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Solid-Liquid Equilibrium in the System 2-Keto-*L*-Gulonic Acid + *L*-Ascorbic Acid + Water

The solid-liquid equilibrium (SLE) in the ternary system 2-keto-*L*-gulonic acid (HKGA) + *L*-ascorbic acid (vitamin C) + water was investigated experimentally at temperatures between 276 K and 308 K at ambient pressure, i.e., under conditions that are of particular interest for industrial applications. Phase diagrams with one eutonic point were obtained for all temperatures. The dissociation constant and the solubility constant of vitamin C were determined as a function of temperature. Based on an extended version of the Debye-Hückel theory, a physicochemical model was developed that describes the SLE in the ternary system. The agreement between experimental data and results from the model is excellent.

Supporting Information available online

Keywords: Debye-Hückel theory, 2-Keto-*L*-gulonic acid, Solid-liquid equilibrium, Thermodynamic model, Vitamin C

Received: May 16, 2018; *revised:* June 20, 2018; *accepted:* August 30, 2018

DOI: 10.1002/ceat.201800240

1 Introduction

L-Ascorbic acid (vitamin C) is produced on a large scale as it is an important product for several industries, such as food, animal nutrition, and pharmaceutical industry. The first synthesis route was proposed by Reichstein and Grüssner [1] in 1934, which was the predominant production process for vitamin C for several decades. In recent years, several improved processes have been developed that are based on fermentation [2–5]. Today, most of the vitamin C is produced by fermentation [3]. In the original process from Reichstein and Güssner as well as in most other processes, 2-keto-*L*-gulonic acid (HKGA) is the key intermediate. In the fermentation process, it is produced biotechnologically. Since HKGA is an acid, the pH has to be adjusted during fermentation. This is usually done by adding basic sodium-containing components [6–10].

Crystallization is an interesting option for the downstream processing of HKGA. However, different species may precipitate from the solutions depending on the concentration of sodium ions and the pH of the solution. From strongly acidic solutions, the acid form HKGA precipitates. With increasing pH, more and more of the crystallizing species is the sodium salt sodium-2-keto-*L*-gulonate (NaKGA). From neutral solutions, NaKGA precipitates exclusively. Both species crystallize exclusively as monohydrates from solution at ambient pressure: HKGA·H_2O and NaKGA·H_2O, respectively. The solid-liquid equilibrium (SLE) of the system HKGA + NaKGA + water was subject of a recently published study of our group [11].

Besides yield losses in the HKGA production process due to the precipitation of its sodium salt, HKGA may also be chemically degraded. At elevated temperatures and strongly acidic conditions, HKGA is converted to vitamin C [12], which may arise during downstream processing of HKGA. Therefore, the solid-liquid phase diagram of the system HKGA + vitamin C + water is of great importance for the conceptual process design of crystallization units for both, the downstream process of HKGA and the downstream process of vitamin C.

Solubility data for pure HKGA in water are given in an earlier work of our group [11], the data for pure vitamin C in water at temperatures between 273 K and 373 K are available in the literature [13–15]. However, no information on the solid-liquid equilibrium in the ternary system HKGA + vitamin C + water has been reported so far. Therefore, in the present work, the phase diagram of the system HKGA + vitamin C + water was determined experimentally in the temperature range 276–308 K at ambient pressure, i.e., under conditions that are of particular interest for industrial applications. Furthermore, the dissociation constant and the solubility constant of vitamin C were determined as a function of the temperature. Based on results of the present work and using data on the equilibrium constants of HKGA from a previous work of our group [11], a thermodynamic model of the SLE in the studied system

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was developed. It is based on an extended version of the Debye-Hückel theory. This approach was already shown to yield good results for describing the solid-liquid equilibrium in the system HKGA + NaKGA + water [11] and so it does for the system HKGA + vitamin C + water.

Table 1. Suppliers and purities of the chemicals used in this work.

Chemical name (abbreviation)	Formula	Supplier	Purity[a)]
2-Keto-*L*-gulonic acid (HKGA)	$C_6H_{10}O_7$	Cargill	> 0.98 g g^{-1}
L-Ascorbic acid (vitamin C)	$C_6H_8O_6$	Sigma-Aldrich	> 0.99 g g^{-1}
Sulfuric acid 1 M	H_2SO_4	Carl Roth	± 2 %

[a)] Supplier specification.

