



# Dehydration mechanism of caffeine hydrate and structural description of driven metastable anhydrates analyzed by micro Raman spectroscopy



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## ABSTRACT

This study shows the contribution of Raman spectroscopy to carefully describe the mechanism of solid-state transformation at the molecular level, by simultaneously monitoring the molecular reorganization and the water escape during the dehydration kinetics. Dehydration of monohydrate caffeine was analyzed at various temperatures. In-situ low- and high-frequency Raman investigations provide information on the long-range and local arrangement of caffeine molecules, during the dehydration kinetics and in the anhydrate state. The nature of the anhydrate was determined, from the analysis in the low-frequency region, as metastable and transient between both polymorphic forms of anhydrous caffeine. It was shown that changing the temperature mainly induces structural reorganization of caffeine molecules in the hydrate state, leading to an anhydrate more or less transformed in form I of anhydrous caffeine.

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## 1. Introduction

During the drug manufacturing process, active pharmaceutical ingredients (APIs) are exposed to environmental conditions and encounter various stresses through the production cycle (Morris et al., 2001). The stability of hydrates can vary extremely (Byrn, 1982; Griesser and Burger, 1995), and low or high humidity can induce solid-state transformation of hydrates or anhydrous forms during manufacturing or storage. These phase transformations can involve crucial changes in the physical properties of APIs, in relation with differences in solubility, bioavailability and in the stability conditions of their physical state. For example, dehydration may occur under milling or during tableting process, inducing the formation of lower hydrate, metastable or stable anhydrate or amorphous form. In this context, information on the mechanism of solid-state transformation induced by dehydration is important.

Caffeine (C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>) is a well-known agrochemical and therapeutic agent. Anhydrous caffeine is known to occur in two different polymorphic forms (called I and II, or α and β) which constitute an enantiotropic system (Bothe and Cammenga, 1979). The commercial form (II) is thermodynamically stable at room

temperature and transforms upon heating at about 426 K into form I (Cesaro and Starec, 1980) which is characterized as a disordered crystalline state from calorimetric and X-ray investigations. The I → II transformation is hindered at room temperature (Lehto and Laine, 1998) but kinetics of transformation are significantly faster around 363 K. Dielectric (Descamps et al., 2005), X-ray diffraction (Derollez et al., 2005) and Raman investigations (Hédoux et al., 2011a) have revealed that form I is a dynamically and orientationally disordered state, called rotator phase. The comparison of Raman spectra of both crystalline forms collected in the low- and high-frequency regions clearly demonstrates that an orientational disorder of caffeine molecules, similar to that in form I, subsists in form II (Hédoux et al., 2011a). In this context, X-ray diffraction refinement in form II, without consideration of orientational disorder can be considered as leading to an approximated structural description of form II. The unusual large monoclinic unit cell (Z=20) determined from the more recent X-ray investigations (Enright et al., 2007; Lehmann and Stowasser, 2007), generates a lot of orientational positions of caffeine molecules, suggesting the existence of an orientational disorder which should be considered to obtain a correct description of the stable form.

It is recognized that caffeine hydrate is not rigorously monohydrate but 4/5 hydrate (Bothe and Cammenga, 1980) and can be classified as a non-stoichiometric hydrate (Authelin, 2005).

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Caffeine hydrate is characterized by a very low stability (Bothe and Cammenga, 1980; Griesser and Burger, 1995). It was also found that dehydration of caffeine is a phase transition toward form II of anhydrous caffeine (Griesser and Burger, 1995). Raman spectroscopy is non-invasive, requests no specific sample preparation, and fast acquisition data made it possible the direct quantitative monitoring I → II phase transformations in-situ during isothermal aging at 90 °C (Hédoux et al., 2011a), and during milling at room temperature (Hédoux et al., 2013). Raman spectroscopy appears as a technique very suited to the analysis of the solid-state transformation during dehydration of caffeine hydrate. The low-frequency Raman spectroscopy (LFRS, 5–100 cm<sup>-1</sup>) is a very powerful indirect structural probe, especially for disordered systems (Hédoux et al., 2011c) providing information which cannot be obtained by X-ray diffraction experiments (Hédoux et al., 2011a,b, 2001). Consequently, information about molecular reorganization during dehydration can be expected from the analysis of the LFRS. Moreover, Raman spectroscopy investigations carried out at higher frequencies can also be used to detect and identify hydrogen bonds (H-bonds). In hydrate caffeine, water and caffeine molecules are associated via two different kinds of H-bonding. Two types of molecular associations via H-bonding were previously detected by X-ray diffraction (Edwards et al., 1997; Parvez, 1994). The water and caffeine molecules are associated via C=N(9)··H<sub>W</sub> (W = water) H-bonds, while caffeine molecules are hydrogen bonded via C(8)—H··O(11)=C(2) interactions. Atom numbers are given in Fig. 1a. Both kinds of molecular associations are shown by dashed lines in Fig. 1b and c. H-bonded caffeine molecules form linear networks located in layers stabilized by

