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: $^{209}\text{Bi}$ \[\text{Xe}\] 4f$^{14}$5d$^{10}$6s$^2$6p$^3$.

Oxidation state of interest in medicine: Bi$^{\text{III}}$. Bi$^V$ is known but tends to be a strong oxidant. Bi$^{\text{III}}$, with an ionic radius of about 1.03 Å, is similar in size to Ca$^{\text{II}}$, 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:

$$[\text{Bi}(\text{H}_2\text{O})_y]^3+ \rightleftharpoons [\text{Bi}(\text{H}_2\text{O})_8(\text{OH})]^2+ + \text{H}^+ \quad pK_a \ 1.5$$

Further deprotonation to give coordinated **hydroxide** and **oxide** is facile, and oxygen bridged clusters such as $[\text{Bi}_6\text{O}_5(\text{OH})_3]^{5+}$ and $[\text{Bi}_6\text{O}_4(\text{OH})_4]^{6+}$ 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** [\((\text{cit})\text{BiBi(cit)}\)]^{2-}, where cit is **tetra-deprotonated citric acid**, containing **tridentate citrate**, with one carboxylate bridging to the neighbouring Bi$^{III}$. 
The $\text{Bi}^{III}$-O(alkoxide) bond is very short (2.2 Å) and strong, being part of a 5-membered chelate ring. $\text{Bi}^{III}$ 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\textsuperscript{III} citrates react readily with thiols such as the tripeptide \textbf{glutathione (GSH)}, with formation of $[\text{Bi(SG)}_3]$, in which Bi\textsuperscript{III} is bound to the thiolate S. Even though $[\text{Bi(SG)}_3]$ is a highly stable complex the thiolate ligands are kinetically labile and exchange with free thiol on a millisecond time-scale.

Therefore Bi\textsuperscript{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  \textbf{Glu, Cys, Gly}
The bacterium *Helicobacter pylori* lives under highly acidic conditions in the stomach and uses the **Ni enzyme urease** to make NH₃ to neutralise the acid and therefore to survive. Inhibition of urease by Bi³⁺ thiolate complexes may play a role in the antibacterial activity of Bi³⁺.
In general Bi\textsuperscript{III} compounds are relatively non-toxic. Cells are probably protected against Bi\textsuperscript{III} by the thiol-rich protein metallothionein (MT). Bi\textsuperscript{III} can induce the synthesis of MT and pre-treatment with Bi\textsuperscript{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 intoxication...

\[ \text{HS-SH-SO}_3\text{H} \]