STABILITY CONSTANTS OF (RS)-1-ISOPROPYL CITRATE METAL COMPLEXES AND PHASE TRANSITION OF ZINC (RS)-1-ISOPROPYL CITRATE

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The dissociation constants of (RS)-1-isopropyl dihydrogen citrate and the stability constants of its metal complexes with Cu(II), Ca(II) and Zn(II) have been determined in the aqueous state by a potentiometry. The solid-solid phase transition of its Zn(II) complex has been studied by the thermogravimetry/differential thermal analysis (TG/DTA), IR spectrometry and X-ray powder analysis. It was found that the physical properties, this is, the contents of the water molecule of crystallization, the coordination geometries and the crystal structures before and after the transition, were changed.

KEYWORDS dissociation constant; potentiometry; 1-isopropyl dihydrogen citrate; metal complex; phase transition; zinc 1-isopropyl citrate; stability constant; TG/DTA; IR; X-ray powder analysis

Since 1983 isopropyl citrate (IPCit) has been used in Japan as a synergistic antioxidant. IPCit as a food additive is a mixture of citric acid, 1-isopropyl, 2-isopropyl, 1,2-isopropyl, 1,3-isopropyl, and tri-isopropyl citrates.¹⁾ Each component has been purified and its chemical structure been determined.²⁾ Of these components, the (RS)-1-isopropyl dihydrogen citrate (1-IPCit), a staple component of isopropyl citrate, has been obtained with high purity. In this communication, its dissociation constants together with the stability constants of its metal complexes are elucidated. Moreover, the phase transition between zinc (RS)-1-isopropyl citrate (Zn(1-IPCit)) mono- and tetra-hydrates was studied by the thermogravimetry/differential thermal analysis (TG/DTA), IR spectrometry and X-ray powder analysis.

Zn(1-IPCit) was prepared from a mixture of zinc acetate and 1-IPCit in 90% methanol, and crystallized as tetrahydrate from the dilute acetic acid solution.³⁾ The pure 1-IPCit was extracted from its zinc complex with ethyl acetate in aqueous hydrogen chloride solution.⁴⁾

From the potentiometric titration curve in the pH range 2.9~5.5 (Fig. 1. A.), the dissociation constants of 1-IPCit at 25±0.1°C, $\mu = 0.1(\text{KNO}_3)$ were calculated, using Schwarzenbach's equation,⁵⁾ as $\text{p}K_{a1} = 3.24 \pm 0.02$, $\text{p}K_{a2} = 5.05 \pm 0.03$, whereas the

Fig.1. Potentiometric Titration of the 1-IPCit:M = 1:1 Systems by 0.1N NaOH

A: without metal. B: $\text{Ca}(\text{NO}_3)_2$. C: $\text{Zn}(\text{NO}_3)_2$. D: $\text{Cu}(\text{NO}_3)_2$. Conc. of metal: 0.004M. Each soln. contains 0.004M 1-IPCit and 0.1N KNO_3 .

Symbol "a" represents neutralized degree.

corresponding values for citric acid are $pK_{a1} = 2.87$ and $pK_{a2} = 4.35$.⁶⁾ Probably, the steric interaction between the carboxyl and isopropyl groups in 1-IPCit causes its weaker acidity than that in citric acid.

Then the stability constants, $\log K_{MA}$, of its metal complexes with Cu(II), Ca(II) and Zn(II) were also calculated using their potentiometric titration curves (Fig. 1. B-D), and Schwarzenbach's equation. As shown in Table I, it seems likely that the stability constants of the 1-IPCit metal complexes are very similar to those of the citrate metal complexes even at different ionic strength. This indicates that the isopropyl group of 1-IPCit does not participate in the metal coordination as a ligand. This is also supported by the X-ray structural studies⁹⁾ of Zn(1-IPCit) tetrahydrate showing that the 1-IPCit chelates to zinc atoms in a tridentate manner similar to the zinc citrate complex.¹⁰⁾

The weight of Zn(1-IPCit) tetrahydrate decreases gradually with increasing temperature as shown in Fig. 2. The weight losses (TG) at 50°C~110°C and at 120°C~180°C are 15% and 5%, respectively. The weight losses indicate the liberation of the water molecules of crystallization from the crystal. Therefore, Zn(1-IPCit) tetrahydrate loses three water molecules at 100.1°C and the remaining one at 164.5°C. Then it is finally decomposed at 200°C. On the other hand, Zn(1-IPCit) monohydrate¹¹⁾ loses only one water molecule at 164.5°C. By Karl Fischer's method, the moisture contents (%) were: for tetrahydrate, calcd., 19.5 and found, 19.6 and for monohydrate, calcd., 5.7 and found, 7.3 by drying at 100°C for 3 h, or 6.5 by drying together with silicagel for 24 h. The discrepancy may indicate the high hygroscopic character of the monohydrate.

In the IR spectra as shown in Fig. 3, the $\nu(\text{OH})$ of free water at 3560 cm^{-1} found in Zn(1-IPCit) tetrahydrate is not detected in the monohydrate. And each of the peaks, $\nu_{as}(\text{C=O})$ at 1728 cm^{-1} and $\nu(\text{C-O})$ at 1223 cm^{-1} assigned as the esterified carboxyl group in the tetrahydrate was split into two peaks in the monohydrate (the former at 1744 cm^{-1} and 1730 cm^{-1} , and the latter at 1222 cm^{-1} and 1195 cm^{-1}). That is, the (R)- and (S)-isomers in the 6-coordinated octahedral complex polymer are related to each other by the glide plane in the crystal of the tetrahydrate.⁹⁾ The (R)- or (S)-isomers in the monohydrate may chelate with different aquazinc ions and form independent 4-coordinated tetrahedral complexes. This indicates the appearance of two stereochemically complex molecules in the monohydrate crystals.

