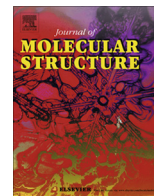




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Polymorphism and disorder in caffeine: Dielectric investigation of molecular mobilities

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HIGHLIGHTS

- In phase 1 two types of molecular rotations are identified.
- Faster dynamics freezes in at ~ -13 °C to give a glassy state.
- In phase 2 dynamical disorder does not correspond to known structural disorder.
- Suggests in plane rotations developing at the surface.

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ABSTRACT

Using dielectric relaxation data we have characterized the molecular mobilities of caffeine both in phase I (stable and metastable) and in phase II. In phase I effects of sublimation and phase transformation kinetics were carefully considered. In plane rotational motions were followed on a wide temperature range. A noticeable antiferroelectric short range order developing at the approach of the glass-like transition is characterized. Condition for occurrence of a critical-like behaviour is discussed. At high temperature the emergence of an additional ultra slow relaxation process is highlighted. Possible molecular mechanisms are proposed for both processes. In phase II the existence of a less intense relaxation process is confirmed. Close similarity with the main process developing in phase I hints at a common origin of the dipolar motions. Careful consideration of recent structure determinations leads to suggest that this process is associated to similar molecular in plane rotations but developing at the surface of crystalline samples. Lower cooperativity at the surface is reflected in the smaller activation entropy of the relaxation.

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Introduction

Plastic crystals [1] are prominent systems for which polymorphism and disorder are intrinsically associated. They are molecular crystals which – upon heating – undergo before melting a phase transformation (first order) between a low temperature crystalline brittle phase and a high temperature crystalline phase where molecules undergo a dynamic orientational disorder. This later “plastic” phase is also sometimes designated by “ODIC” (Orientational Disorder in Crystal). Plastic phases have generally a high crystalline symmetry, cubic or hexagonal. Molecular rotation allows accommodating the generally lower molecular symmetry to the high symmetry of the site. Such compounds are considered as model systems for approaching two remaining challenging issues in material physics: that of melting and that of glass transition. Indeed the transformation to the plastic phase can be perceived

as an orientational melting on an average crystalline lattice. The other, in a sense linked situation, is the possibility sometimes observed to undercool the plastic crystal phase deep enough to achieve a dynamical freezing of the molecules. Such systems give rise to the signature of a conventional glass transition while the structure is crystalline. The latter undercooled systems were named “glassy crystals” by Suga and Seki [2]. They are real analogues of glassy liquids since any dilution of some sort is not necessary to induce a frustration in the system as in spin glass like systems. The latter are also named orientational glasses [3] which may induce some confusion.

Polymorphism of molecular crystals is a very hot topic in the domain of pharmaceutical science [4]. The interest in the polymorphism of drug compounds is linked to the situations of metastability, the associated increases of solubility, and possible influences on bioavailability. Screening of drug polymorphs has become a major activity with the problematic multiplication of poorly soluble active pharmaceuticals.

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Crystalline anhydrous caffeine ($C_8H_{10}N_4O_2$) is a pharmaceutical compound which presents an interesting crystalline polymorphism with two enantiotropically related modifications [5–10]. The room temperature commercial crystalline form II transforms endothermally upon heating above $T_p \approx 140$ – 150 °C into form I which, very early, has been suspected to be disordered [5,6]. It was shown more recently that phase I is hexagonal and highly dynamically disordered [11]. It thus belongs to the class of plastic crystals which may also give rise to a glassy crystal state. Upon cooling below T_p , phase I can be maintained in a long living metastable state. Rotational motions of the molecules could be investigated by dielectric relaxation spectroscopy (DRS) in this low temperature domain [11]. Slowing down of molecular rotations was observed giving relaxation time of about 1 s at room temperature. Molecular rotations eventually freeze at ≈ -15 °C. A glass transition of a conventional nature is clearly detected at this temperature via a sudden drop of the expansivity coefficient [12]. Dynamics could not be investigated above T_p , in the stable domain of phase I, mainly because of a strong sublimation of the sample. The structure refinements of phase I could be performed from powder [12] then from single crystal [13] X-ray diffraction. Results are in many respects similar and confirm the existence of a statistical disorder of the molecules which dynamics was revealed by DRS. Ring planes of the molecules are parallel and stacked along the *c* hexagonal axis. Proposed structures only differ by the number of in-plane orientations that each molecule randomly takes on its site around the hexagonal axis: either three [12] or six [13] orientations. The orientational disorder restores a site symmetry compatible with the Bravais lattice.

