

Perspective

Cages meet gels: Smart materials with dual porosity

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SUMMARY

Soft materials have found uses in many areas, such as medicine, robotics, and battery research. These advances are the result of the properties of gels stemming from both their solid-like and their liquid-like features. However, fine-tuning of these properties and an onset of new applications can be envisaged if gels are coupled to metal-organic cages, discrete three-dimensional structures containing well-defined cavities. In this perspective, we review the types of cage-gel smart materials synthesized to date, their properties, and their potential applications, such as in molecular separation, catalysis, and luminescent materials. Finally, we highlight current challenges and opportunities for future research.

INTRODUCTION

Gels, in particular hydrogels, are emerging as soft materials useful for a wide range of applications from regenerative medicine,¹ artificial life,² and soft robotics³ to soil-free film-based agriculture,⁴ controlled delivery of fertilizers,⁵ catalysis,⁶ and biodegradable batteries.⁷ They are also considered to be environmentally friendly substitutes for plastics.⁸ Gels are semi-solids and typically comprise a network of structures that trap and immobilize a large amount of fluid. When the fluid is water, it is a hydrogel. Hydrogels are widely found in nature and within the human body. They offer an ideal environment for life processes to occur, whereby complex cascades of reactions must be organized with fine spatiotemporal control. We can look beyond biology and envisage translation of this concept to industrial processes, with the possibility of switching to organic solvents as required, to form functional organogels.

The unique positioning of these soft materials at the boundary between liquids and solids offers attractive features, combining the diffusion of small molecules to allow reactions to occur within the occluded solvent with the shape persistency associated with a solid, allowing gels to be shaped as desired.⁹ Thus, each part of a gel can allow a specific reaction (or orthogonal reactions) to occur, and when gels are adjacent to one another, products may meet or diffuse further to become the reactants in a new process.¹⁰ Gels can also be designed to respond to specific stimuli,¹¹ disassemble, re-form, and even convert energy from one form into another.¹² The evolution of these dynamic materials has enjoyed decades of research efforts, as has been described in the excellent reviews noted above.

The maturity of research on gels has led to their encounter with other research areas, with great potential for further innovation. The confluence of gels with metal-organic cages (MOCs), in particular, shows great promise. MOCs are discrete objects that exploit the directionality of metal-ligand coordination to form hollow geometric assemblies that can host a variety of small molecules, sometimes enabling these

Progress and potential

Materials comprising gels and metal-organic cages offer promising solutions to current scientific challenges. Their structures rely on non-covalent interactions and hence can be dynamic and change properties in response to a variety of external stimuli to exert functions, thus providing smart materials for diverse applications. Coupling these two types of materials yields a three-dimensional network with distinct sets of pore sizes and shapes, which may be useful in applications dependent on the transport of molecules at different rates, such as catalysis and chemical separation. Given the dynamic nature of cages and the range of transformations they have been shown to undergo, gels containing stimulus-responsive cages may be developed, whereby a structural transformation of the cage within the gel matrix could be followed by a change in the mechanical properties of the material. This concept might be applied in industrial processes and to develop catalytic cascades. In this perspective, we also discuss current challenges in the field, highlighting areas for exploration at the interface of metal-organic cages and gel chemistry.



guests to rearrange during catalytic transformations.¹³ The presence of non-covalent interactions within the structure of gels that contain MOCs means that the chemical bonds holding the material together can be broken and re-formed in response to a variety of external stimuli (e.g., addition of chemicals, changes in pH or temperature, etc.). As a consequence, the properties of the system can vary to exert desired functions as described further below, thus providing *smart* materials that adapt to the local environment as required for the intended application.

Particular attention has recently been devoted to the formation of hybrid gels consisting of MOCs linked together by polymer chains.^{14–16} MOCs are excellent candidates for the development of such materials due to their unique properties among supramolecular structures. The reversibility of the metal-ligand coordination bond has enabled the construction of an extensive library of two- and three-dimensionally defined structures with complex topologies, including polygons,¹⁷ polyhedra,¹⁸ polymers,¹⁹ and interlocked species.²⁰ This set of diverse architectures has been shown to be well suited to a range of applications such as the encapsulation of specific molecular cargoes,²¹ catalysis,²² stabilization of reactive species,²³ and chemical separation.²⁴ Guidelines and principles for the design of cages for task-specific applications have been extensively reviewed elsewhere^{25–27} and will thus not be explored in this perspective.

