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Lewis, Jamie

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Forum

Developing
sophisticated
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Cavity spaces in metal-organic cages (MOCs) frequently draw parallels with enzyme active sites; a cursory comparison of the relative complexities of the two can lead to bewilderment at this analogy. Strategies are now being developed to imbue these artificial microenvironments with higher-level, sophisticated properties and behaviours, moving towards architectures that may justifiably be viewed as artificial analogues of natural systems.

The self-assembly of ligands and metal ions/nodes can generate discrete, porous, supramolecular host architectures that are remarkable given the simplicity of their components and the ease of their synthesis. Various names have been ascribed to these systems, composited from a descriptor (coordination, metal-organic, metallosupramolecular) and a noun (architecture, assembly, cage, polyhedron); the term ‘metal-organic cage’ (MOC) is used here.

Seminal early work demonstrated the power of metal-organic self-assembly to generate beautiful, high-molecular-weight structures from simple building blocks. Exploitation of the enclosed cavities in both 2D (metallocycle) and 3D (MOC) architectures for guest binding followed instantaneously. The power of this approach is

such that a single ligand and metal ion have been used to construct a nanosphere with molecular weight >30 kDa, a diameter over 8 nm, and an interior space of $1.6 \times 10^5 \text{ \AA}^3$ [1].

The interest that guest encapsulation in the cavities of MOCs has generated, particularly when used to promote chemical transformations, has drawn parallels with enzymes. The relative simplicity of MOCs can be considered a positive attribute: more in-depth detail can be garnered about the structure of, and behaviour within, their cavities. This allows tailoring of these artificial systems to suit particular tasks in an, ostensibly, easy fashion [2]. In the continual pursuit of advancing these artificial analogues of biological machinery, however, it is important to strive to create, and understand, cavities in MOCs possessing underexplored properties and displaying more sophisticated behaviours [3].

Sophisticated microenvironments

MOCs possess endohedral sites of interaction around metal ion nodes and within ligand frameworks. Given the generally high symmetry of MOCs, precision control over the relative spatial organisation of these sites can be challenging. This has limited investigations into shape complementarity as a significant factor in host-guest interactions, despite its known importance in biological molecular recognition events [4]. Limited examples have shown the promise of using specific noncovalent interactions in artificial hosts for selective recognition of biologically relevant molecules [5] and catalysis [6]. Consequently, there is a growing trend towards the development of lower-symmetry MOCs [7,8], creating more anisotropic recognition sites, despite the challenge of biasing the self-assembly process to avoid statistical mixtures of products. In this manner, spatial organisation of recognition motifs could be used for defined shape differentiation to target selectivities rivaling biological systems.

Heteroleptic, or mixed-ligand, $\text{Pd}_2\text{L}_2\text{L}'_2$ -type MOCs have been prepared from mixtures of geometrically matched ligands. The planes of the Pd coordination environments in the resulting cages, in contrast to prototypical homoleptic Pd_2L_4 systems with (pseudo-) D_{4h} symmetry, deviate from parallel. In one such example, this was shown to significantly impact the relative binding affinities of two regioisomers of disulfonate guests, resulting from the better shape match of one for the unsymmetrical cavity space (Figure 1A) [9].

Differences between the microenvironments of MOC cavities and bulk solution arise from such endohedral interaction sites. Targeting MOCs with other properties that deviate from normal solution-phase environments is underexplored and would be of great interest. By lining the edges of an Fe_4L_6 tetrahedron with antiaromatic Ni(II)-porphyrinoids, a very unusual paramagnetic environment was able to be engineered within the cavity (Figure 1B). NMR resonances of bound guests were observed to shift downfield by up to 14.9 ppm [10].

Combining such unusual environments with spatial confinement effects and host-guest interactions could open new areas of reactive chemical space. The ability to modulate the properties of the environment in response to stimuli would further advance the sophistication and utility of these spaces.

Allosteric guest binding

Allosteric regulation – modulating molecular recognition events through binding a second guest at a distal site – is a well-known behaviour in biology. Emulating allostery in MOCs is a significant challenge due to the requirement for multiple, guest-selective recognition sites, mechanically coupled to enable controlled conformational distortion of the cage framework to change host-guest interactions to a large extent, without destroying the host entirely.

