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Supramolecular and molecular capsules, cages and containers

Cameron J. T. Cox, † Jessica Hale, † Paulina Molinska † and James E. M. Lewis *

Stemming from early seminal notions of molecular recognition and encapsulation, three-dimensional, cavity-containing capsular compounds and assemblies have attracted intense interest due to the ability to modulate chemical and physical properties of species encapsulated within these confined spaces compared to bulk environments. With such a diverse range of covalent motifs and non-covalent (supramolecular) interactions available to assemble building blocks, an incredibly wide-range of capsular-type architectures have been developed. Furthermore, synthetic tunability of the internal environments gives chemists the opportunity to engineer systems for uses in sensing, sequestration, catalysis and transport of molecules, just to name a few. In this tutorial review, an overview is provided into the design principles, synthesis, characterisation, structural facets and properties of coordination cages, porous organic cages, supramolecular capsules, foldamers and mechanically interlocked molecules. Using seminal and recent examples, the advantages and limitations of each system are explored, highlighting their application in various tasks and functions.

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Key learning points

(1) Capsules can be prepared under both thermodynamic and kinetic control that display a wide range of structural, chemical and physical properties.
(2) Through careful design, building blocks can be prepared that self-assemble to form supramolecular capsules using various non-covalent interactions.
(3) The varying properties of different classes of capsules provide a range of systems to choose from depending on the intended application and operating environment.
(4) The host–guest chemistry of capsule-type systems can be exploited for applications in sequestration, sensing, separation, stabilisation and catalysis, amongst others.

Introduction

In 1967, Charles J. Pedersen reported the discovery of a new class of macrocyclic compounds, the crown ethers,[1] and their ability to bind alkali metal ions within their cavities that would later be described as if the "ion had fallen into the hole in the center of the molecule."[2] Jean-Marie Lehn's subsequent work on bicyclic analogues of the crown ethers – named cryptands – demonstrated the power of extending these host systems into three dimensions (Fig. 1).[3] This work would see Pedersen[4] and Lehn,[5] alongside Donald J. Cram,[6] win the 1987 Nobel Prize in Chemistry "for their development and use of molecules with

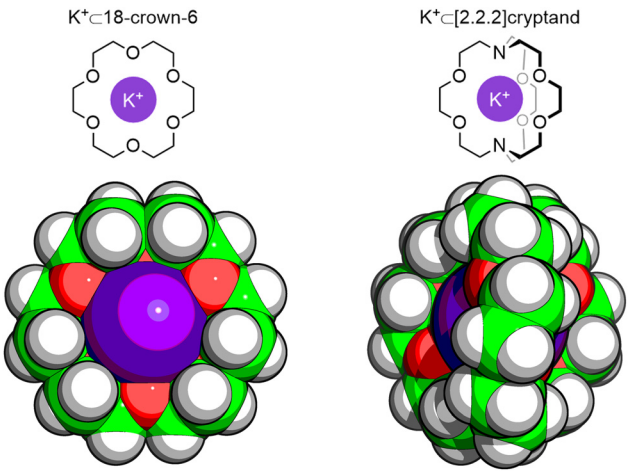


Fig. 1 Single-crystal X-ray diffraction (SCXRD) structures of K^+ complexes of Pedersen's macrocyclic 18-crown-6 ether and Lehn's macrobicyclic [2.2.2]cryptand.

School of Chemistry, Molecular Sciences Building, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. E-mail: j.e.m.lewis@bham.ac.uk; Web: https://lewisgroup.org.uk
† These authors contributed equally and are listed in alphabetical order.

structure-specific interactions of high selectivity.'' The concept of host–guest chemistry had been born.[7]

Since this seminal work (and inspired by increased understanding of natural architectures like enzymes), chemists have been fascinated by the idea and challenges of preparing three-dimensional artificial host systems, often termed capsules, cages or containers. These include covalent systems (of which cryptands are arguably the progenitors), which can incorporate dynamic covalent bonds (such as imines), as well as those assembled using non-covalent (supramolecular) interactions.

Applications, both potential and realised, for molecular capsules are manifold. Encapsulation of guest species[8] within the confined cavity spaces of these systems can result in unusual effects on properties and behaviours.[9] Reactivity, in particular, can be altered upon encapsulation,[10] which can be exploited for both stabilisation[11] and promotion of chemical reactions.[12]

In this Tutorial Review, we introduce the most commonly investigated (supra-)molecular host architectures, outlining their key design principles, structural facets and properties, and link to relevant reviews and articles covering applications for which particular systems have been investigated. In this manner, we aim to provide a broad overview of the various capsule-type hosts and their suitability for use in different environments.

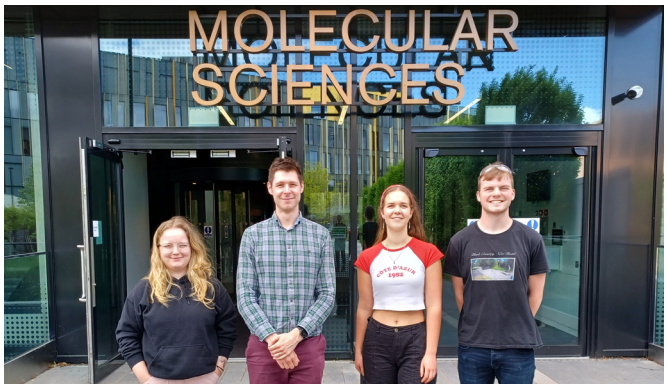
The terms capsule, cage and container are sometimes used interchangeably and sometimes with specific intent to distinguish between systems. In this review we have taken the former route, with no implied comment on the properties of a system from the noun applied. We have also limited our discussion of host–guest chemistry to reversible, supramolecular systems, the assembly of which is driven by non-covalent interactions between the host and guest and/or solvophobic forces.[8,13] Such hosts and host–guest complexes are termed *hemicarcerands* and *hemicarceplexes* in the nomenclature of Cram, as opposed to kinetically trapped *carceplexes* in which destruction of the host is required for guest release.[14]

The systems discussed herein include coordination cages, anion-coordination-directed assemblies, porous-organic cages, assemblies held together by alternative non-covalent interactions (hydrogen, halogen and chalcogen bonds, π–π interactions and hydrophobic effects), foldamers and mechanically interlocked molecules, with selected examples chosen to highlight key principles. For each system, readers are directed to more in-depth reviews to provide greater detail.

Coordination cages

Coordination cages, or metal–organic cages/polyhedra (MOCs/MOPs), are self-assembled container molecules formed through coordination bond interactions between metal ions/nodes and ligand donors, generally under thermodynamic control. We note that these terms are sometimes applied explicitly to architectures assembled from ligands with neutral (often pyridyl) donors (coordination cages) and anionic carboxylate donors (MOCs/MOPs).[15] We do not make such a distinction here, but rather view these as different motifs that can be employed for related assemblies depending on the desired properties of the target cage.

The topology of the thermodynamic product is determined by a balance of entropic and enthalpic factors, with the components tending to fulfil Lehn's concept of maximal site occupancy,[16] *i.e.* to form the greatest number of coordination bonds according to the denticity of the ligand and coordination number of the metal ion/node. For example, square-planar Pd(II) ions in combination with ditopic, or bis-monodentate, ligands will preferentially form Pd_nL_{2n}-type assemblies. As demonstrated by extensive ligand engineering studies from



From left to right: Jessica Hale, Jamie Lewis, Paulina Molinska and Cameron Cox

Cameron Cox (right) is a PhD student under the supervision of Jamie Lewis. He obtained his MChem from the University of Edinburgh in 2023 with a research project at The Australian National University. His research is focused on the synthesis of low-symmetry and template-directed covalent cages. Jessica Hale (left) obtained her MChem (Honors) at Lancaster University completing a research thesis on the enantioselective synthesis of azetidines with Vilius Franckevičius. In 2023, she joined the University of Birmingham to pursue her PhD under the supervision of Jamie Lewis and Chiara Arno on mechanically interlocked molecules in polymeric materials. Paulina Molinska (centre right) obtained her MSci from the University of Birmingham, with her master's project focusing on self-assembly of metal–organic cages in the Lewis Group. She started her PhD work, under the supervision of Jamie Lewis, in 2024. Her research interests include self-assembly and design principles of low-symmetry metal–organic cages. Jamie Lewis (centre left) obtained his PhD (2014) from the University of Otago, New Zealand, under the supervision of Prof. James Crowley. He then joined the group of Prof. Steve Goldup at the University of Southampton, initially as a PDRA and subsequently a Marie-Skłodowska-Curie Fellow. He began his independent career at Imperial College London in 2017. In 2022 Jamie moved to the University of Birmingham, with the award of a Royal Society University Research Fellowship, where he is now an Associate Professor in Supramolecular Chemistry.

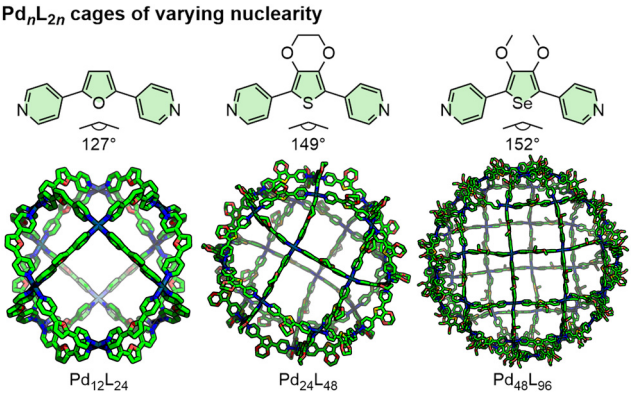


Fig. 2 Different nuclearity Pd_nL_{2n} coordination cages assembled from bis-monodentate ligands and Pd(II) ions (n = 12, 24 and 48 from left to right).

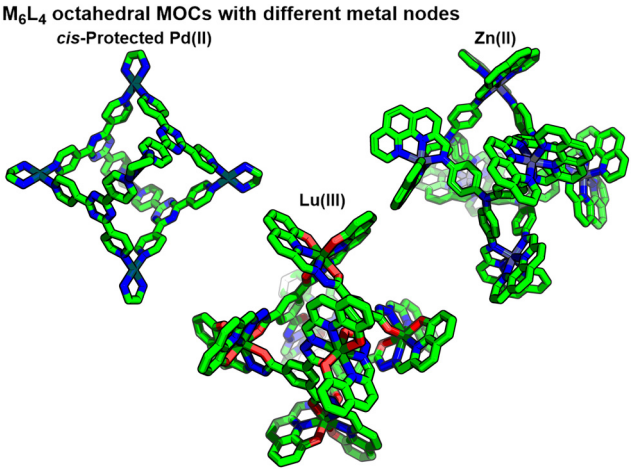


Fig. 3 Octahedral M_6L_4-type coordination cages assembled from metal ions/nodes with different coordination numbers and ligands with different denticities.

the Fujita group, the value of n, in the absence of other factors, is largely controlled by the ligand structure, with the smallest possible assembly forming based on accessible conformations of the ligand (Fig. 2).[17] Although structural factors are some of the most important considerations in designing MOCs, guest-induced/-templated transformations, including by counter-anions, can lead to the formation of unexpected species or structural rearrangements.[18]

Whilst MOCs are most often formed as the thermodynamic product of self-assembly, there are notable examples of kinetically (meta)stable species. The Mirkin group has pioneered the concept of the weak-link approach (WLA), in which a thermodynamic architecture is used to pre-organise components; subsequent modification of the structure leads to formation of a kinetically trapped assembly that cannot be formed through direct reaction of the building blocks.[19]

The range of building blocks, and therefore accessible structures, that can be used to assemble MOCs is essentially infinite. Transition metal ions with coordination numbers typically between 3 and 6, as well as lanthanide ions able to coordinate to up to 12 donors,[20] and a range of coordination geometries have been used. Additionally, capping ligands can be used to form kinetically stable metal nodes with limited coordination numbers and geometries; the most extensively studied of these is the *cis*-protected Pd(II) ion, with two coordination sites blocked *via* a chelating bidentate ligand such as ethylenediamine (en).[21] Through selection of ligand denticity and metal ion/node coordination number, topologically related assemblies can be obtained from different building blocks (Fig. 3).[22]

With regards to the ligand structure, donor units can be neutral or anionic, with a range of denticities, and arranged in any number of geometries from acyclic or cavitand-based ligand scaffolds. Through the balance of charges between the metal ions and ligands, MOCs can be prepared that are cationic, neutral, or anionic (Fig. 4).[23] Myriad studies have also been reported on the appendage of functional groups to both the external[24] and internal[25] surfaces of cages, endowing them with particular properties and functions. To limit formation of a distribution of products, including polymeric assemblies, relatively rigid ligands are generally used; flexible architectures, however, are not unprecedented.[26]

Various design principles have been explicated for the targeted formation of MOC structures, often based on commonly recognised polyhedra, such as the Platonic solids

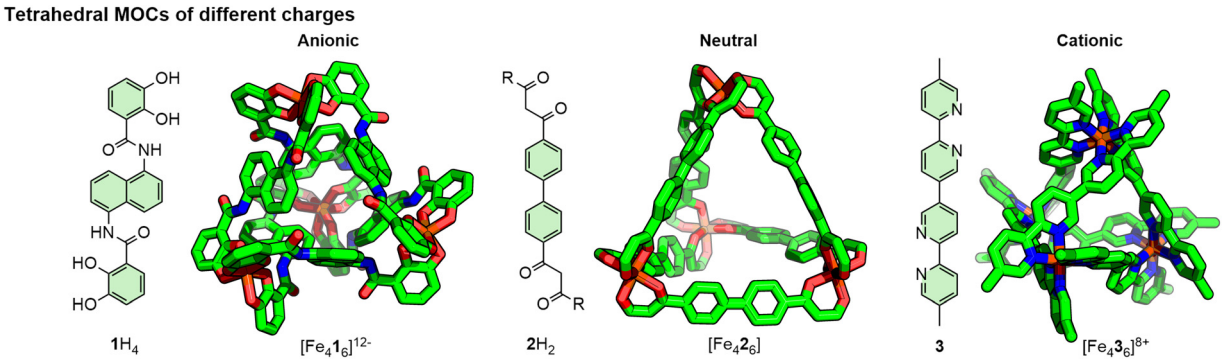


Fig. 4 Tetrahedral Fe_4L_6 assemblies where the balance of charges between the ligands and metal ions results in anionic, neutral and cationic assemblies. R groups omitted from SCXRD structures for clarity.

