Terahertz Spectroscopy and Solid-State Modeling of Crystalline Polymorphs: Conformation vs. Cohesion

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***Abstract*—The detection, identification, and characterization of crystalline polymorphs of molecular solids such as pharmaceuticals and related compounds has long been an active area of terahertz research. The terahertz spectroscopic response of such materials originates from the identities of the molecules, and also from the various three-dimensional solid-state arrangements (or polymorphs) achievable by the components. Detailed analyses will be described of the internal molecular conformations and the external cohesive interactions in these crystals that have been investigated using pulsed time-domain terahertz spectroscopy and solid-state density functional theory simulations.**

I. INTRODUCTION

Polymorphism in molecular crystals (generally defined as modifications in the three-dimensional molecular packing) is a subject of great interest to the pharmaceutical industry since it directly impacts the physical properties of drugs, such as melting point and solubility. Polymorph formation and stability is highly dependent on environmental factors including temperature, pressure, and humidity. It is this sensitivity that creates a need for rapid and accurate analytical methods for characterizing such samples. Terahertz spectroscopy provides a compelling solution to this problem and has become a leading application of terahertz radiation.

Different polymorphs of the same compound will each yield a unique and identifying terahertz spectrum that enables differentiation between the multiple possible solid forms to be readily achieved. While the collection and tabulation of the terahertz spectra of many pharmaceuticals has been performed, the understanding of the exact origins of these spectra remains a challenge. The terahertz spectra of molecular crystals represent vibrations both within the molecules and also those that are a product of the bulk (translations and rotations). The nature of the motions in this region makes unambiguous assignment of the observed features nontrivial. Quantum mechanical simulations, specifically solid-state density functional theory approaches, have proven excellent for assigning the spectral peaks to specific atomic motions and for understanding the relative energetic stabilities of the numerous polymorphic forms.[1]

II. RESULTS

The terahertz spectra of several pharmaceuticals, amino acids, and their hydrated variations [2] have been collected using both standard (≤3 THz, ZnTe optical rectification) and high-bandwidth (≤7 THz, $LiNbO_3$ Cherenkov-type source) pulsed terahertz instruments over a range of temperatures. The data have been analyzed using solid-state density functional theory where the quality of the crystal structure reproductions have been verified using single-crystal X-ray diffraction measurements. The initial focus will be on comparisons within the glutamic acid family of compounds, specifically: the conversion of α and β polymorphs in L-glutamic acid (Fig. 1), hydration mechanisms in DL-glutamic acid, and the assignment of the terahertz spectrum of monosodium glutamate (MSG). The analysis of these zwitterionic species will then be compared and contrasted with non-zwitterions including sugars such as mannitol and sorbitol, where hydrogen bonding dominates. These investigations establish the importance of considering both conformational flexibility and optimized intermolecular bonding in the evaluation of terahertz spectra and polymorph formation.

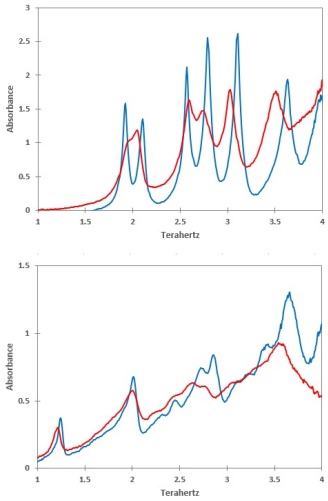

Fig. 1. Terahertz spectra of the α (top panel) and β (bottom panel) polymorphs of L-glutamic acid obtained at 295 K (red) and 100 K (blue).

III. SUMMARY

Terahertz spectroscopy is a powerful tool for studying polymorphic organic compounds. Combining it with solid-state density functional theory enables remarkable insight to be achieved into the fundamental characteristics and properties of complex molecular solids. The studies detailed here reveal that the terahertz spectroscopic signatures of crystalline polymorphs, and indeed the very existence of these forms, arise from a complicated energetic balance between intramolecular and intermolecular forces that coexist in the solid state.

REFERENCES

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[2]. T.R. Juliano and T.M. Korter, "Origins of hydration differences in homochiral and racemic crystals of aspartic acid," *Journal of Physical Chemistry A*, 119(8), pp. 1396-1403, 2015.