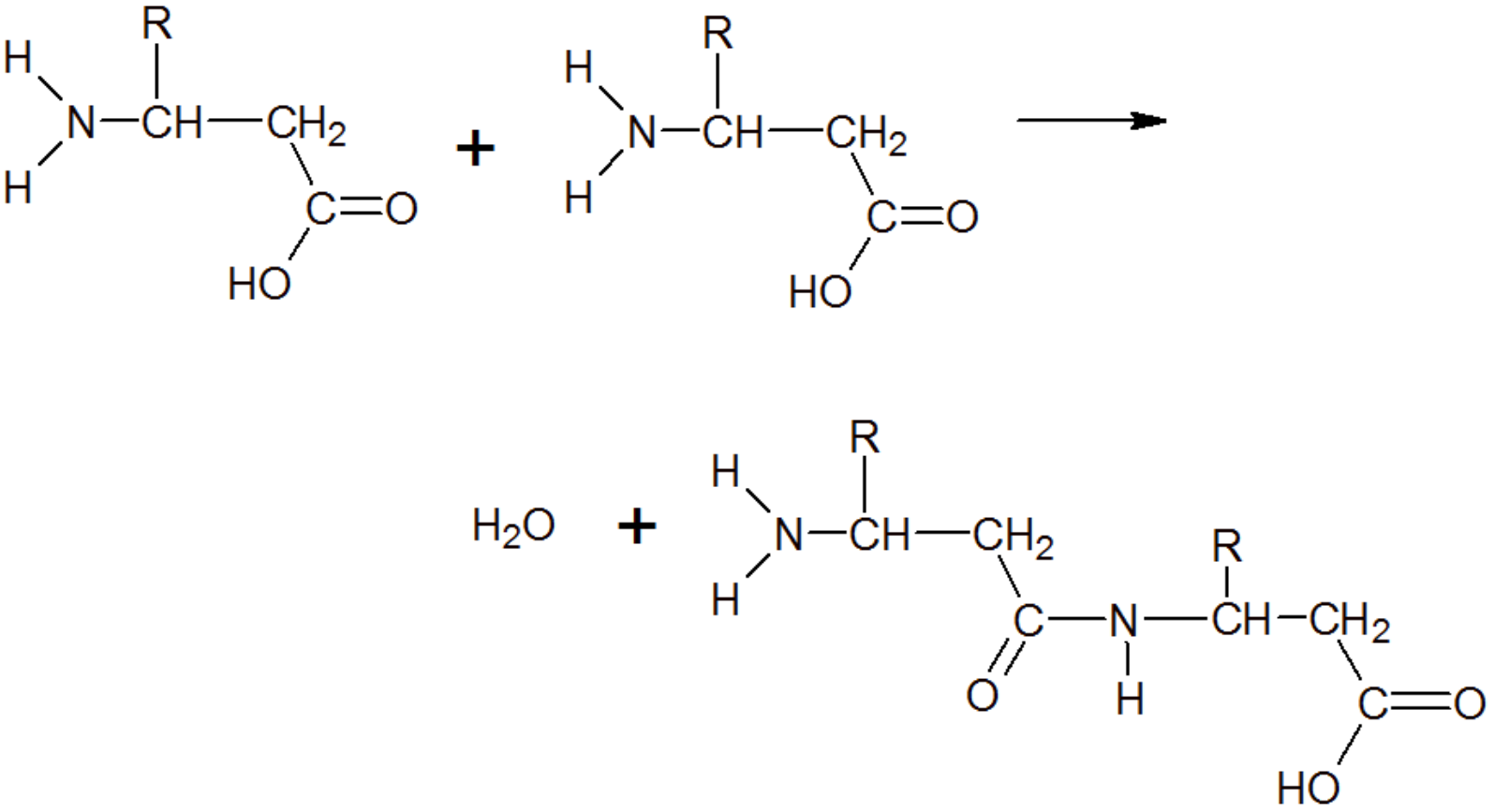
Glutamine



Glycine

Condensation of amino acids

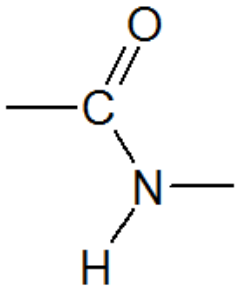
Loss of H_2O

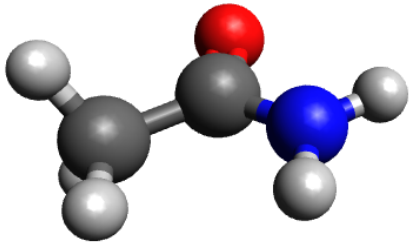


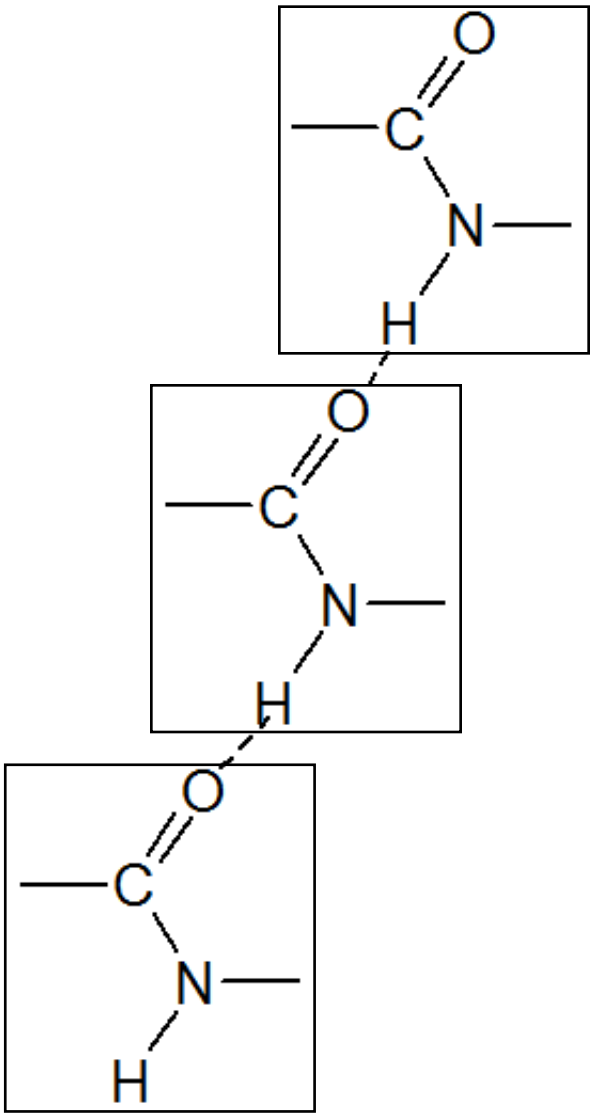
Peptide bond

A fundamental element of a protein backbone

Peptide group







Atoms in the peptide group are planar indicating on delocalization of π electrons, which stabilize the structure

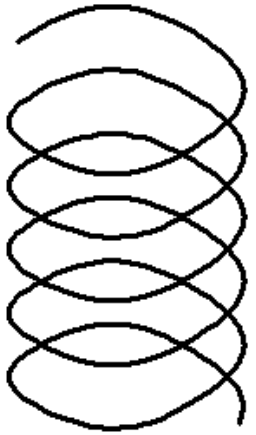
Hydrogen bonds

There are hydrogen bonds between peptide groups forming final 3D structures of proteins

Two main arragngements

α Helix

Formed by hydrogen bonds within one polypeptide chain

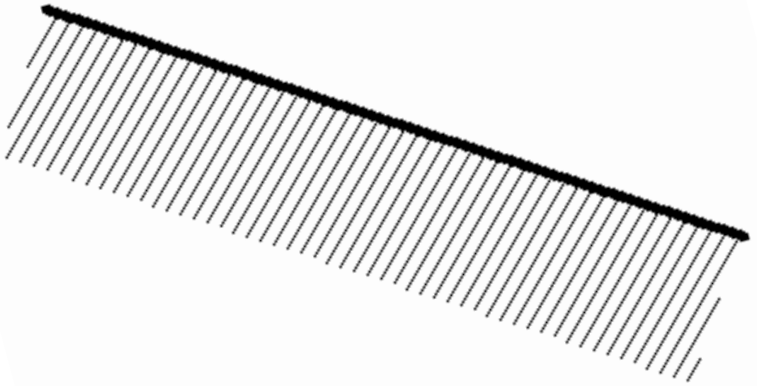


β Sheet

Formed by hydrogen bonds between two polypeptide chains

- parallel

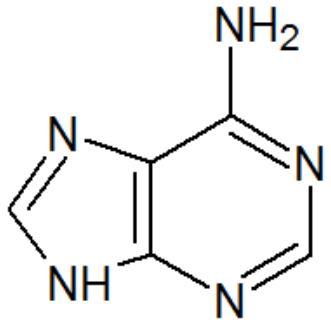
- antiparallel



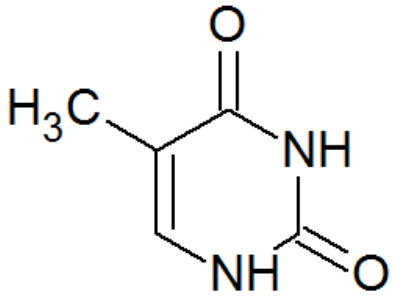
Nucleic Acids (DNA, RNA)

- Also condensation polymers
- Phosphate groups
- Sugar molecules
- 4 bases (purines and pyrimidines)
- Monomer contains all three units - one nucleotide
- Structure dominated by hydrogen bonding
- Base pairs (A-T and C-G)

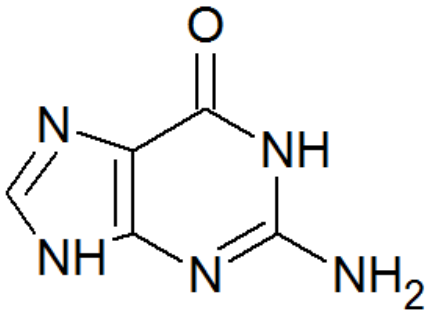
DNA bases



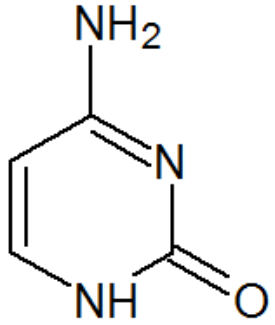
Adenine



Thymine

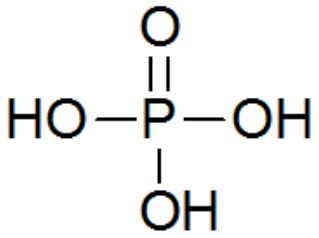


Guanine

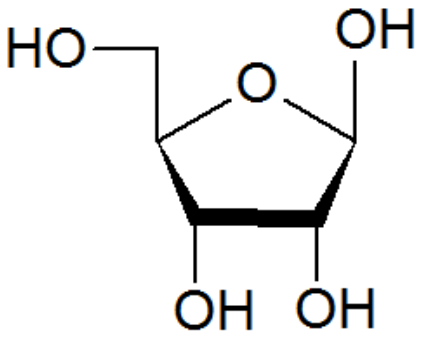


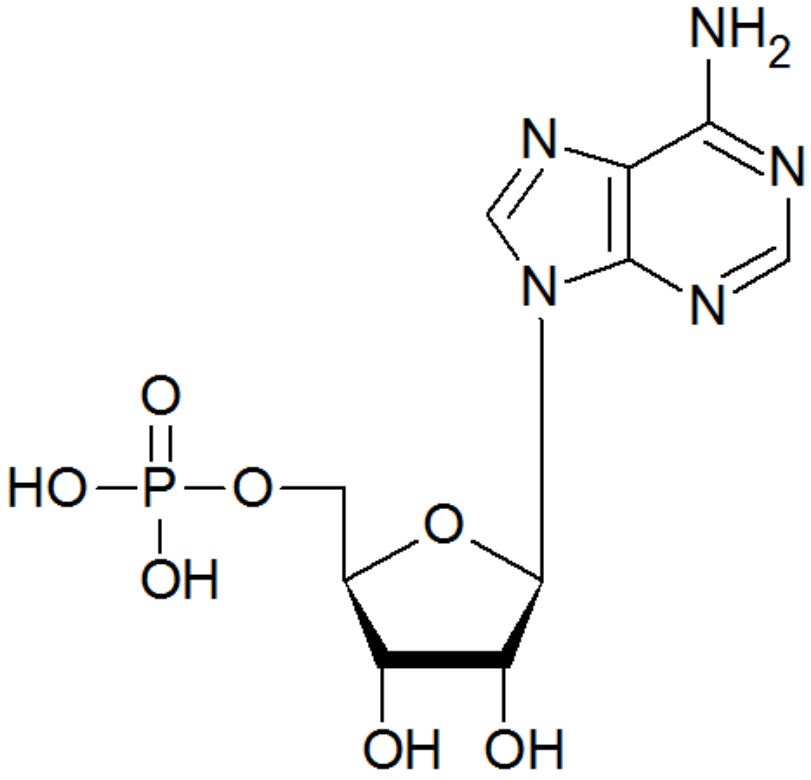
Cytosine

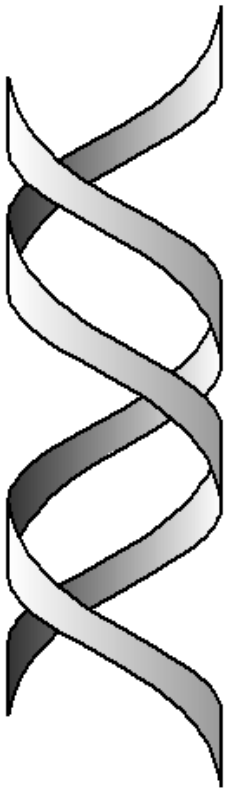
Phosphate unit



Sugar unit

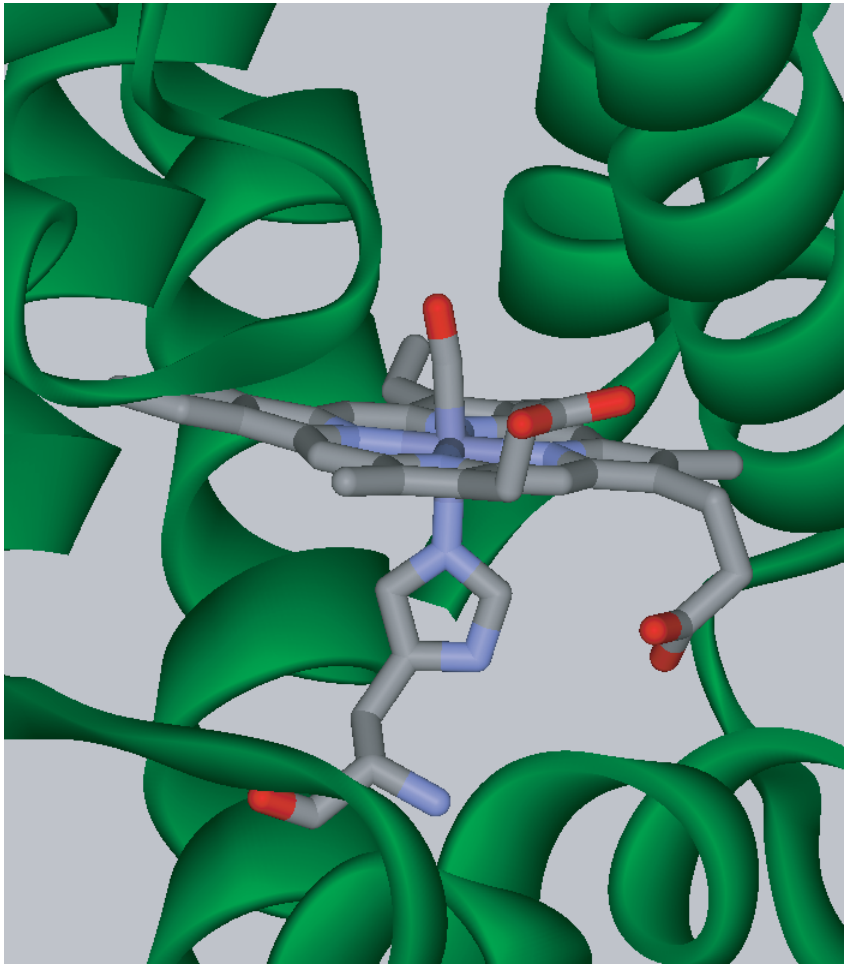






Hemoglobin

The iron and oxygen-binding protein protein which is responsible for oxygen (O_2) transport and storage. The protein is formed of four units (myoglobin like)



