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Thermochimica Acta 354 (2000) 7–13

thermochimica acta

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Dissolution enthalpies of uric acid and uric acid dihydrate

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Received 13 December 1999; received in revised form 29 February 2000; accepted 2 March 2000

Abstract

The dissolution enthalpies of uric acid and its dihydrate in Tris–buffer solutions were measured calorimetrically for the first time. It was found that these quantities do not depend significantly on pH (7.2–8.9), temperature (t=25–37°C), ionic strength (I=0.010–0.045 mol dm^{-3}) and uric acid concentration (c=3.4–8.5 mmol dm^{-3}). After subtracting the protonation enthalpy of Tris, the present results

$$H_2U(s) \rightarrow H^+(aq) + HU^-(aq), \quad \Delta_r H = (56.3 \pm 0.4)\,kJ\,mol^{-1}$$

$$H_2U \cdot 2H_2O(s) \rightarrow H^+(aq) + HU^-(aq) + 2H_2O(aq), \quad \Delta_r H = (64.5 \pm 0.2)\,kJ\,mol^{-1}$$

are consistent with those obtained from the temperature dependence of the solubility equilibrium constants reported in our previous work. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Calorimetry; Solubility; Uric acid; Urolithiasis; Thermodynamics

1. Introduction

Uric acid, the end-product of purine metabolism, is a sparingly soluble substance. Since uric acid anhydrate and dihydrate are found as constituents of renal calculi, the epidemiological and clinical characteristics of uric acid lithiasis have been described frequently, e.g. in [1]. The prevention and treatment of uric acid lithiasis can certainly benefit from a better knowledge of the physico-chemical principles underlying uric acid stone formation. In our previous work, highly reproducible solubility data of uric acid anhydrate and dihydrate and the dependencies of solubility on temperature, solution composition and pH were obtained under conditions most pertinent to urolithiasis [2,3].

Owing to the sparing solubilities and low dissolution rates near saturation, the dissolution enthalpies of uric acids have not been measured directly but have only been derived from the temperature dependence of solubilities, e.g. in [2,4]. However, the dissolution enthalpies obtained in this way are very sensitive even to small changes of the solubility data so that the values calculated from the reported solubility data [2,4–8] scatter considerably.

Consequently in this work, for the first time, the dissolution enthalpies of anhydrous uric acid and uric acid dihydrate were determined calorimetrically in a

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PII: S0040-6031(00)00492-5

systematic study. Care was taken to minimise the experimental uncertainties resulting from the difficulties mentioned above. It is thus expected that the results obtained here will contribute to a sound thermodynamic database for this biologically important system.

2. Experimental

2.1. General considerations

The solubility of uric acid anhydrate and dihydrate can be calculated as a function of the H^+ concentration from the relation $[H_2U]_{tot}=K_s(1+(K_1/[H^+]))$ employing the solubility, K_s, and first dissociation, K_1, constants given in Table 1 [2]. Although these constants were determined in NaCl solutions of ionic strength $I=0.15$ mol dm^{-3}, it was shown that they can be used to predict solubilities in a variety of salt solutions in the ionic strength range of 0.15–0.30 mol dm^{-3} and in artificial urine [3]. These calculations show that solubilities are very low at $pH<pK_1$; however, for $pH>pK_1$, $\log([H_2U]_{tot})$ increases linearly with pH. Consequently, the enthalpy measurements should be performed in a pH range of about 7–9, in order to (i) achieve a significant thermal effect since in that pH range a larger amount of sample can be dissolved and (ii) have a defined final state of predominantly hydrogenurate ions in solutions. To avoid precipitation of sodium hydrogenurate monohydrate at higher pH [2], sodium-free Tris–buffer solutions were chosen for the enthalpy measurements. The experimental conditions of this study are summarised in Table 2.

2.2. Materials

Uric acid anhydrate ($C_5H_4N_4O_3$, high-purity ≥99%), purchased from Aldrich, was used directly. The preparation of uric acid dihydrate is described in [2], however in this study, the sample was not used immediately but washed with acetone and dried. These two substances were characterised by X-ray diffraction analysis, scanning electron microscopy and thermogravimetric analysis.

