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Solubility equilibria in the uric acid–sodium urate–water system[1,2]

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Abstract

In a constant ionic medium, corresponding to a physiological environment ($I_c = 0.15\ \mathrm{mol\ dm^{-3}}$ NaCl), the solubilities of anhydrous uric acid, uric acid dihydrate and monosodium urate monohydrate have been measured as a function of $\mathrm{p[H]} = -\log[\mathrm{H^+}]$(2–8) and temperature (25°, 32°, 37° and 42°C). The solubility equilibria in the uric acid–sodium urate–water system are discussed on the basis of the solubility constants (K_s) and the first dissociation constant (K_1) of uric acid and the solubility product (K_{s0}) of monosodium urate. The quantities measured in this work are in good agreement with literature values, however, the present solubility data have a much higher precision. © 1998 Elsevier Science B.V.

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1. Introduction

It is well known that the precipitation of uric acid and monosodium urate in the human body is closely related to many diseases, e.g. formation of calculi in the urinary tract, uric acid nephropathy and gouty arthritis [1–7]. In order to investigate the mechanisms leading to uric acid or monosodium urate precipitation, many factors, e.g. influences on nucleation by pH [4], proteins [5], antibodies [6], biological milieu in general [7], etc. have been studied and discussed. However, in spite of numerous solubility studies published in the available literature, accurate solubilities of uric acid and monosodium urate, e.g. in physiological NaCl solution are not well known. More recently, only a few experimental investigations on the uric acid–sodium urate–water system have been performed [8–12], whereas data given in most papers have just been recalculated or cited from other sources, e.g. [9,13]. Since sound physico-chemical data are indispensable for a discussion of medical implications, a detailed investigation of solubility equilibria in the uric acid–sodium urate–water system was carried out.

2. Experimental

2.1. Materials

High-purity uric acid $C_5H_4N_4O_3$ (99%+), purchased from ALDRICH, was used directly. X-ray diffraction analysis and scanning electron microscopy (SEM) confirmed that this commercial sample was

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pure anhydrous uric acid. Other chemicals used were of analytical reagent grade.

Uric acid dihydrate was prepared as follows:

Since uric acid dihydrate crystallises from slightly acidic, highly supersaturated solutions obtained by rapid cooling [14], ca.130 mg of commercial anhydrous uric acid were dissolved in 500 cm^3 of boiling bidistilled water. The pH of the solution was adjusted to ca. 3, with glacial acetic acid. The solution was filtered, rapidly cooled in an ice bath and kept in a refrigerator for 3 h. The transparent, platelike crystals formed were filtered, washed with cold bidistilled water and immediately used for the solubility experiments. The crystals were identified to be pure uric acid dihydrate by optical and scanning electron microscopy as well as X-ray diffraction analysis.

Monosodium urate monohydrate was prepared as follows:

An amount of 2 g uric acid was suspended in 4 cm^3 of 0.01 mol dm^{-3} NaOH solution, diluted with bidistilled water to 600 cm^3 and warmed up to ca. 70°C. Solid NaOH was gradually added to the well-stirred solution until it was clear. At this moment, the pH of the solution was ca. 9. The solution was filtered and slowly evaporated at ca. 70°C to a final volume of 500 cm^3. For the crystallisation of monosodium urate monohydrate, the solution was kept at room temperature for about 40 h. The formation of the needle-shaped crystals was checked under a microscope. Then the suspension was cooled in a refrigerator for 2 h. The crystals were filtered under vacuum, washed with cold bidistilled water and dried at 110°C in an oven for 2 h. The yield was usually ca. 1.4 g monosodium urate monohydrate. The purity of the crystals was confirmed by X-ray diffraction analysis and SEM.

2.2. Equipment

The experiments were performed using a thermostatted, percolation-type solubility cell [15]. SCHOTT H2680 glass electrodes and a home-made silver–silver chloride reference electrode with Wilhelm-type salt bridge [16] were connected to an ORION 940 pH-meter. The concentration of uric acid was measured in 0.1 mol dm^{-3} NaOH solution using a Perkin–Elmer LAMBDA 15 UV/VIS spectrometer.

