# Bismuth Antiulcer Drugs…

Bismuth compounds have been used in medicine for over 200 years to treat a wide variety of conditions, including **gastrointestinal disorders** and **syphilis**. Current interest centres on their antiulcer activity, in particular antimicrobial activity against Helicobacter pylori, a bacterium which can prevent ulcers from healing…

Bi: atomic number 83,
heaviest stable element in the periodic table,
occurs as a single isotope in nature: $^{209}Bi$
$[Xe]\ 4f^{14}5d^{10}6s^{2}6p^{3}$


Oxidation state of interest in medicine: **$Bi^{III}$**. $Bi^{V}$ is known but tends to be a strong oxidant. $Bi^{III}$, with an ionic radius of about 1.03 Å, **is similar in size to $Ca^{II}$**, and adopts variable coordination numbers from ***3* – 10** with a wide range of geometries. The $6s^2$ lone pair of electrons sometimes exhibits a stereochemical effect, the "**inert pair effect**".

$Bi^{III}$ is a **highly acidic** metal ion. The first deprotonation of the aqua ion has a $pK_a$ of 1.5:

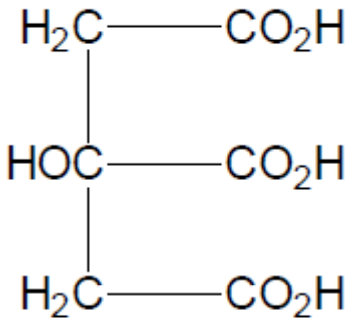
$$[Bi(H_2O)_9]^{3+} \rightleftharpoons [Bi(H_2O)_8(OH)]^{2+} + H^+ \qquad \mathbf{pK_a\ 1.5}$$

Further deprotonation to give coordinated **hydroxide** and oxide is facile, and oxygen bridged clusters such as $[Bi_6O_5(OH)_3]^{5+}$ and $[Bi_6O_4(OH)_4)]^{6+}$ readily form in aqueous solution.

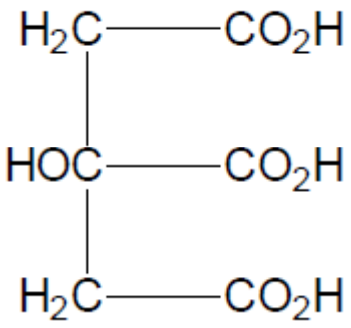
Most widely used Bi compounds for treating **gastrointestinal disorders** are: bismuth subsalicylate (BSS, e.g. Pepto-Bismol), colloidal bismuth **sub**-citrate (CBS, e.g. De-Nol), and ranitidine bismuth citrate (RBC, Pylorid). The chemical nature of the bismuth compounds in these preparations not fully understood.

(**Sub**= containing $OH^-$, and/or $O^{2-}$)

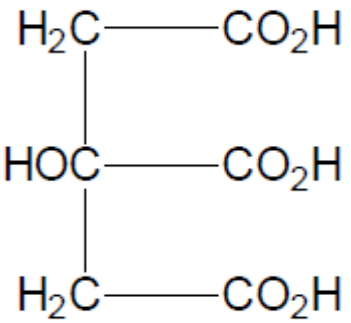
$Bi^{III}$ citrate [Bi(Hcit)] is insoluble but can be solubilised with alkali (including ammonia and amines such as ranitidine – itself an antiulcer drug).