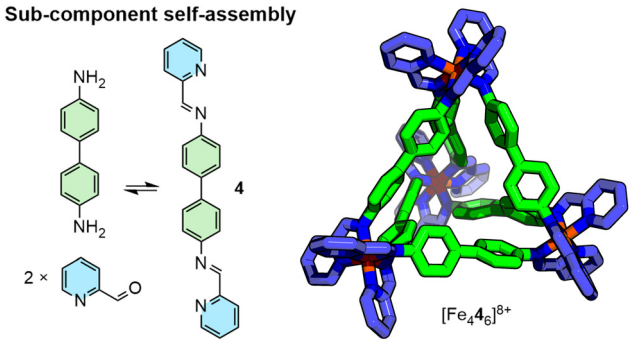


Fig. 5 In sub-component self-assembly strategies, ligands are formed *in situ* using DCC.

(tetrahedron, cube, octahedron *etc.*), that position ligands on the edges, faces or vertices of these shapes.[27] These include the symmetry interaction,[28] directional bonding[29] and molecular panelling[30] approaches, with several excellent reviews available that cover these design strategies in detail.[31] A subset of these design principles is the concept of sub-component self-assembly,[32] in which the complete ligand scaffold is assembled *in situ* through dynamic covalent chemistry, such as the condensation of an amine building block with 2-formylpyridine to form bidentate pyridylimine moieties (Fig. 5).[33]

It is noted that topologically similar architectures can often be obtained from different building blocks. The tetrapyridyl, square planar Pd(II) motif, for example, is structurally analogous to the tetracarboxylate dicopper(II) paddlewheel node and these can be used to form geometrically isostructural assemblies (Fig. 6).[34] Thus, the choice of particular structural features can be dictated by restrictions imposed by the intended application without wholesale redesign of the assembly topology.

Most commonly, MOCs are assembled from a single type of ligand, referred to as homoleptic cages, and a single type of

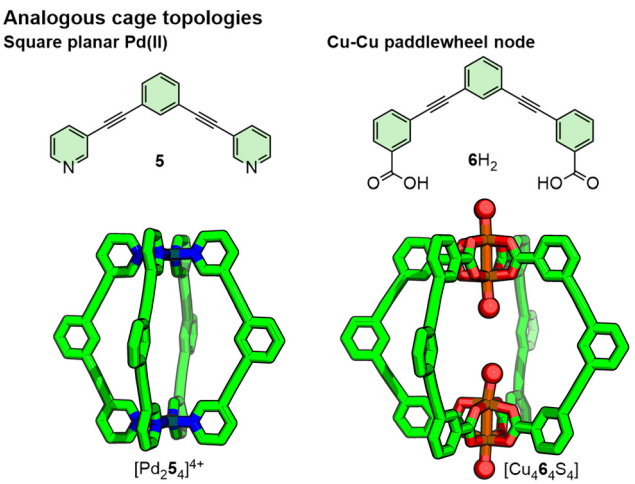


Fig. 6 Topologically analogous architectures can be prepared from ligands and metal nodes with comparable geometries. Axial ligands (S) of $[Cu_4\mathbf{6}_4S_4]$ have been simplified to red balls.

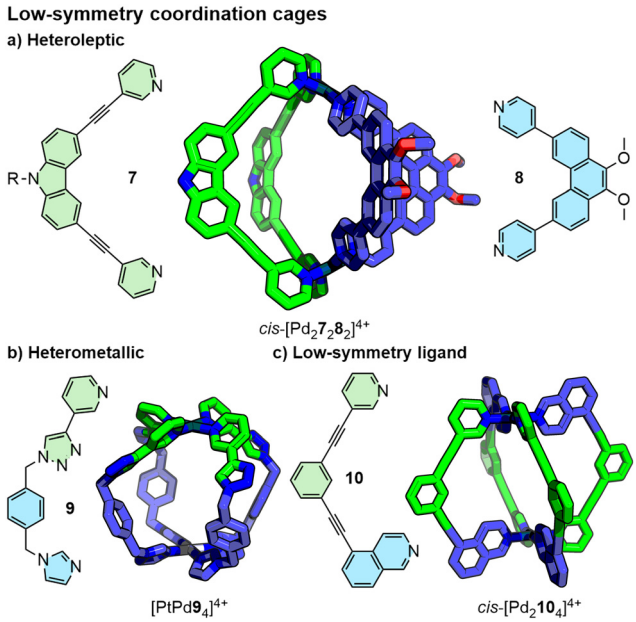


Fig. 7 Low-symmetry coordination cages can be prepared *via* different strategies. R groups omitted from SCXRD structures for clarity.

metal ion/node (homometallic or homonuclear). To increase the structural complexity of these systems,[35] design principles have been developed to form low-symmetry cages (Fig. 7). These include heteroleptic (mixed-ligand) MOCs[36] (Fig. 7a) from the self-assembly of ligand mixtures (a process referred to as integrative self-assembly)[37] and heterometallic cages[38] incorporating different metal ions (Fig. 7b).[39] Additionally, investigations into directing the orientation-selective assembly of low-symmetry ligands,[40] that would otherwise form a mixture of isomeric MOCs, have been reported (Fig. 7c).[41] Recently, using different design strategies, examples of M_2L_4-type cages assembled from four different ligands have been reported, representing the state-of-the-art in this area.[42]

The range of solvents across which a particular MOC is soluble tends to be quite limited. Cationic MOCs, for instance, are generally only soluble in high polarity solvents, such as acetonitrile and DMSO. The identity of counter-anions, however, can be used to dramatically alter solubility profiles; the highly lipophilic BAr^{F-} (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) anion was demonstrated to render Pd_2L_4-type MOCs soluble in apolar dichloromethane and chloroform,[43] whilst sulfate anions were shown to make Fe(II) MOCs water-soluble.[44] For MOCs based on carboxylate paddle-wheel motifs, exchanging axial ligands can be used to similar effect; 4-*tert*-butylpyridine, 4-trifluoromethylpyridine and L-proline were shown to make a $Rh_{24}L_{24}$ cuboctahedron soluble in DMF, CH_2Cl_2/THF and water, respectively (Fig. 8).[45] Solubilising groups appended to ligand scaffolds are also commonly used to modify solubility. As the solvent of life, water-solubility is a commonly targeted property of MOCs, with various approaches investigated to achieve this.[46]

Due to the relatively strong nature of metal–ligand bonds, in comparison to other non-covalent interactions, MOCs are often

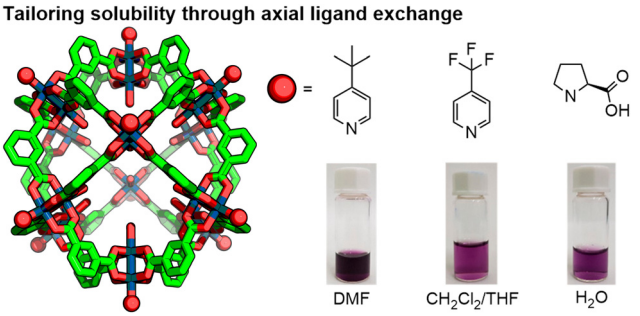


Fig. 8 Through exchange of the exohedral axial ligands of the dirhodium paddlewheel nodes, the $Rh_{24}L_{24}$ cuboctahedron was rendered soluble in various solvents. Adapted with permission from ref. 45. Copyright 2019 American Chemical Society.

stable under a range of conditions, and can be designed to undergo post-synthetic modifications.[47] That being said, paddle-wheel nodes are known to be hydrolytically unstable,[48] and metal–ligand bonds are susceptible to competing nucleophiles.[49] If well understood, these can be used to prepare stimuli-responsive architectures.[50] Attempts have been made to enhance the stability of MOCs[51] through increasing the donor strength of the ligand,[52] using more inert metal ions (*e.g.* Pt rather than Pd)[53] and steric protection around the coordination sphere.[54]

The characterisation and study of MOCs in solution is most often carried out by NMR techniques, including diffusion-orientated spectroscopy (DOSY).[55] This is generally simpler for systems assembled from diamagnetic metal ions, such as Pd(II) and low-spin Fe(II), although useful information can often be obtained for paramagnetic systems too.[56] Mass spectrometry (MS) is also ubiquitous, although often challenging, particularly for larger systems, due to instability of MOCs under MS conditions, although various "softer" techniques have been successfully employed.[57] Characterisation of MOCs in the solid-state by SCXRD is often considered the gold-standard for unambiguous structure determination; however, structures that successfully pack to form X-ray diffraction quality crystals are not necessarily representative of what is predominantly in solution. Thus, when used to make conclusions about the structure of metal–organic assemblies, SCXRD data should always be used to support solution-phase data, rather than *in lieu* of it.

As one of the most commonly explored classes of supramolecular capsules, there is a vast body of literature on the design and molecular engineering of MOCs.[58] The relatively high strength and directionality of metal–ligand bonds, predictable coordination geometries of transition metal ions, and innumerable combinations of components that can be incorporated into functional ligand scaffolds make MOCs one of the most versatile and useful classes of molecular capsules. As a result, coordination cages have been investigated for wide-ranging applications in catalysis,[59] molecular separations,[60] sensing,[61] stabilisation of reactive species,[11] and in biomedical applications,[62] with a multitude of reviews written over the years, a small selection of which the reader is directed to for more detailed discussion.

Anion-coordination-directed assemblies

Conceptually analogous to coordination cages, so-called anion-coordination-directed assemblies (ACDAs) are composed of ligand units bridging between anionic nodes. Rather than the dative covalent, metal–ligand interactions used within coordination cages, ACDAs exploit hydrogen bonding and other electrostatic interactions between anions and ligands to hold the structure together. The notion of anion coordination chemistry has been in discussion since at least the late 1970s,[63] however it is only relatively recently that the field has reached sufficient maturity to enable the design and assembly of polyhedral architectures. Detailed historical overviews of ACDAs have been covered in recent reviews.[64]

In contrast to transition metals, with their often-predictable coordination numbers and geometries, the "coordination" environment around anions is less well-defined and more flexible. Phosphate, PO_4^{3-}, has become the most intensely studied anion for self-assembly, presumably due to its defined tetrahedral shape and ability to form coordinatively saturated complexes with 12 hydrogen bonds.[65] In contrast, sulfate, SO_4^{2-}, is known to form coordinatively unsaturated assemblies, although capsules analogous to those with phosphate have been reported;[66] assemblies formed from tris-carboxylate anions have also been realised.[67]

In terms of "coordinating groups", urea moieties are popular choices, with ligands often consisting of bis- or tris-urea units (capable of forming 4 and 6 hydrogen bonds, respectively), and the manner in which these are arranged directing the topology of assembly formed (Fig. 9). In this manner, coordination of three bis-urea units around a PO_4^{3-} anion is analogous to binding three bidentate ligands around an octahedral metal ion. For example, bis- and tris-(bis-urea) ligands (**11** and **12**, respectively) have been shown to assemble with PO_4^{3-} anions to form edge-based A_4L_6[68] and face-based A_4L_4 tetrahedra,[69] respectively (Fig. 9). Subtle structural modification of ligands, however, can result in significant changes to the resultant assembly. Whilst ligand **12** with a triphenylamine core assembled with PO_4^{3-} to form an A_4L_4 tetrahedron, its phosphine oxide congener, **13**, formed an A_6L_6 trigonal antiprism instead (Fig. 9).[70]

