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Thermodynamic stability and crystallization behavior of molecular complexes with TEP host

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ABSTRACT

In the crystallization of molecular complex (co-crystal, clathrate complex), polymorphism in regard to the host structure frequently appears. Previously, we studied the release process of the biocide, CMI (5-chloro-2-methyl-4-isothiazolin-3-one) from the molecular complex with TEP (1,1,2,2-tetrakis(4-hydroxyphenyl)ethane) (TEP · 2CMI) in methanol–water mixed solvents. It was clear that the release process of the biocide (CMI) is composed of the transformation from the TEP · 2CMI crystal to a more stable molecular complex crystal with solvent. In this work, the crystallization was performed in the methanol solutions including TEP and CMI at constant temperature (298 K and 308 K). It appeared that two kinds of TEP molecular complexes (TEP · 2CMI and TEP · 2MeOH) crystallize competitively. The crystallization zone of each molecular complex was shown in the map using the coordinates of initial concentrations of TEP and CMI. In the boundary zone both molecular complexes appeared and the transformation from TEP · 2CMI to TEP · 2MeOH was observed, indicating that the stable form is TEP · 2MeOH. Without the boundary zone the corresponding stable form crystallized in each zone. The value of the initial concentration ratio of CMI/TEP for the selective crystallization of TEP · 2CMI was higher at 298 K (1.54) than that (1.36) at 308 K. The equilibrium concentrations of TEP and CMI in the presence of two molecular complexes were expressed using the dissociation constants of the molecular complexes and it was indicated that the dissociation of TEP · 2CMI highly increases with temperature

1. Introduction

It is known that the molecular complex crystals (clathrate, inclusion complex, co-crystal) with various host compounds can be used to separate organic isomers and to improve various properties of guest molecule, e.g. solubility and stability [1–7]. We have previously examined the application of a TEP host (1,1,2,2-tetrakis(4-hydroxyphenyl)ethane) (Fig. 1(a)) to control the release of the biocide CMI (5-chloro-2-methyl-4-isothiazolin-3-one) (Fig. 1(b)) [8,9] in water–methanol mixed solvents. The TEP host forms the molecular complex with CMI in a molar ratio of 2.0 [10,11]. We reported that using the molecular complex (TEP · 2CMI), the CMI concentrations in solutions can be suppressed at a low level and slowly released [12,13]. It was also reported that the release process of the biocide (CMI) from the molecular complex is composed of the transformation from the TEP · 2CMI to a more stable molecular complex crystal with solvent (water and methanol).

In this paper, the crystallization of the molecular complex was performed in methanol solutions including various concentrations of TEP and CMI at constant temperatures. The preferential crystallization behavior of the molecular complex between TEP and CMI was investigated.

2. Experimental

In this paper, the crystallization behavior of the molecular complex was examined at various initial concentrations of TEP (120–250 mmol/l-solvent) and CMI (50–300 mmol/l-solvent) in methanol solutions. The initial concentrations of TEP and CMI were controlled by adding certain amount of solids of TEP and TEP · CMI to MeOH (80 ml). The suspended solution was heated up to about 338 K to dissolve the solids completely, and then the solution was rapidly cooled to the crystallization temperature (298 K and 308 K). The crystallization was carried out at a constant temperature under a constant stirring rate (90 rpm) with an impeller. The slurry was periodically sampled and filtrated, and then the structural change of the crystals was examined using an X-ray diffraction instrument (XRD) (RINT 2200, Rigaku Corporation). Concentrations of TEP and CMI in

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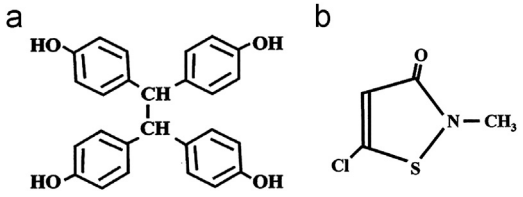

Fig. 1. TEP (a) and CMI molecules (b).

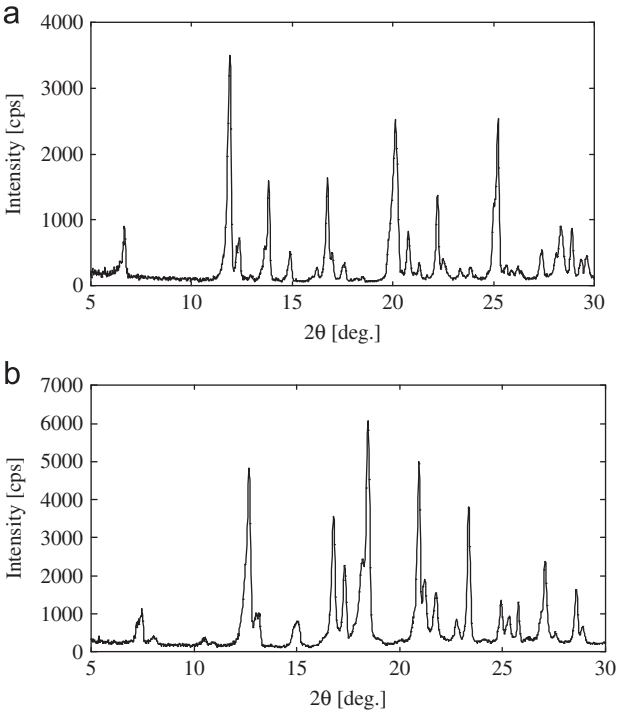

Fig. 2. (a) XRD pattern of TEP · 2CMI obtained at 180 mmol/l-solvent of TEP and at 300 mmol/l-solvent of CMIand (b) XRD pattern of TEP · 2MeOH obtained at 180 mmol/l-solvent of TEP and at 180 mmol/l-solvent of CMI.

solutions were analyzed by HPLC (Shimazu LC). The thermal analysis (TG) (Seiko Instruments TG/DTA 220) was carried out by increasing the rate of temperature, 10 K/min. The composition of crystals was also determined by HPLC using the solution after dissolving the crystals (5 mg) in ethanol (20 ml).