2.3. Procedure

In the solubility cell, the initial solution ($[Na^+]_{ini} = I_c$ mol dm^{-3}, $[OH^-]_{ini}$ = OH mol dm^{-3}, $[Cl^-]_{ini} = (I_c - OH)$ mol dm^{-3}) was percolated by a H_2O-presaturated N_2-gas stream through the solid phase of uric acid. In the case of monosodium urate, the initial solution contained $[Cl^-]_{ini} = I_c$ mol dm^{-3}, $[H^+]_{ini}$ = H mol dm^{-3}, $[Na^+]_{ini} = (I_c - H)$ mol dm^{-3}. In the pH variation method [17] employed here, $I_c = 0.15$ mol dm^{-3} and H or OH were varied systematically from one experiment to another. During the reaction with the solid phase, the p[H] value of the solution was followed by the galvanic cell

$$\text{Ag} \mid \text{AgCl} \mid I_c \,\text{mol dm}^{-3}\, \text{NaCl} \mid I_c \,\text{mol dm}^{-3} \times \text{NaCl} \mid S_A \text{ or } S \mid \text{glass electrode} \qquad (A)$$

and recorded by the pH-meter. After 6–48 h, depending on the compound and temperature, a constant p[H] value was obtained which indicated the (metastable) solubility equilibrium.

The cell (A) was calibrated with a solution $S_A = 0.14$ mol dm^{-3} NaCl/0.01 mol dm^{-3} HCl before and after the solubility measurement. The liquid junction potential E_j in NaCl must be considered in the p[H] range at calibration. It was calculated using the relation $E_j/\text{mV} = -51.2[H^+]/I_c$ which can be derived from a simplified form of the Henderson equation [18].

The resulting solution was separated from the solid phase and diluted 5, 10, or 20 times with 0.1 mol dm^{-3} NaOH solution, thereby uric acid, H_2U, and hydrogen urate, HU^-, were transformed to urate, U^{2-}. The total concentration of urate was determined spectrophotometrically at 293.6 nm wavelength with 0.1 mol dm^{-3} NaOH as the reference solution. It should be noted that, after separation from the solid phase, the urate dissolved in the solution decomposed at room temperature due to atmospheric O_2 absorption. Therefore, the measurement must be carried out as soon as possible.

3. Results and discussion

For this heterogeneous system, at least three equilibria must be considered:

$$H_2U(\cdot 2H_2O)_{(s)} \rightarrow H_2U_{(aq)}(+2\,H_2O) \quad K_s \qquad (1)$$

$$H_2U_{(aq)} \rightarrow H^+_{(aq)} + HU^-_{(aq)} \quad K_1 \qquad (2)$$

$$NaHU \cdot H_2O_{(s)} \rightarrow Na^+_{(aq)} + HU^-_{(aq)} + H_2O \quad K_{s0} \qquad (3)$$

The results of the uric acid and monosodium urate monohydrate solubility measurements at $I_c = 0.15\ \mathrm{mol\,dm^{-3}}$ NaCl and at temperatures of 25°, 32°, 37° and 42°C are shown graphically in Fig. 1.

Anhydrous uric acid – When $p[H] \leq 3$, the solubility of uric acid was low and independent of p[H]. At high concentration of hydrogen ions, $H_2U_{(aq)}$ is the predominant species due to the negligible dissociation of uric acid. From these data, the solubility constant of uric acid, which corresponds to reaction (1), was calculated for 25°, 32°, 37° and 42°C.

When $3 < p[H] < 5$, the solubility of uric acid increased with p[H]. A decrease in the concentration of hydrogen ions in the initial solution enhances the dissociation of $H_2U_{(aq)}$ so that HU^- contributes significantly to the total uric acid concentration. When $5 < p[H] < 7$, the solubility of uric acid still increased continuously with p[H], although the ionic product of hydrogen urate ions and sodium ions by far exceeded the solubility product of monosodium urate. Thus, the equilibrium between solid uric acid and the solution was metastable with respect to the formation of solid monosodium urate. Obviously, the nucleation of monosodium urate was retarded, it only occurred at a high degree of supersaturation.