Table 1
Solubility equilibrium constants of uric acids at $I=0.15$ mol dm^{-3} NaCl [2]

t (°C)	pK_s ($H_2U\cdot 2H_2O$)	pK_s (H_2U)	pK_1
25	3.55±0.01	3.76±0.03	5.26±0.04
32	3.35±0.01	3.63±0.01	5.21±0.01
37	3.21±0.01	3.49±0.03	5.19±0.04
42	3.08±0.01	3.41±0.01	5.13±0.01

Table 2
Experimental conditions of dissolution enthalpy determinations (70 g Tris–buffer solution was used throughout)

Solute	t (°C)	m (mg)	pH$_{ini}$ at 25°C	I (mol dm^{-3})
H_2U	25	40	7.9	0.035
	37	40, 80, 100	7.9	0.035–0.040
			8.9	0.010
$H_2U\cdot 2H_2O$	25	40	7.2	0.045
			7.9	0.035
			8.9	0.010

Buffer solutions (pH=7.2, 7.9 and 8.9) were prepared with tris-(hydroxymethyl)-aminomethane ($C_4H_{11}NO_3$, abbreviated as Tris, ultra pure, Biomol) and HCl (standard solution ampoules, Fluka and Riedel-de Haën) according to [9].

Original LKB ampoules (LKB Stockholm, Sweden) were used throughout. Beeswax adhesive (colophony: beeswax=1:1, VEB Jenapharm Laborchemie Apolda) and silicone stoppers (SCRINTEC 600, SCRINT GmbH) were employed to seal ampoules.

2.3. Equipment

All calorimetric measurements were carried out in LKB precision calorimetry systems 8700 and 8710 (hereafter referred to as LKB 1 and 2, respectively) which have been modified by using 70 ml reaction vessels instead of the original 100 ml vessels. The output data were recorded graphically by Ω-time recorders (endim 621.02, VEB Messapparatewerk Schlotheim) and digitally by computers. The enthalpy values were evaluated using a well-tested program written on 'MATLAB' basis (The MathWorks, Inc.) with optimisation of the deconvolution parameters [10]. The original LKB ampoules and substances were weighed exactly with a microbalance (MP 20, 20 g/0.01 mg, VEB Feinmechanische Werkstätten Freiberg). The reaction vessels and Tris-buffer solution were weighed with an electronic balance (AC 2115,

Table 3
Dissolution enthalpies of H_2U in Tris–buffer solution with initial pH=7.9

t (°C)	LKB	Stirrer speed	$m(H_2U)$ (mg)	$\sum \Delta_r H$ (kJ mol^{-1})	$(\Delta_r H_1+\Delta_r H_2)$ (kJ mol^{-1})
37	2	H	39.66_4	9.14_5	56.04
37	2	H	42.58_3	9.26_0	56.16
37	2	M	44.12_2	9.18_8	56.09
37	2	H	44.98_8	9.16_2	56.06
37	1	H	84.21_6	8.89_8	55.80
37	2	H	84.63_5	9.29_9	56.20
37	1	H	85.75_7	9.12_6	56.03
37	1	H	95.85_3	9.47_5	56.38
37	2	M	101.77_7	9.21_3	56.11
37[a]	2	H	49.31_0	9.23_0	56.13
25	2	H	37.15_4	9.10_0	56.70
25	2	H	40.46_8	9.17_8	56.78
25	2	H	40.99_4	9.17_5	56.78
25	2	H	42.69_5	8.69_5	56.30
				9.15±0.17[b]	56.25±0.36[b,c]

[a] Initial pH=8.9.
[b] ±1σ.
[c] Uncertainty of Tris protonation enthalpy [15] included.

210 g/0.1 mg, Sartorius). pH values and temperatures of the Tris-buffer solution were measured simultaneously with a pH meter (Knick 763 Multi-Calimatic).

2.4. Preparation for measurements

The performance of all equipment and materials used in this work were checked for their reliability and precision before the measurements of interest were carried out. First of all, the breaking enthalpy of the original LKB ampoules was measured and found to be negligible. Furthermore, the overall accuracy of the two calorimeters used independently for all measurements was tested with a standard substance. For this purpose, the enthalpy of dissolution in H_2O of ultra pure KCl, which was prepared and characterised as described by Günther et al. [11], was measured at 37°C. About 0.002 mol KCl was weighed exactly and the appropriate mass of bidistilled water was added to make a ratio of 1 mol KCl:2000 mol H_2O. The result obtained was $\Delta_{sol}H_{310.15}=(15.62\pm0.18)$ kJ mol^{-1} which is in good agreement with the calculated value $\Delta_{sol}H_{310.15}=15.82$ kJ mol^{-1} (using data given in [12]). This verified that the performance of the calorimeters was reliable.