Such structures can be inherently chiral; A_4L_6 tetrahedra, for example, have vertices composed of anions surrounded by three coordinating units that can adopt Δ or Λ configurations. Chiral induction of ΔΔΔΔ- and ΛΛΛΛ-A_4L_6 tetrahedra has been demonstrated through the incorporation of chiral auxiliary units into the ligand scaffold[71] and through interactions with chiral cations.[72]

Unsurprisingly, given their anionic nature, ACDAs are prone to binding cationic guests, although encapsulation of neutral molecules including halocarbons[73] and P_4 and As_4[74] has been demonstrated. As with coordination cages, guest molecules

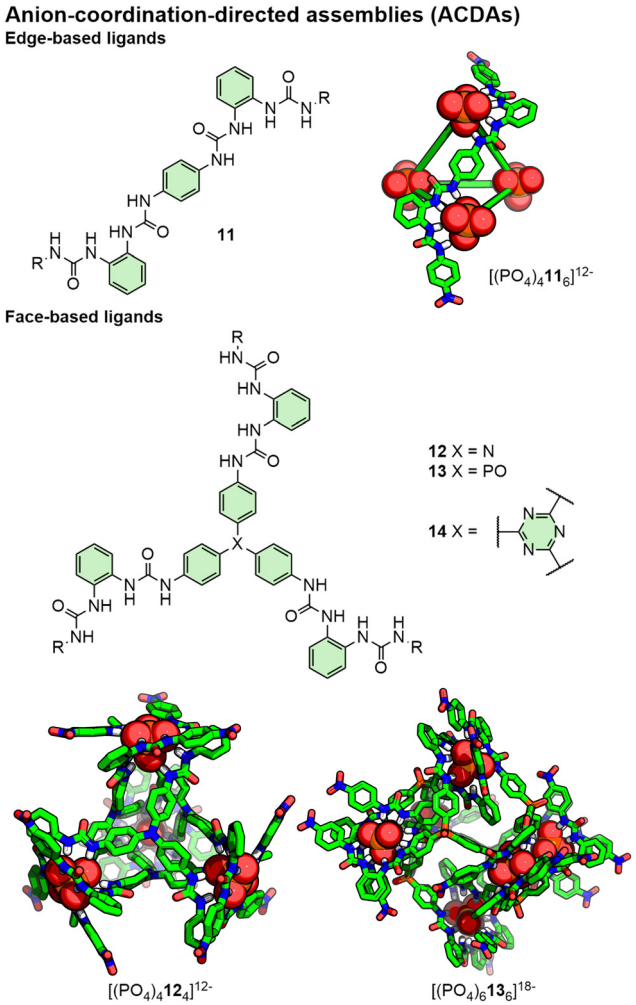


Fig. 9 Ligands incorporating bis-urea "coordinating" groups can be used to assemble ACDAs of different geometries with ligands occupying edge- or face-based positions using design principles analogous to those for coordination cages. R groups omitted from SCXRD structures for clarity.

(or lack thereof) can template the formation of different topologies. $[(PO_4)_4\mathbf{11}_6]^{12-}$, for example, formed in the presence of a tetramethylammonium guest; with tetrabutylammonium as the countercation, however, which was too large to fit within the cavity of the tetrahedron, an A_2L_3 helicate was formed.[68] In contrast, tetrahedral cage $[(PO_4)_4\mathbf{14}_4]^{12-}$ was found to form with or without a suitably sized cationic template, and exhibited conformational flexibility to the encapsulation of different sized ammonium cations.[75]

ACDAs are generally assembled, soluble, and stable in high polarity solvents such as acetonitrile, DMF and DMSO. As such, they can be characterised in solution using standard NMR, DOSY and MS techniques, as well as in the solid-state using SCXRD. The combined effects of multiple hydrogen bonds impart structural stability; the total dissociation energy of $[(PO_4)_4\mathbf{12}_4]^{12-}$, assembled from 48 hydrogen bonds, was calculated to be 1709 kJ mol^{-1}.[69] Acidic conditions, however, can protonate anions like PO_4^{3-}, resulting in disassembly of the architecture.[69]

In summary, the key design principles of ACDAs are similar to those of coordination cages; ligands can be designed to be edge- or face-based, with the anion/ligand ratio controlled by the number of donor moieties, akin to the principal of maximal site occupancy,[16] and the assembly stoichiometry controlled by the ligand geometry. The good solubility of ACDAs makes them suitable for study both in solution and the solid-state. Their anionic nature makes them particularly suited to the binding of cationic guests, while the ligand structure can be tailored to promote non-covalent interactions with encapsulated species. Whilst generally stable in the presence of bases, acidic conditions can lead to disassembly through protonation of the anionic nodes. As the first report of an ACDA capsule is little more than a decade old, it is perhaps unsurprising that applications for these systems have not been thoroughly explored. With rapidly growing developments in design principles, however, ACDAs have potential as highly useful supramolecular capsules. For a more detailed overview and analysis of ACDAs, including beyond capsule-type systems, the reader is directed to recent reviews in the area.[64]

Porous organic cages

The term porous organic cage (POC) is used to refer to capsular molecular systems that contain only covalent organic bonds within their structural scaffold. Several existing reviews provide an historical overview and comprehensive discussion of these systems.[76] In this review, we have chosen to specifically distinguish between capsules, typically formed under thermodynamic control, that exploit reversible covalent bonds, and those formed under kinetic control (covalent-organic cages; COCs). It is noted, however, that the reversibility of "dynamic" bonds is dependent upon the conditions. A stark example of this are alkynes; generally considered kinetically robust, alkynes can be rendered dynamic under specific metathesis conditions.[77] A prolonged discussion on this will not be provided here, but we simply wish to highlight this blurring of lines between different types of POCs.

Dynamic covalent cages

Dynamic-covalent/combinatorial chemistry (DCC) has become an increasingly important tool in supramolecular chemistry,[78] allowing the high-yielding formation of organic molecular architectures from simple precursors in minimal steps and under thermodynamic control. Some of the most widely used dynamic covalent bonds include imines, boronic esters, disulfides, and alkenes and alkynes, each of which has been used to form covalent molecular capsules under thermodynamic control.

As with MOCs and ACDAs, the thermodynamic product(s) formed from a dynamic combinatorial library will be determined by a balance of entropic and enthalpic effects. POCs can, however, be formed as kinetic products,[79] although it may not always be obvious when this is the case.[80] Regardless of whether cages are kinetic or thermodynamic products, the solvent/conditions in which they are formed can have a

significant impact on both the identity of the cage formed[81] and its isolation.[80] Additional guest species can also affect self-assembly outcomes by acting as templates.[82]

A significant determinant of what cage(s) can be/is formed will be the relative numbers and positions of the reactive functional groups in the sub-components. While early seminal examples were assembled from condensation of aldehyde-functionalised cavitands with diamine linking units,[83] smaller, often commercially available, building blocks are now commonly used.

Jelfs and co-workers have outlined a simple system of nomenclature[84] in which building blocks with complementary functionality, depending on the covalent bond being targeted (*e.g.* aldehyde and amine for imines, boronic acid and diol for boronic esters), are assigned as ditopic (**Di**), tritopic (**Tri**), or tetratopic (**Tet**) based on the number of reactive end groups. The stoichiometry of building blocks in the resultant assembly will be determined by their topicity, following analogous principles to Lehn's maximal site occupancy, *e.g.* a ditopic unit combined with a tritopic unit will likely give species with a 2 : 3 ratio ([2*n*+3*n*]) of **Tri** and **Di** units (**Tri**^{2n}**Di**^{3n}), with the precise formula dependent on the building block structures and external factors (Fig. 10a). It is noted, however, that there are exceptions to this rule, in which the stoichiometry of building blocks in a POC does not align with the ratio of their reactive groups.[81b,85] By careful design of the building blocks, topologically comparable structures can be assembled using different reactions (Fig. 10b). Triformylbenzene, **15**, and diamine **16** assemble to form the [4+6] (or **Tri**^{4}**Di**^{6}) tetrahedron **17**;[86] alternatively triamine **18** and dialdehyde **19** also form a [4+6] imine-based tetrahedron (**20**),[87] whilst a boronic ester analogue (**23**) was formed from the combination of tris-diol **21** and bis-boronic acid **22**.[88]

While imines[89] and boronic esters[90] are some of the most commonly used dynamic covalent systems, various others have been reported. These include the condensation between resorcinol and dialdehydes forming noria (**26**)[91] and oligoresorcinarene macrocycles,[92] alkyne metathesis,[93] and formation of disulfides[94] and boroxines (Fig. 11).[95] Orthogonal dynamic covalent linkages have also been used in concert, including imines and boronic esters,[96] and imines and alkynes.[97] Using these chemistries, and through careful design of building blocks, impressive architectures have been realised, including a 5.3 nm **Tet**^{12}**Di**^{24} cuboctahedron assembled from a porphyrin tetramine and a dialdehyde.[98]

Although often characterised and studied in the solid-state as porous materials,[99] POCs are usually solution processable and have been used as components of porous liquids,[100] and can be engineered to have sufficiently low melting points to render them as neat liquids.[101] The conditions under which POCs are stable will depend on the nature of the structure and DCC being used. Imines, for example, are generally susceptible to hydrolysis, although examples of hydrolytically stable systems are known;[102] structural tailoring has been used to enhance the stability of imine-based cages,[103] or alternatively exploitation of keto-enol tautomerisation[104] or use of more robust hydrazones[105] provide access to more stable analogous systems. For some systems this is less of a consideration. Alkynes, for example, require a catalyst for metathesis; otherwise, they remain kinetically stable under a wide range of conditions. The dynamic nature of these organic cages can be exploited for stimuli-responsive transformations, such as the exchange of components in cage-to-cage conversions.[106]

With a wide range of dynamic covalent chemistries to choose from, and with a choice of building blocks only limited by synthetic accessibility,[107] dynamic covalent cages are a versatile class of molecular capsules. Systems can be designed of different geometries and sizes with precise control over pore and cavity size[108] and solubility,[109] and covalent linkages chosen to be stable under a set of required conditions. Indeed, orthogonal DCCs can be combined to enable bond cleavage at specific sites upon application of specific stimuli,[97] making them suitable for

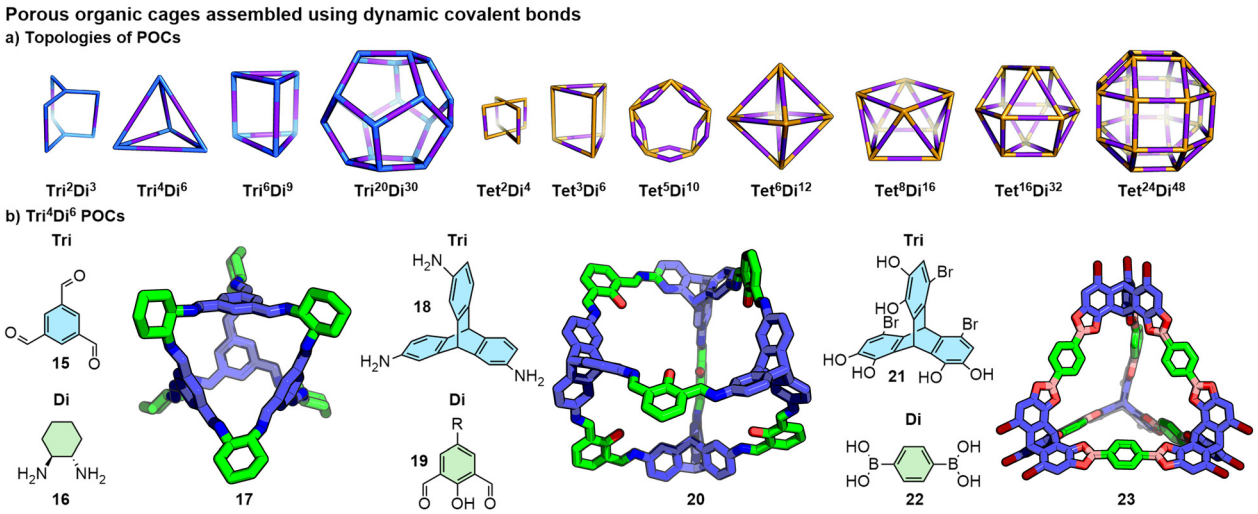


Fig. 10 (a) The topologies of POCs formed through DCCs can be designated formulations based on the number of reactive groups on the building blocks. Reproduced from ref. 84 with permission from the Royal Society of Chemistry. (b) Through careful design, topologically analogous systems can be prepared with functional groups on different building blocks or using alternative reactions. R groups omitted from SCXRD structures for clarity.

