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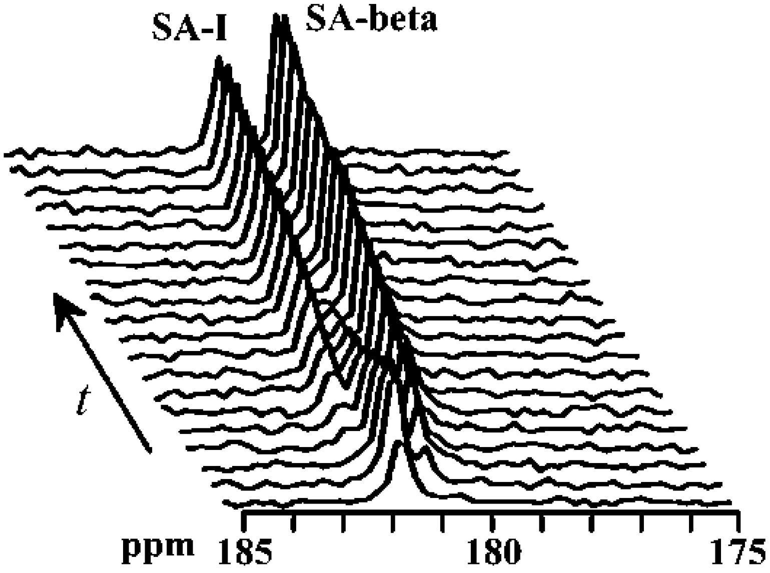

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Altering the Polymorphic Product Distribution in a Solid-State Dehydration Process by Rapid Sample Rotation in a Solid-State NMR Probe

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In the field of molecular crystals, the term polymorphism refers to situations in which a given type of molecule is able to form different crystal structures.[1] Although the different polymorphs have the same chemical composition, their solid-state properties (e.g., reactivity[2]) are generally different (often appreciably so) as a consequence of their different crystal structures. Different polymorphic forms of a given molecule can be produced by a variety of different strategies, including conventional crystallization from solution using different solvents, different crystallization conditions, or crystallization in the presence of additives that promote the nucleation of a specific polymorphic form. Another means of producing different polymorphs is by solid-state transformations, for example, by dehydration of a hydrate crystal phase or desolvation of a solvate crystal phase. In some cases, solid-state transformations yield polymorphic forms that cannot be prepared by conventional solution-state crystallization. It may be surmised that the specific polymorphic form produced by dehydration/desolvation processes is the one that is formed most directly by structural reorganization following loss of the water/solvent molecules from the hydrate/solvate crystal structure, and that topochemical factors[2] may play a role in governing such transformations. It may be envisaged that by carrying out the solid-state dehydration/desolvation process under different experimental conditions, it may be possible to open up a different mechanism for the escape of the water/solvent molecules from the parent crystal structure, which may in turn yield a different polymorphic form of the dehydrated/desolvated product.

In this paper, we demonstrate that the polymorphic form of sodium acetate (SA) obtained by dehydration of sodium acetate trihydrate ($SA\cdot 3H_2O$) is altered by carrying out the dehydration process under conditions of rapid (several kilohertz) sample rotation in a solid-state magic-angle-spinning (MAS) NMR probe. This observation suggests a new opportunity to influence the outcome of solid-state dehydration/desolvation processes and, in particular, to alter the polymorphic form obtained.

SA is known[3] to form a trihydrate crystalline phase, $SA\cdot 3H_2O$, and three anhydrous polymorphs of SA (called form I, form II, and the beta form; here denoted SA-I, SA-II, and SA-beta, respectively) have so far been reported.[4] SA-I and SA-II may be obtained (often as concomitant polymorphs[1c]) by crystallization from aqueous solution at sufficiently high temperature (above ca. 333 K); SA-II is also obtained by crystallization from methanol.[4a] SA-beta is known to be obtained by dehydration of $SA\cdot 3H_2O$ under vacuum.[4b] It has been suggested from DTA/TGA studies[5] that dehydration of $SA\cdot 3H_2O$ occurs directly to give the anhydrous product without passing through any lower hydrate phase (e.g., a monohydrate or dihydrate).