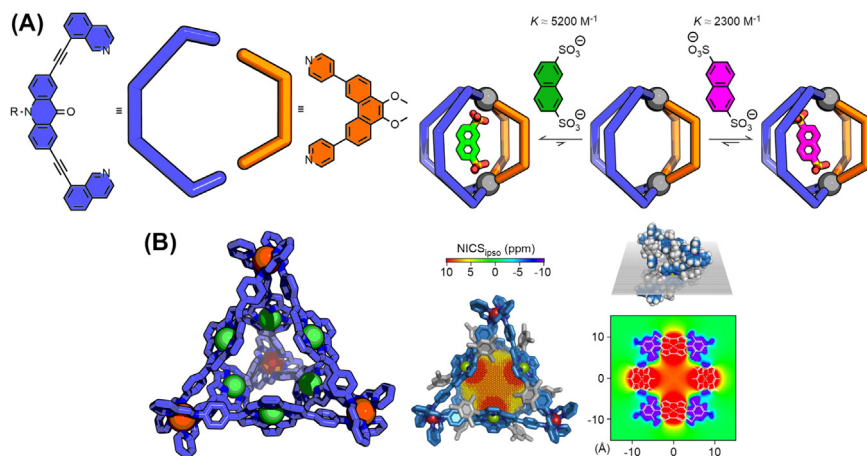


Figure 1. Cavities in metal-organic cages exhibiting sophisticated properties. (A) A heteroleptic $Pd_2L_2L'_2$ cage with C_{2v} symmetry is better able to bind the 2,7-regioisomer of naphthalene disulfonate due to the shape complementarity between guest and host. (B) Lining the edges of a Fe_4L_4 tetrahedron with antiaromatic Ni-porphyrinoid components generates an unusual paramagnetic environment in the cage. Insets show calculated nucleus-independent chemical shifts (NICS) within the cavity. Adapted, with permission, from [10]. Copyright 2019 Springer Nature.

Interlocked dimers of Pd_2L_4 -type (and other) MOCs have been reported that possess three binding sites – two at the termini of the interlocked structure and a central cavity. As the component cages

are able to move relative to each other along the $Pd \cdots Pd$ axis, the size of each cavity can be modulated by this sliding mechanism. One such system has been shown to bind three BF_4^- anions within

cavities of approximately equal size. The addition of two equivalents of Cl^- displaced the outer BF_4^- anions, reducing the cavity size by approximately 20%. Concomitant with this, the central cavity underwent an expansion, decreasing the affinity for the third BF_4^- anion, allowing its displacement by neutral guests cyclohexane and benzene (Figure 2A) [11].

In an alternative approach, a Pd_3L_4 MOC was reported with two chemically equivalent cavities; binding of bulky guests in one of these, however, induced a conformational distortion of the ligand framework, leading to the two cavities being of different volumes. This inhibited binding of the same guests in the second cavity, allowing different species to be encapsulated in each of the two binding sites (Figure 2B) [12]. The engineering of multicavity systems with different cavities for segregated guest binding has been reported [13]; coupling this site-selective binding strategy with allosteric binding mechanisms would advance the utility of both behaviours.

