

Physico-chemical understanding of polymorphism and solid-state dehydration/rehydration processes for the pharmaceutical material acrinol, by *ab initio* powder X-ray diffraction analysis and other techniques

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Introduction

Acrinol (2-ethoxy-6,9-diaminoacridine monolactate) is a crystalline material comprising ethacridinium cations and lactate anions in a 1:1 ratio. It is used in pharmaceutical applications as an antibacterial agent. The crystal structure of the monohydrate form of acrinol (denoted **H**) has been reported, although the thermal behavior of **H** and the structural changes associated with dehydration of **H** have not been reported previously. Recently we found two different polymorphic anhydrous forms for this compound. One can be obtained by dehydration of **H** (denote: anhydrous phase I, **AI**) and the other can be obtained by polymorphic transformation of **AI** (denote: anhydrous phase II, **AII**) by heating. Unfortunately, **AI** and **AII** only can be obtained by the dehydration and the polymorphic transformation which accompany the disintegration of the parent single crystal form. In the present work, therefore, the crystal structures of **AI** and **AII** were determined from high resolution powder X-ray diffraction data and the mechanistic aspects on the structural transformations were revealed.

Results and Discussions

High resolution synchrotron X-ray powder diffraction data were recorded at ambient condition on beamline 4B2 (Multiple Detector System) at Photon Factory with wavelength 1.20853(2)Å. The sample was mounted on flat sample holder and diffraction measurement was carried out using reflection mode with rotation of sample holder. Data collection time was ca. 12 hours. From high resolution diffraction data, the crystal structures of **AI** and **AII** were successfully determined using the programs DICVOL, EAGER and GSAS.

The crystal structures of **H** and **AI** are shown in Figure 1 a,b and Figure 1 c,d respectively. The crystal structure of **H** comprises stacking of ethacridinium cations and lactate anions along the *a*-axis. The water molecules are arranged along the *a*-axis, and may be described as a water channel. The crystal structure of **AI** retains several of the structural features present in the parent hydrate phase **H**, and contains similar stacks of ethacridinium cations and lactate anions. Although the ethacridinium cations retain their molecular conformation during the transformation from **H** to **AI**, they undergo slight displacements into the vacant space created by removal of the water molecules from **H**. In addition, the positions and orientations of the lactate anions undergo some adjustment, resulting in a modified hydrogen bonding network.

Insights concerning the mechanism of dehydration of **H** can be gained by comparing the crystal structures of **H** and **AI**. As the structure of **H** has a water channel along the *a*-axis (Figure 1b), dehydration of **H** is expected to proceed by loss of water molecules along the water channel. Although the resulting molecular displacements are such that **AI** does not contain an "empty" channel, the structure of **AI** nevertheless retains several

features of the parent structure **H**. Our observation that the reverse process (i.e. hydration of **AI** to produce **H**) occurs readily is consistent with the fact that there are only relatively small structural differences between **AI** and **H**.

The crystal structure of **AII** (shown in Figure 1c, d) is significantly different from the structures of **H** and **AI**. The stacking of ethacridinium cations in **AII** may be described as half-overlapped offset stacking, which is different from the overlapped stacking in the crystal structures of **H** and **AI**. Given the significant differences between the crystal structures of **AI** and **AII** (compare Figure 1 c,d and e,f), substantial molecular movements are implicated in the polymorphic transformation between **AI** and **AII**, involving essentially complete reconstruction of the crystal structure and significant changes in the hydrogen bonding arrangement.

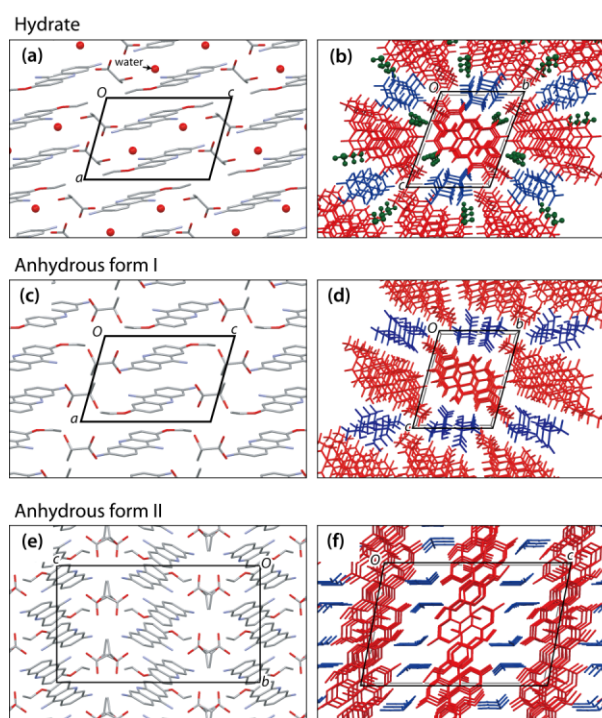


Figure 1 : Crystal structures of acrinol (a, b) monohydrate(**H**), (c, d) anhydrous phase I (**AI**) and (e, f) anhydrous phase II (**AII**), view along the *b* axis. In b, d, f, red molecules are ethacridinium cations, blue molecules are lactate anions and green molecules are water.

References

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