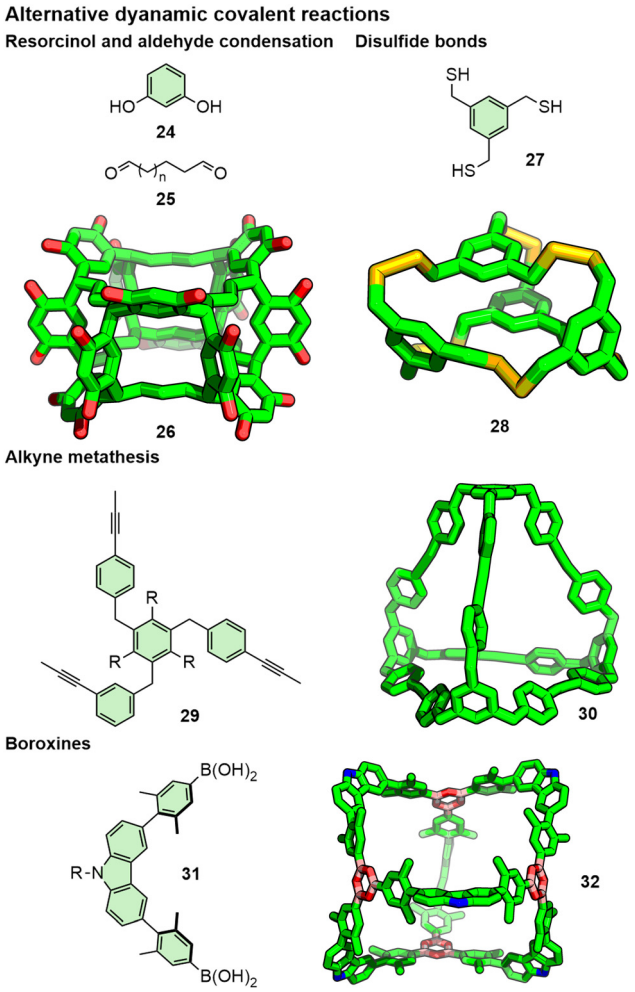


Fig. 11 Alternative dynamic covalent reactions used to generate thermodynamically favoured organic capsules. R groups omitted from SCXRD structures for clarity.

developing stimuli-responsive architectures. Detailed reviews on dynamic covalent POCs,[76] and practical considerations for their synthesis and characterisation,[110] providing in-depth information, are available for the reader's consumption.

Covalent-organic cages

Covalent-organic cages (COCs) are differentiated from dynamic POCs by virtue of containing no reversible linkages, making them generally more kinetically robust. This can, however, make their synthesis more challenging as, once an irreversible covalent bond has been formed, no error correction is possible.

COCs can be synthesised *via* direct covalent-bond forming reactions between components, either *via* a step-wise approach, or "one-pot" methods. Cryptands, arguably the first COCs, first reported by Lehn and co-workers in the late 1960s, were originally synthesised using the former method; iterative amide bond formation followed by reduction were used to synthesise first a macrocyclic precursor (**35**) and subsequently the macrobicyclic cryptand in an overall yield of ~25% (Fig. 12a).[3a] In a similar vein, the stepwise formation of amide[111] and ether-based[112] systems (*e.g.* **38**) have been demonstrated. Ring-closing of acyclic precursors is also possible: Lee and Moore reported the elegant multi-step synthesis of cage **39** (Fig. 12b) *via* a series of Sonogashira reactions and use of protecting group strategies, with a final, intramolecular, double Sonogashira step.[113]

Conversely, "one-pot" approaches, entailing multiple bond-forming reactions between components, have been reported. The simplest of these involve reactions between two complementary building blocks to form [1+1] products. Macrobicyclic systems have been synthesised in this manner through homodimerisation of self-complementary units (Fig. 12c), such as by alkyne homocoupling (*e.g.* **41**)[114] and Yamamoto coupling (*e.g.* **43**),[115] and through heterodimerisation (Fig. 12d) using CuAAC chemistry (*e.g.* **46**),[116] Sonogashira coupling,[117] and nucleophilic substitution (*e.g.* **49**).[118]

Likewise, multi-component one-pot approaches have been reported. Such multi-component reactions are advantageous as the building blocks are relatively easy to access; however, yields can often suffer. Vögtle reported the synthesis of a macrotricyclic system through amide condensation: synthesis of the cage directly from a bis-acid chloride and trisamine in a [3 + 2] reaction yielded the desired cage in only 1.5% yield, whilst the [1+1] reaction between a tris-acid chloride, requiring a multi-step synthesis, and trisamine proceeded in 13% yield.[119]

Capsules have been prepared from oligomerisation of precursors (Fig. 12e), such as tetrameric capsule **51** that was synthesised from the condensation of **50** with paraformaldehyde,[120] and cages such as **53** were synthesised through Rh-catalysed [2+2+2] cycloaddition of bis-alkyne precursors.[121] Reactions between complementary building blocks have also been used to good effect, such as the [3+2] CuAAC reaction between bis-azide **54** and trialkyne **55**[122] and bicyclooxacalixarenes (*e.g.* **58**) synthesised *via* nucleophilic aromatic substitution.[123] Reactions involving more than two reactive groups, such as the Ugi reaction, have also been used to generate structurally complex COCs (*e.g.* **62**; Fig. 12f).[124] Whilst far from exhaustive, these examples demonstrate the versatility of chemistries that can be used for the synthesis of COCs.

To enhance the yields of cage-forming reactions, high, or pseudo-high, dilution conditions are often employed, as are relatively rigid precursors. Alternatively, templates can be used to pre-organise components and promote formation of the desired architecture (Fig. 13). The predictable coordination geometry of transition metal ions can make them very useful for such applications. Raymond, for example, demonstrated the efficiency of using an iron(III) template (Fig. 13a) to pre-organise catecholate units that were subsequently linked *via* amide bond formation with triamine **64**, forming the iron complex of the cage (**67**) in 70% yield; by comparison, the [3+2] condensation of bis-acid chloride **63** with **64** under high dilution yielded cage **65** in 3.5% yield.[125] Step-wise formation of a porphyrin nanoball *via* a macrocyclic intermediate was achieved using sequential coordination templates by Anderson and co-workers.[126] Post-synthetic modification of pre-formed coordination cages, followed by demetallation, has also been used.[127] Guest templates that interact with the incipient cage framework *via* alternative

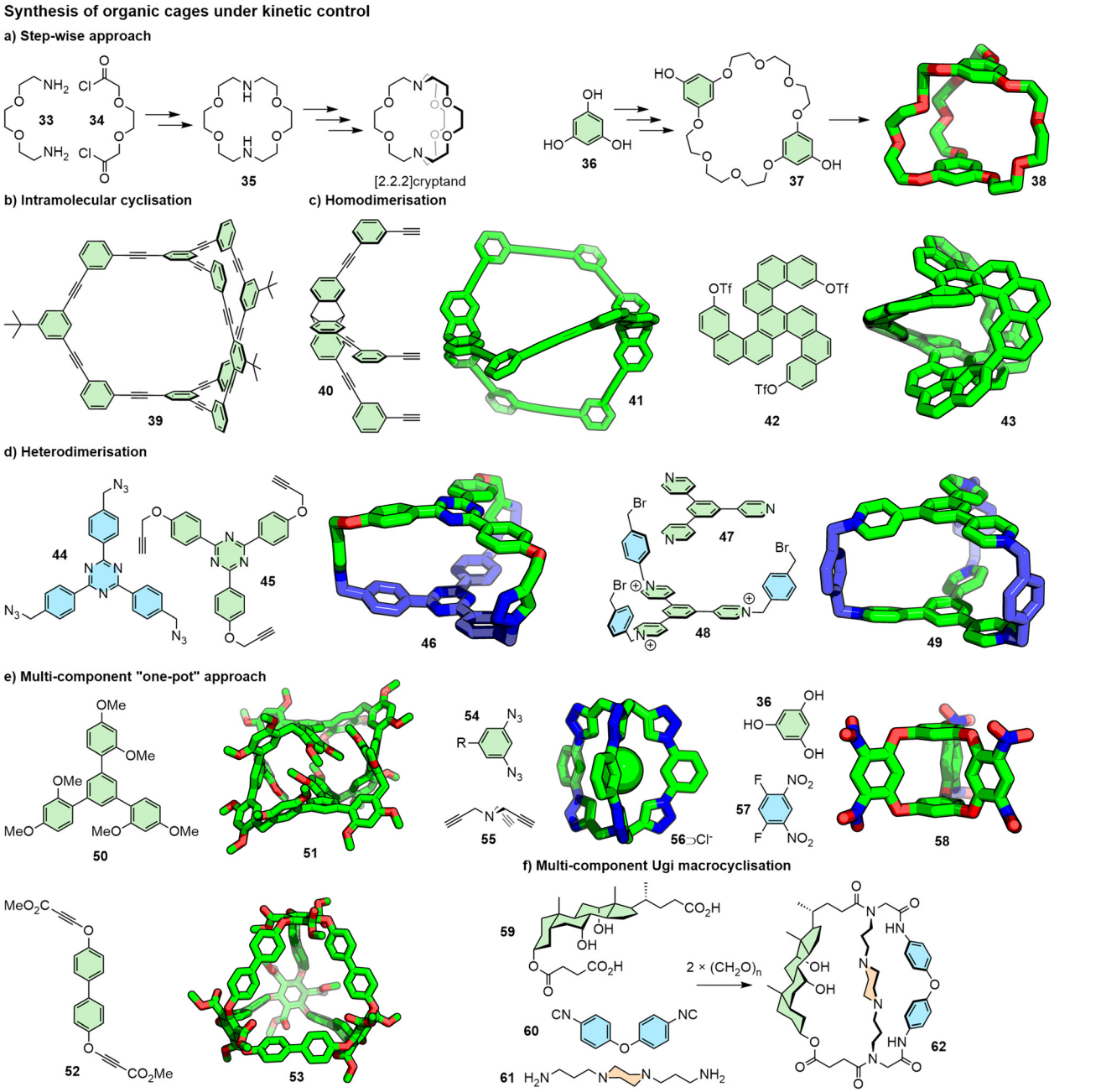


Fig. 12 Kinetically stable organic cages can be prepared *via* a variety of methodologies and using myriad reactions. R groups omitted from SCXRD structures for clarity.

interactions, such as π–π[118a,b] and hydrogen bonding,[128] have also been reported. Solvent choice can be critical for the successful formation of desired products,[129] including through playing the role of template,[116a] dramatically affecting the yield of cage formation under kinetic control.

Alternatively, assemblies can be initially formed under thermodynamic control using dynamic bonds, with subsequent modification used to kinetically "lock" the structure. A number of examples have been reported of transforming POCs into COCs through transformation of imines to amines,[130] amides,[131] aminals,[132] carbamates,[133] quinolines,[134] hydrocarbons,[135] and, through an azedefluorination reaction of a reduced amine with an isocyanate, cyclic ureas.[136] In a similar vein, Yamogo and co-workers reported the transformation of a Pt_6L_4 octahedral coordination cage (**68**) into a COC (**69**) through reductive elimination (Fig. 13b).[137]

With this incredibly wide range of available synthetic strategies and reactions, COCs offer some of the highest levels of structural diversity of molecular capsules. The caveat to this is that the irreversibility of reactions can result in much reduced yields compared to alternative systems. Regardless, the versatility of COCs means they can be designed to be rigid or relatively

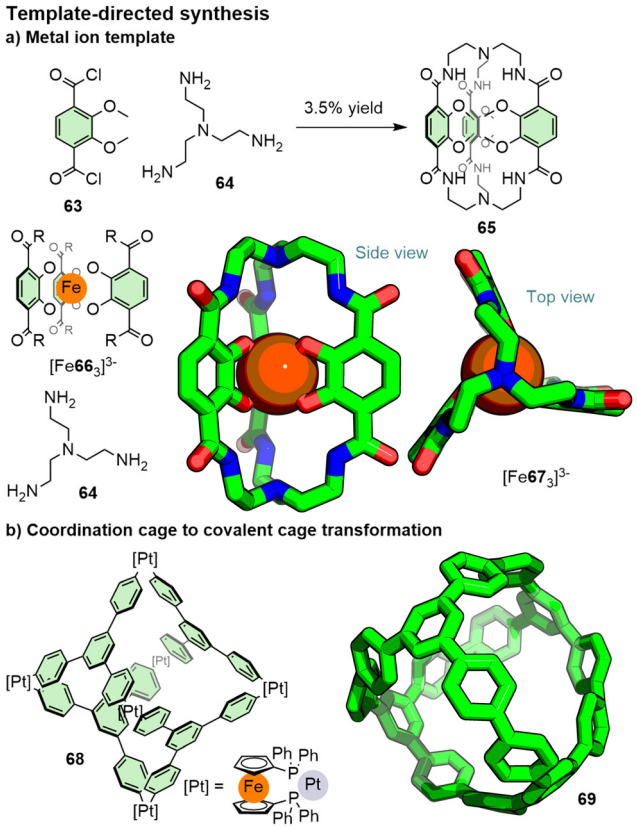


Fig. 13 Templates can be used to increase the yields of covalent cages formed under kinetic control through pre-organisation of a thermodynamic precursor.

flexible, of various sizes and geometries. They can also be rendered soluble in various media,[138] and porosity in the solid-state can be tailored through substituents.[139] In terms of characterising and studying POCs, solid-state analysis by SCXRD is common, as is the use of NMR and MS in solution.