2 Materials and Methods

2.1 Materials

Anhydrous HKGA was obtained from Cargill. *L*-Ascorbic acid (vitamin C) was purchased from Sigma-Aldrich. For all experiments, ultrapure water was used, produced with a Milli-Q apparatus (Elix Essential 5, Millipore). Tab. 1 gives an overview of the chemicals used in this work, including sulfuric acid, which was used for eluent preparation for the analysis.

2.2 Experimental Procedure

The experimental procedure was the same as described in [11]. Suspensions containing HKGA, vitamin C, and water were prepared gravimetrically with a laboratory scale (AG204, Mettler Toledo) by pouring about 5 g of water into 30-mL glass vessels and adding 5–10 g of a mixture of the solids HKGA and vitamin C. Thereby, the ratio of HKGA to vitamin C was varied to achieve samples with high contents of HKGA, samples with high contents of vitamin C, and samples with similar contents of both solids. Also, binary samples containing water and only HKGA or only vitamin C were prepared. After the preparation of the mixtures, a solid phase was observed in all vessels. The vessels were sealed and equilibrated at constant temperature in an incubator (ICP600, Memmert) for three days. The solid phase was kept suspended during the equilibration by magnetic stirring. The temperature was measured with a calibrated PT100 thermometer connected to a digital multimeter (5017, Prema) with an accuracy of ± 0.1 K.

After equilibration, the stirring was stopped to allow the solid phase to settle. Samples were drawn from the clear supernatant using syringes with syringe filters (5 µm pore size, Rotilabo, Carl Roth), which had been thermostated previously at the temperature of the experiment. The samples were gravimetrically diluted with water using the laboratory scale and analyzed by high-performance liquid chromatography (HPLC; 1200 series, Agilent). For the separation of the components, a weak anion-exchange column (Hi-Plex H, 7.7×300 mm, Agilent) with 10 mM sulfuric acid as eluent was used at room temperature. The concentrations of HKGA and vitamin C were determined with a refractive index detector (1260 Infinity, Agilent).

To elucidate the stoichiometry of the precipitated species, the solid phase was separated from the liquid by filtration, dried in a drying chamber at 323 K and ambient pressure, dissolved in water, and analyzed as described before. In preliminary experiments, it was confirmed that an equilibration time of three days is sufficient to reach the solid-liquid equilibrium in the investigated system under the studied conditions. For the determination of the dissociation constant of vitamin C as a function of the temperature, a liquid sample of vitamin C and water with a defined concentration was prepared gravimetrically. The pH of this sample was measured at different temperatures in the studied range with a pH meter (780, Metrohm). The chemical stability of the solutes during the equilibration was proven by ^{13}C NMR spectroscopy using a 400-MHz NMR spectrometer (Avance, Bruker). For details, see the Supporting Information.

3 Model

The model of the SLE in the system HKGA + vitamin C + water is presented schematically in Fig. 1. The model takes into account the dissociation of HKGA and vitamin C in the liquid phase as well as the autoprotolysis of water in the liquid phase. Since HKGA and vitamin C (also labeled as HAsc in the following) are weak electrolytes, the two solutes are present in both, the dissociated form, i.e., $H^+ + KGA^-$ and $H^+ + Asc^-$, respectively, and the undissociated form, i.e., HKGA and HAsc, respectively. The degree of dissociation of HKGA and vitamin C is characterized by the dissociation constants K^D_{HKGA} [1)] and K^D_{HAsc}, respectively. The equilibrium constant of the autoprotolysis of water (H_2O) is $K^D_{H_2O}$. The solid phase in equilibrium can either be pure HKGA monohydrate (HKGA·H_2O) or pure vitamin C (HAsc) or both. The solid-liquid phase equilibrium is characterized by the solubility constants $K^S_{HKGA\cdot H_2O}$ and K^S_{HAsc}.

