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Preparation and characterization of uniform particles of uric acid and its salts

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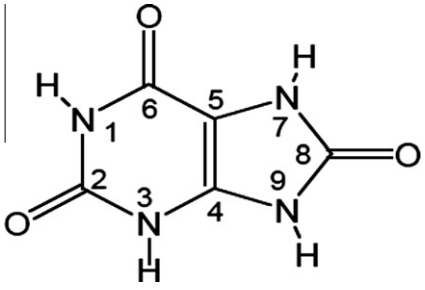
ABSTRACT

Uric acid, the major component in many kinds of kidney stones, as well as its sodium, ammonium, calcium, and barium salts were successfully prepared as uniform dispersions by precipitation in basic aqueous solutions. The effects of the reactant concentrations, pH, and the stabilizers were evaluated in detail. Except for the platelets of the pure acid, all prepared compounds appeared as needles or their aggregates. The electron micrographs showed that kidney stones consisted of such aggregates although less regular in size and morphology. All prepared urate salts had a 1:1 cation/uric acid ratio, regardless of the valence of the cation. The electrokinetic measurements showed all these particles to have negative ζ-potentials over the pH range 3–9. The precipitated salt particles were chemically and morphologically unstable at low pH values by decomposing into ill-defined aggregates of the pure uric acid.

1. Introduction

Uric acid, the final product of the catabolism of purine nucleosides in the human system, is considered to be an important marker molecule causing problems related to variations of the plasma urate levels, such as cardiovascular diseases, high blood pressure, hyperuricemia (gout), ketoacidosis, lactate excess, Lesch–Nyhan syndrome, leukemia, and renal impairment [1–7]. It is also the dominant component of the calculi, which represent a sizeable proportion (~13%) of all human kidney stones [8]. In some cases these stones contain different uric acid compounds, such as ammonium, sodium, or calcium urates [9,10].

Uric acid is a heterocyclic compound of the composition:



It is essentially insoluble in all organic solvents and only slightly soluble in water, except at sufficiently high pH. It exists primarily in its neutral form at low pH. However, above its pKa of 5.4, the nitrogen at position 3 becomes deprotonated, so that the major species in solution is the urate ion. This pH dependence is an important factor in the kidneys and all along the renal tract [11,12].

Research on uric acid can be classified into two categories. The majority of studies describe several effective analytical methods for the determination of its concentration in urine or blood [13–17]. The others deal with the precipitation of uric acid as ultrafine colloids [10,18] or single crystals [19–21] in order to establish the mechanism of the uric acid kidney stones formation. However, it seems that no successful method was developed to produce uniform particles, in size and shape, of this acid and its salts. This work describes the preparation of such well-defined dispersions of the acid and its ammonium, sodium, calcium, and barium salts with special emphasis on the effects of the reactant concentrations, pH, and additives on the morphology and uniformity of the resulting particles.

2. Experimental

2.1. Materials

Uric acid (Sigma) was 99% pure and used without further purification. Two additives, i.e. Igepal CO 630 95% pure

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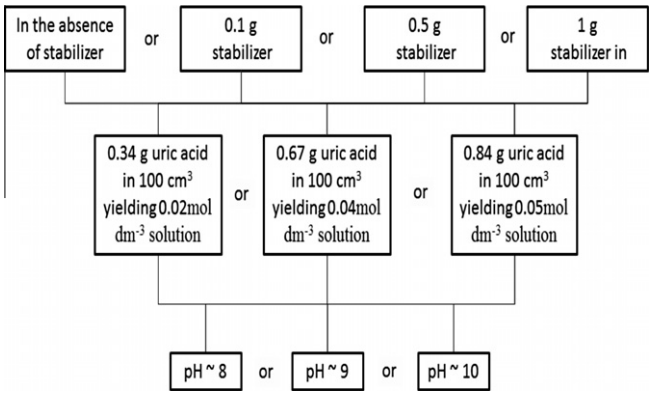
(Rhodia Novecare), and hydroxypropyl cellulose (HPC-SL, Nisso Chemical, lot DL-0881) were employed in the preparation of uniform particles of this acid and its compounds.