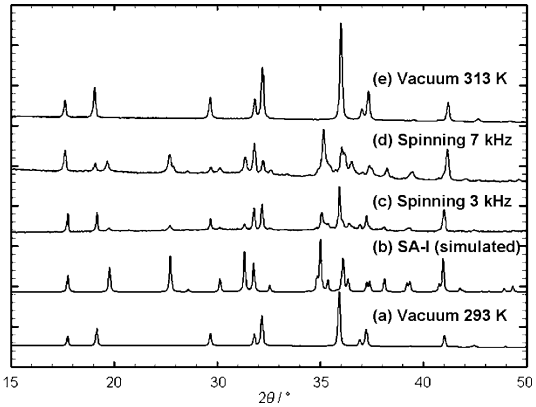

Figure 1. Powder XRD patterns of (a) SA-beta (obtained by dehydration of $SA\cdot 3H_2O$ under vacuum at 293 K), (b) SA-I (simulated from known crystal structure), (c) product from dehydration of $SA\cdot 3H_2O$ with sample rotation at 3 kHz and (d) 7 kHz, and (e) product from dehydration of $SA\cdot 3H_2O$ under vacuum at 313 K.

In the present work, dehydration of $SA\cdot 3H_2O$ was carried out in two ways: (i) under normal laboratory conditions with the sample under vacuum (10^{-2} mbar) and not subjected to sample rotation, and (ii) under conditions of sample rotation in a solid-state MAS NMR probe (such experiments clearly cannot be carried out under vacuum as the sample rotation mechanism requires a flow of gas, in the present case, nitrogen (the drive and bearing gas for the solid-state NMR rotor)). For experiments of type (ii), crystals of $SA\cdot 3H_2O$ (crystal size of several millimeters) were loaded without grinding into a PENCIL rotor[6] (7.5 mm diameter). Sample masses were measured before and after dehydration to provide an independent check that complete dehydration had occurred. For all experiments (types (i) and (ii)), the samples obtained in the dehydration process were characterized by powder XRD[7] and solid-state ^{13}C NMR.[8]

As shown in Figure 1a, dehydration of $SA\cdot 3H_2O$ under vacuum at 293 K leads to a monophasic sample of SA-beta, as also described in the literature.[4b] Figure 1b is the simulated powder XRD pattern of SA-I. Figure 1c shows the powder XRD pattern of the material obtained by dehydration of $SA\cdot 3H_2O$ under sample rotation at 3 kHz in the solid-state NMR probe (nominally at 293 K; see below). In addition to the dominant SA-beta phase, a significant amount of SA-I is also present, suggesting that rapid sample rotation opens up an alternative pathway for dehydration, leading to SA-I. The change in polymorphic product distribution is even more significant at higher rotation frequency (7 kHz), for which a higher proportion of SA-I is obtained (Figure 1d). Furthermore, the rate of dehydration is also found to depend on the rotation frequency. Below 2 kHz, the rate of dehydration is very low (at 2 kHz, there is only ca. 17% loss of water after 5 days), whereas at spinning frequencies of 3 and 7 kHz, complete dehydration occurs in ca. 5 and 2 days, respectively. These observations suggest that sample rotation plays a key role in the formation of the SA-I phase in the dehydration of $SA\cdot 3H_2O$ in experiments of type (ii).

Two immediate questions arise. Is the change in polymorph selectivity caused directly by sample rotation or by other effects (e.g., increase of temperature) that are induced by sample rotation?

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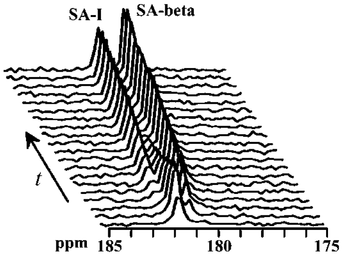

Figure 2. Solid-state ^{13}C NMR spectra recorded as a function of time during dehydration of $SA{\cdot}3H_2O$ (150 scans (5 h) per spectrum). The tuning and match of the NMR probe were re-established at regular intervals during the experiment. Note that the anomalously low signal intensity in the first spectrum is observed reproducibly and is attributed to instrumental factors.

Is SA-I produced directly by dehydration of $SA{\cdot}3H_2O$ or by a sample rotation induced transformation from another phase (e.g., SA-beta) that is produced initially upon dehydration?

First, it is well-known that sample rotation in solid-state MAS NMR experiments can increase the sample temperature.[9] Our temperature calibration experiments using lead nitrate[9] indicate that, for a nominal sample temperature of 293 K (recorded using the thermocouple in the solid-state NMR probe), the actual sample temperature for rotation at 3 kHz was 294 K and at 7 kHz was 317 K. To assess independently whether such increases of temperature could influence the polymorphic product distribution, experiments of type (i) (dehydration of $SA{\cdot}3H_2O$ with no sample rotation) were carried out at elevated temperature (313 and 323 K). These experiments produced only SA-beta, with no detectable amounts of SA-I (Figure 1e).