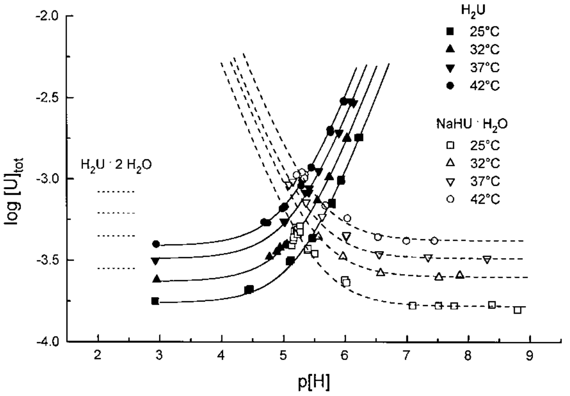

Fig. 1. Summary of the solubility relationships in the uric acid–monosodium urate–water system at $I_c = 0.15\ \mathrm{mol\,dm^{-3}}$ NaCl. Solid (anhydrous uric acid) and dashed (monosodium urate monohydrate) lines were calculated from Eqs. (4) and (5) using the thermodynamic quantities given in Tables 1 and 2, respectively. Solubilities of uric acid dihydrate at low p[H] (dotted lines) are shown for comparison.

The solubility constant, K_s, and the first dissociation constant, K_1, of uric acid were obtained by a least-squares analysis of data measured in the entire p[H] range under different starting conditions. The experimental quantity $[U]_{tot}$ equals the sum of $[H_2U]$ and $[HU^-]$ which can be rearranged to yield the following equation

$$[U]_{tot} \equiv [H_2U] + [HU^-] = K_s(1 + K_1/[H^+]), \qquad (4)$$

where $[U]_{tot}$ and p[H] were measured at the solubility equilibrium with solid uric acid. The values obtained for K_s in this way agreed very well with those determined directly (see above). It can also be seen in Fig. 1 that consistent results were obtained.

Monosodium urate monohydrate – The solubility of monosodium urate did not exceed an almost constant, maximum value even if the p[H] of the initial solutions changed from 1.6 to 3. Since the equilibria (2) and (1) are shifted to the left at low p[H], the explanation for this phenomenon is obviously the precipitation of solid uric acid whose crystals were actually detected under an optical microscope. It seems that the nucleation of uric acid occurs at much lower supersaturation than that of monosodium urate.

At $7 < p[H] < 8$, the concentrations of uric acid and urate ions are negligible, i.e. $[U]_{tot} \approx [HU^-]$. The solubility of monosodium urate depends on the initial concentration of sodium ions which is much higher than that resulting from the dissolution of monosodium urate. Since the initial Na^+ concentration was essentially kept constant, the concentration of hydrogen-urate ions was also constant in this p[H] range. Thus, the solubility product of monosodium urate monohydrate could be calculated.

The solubility of monosodium urate increased with decreasing concentration of sodium ions and increasing concentration of hydrogen ions in the initial solution. If the total concentration of urate

Table 1

Solubility and first dissociation constants of uric acid at $I_c = 0.15$ mol dm^{-3} NaCl as derived from solubility measurements on anhydrous uric acid (H_2U) and uric acid dihydrate ($H_2U{\cdot}2H_2O$)

t/°C	pK_s (exp) [a] ($H_2U{\cdot}2H_2O$)	pK_s (exp) [a] (H_2U)	pK_s (fit) (H_2U)	pK_1 (fit)
25	3.55 ± 0.01	3.75 ± 0.01	3.76 ± 0.03	5.26 ± 0.04
32	3.35 ± 0.01	3.62 ± 0.02	3.63 ± 0.01	5.21 ± 0.01
37	3.21 ± 0.01	3.50 ± 0.01	3.49 ± 0.03	5.19 ± 0.04
42	3.08 ± 0.01	3.40 ± 0.01	3.41 ± 0.01	5.13 ± 0.01

[a] Derived from direct solubility measurements at p[H] ≤ 3.