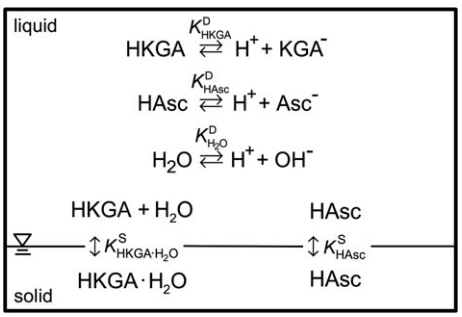

Figure 1. Scheme of the model of the solid-liquid equilibrium in the ternary system HKGA + vitamin C (HAsc) + water.

1) List of symbols at the end of the paper.

The thermodynamic equilibrium constants are defined by Eqs. (1)–(5):

$$K^{D}_{HKGA} = \frac{m_{H^+} m_{KGA^-}}{m_{HKGA} m_0} \frac{\gamma_{H^+}\gamma_{KGA^-}}{\gamma_{HKGA}} \quad (1)$$

$$K^{D}_{HAsc} = \frac{m_{H^+} m_{Asc^-}}{m_{HAsc} m_0} \frac{\gamma_{H^+}\gamma_{Asc^-}}{\gamma_{HAsc}} \quad (2)$$

$$K^{D}_{H_2O} = \frac{m_{H^+} m_{OH^-}}{m_0^2} \frac{\gamma_{H^+}\gamma_{OH^-}}{a_{H_2O}} \quad (3)$$

$$K^{S}_{HKGA\cdot H_2O} = \frac{m_{HKGA}}{m_0} a_{H_2O}\gamma_{HKGA} \quad (4)$$

$$K^{S}_{HAsc} = \frac{m_{HAsc}}{m_0}\gamma_{HAsc} \quad (5)$$

The variables m_k and γ_k represent the molality and the activity coefficient of species k in the liquid phase, respectively; m_0 is defined as 1 mol kg^{-1}. The variable a_{H_2O} denotes the activity of water in the liquid phase, which is normalized according to Raoult's law, whereas the activity coefficients of all other components (the solutes) are normalized similar to Henry's law. The activity coefficients γ_i of the ionic species i in the liquid phase are calculated as a function of the ionic strength I in the liquid phase using an extended version of the Debye-Hückel theory [16], which is given in Eqs. (6)–(8):

$$\ln\gamma_i = -A^{\Phi}\left(\frac{\sqrt{I}}{1+b\sqrt{I}} + \frac{2}{b}\ln\left(1+b\sqrt{I}\right)\right) \quad (6)$$

$$A^{\Phi} = \frac{1}{3}\left(2\pi N_A \rho_{H_2O} m_0\right)^{\frac{1}{2}}\left(\frac{e^2}{4\pi\varepsilon_0\varepsilon_{H_2O}kT}\right)^{\frac{3}{2}} \quad (7)$$

$$I = \frac{1}{2}\sum_i \frac{m_i}{m_0} z_i^2 \quad (8)$$

The nomenclature of the symbols is as follows: b is the Debye-Hückel parameter, set to 1.2 as suggested by Pitzer [16], N_A is Avogadro's number, ρ_{H_2O} denotes the specific density of water, e is the absolute elementary charge, ε_0 is the vacuum permittivity, ε_{H_2O} means the relative permittivity of water, k is Boltzmann's constant, T is the absolute temperature, and z_i denotes the charge number of ion i. The activity coefficients of the neutral species HKGA and HAsc are assumed to be unity and the activity of water is calculated using the Gibbs-Duhem equation.

The equilibrium constant of the autoprotolysis of water ($K^{D}_{H_2O}$) was taken from the literature [17]. The equilibrium constants of the dissociation and the solubility of HKGA in water, i.e., K^{D}_{HKGA} and $K^{S}_{HKGA\cdot H_2O}$, respectively, were taken from a previous work of our group [11]. The equilibrium constants of the dissociation and the solubility of vitamin C in water, namely, K^{D}_{HAsc} and K^{S}_{HAsc}, respectively, were fitted to experimental data of the present work. Thereby, the values of K^{D}_{HAsc} were determined from experimental data on the pH of an aqueous solution with a known concentration of pure vitamin C at different temperatures (cf. Supporting Information), and the values of K^{S}_{HAsc} were assessed from experimental data on the solubility of pure vitamin C in water at different temperatures.

