Probing solids through THz spectroscopy: Differentiation of chiral and racemic forms of isostructural and non-isostructural cocrystals

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***Abstract*—Cocrystals of theophylline (tp) and racemic and chiral forms of both tartaric acid (tart) and malic acid (mal) were investigated using terahertz time-domain-spectroscopy (THz-TDS). Using X-ray powder diffraction (XRPD) the racemic and chiral malic acid cocrystal forms were found to be nearly isostructural and therefore almost indistinguishable using XRPD. Using THz-TDS clear differences were observed both at room temperature and at 109 K. This was rationalized using lattice energy calculations and attributed to a difference in the conformational strain of the acid groups between the two cocrystal forms.**

I. Introduction And Background

COCRYSTALS are defined as organic molecular crystals that contain two non-volatile materials. Characterization of these solid state modifications has developed rapidly and the "gold standard" of XRPD has now been joined by solid state NMR methods and most recently by THz-TDS.[1] THz-TDS has certain advantages over the other analytical techniques including its non-destructive nature, use of non-ionising radiation, acquisition speed and the simplicity of sample preparation. Using computational models considerable advances have been made to assign specific vibrational modes to spectral features allowing for spectral "fingerprinting" of the crystal structures.[2, 3]

It is shown that chiral and racemic forms of cocrystals differ in the handedness of one or more of their constituents. In many cases, such as in the cocrystals of **tp** and **tart**, this results in a completely different molecular arrangement which can easily be detected using XRPD.[4] There are, however, some sets of cocrystals, such as cocrystals of **tp** and **mal**, for which the cocrystals formed of either the racemic or chiral forms of **mal** are very nearly isostructural. In these cases techniques such as XRPD, which probe atomic positions, are unable to easily differentiate between the two forms. THz-TDS probes the intermolecular modes and low energy intramolecular modes. These are highly dependent on the structural constraints of the unit cell and so THz-TDS may be able to differentiate between such isostructural cocrystals because of changes in the conformation of the molecular units. To investigate this we have acquired THz-TDS data of the chiral and racemic forms of both the **tp** and **tart** system and the **tp** and **mal** system at room temperature and 109 K and rationalized the results using lattice energy calculations.

II. Results and Discussion

As can be seen in Figure 1a very few differences were observed for the isostructural cocrystals of (tp)·(DL-mal) and (tp)·(L-mal) using XRPD. There are no pronounced extra diffraction peaks in either form and the traces only differ by very small shifts in 2θ below the resolution of most routine XRPD measurements. However, clear differences were observed in the THz-TDS absorption spectra between the two cocrystals, especially at 109 K (Figure 1b). Here, five distinct peaks were observed between 1.25 and 2.2 THz in the chiral cocrystal in comparison to just three seen in the racemic cocrystal within the same frequency range. In fact one of those peaks in the racemic spectrum (at 1.28 THz) was attributed to unreacted **DL-mal** known to still be present in the racemic cocrystal product through other techniques such as DSC.

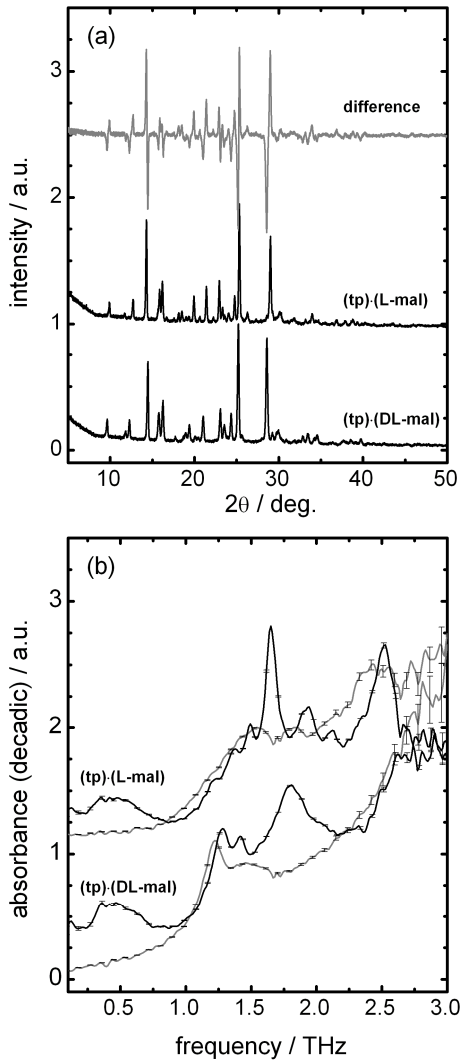

Figure 1: XRPD diffractograms (a) and terahertz spectra (b) for the **tp** and **mal** cocrystals. Both room temperature (grey lines) and 109 K (black lines) terahertz spectra are shown.

