**Serendipitous Discovery of a New Polymorph of L-Serine**

**A. Skórska-Stania1, Sz. Grabowski1,2, M. Gryl1**

*1Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, Kraków, 30-387, Poland, 2Doctoral School of Exact and Natural Sciences, Jagiellonian University, Prof. St. Łojasiewicza 11, Kraków, 30-348, Poland*

*agnieszka.skorska-stania@uj.edu.pl*

A new anhydrous polymorph of L-serine (form V) was obtained under ambient pressure conditions via additive-mediated crystallization. This polymorph represents the second anhydrous form of L-serine crystallized at ambient pressure (form I), in contrast to other known forms that require high-pressure conditions (form II, III, IV) [1-4].

Structural analysis reveals that form V shares key hydrogen-bonding motifs with the hydrate (form IH), including zwitterionic dimers stabilized by N–H⋯O and O–H⋯O interactions (Fig 1). In form V, these dimers propagate into a three-dimensional network without incorporating solvent molecules suggesting a solvent-mediated nucleation pathway, where the hydrogen-bonding motifs observed in the final structure may originate from pre-organized aggregates in solution.

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| Form V | Form I | Form IH |

**Figure 1**. Dimers of L-serine in form V, I and IH-monohydrate

Thermodynamic calculations using periodic DFT indicate that form V has lower lattice energy than the stable form I at 0 K. However, temperature-dependent Gibbs free energy calculations reveal a stability crossover, with form V favored at lower temperatures and form I becoming more stable above a certain threshold, supported by experimental observations of solid-state transformations over time or upon heating. These results highlight the importance of supramolecular assembly and solution environment in directing polymorphic outcomes and illustrate the necessity of integrating crystallographic and thermodynamic perspectives in polymorph discovery.

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