



Chemical Education

A CHIMIA Column

Topics for Teaching: Chemistry in Nature

What Goes in Must Come out: The Story of Uric Acid

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Abstract: Birds and reptiles convert waste ammonia into uric acid, while mammals excrete urea, with only small amounts of uric acid ending up in urine. This column explores the varying roles of uric acid and important calcium and sodium salts, and introduces π -stacking interactions in solid-state structures.

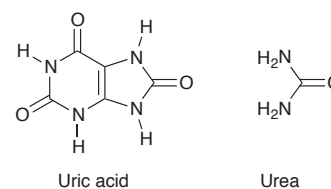
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We are all familiar with the colour and consistency of bird droppings – best to avoid a direct hit (Fig. 1)! However, when birds nest in large colonies, their droppings have agricultural significance. The term *guano* is used to describe the amassed excrement of birds, characteristically seen as white or grey deposits on cliffs inhabited by colonies of seabirds. The European herring gull (Fig. 1), for example, forms colonies of thousands of breeding pairs. In hot and dry climates, guano accumulates in large amounts and, because it is rich in nitrogen and phosphorus, it has applications as a fertilizer. With its long coastlines and many islands which host huge colonies of seabirds, South America features strongly in the history of guano harvesting, and the word *guano* originates in the Quechua (language of the indigenous people of Peru) word *huano*, meaning dung or fertilizer. Guano was being used as a fertilizer in South America as early as the 5th Century BCE, and the Incas recognized its importance as a natural, sustainable manure in the 1500s.^[1] In 1805, Alexander von Humboldt returned to Europe from Peru, bringing with him samples of guano that he sent to Antoine François de Foucroy and Louis Nicolas Vauquelin in Paris, and Sir Humphry Davy in the UK, for chemical analysis. The identification of *uric acid* (Scheme 1) linked guano, so prized as a fertilizer in Peru, to bird excrement. It took another forty years before the commercial importation of South American guano into Europe began.^[1] Whereas local agricultural use of guano by the Incas had been sustainable, large-scale harvesting and export to Europe by the end of the 19th Century CE was not, and action to protect the breeding colonies of seabirds was taken. With the growth of industrially manufactured fertilizers, the commercial trading of guano eventually ceased at the start of the 20th Century.

A high percentage of bird excrement is crystalline uric acid. This is a good opportunity to reiterate the role of hydrogen bonding in solid-state structures (introduced in an earlier Chemical Education column^[2]), and to look at another important crystal-packing interaction: π -stacking. Fig. 2 illustrates the packing of molecules of uric acid in the crystal lattice. In addition to N–H...O hydrogen bonds (Fig. 2a), uric acid molecules are arranged so that the 6-membered aromatic rings lie over the top



Fig. 1. Left, a common buzzard (*Buteo buteo*) – spot the uric acid in a colloidal form (see text). Right, a European herring gull (*Larus argentatus*). ©Edwin C. Constable 2021



Scheme 1. The structures of uric acid and urea.

of one another but in an offset manner (Fig. 2b). This leads to a π -stacking interaction (Fig. 2c)^[3] which, like hydrogen bonding, is an important intermolecular interaction in the crystal structures of aromatic organic molecules and in biological systems. For an efficient π -stacking interaction, the distance between the centroids of the arene rings is typically around 3.8 Å,^[4] and the angle between the planes of the rings should be close to 0°, but is usually in the range 0–20°. For educational purposes, the stabilizing influence of π -stacking interactions can be confirmed in a simple experiment: both hexafluorobenzene and 1,3,5-trimethylbenzene are liquids at room temperature, but mixing equimolar amounts of these aromatic compounds yields a white crystalline solid that melts at 34 °C. The electron-withdrawing fluoro-substituents in hexafluorobenzene render the molecule π -acidic, while 1,3,5-trimethylbenzene is π -basic.^[5]

We now return to uric acid. In birds and reptiles, uric acid is the end product of amino acid catabolism; *catabolism* is the term used for metabolic pathways that degrade large molecules into smaller ones. Before excretion, levels of uric acid in the blood of birds can reach 15–300 mg dm⁻³, and during excretion, crystalline uric acid is bound with mucus and organic matter to produce the colloidal excretion shown in Fig. 1.^[6] In contrast to birds, aquatic organisms excrete NH₃ directly, while mammals convert NH₃ into urea (Scheme 1) *via* the *urea cycle*, details of which can be found in ref. [7]. In humans, uric acid is produced from adenine and guanine,^[8] and is usually excreted in urine in small quantities. However, if levels of uric acid are especially high, *calcium urate* or complex urates containing Ca, Na and K crystallize as kidney stones (also known as renal calculi). The

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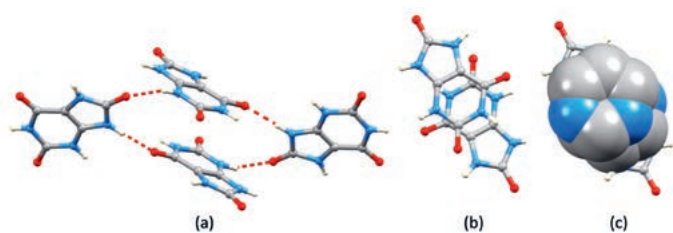
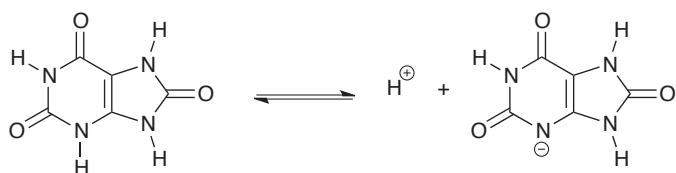