The structural versatility available to POCs, both dynamic and kinetically stable, enables their design for binding a wide range of guests in solution, including anions[140] (of particular note, cage **56** exhibited attomolar affinity (K_a ~10^{17} M^{-1}) for Cl^-,[122] and a urea-based cryptand bound SO_4^{2-} in 100% water)[141] and cations[142] as well as neutral molecules such as saccharides,[143] small aromatics,[144] polycyclic aromatic hydrocarbons[116d,118] and fullerenes.[145] Such host–guest chemistry can be exploited for sensing and separations,[146] and the cavity space can be engineered to possess endohedral catalytic sites.[147] In the solid-state, many POCs have been explored as porous materials for applications involving the uptake and separation of gases.[99] As such, POCs are an incredibly versatile class of molecular capsules that lend themselves to applications as both solution- and solid-phase materials.

Hydrogen, halogen and chalcogen bonding capsules

One of the most commonly encountered non-covalent interactions is the hydrogen bond (HB; Fig. 14). Ubiquitous in nature,

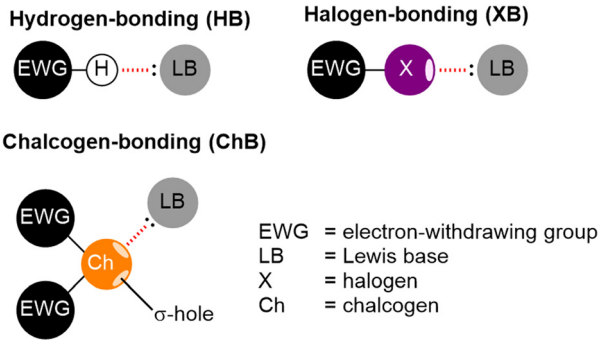


Fig. 14 Cartoon representations of hydrogen-, halogen- and chalcogen-bonding electrostatic interactions.

the relatively weak nature of HBs (typically <40 kJ mol^{-1} although estimates vary[148]) is both a gift and a curse. The low energy barrier to rearrangement allows funnelling of self-assembled mixtures down to their thermodynamic minimum with relative ease. The susceptibility of the HB to unwanted disruption, however, limits the stability of such systems, and makes their design a significant challenge.

The simplest form of HB capsules would therefore arise from homomeric dimerisation of self-complementary building blocks (Fig. 15). In 1993, Rebek and co-workers introduced curved glycouril-based monomer **70** that was shown to self-assemble into a dimeric capsule in chloroform, forming a molecular tennis-ball held together by a seam of 8 HBs between the glcouril units.[149] Encapsulation of small molecule guests (chloroform, dichloromethane, methane, ethylene) was demonstrated by NMR, with slow exchange evidenced by observed signals for both the *empty* capsule and host–guest adduct.[150] Since this seminal work, other examples of hydrogen-bonded dimers have been reported from interactions between various functional groups (Fig. 15), such as peptides,[151] oximes,[152] amides,[153] ureas (*e.g.* **71**),[154] and resorcinarenes (*e.g.* **72**, **73**).[155,156] For each of these, self-assembly in chloroform proceeded readily, whilst addition of competing solvents (methanol, DMSO) served to disrupt the HB interactions between monomers.

Although apparently forming without an explicit template, subsequent studies suggested that appropriately-sized solvent molecules could take on this role. An extended version of Rebek's glycouril monomer, for example, dimerised in benzene, but only did so in *p*-xylene in the presence of a suitable guest.[157] Likewise, resorcinarene-based cavitands have been shown to cleanly dimerise in chloroform, benzene or toluene, as these were small enough to readily fit within the cavity of the host, whilst bulkier mesitylene as solvent required addition of suitable guests to template the assembly.[158] Resocinarene tetraester **73**, for example, existed in monomer form in chloroform, but assembled into a dimeric host in the presence of a tropylium cation (**74**) template.[155] Such host–guest interactions can be incredibly powerful in imparting stability to HB capsules: resorcinarene **72** did not spontaneously dimerise in acetone but could be induced to do so upon addition of $^+NEt_4$ as a suitable template.[155]

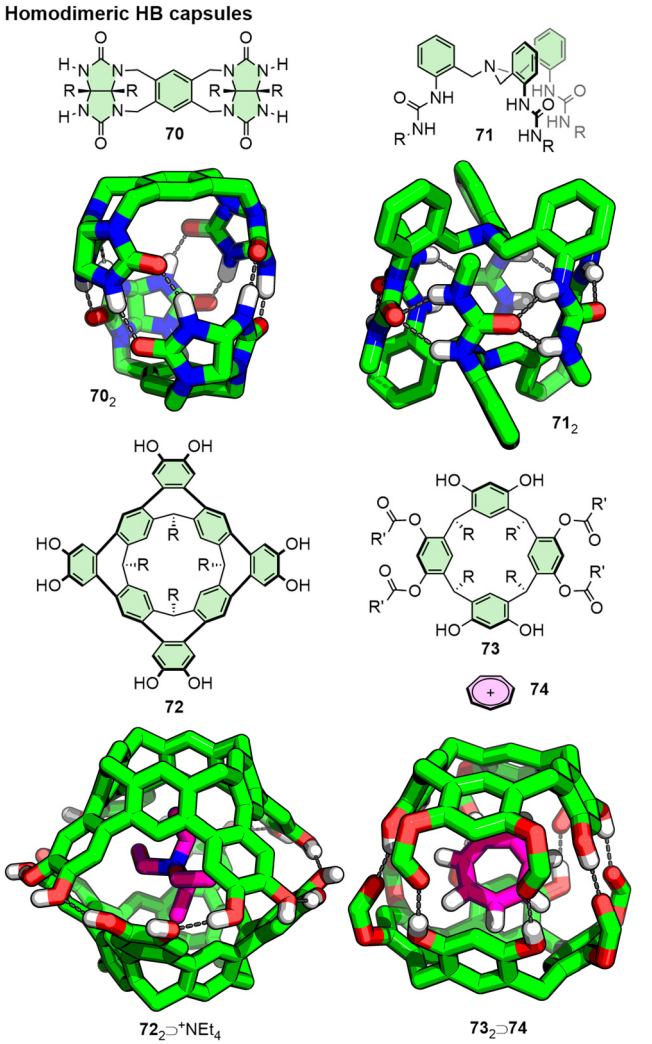


Fig. 15 Homodimeric capsules formed through HB interactions between self-complementary units. R groups omitted from SCXRD structures for clarity.

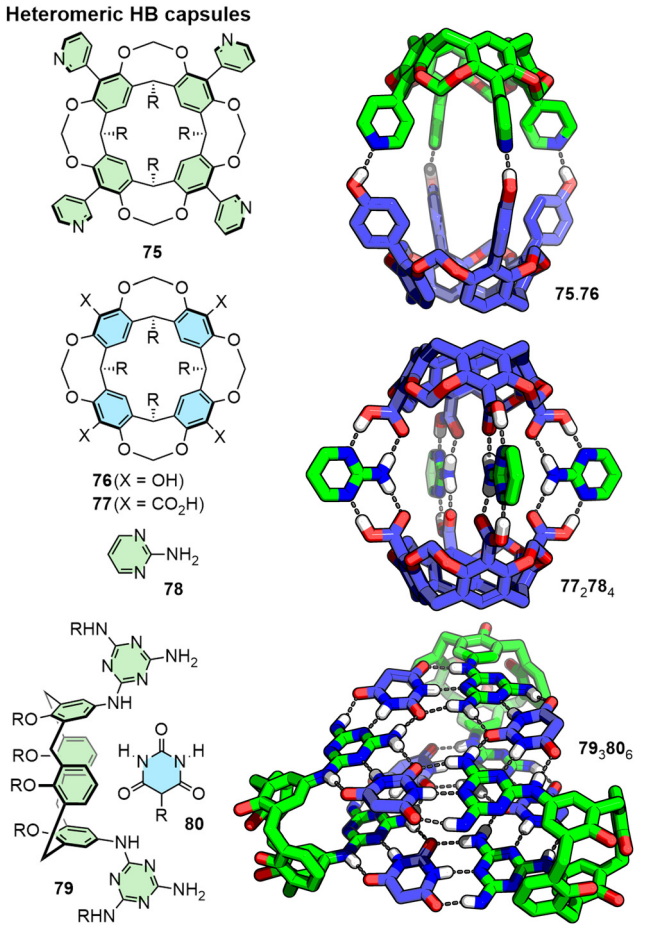


Fig. 16 Heteromeric capsules formed through HB interactions between complementary building blocks. R groups omitted from SCXRD structures for clarity.

Larger homomeric HB assemblies beyond dimers have also been investigated. Tetramers,[159] hexamers and octamers[160] have all been realised, with a large hexameric assembly 2.3 nm in diameter and a cavity volume of 2800 Å^3 recently reported.[161] Seminally, MacGillivray and Atwood reported the solid-state structure of a hexamer formed from the self-assembly of a resorcinarene with 8 molecules of water through a concerted network of 60 hydrogen bonds.[162] The solution-phase persistence of this structure, and its ability to encapsulate guests, in water-saturated chloroform, was subsequently demonstrated.[163]

In addition to these homomeric systems, heteromeric assemblies have been reported from interactions between complementary building blocks (Fig. 16). Combining resorcinarenes functionalised with HB donors, such as carboxylic acids (*e.g.* **77**) and alcohols (*e.g.* **76**), and acceptors such as pyridines (*e.g.* **75**), has been shown to lead to the formation of heterodimeric capsules (*e.g.* **75.76**).[164] Related architectures assembled from quite different building blocks, such as acid-functionalised resorcinarenes and tetrapyridyl porphyrins (including double-cavity systems) have also been reported.[165] Charge-assisted HBs have been exploited to prepare heterodimeric capsules that have demonstrated enhanced stability in polar media including methanol and water.[166]

Through careful design, multi-component heteromeric HB architectures have also been realised. [4+2]-type assemblies have been reported from cavitands assembled with complementary struts (*e.g.* 77_278_4),[167] whilst a [6+3] architecture was shown to assemble from functionalised calixarene **79** and barbituric acid derivative **80**.[168]

In summary, supramolecular capsules assembled through cooperative hydrogen bonds between subcomponents can be realised of varying topology, including both homomeric and heteromeric architectures. Perhaps unsurprisingly, these assemblies tend to only be stable in apolar, aprotic media, although there are exceptions.[169] Systems held together by charge-assisted HBs, however, have demonstrated enhanced stability in highly competitive solvents, as have hosts that are additionally stabilised by interactions with guest molecules. A wide range of structures for the monomer units have been reported, in addition to the commonly explored calixarene and resorcinarene cavitands, with various HB units that are

capable of interacting with themselves or complementary motifs.

Under suitable conditions, HB capsules have been shown to be capable of encapsulating a variety of guest species, both neutral and charged, and to exhibit guest selectivity.[158] Such host–guest chemistry has been exploited for applications in catalysis,[170] molecular separations,[171] and stabilisation of reactive species.[172]

Conceptually similar to HBs, electrostatic interactions arising from the donation of electron density into electropositive regions, labelled σ-holes, on halogen and chalcogen atoms have been termed halogen bonds (XBs) and chalcogen bonds (ChBs), respectively (Fig. 14). Whilst less well studied than their HB congeners, XBs and ChBs have been investigated as alternatives non-covalent interactions in supramolecular chemistry, including for self-assembled architectures.