2.5. Procedure of experiment and calibration

The reaction vessel was thermostatted in the calorimeter and the test solution was agitated under constant stirrer speed (either medium, M or high, H, see Tables 3 and 4) for at least 15 h to attain thermal equilibrium between the reaction vessel and the thermostat bath. Then the reaction was started by breaking the ampoule containing the sample. Since uric acids dissolved within 10 min (dihydrate) to 20 min (anhydrate), long fore and after-periods were recorded. Fore-periods ran for about 1–2 h, main and after-periods for more than 4 h in order to determine reliably the end of the main-periods as well as the cooling constants. After that period of time, the temperature (converted from the thermistor resistance) of the reaction vessel had approached a constant value.

Calibration was carried out immediately after every experiment by means of electric heating. After the thermal equilibrium between reaction vessel and thermostat bath was re-attained, the fore-period of calibration ran for about 1 h. Care was taken that the shape of the resistance versus time curve of calibration was as similar as possible to that of the experiment. The heating power was 50 mW and heating time was chosen in the range of 25–110 s depending on the

Table 4
Dissolution enthalpies of $H_2U{\cdot}2H_2O$ in Tris–buffer solution at t=25°C

LKB	Stirrer speed	pH_{ini}	$m(H_2U{\cdot}2H_2O)$ (mg)	$\sum \Delta_r H$ (kJ mol^{-1})	$(\Delta_r H_1+\Delta_r H_2)$ (kJ mol^{-1})
2	H	7.2	37.52_6	16.81_6	64.42
2	H	7.2	39.16_9	16.85_1	64.45
1	M	7.9	40.96_7	17.08_4	64.68
2	H	7.9	41.12_6	17.26_2	64.86
1	M	7.9	41.47_2	16.71_1	64.31
2	H	7.9	42.79_5	16.76_7	64.37
2	H	8.9	41.31_4	16.75_1	64.35
2	H	8.9	43.53_0	16.86_1	64.46
				16.89±0.18[a]	64.49±0.20[a,b]

[a] $\pm 1\sigma$.

[b] Uncertainty of Tris protonation enthalpy [15] included.

heat effect of the corresponding experiment. Main and after-periods ran for more than 2 h.

The change of the thermistor resistance during both experiment and calibration was measured and digitally recorded at 20 s intervals by a computer. The pH of the buffer solution was measured at the reaction temperature before and after each experiment.

3. Results and discussion

3.1. Dissolution enthalpies measured calorimetrically

All calorimetric results of total dissolution enthalpies in Tris–buffer solutions, $\sum \Delta_r H$, are shown in Tables 3 and 4. From Table 3, it can be seen that on increasing the mass of anhydrous uric acid from 40–100 mg, no significant difference in dissolution enthalpies was detected. Thus in this range, the dissolution enthalpy of anhydrous uric acid is independent of concentration. Also, no temperature dependence was observed between data obtained at 25 and 37°C. The heat capacity, $\Delta_r C_p$, of reaction of anhydrous uric acid with Tris–buffer solution is obviously negligible in such a small temperature range.

It can be seen from Table 4 that on changing the pH of the Tris–buffer solution from 7.2 to 8.9, the dissolution enthalpies obtained in different buffer solutions are in good agreement with each other. Therefore, the dissolution enthalpies of uric acid dihydrate, as well as anhydrous uric acid, are independent of the pH of initial solution in the range 7.2<pH<8.9, since in this pH range, hydrogenurate is the predominant species in both cases. Moreover, as the enthalpies of dehydration, in the present case corresponding to $H_2U{\cdot}2H_2O(s) \rightarrow H_2U(s)+2H_2O(aq)$, are always positive [13], the enthalpies of dissolution should become progressively more endothermic with extent of hydration. This rule, which has already been noticed 120 years ago [14], was actually confirmed in this study.