MOCs make good linkers within gels because the rules governing their formation are relatively well understood. These rules can be inferred from the coordination chemistry of their metal-ion vertices, together with the lengths and geometries of the multiply binding, i.e., multitopic, organic ligands that link these metal ions together.^{28–30} The host-guest chemistry of these cages can then be probed and rationalized, particularly for compact, isotropic guests that fit well within relatively spherical cavities.³¹

It is more challenging to design cages that do not correspond to high-symmetry polyhedra—the Platonic and Archimedean solids and their derivatives. Lower-symmetry cages are of potentially greater interest for binding isotropic guests with more complex structures. This class of guests includes drug molecules of the sort that cage-gel hybrid materials might be used to deliver. By contrast, flexible biomolecules such as proteins can accommodate defects to yield geometrically “impossible” cages,³² thus potentially opening new directions in supramolecular assembly, although general design rules are yet to be identified. By virtue of their very different supramolecular behaviors, protein-³³ and nucleic acid-based³⁴ cages are beyond the scope of this Perspective.

Gels containing cages possess well-defined cavities stemming from the cages, in addition to the mesoscopic pores of the gel, which contain entrained solvent. However, embedding cages into porous materials not only might endow gels with features characteristic of the cages, but also could lead to the development of new properties that have not been observed in soft materials before. Therefore, new functions could be programmed into the cage-gel systems. Research in this area has resulted in the design of self-healing porous polymers, as well as materials that show promise for targeted drug delivery. However, further work is required to enable the precise control and design of such systems so as to obtain hierarchical structures from a bottom-up approach.

Advances in this field may ultimately contribute to the development of next-generation materials for molecular separation. In addition, cages within the gels may act

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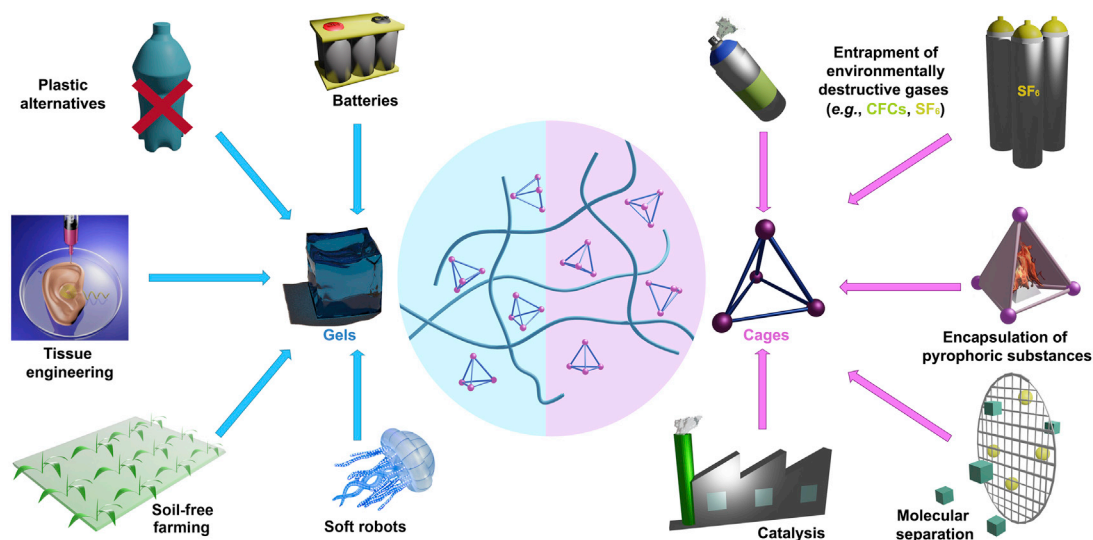


Figure 1. Applications for gels (left) and cages (right) can be combined in innovative materials (center)

Applications include batteries,⁷ plastic alternatives,⁸ tissue engineering³⁵ (copyright, 2013, American Chemical Society), soil-free farming,⁴ and soft robots³ (left) for gels and entrapment of environmentally destructive gases,³⁶ encapsulation of pyrophoric substances,²³ molecular separation,³⁷ and catalysis (right) for cages.²²

catalytically, or hold catalysts, allowing incompatible catalytic processes to be spatially separated. The cages that cross-link these materials may also transform from one architectural framework to another, thus changing the pore shapes and the connectivity between them, in turn altering the material properties of the gel.

