National Student Team Contest (first stage)
Solution of task 10. Nanobattle for iron

1. These molecules are named siderophores. Iron is present in anaerobic conditions (i.e. in ground water) in ferrous state. In aerobic conditions it is rapidly oxidized to the ferric state which almost insoluble in neutral medium. So to take iron it is necessary to use complexants to transfer iron into soluble (and thus bioavailable) form.

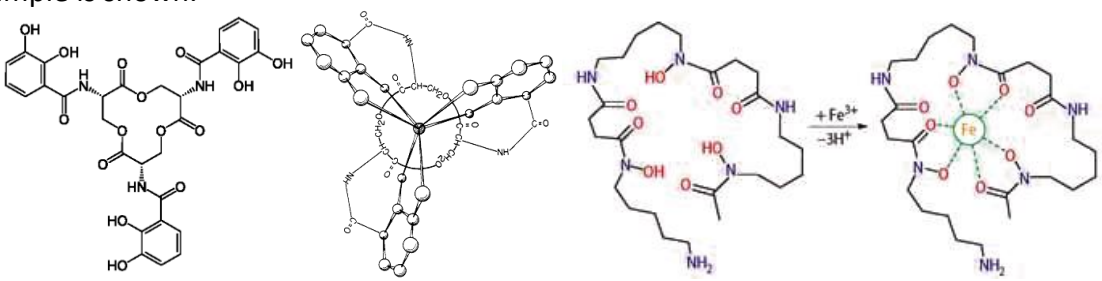
2. Iron is the most abundant transition metal so it is no wonder that during the evolution organisms adapted to utilize its main chemical properties (ability to form complexes and to catalyze redox reactions by one electron transfer) in great number of metalloproteins and enzymes which control over vital processes such as transport, respiration and DNA synthesis. In example, iron is used in hemoglobin, cytochromes, nitrogenases, reductases, catalases, alcohol dehydrogenases.

   Free iron is potentially toxic because of different possible interactions with wide range of biomolecules, peptides and enzymes (i.e. it has an affinity to sulfur containing groups) but mainly because of easy Fenton Reaction with peroxides which leads to free radicals production (which makes oxidative damage). So the same chemical properties of iron which are used by organisms make them to bound iron in order to keep it under control.

   The main iron storage molecule in human body is ferritin (was shown in the figure) which is the primary intracellular iron-storage protein. Hemosiderin is another iron storage complex which function is to deposit in inactive form the excess of iron, often during pathological organism's sate (hemolysis or iron utilization deceases). Transferrin is used in biological fluids to transfer iron to different tissues and it serves as fast and reversible iron carrier, thus it is also used as quick access storage. Transferrin is also associated with the innate immune system, it is found in the mucosa and suppress bacterial growth by withdrawing iron. Though hemoglobin and myoglobin also contain iron, they are not used directly for its storage.

3. Because **A** is one of the strongest iron complexing agents, the corresponding organisms must inhabit a medium with very strong iron deficit and must be in permanent competition for iron. Animals don't compete for iron, so **A** evolved during the competition of bacterial siderophores with each other and/or with animals' ones, for example in intestines or in blood of animals. **A** is enterobactin which is found in bacteria such as *Escherichia coli* and *Salmonella typhimurium*.

4. Each fragment of **A** is a bidentate catechol-based ligand which after deprotonation "catch" iron ion like claws into increased stability five-membered ring. Altogether the ligands complete the coordination sphere of iron. Other siderophores behave similarly, an example is shown.



Aminoacid polyester ring moiety is used to hold together three bidentate ligands so that metal complex formation entropy is greatly increased (by reducing three times the number of ligand molecules in the reaction) which greatly stabilize overall complex (so called chelate effect).

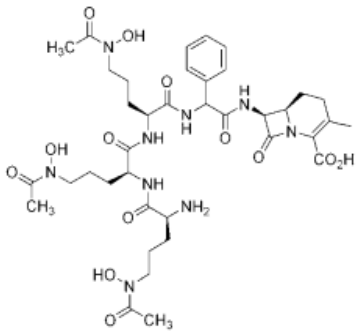
To obtain free iron it is necessary to reduce the complex stability, which could be achieved by several ways:

a. by reducing the chelate effect, i.e. by cutting a link between ligands. As we can see, the building blocks of siderophores are connected by ester and/or peptide bonds which are easily cut by standard cell toolkit (esterases and peptidases).
b. by reduction to ferrous state and/or by ligand oxidation.
c. by pH change (by protonation).

5. Bacterial siderophores in iron free form could be used for binding and excretion of metal excess from human organism which has no special mechanisms for iron removal, i.e. in a case of poisoning by iron (and even by some other metals, i.e. Al), for treatment of transfusion hemosiderosis (frequent blood transfusions lead to iron overload) or hereditary hemochromatosis (a hereditary disease when excessive intestinal absorption leads to increased iron content in body).

   Human originated complexes with iron could be used as a source of bioavailable iron, for example, to increase hemoglobin level (i.e. in anemia). Strong bacterial siderophores in iron free form could also act as antibacterial agents (by suppressing iron uptake and then growth of bacteria which produce weaker siderophores), and as was mentioned above so does human transferring. Since the bacteria due to strong evolutionary selection have a great variety of siderophores, there are different corresponding bacterial transport systems which could be used for selective antibacterial therapy, when bacterial sidefophores serve as drugs carriers (see below).

6. The compound has a *β*-lactam cephalosporin like antibiotic fragment attached to a siderophore which serves as a pass into a bacterial cell, where after cleavage the antibiotic inhibits cell wall biosynthesis. Thus the antibiotic concentration in the bacterial cell is increased many times, increasing its effectiveness.



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