Myoglobin

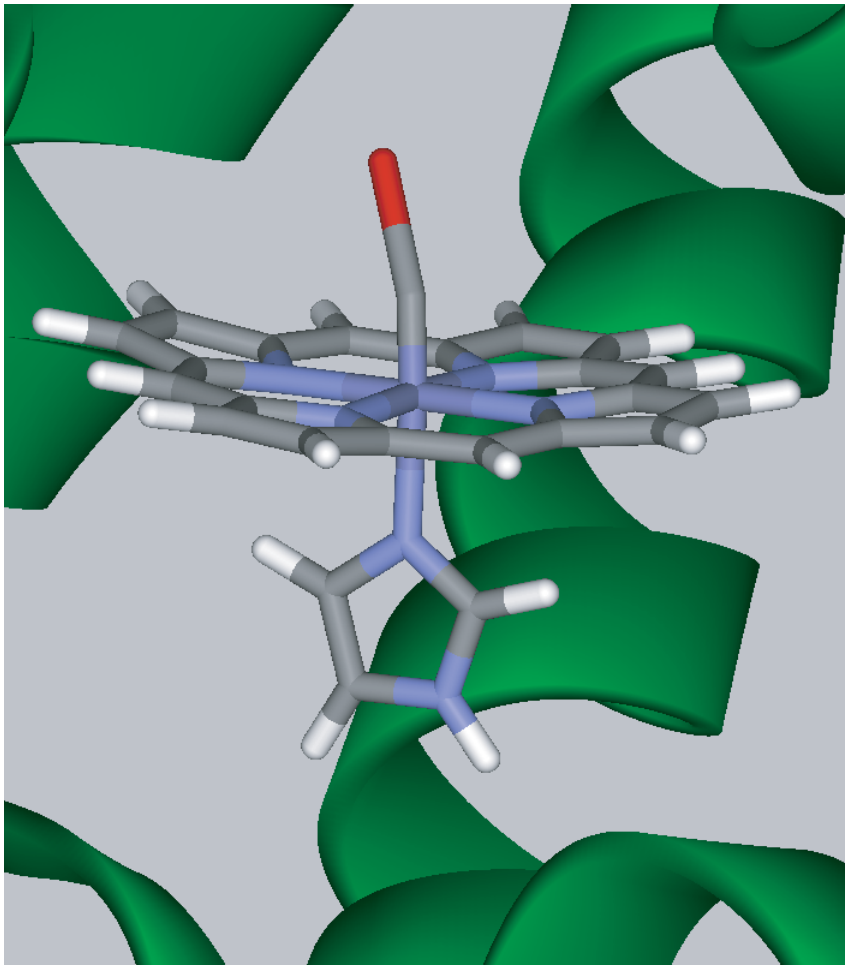
The x-ray structure of myoglobin

The protein is found in the muscle tissue in almost all mammals. It is related to hemoglobin, which is the iron and oxygen-binding protein in blood, specifically in the red blood cells

Myoglobin with CO

The computational model of myoglobin with CO

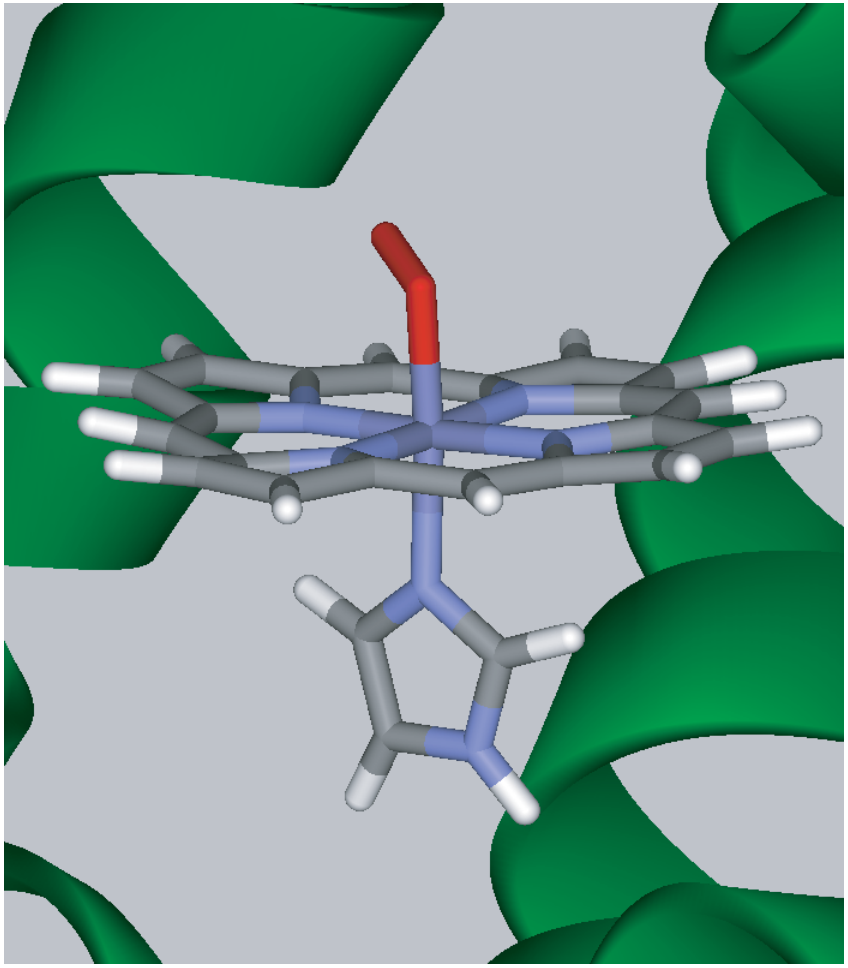
CO binds to the heme group 25000 times stronger than O_2 in the gas phase, in the protein the CO affinity is reduced to only 30 times



Myoglobin with O_2

The computational model of myoglobin with O_2

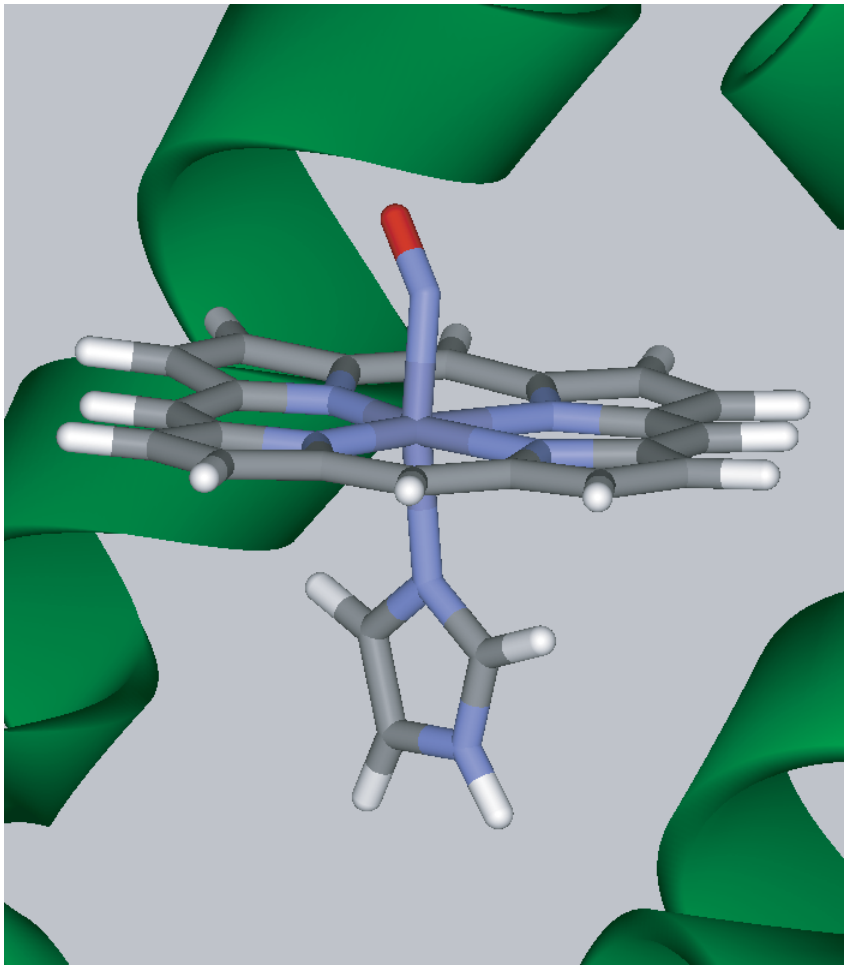
The physiological function of myoglobin is to store molecular oxygen in muscle tissue so that there is a reserve of O_2 over and above that bound to the hemoglobin in the blood



Myoglobin with NO

The computational model of myoglobin with NO

In the 1980s, it was reported that nitric oxide (NO) can be synthesized in mammals cells to generate vascular muscle relaxation, which significantly changed fundaments of cell signal transduction



Nobel prize

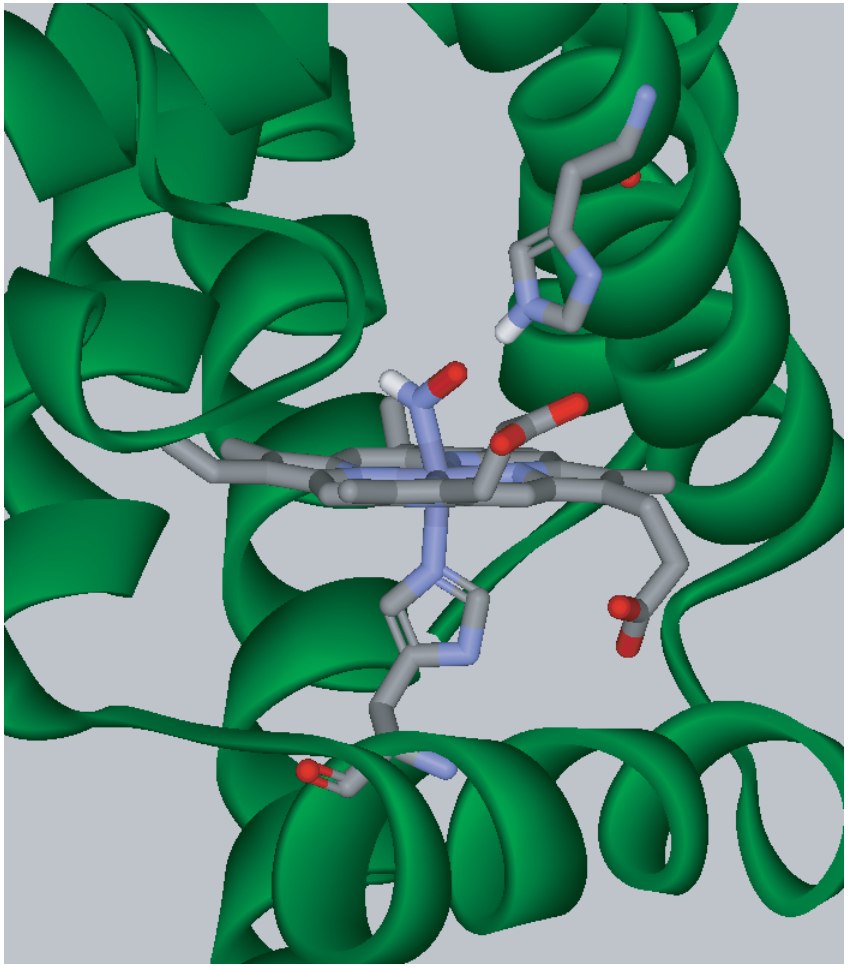
- NO is improving relaxation of the heart muscle

- NO is decreasing heart capacity for blood pumping

Myoglobin with HNO

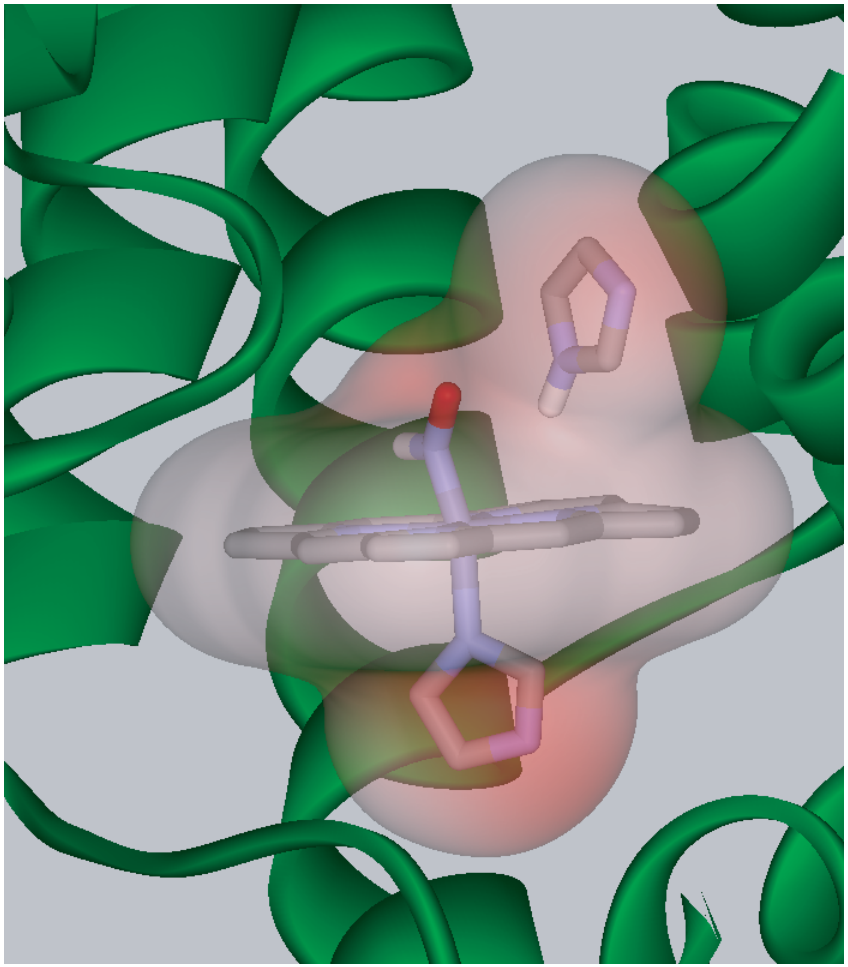
The experimental structure of myoglobin with HNO