In Tables 3 and 4, the results are the total enthalpy changes ($\sum \Delta_r H$) involving the reactions (1–3) given below (taking anhydrous uric acid as example):

$$H_2U(s) \rightarrow H_2U(aq), \quad \Delta_r H_1 \tag{1}$$

$$H_2U(aq) \rightarrow H^+(aq) + HU^-(aq), \quad \Delta_r H_2 \tag{2}$$

$$\mathrm{Tris}(aq) + H^+(aq) \rightarrow \mathrm{Tris\,H}^+(aq), \quad \Delta_r H_3 \tag{3}$$

In order to obtain the sum of the enthalpies of dissolution ($\Delta_r H_1$) and dissociation ($\Delta_r H_2$), the contribution from protonation of Tris ($\Delta_r H_3$) should be subtracted from the total value. Since $\Delta_r H_3$ depends only slightly on the ionic strength, the corresponding values for I=0.1 mol dm^{-3} NaCl, $\Delta_r H_3=-(47.6\pm0.1)$ and $\Delta_r H_3=-(46.9\pm0.2)$ kJ mol^{-1} for t=25 and 37°C, respectively, were taken from a comprehensive review [15]. The resulting values of $(\Delta_r H_1+\Delta_r H_2)$ are also given in Tables 3 and 4. The uncertainties of these quantities reflect the internal precision of these measurements while the overall accuracy of the batch calorimetric method applied is estimated to 1–2%.

3.2. Dissolution enthalpies derived from temperature dependence of equilibrium constants

According to the fundamental thermodynamic relation

$$\Delta_r H^0 = -R\left[\frac{\partial \ln K^0}{\partial(1/T)}\right] \tag{4}$$

the total enthalpy change of dissolution and dissociation of uric acids (anhydrous and dihydrate) can also be derived from the temperature dependence of equilibrium constants of these reactions (in Eq. (4), $\Delta_r H^0$ is the standard enthalpy change of the reaction, R the universal gas constant and T is the absolute temperature). However, our previous solubility study [2] was performed at constant ionic strength I=0.15 mol dm^{-3} NaCl, thus yielding constants K^I which are expressed in terms of concentrations rather than activities. Following e.g. Williamson's [16] derivations of the temperature dependence of solubilities, and modifying these for constant I, leads to the result

$$\Delta_r H^I = -R\left[\frac{\partial \ln K^I}{\partial(1/T)}\right] \tag{5}$$

where $\Delta_r H^I$ is the enthalpy of reaction valid for ionic strength I. This quantity is given by $\Delta_r H^I = \Delta_r H^0 + \nu L_2^I + x L_1^I$, where ν and x are the moles of ions (ν=2) and water (x=0 or 2) resulting from the dissolution of 1 mol of the solid substance, whereas L_2^I and L_1^I are the relative partial molar enthalpies of solute and solvent at ionic strength I, respectively. L_1^I can certainly be neglected, and for the ionic strength range (I=0.010–0.045 mol dm^{-3}) investigated in the present calorimetric study, the change in 2 L_2^I for a 1:1 electrolyte is estimated to ca. 0.2 kJ mol^{-1} which is also within the experimental error. This explains the fact that no significant pH, and hence ionic strength dependence of the present results, was detected.

Table 5
Enthalpies of dissolution and dissociation of uric acids obtained from solution calorimetry and temperature dependence of equilibrium constants

Reaction	$\Delta_r H$ (kJ mol^{-1})	Reference
$H_2U(s) \rightarrow H_2U(aq)$	39.4±2.0	[2]
	23.9[a]	[4]
	39.7±1.5	[5]
	37.0±0.8	[6]
$H_2U \cdot 2H_2O(s) \rightarrow H_2U(aq)+2H_2O(aq)$	49.8±0.2	[2]
	47.3±2.7	[6]
	31.8[a]	[7]
$H_2U(aq) \rightarrow H^+(aq)+HU^-(aq)$	14.5±0.9	[2] (I=0.15 mol dm^{-3})
	14.4[a]	[4] (Solubility)
	20.6±1.3	[4] (Spectroscopy)
	18.3±0.8	[5] (Conductivity)
	17.2±0.1	[8] (emf)
$H_2U(s) \rightarrow H^+(aq)+HU^-(aq)$	56.3±0.4	Calorimetry, this work
	53.9±2.2	[2]
	38.3[a]	[4] (Solubility)
	44.5	[4] (Spectroscopy)
	58.0±1.7	[5]
	55.3±1.1	[5,6]
$H_2U \cdot 2H_2O(s) \rightarrow H^+(aq)+HU^-(aq)+2H_2O(aq)$	64.5±0.2	Calorimetry, this work
	64.3±0.9	[2]
	65.6±2.8	[5,6]
	50.1	[5,7]

[a] Two data points only.

