doi:10.2533/chimia.2023.544 Chimia 77 (2023) 544–545

Chemical Education

A CHIMIA Column

Topics for Teaching: Chemistry in Nature

Anti-UV the Hippo Way

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Abstract: The hippopotamus secretes a liquid from its skin that may act both as a sunscreen and an antibiotic.

Keywords: Acid–base · Chemical education · Hippopotamus · Sunscreen

Folklore from the Ndebele people in Africa tells how the hippopotamus (*Hippopotamus amphibius*) was once hairy.[1] In reality, a hippopotamus's (hippo's) skin lacks hair and, although the skin is very thick (*ca*. 5 cm), it is extremely sensitive to drying out and sunburn. Hippos spend most of the daytime largely submerged under water (Fig. 1). Although hippos regularly graze on land, they do so mainly at night, and daylight sightings (Fig. 2) are relatively infrequent. Hippos exhibit an unusual phenomenon: they secrete a colourless fluid from their skin which quickly turns red on exposure to air. The secretion is often likened to sweat. However, unlike human sweat which originates from the eccrine glands close to the surface of the skin, hippo 'sweat' derives from deep in the skin and is more viscous than human sweat. The observation that hippos secrete a red liquid led to the ancient Egyptian belief that hippos intentionally pierce their skin to let blood flow (Fig. 3). This myth appears to be associated with the medical practice of bloodletting, known to ancient Greek and Arabic scholars, and continuing into the 1800s. In his 1613 bloodletting handbook, the Italian surgeon Tarduccio Salvi da Macerata wrote (the text being freely translated from old Italian[2]): "Naturalists say that the Hippopotamus, who is similar in size to a Frisian horse and lives near the river Nile, was the inventor of phlebotomy; he is of terrestrial and aquatic nature, and when he feels aggravated by an excess of blood, goes into a reedbed, or similar, and instinctively wounds a vein, letting out enough blood, until he feels comfortable: then he finds a swamp and uses mud to seal the wounds."

Definition: Phlebotomy is the procedure of taking blood directly from a vein, such as when taking a blood sample from a patient.

Initial attempts to collect and isolate the red secretion from hippos were fraught with difficulty, not simply because hippos can be very aggressive, making it non-trivial to collect samples – the researchers reported that they collected samples from the hippos by "wiping their bodies with paper towels along with the cooperation of the animal keepers".[3] The major difficulty was that the red liquid comprised molecules that rapidly polymerized to a brown material. Their extreme sensitivity meant that several standard procedures had to be avoided: evaporation of aqueous solutions of the samples to dryness, the addition of certain organic solvents (*e.g.* ethyl acetate), storage of aqueous extracts at am-

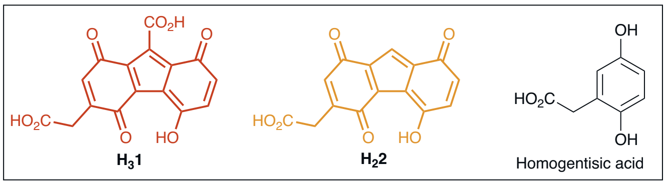
Fig. 1. The hippopotamus (*Hippopotamus amphibius*) spends most of the daytime largely submerged under water. Photo credit: Edwin Constable.

Fig. 2. A hippopotamus grazing on land. Photo credit: Edwin Constable.

Fig. 3. Engraving of a 'bleeding' hippopotamus. (Wellcome Collection, item c3yd28w7. Licence: public domain mark. https://wellcomecollection.org/search?query=item+c3yd28w7).

doi:10.2533/chimia.2023.545 Chimia 77 (2023) 545–545 © Swiss Chemical Society

bient temperatures, freezing of aqueous extracts, and the use of some separation phases including silica gel and octadecyl-bonded silica (ODS) columns for high-performance liquid chromatography (HPLC). Furthermore, the red secretion was alkaline (pH 8.5–10.5), and neutralization with aqueous hydrochloric acid resulted in the polymerization of the targeted compounds.[3] With the pH controlled, the highest solution concentration that could be used before the onset of polymerization was of the order of 10^{-5} mol dm^{-3}. Once optimal conditions had been determined, two pigments (red and orange) were isolated using gel filtration and ion exchange methods.[3,4] The structures of the red and orange pigments (**$H_3$1** and **$H_2$2**, respectively) are shown in Scheme 1, and Saikawa *et al.* gave these compounds the trivial names of hipposudoric and norhipposudoric acids, respectively. They are probably produced by the oxidative dimerization of homogentisic acid (Scheme 1), a metabolite of the amino acids tyrosine and phenylalanine. Compounds **$H_3$1** and **$H_2$2** are highly hydrophilic ('water loving') due to possessing many sites for hydrogen bond formation. Critically, the absorption spectra of aqueous solutions of the red and orange pigments exhibit maxima at 240, 411 and 530 nm for **$H_3$1**, and 243, 418 and 511 nm for **$H_2$2**, with the most intense absorptions being in the high energy (low wavelength) region. This is consistent with the compounds absorbing light in the UV (*ca.* 200–400 nm) and visible regions of the Sun's spectrum and, therefore, acting as a natural sunblock for the hippo.