HNO is improving relaxation of the heart muscle without decreasing heart capacity for blood pumping



Myoglobin with HNO

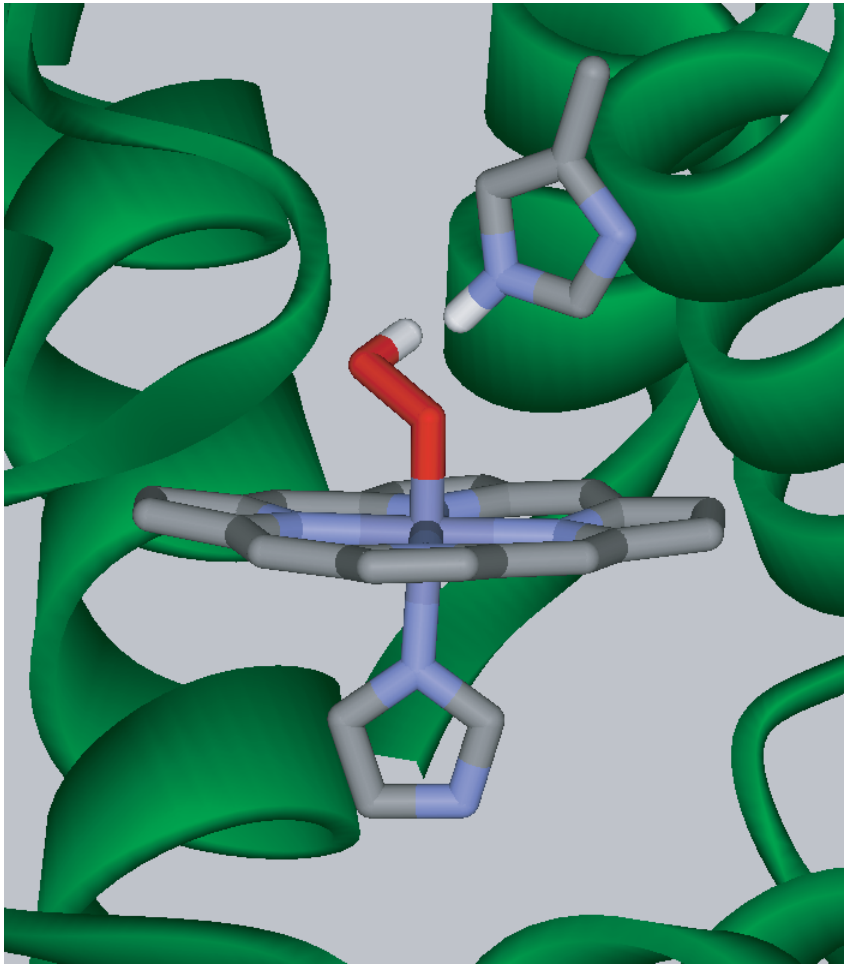
The computational model of the active site of myoglobin with HNO showing a hydrogen bonding with distal histidine



Myoglobin with OOH

The computational model of the active site of myoglobin with OOH showing a hydrogen bonding with distal histidine

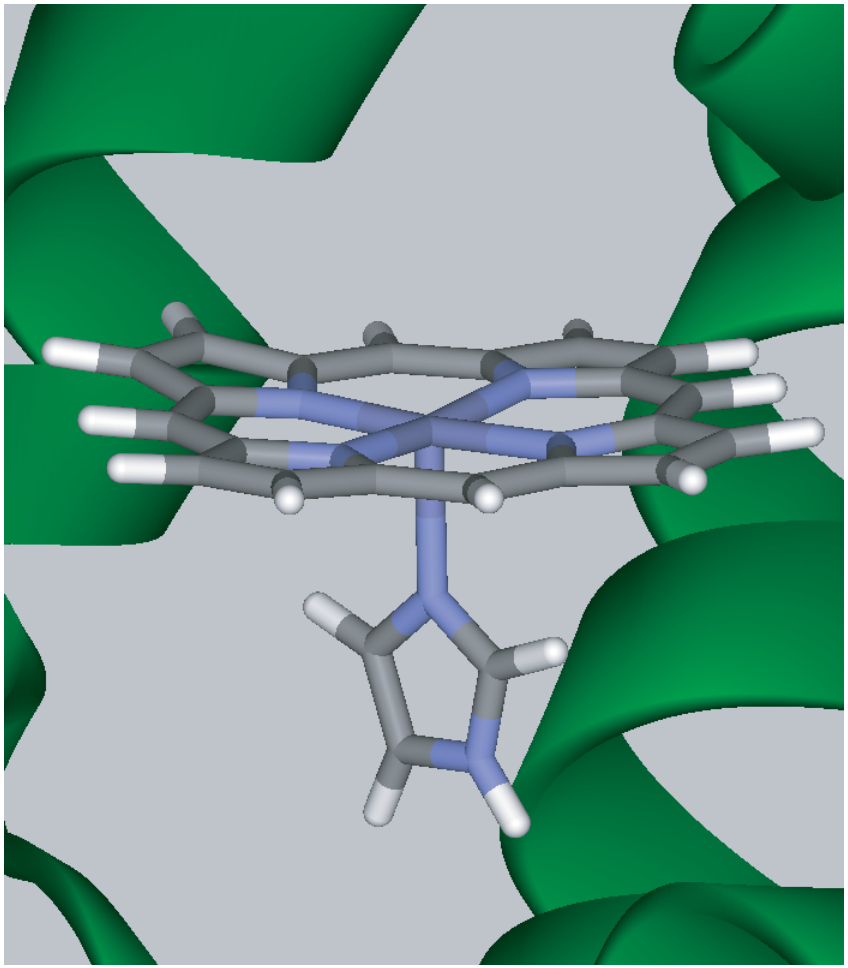
The Fe-OOH interaction in the protein is a precursor of the *compound I* (Fe-O) a very active species resposible for catalytic activity of cytochrome P450



Deoxymyoglobin

The computational model of deoxymyoglobin

Deoxymyoglobin readily converts to oxymyoglobin in the presence of oxygen



Meat color

- red myoglobin with O_2
- pink myoglobin with NO
- brown myoglobin with H_2O
- dark myoglobin with CO

SGC

The x-ray structure of Soluble Guanylate Cyclase (sGC)

sGC catalysis the GTP into cGMP conversion (400 times)