2.2. Preparation of stock solutions

To study the effects of the pH, reactants concentrations, and additives on the morphology and uniformity of the resulting particles of uric acid and its salts, a series of stock solutions of different concentrations and pH values were prepared using the following steps. The desired weights of the stabilizer (Igepal CO 630 or HPC) were dissolved in 10 cm^3 of deionized water, and then predetermined weights of uric acid were suspended in the stabilizer solutions. To this suspension, 0.10 mol dm^{-3} NaOH solution was slowly added under magnetic stirring until the uric acid was completely dissolved. The so obtained clear solutions were increased up to 100 cm^3 with deionized water. Additionally, a few drops of 0.10 mol dm^{-3} NaOH solution were required to adjust the pH to values of ~8, 9, or 10. These volumes of the base had a negligible effect on the final concentrations of the reactants. The weights and the concentrations of the uric acid and the stabilizers, as well as the pH of the so prepared stock solutions are summarized in the following chart:



2.3. Preparation of uric acid and its salts dispersions

2.3.1. Uric acid

In general, uric acid dispersions were obtained by a slow addition of a 0.10 mol dm^{-3} HCl solution to 20.0 cm^3 of the basic uric acid stock solutions (Section 2.2), under magnetic stirring, until reaching the pH ~ 5.0. These dispersions were stirred for 5 min, followed by aging for 15 min, and then the precipitated particles were collected on 0.8 μm pore-size polycarbonate membranes.

2.3.2. Uric acid salts

Dispersions of sodium, ammonium, calcium, and barium salts of the uric acid were prepared as follows. The monosodium urate particles were obtained by the same method as that for the pure acid (Section 2.3.1.), except by acidifying the uric acid stock solution to pH ~ 7. The dispersions of other salts were produced by adding 10 cm^3 of NH_4NO_3, $Ca(NO_3)_2$, or $Ba(NO_3)_2$ solutions to 10 cm^3 of the uric acid stock solutions (Section 2.2). The molar concentrations of $Ca(NO_3)_2$, and $Ba(NO_3)_2$ solutions were chosen to be the same as those of the uric acid solutions, while NH_4NO_3 molar concentrations doubled those of the pure uric acid. After mixing the reactants, the resulting dispersions were magnetically stirred for 5 min and then aged for 15 min.

All prepared samples were examined with a JEOL JSM-7400F field emission scanning electron microscope, their crystallinity evaluated with a Bruker D8 Axis X-ray diffractometer, and the electrokinetic properties studied using the BIC Zeta Plus analyzer under constant ionic strength of 0.1 mol dm^{-3} KCl.

3. Results

The morphology of the prepared uric acid or urate particles depended on the pH, the concentration of the reactants, and the presence of the stabilizers, as described in the following sections.

3.1. Uric acid

The scanning electron micrograph of the uric acid as received (Fig. 1a) shows that the solid consisted of ill-defined non-uniform aggregates. The platelets in Fig. 1b were obtained when 0.04 mol dm^{-3} uric acid solution of pH ~ 10 was acidified with HCl to pH ~ 5, in the absence of any stabilizers. The collected particles were proven to be pure uric acid by the energy dispersive X-ray spectroscopy (EDS) (Fig. 2). Changing the pH (8, 9, or 10), the initial uric acid concentration (0.02, 0.04, or 0.05 mol dm^{-3}), or the presence of stabilizers, had no significant effects on the shape and the size of the obtained particles or the degree of their uniformity. The platelets were similar in shape to what was revealed in the literature [10], although the latter were aggregated due to a high ionic strength of the artificial "urine solution" in which the uric acid was precipitated.

The X-ray diffractogram of the commercial uric acid (Fig. 3a) matches the results found in the database [22], and that of particles precipitated at pH ~ 5 (Fig. 1b). However the latter shows preferable planes of growth (Fig. 3b).

3.2. Salts of the uric acid

In general, finely dispersed particles of uric acid salts can be obtained by precipitation in basic aqueous solutions as described in Section 2.3.2.

3.2.1. Monosodium urate

The scanning electron micrograph in Fig. 4a displays the structure of hollow spheres obtained by acidifying the same uric acid solution as in Fig. 1b to pH ~ 7. The EDS (Fig. 4b) verifies that these particles are the monosodium salt of the uric acid, which would explain the different morphology from that of the pure acid.

Repeating the experiment as in Fig. 4a, with solutions containing either Igepal CO 630 or HPC, also produced internally composite particles as those obtained in the absence of any additives, except much smaller in size (Fig. 5a). Interestingly, their internal structure consists of small rod-like subunits displayed in Fig. 5b. Starting with solutions of different concentrations of the uric acid (0.02, 0.04, or 0.05 mol dm^{-3}), or of the stabilizer (0.1, 0.5, 1.0 wt%), as well as of the pH (8, 9, or 10) had a negligible effect on the properties of the precipitated particles.

Fig. 6 displays the X-ray diffractograms of the monosodium salt shown in Fig. 3a, obtained at pH ~ 7 in the absence of a stabilizer, and of those obtained in the presence of HPC. The two diffractograms are matched but differ from that of the pure uric acid (Fig. 3b).

3.2.2. Ammonium urate

Fig. 7 displays the scanning electron micrographs of the rod-like ammonium urate particles precipitated by adding 10 cm^3 of 0.08 mol dm^{-3} NH_4NO_3 solution to 10 cm^3 of a 0.04 mol dm^{-3} uric