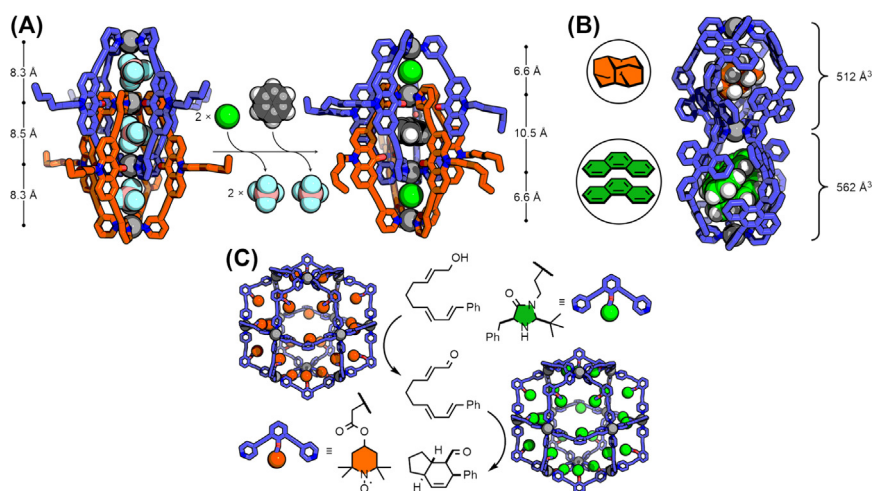


Figure 2. Advanced behaviours of cavity spaces in metal-organic cages. (A) The individual cages in an interlocked $[Pd_2L_4]_2$ metallo-catenane are able to slide relative to one another along the $Pd \cdots Pd$ axis in response to guest exchange, allowing modulation of the size of the terminal and central cavities. (B) Induced fit of guests within one cavity of a double-decker Pd_3L_4 cage distorts the ligand framework, reducing the size of the second cavity, promoting selective binding of a different guest. Solubilising chains omitted from model for clarity. (C) Segregation and stabilisation of incompatible catalytic units within kinetically robust $Pd_{12}L_{24}$ nanospheres allows one-pot sequential catalytic oxidation and Diels-Alder cyclisation of a substrate.

Sequential reaction cascades

As an alternative to single MOCs with multiple binding sites, exciting systems behaviour could be achieved with selective binding between multiple MOCs. In cells enzymes coexist, sequentially catalysing reactions within a cascade in the biosynthesis of natural products. Emulating such 'one-pot' transformations is an enviable goal of synthetic chemists [14]; the ability of multiple functional MOCs to sequentially interact with guest species, albeit in a stochastic fashion, would be a significant step forward.

Efforts towards this have included the encapsulation of incompatible catalytic units within the cavities of kinetically robust $Pd_{12}L_{24}$ nanospheres. In this manner, a TEMPO oxidation catalyst and an organocatalyst were able to effect the sequential oxidation of an alcohol and

stereoselective Diels–Alder (DA) cyclisation of the resultant aldehyde (Figure 2C). Isolation of the catalytic units inside the nanospheres inhibited deactivation of the organocatalyst from oxidation by TEMPO, allowing the one-pot, two-step reaction to proceed that was not feasible with a mixture of the catalysts by themselves [15].

This proof-of-concept study beautifully demonstrates the potential for MOC cavities to segregate reactivities. The large pore size of these Pd₁₂L₂₄ nanospheres should allow the ingress and egress of a range of reactants, making them useful for general chemical transformations. Alternatively, if this concept was combined with high substrate specificity, using the approaches outlined above, it might find utility in mimicking the selectivity of enzymatic reactions that occur in the milieu of biological media.

Concluding remarks

Chemists have always been inspired by nature. Despite what can be, and has been, achieved with guest encapsulation in ‘simple’ MOCs, the development of host systems with more sophisticated behaviours is highly desirable. Efforts have been made towards developing individual aspects of such MOC characteristics. The next big advance in the area would be to combine these behaviours, working in unison, to create truly sophisticated microenvironments. Likewise,

multiple architectures operating synergistically in a cohabited environment would pave the way for artificial systems chemistry. The (significant) challenge lies in gaining complete understanding of individual behaviours before they can be combined in a controlled manner. Achieving, and continually advancing, these feats of molecular design and synthesis would strengthen the comparison between MOCs and enzymes and lead to exciting new functional materials and systems with sophisticated behaviours akin to natural architectures.

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Declaration of interests

James E.M. Lewis is in a close family relationship with the current editor of *Trends in Chemistry*, who took up the role after this paper had been submitted to the journal.

Publisher statement

Because of the close family relationship with the author, the editor of *Trends in Chemistry* was not involved in the peer review of this manuscript, nor did they participate in the decision making process.

¹School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

*Correspondence:
j.e.m.lewis@bham.ac.uk (J.E.M. Lewis).
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