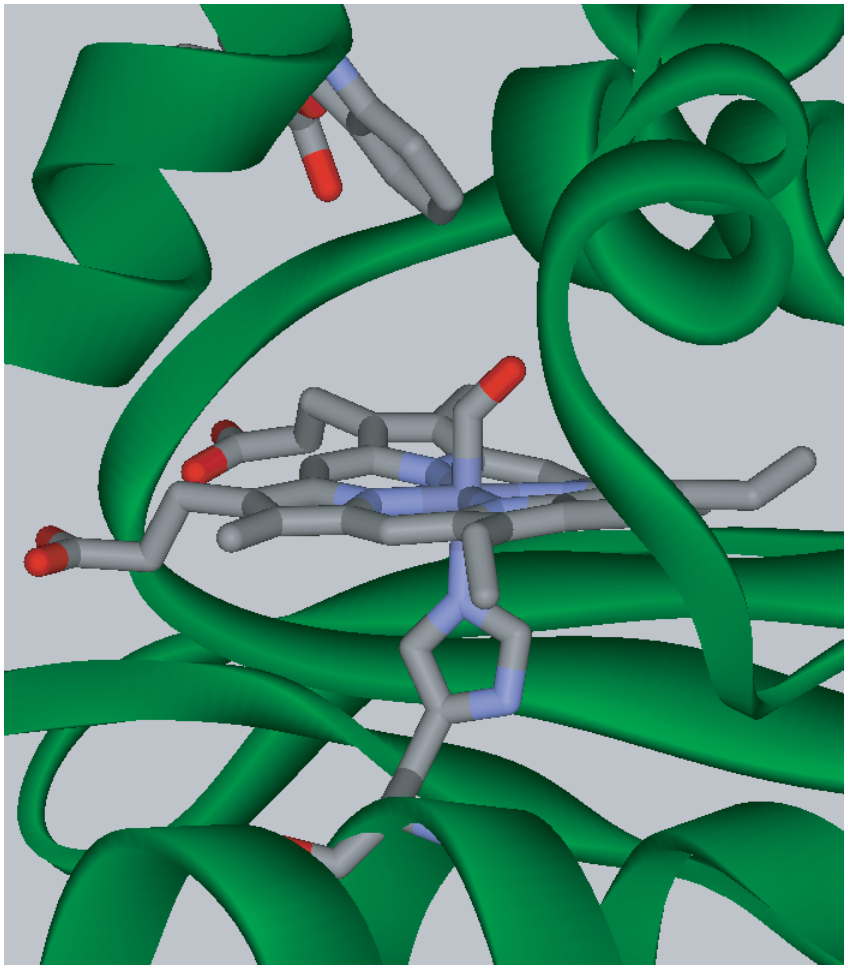
- Smooth muscle relaxation

- Blood pressure regulation

- Platelet aggregation

- Neurotransmition

- Depression



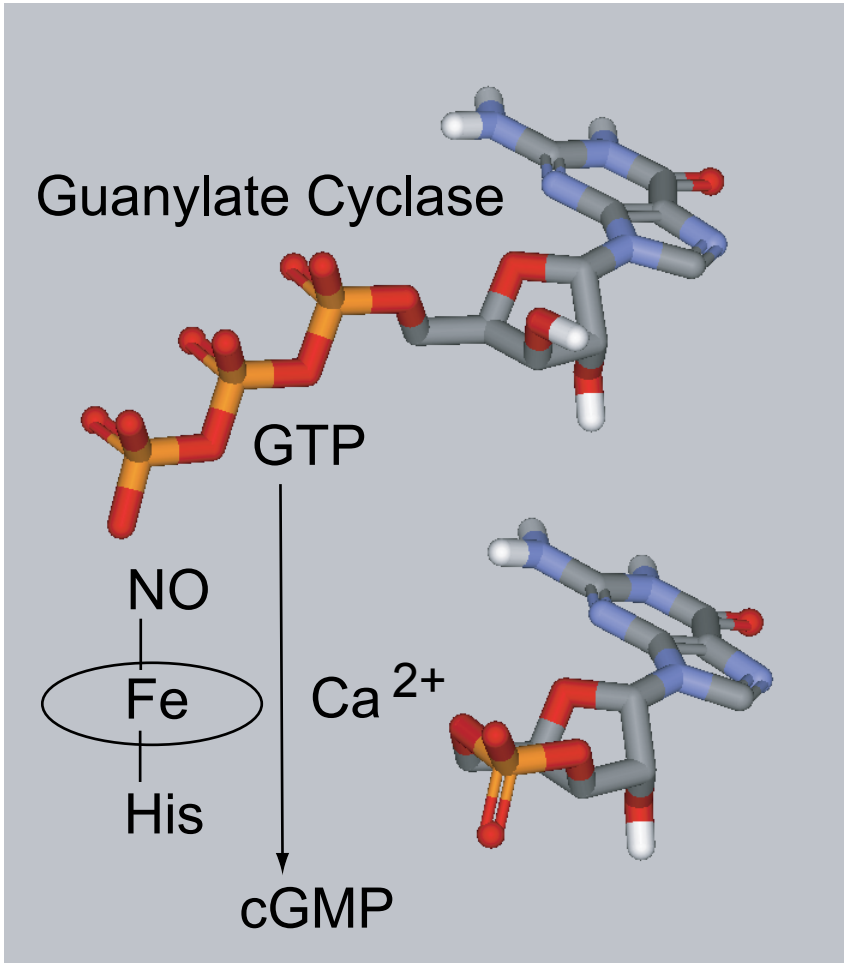
SGC

Conversion of GTP into cGMP

- GTP guanosine triple-phosphate

- cGMP cyclic guanosine mono-phosphate

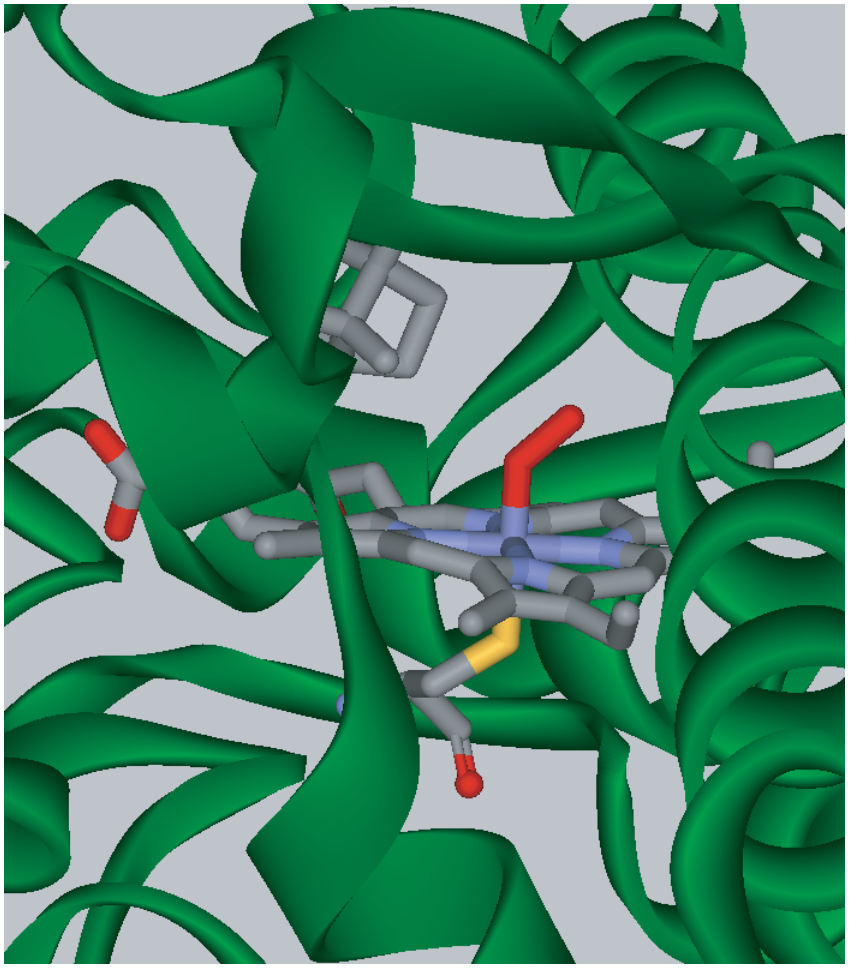
- Crucial role of NO



Cytochrome P450

The x-ray structure of cytochrome P450

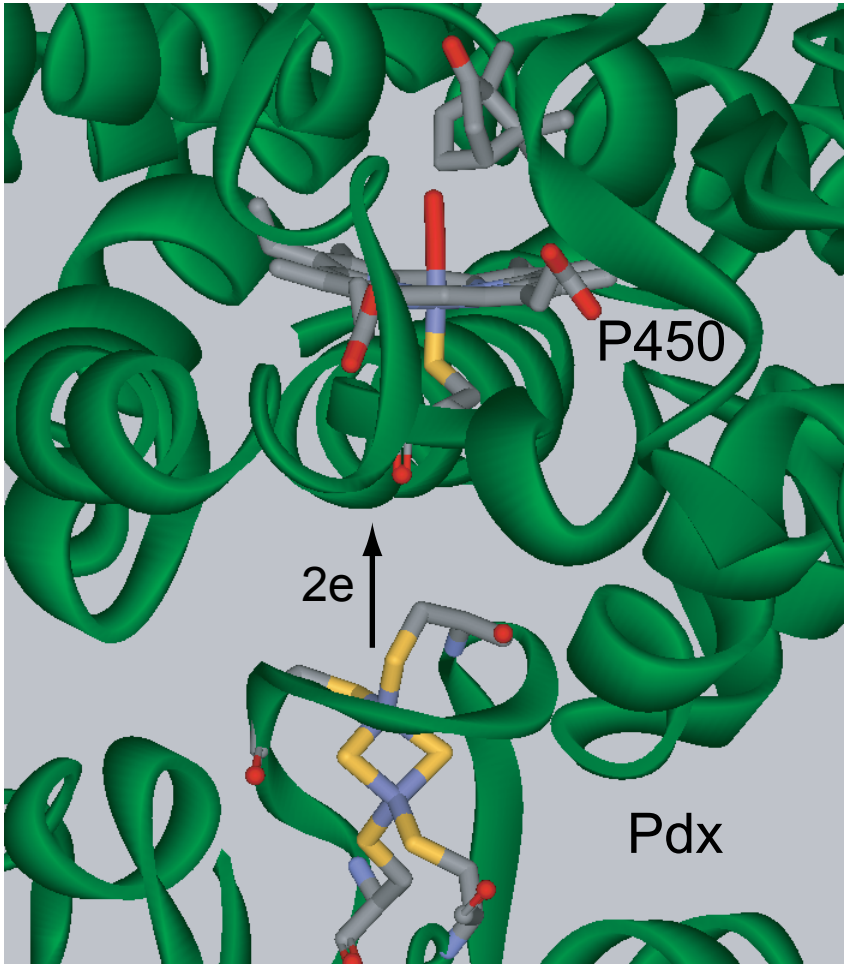
The major enzymes involved in drug metabolism and bioactivation, accounting for about 75% of the total number of different metabolic reactions



Cytochrome P450

The computational model of P450 and Pdx

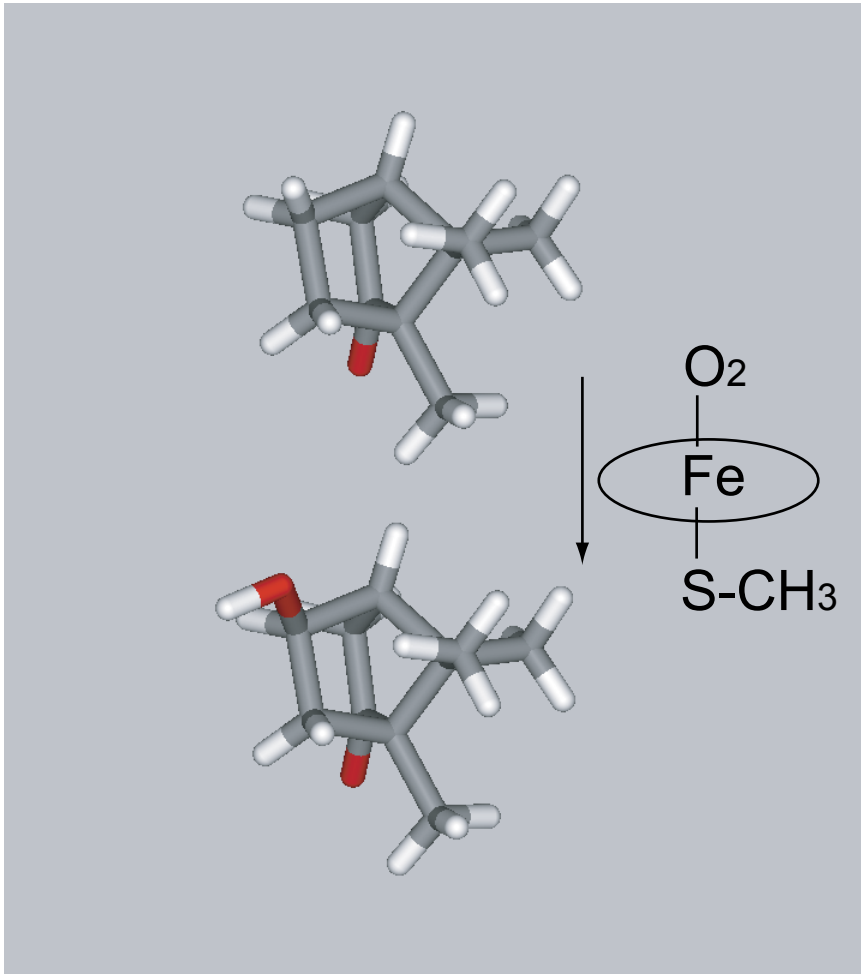
Catalytic activity of P450 requires two electrons, both electrons are tranfered to P450 from Putidaredoxin (Pdx), after protein binding



Cytochrome P450

Catalytic reaction of hydroxylation

The reactant and the product of the reaction, which is catalyzed by cytochrome P450 in a presence of molecular oxygen



Bacteriorhodopsin

The x-ray structure of bacteriorhodopsin (bR) with retinal

Interaction of bR with light triggers reactions leading to visual processes

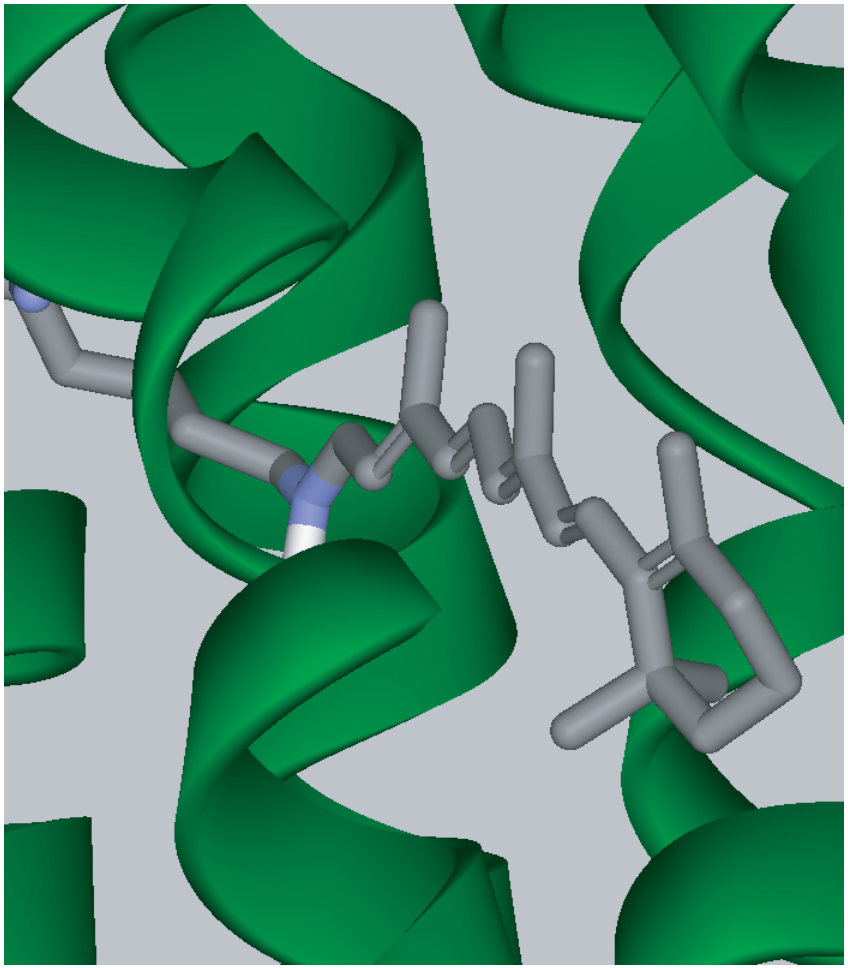
- Light absorption

- Photoisomerisation of the active site

- Hydrogen atom transfer

- GTP to sGMP transformation

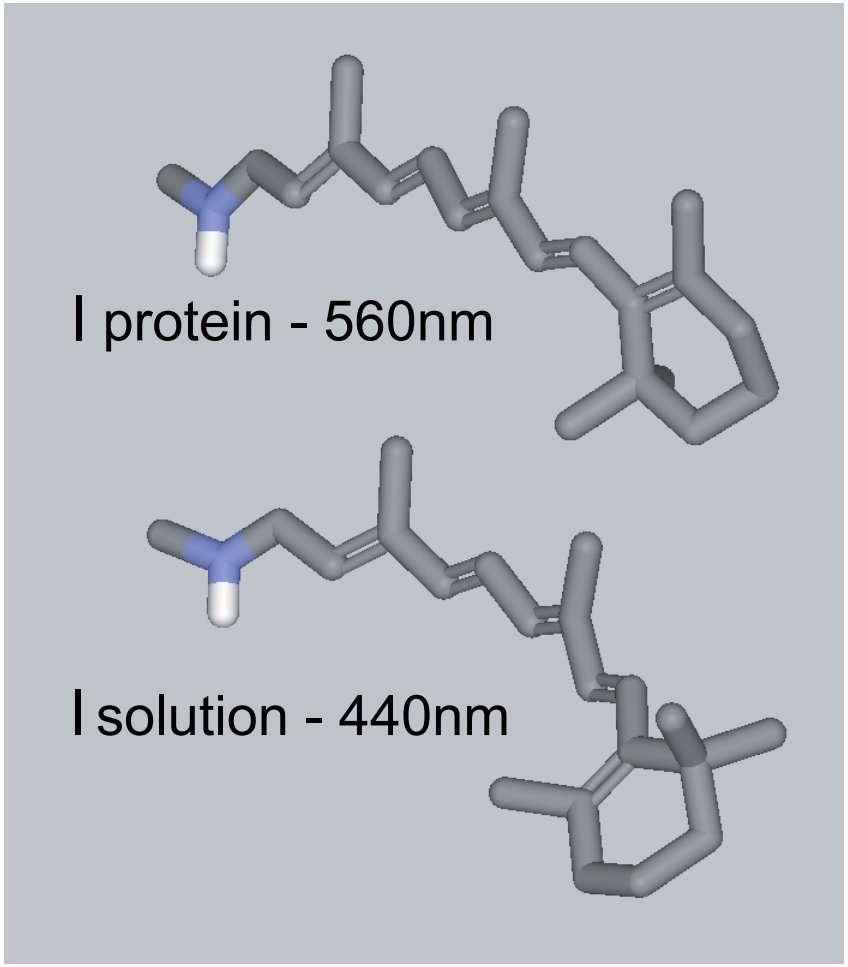
- Calcium cations



Bacteriorhodopsin

Two different conformations of retinal

External light induces *cis* to *trans* transformation

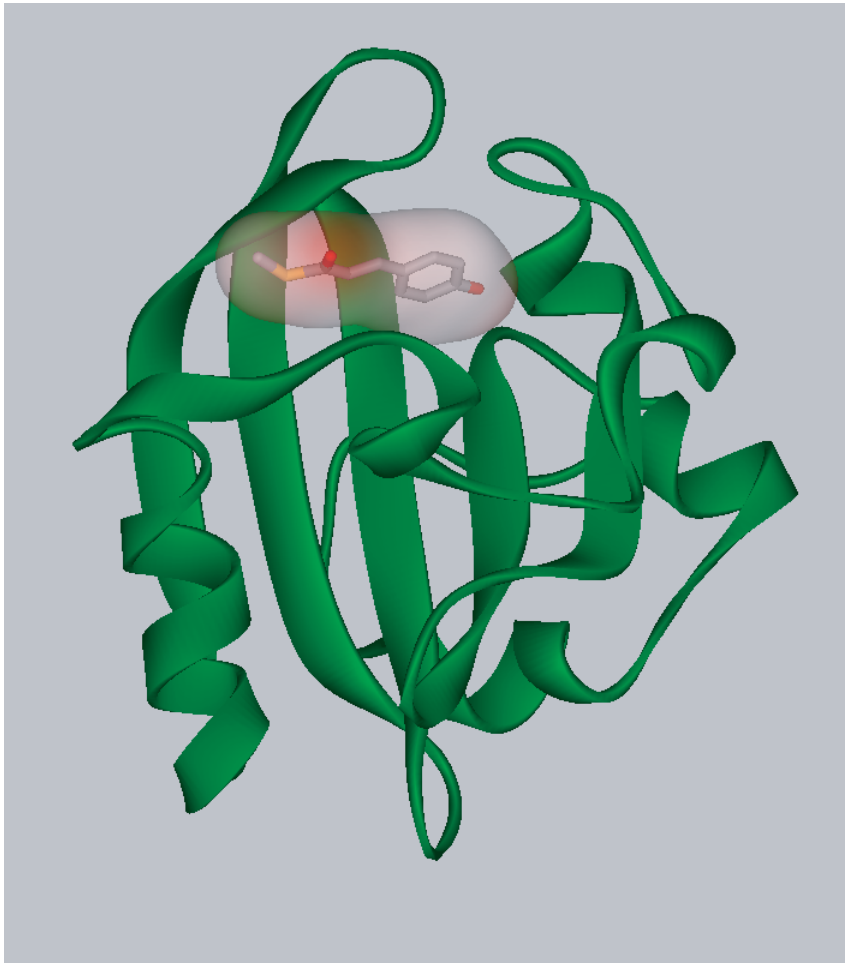


Photoactive yellow protein

The x-ray structure of photoactive yellow protein (PYP)

PYP is a simple model of rhodopsin proteins, which are responsible for signal transduction

