Using terahertz time-domain-spectroscopy to follow the kinetics and mechanism of cocrystal formation

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***Abstract*—The mechanically-assisted formation of a cocrystal from theobromine (Tb) and oxalic acid (ox) is studied using terahertz time-domain-spectroscopy (THz-TDS). The cocrystal formation was investigated by taking terahertz spectra at various time points throughout the solid-state reaction. This result suggests that THz-TDS may be a useful tool in understanding particular cocrystallisation reactions.**

I. Introduction And Background

ORGANIC molecular crystals in which both molecules that form the crystal are solids at room temperature are known as cocrystals.[1] Cocrystals provide an advantage in the construction of functional (e.g. optical, electronic, pharmaceutical) solid materials,[2,3] since they can be constructed following a design based on non-covalent interactions. One very successful approach to forming cocrystals has been to grind together the pure starting materials, either on their own (neat grinding) or aided by a small amount of liquid (liquid-assisted grinding). However, it is still not clear what factors control the formation of cocrystals under the conditions of neat and liquid-assisted grinding. Thus, there exists a growing interest in the elucidation of the mechanisms behind mechanochemical cocrystal formation.[4] Various mechanisms have been suggested for the formation of cocrystals such as the formation of a eutectic intermediate[5] and nucleation from an amorphous phase.[6] The effect of moisture has also been suggested as an important factor in cocrystallisation.[7]

For the study of cocrystal formation, techniques such as Raman spectroscopy and X-ray powder diffraction (XRPD) have been used. THz-TDS,[8] due to its unique ability to probe the intermolecular interactions as opposed to simply measuring the atomic positions (XRPD) may elucidate further the conformational states and interactions in the cocrystal, formers and any intermediates. In the present study the formation of a 1:1 hydrogen-bonded cocrystal from theobromine (**Tb**) and oxalic acid (**ox**) is followed using THz-TDS (Figure 1).

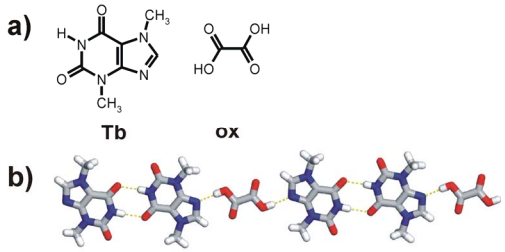

Figure 1: (a) Schematic diagrams of **Tb** and **ox**; (b) fragment of the crystal structure of the hydrogen-bonded cocrystal (**Tb**)(**ox**).