was calculated with the help of Eq. (5), using K_1 obtained from uric acid solubilities (Table 1),

$$\begin{aligned}[U]_{tot} \equiv [H_2U] + [HU^-] &= [HU^-]\,[H^+]/K_1 \\ &+ [HU^-] = [HU^-]\{[H^+]/K_1 + 1\} \\ &= K_{s0}\{[H^+]/K_1 + 1\}/[Na^+], \qquad (5)\end{aligned}$$

the experimental values were higher than the calculated ones. This cannot be explained by the formation of $NaHU_{(aq)}$ complexes, because it can be shown that this would affect the solubilities of both, uric acid and sodium urate in the same way. Therefore, in the case of complex formation, $[U]_{tot} = [H_2U] + [HU^-] + [NaHU]$, K_1 in Eqs. (4) and (5) has to be replaced by

$$K_1' = K_1(1 + K'[Na^+]) \qquad (6)$$

where K' is the formation constant of $NaHU_{(aq)}$. In Eq. (5), K_{s0} has to be replaced by $K_{s0}\{1 + K'[Na^+]\}$ as well. Since, in this study, $[Na^+]$ is essentially kept constant, a complex-formation constant cannot be derived from these measurements directly. However, Fig. 1 shows that the solubility data for monosodium urate monohydrate can be fitted to Eq. (5), but the resulting K_1 (or K_1') values (Table 2) are consistently higher than those obtained for uric acid solubilities (Table 1). Although the uncertainty in monosodium urate solubilities is greater, the difference in K_1 (or K_1') is significant and may be attributed to either the use of an oversimplified speciation model for the aqueous phase or, more likely, the tendency of monosodium urate monohydrate to form supersaturated solutions [19]. In this study, supersaturated solutions may have actually formed in the measurements with acidic initial solutions. Anyway, the pK_1 values given in Table 2 are regarded to be less reliable than those in Table 1.

Uric acid dihydrate – The solubility constant of uric acid dihydrate was determined by directly measuring

Table 2

Solubility product of monosodium urate monohydrate and first dissociation constant of uric acid at $I_c = 0.15$ mol dm^{-3} NaCl as derived from solubility measurements on monosodium urate monohydrate

t/°C	pK_{s0} (exp) [a]	pK_{s0} (fit)	pK_1 (fit) [b]
25	4.61 ± 0.01	4.57 ± 0.04	(5.44 ± 0.06)
32	4.43 ± 0.01	4.42 ± 0.01	(5.45 ± 0.03)
37	4.31 ± 0.01	4.28 ± 0.03	(5.35 ± 0.05)
42	4.20 ± 0.01	4.19 ± 0.03	(5.45 ± 0.07)

[a] Derived from direct solubility measurements at $7 \leq$ p[H] ≤ 8.5.

[b] For reasons stated in the text, the pK_1 values reported here are regarded to be less reliable than those given in Table 1.

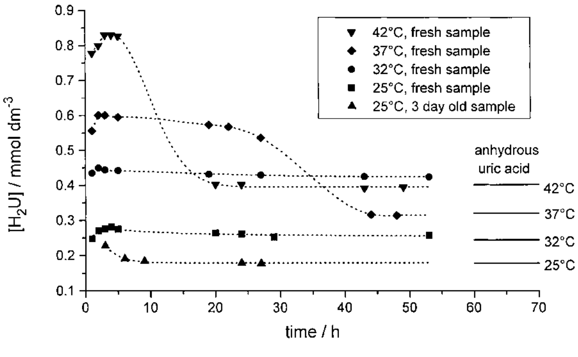

Fig. 2. Uric acid concentration vs. time measured for uric acid dihydrate at p[H] ≈ 3 and $I_c = 0.15$ mol dm^{-3} NaCl. Maximum values were interpreted as solubility of uric acid dihydrate at metastable equilibrium with the solution. Solubilities of anhydrous uric acid at low p[H] (solid lines) are shown for comparison.