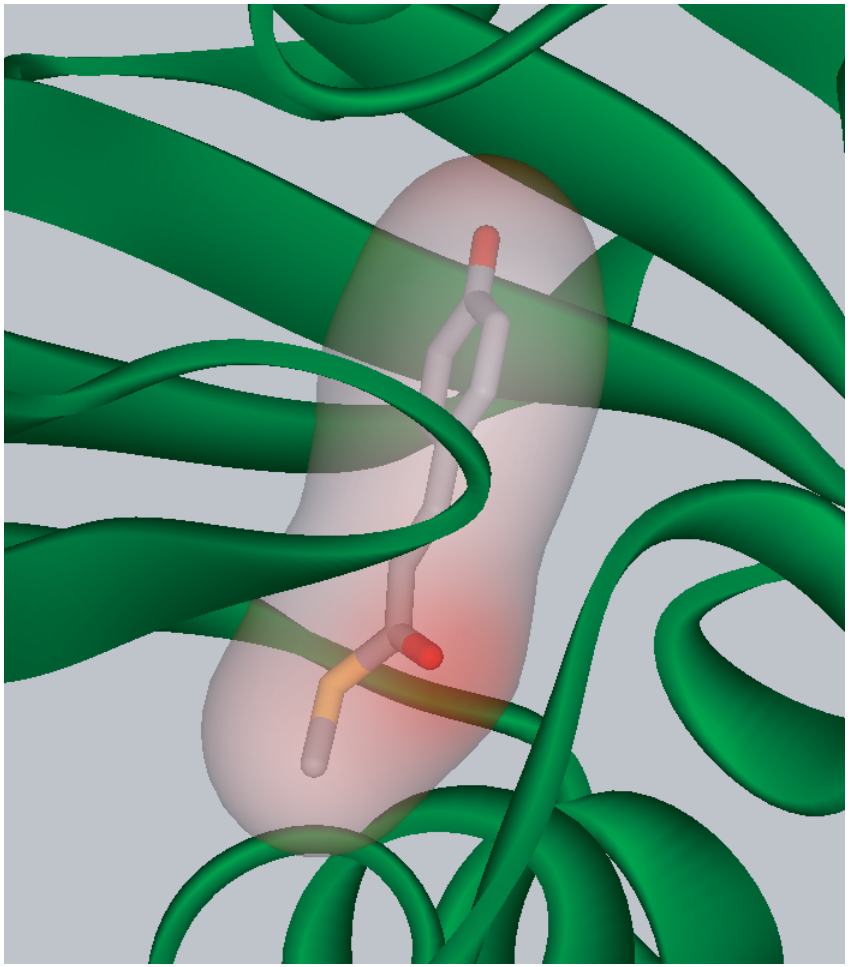
It been isolated from a bacterium, which exhibits a repulsive response to blue light



Photoactive yellow protein

The active site of the yellow protein

PYP is a genetic mutant of green fluorescent protein (GFP). Like green fluorescent protein, it is a useful tool in cell and molecular biology



DHFR enzyme

The x-ray structure of dihydrofolate reductase (DHFR) enzyme

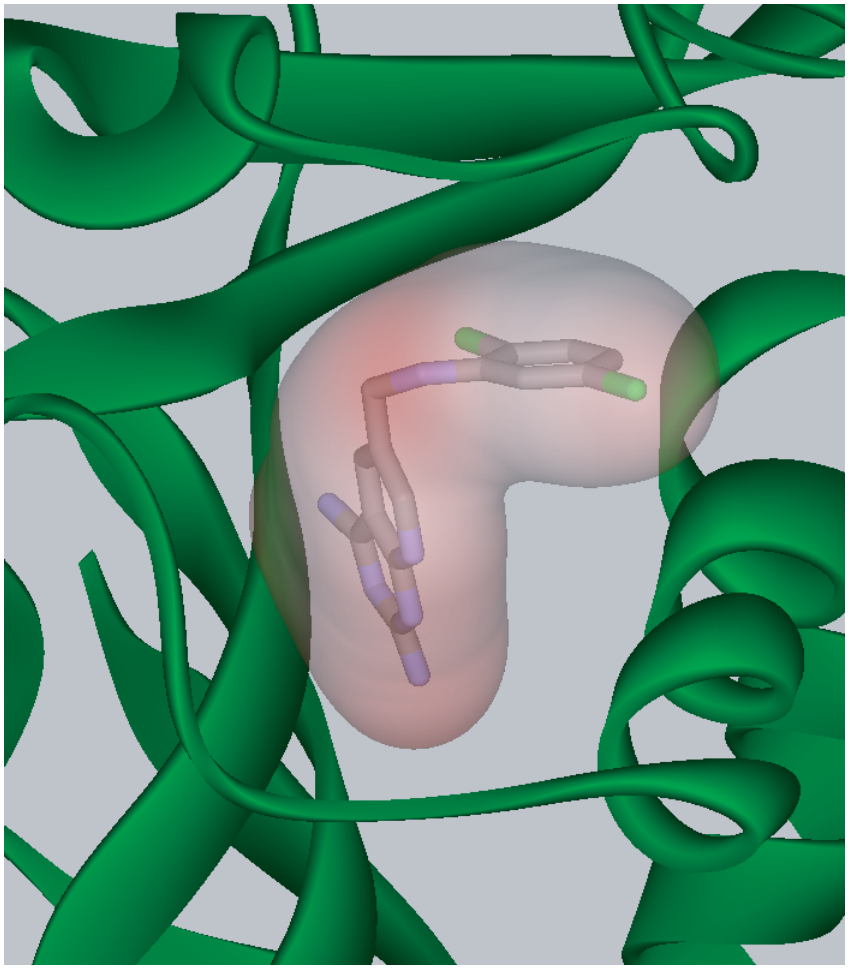
Antifolate is a substance (a drug) that blocks the activity of folic acid

Folic acid is necessary for the production of new cells. Therefore antifolates are used to treat cancer

An antifolate was the first clinically used anticancer drug

DHFR enzyme

The computational mode of the active site of a protein with the antifolate molecule

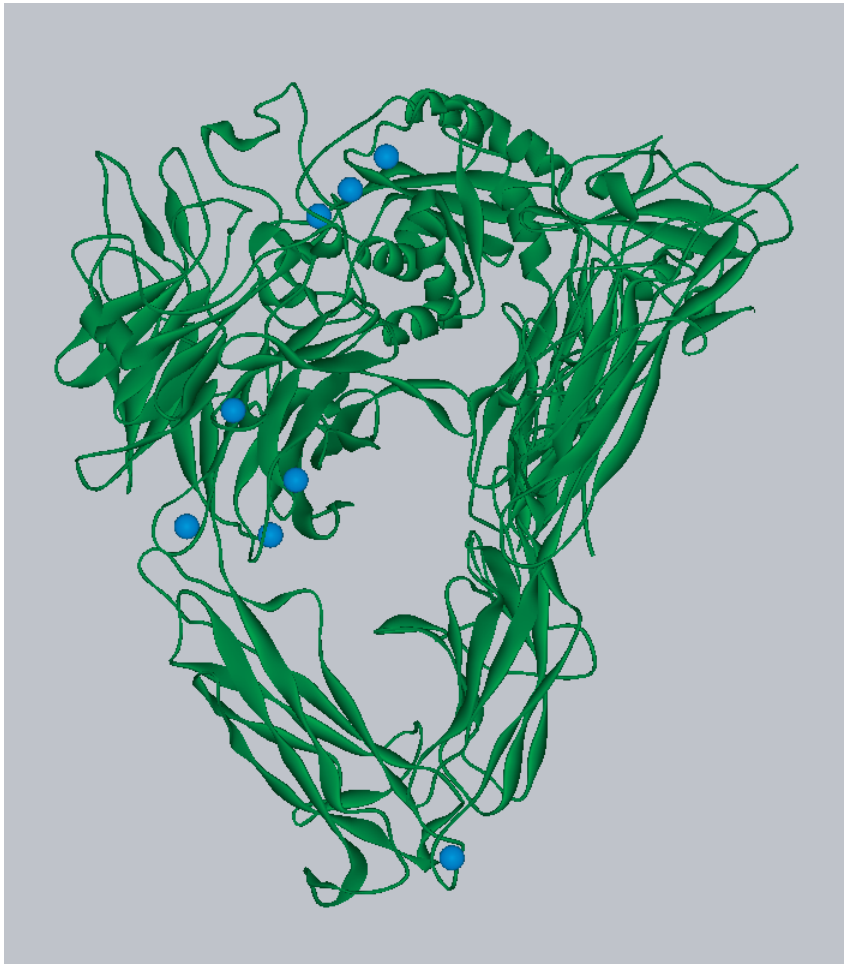


Integrin protein

The x-ray structure of the integrin protein

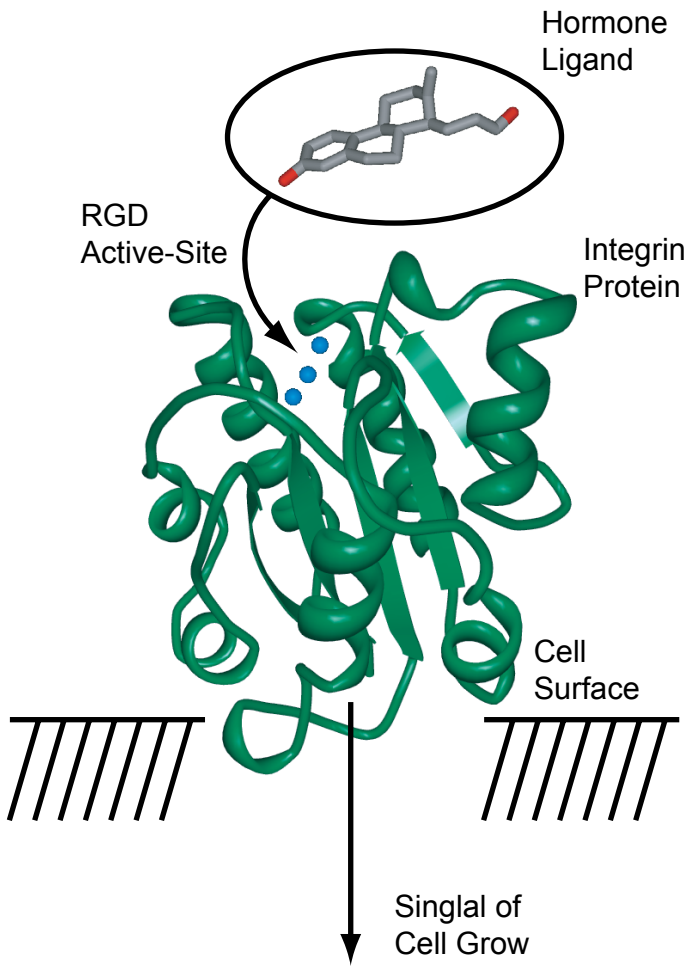
Integrins are cell membrane proteins responsible for cell growing, and uncontrolled activity of these proteins is responsible for cancer

Blue spheres indicate presence of Ca^{2+} cations



Integrin protein

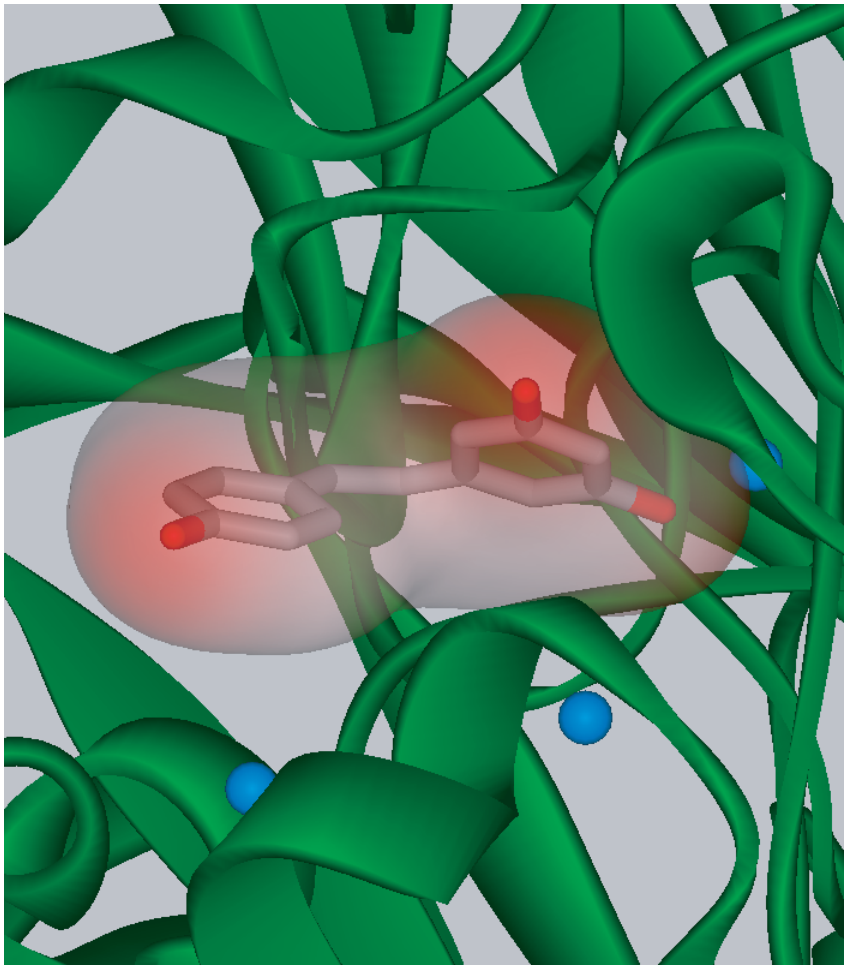
Experimental data showed that the ratio of Mg^{2+}/Ca^{2+} in cells is responsible for the cancer grow



Integrin protein

The computational model of the active site of the integrin protein with the inhibitor molecule

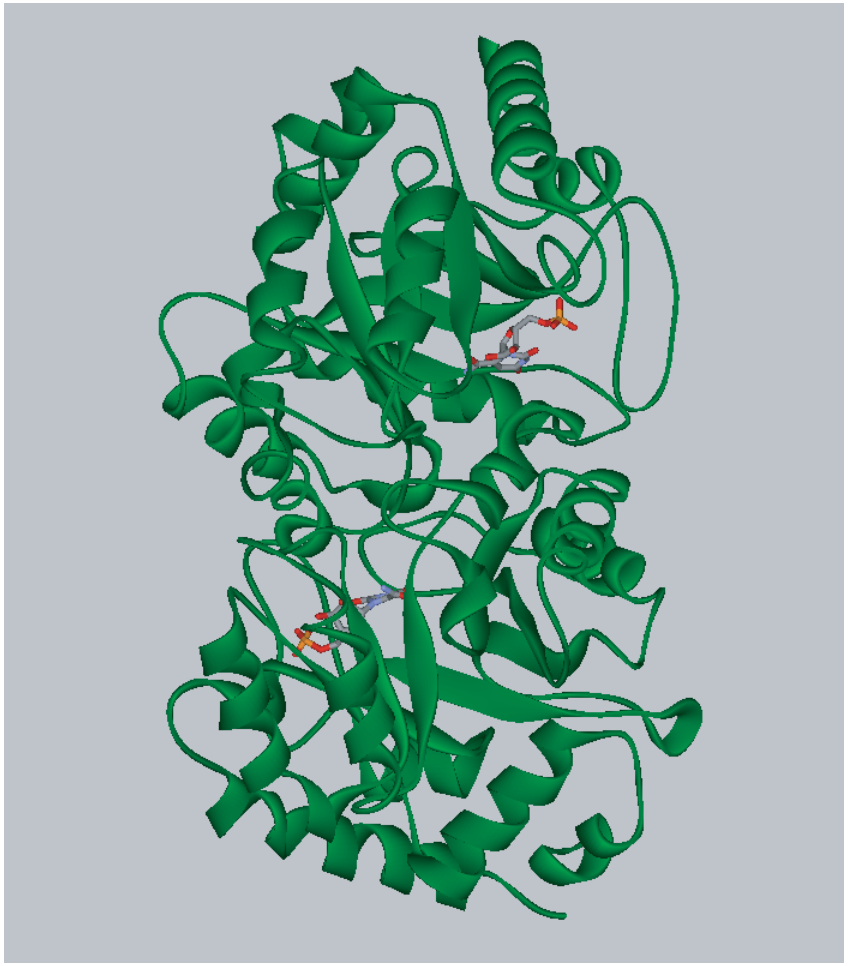
An enzyme inhibitor is a molecule that binds to enzymes and decreases their activity