Table I. Stability Constants of (RS)-1-Isopropyl Citrate Complexes with Various Metals

Metal	pH range	$\log K_{MA}$ ($\log K_{MA}$ of Cit)
Cu^{2+}	2.54~2.85	5.51 ± 0.05 (5.2, $\mu=1^*$)
Ca^{2+}	3.40~4.52	3.28 ± 0.06 (3.16, $\mu=0.16^{**}$)
Zn^{2+}	2.88~3.47	4.31 ± 0.02 (4.69, $\mu=0.16^{**}$)

$\mu=0.1$

*Ref. 7).

**Ref. 8).

Fig.2. TG/DTA Patterns of Zinc (RS)-1-Isopropyl Citrate

- (a) Zn(1-IPCit) tetrahydrate —
(b) Zn(1-IPCit) monohydrate - - -

TG/DTA patterns were determined by Seiko TG/DTA220. Heating rate: 5°C/min, gas flow: N_2 at 200 ml/min, pseudo-sealed sample.

Fig.3. IR Spectra of Zinc (RS)-1-Isopropyl Citrate

- (a) Zn(1-IPCit) tetrahydrate —
(b) Zn(1-IPCit) monohydrate - - -

Arrows represent the separated peaks in its monohydrate.

IR spectra (KBr) were determined using JASCO IR-700.

Fig.4. X-Ray Diffraction Patterns of Zinc (RS)-1-Isopropyl Citrate

(a) Zn(1-IPCit) tetrahydrate
(b) Zn(1-IPCit) monohydrate

Rigaku RINT 1100 was used.
Cu K α : 1.54056Å, 40KV, 40mA,
scanning rate: 4°/min.

Table II. X-Ray Diffraction Peaks of Zinc (RS)-1-Isopropyl Citrate

2 θ (°)	d(Å)	I/I ₀	h k l	d(Å)	2 θ (°)	d(Å)	I/I ₀
(Single crystal data)*							
Zn(C ₉ H ₁₂ O ₇) ₄ H ₂ O (tetrahydrate)				Zn(C ₉ H ₁₂ O ₇)H ₂ O (monohydrate)			
5.35	16.50	24	----	----	4.78	18.47	24
5.90	14.97	100	0 2 0	14.85	5.30	16.66	100
10.45	8.46	3	-1 1 1	8.48	8.00	11.04	2
10.75	8.22	3	----	----	10.68	8.28	5
11.55	7.66	14	-1 2 1	7.60	12.71	6.96	2
11.90	7.43	12	0 4 0	7.42	13.23	6.69	4
13.35	6.63	1	-1 3 1	6.60	14.30	6.19	2
13.90	6.37	3	----	----	15.70	5.64	4
14.90	5.94	2	0 5 0	5.94	19.81	4.48	1
15.40	5.75	14	1 0 0	5.73			
16.10	5.50	4	1 1 0	5.63			
16.50	5.37	8	1 2 0	5.35			
17.40	5.10	2	0 1 1	5.08			
17.85	4.97	17	1 3 0	4.96			
18.85	4.70	1	0 2 1	4.87			
19.35	4.58	2	0 3 1	4.58			
19.80	4.48	4	-2 1 1	4.47			

*Ref.9)

The X-ray diffraction patterns of Zn(1-IPCit) tetra- and mono-hydrate are different from each other as shown in Fig. 4. The reflection angles (2θ), the spacings (d) and the Miller indices ($h k l$) of the X-ray diffractions of both hydrates are summarized in Table II. The strongest peak at $d = 14.97$ Å of the tetrahydrate corresponds to the (0 2 0) reflection of its single crystal, and the d (0 2 0) is just the distance between the Zn atoms related by the screw axis in the tetrahydrate crystal. After the release of three water molecules from the tetrahydrate crystal, the rearrangement of molecules in the monohydrate crystal occurs, where the zinc atom coordinates to one 1-IPCit and also to one water molecule, thus forming a 1:1:1 (Zn:1-IPCit:H₂O) complex. Probably this rearrangement makes the Zn-Zn distance longer (from 14.97 Å to 16.66 Å), because these reflections having these interplanar spacings show the strongest intensities in the tetra- and monohydrate crystals, respectively, as indicated in Fig. 4 and Table II.

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- 3) Mp decomp. >200°C. *Anal.* Calcd. for Zn(II)C₉H₁₂O₇(H₂O)₂·2H₂O: C, 29.25; H, 5.45; N, 0.00. Found: C, 29.16; H, 5.09; N, 0.00.
- 4) Mp 122°C. *Anal.* Calcd. for C₉H₁₄O₇: C, 46.15; H, 6.03; N, 0.00. Found: C, 45.95; H, 6.03; N, 0.00.
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- 11) Mp decomp. >200°C. *Anal.* Calcd. for [Zn(II)C₉H₁₂O₇(H₂O)]: C, 34.25; H, 4.33; N, 0.00. Found: C, 34.00; H, 4.37; N, 0.00

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