the uric acid concentration in the $2 < p[H] < 3$ range. Fig. 2 shows that, after 2–5 h, $[H_2U]$ reaches a maximum value which is interpreted as the solubility of uric acid dihydrate at metastable equilibrium. The concentration then drops to lower values and eventually arrives at the equilibrium solubility of anhydrous uric acid. At 42°, 37° and 32°C, this occurred after 20, 45 and 150 h, respectively. At 25°C, however, $[H_2U]$ still agreed with the solubility of the dihydrate after 150 h, even in an experiment with seed crystals of anhydrous uric acid added after ca. 100 h. The complete conversion of the dihydrate to the anhydrous form at 42°C was confirmed by X-ray diffraction and SEM, whereas the sample collected after the solubility experiment at 25°C still consisted of uric acid dihydrate with no anhydrous uric acid being detected. These results were obtained with samples used for the solubility experiments immediately after preparation (without drying), whereas in the 25°C experiment, a three-day old sample of dihydrate was converted to anhydrous uric acid within 8 h. Obviously, this sample was partly decomposed since it is well known that uric acid dihydrate looses water in contact with dry and even moist air within a few hours to two days [3]. However, our experiments with fresh samples support the earlier observation [12] that sodium chloride solutions stabilise the metastable dihydrate.

The constants obtained by direct measurement (at solubility minimum) and nonlinear least-squares analysis (using data measured in the whole p[H] range) are listed in Tables 1 and 2. The results of this study are compared with literature data in Figs. 3 and 4. While the solubility constant of anhydrous uric acid and uric acid dihydrate agree with literature values [11,12] at 25° and 37°C, respectively, the temperature dependence of pK_s determined in this work differs from that previously reported. Table 3 shows the corresponding $\Delta_r H$ values for comparison.

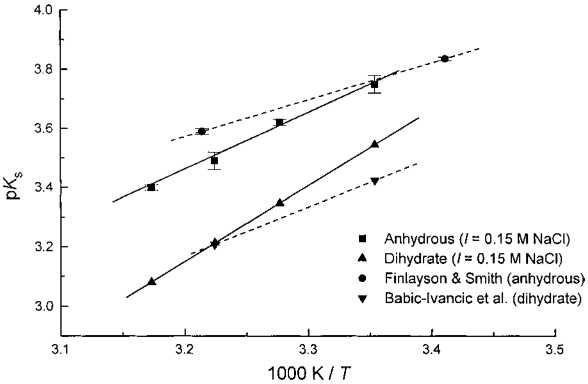

Fig. 3. Temperature dependence of uric acid solubility constants. Solid lines – this work; and dashed lines – literature values. The corresponding enthalpies of reaction are given in Table 3.

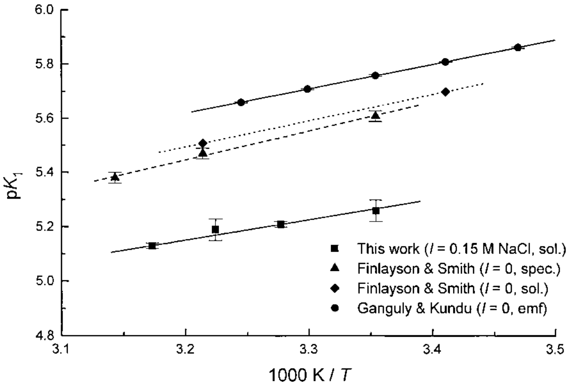

Fig. 4. Temperature dependence of the first dissociation constant of aqueous uric acid as compared to literature values. The corresponding enthalpies of reaction are given in Table 3.

Using the Davies equation, an activity-coefficient correction for pK_1 at 25°C (5.26) is calculated as 0.24. Comparison with Ganguly and Kundu's [20] pK_1, valid for $I_c = 0$ (5.76), suggests the formation of $NaHU_{(aq)}$ complexes. From Eq. (6),

Table 3
Enthalpies of reaction derived from the temperature dependence of the corresponding equilibrium constants

$H_2U(\cdot 2H_2O)_{(s)} \rightarrow H_2U_{(aq)}(+2\,H_2O_{(aq)})$			$H_2U_{(aq)} \rightarrow H^+_{(aq)} + HU^-_{(aq)}$	
	$\Delta_r H/(\mathrm{kJ\,mol^{-1}})$	Reference	$\Delta_r H/(\mathrm{kJ\,mol^{-1}})$	Reference
Anhydrous	36.6	This work	14.5	This work
	23.9	[11]	17.3	[20] (e.m.f.)
Dihydrate	49.0	This work	18.7	[11] (solubility)
	31.8	[11]	20.7	[12] (spectroscopy)

$K' \approx 5.5\ \mathrm{mol^{-1}\ dm^3}$ can be calculated which may be compared to $K' \approx 13\ \mathrm{mol^{-1}\ dm^3}$ as derived by Finlayson and Smith [11] from the early solubility measurements by Hammarsten [21].

