Exploration of the polymorphic solid-state landscape of an amide-linked organic cage using low-cost computation and automation

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Organic cages can possess complex, functionalised internal cavities that make them promising candidates for synthetic enzyme mimics.[1] Conformationally flexible but chemically robust structures are needed for adaptable guest binding and catalysis, but these rapidly exchanging systems are difficult to resolve in solution. Amide-linked cage **1** was previously studied in solution, where it gave rise to a symmetrical set of ^{1}H NMR signals. However, it was found to crystallise as a significantly less symmetrical – and perhaps much more interesting – conformer.[2] In fact, there are 13 possible conformers that arise from permutations of amide linker orientations (see Figure 1).

Using modelling, we identified five different relative orientations of the amide bonds in the scaffold that should lead to accessible structures. Basis-set validation and completeness confirms the shallow potential energy surface required for conformational promiscuity. By leveraging an automated solvent-antisolvent crystallization workflow, we were able to experimentally isolate and characterize these five different conformers. Observed structures exhibit a wide range of distances between the internal acid groups that are accessible for guest binding ("cavity heights" from 8.2 to 9.2 Å), demonstrating the flexibility and tunability of this artificial supramolecular receptor for potential functional applications.[3]

Our workflow is directly relevant to the broader chemical sciences where understanding structural diversity aids the design of functional molecules. The complexity of the observed crystal structures goes beyond what is possible with state-of-the-art crystal structure prediction. We detail the workflow required to apply our discovery methodology to other systems, such as modern molecular materials, active pharmaceutical ingredients, catalysts, or molecular machines. Our automation-based approach to crystallisation will help curate reliable FAIR datasets and promote reproducibility in a field that is dominated by serendipity of almost "magical" character.

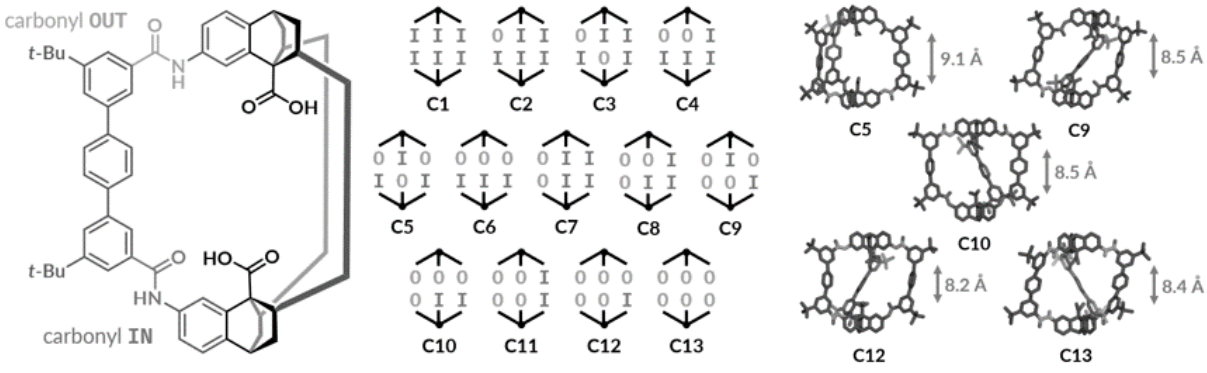

Figure 1. Chemical structure of cage **1** and its thirteen possible amide configurations, shown alongside the five distinct cage **1** conformations found in experimentally obtained crystal structures. Cavity heights (acid-acid distances) are listed for reference.

Bibliography:

[1] Montà-González *et al.*, *Chem. Rev.*, 2022, **122**, 13636–13708.
[2] Andrews and Christensen, *Chem Eur. J.*, 2023, **29**, e202300063.
[3] Shields *et al.*, *chemRxiv*, 2024, 10.26434/chemrxiv-2024-6cwvw.