

## Unveiling The Mysteries of Crystal Nucleation: Insights From Single Crystal Nucleation Spectroscopy (SCNS)

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Crystallization plays a key role in numerous scientific and industrial areas. Despite extensive research, the fundamental principles of crystal formation at the molecular level remain unclear. Current research indicates that the crystal nucleation process is more complex than what classical nucleation theory proposes. It is vital to investigate the initial stages of crystal formation at the molecular level to establish a fundamental understanding, thereby enabling rational control over the crystallization process. The use of *in situ* optical spectroscopy is a promising approach for revealing detailed information about the nucleation process. However, the stochastic and heterogeneous nature of crystal nucleation has previously limited the application of optical spectroscopy. To address this problem, we have developed Single Crystal Nucleation Spectroscopy (SCNS), a method capable of locally inducing the nucleation of single crystals, while providing *in situ* spectroscopic information of the process. In an initial study<sup>1</sup>, we examined the nucleation of glycine from an aqueous solution and discovered Raman spectral evidence of pre-nucleation aggregates, pointing towards a non-classical nucleation mechanism. We have also observed the consistent formation of the metastable  $\beta$ -glycine polymorph as the first short-lived nucleation step, which subsequently transforms into a more stable  $\alpha$ -glycine polymorph. Recently, we demonstrated that SCNS further enabled us to study the effect of chemical environments on polymorph formation pathways. It is well known that the addition of salts in glycine aqueous solution results in  $\gamma$ -glycine instead of  $\alpha$ -glycine. Our latest results revealed a previously unseen nucleation pathway of  $\gamma$ -glycine in saltwater. This presentation aims to provide an overview and insights into the study of single crystal nucleation events, enhancing our understanding of the pre-nucleation and initial stages of crystal formation through SCNS.

### References:

- [1] Urquidi, O., Brazard, J., LeMessurier, N., Simine, L., Adachi, T. B. M., *Proc. Natl. Acad. Sci. U.S.A.* **2022**, 119 (16), e2122990119.