3. Results and discussion

3.1. Crystallization behavior of molecular complex at 298 K

Crystallization could not be performed at initial concentrations lower than 130 mmol/l-solvent for TEP (C_T) and 160 mmol/l-solvent for CMI (C_C), because the induction time of nucleation was too long (more than a few weeks). When the crystallization was carried out at the initial concentrations of 150–190 mmol/l-solvent for TEP and at the constant concentrations of CMI (300 mmol/l-solvent), the same crystals were obtained. The typical XRD pattern of the crystals is shown in Fig. 2(a), showing from the previous report [12] that the crystal is TEP · 2CMI molecular complex. However, with decrease of the initial concentration of CMI to 180 mmol/l-solvent at the same TEP concentration (300 mmol/l-solvent), crystals with different structures were obtained. It can be confirmed by the XRD pattern in Fig. 2(b).

In Fig. 3(a) the result of the thermal gravity analysis (TG) for the crystal in Fig. 2(b) is shown, and compared with the result for TEP · 2CMI crystal (Fig. 3(b)). The large weight decrease (41%) at about 430 K of TEP · 2CMI crystal (Fig. 3(b)) is due to the loss of CMI and the weight loss near 580 K in the TG curve is by the decomposition of TEP as shown in the previous report [13]. From the TG curve in Fig. 3(a) 14% weight loss is observed at about 350 K. It was confirmed by the composition analysis by HPLC that in the crystals no CMI is included. Therefore, the 14% weight loss is considered to correspond to two moles of MeOH per one mole of TEP · 2MeOH molecular complex.

With increase of initial concentrations of TEP and CMI, the simultaneous crystallizations of TEP · 2CMI and TEP · 2MeOH were observed. It can be confirmed by XRD analysis in Fig. 4, which is the XRD pattern for the crystals obtained at 210 mmol/l-solvent of TEP and at 300 mmol/l-solvent of CMI.

The crystallization zones of TEP · 2CMI and TEP · 2MeOH at 298 K were shown in the map using the coordinates of initial

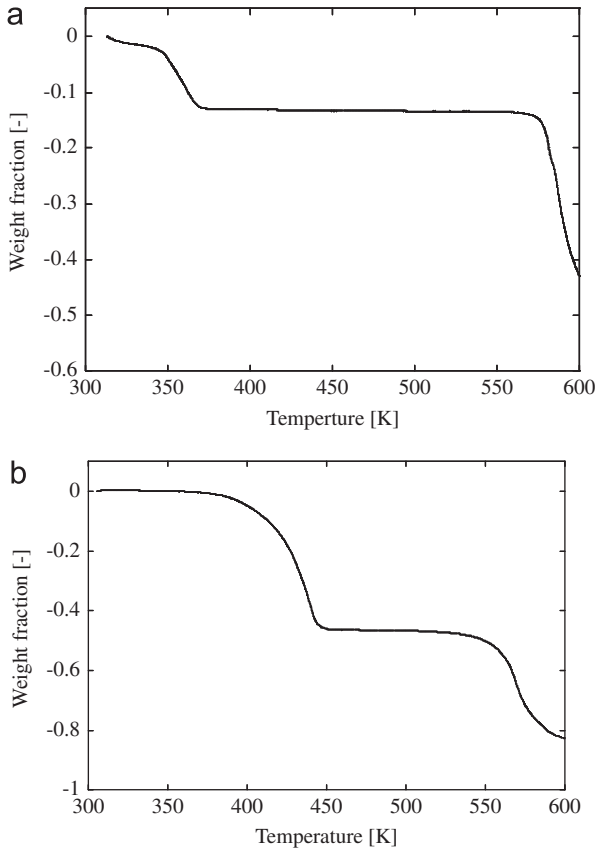

Fig. 3. TG curves for TEP · 2MeOH (a) and TEP · 2CMI (b).

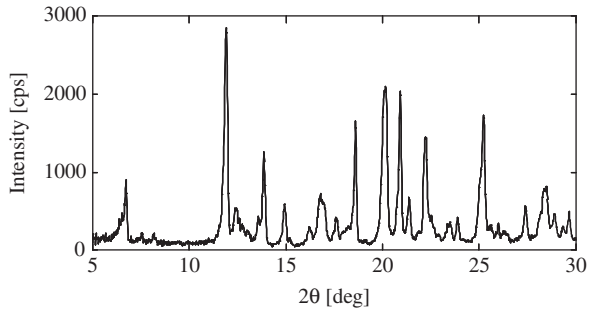

Fig. 4. XRD pattern of crystals obtained at 210 mmol/l-solvent of TEP and at 300 mmol/l-solvent of CMI.