Fig. 2. The crystal structure of uric acid. (a) Hydrogen bonding (red hashed lines) between molecules. (b) For the central two molecules in (a), note the offset arrangement of the two 6-membered arene rings with respect to one another. This leads to (c) a π -stacking interaction, shown in space-filling representation. Data: Cambridge Structural Database refcode GADGIF.

first description of the isolation of uric acid from kidney stones came from Scheele (also one of the discoverers of oxygen^[9]) in 1776: “Having collected a sufficient number of calculi, taken from persons of both sexes, I undertook an inquiry into their nature ... According to these experiments, all urine contains besides the substances already known ... a concrete acid, hitherto unknown.”^[10] The ‘concrete acid’ was uric acid. Under physiological conditions, uric acid (HUr , $\text{p}K_{\text{a}} = 5.5$) is present mainly as its conjugate base (Scheme 2).



Scheme 2. Uric acid and its conjugate base.

Crystalline calcium urate hexahydrate, $\text{CaUr}_2 \cdot 6\text{H}_2\text{O}$ can be prepared by the reaction of uric acid with CaCl_2 under alkaline conditions (pH 10.5). The crystal structure of $\text{CaUr}_2 \cdot 6\text{H}_2\text{O}$ (Fig. 3) reveals an 8-coordinate Ca^{2+} ion bound by six H_2O molecules and one bidentate urate ion. The second urate ion is involved in hydrogen bonded interactions as shown in Fig. 3a. Additional hydrogen bonds are supplemented by π -stacking interactions between adjacent urate ions (coordinated and non-coordinated) to complete the overall crystal packing (Fig. 3b).

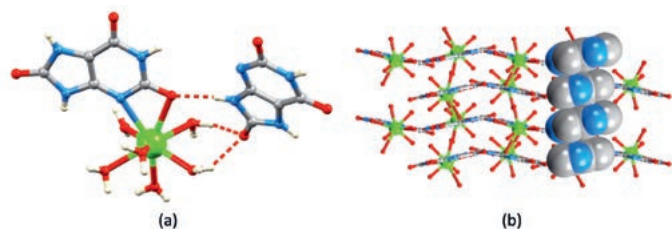


Fig. 3. (a) The crystal structure of calcium urate hexahydrate. Hydrogen bonds are shown as red-hashed lines. (b) In addition to hydrogen bonding, packing of molecules also involves π -stacking interactions between heterocyclic rings. Data: Cambridge Structural Database refcode YODJAE.

Uric acid is also associated with gout which causes painful swelling of human joints (Fig. 4) resulting from the deposition of sodium urate monohydrate, $\text{NaUr} \cdot \text{H}_2\text{O}$. In 2020, a study revealed that around 1 in 100 people in Switzerland has a prevalence for

gout.^[11] Crystals of $\text{NaUr} \cdot \text{H}_2\text{O}$ have a needle-like morphology and this facilitates their incorporation into cartilage in joints. At present, there is no cure for gout without incurring harmful side-effects.^[12] Fig. 5 illustrates the solid-state structure of sodium urate monohydrate.^[13] The heterocyclic anions are hydrogen bonded to one another to form 2-dimensional sheets with Na^+ ions residing in cavities within each sheet (Fig. 5a). Each Na^+ ion interacts with three urate anions within a sheet, and with one H_2O molecule (Fig. 5a) which lies between the sheets (Fig. 5b). As in $\text{CaUr}_2 \cdot 6\text{H}_2\text{O}$, the heterocyclic anions in $\text{NaUr} \cdot \text{H}_2\text{O}$ engage in π -stacking interactions to lock the sheets together (Fig. 5b).



Fig. 4. ‘The Gout’ by James Gillray. Published May 14th 1799. [https://commons.wikimedia.org/wiki/File:The_gout_james_gillray.jpg]

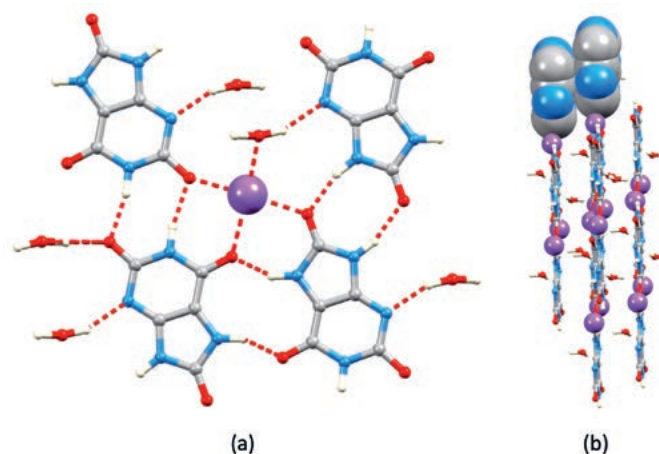


Fig. 5. (a) The crystal structure of sodium urate monohydrate. Hydrogen bonds and electrostatic $\text{Na}^+ \dots \text{O}$ interactions are shown as red-hashed lines. (b) Packing of 2D-sheets. Data: Cambridge Structural Database refcode NAURAT.

This column has illustrated the role of uric acid as an end-product in birds, and as a minor component of urine in mammals. We have also focused on packing interactions in crystalline materials.

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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.