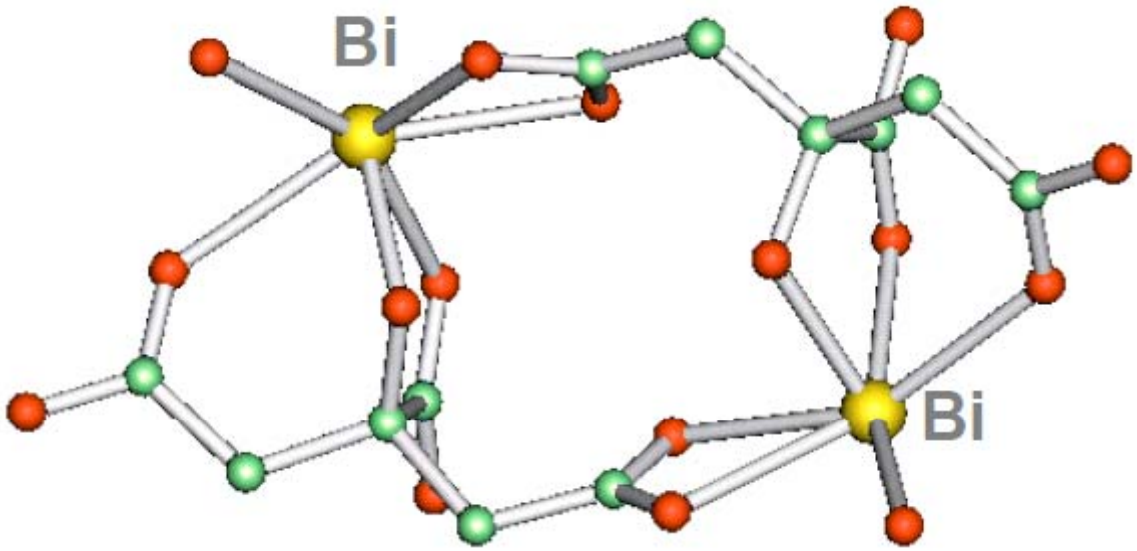


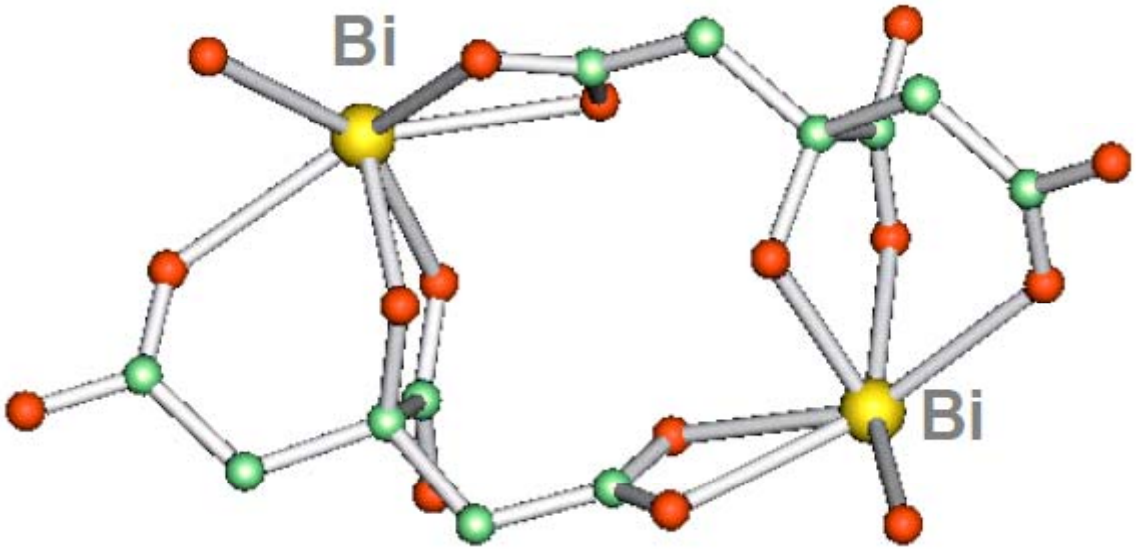
Citric acid, with pKa values of 2.9, 4.3, and 5.6, exists as a **trianion** at pH 7. In addition, metal ions such as $Al^{3+}$, $Fe^{3+}$, $Ga^{3+}$ as well as $Bi^{3+}$ can displace the proton from the central hydroxyl group...



$Bi^{III}$ citrate complexes have complicated structures, which are often based on the **dimeric unit $[(cit)BiBi(cit)]^{2-}$**, where cit is **tetra-deprotonated citric acid**, containing **tridentate citrate**, with **one carboxylate bridging to the neighbouring** $Bi^{III}$.



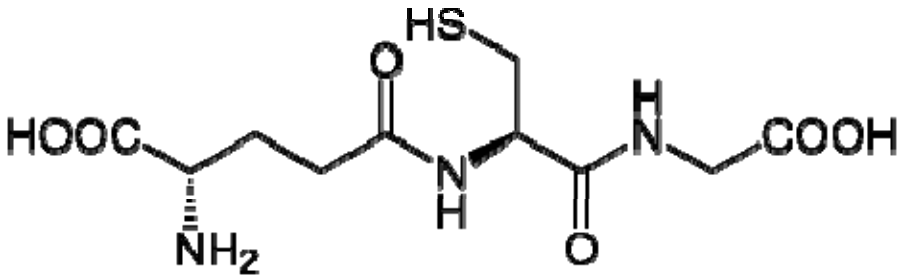






The **$Bi^{III}$-O(alkoxide) bond is very short (2.2 Å) and strong**, being part of a **5-membered chelate ring**. $Bi^{III}$ citrate dimers can associate to give chain and sheet structures via further bridging and H-bonding. Such polymers may be deposited on the surface of ulcers. At pH values < 3.5 in dilute HCl, BiOCl precipitates

$Bi^{III}$ citrates react readily with thiols such as the tripeptide **glutathione (GSH),** with formation of $[Bi(SG)_3]$, in which $Bi^{III}$ is bound to the thiolate S. Even though $[Bi(SG)_3]$ is a highly stable complex the **thiolate ligands are kinetically labile and exchange with free thiol on a millisecond time-scale.**

Therefore $Bi^{III}$ may be a highly mobile ion inside biological cells.




**Unusual peptide bond between the amine group of Cys and the -COOH group of the Glu side chain**

GSH: tripeptide **Glu, Cys, Gly**

The bacterium *Helicobacter pylori* lives under highly acidic conditions in the stomach and uses the **Ni enzyme urease** to make $NH_3$ to neutralise the acid and therefore to survive. Inhibition of urease by $Bi^{III}$ thiolate complexes may play a role in the antibacterial activity of $Bi^{III}$.

In general $Bi^{III}$ compounds are relatively non-toxic. Cells are probably protected against $Bi^{III}$ by the **thiol-rich protein metallothionein (MT). $Bi^{III}$ can induce the synthesis of MT** and pre-treatment with $Bi^{III}$ is an effective mechanism for minimising the toxicity of **Pt drugs**. Curiously, Bi is deposited in membrane-bound vesicles in the nuclei of cells as "**bismuth inclusion bodies**", but the chemical nature of these deposits is unknown…

The most serious side effects of bismuth drugs were encountered in France and Australia in the 1960s and 1970s when out-breaks of **encephalopathy** were reported. The chelating agent 2,3-dimercapto-1-propanesulfonic acid (DMPS) is an effective antidote for acute Bi intoxification...