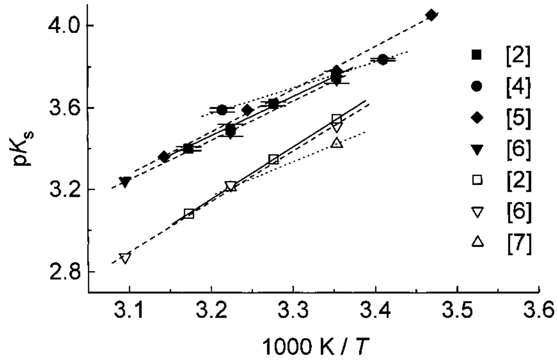

Fig. 1. Temperature dependence of uric acid solubility constants. Solid symbols: anhydrous uric acid, open symbols: uric acid dihydrate. The lines were calculated by linear regression and the corresponding enthalpies of reaction are given in Table 5.

The reaction enthalpies calculated from the solubility equilibrium constants evaluated in our previous work [2] (listed in Table 1), as well as from those reported in literature are presented in Table 5 and shown in Figs. 1 and 2. From Tables 1 and 5 it is obvious that the calculated enthalpy change is very sensitive even to small changes in the equilibrium constants, as the small uncertainties of these constants cause large uncertainties in enthalpy. The change in 2 L_2^J for a 1:1 electrolyte from the ionic strength range investigated in the present calorimetric study to I=0 [5,6,8] and to I=0.15 mol dm^{-3} [2] is estimated to ca. 0.3 and 0.5 kJ mol^{-1}, respectively, which is within the uncertainty of most of the enthalpy values reported in Table 5. It can thus be concluded that the dissolution enthalpies derived form the solubility equilibrium constants of our previous work [2] as well as from [5,6] are thermodynamically consistent with the present calorimetric results, while the uric acid anhydrate and dihydrate solubilities of [4,7], respectively, have incorrect temperature dependencies.

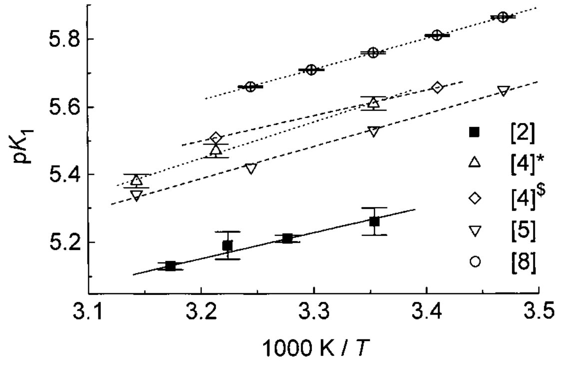

Fig. 2. Temperature dependence of the first dissociation constant of aqueous uric acid. The corresponding enthalpies of reaction are given in Table 5. The values indicated by (*) and ($) were obtained by spectrophotometric and solubility measurements, respectively.

4. Conclusions

1. Despite the very low solubilities of anhydrous uric acid and uric acid dihydrate, the total enthalpy changes of dissolution and dissociation of these substances were successfully determined by direct calorimetric measurements.
2. These quantities were found to be independent of temperature between 25 and 37°C, pH from 7.2 to 8.9, ionic strength in the range I=0.010–0.045 mol dm^{-3} and uric acid concentration from 3.4 to 8.5 mmol dm^{-3}.
3. The thermodynamically consistent results obtained from direct calorimetric measurements and from the temperature dependence of equilibrium constants [2] have shown that both methods used in our laboratories are accurate and reliable.
4. The thermodynamic data provided by this work are considered to be helpful for the further investigation of crystal deposition diseases.

Acknowledgements

The authors would like to thank Ms. Dagmar Süßner (Technical University of Freiberg) for her help with the calorimetric measurements, Ms. W. Dolezel (Veitsch-Radex AG, Leoben) for performing the X-ray diffraction analyses, Mr. G. Hawranek (University of Leoben) for taking scanning electron micrographs and Mr. M. Jobst (Technical University of Freiberg) for performing the thermogravimetric analyses. Financial support by the Austrian National Bank (Jubiläumsfondsprojekte Nos. 5683 and 6850) and the ERASMUS/SOCRATES program of the European Union is gratefully acknowledged.

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