OMP Decarboxylase

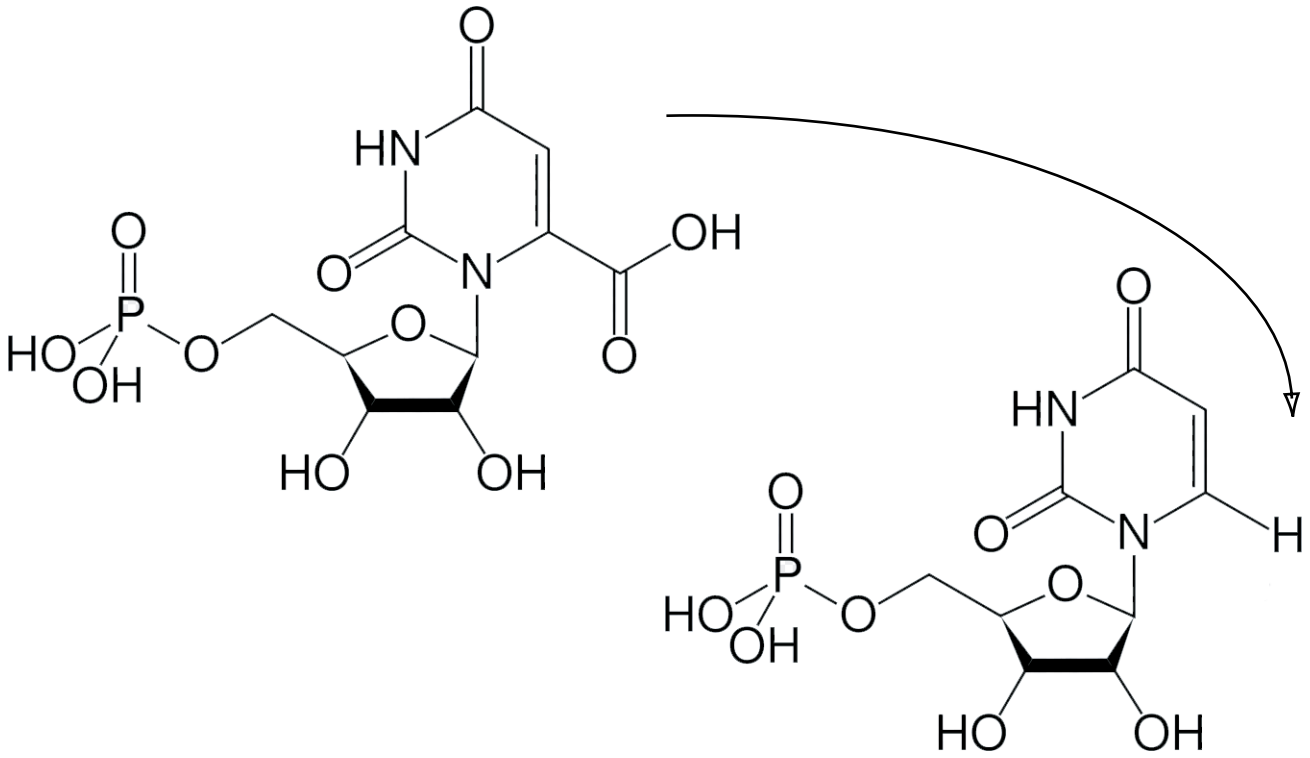
The x-ray structure of orotidine phosphate decarboxylase (OMP)

OMP is an enzyme responsible for synthesis of uridine phosphate (UMP), an essential precursor of RNA and DNA



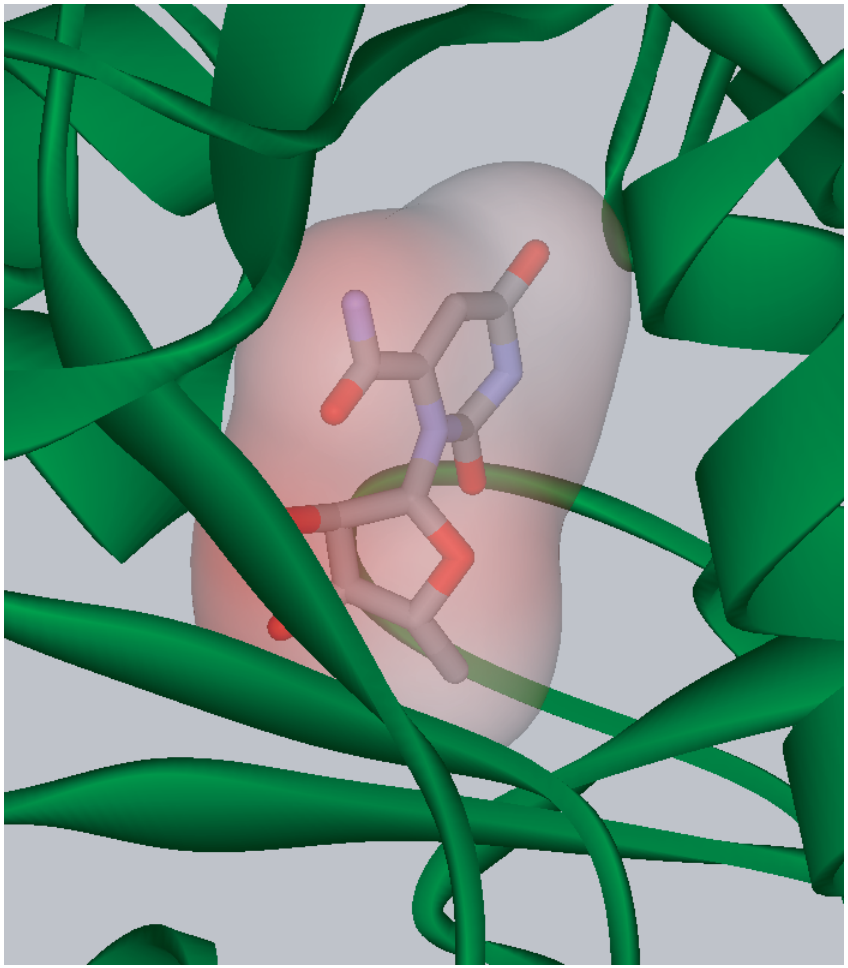
OMP Decarboxylase

In solution, the OMP to UMP reaction runs with a half-time of 78 million years. In the enzyme, the same reaction proceeds with a half-time of 18 msec



OMP Decarboxylase

The computational model of the active site of the OMP enzyme with the inhibitor molecule



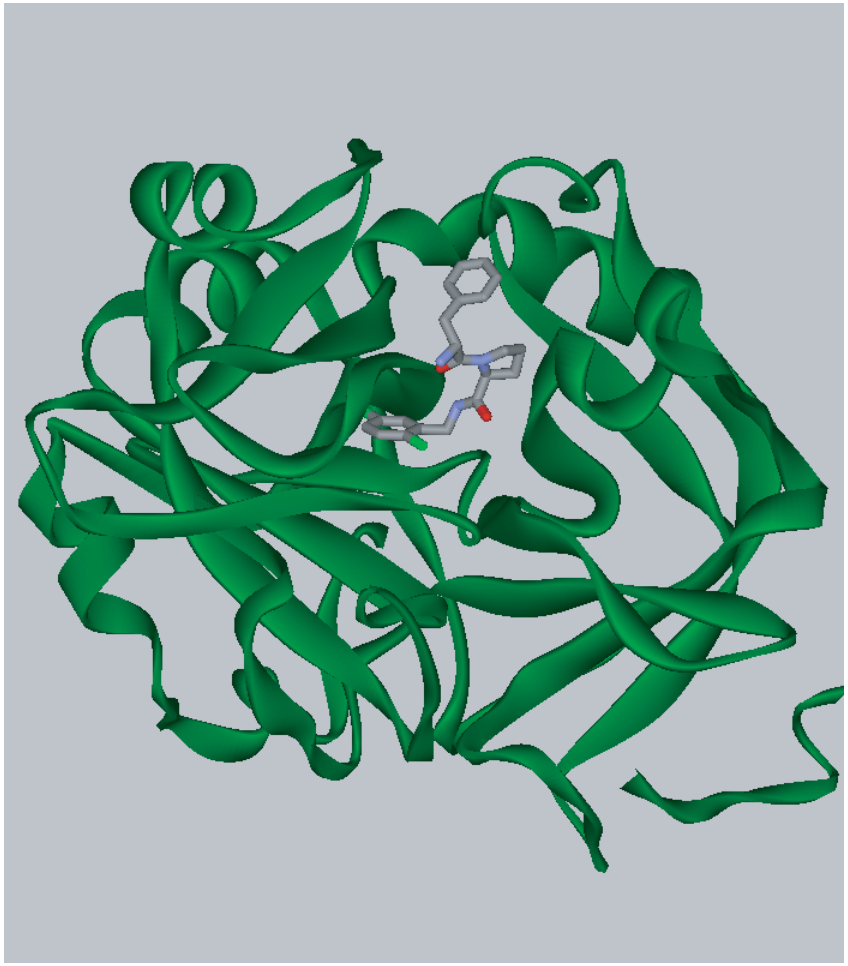
Thrombin

The x-ray structure of thrombin protein

Thrombin is a human protein, converting fibrinogen in fibrin, and uncontroled activity of thrombin leads to formation of blood clots

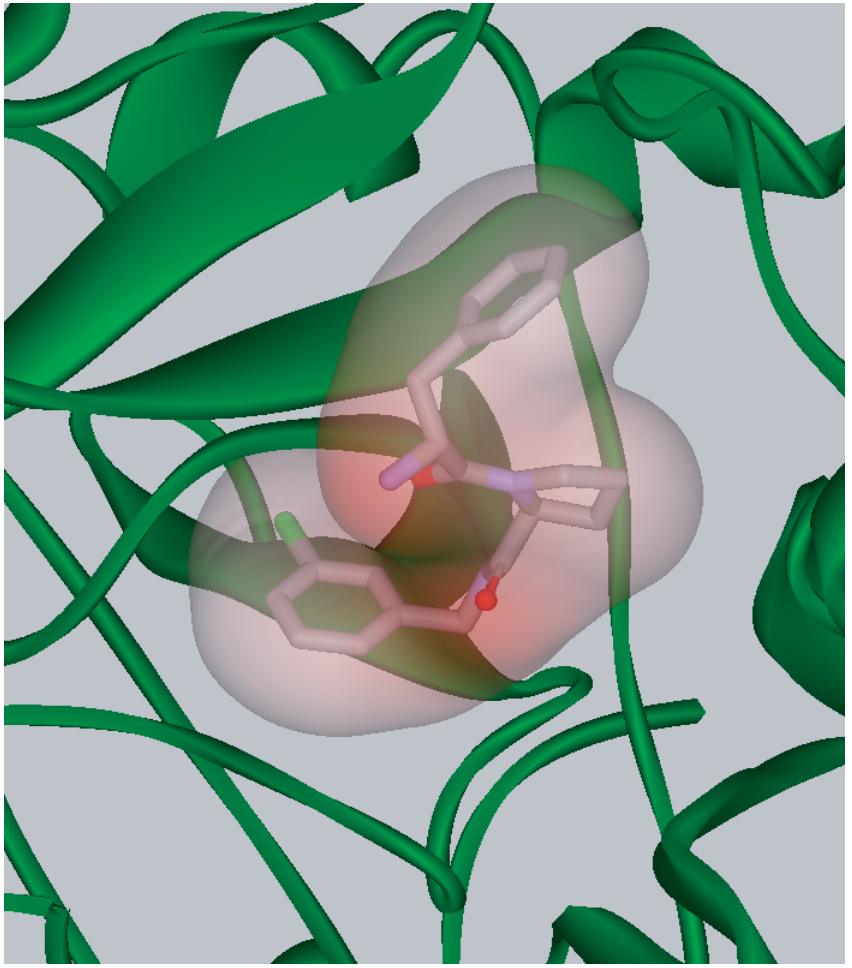
The activity of this enzyme can be regulated by enzyme inhibitors

An enzyme inhibitor is a molecule that binds to enzymes and decreases their activity



Thrombin

The computational model of the activity site of thrombin with the inhibitor



B_{12} protein

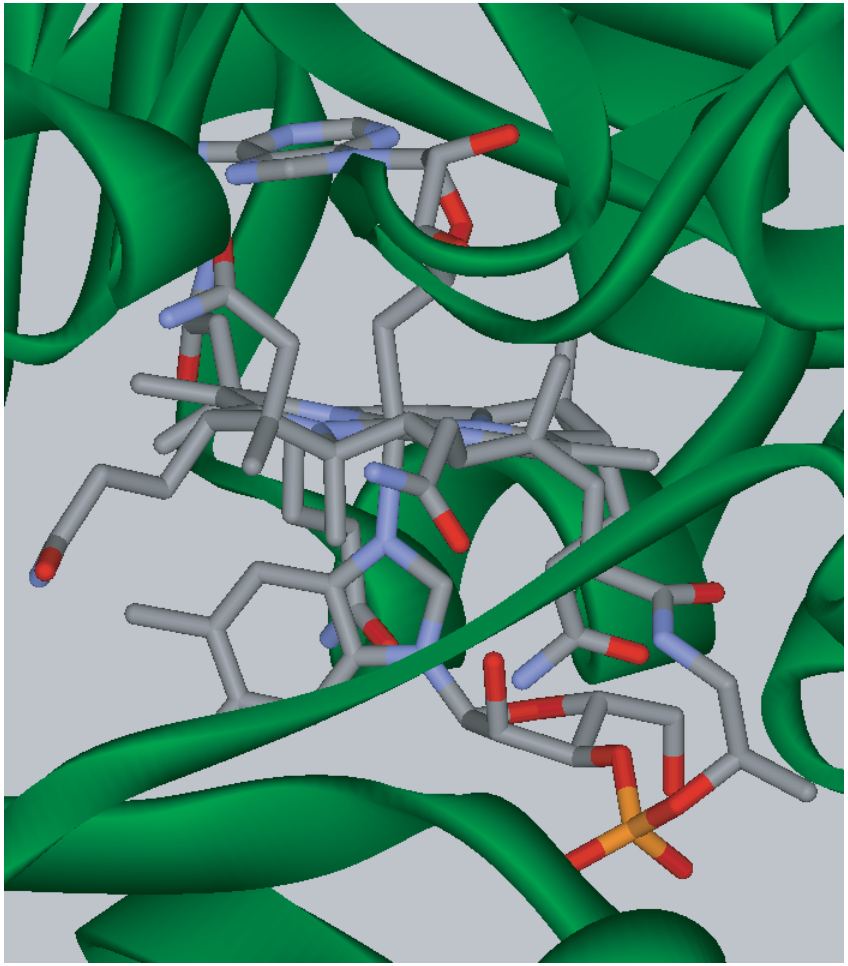
The x-ray structure of B_{12} protein

Vitamin B_{12} is an active site of B_{12} protein. Vitamin B_{12} is normally attached to a protein either for transport or storage