Second, it is conceivable that the SA-I phase obtained under conditions of sample rotation is not formed directly by dehydration of $SA{\cdot}3H_2O$, but is instead produced from an initially formed phase (SA-beta) by a transformation that is induced by sample rotation. To assess this issue, high-resolution solid-state ^{13}C NMR has been used as an in situ probe of the dehydration process. Solid-state ^{13}C NMR spectra recorded as a function of time during dehydration are shown in Figure 2, and isotropic ^{13}C chemical shifts (measured independently of the in situ study) for $SA{\cdot}3H_2O$ and the anhydrous polymorphs of SA are listed in ref 10. At the start of the in situ experiment, the signal at 181.8 ppm is characteristic of the $SA{\cdot}3H_2O$ starting material. The intensity of this signal decreases as a function of time, while a new signal at 181.2 ppm arises from the formation SA-beta, and a weaker signal at 182.1 ppm indicates the concomitant formation of SA-I.[11] The solid-state ^{13}C NMR results indicate[12] that both SA-beta and SA-I are produced from the start of the dehydration process, and there is no evidence (e.g., from integrated peak areas for SA-I and SA-beta as a function of time) that SA-I is produced by a transformation from SA-beta. In further support of this conclusion, pure SA-beta (obtained by dehydration of $SA{\cdot}3H_2O$ in experiments of type (i)) was subjected to sample rotation for ca. 12 h (nominal temperature 293 K) in separate experiments at 3 and 7 kHz; in each case, there was no change in the solid-state ^{13}C NMR spectrum.[13]

Sample rotation produces a centrifugal force in the radial direction with respect to the rotation axis, and the magnitude of this force is higher as distance from the rotation axis increases. For the polycrystalline sample within the solid-state NMR rotor, the crystals are oriented randomly. Clearly, the magnitude of the centrifugal force exerted on a given crystal depends on the distance of the crystal from the rotation axis, and the direction in which this force is applied within the crystal depends on the orientation of the crystal relative to the rotation axis. It is reasonable to propose that a different dehydration mechanism, leading to the formation of the SA-I phase, might be induced if the magnitude of the centrifugal force is sufficiently high and if this force is applied in an appropriate direction within the $SA{\cdot}3H_2O$ crystal. The fact that this effect depends on both the position of the crystal relative to the rotation axis and on the orientation of the crystal relative to this axis can explain why some crystals can undergo the "new" dehydration mechanism to yield SA-I, whereas other crystals still yield SA-beta. In addition, rapid sample rotation can produce acoustic vibration, and we cannot, at this stage, exclude the possibility that acoustic vibration might also influence the mechanism for dehydration of $SA{\cdot}3H_2O$. Further experiments are in progress to yield a more detailed fundamental understanding of the change in polymorphic product distribution induced by rapid sample rotation.

While the SA-I phase obtained by dehydration of $SA{\cdot}3H_2O$ under conditions of rapid sample rotation is a known polymorph (although not previously known to be accessible by dehydration of $SA{\cdot}3H_2O$), it is conceivable that, for other systems, carrying out solid-state desolvation processes under rapid sample rotation may provide a viable route for the formation of new, hitherto unknown, polymorphic forms.

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(6) The PENCIL rotor (Varian) comprises a zirconia sleeve, a removable drive tip, a sample spacer, and a Teflon end-cap. The end-cap designed for high-temperature operation has a vent hole to relieve pressure in the rotor, which provides an escape route for loss of water from the rotor during the in situ dehydration experiments.

(7) Powder XRD patterns were recorded on a Bruker D8 instrument operating in transmission mode (Cu Kα1 radiation).

(8) All solid-state ^{13}C NMR spectra were recorded under conditions of $^{13}C \leftarrow {}^{1}H$ cross-polarization, high-power ^{1}H decoupling, and MAS, at 75.48 MHz on a Chemagnetics CMX-Infinity 300 spectrometer (CP contact time, 1 ms; recycle delay, 120 s).

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(10) Isotropic ^{13}C chemical shifts (ppm): $SA{\cdot}3H_2O$, 26.0 (CH_3), 181.8 (CO_2^-); SA-I, 26.6 (CH_3), 182.1 (CO_2^-); SA-II, 26.8 (CH_3), 183.6 (CO_2^-); SA-beta, 27.2 (CH_3), 181.2 (CO_2^-).

(11) Similar changes in the signals for the methyl carbon environment (not shown in Figure 2) are in agreement with these conclusions.

(12) High-resolution solid-state ^{23}Na NMR spectra, again recorded as a function of time during the dehydration process, also lead to the same conclusions as the in situ solid-state ^{13}C NMR study.

(13) In another experiment, the product (SA-I plus SA-beta) following complete dehydration of $SA{\cdot}3H_2O$ was subjected to sample rotation at 3 kHz for ca. 12 h (in separate experiments at nominal temperatures of 293 and 393 K). There was no evidence from the solid-state ^{13}C NMR spectra of any change in the relative amounts of SA-I and SA-beta.

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