Heteromeric XB capsules have been reported from the self-assembly of suitably functionalised cavitands (Fig. 17a). Aakeröy and co-workers observed such a structure in the solid-state from interactions between a calixarene macrocycle with four iodotetrafluorobenzene arms and a tetrapyridyl resorcinarene.[173] Subsequently, Diederich and co-workers demonstrated the persistence of related architectures (**81**.**82**) in solution by NMR and were able to determine an association constant between the two components. Critically, small quantities of an alcohol were required to stabilise the structures through hydrogen-bonding interactions between the arms of the resorcinarene-based cavitands. The ability of these XB capsules to bind small guest molecules both in the solid state and in solution was also demonstrated.[174]

As an alternative design strategy, homomeric systems have also been reported in which XB acceptor-functionalised cavitands are assembled through interactions with iodonium ions (I^+), generally prepared *via* a pre-organised Ag(I) metallocapsule intermediate (Fig. 17b). In this way, the halonium ions act as analogues of metal ions in coordination cage structures. Using this approach, Rissanen and co-workers have reported dimeric I_3L_2[175] and I_4L_2 assemblies,[176] I_6L_4 tetrahedra,[177] and a 4 nm $I_{12}L_6$ octahedron.[178] As with MOCs, subtle changes to the ligand structure can have a significant impact on the resultant assembly: whilst ligand **83** with imidazole donor units yielded an I_3L_2 prismatic cage, DABCO ligand **84** formed an I_6L_4 tetrahedron.[177] Aside from characterisation by SCXRD in the solid-state and by MS, the persistence of these species in solution has been demonstrated by NMR and DOSY. Typically, these experiments have been run in low polarity solvents such as dichloromethane or chloroform, although stability in acetonitrile has also been demonstrated.[177]

Dimeric capsules assembled through chalcogen-bonding interactions have also been reported (Fig. 17c). By incorporating benzotelluradiazole and benzothiadiazole moieties into resorcinarene cavitands, Diederich and co-workers showed that these were capable of self-assembly into [1+1] capsules in solution and the solid-state. Crucially, for the capsule dimers to form, the cavitands were required to adopt a *vase* conformation. The significantly stronger ChB interactions with tellurium

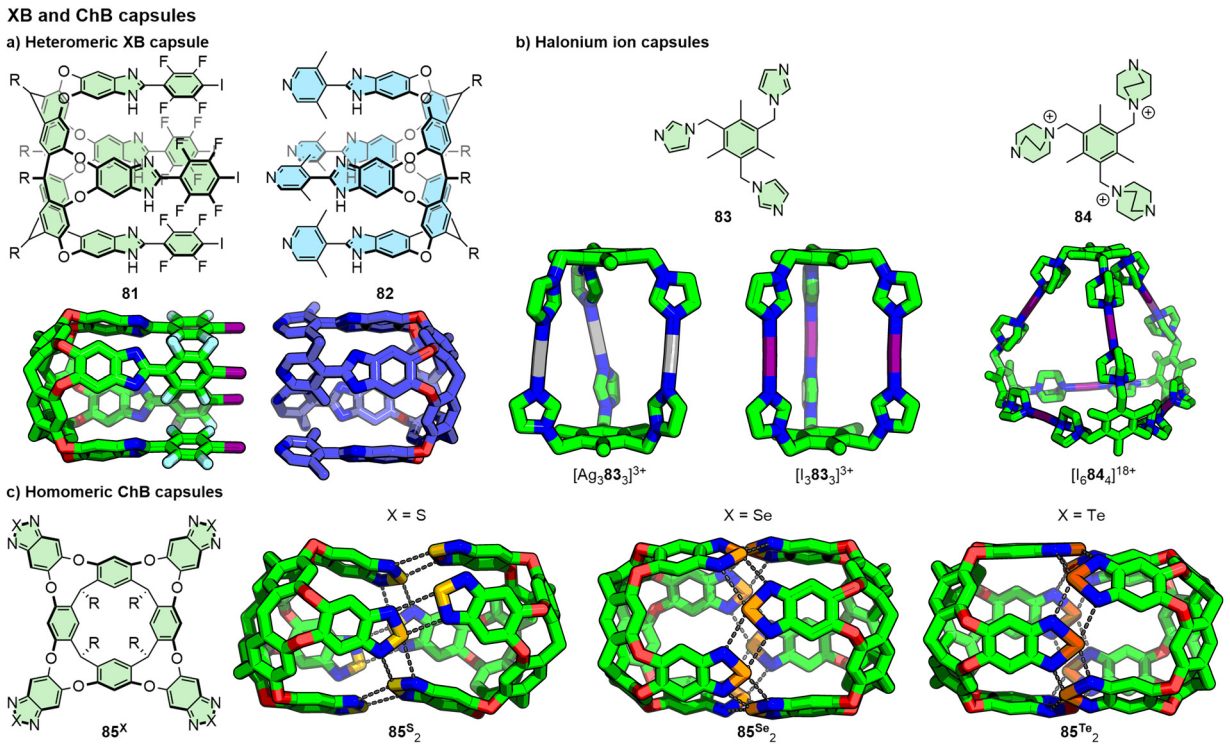


Fig. 17 Halogen- and chalcogen-bond interactions, including with halonium ions, can be used to assemble both homo- and heteromeric capsules. R groups omitted from SCXRD structures for clarity.

resulted in persistence of $\mathbf{85^{Te}}_2$ across a range of solvents (dichloromethane, benzene and THF) and concentrations (down to 40 μM in THF). In contrast, $\mathbf{85^{S}}_2$ only formed in benzene and THF, resulting from complementary binding of solvent molecules within the cavitand cavity favouring the *vase* form, whilst in dichloromethane $\mathbf{85^{S}}$ adopted a *kite* conformation, preventing capsule formation.[179] Rebek, Yu and co-workers investigated related benzoselenadiazole systems with water-solubilising substituents attached to the lower rim. Although by itself cavitand $\mathbf{85^{Se}}$ adopted a *kite* conformation in D_2O, addition of suitable guests induced formation of [1+1] capsules templated through incorporating one (*e.g.* *n*-nonane) or two (*e.g.* *n*-pentane, cyclohexane) guest molecules.[180]

HB, XB and ChB capsules can be studied in solution by NMR techniques, including DOSY. Of special note, self-assembly of the XB capsules reported by Diederich and co-workers (**81.82**), that incorporated perfluorinated iodophenyl XB donors, could be followed by ^{19}F NMR, and close spatial proximity of the acceptor and donor cavitands evidenced by ^{1}H,^{19}F HOESY experiments.[174] MS is also commonly employed, as is SCXRD in the solid-state, although the relatively weak nature of some HB/XB/ChB interactions can make successful crystallisation of these capsules difficult.

The study of capsules assembled through XB and ChB interactions is still in its infancy, with the first example of a solution-persistent capsule only reported within the last decade. Similarly, preliminary results have shown these systems to be capable of binding guest molecules, although exploitation of this for applications remains very much underexplored. There has been one report, however, of a ChB capsule demonstrating selective encapsulation of oxime isomers and their isomerisation under confinement.[181]

To date, systems assembled from donor- and acceptor-functionalised build blocks have been reported solely from suitably functionalised cavitands. Despite this limited structural diversity, there is nothing inherent to the design of these capsules that suggests alternative building blocks could not be used. In contrast, those assembled using halonium ions have been demonstrated with a range of ligands of different geometries and denticities. The potential to exhibit stability in various solvents and across a range of concentrations has also been demonstrated, although less robust systems remain predominant. As such, XB and ChB capsules[182] at this nascent stage of their study show promise as robust supramolecular architectures.

π−π capsules

π–π, or π–stacking, interactions are relatively weak and poorly directional in comparison to other non-covalent interactions such as dative covalent and hydrogen bonds. This helps to explain the relative paucity of capsules assembled using π–π interactions, as it can be difficult to design systems for controlled self-assembly. Due to their relatively weak nature, the directing effects of π–π interactions are often assisted by solvophobic forces that act as significant drivers of the self-assembly process. In this section we will consider systems that assemble in organic solvents, whilst assemblies that form in aqueous media (*i.e.* driven specifically by hydrophobic forces) will be discussed in the subsequent section.

Cram and co-workers reported the synthesis of resorcinarene-derived macrocyclic cavitands with extended aromatic units. These were able to adopt conformations referred to as *vase*,[183] in which the aryl arms are axial, *i.e.* perpendicular to the plane of the resorcinarene base, and *kite*, in which the arms splay outwards in an equatorial fashion (Fig. 18). By introducing substituents (*e.g.* methyl group) onto the 2-position of the resorcinol components (X-substituent of **86** in Fig. 18), the structures could be locked into the *kite* conformation.[184] The *kite* conformers provided a suitable π-surface for dimerisation, observed in the solid-state by SCXRD analysis,[185] and in solution by vapour pressure osmometry and NMR in $CDCl_3$ (*e.g.* evidenced by shielding of methyl groups directed internally in the dimer).[186] Such capsule-type dimers were termed *velcraplexes*.

In addition to homodimers, heterodimers were observed to form in some instances from mixtures of cavitands, including when one of the components did not dimerise with itself. Narcissistic self-sorting behaviour of some cavitands was also observed, in which only homodimers self-assembled from mixtures of cavitands.[187]

Cram observed that dimer formation was highly dependent on both temperature and concentration. The nature of the solvent was also important, with more polar solvents (*e.g.* acetonitrile, methanol) promoting cavitand dimerisation through solvophobic effects.[186b,187] A similar observation was made by Paek and co-workers, who determined the association constant for one homodimer in $CDCl_3$ to be 4.9×10^{-4}; increasing the solvent polarity resulted in enhancement of

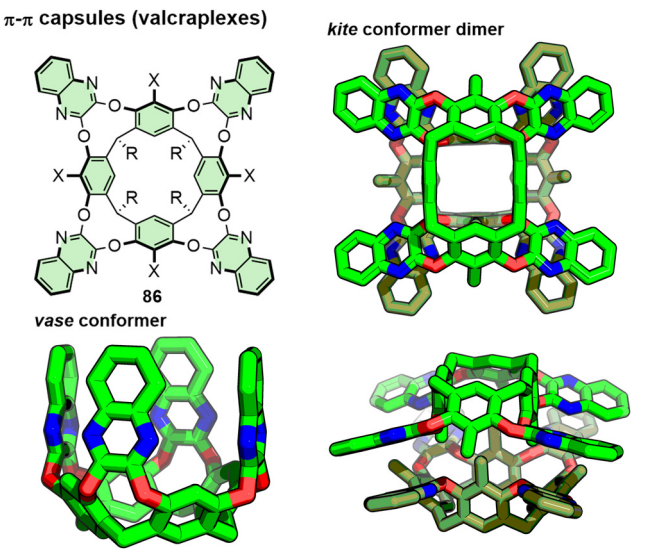


Fig. 18 Cavitands can adopt *vase* conformations in which the arms are orthogonal to the base, or a splayed *kite* conformation that allows dimerisation through π−π interactions. R groups omitted from SCXRD structures for clarity.

the association constant by two orders of magnitude in 10% CD_3OD.[185]

Within these systems, structural modifications to the cavitand could have profound effects on their self-assembly. Whilst larger resorcinol substituents, *e.g.* ethyl groups, still promoted the *kite* conformer, they prevented homodimerisation through steric hindrance.[184] Dalcanale and co-workers observed that tethering groups on the lower rim of the cavitand also impeded dimerisation through restricted conformational flexibility.[188]

Due to the difficulty of their design and fragility with respect to concentration, temperature and solvent, the host–guest chemistry of velcraplexes have not been studied. Although they have been investigated as supramolecular junctions within polymers,[189] their use remains extremely limited.

Hydrophobic capsules

Within the context of this discussion, the hydrophobic effect[190] is (very) broadly defined as the propensity for apolar moieties to aggregate in aqueous solution due to the sum of interactions between solvent and solute being less energetically favourable than interactions between water molecules. This allows relatively weak, and often ill-defined and poorly directional, non-covalent interactions (van der Waals forces, π–π interactions) to exist between the apolar moieties that might be ineffective at directing any semblance of molecular ordering in alternative solvents. Thus, while polar solvents can be detrimental to the stability of many other supramolecular capsules due to competing interactions between the components and solvent molecules, exploiting the hydrophobic effect can lead to the formation of capsules in one of the most competitive solvents – water (Fig. 19).

Gibb and co-workers have extensively investigated so-called "deep-cavity" cavitands,[191] such as **87** and **88**, the latter of which consists of a hydrophilic surface functionalised with carboxylic acid groups, and a hydrophobic cavity, the entrance to which is surrounded by a hydrophobic rim (Fig. 19a). By itself, the cavitand was shown to exist in monomeric form in basic aqueous solution; addition of a suitable hydrophobic template (*e.g.* estradiol), however, led to formation of a dimeric capsule.[192] Depending on the size of the guest, one (*e.g.* estradiol) or two (*e.g.* butane, naphthalene)[193] molecules might be encapsulated within the host dimer. Whilst remarkably stable in water at various concentrations (suggesting a minimum association constant of 10^8 M^{-1}),[192] addition of other solvents (acetonitrile, THF, acetone, DMSO) led to capsule degradation to varying extents.[194] Successful deposition of capsule host–guest complexes on silica surfaces has been demonstrated, with retention of the capsular structure.[195] Cationic analogues of these have been reported by replacing the carboxylic acid moieties with amine/ammonium functionalities, enabling capsule formation in acidic media.[196] Through small structural modifications and choice of guest template, higher-order assemblies including tetramers and hexamers have been reported,[197] as have heteromeric assemblies[198] and externally functionalised systems.[199]

Hiraoka, Shionoya and co-workers reported the self-assembly of a remarkable hexameric cube from the gear-shaped monomer, **89**, in a water/methanol solvent mixture (Fig. 19b). The solid-state SCXRD structure showed the hexamer to apparently be held together by van der Waals, π–π and CH–π interactions; the delicate balance of these interactions was demonstrated by comparison with an analogous monomer in which the tolyl substituents were replaced with phenyl units, which did not form an analogous assembly.[200] Whilst this hexameric structure was able to encapsulate appropriately sized substituted benzenes, adamantane

