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Editorial

# Conformationally adaptive metal–organic cages for dynamic guest encapsulation

Dynamic adaptability is a key feature in biological macromolecules, enabling selective binding and catalysis [1]. From DNA supercoiling to enzyme conformational changes, biological systems have evolved intricate ways to dynamically adjust their structures to accommodate functional needs. Mimicking this adaptability in synthetic systems is an ongoing challenge in supramolecular chemistry.

Metal-organic cages (MOCs) have gained significant interest due to their potential to encapsulate a variety of guest molecules, making them valuable in catalysis, drug delivery, and separation technologies [2,3]. Traditional MOCs typically exhibit rigid structures that restrict their ability to accommodate different guests, limiting their broader applicability. To overcome this limitation, researchers have sought to design MOCs with enhanced flexibility by introducing mechanically interlocked ligands, incorporating responsive linkers, or leveraging dynamic coordination bonds [4]. However, achieving a balance between flexibility and structural stability remains an ongoing challenge.

In a recent contribution to the field of supramolecular chemistry published in *Nature Chemistry*, Nitschke and co-workers presented a $Zn_8L_6$ *pseudo*-cubic cage with inherently switchable facial conformations that allow it to expand or contract its cavity based on the size and shape of encapsulated guests [5]. Unlike traditional MOCs, which rely on preorganized cavities, this system offers a dynamic approach to guest encapsulation by leveraging cooperative conformational changes. This structural flexibility mirrors biological host–guest systems, offering a new paradigm for designing adaptive molecular hosts with enhanced versatility in chemical separations, sensing, and drug delivery.

The *pseudo*-cubic $Zn_8L_6$ cage consists of eight zinc(II) ions, twenty-four 2-formylpyridine and six tetramine-based ligands featuring 2,6-naphthalene arms (Fig. 1A). These arms induce a non-planar conformation in the ligand framework, allowing each face to independently switch between *endo* (inward-facing) and *exo* (outward-facing) states (Fig. 1B). The discrete cage structure was confirmed by NMR spectroscopy, electrospray ionization mass spectrometry (ESI-MS), and single-crystal X-ray diffraction. Notably, the structure maintains its integrity while permitting dynamic reconfiguration, balancing rigidity with adaptability.

Host–guest binding studies revealed that the cage accommodates a diverse range of guests, from small hydrocarbons to large anionic species. The cage's adaptability enables it to accommodate guests spanning 46% to 154% of its empty cavity volume. NMR spectroscopy and ion mobility mass spectrometry (IMS) confirmed that larger guests induce a shift from an all-*endo* to a mixed *endo*-*exo* or fully *exo* conformation (Fig. 1C). This transformation allows the cage to optimize its cavity volume, enhancing guest encapsulation efficiency. NOESY NMR experiments revealed guest positioning within the cage, revealing that different guests preferentially interact with either *endo* or *exo* ligand protons. These interactions indicate site-specific conformational switching, confirming the adaptive nature of the host structure. Energy landscape simulations confirmed that guest binding lowers the energetic barrier for conformational switching, making the cage highly responsive to different molecular environments.

The ability of the *pseudo*-cubic cage to undergo quantized structural changes in response to guest binding has significant implications for molecular recognition, drug delivery, and chemical separations. The dynamic nature of the cage suggests its potential for selective guest encapsulation based on molecular properties, making it a promising candidate for adaptive material design. Future work could explore modifications to ligand structures to fine-tune the adaptive behavior or extend this approach to other metal-organic architectures.

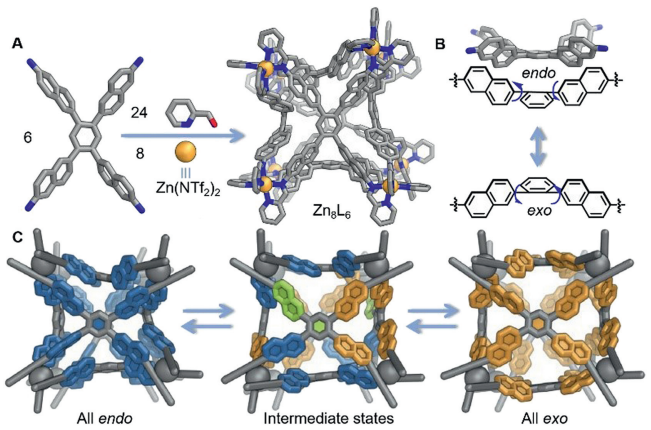


**Fig. 1.** Preparation and illustration of possible conformations of *pseudo*-cube $Zn_8L_6$. (A) The synthesis of pseudo-cube $Zn_8L_6$ from tetramine subcomponent. (B) The two conformations of each face, as a result of the 2,6-naphthalyl rotational units. (C) An illustration of the pathway for conversion between the all-*endo* to the all-*exo* conformation of $Zn_8L_6$, calculated with the GFNFF potential and computational tools from the energy landscape framework. The metal vertices are simplified for clarity. Blue, lime and orange denotes *endo*, intermediate and *exo* states of the structure, respectively. Copied with permission [5]. Copyright 2025, Nature Publishing Group.

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In summary, this study highlights the potential of conformationally adaptive metal-organic cages to enhance host–guest interactions through dynamic structural changes. By integrating switchable ligand conformations into a well-defined cage architecture, this work paves the way for the development of next-generation supramolecular systems with enhanced versatility and responsiveness. These findings offer a blueprint for designing adaptable molecular hosts that can accommodate a broad spectrum of guest molecules with optimized affinity.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Yujuan Zhou:** Writing – review & editing, Writing – original draft, Funding acquisition. **Kecheng Jie:** Writing – review & editing, Writing – original draft, Funding acquisition.

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