Generally, the precision of the present solubility data is much better than in previous studies. Thus, a discrepancy in the K_1 (or K_1') values, derived form uric acid and monosodium urate solubilities, respectively, was detected. However, this difference cannot be explained by the equilibrium model employed in this work. To resolve this discrepancy, possibly a more complex speciation model of the aqueous phase is needed or, more likely, supersaturated monosodium urate solutions are assumed to have been formed.

4. Conclusion

- The solubility relations in the uric acid–sodium urate–water system at $I_c = 0.15\ \mathrm{mol\ dm^{-3}}$ NaCl can be summarised as follows:
  - At low $p[H] (< 5)$, uric acid concentrations are limited by the low solubility of uric acid which readily precipitates from supersaturated urate solutions.
  - At higher $p[H] (> 6)$, the low solubility of monosodium urate limits the urate concentrations in the solution. However, metastable uric acid solutions exist up to $p[H] \approx 6$. They are highly supersaturated with respect to monosodium urate.

  Thus, it can be concluded that the nucleation of uric acid occurs much easier than that of monosodium urate.
- Whereas uric acid dihydrate is readily transformed to the anhydrous form when in contact with air, it is stabilised by $0.15\ \mathrm{mol\ dm^{-3}}$ NaCl solution for a much longer period of time.
- The good agreement with literature data and the high precision of the results obtained from this work indicates that the equipment and method used are very reliable for solubility studies on sparingly soluble acids and salts with basic anions. The data obtained in this work contribute to a sound physicochemical basis of the research on diseases like formation of calculi in the urinary tract, uric acid nephropathy and gouty arthritis.

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References

[1] E. Matouschek, R.-D. Huber, Urolithiasis, F.K. Schattauer Verlag, Stuttgart, 1981, 198 p.
[2] T.D. Peters, G.V. Ball, Current Opin. Rheumatol. 4 (1992) 566.
[3] F. Grases, A.I. Villacampa, A. Costa-Bauzá, O. Söhnel, Uric acid calculi, Scanning Microsc., submitted (1997).
[4] B. Hess, U. Binswanger, Klin. Wochenschr. 68 (1990) 874.
[5] E. Ortiz-Bravo, M.S. Sieck, H.R. Schumacher Jr., Arthritis Rheum. 36 (1993) 1274.
[6] R.A. Terkeltaub, Current Opin. Rheumatol. 5 (1993) 510.
[7] N.W. McGill, A. Hayes, P.A. Dieppe, Scand. J. Rheumatol. 21 (1992) 215.
[8] D.J. Allen, G. Milosovich, A.M. Mattocks, Arthritis Rheum. 8 (1965) 1123.
[9] W.R. Wilcox, A. Khalaf, A. Weinberger, I. Kippen, J.R. Klinenberg, Med. and Biol. Eng. 10 (1972) 522.
[10] A.A. Khalaf, W.R. Wilcox, J. Cryst. Growth 20 (1973) 227.
[11] B. Finlayson, A. Smith, J. Chem. Eng. Data 19 (1974) 94.
[12] V. Babic-Ivancic, H. Füredi-Milhofer, W.E. Brown, T.M. Gregory, J. Cryst. Growth 83 (1987) 581.
[13] J.N. Loeb, Arthritis Rheum. 15 (1972) 189.
[14] C. Rinaudo, R. Boistelle, J. Cryst. Growth 49 (1980) 569.
[15] H. Gamsjäger, F. Reiterer, Environment International 2 (1979) 419.
[16] W. Forsling, S. Hietanen, L.G. Sillén, Acta Chem. Scand. 6 (1952) 901.
[17] P. Schindler, Chimia 17 (1963) 313.
[18] G.T. Hefter, Anal. Chem. 54 (1982) 2518.
[19] R. Kohler, Z. Klin. Med. 78 (1913) 205.
[20] S. Ganguly, K.K. Kundu, Indian J. Chem. 34A (1995) 47.
[21] G. Hammarsten, C.R. Trav. Lab. Carlsberg 19 (1932) 1.