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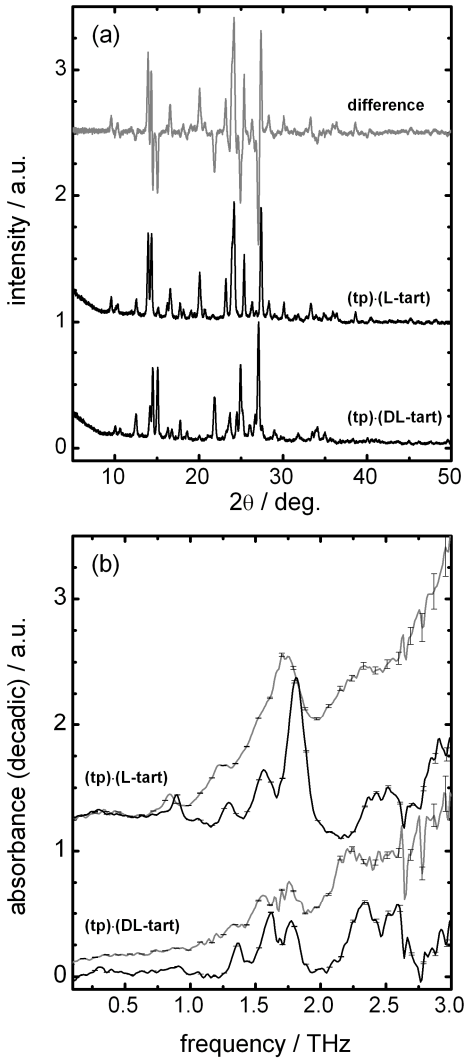

Figure 2: XRPD diffractograms (a) and terahertz spectra (b) for the **tp** and **tart** cocrystals. Both room temperature (grey lines) and 109 K (black lines) terahertz spectra are shown.

Analysis of the lattice dynamics calculations attributed this difference to the conformational change in the chiral cocrystal compared to the racemic cocrystal, resulting in a more pronounced mixing of inter- and intra-molecular modes in the former. In the chiral cocrystal one of the **L-mal** acids takes the place of a **D-mal** acid in the racemic crystal, requiring a high energy molecular geometry. There is a resulting loss of symmetry in the unit cell, leading to an increased number of vibrational modes compared to the racemic crystal. Furthermore, the intramolecular vibrations of the strained molecular conformation in the chiral crystal are more likely to couple strongly with the lattice modes, leading to a very different THz spectrum from that of the racemic cocrystal, where the acid molecules are close to their most stable conformation. This is further supported by consideration of the lattice energies of the two different forms. Calculations suggest that the chiral form is overall 7.52 $kJ \cdot mol^{-1}$ less stable than its racemic analogue, consistent with the earlier explanation for the increased number of vibrational modes in the chiral cocrystal.

XRPD of the non-isostructural cocrystals of $(tp)_2$·(DL-tart) and $(tp)_2$·(D-tart) show some obvious differences in comparison to the isostructural cocrystals discussed above (Figure 2a) with much larger peak shifts being observed between the two forms. This is to be expected as the cocrystals are no longer as similar in their structural form, and as XRPD probes the average atomic positions a different diffractogram is expected. However, a clear discrimination of the two forms still requires a high resolution diffractogram.

The room temperature THz spectra (Figure 2b grey lines) of the two **tart** cocrystals reveals a number of broad spectral features that have similar vibrational frequencies but different relative intensities. Cooling to 109 K (Figure 2b black lines) resolved these peaks more clearly and revealed subtle changes in the vibrational frequencies between the chiral and racemic forms for these similar frequencies. However, preliminary lattice dynamics calculations suggested that these similar frequencies were purely serendipitous and that the vibrational oscillations in the different cocrystal forms corresponded to very different intermolecular modes. The additional peak observed in the chiral form at 0.84 THz is attributed to a bending of the hydrogen bonds between the **tp** and **D-tart** molecules. A similar mode was predicted for the racemic analogue, but with a significantly lower intensity, which may explain why it was not observed in the terahertz spectrum.

III. Conclusions

In this investigation we have employed THz-TDS to differentiate between isostructural cocrystals and used lattice energy calculations to provide tentative interpretations for the observed differences. Whilst in most cases, such as the non-isostructural cocrystals presented herein, XRPD is able to distinguish between racemic and chiral cocrystals, in situations such as the isostructural cocrystals it struggles due to the similarity in atomic position. As THz-TDS is probing the strength of the interactions it does not suffer from this problem and instead is able to pick up changes in the energy state of the different cocrystals. This means it could be an ideal probe for understanding compound stability when considering the different structural forms of solid-state modifications and an excellent addition to complement existing classification techniques such as XRPD and Raman spectroscopy.

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