4 Results and Discussion

The experimental SLE data for the system HKGA + vitamin C + water are presented in Tab. 2.

The solubility of pure vitamin C in water is plotted in Fig. 2 as a function of the temperature. The experimental results of this work agree well with the solubility data of vitamin C reported in the literature [13–15].

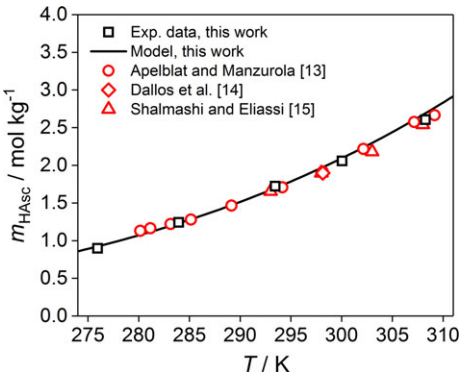

Figure 2. Solubility of vitamin C (HAsc) in molality m in water as a function of the temperature T. Results from this work and data from the literature [13–15].

The values of K^{D}_{HAsc} and K^{S}_{HAsc} determined from experimental data of this work are indicated in Fig. 3 in a logarithmic plot over the inverse temperature. Linear relations are found for

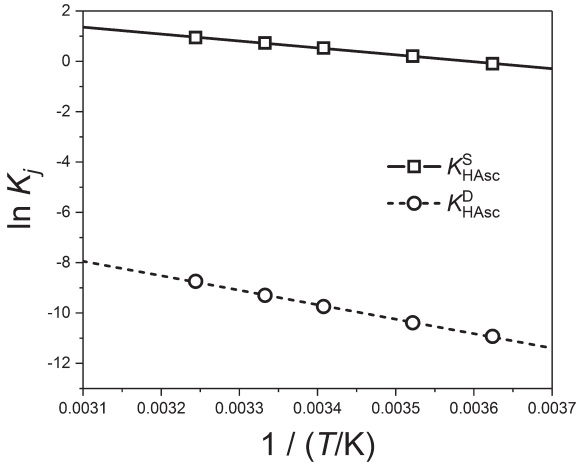

Figure 3. Equilibrium constants K_j in a logarithmic plot over the inverse temperature T. Symbols: calculated from experimental data of this work. Lines: model.

Table 2. Experimental SLE data for the ternary system HKGA + vitamin C + water at ambient pressure.

x_{HKGA} [g g^{-1}]	x_{HAsc} [g g^{-1}]	Solid phase	x_{HKGA} [g g^{-1}]	x_{HAsc} [g g^{-1}]	Solid phase
T = 276.0 K					
0.000	0.137	B	0.211	0.103	A + B
0.113	0.127	B	0.212	0.104	A + B
0.140	0.133	B	0.212	0.103	A + B
0.206	0.100	A + B	0.218	0.103	A + B
0.209	0.104	A + B	0.220	0.076	A
0.209	0.102	A + B	0.243	0.000	A
0.211	0.104	A + B			
T = 284.0 K					
0.000	0.180	B	0.238	0.122	A + B
0.059	0.176	B	0.240	0.123	A + B
0.089	0.153	B	0.240	0.116	A + B
0.131	0.148	B	0.241	0.124	A + B
0.179	0.136	B	0.243	0.125	A + B
0.234	0.118	A + B	0.262	0.057	A
0.238	0.123	A + B	0.283	0.000	A
T = 293.5 K					
0.000	0.233	B	0.281	0.150	A + B
0.069	0.207	B	0.281	0.128	A
0.200	0.176	B	0.303	0.064	A
0.240	0.156	B	0.337	0.000	A
0.260	0.151	B			
T = 300.1 K					
0.000	0.266	B	0.263	0.181	B
0.062	0.250	B	0.299	0.160	A + B
0.115	0.225	B	0.303	0.165	A + B
0.169	0.211	B	0.328	0.113	A
0.231	0.195	B	0.369	0.000	A
T = 308.3 K					
0.000	0.315	B	0.337	0.182	A + B
0.052	0.297	B	0.372	0.105	A
0.122	0.289	B	0.398	0.058	A
0.196	0.240	B	0.415	0.000	A
0.295	0.201	B			