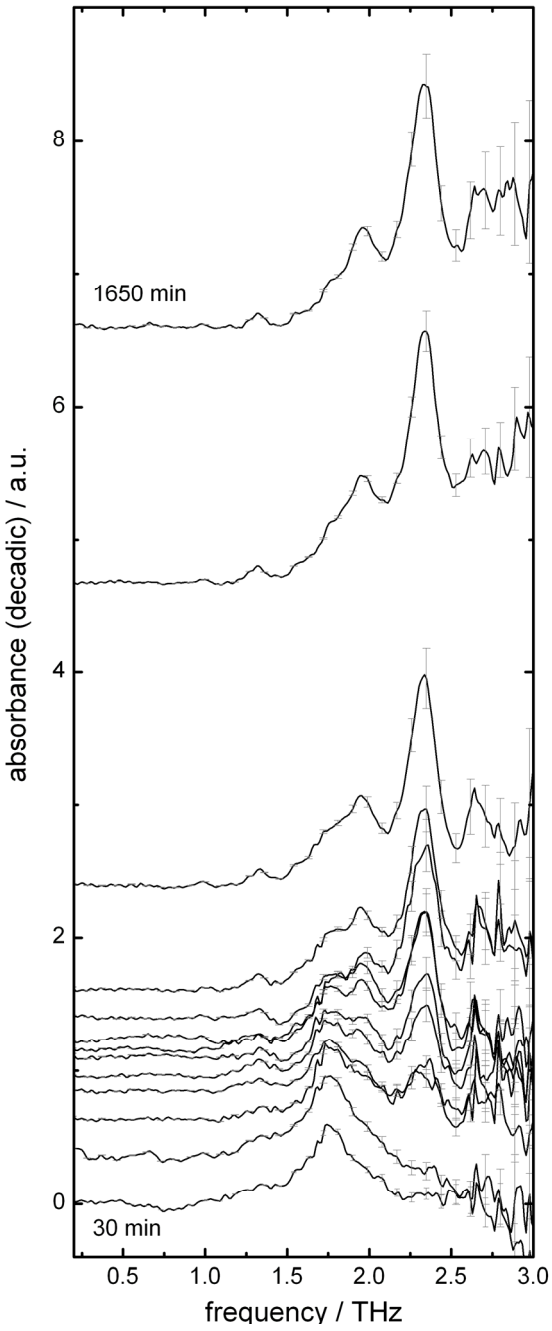

Figure 2: Observed room temperature evolution of the cocrystal from the initial state after grinding to the final spectrum as measured 1650 minutes after the end of grinding. The spectra are offset by relative amounts as corresponds to the time they were recorded and have had their absorbance background subtracted using a quadratic function.

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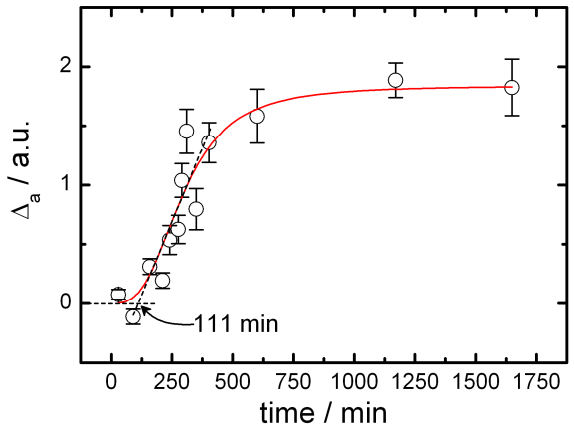

Figure 3: Observed change in absorbance relative to the background for the feature at 2.33 THz as a function of time after the end of grinding.

II. Results And Discussion

Figure 2 documents the changes in the terahertz absorption at room temperature for the **(Tb)·(ox)** cocrystal formation. The samples of mixed **Tb** and **ox** have been ground for 20 minutes and then left to stand at 43 % relative humidity. Terahertz spectra were acquired by mixing 20 mg of the ground material with polyethylene at each time point and measuring the spectrum of a pellet of this mixture. After resting for 30 minutes the terahertz spectrum resembles neither a simple mix of the spectra for the pure cocrystal components (not shown here) nor the final cocrystal product. There is, however, a broad spectral feature centered at 1.75 THz suggesting the possible presence of some as yet unreacted **ox** in the mixture. The spectra recorded at later time points are observed to evolve to the final cocrystal over the course of 1 day. Four distinct spectral features are observed to change during this reaction. The first is the peak at 1.75 THz tentatively assigned to unreacted **ox** within the cocrystal mix. From the initial spectrum this is observed to decrease during the measured time. The three other peaks at 1.31, 1.95 and 2.33 THz are observed to increase over time, and from the liquid assisted cocrystal these are known to be spectral features present in the pure cocrystal form. The increase in these spectral features suggests a continuation of the cocrystal formation reaction whilst the sample stands in the 43 % relative humidity environment.

Further analysis of the large spectral feature at 2.33 THz tentatively attributed to the cocrystal formation may reveal further information as to the kinetics of the reaction, as plotted in Figure 3. From this it appears that much of the cocrystal formation occurs within the first 300 minutes after grinding has ceased. Extrapolation of the gradient of the curve at this point and comparing the intersection with the zero peak height value gave a lag time before commencement of cocrystal formation of 111 minutes. This is in agreement with the time lag before observation on cocrystal formation observed using other techniques such as XRPD.

III. Conclusions

This investigation has begun to probe the kinetics and mechanism of a cocrystal formation using terahertz and suggests that THz-TDS may be useful in characterizing these systems and providing a timescale for the conversions. This technique, coupled with lattice dynamics calculations and in collaboration with other techniques for probing the solid-state, such as XRPD, may be able to provide new insights into the mechanisms behind cocrystal formation by mechano-grinding. A further possibility would be the potential ability for THz-TDS to be used to monitor the formation of molecular assemblies such as cocrystals *in-situ*.

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