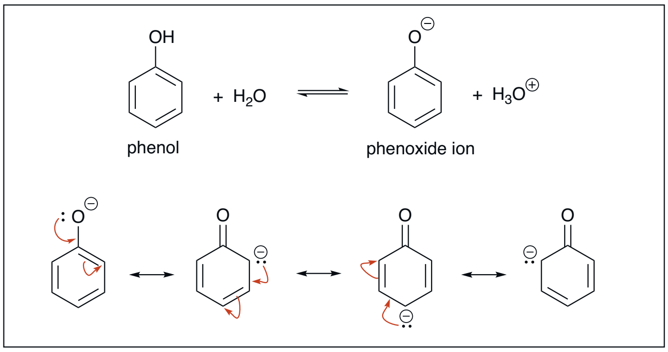


Scheme 1. Structures of the red (**$H_3$1**) and orange (**$H_2$2**) pigments isolated from the liquid secreted from the hippo's skin, and the structure of their precursor.

The red pigment **$H_3$1** appears to have a second function. At concentrations lower than is present in the skin of a hippo, **$H_3$1** inhibits the growth of pathogenic bacteria. Rival male hippos fight with extreme aggression (Fig. 4) and the natural antibacterial properties of the secretion from their skin may assist in lessening the effects of wounds.

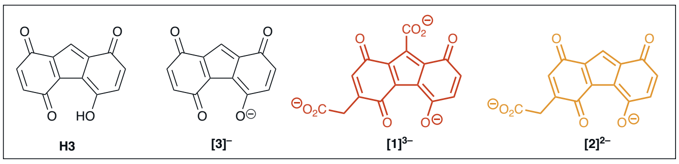
Compounds **$H_3$1** and **$H_2$2** contain phenolic and carboxylic acid functionalities, both of which are acidic in aqueous solution. Phenol is a weak acid (pK_a = 9.89), and the equilibrium shown at the top of Scheme 2 is driven to the right-hand side by the resonance stabilization of the conjugate base (bottom of Scheme 2). This means that the negative charge of the conjugate base is not localized on the O atom but is delocalized over the arene π-system, thus stabilizing the negative charge.

Fig. 4. Male hippos engage in fierce, territorial fights. Photo credit: Catherine Housecroft.



Scheme 2. Phenol is acidic in aqueous solution, and the lower part of the scheme shows resonance stabilization of the conjugate base (phenoxide ion).

Due to the difficulties in handling pigments **$H_3$1** and **$H_2$2**, Hashimoto and coworkers synthesized a model compound, **H3** (Scheme 3) and used it to investigate the acid–base behaviour of the pigments.[3–5] Note, however, that the model compound lacks the CO_2H groups present in **$H_3$1** and **$H_2$2**, so the focus is only on the behaviour of the phenolic proton. The dissociation of **H3** to **[3]$^-$** (Scheme 3) was studied in a 1:1 mixture of MeOH and H_2O and under these conditions, a value of pK_a in the range 2.7 to 3.3 was determined. This extrapolates to pK_a of between 1 and 2 in a purely aqueous solution, *i.e.* compound **H3** is a strong acid. Just as a series of resonance structures can be drawn for the phenoxide ion (Scheme 2) leading to resonance stabilization, so the conjugate base **[3]$^-$** gains substantial resonance stabilization through delocalization of the negative charge over the whole molecule. This in turn favours the dissociation of **H3**, rendering it a strong acid. By analogy, it can be concluded that the red and orange pigments secreted by a hippo exist in their tri- and dianionc forms **[1]$^{3-}$** and **[2]$^{2-}$**, respectively (Scheme 3).



Scheme 3. Left: Structure of model compound **H3**, and one resonance form of the anion **[3]$^-$**. Right: The fully deprotonated forms of the red and orange pigments in the secretion from hippo skin.

In this article, we have described the scientific origin for the ancient myth of the 'bleeding' hippo. The secretion from the hippo's skin may act both as a sunscreen and an antibiotic, with the pigments being strongly acidic due to resonance stablization of the negative charge over the molecular structures of **[1]$^{3-}$** and **[2]$^{2-}$**.

Received: May 17, 2023

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This column is one of a series designed to attract teachers to topics that link chemistry to Nature and stimulate students by seeing real-life applications of the subject