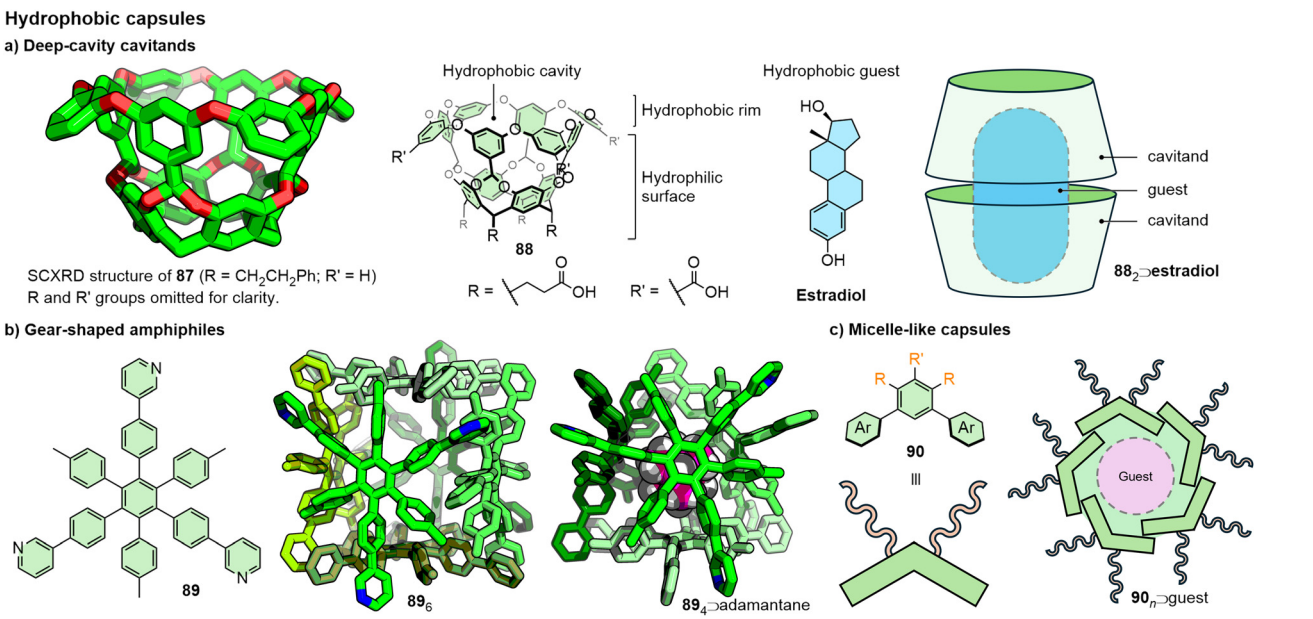


Fig. 19 Hydrophobic capsules assemble from components that contain both hydrophobic moieties, that are forced to interact with themselves *via* relatively weak and poorly directional interactions, and hydrophilic units capable of externally interacting with water molecules to solubilise the assemblies.

induced a rearrangement of the host to give a tetrameric architecture (**89**$_4$, Fig. 19b).[201] Methylation of two of the pyridine rings to cationic pyridinium moieties gave a fully water-soluble monomer that, in the absence of a template, assembled into a hexameric cube,[202] the thermal stability of which could be modified by tailoring the electronics and sterics of the non-pyridinium arm of the monomer.[203]

Detailed reviews on well-defined capsules assembled using the hydrophobic effect are available for perusal.[204] For these systems, the precise number of component building blocks incorporated into the self-assembled structures can be determined. For others, there can be a distribution of compositions. Yoshizawa and co-workers have extensively studied micelle-like structures assembled from small-molecule amphiphiles incorporating hydrophobic aromatic shells (Fig. 19c).[205] Amphiphiles with the general structure of **90** incorporating anthracene,[206] naphthalene, phenanthrene,[207] phenothazine[208] and even aliphatic adamantane[209] have been investigated. NMR spectroscopy was used to confirm the formation of aggregates, whilst dynamic light scattering (DLS) and atomic force microscopy (AFM) reveal the approximate size and narrow size distribution of the assemblies. A U-shaped amphiphile was shown to assemble into a dimeric capsule,[210] whilst an anthracene-based amphiphile formed capsules composed of 4-6 sub-components,[206] and an adamantly-functionalised monomer formed a larger assembly with approximately 16 sub-components,[209] demonstrating that, through structural design, some control over the aggregate size is possible, although formation of different sized aggregates through encapsulation of smaller or larger guests has been observed.[209]

Given the inherently low directionality of relatively weak forces that contribute to self-assembly under hydrophobic conditions, the rational design of hydrophobically-driven assemblies is somewhat challenging. Structural factors common to the different systems discussed herein include hydrophilic solubilising groups and accessible hydrophobic surfaces that can aggregate together in aqueous media. ^{1}H NMR, NOESY, DOSY and MS have all been used to demonstrate the persistence of structures self-assembled by the hydrophobic effect in solution, with some structures able to be confirmed in the solid-state by SCXRD. Other analytical techniques that have been used include dynamic light scattering (DLS) and atomic force microscopy (AFM), which can also reveal size-distribution of non-uniform assemblies. Although often limited to the binding of guests that are themselves hydrophobic, this class of capsules has demonstrated utility in a number of areas, including as molecular reaction flasks,[211] in molecular separations,[193a] modulation of photophysical/photochemical properties,[212] and solubilisation of hydrophobic species.[192,206]

Mechanically interlocked molecules and foldamers

Although not traditionally considered as molecular capsules *per se*, mechanically interlocked molecules (MIMs) – species held together through mechanical entanglement of molecular components rather than covalent bonds – and foldamers – oligomers that adopt a defined folded conformation through intramolecular interactions – can possess confined cavities described by the three-dimensional structure of the molecules. For completeness, we include brief discussions of each of these host architectures. Where MIMs are concerned, the discussion will be split into two parts covering (i) the interlocking of components that are capsules in their own right, resulting in the formation of new cavity spaces distinct from the constituents, and (ii) MIMs in which the components are acyclic or macrocyclic, therefore not considered capsules individually, but through their interlocking generate confined spaces.

Interpenetrated capsules

The same non-covalent forces that drive the encapsulation of guests within hosts can also result in interactions between capsules which can give rise to interpenetrated systems (Fig. 20).[213] For supramolecular capsules, interlocking can arise spontaneously as a thermodynamic process resulting from interactions ostensibly either directly between cage components or with a template. Kinetically robust interpenetrated

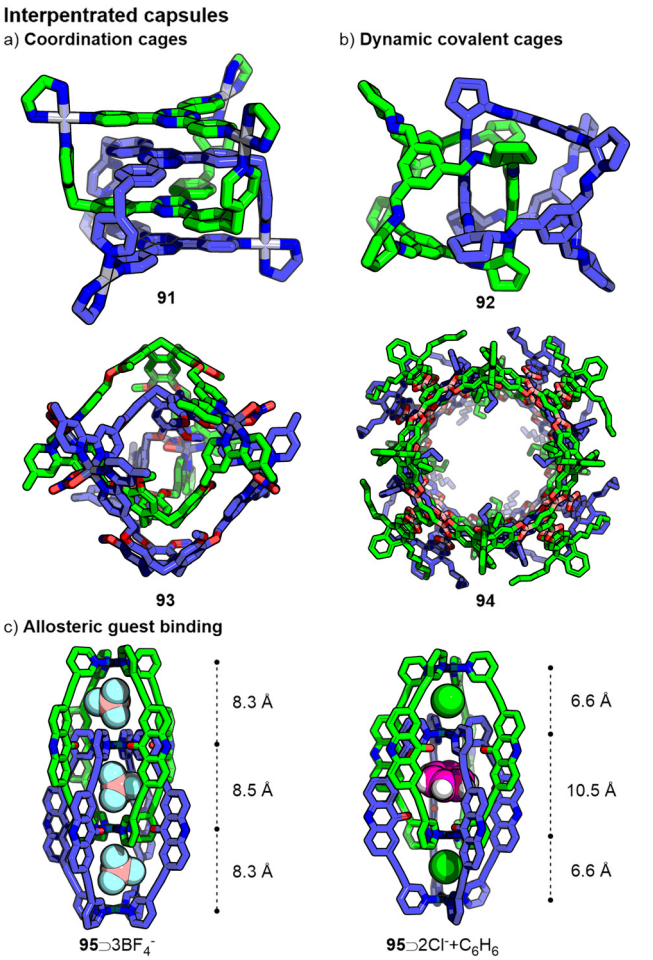


Fig. 20 Examples of metal–organic and covalent interpenetrated cage structures have been reported, some of which retain appreciable cavity space. These systems have the potential to exhibit interesting host–guest chemistry such as allostery.

capsules have also been prepared through reaction of suitably templated precursors.[214]

In 1999, Fujita and co-workers reported the spontaneous interlocking of two trinuclear coordination cages in water, driven by π–π interactions between the ligands (**91**).[215] Due to the tight packing between the cage components, any cavity space was occluded, preventing further guest binding. Subsequently, additional examples of interpenetrated coordination[216] (Fig. 20a) and dynamic covalent[217] cages (Fig. 20b) have been reported *via* "self-templation", although accessible cavity space is often severely reduced, limiting potential host–guest chemistry. Exceptions to this include Hardie's catenanted coordination cage (**93**) based on cyclotriveratrylene ligands[218] and Mastalerz's giant dynamic covalent cages (**94**).[219] Perhaps unsurprisingly, the choice of solvent can have a significant impact on the formation of such interpenetrated species.[219b]

In 2008 Kuroda reported a Pd_2L_4 coordination cage that, in the presence of suitably sized anions acting as templates, could form a quadruply-interpenetrated catenane.[220] Due to the difference between the external cavities and the central one, it was shown to be possible to encapsulate both BF_4^- and NO_3^- anions in a site-selective manner.[221] Subsequent work on related systems (*e.g.* **95**) has shown that guest binding can cause the interlocked cages to move relative to each other, altering the sizes of the cavities and affecting their host–guest chemistry, akin to allosteric binding (Fig. 20c).[222]

Despite the potentially limited cavity space offered by interpenetrated capsules, there have been reports of these systems being used for molecular recognition[223] and separations.[224] The targeted synthesis of such interlocked architectures, however, remains a significant challenge, limiting their rational design and use as molecular capsules.

Mechanically interlocked molecules

The two most common classes of MIMs are catenanes (consisting of interlocked macrocycles)[225] and rotaxanes (consisting of macrocyclic and dumbbell-shaped components).[226] The entanglement and relative orientation of the components in MIMs creates a three-dimensional cavity space between them, enabling encapsulation of guest species (Fig. 21a). The mechanical bond has been exploited to tailor environments for the interlocked components themselves, essentially acting as kinetically stable host–guest assemblies. In this manner, mechanically-enforced proximity of components can alter the reactivity[227] of, or interactions[228] between, functional units. These effects of the mechanical bond have been investigated for applications in caging the activity of biomolecules,[229] catalysts[230] and cytotoxic agents,[231] just to name a few. The discussion in this review, however, will be limited to MIMs as hosts for guest ions/molecules that are distinct from the interlocked units.

Even just within catenanes and rotaxanes there is scope for a huge amount of structural variation dependent upon the number of components, the manner in which they are interlocked, and their chemical structure. The literature on MIMs is vast; reviews detailing synthetic strategies based on anions and metal cations are indicated in the relevant sections below, with alternative template motifs covered in other reviews.[232]

Perhaps unsurprisingly, given their critical role in the development of high-yielding synthetic methods to access MIMs,[233] the binding of transition metal ions has been explored extensively (Fig. 21a).[234] The mechanically-enforced proximity of coordinating units on sub-components induces a "mechanical chelate" effect (originally termed the *catenand* effect by Sauvage).[235] In this manner, MIM ligands have been used to stabilise oxidation states or enforce unusual coordination environments of metal ions[236] and for selective detection.[237]

Like transition metal ions, anions have been used to template the formation of MIMs.[238] As such, various interlocked molecules have been engineered to possess units capable of interacting with anions (Fig. 21a)[239] through non-covalent interactions. In this manner, MIMs have been synthesised that demonstrate binding of various anions, including preferences between halides,[240] selective binding of polyatomic anions such as NO_3^-,[241] SO_4^{2-},[242] and encapsulation in aqueous media.[243]

Whilst most commonly employed for the binding of charged species, encapsulation of small neutral molecules by MIMs has been reported, albeit often serendipitously (Fig. 21b). Stoddart and co-workers have developed stepwise syntheses of both oligo[*n*]catenanes and rotacatenanes that proceed through the (transient) formation of a pseudorotacatenane, *i.e.* an unstoppered axle component bound between the components of a catenane *via* π–π and hydrogen bonding interactions, the solid-state structure of one of which (**101**⊃**100**) was reported.[244] Related to this work, the authors were able to generate a redox-active [2]catenane host in which guests could bind within different pockets between the constituent components.[245] Loeb and co-workers reported the binding of a dibenzo-24-crown-8 macrocycle between the components of a [3]catenane through π–π and CH–π interactions (**102**⊃**103**).[246]

It is possible to specifically engineer recognition components within the sub-components of MIMs for binding to small-molecule guests (Fig. 21c). Smithrud and co-workers, for example, have designed rotaxane hosts incorporating macrocyclic recognition units into the axle components, with additional host–guest interactions from the macrocyclic components (*e.g.* **104** in Fig. 21c), for the intracellular delivery of various guests.[247] Niemeyer and co-workers synthesised [2]catenane **105** incorporating chiral BINOL-phosphate units within each of the macrocycles and demonstrated its ability to bind diamine guests in DMSO, observing stereoselective binding of chiral guests;[248] Beer and co-workers showed binding of dicarboxylates within a [3]rotaxane, also reporting chiral discrimination.[249] A [3]rotaxane with porphyrin units attached to the two macrocycles was shown by Morin and co-workers to bind fullerenes in a tweezer-like fashion.[250]

The ability for MIM sub-components to move relative to each other make such cavity spaces highly flexible, particularly for systems large enough to encapsulate polyatomic molecules. Although this could potentially be exploited for adaptive host systems, uncontrolled dynamics might explain the relative paucity of examples reported of binding molecules larger than simple cations and anions.