The solid phase is either HKGA monohydrate (A) or vitamin C (B) or both (A + B). The composition of the liquid phase in equilibrium is specified using the mass fractions x_{HKGA} and x_{HAsc} of the solutes HKGA and vitamin C, respectively. The standard uncertainties are: temperature $u(T)$ = 0.1 K, mass fraction $u(x)$ = 0.007 g g^{-1}.

both equilibrium constants. Thus, the temperature dependence of K^{D}_{HAsc} and K^{S}_{HAsc} is modeled using the van't Hoff equation assuming values for the enthalpy change Δh_j and the entropy change Δs_j that are independent of the temperature, cf. Eq. (9).

$$\ln K_j = -\frac{\Delta h_j}{R}\frac{1}{T} + \frac{\Delta s_j}{R} \tag{9}$$

where R is the universal gas constant. The results for the parameters Δh_j and Δs_j from the fit are given in Tab. 3. The values of the corresponding parameters for K^{D}_{HKGA}, $K^{S}_{HKGA\cdot H_2O}$, and $K^{D}_{H_2O}$ were taken from [11]. The solubility of vitamin C calculated with the model based on these data is displayed as a line in Fig. 2. There is excellent agreement with the experimental results of this work as well as with the solubility data from the literature [13–15].

Table 3. Parameters for the correlation of the temperature dependence of the equilibrium constants in Eq. (9).

Equilibrium constant	Δh_j [kJ mol^{-1}]	Δs_j [J mol^{-1}K^{-1}]	Ref.
K^{D}_{HAsc}	47.8	82.3	This work
K^{S}_{HAsc}	22.8	82.1	This work
K^{D}_{HKGA}	63.7	165.0	[11]
$K^{S}_{HKGA\cdot H_2O}$	15.1	58.7	[11]
$K^{D}_{H_2O}$	52.3	–99.2	[17]

The topology of the solid-liquid phase diagram of the ternary system HKGA + vitamin C + water is the same for all investigated temperatures. As an example, Fig. 4 shows the phase diagram for 284 K. The diagram is divided into four regions that meet in one eutonic point. These regions are: L, unsaturated solution; L+A, saturated solution in equilibrium with solid HKGA monohydrate; L+B, saturated solution in equilibrium with solid vitamin C; L+A+B, saturated solution in equilibrium with solid HKGA monohydrate and solid vitamin C. The symbols in Fig. 4 indicate the experimental data of this work for the composition of the liquid phase in equilibrium. The line shows the composition of the liquid phase in SLE calculated with the model, which was adjusted to the experimental results of this work. Excellent agreement between experiment and model is found.

Fig. 5 illustrates the corresponding results for all studied temperatures. The agreement between experimental SLE data and the results calculated with the model is again excellent.

In this work, a simple approach was used to calculate the activity coefficients of the species in the liquid phase, i.e., extended Debye-Hückel theory and the assumption $\gamma_{HKGA} = \gamma_{HAsc} = 1$. This approach is shown to yield sufficiently good results for describing the SLE in the studied system at the studied conditions. However, the experimental data of this work do not allow a deeper validation of the activity coefficient model, since possible errors are veiled by the fit of the equilibrium constants.

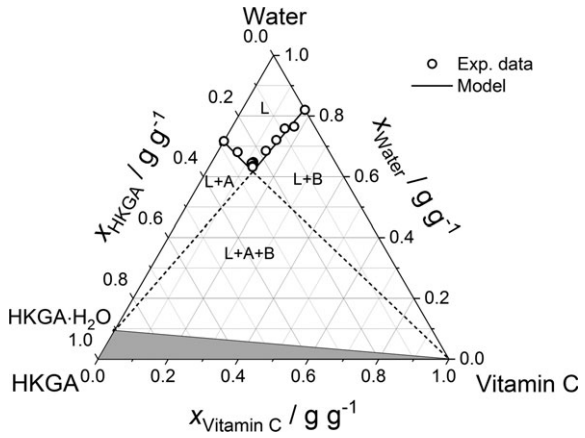

Figure 4. Solid-liquid phase diagram of the system HKGA + vitamin C + water at 284 K and ambient pressure. L, unsaturated solution; L+A, SLE with pure HKGA monohydrate as solid phase; L+B, SLE with pure vitamin C as solid phase; L+A+B, SLE with HKGA monohydrate and vitamin C as solid phase. Symbols: experimental data, this work. Lines: model. In the shaded area, only solid is present. This area was not subject of this study.