B_{12} is responsible for biosyntheses of nucleic acids, proteins and lipids

B_{12} is also responsible for maintaining a normal function of nervous cells

A central element of the B_{12} biochemical activity, is the Co metal atom

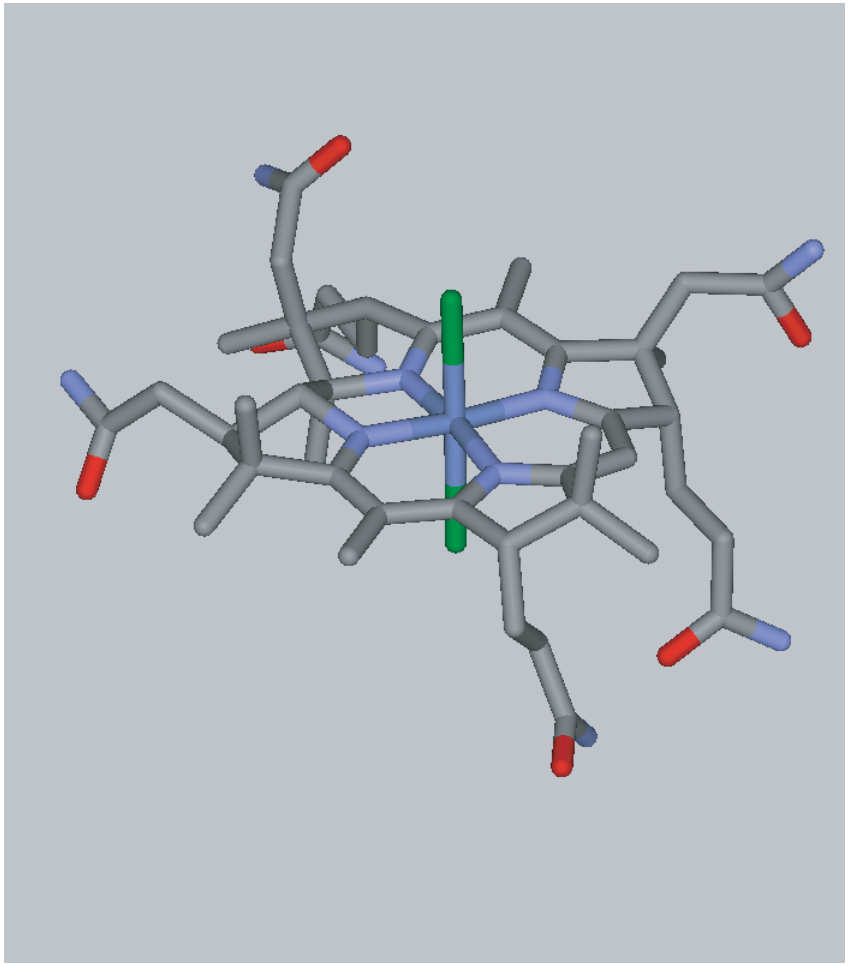


B_{12} protein

The computational model of vitamin B_{12}

In B_{12} analogous, the axial metal coordination of Co is filled out by different groups, referred as different cobalt corrinoids, and in recent years there are known about 30 of them

A central element of the B_{12} biochemical activity, is a Co-C covalent bond



B_{12} protein

The computational model of the active site of B_{12} in the protein

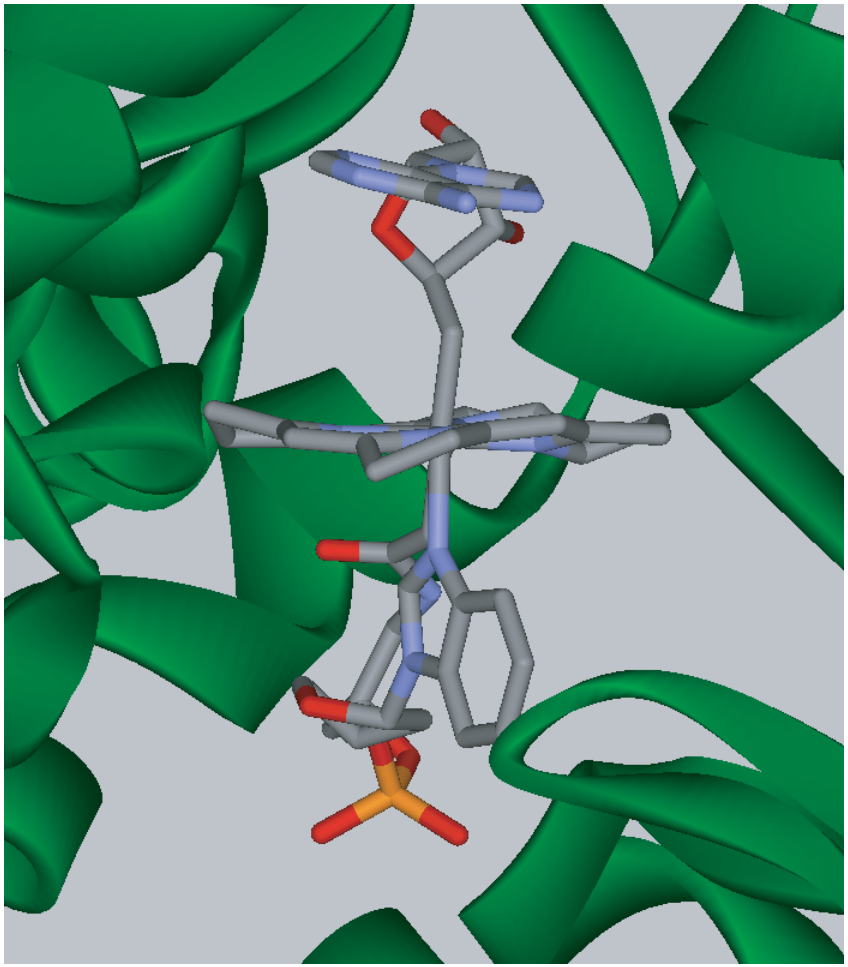
A central element of the B_{12} biochemical activity, is a Co-C covalent bond

Bond dissociation energy:

Solution - 30kcal/mol

Protein - 13kcal/mol

Trillion-fold rate acceleration

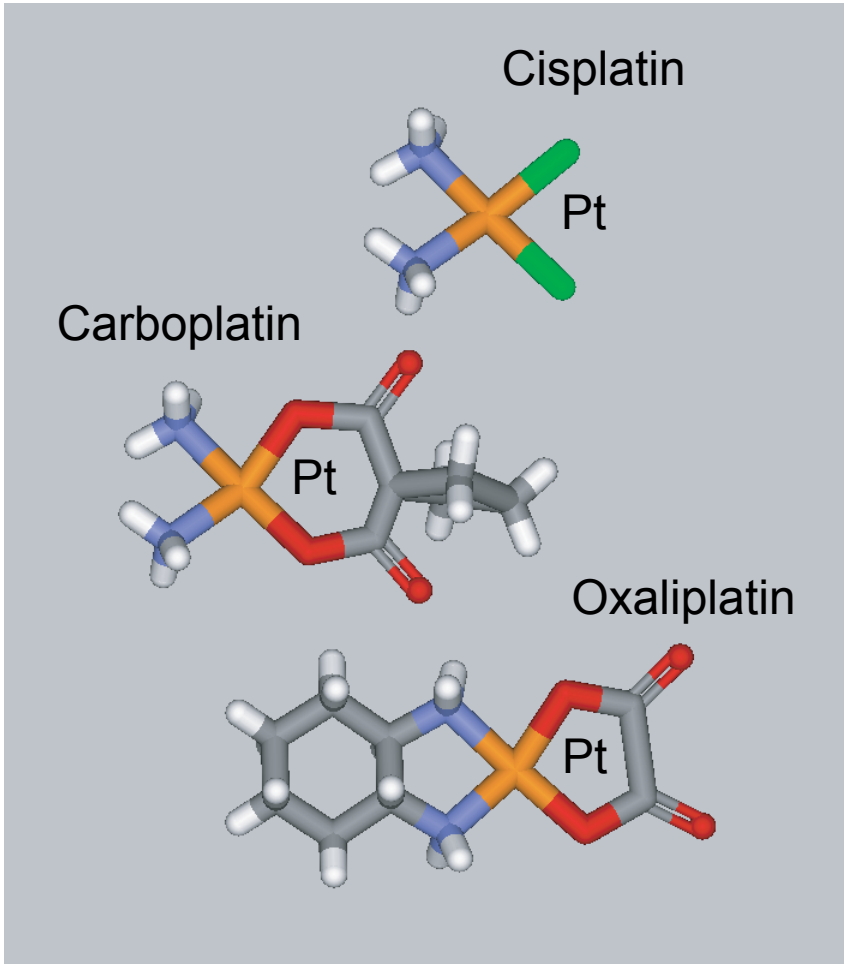


Cisplatin

Cisplatin has been discovered in 1970, and now is one of three most widely utilized antitumor drugs in the world

- Limited to narrow range of tumors

- Too toxic (anemia)

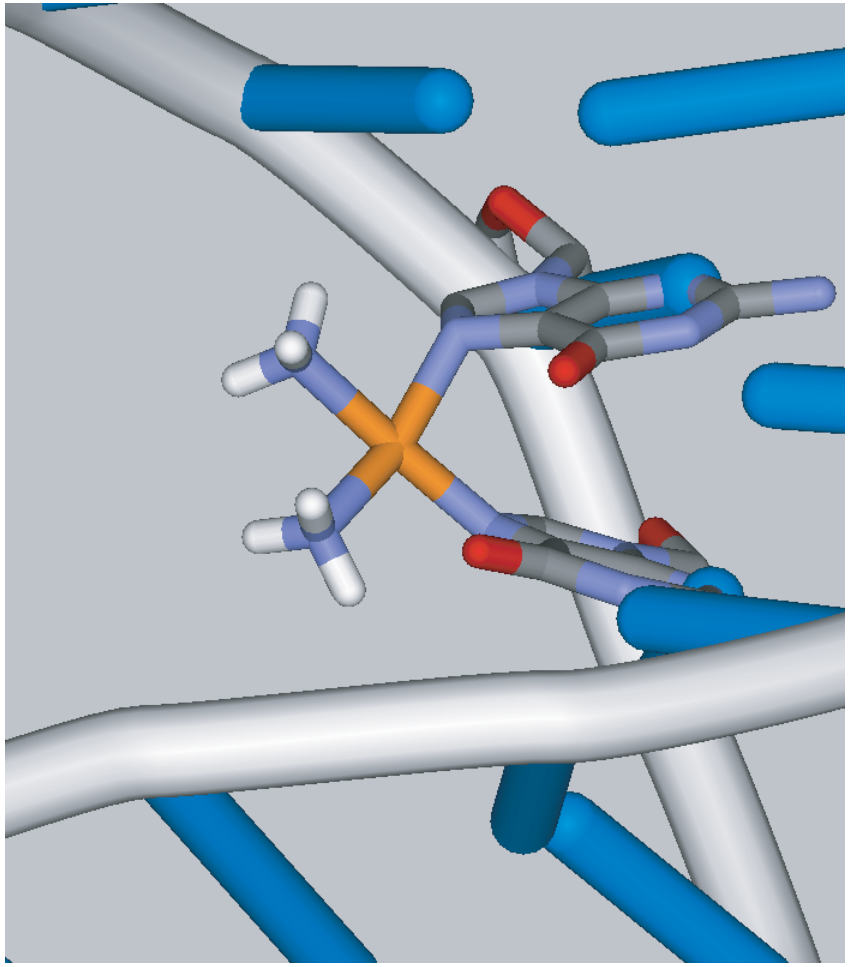


Cisplatin

The x-ray structure of cisplatin with DNA

Cisplatin binds to DNA (1,2-intrastrand GG adduct) and strongly bends the double strand DNA helix

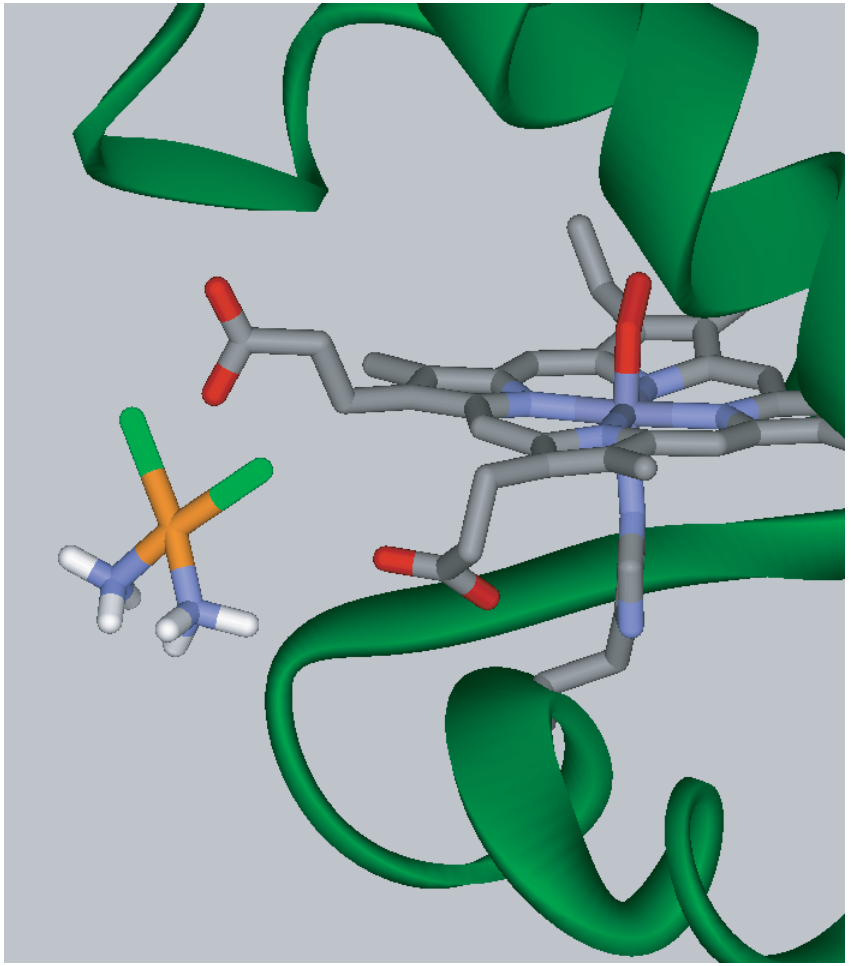
Cisplatin is forming a platinum complex inside of a cell which binds to DNA and cross-links DNA. When DNA is cross-linked in this manner, it causes the cells to undergo systematic cell death