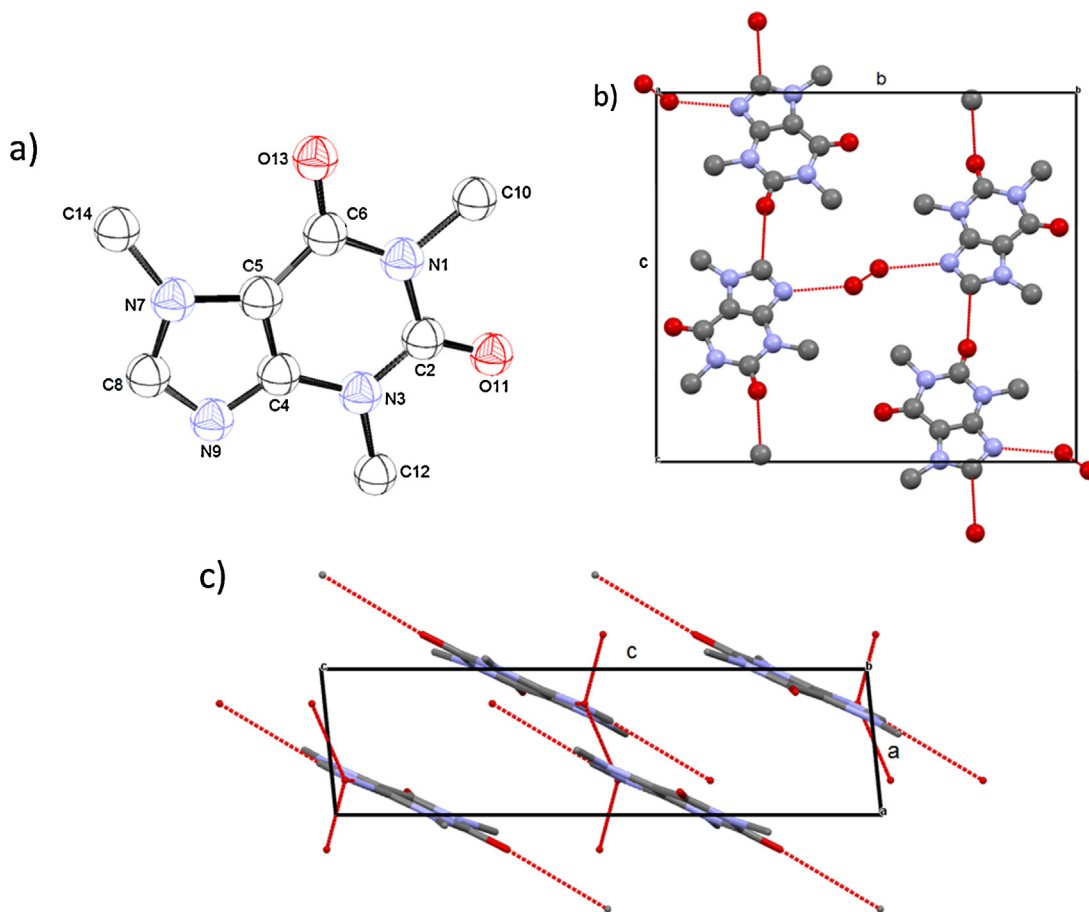
water molecules linked to caffeine molecules via H-bonding. It can be expected that the nature of these H-bonds between caffeine and water molecules is closely connected with the stability of hydrate caffeine, and then Raman spectroscopy should bring out information on the local molecular changes involved in the water escape. Combining low and high-frequency investigations should provide a detailed description of the mechanism of solid-state transformation in the close molecular neighboring of individual caffeine molecules and in the long-range molecular organization.

In a first step, the Raman spectrum of hydrate caffeine was analyzed to determine Raman bands associated to H-bonds between caffeine and water and between caffeine molecules. In a second step, kinetics of dehydration have been analyzed in selected low and high frequency spectral domains to describe molecular reorganization with respect to the water escape. The solid–solid phase transformation has been described with respect to the escape of water to understand the mechanism of dehydration at the molecular level.

## 2. Materials and methods

### 2.1. Chemicals

Caffeine (purity = 98.5%) was purchased from Acros Organics. Crystallites of hydrate caffeine were obtained by slow crystallization from an aqueous solution. Samples were stored in a sealed vessel at 75% RH. Experiments were performed on crystallites characterized by similar shape (spherical) and similar size (~50 μm).



**Fig. 1.** Structural representation of hydrate caffeine using data from (Edwards et al., 1997) (a) the molecular structure of caffeine, (b) the crystal packing of monohydrate caffeine in the (b, c) plane, (c) in the (a, c) plane of P2<sub>1</sub>/c space group, dashed lines correspond to H-bond between caffeine and water molecules (N9··H<sub>W</sub>, W = water) observed in (b, c) plane, and between caffeine molecules (O11H··HC8) observed in (a, c) and (b, c) planes. Hydrogen atoms are not represented.

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