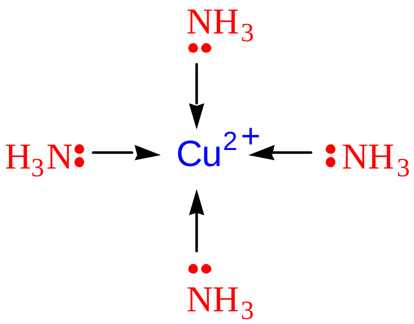
What is chelation, and how can it help copper to be excreted?

How other substances bind to copper

An atom of the metal copper (Cu) can gain two positive charges by losing two electrons to become Cu^{2+}, a copper ion (an atom that possesses electrical charge is called an ion) This turns the metal copper into a copper salt (an assembly of the positively charged Cu^{2+} ions and negatively charged ions). Many substances bind well to Cu^{2+}, and nearly all of them do so because they have negative charges that are attracted to the positively charged Cu^{2+} ion. Here we consider binding when the copper salt is in solution in water, as it will largely be in the human body.

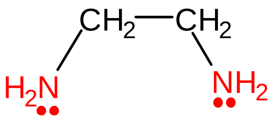
An example of a substance that can bind copper ions in solution is ammonia, NH_3. The nitrogen atom of this molecule has, in addition to the electrons that bind it to the three hydrogen atoms, a spare pair of electrons known as a 'lone pair'. These are sometimes represented by two dots on the N, thus: $:NH_3$. These are available to bind the ammonia to the copper, and this can be shown as $Cu^{2+} \leftarrow :NH_3$. The negatively charged electron pair of the nitrogen is pulled towards the positive charge of the copper ion. (Here the copper ion is shown in blue, the colour it possesses in solution, and the groups that bind it are shown in red.) Further molecules of ammonia can bind, to give finally:



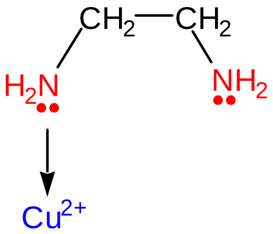
The first ammonia molecule binds tightly, and the second, third and fourth progressively less so. This is because the positive charge on the copper becomes less, as it is partly shared with the electrons of the lone pairs of the previously bound ammonia molecules.

How chelation enhances binding

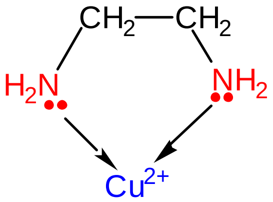
There is a natural tendency for things to fly apart. If we open a gas cylinder the gas spreads throughout the room. Hence when ammonia binds to copper ions as above, it only does so because the attrraction of the ammonia for the Cu^{2+} is enough to overcome the tendency of the ammonia molecules to fly apart. But suppose we replace two ammonia molecules with a single molecule that has two of the groups like ammonia, then we can get, for example, a molecule of



When it binds Cu^{2+} the first product will be



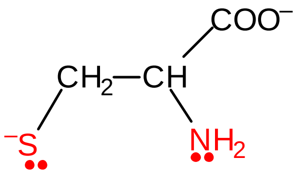
just as with ammonia. But the second $-NH_2$ group also has affinity for the copper. It cannot have the tendency to fly away, since it is linked to the first. Hence it will easily form



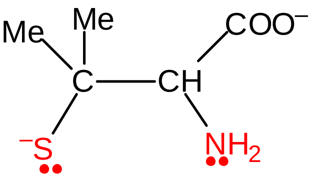
This behaviour leads to very strong binding. Since this double binding resembles the way a claw can act, the term 'chelation', based on the Greek word for a claw, has been used by chemists to describe it. Hence a chelating agent is a substance that binds twice over, with different parts of its molecule, and hence very tightly.

Chelation and Wilson's disease

Dr John Walshe found an unusual substance in the urine of patients who were being treated with penicillin, which led him to an impressive series of conclusions. Penicillamine, a breakdown product of penicillin, is an amino acid. Amino acids are the building blocks of proteins; the molecules of proteins are long chains made of 20 different amino acids, just as a paragrpah is a chain made of the 26 different letters of the alphabet. Penicillamine is similar in its structure to cysteine (one of the 20 common amino acids that make up our proteins).

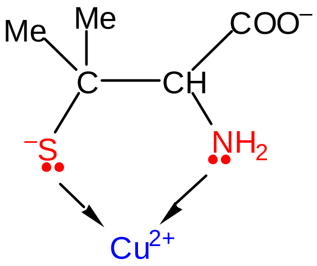


cysteine



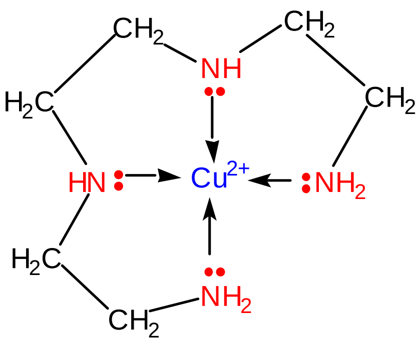
penicillamine

It just has two methyl groups (–CH_3, shown here simply as –Me) added in place of two hdyrogen atoms. Cysteine does not come out in the urine partly because it is used up in many reactions in our bodies. He also realized that this structure means that penicillamine, like cysteine, binds copper tightly by chelation:



He then realized that the penicillamine, able to get through the kidneys to the urine, might be able to do this even when it had copper bound to it. It proved to do so, and hence to have its wonderful effect in helping patients with Wilson's disease to excrete copper.

It is similar chelation that allows trientine to have the same effect. Here it is not just one claw (two groups) that bind the copper, but four groups, as follows:



Again the wrapping up of the copper ion, and spreading its charge over a larger molecule, allows it to pass through the barriers in the kidney and be excreted.

Chelation thus makes binding especially tight, and so is the basis for the methods used to treat Wilson's disease.