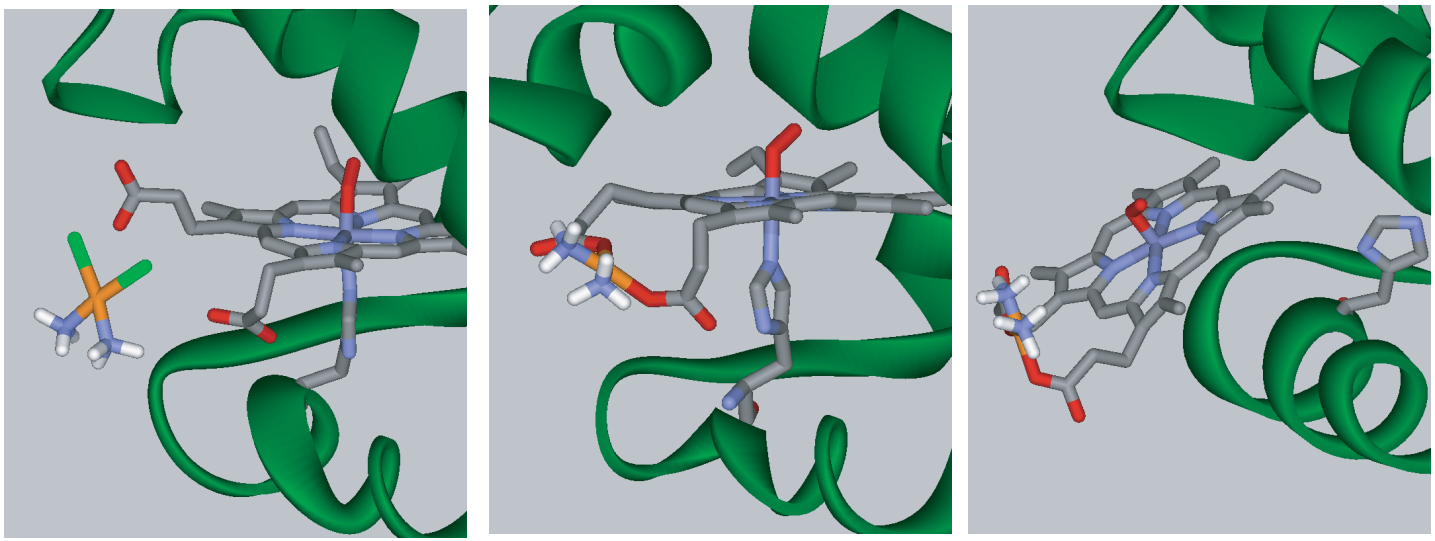


Cisplatin

The computational model of the interaction between cisplatin and heme in the protein

Cisplatin can bind the heme group of hemoglobin and remove the heme group from the active site of the enzyme





1. Docking

Binding Reaction

. Binding

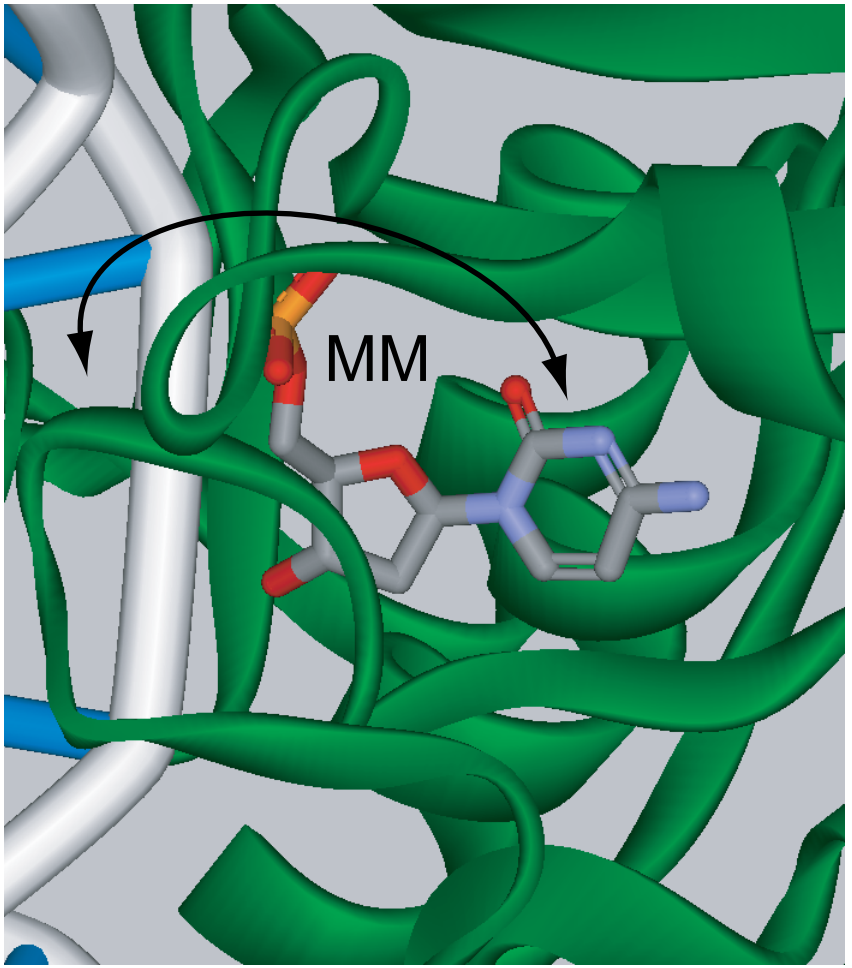
Releasing Reaction

. Releasing

DNA base flipping

The computational model of DNA with a based flipped out of DNA

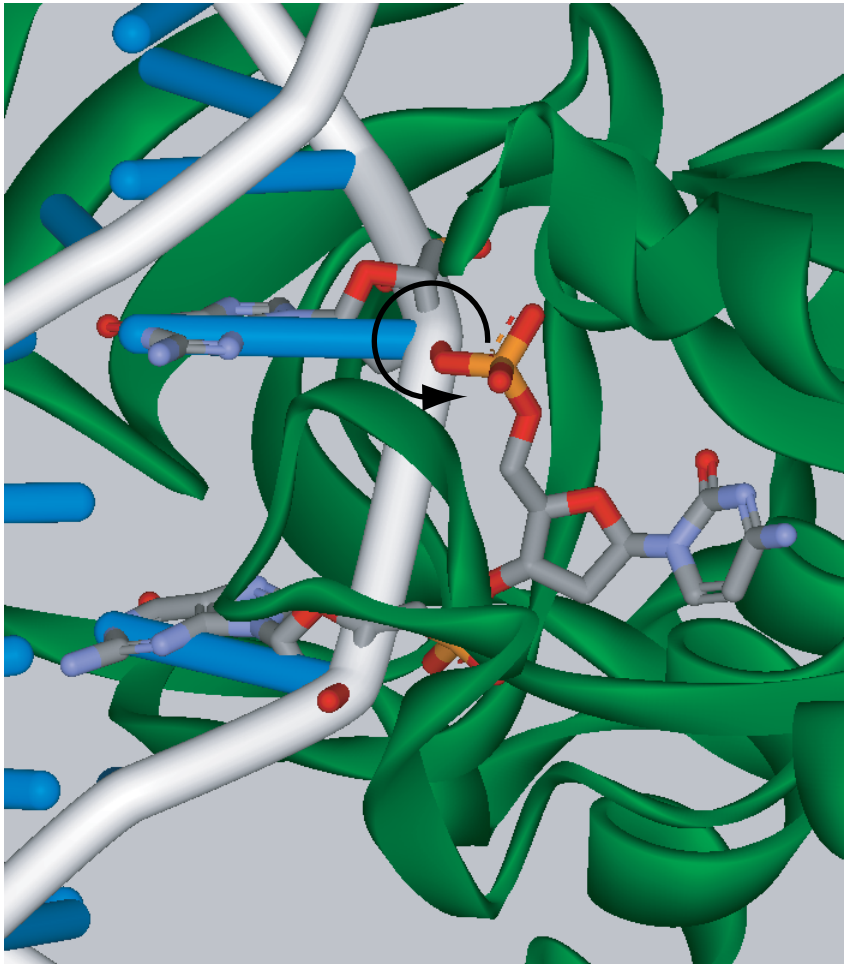
Base flipping is a simple structural change that may be the first step in replication and transcription of DNA and is essential for other processes in which enzymes interact with the base



DNA base flipping

The computational model of DNA with a based flipped out of DNA

After the base flipping, the base interacts further with the enzyme, until the enzyme-cofactor complex stabilizes the fully flipped state



DNA methylation

The x-ray structure of DNA and protein showing one base flipped out of DNA

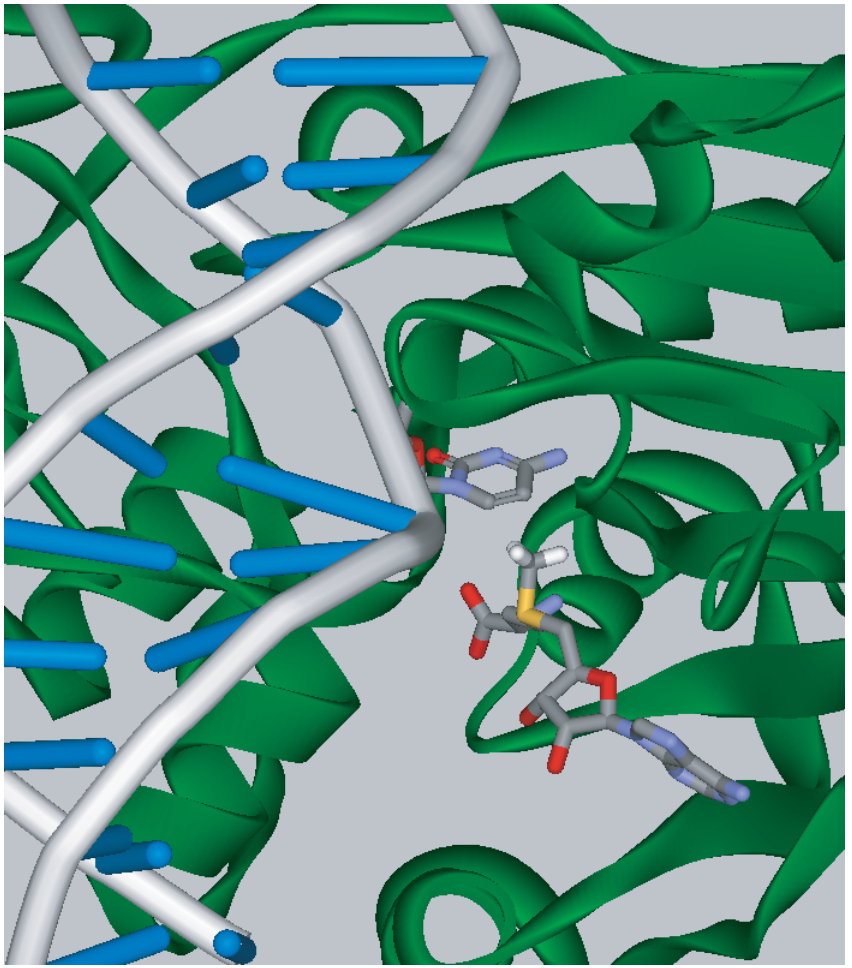
DNA methylation occurs in living species from bacteria to mammals

- DNA modification and repair

- Gene regulation

- Develpoment of cancer

- Novel antibiotic drugs



DNA methylation

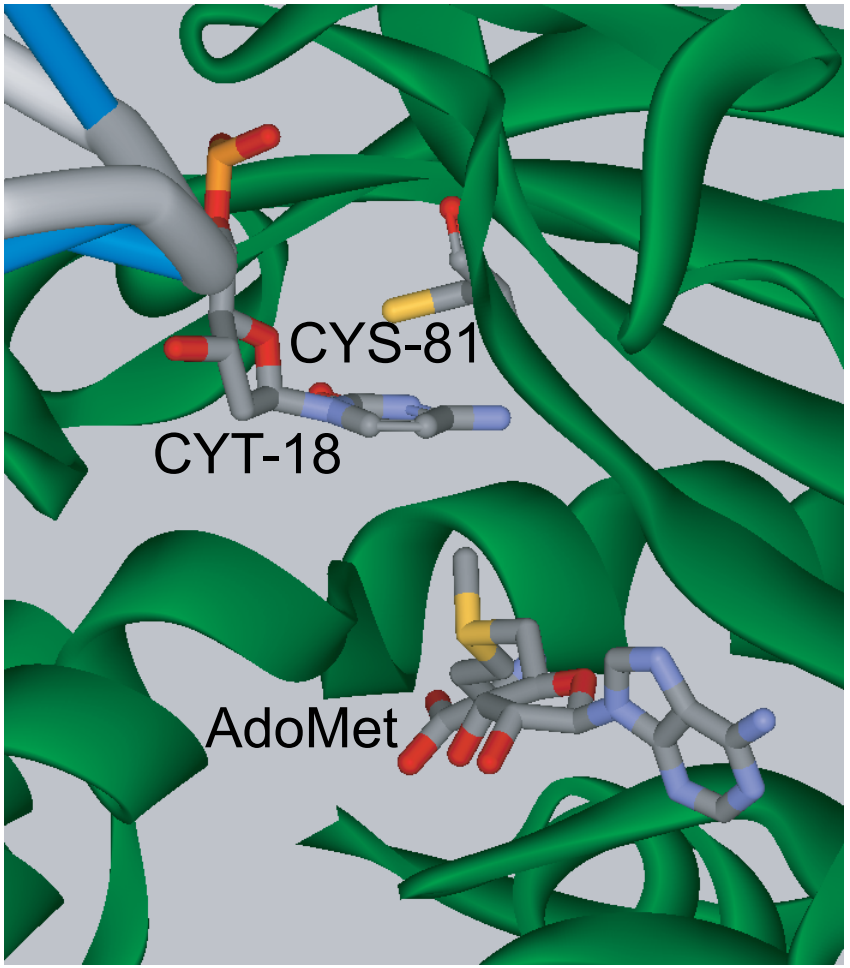
The computational model of the interaction between DNA base and the protein

The active site of DNA methylation

- AdoMet cofactor

- Cytosine CYT-18

- Cysteine CYS-81



DNA methylation

The proposed mechanism of the C5-methylation of CYT-18