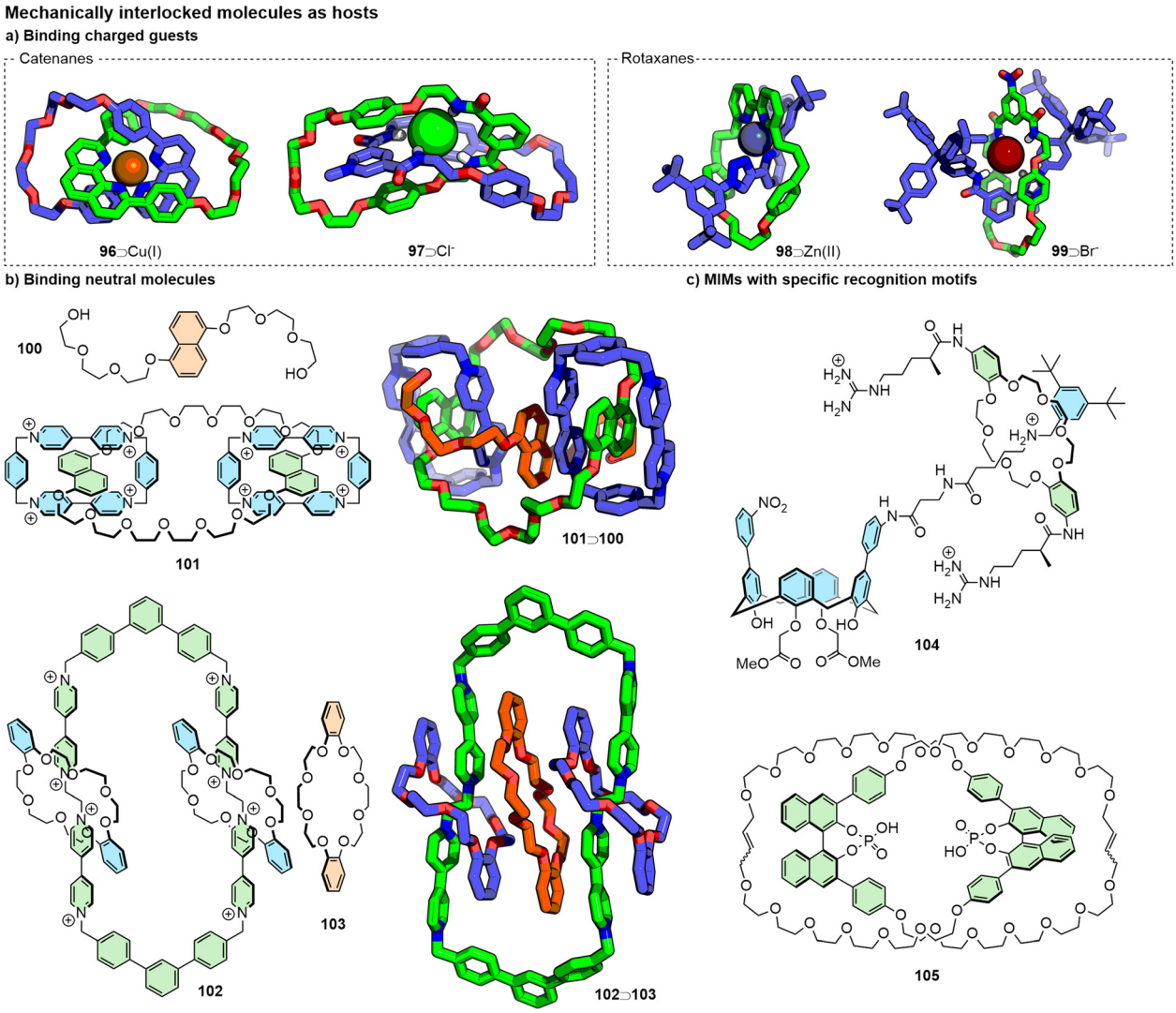


Fig. 21 MIMs are well suited to the binding of small, charged guests such as Cu(I), Cl^- and Br^- due to the mechanically-enforced proximity of interacting motifs. Less well explored is the binding of neutral guest molecules through interactions between the mechanically interlocked components.

The diversity of MIM structures that can be accessed make them one of the most tuneable classes of host systems; the type, number and manner of interlocking of the components are all variable, as are their covalent structures, allowing the installation of myriad recognition and solubilising groups. Anion-binding MIMs, for example, have been prepared with recognition groups that interact *via* hydrogen bonds, halogen bonds, chalcogen bonds and can be charged or neutral.[251] Furthermore, so-called "impossible" MIMs have been reported that lack specific binding motifs.[252] External functionalisation of MIMs has also allowed their incorporation into polymeric materials, resulting in soft matter with switchable properties dependent on the binding of a guest within the MIM cavity.[253] Due to their unusual topology, MIMs have found wide-ranging use for various applications. Specifically related to their ability to bind guest species with the endohedral cavity defined by the intersection of their components, MIMs have been used for sensing,[254] transport[255] and catalysis.[256]

MIMs are usually readily characterised using standard techniques for covalent molecular systems: NMR and MS in solution, with NOESY often being useful for identifying co-conformations of the interlocked components, and SCXRD in the solid-state, all of which can also be used to probe host–guest interactions. Mechanical linking of the components means that covalent bonds must be broken to separate them, making MIMs highly robust. As hosts of small, often charged, species such as cations and anions, MIMs are incredibly versatile hosts that can be engineered with high precision. Although the potential for multiple co-conformations has been exploited in the design and synthesis of molecular switches and machines,[257] with more complex systems, and for binding of larger guest molecules, this flexibility may be detrimental to strong and selective recognition events.

Foldamers

Foldamers are abiotic oligomers that adopt well-defined folded conformations driven by interactions between components of

their primary structure.[258] Although foldamers can be very compact, precluding their use as molecular capsules, it is possible to design systems with appreciable cavity spaces, described by the folded conformation of their scaffolds, that can be used to encapsules guests.[259]

Various monomeric units have been used to construct foldamer scaffolds (Fig. 22a), including peptidomimetics,[260] phenylacetylenes[261] (*e.g.* **106**),[262] aromatic amides[263] (*e.g.* **108**),[264] ureas[265] (*e.g.* **109**)[266] and triazoles[267] (*e.g.* **107**).[268] This diversity of building block types and monomer structures, and the quantities and sequences in which they can be combined, allows a wide range of structures to be accessed. Although a detailed discussion of their synthesis will not be included here, we note that solid phase synthetic methods have been applied to a range of foldamer structures,[269] allowing automation of what can otherwise be a very tedious process.

As the conformation of foldamers is directed by non-covalent interactions such as hydrogen bonding, π–π stacking and solvophobic forces, it is unsurprising that solvents can dramatically affect the conformational state of oligomers;[270] the incorporation of additional supramolecular interactions along the backbone has been shown to aid stabilisation of folded conformations.[271] The impact of binding anions[272] and cations[273] on the conformation of foldamers is also well known.

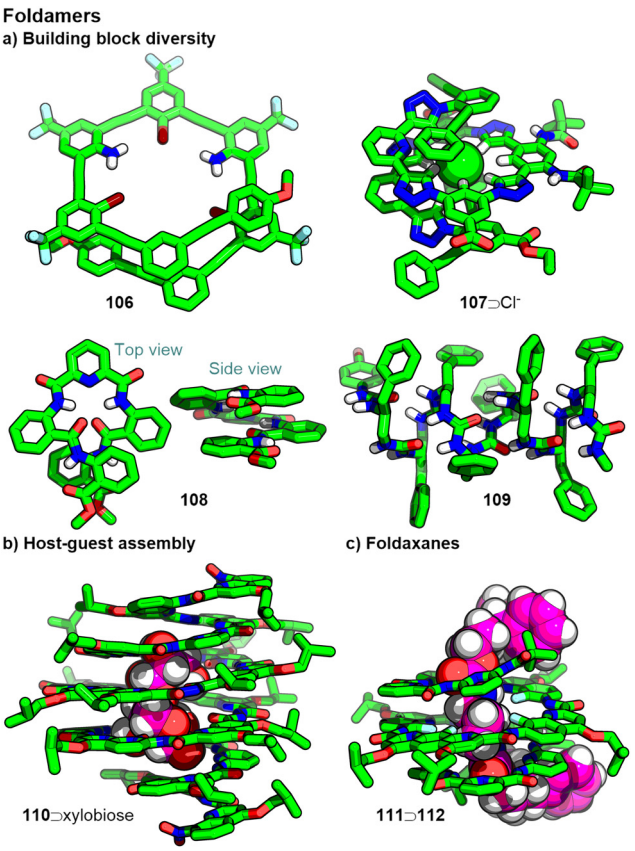


Fig. 22 Foldamers adopt well-defined conformations arising from interactions between units within their scaffold. These can create well-defined cavity spaces that can be used to encapsulate guest species.

The well-defined folded structure of foldamers allows them to possess a three-dimensional cavity space capable of encapsulating guest species; the binding of solvent/small organic molecules,[274] hydrocarbons,[275] and saccharides (Fig. 22b)[276] have all been reported. Additionally, the helical nature of many foldamers has been exploited in the stereoselective binding of chiral guests.[277] A report on the selective binding of a heteromeric pair of saccharides demonstrates the potential for cooperative binding of multiple guests.[278] The term *foldaxane* has been coined to describe assemblies formed from linear, dumbbell-shaped molecules (akin to the axles of rotaxanes) encapsulated within foldamers with the bulky terminal groups located outside of the helical structure (Fig. 22c).[279]

Although the primary structures of foldamers, being generally covalent, are robust, their folded nature that gives rise to a defined cavity is highly susceptible to external conditions, such as solvent and temperature. While foldamers in general are of interest for their (potential) biomedical[280] and catalytic applications,[281] their use as capsules has been exploited for selective molecular recognition,[282] sensing,[283] catalysis,[284] separations[285] and controlling the second coordination sphere of metal complexes.[286]

Conclusions

The study of molecular capsules, capable of encapsulating guest species, has grown exponentially since the early work of Pedersen and Lehn. Stemming from these seminal contributions, research in this area has been pushed forward dramatically in terms of both the design of capsules and demonstration of their function, particularly related to chemistry within the confined spaces of their internal cavities. In the design of capsule systems themselves, molecular engineering strategies have been developed to prepare architectures across scale lengths, that are robust, structurally sophisticated, and that incorporate functional units to change physical and chemical properties. In terms of function, the effects of encapsulation on the properties of guest species have been shown to stabilise reactive species or promote reactivity in benign molecules, and to allow their selective recognition or separation from mixtures.

Combined with advances in computational chemistry to aid in their design,[287] the chemistry of capsules is moving away from serendipitous discoveries towards the targeted design of specific structures as solutions to scientific challenges. Some of these are clearly pertinent for extant problems, such as the highly selective recognition of glucose[128] and extraction of hydrophilic anions from water.[122] Others push the boundaries of what can be achieved from a purely fundamental, curiosity-driven perspective, such as the generation of an antiaromatic confined space.[288]

The breadth of architectures that fall under the umbrella-term *capsule* is enormous, something that has hopefully been demonstrated in this article. As such, when searching for a class of capsule to achieve a certain task, researchers can be guided by system requirements in terms of stability, chemical

compatibility, flexibility *etc.* Another key consideration is often synthetic accessibility, for which there is usually a trade-off with (i) stability and (ii) structural complexity. Structures formed under thermodynamic control can be assembled from simple building blocks in high yields but are often susceptible to degrading reactions, whilst the synthesis of reduced-symmetry systems and the installation of functional groups can be non-trivial. The essentially infinite diversity of (supra-)molecular capsule structures, however, allows researchers to design systems very specifically to their circumstances.

The study of capsules and their functions is still in a period of maturation. Multiple spectacular examples in the literature have shown what can be achieved within the confined environments of capsule cavities. Building on these, and inspired by nature's use of confinement effects to achieve astounding recognition and reaction selectivity, combined with advances in molecular design, we anticipate that increasingly sophisticated structures and behaviours of capsule systems will emerge over the coming years. Based on current trends, we are sure that (supra-)molecular capsules will become invaluable tools in the development of advanced catalysts, sensors and artificial systems/networks.

Author contributions

All authors contributed to the writing of the manuscript.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts of interest to declare.

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