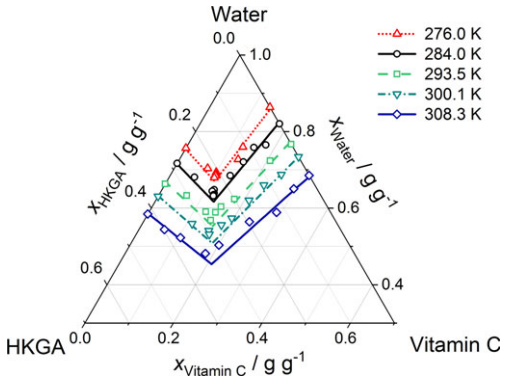

Figure 5. Solid-liquid phase diagram of the system HKGA + vitamin C + water for the studied temperatures at ambient pressure. Symbols: experimental data, this work. Lines: model.

A molality-based equilibrium model, which does not require the calculation of activity coefficients in the liquid phase, is described in the Supporting Information. The description of the SLE of the studied system using the molality-based model is comparable to the results from the activity-based model.

5 Conclusions

L-Ascorbic acid (vitamin C) and its precursor 2-keto-*L*-gulonic acid (HKGA) are produced on a large scale since vitamin C is an important product for different industries. For the conceptual process design of efficient downstream processes for HKGA and vitamin C, the knowledge of the solid-liquid equilibrium (SLE) of the system HKGA + vitamin C + water is crucial, especially if crystallization is considered. Data on this SLE were not available in the literature until now. Therefore, in the present work, the SLE in the system HKGA + vitamin C + water was investigated in the industrially relevant temperature range between 276 K and 308 K at ambient pressure.

The solid-liquid phase diagram shows the same qualitative behavior with one eutonic point for each temperature. A physicochemical model describing the SLE in the system was developed. It is based on an extended version of the Debye-Hückel theory for the calculation of the activity coefficients of the ionic species in the liquid phase. The dissociation of HKGA and vitamin C, which are both weak electrolytes, in the liquid phase is considered with the respective dissociation constants. For vitamin C, the dissociation constant and the solubility constant in water were determined as a function of the temperature from the data of this work.

Acknowledgment

The authors gratefully acknowledge financial support from the European Commission's Framework Program for Research and Innovation Horizon 2020 (2014–2020) under grant agreement no. 636077.

The authors have declared no conflict of interest.

Symbols used

a	[–]	activity
b	[–]	Debye-Hückel parameter
e	[C]	absolute elementary charge
h	[J mol^{-1}]	molar enthalpy
I	[–]	ionic strength
K	[–]	equilibrium constant
k	[J K^{-1}]	Boltzmann's constant
M	[g mol^{-1}]	molar mass
m	[mol kg^{-1}]	molality
N_A	[mol^{-1}]	Avogadro's number
R	[J mol^{-1}K^{-1}]	universal gas constant
s	[J mol^{-1}K^{-1}]	molar entropy
T	[K]	temperature
x	[g g^{-1}]	mass fraction
z	[–]	relative charge number

Greek letters

Δ	[–]	difference, change
γ	[–]	activity coefficient
ε_0	[F m^{-1}]	vacuum permittivity
ε_{H_2O}	[–]	relative permittivity of water
ρ	[kg m^{-3}]	specific density

Sub- and superscripts

0	reference
D	dissociation
i	ionic species
j	equilibrium reaction
k	species
S	solubility

Abbreviations

Asc^-	*L*-ascorbate ion
HAsc	*L*-ascorbic acid (vitamin C)
HKGA	2-keto-*L*-gulonic acid
HPLC	high-performance liquid chromatography
KGA^-	2-keto-*L*-gulonate ion
NaKGA	sodium-2-keto-*L*-gulonate
NMR	nuclear magnetic resonance
SLE	solid-liquid equilibrium

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