This perspective will focus on recent progress made in the design of porous soft materials comprising MOCs that are cross-linked or embedded into gels by either covalent chains or supramolecular interactions (Figure 1). Our discussion will focus on the strategies currently implemented to design cage-containing porous soft matter and the applications that have been devised so far. We also offer future perspectives, with an emphasis on catalytic systems and smart materials.

TYPES OF GELS

In this section, gels are divided into groups, depending on the nature of the interactions that keep the cage network together. Some of the key examples of gels incorporating MOCs into their networks are based on non-covalent interactions, such as hydrogen bonding, ionic interactions, π -stacking, metal-ligand coordination, and combinations thereof. The synthesis of these polymers typically takes place in two steps: (1) the formation of the MOC and, subsequently, (2) non-covalent cross-linking of the cages into a gel network. The design principles that proved successful thus far for this two-step approach are based mainly on three different strategies, as shown in Figures 2, 3, and 4. Successful approaches enabled cages to be interconnected by means of non-covalent bonds (Figure 2), physically embedded within a supramolecular gel based on orthogonal chemistry (Figure 3), and covalently bound within a 3D network (Figure 4).

Gels with cages embedded by means of non-covalent bonds

Gels of this type have been obtained in three different ways (Figure 2). MOCs can be designed to display empty macrocycles, such as pendant crown ethers, or pillar[n]arenes, which then, upon host-guest complexation with suitable linkers, connect the MOCs to form a 3D network (Figure 2A). Alternatively, non-structural binding

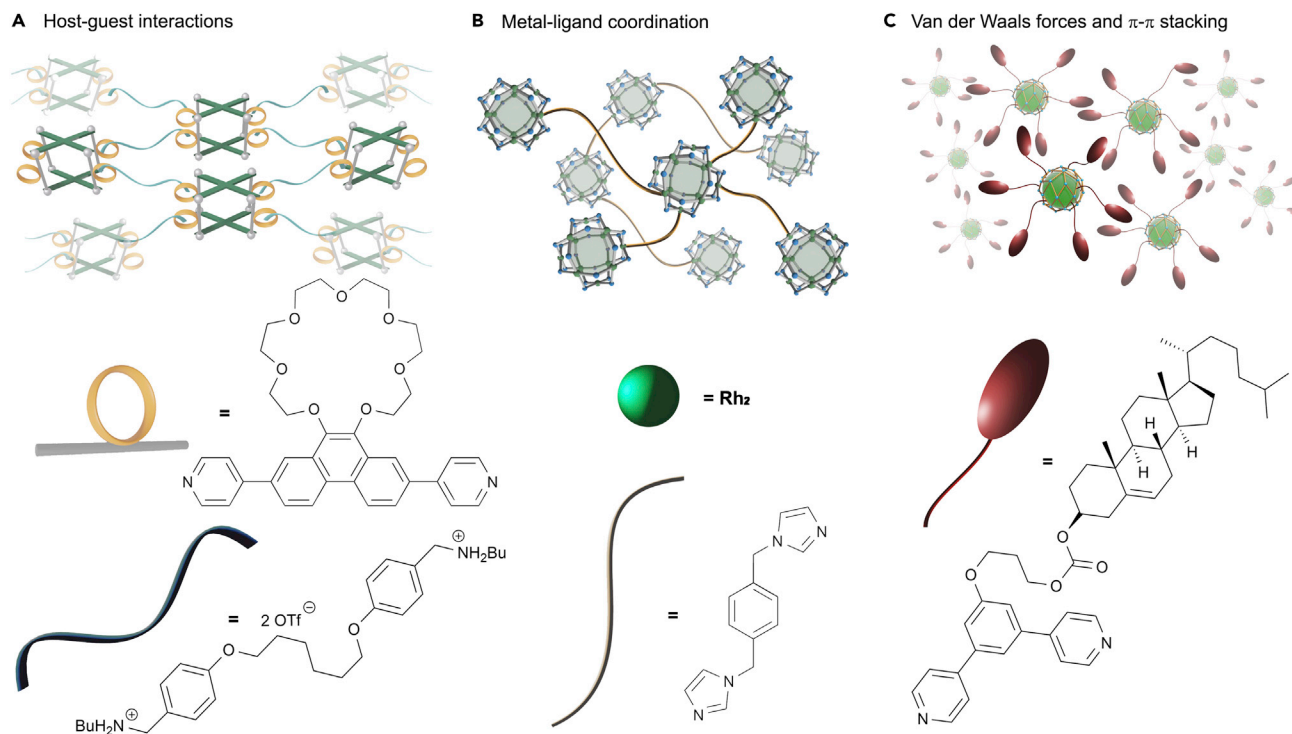


Figure 2. Examples of non-covalent interactions used as connection points in the design of gels containing MOCs