Structure of phase II was recently solved on single crystal [13]. The monoclinic lattice of form II is based on a surprisingly large ($Z = 20$) unit cell. It contains 3 types of sites: one where molecules are orientationally ordered and two others where molecules are independently disordered. These two types of disorders are furthermore fully different from that expected in phase I. They involve that time out of plane 180° reorientations around in-plane axis. Preliminary DRS data on phase II [14,11] allowed to detect a signal similar to that of metastable phase I but less intense. Considering the structural results and the very different types of motions that could be expected in the two phases, the similarity of the signals is highly questionable.

Crystallography only provides a static averaged view of the disordered molecular organizations and cannot give information about the dynamics of the process. To gain information about dynamics it is necessary to progress in the understanding of the structural instabilities of solid caffeine which is a long standing challenge. In the present paper we report a characterization by DRS of the molecular mobility in phase I both above (stable form) and below T_p (metastable form) and in phase II. Methodical investigation of kinetic and history dependent effects was needed. It allowed circumventing difficulties linked to sublimation at high temperature and slow kinetics of conversion from I to II at low temperature. The study gives access to an extended view of the evolution of the complex disorder existing in phase I and the glass like formation. It peculiarly reveals an additional, till now unsuspected, ultra slow relaxational component which may play a decisive role in the phase transformations and their slow kinetics.

Concerning phase II we may wonder if the previously detected DRS signal results or not from the contamination by remaining traces of metastable phase I. This question is pertinent since kinetics of conversion from I to II are incredibly slow at room temperature (weeks to months) [15–17]. In order to investigate “pure” phase II we have prepared samples in this phase by specific very long annealing. Results will allow proposing a reasonable way to accommodate the apparently contrasting information provided by structure and dynamics.

For the two phases, interpretation of data will be helped by the use of two recent papers which intend to numerically model the disorders: Monte-Carlo simulation for phase I [18] and symmetry adapted approach for phase II [19].

Experimental details

Caffeine was purchased from Acros Organics. Commercial caffeine was purified by cold sublimation at 493 K and 10^{-3} Torr onto a coldfinger at 285 K. For investigation in phase II, one year annealing was performed at 90 °C where metastable phase I converts more readily to phase II.

The dielectric measurements were performed with the analyser DEA 2970 of TA instruments which supplies more than 7 decades of frequency (1 mHz to 300 kHz). A nitrogen cooling accessory provides testing capability from 120 K to 700 K. The dielectric cell consists in two ceramic parallel plate sensors, with gold circular electrodes. Samples of caffeine are used in a form of a disk (25 mm of diameter and 2 mm of thickness) prepared by compressing 1.3 g of caffeine powder under a pressing force of 50 kN.

X-ray diffraction experiments were performed with an INEL CPS 120 diffractometer ($\lambda_{CuK\alpha} = 1.540$ Å) equipped with a 120° curved sensitive detector.

Experimental results

The low symmetry of caffeine molecule results in a sizeable permanent dipole moment ($\mu_D = 3.70$ Debye). As a consequence dielectric relaxation spectroscopy (DRS) is very suitable to characterize the molecular mobility in this compound. In a previous investigation DRS was used to investigate the temperature domain ranging up to the transition temperature T_p . So doing, only the metastability domain of phase I could be characterized. Investigation above T_p , in the stability domain of phase I, is made very difficult due to a strong sublimation of the sample. Careful investigation at higher temperatures is however very suitable to get an extended picture of the evolution of the dynamics and also because of the detection with the TSDC (Thermo Stimulated Depolarization Current) technique [15] of a very slow mode which exists in the low temperature domain in addition to the relaxation one already identified with DRS. With TSDC such a mode would correspond to relaxation times of about 100–1000 s. It was found peaking in the 30–100 °C temperature range which leads to presuppose possible additional complexity for the slow molecular mobility in phase I at higher temperature. Isothermal DRS measurements were thus carried out in the stable domain of plastic phase I ($T > T_p$). The study was completed by new investigations at $T < T_p$ both in the metastable phase I and with samples carefully annealed for a very long time to assure a full conversion in phase II.

Stable phase I ($T > T_p$)

In this temperature domain measurements were performed between 188 °C and 155 °C by steps of 2 °C. The frequency domain was explored between 10^5 and 0.5×10^{-2} Hz. The effects of the strong occurring sublimation will be discussed latter. It is thus important to already notice that the duration of the frequency sweep for a global frequency investigation at one given temperature is of 25 min and the equilibration time between two temperatures is of 5 min. Sublimation may thus affect the results obtained during such necessarily long investigations. Fig. 1 shows the real and imaginary part of the isothermal dielectric susceptibility $\varepsilon^*(\omega) = \varepsilon' - i\varepsilon''$. Two relaxation peaks are clearly observed. A high frequency contribution (A_1) which is the manifestation of the mode still identified in the low temperature metastable domain. Another

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