- (A) Host-guest interactions.³⁸
 (B) Metal-ligand coordination.³⁹
 (C) Van der Waals forces and π - π stacking.⁴⁰

sites can be used for labile metal-ligand exchange, to allow a linker to displace a labile ligand and bind the cages into a gel network (Figure 2B). Finally, MOCs can have ligands that display pendant motifs that can aggregate and gel, for instance, via van der Waals or π -stacking interactions (Figure 2C).

Host-guest interactions

In a pioneering study, Stang and coworkers reported the formation of a tetragonal prismatic MOC consisting of tetraphenylethene (TPE) ligands that bridge platinum(II) cage corners.³⁸ Because each cage is decorated with four crown ether functionalities, it could act as a host for four linear bis(ammonium) linkers (Figure 2A). The addition of these linkers to the cages resulted in host-guest complexation, and subsequent gelation occurred as ammonium-crown-ether binding linked neighboring cages together. This approach has been expanded upon by Wang and coworkers, who appended two crown ether moieties to Zn^{2+} - or Fe^{2+} -based MOCs, which then polymerized into a gel following the addition of a suitable bisammonium salt, ultimately forming a network of cages held together by non-covalent interactions between the cages and the linkers.⁴⁵

Huang and coworkers demonstrated the promise of the approach to obtain gels on the basis of host-guest chemistry. As pillar[*n*]arenes display useful host-guest recognition capabilities, they showed that a $Pd^{II}_2L_4$ cage containing four pillar[5]arene macrocycles can form host-guest interactions with suitable ditopic guest molecules that again acted as linkers between the cages in the gel matrix.⁴⁶ A subsequent advance was accomplished by Haino and coworkers, who showed that functional cage-based gels can be formed without modifying cage subcomponents further

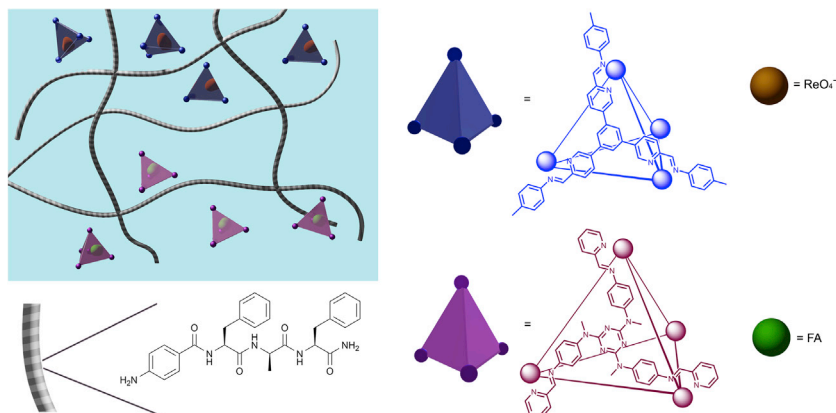


Figure 3. Supramolecular peptide-gel embedding two MOCs for molecular separation

Supramolecular gel based on a self-assembling tripeptide that embeds two MOCs soluble in the same solvent (acetonitrile) and allows for their physical separation in different layers (i.e., top and bottom of the gel). FA, fluoroadamantane.³⁷

to provide sites that would act as hosts. Instead, this study was based on the premise that the inherent cavities of the cages can be used to encapsulate guest molecules that would act as linkers to induce gelation. Specifically, a linear polyester containing multiple guest sites was found to be encapsulated by a polymer-appended cavitated-based cage, forming a supramolecular graft polymer that underwent gelation in halogenated solvents.⁴⁴

Metal-ligand coordination

Metal-ligand interactions have also been successfully used to link MOCs into gel networks.⁴⁷ These interactions have been fruitfully applied for the construction of supramolecular systems because of their dynamic nature. They are stronger than hydrogen bonds and van der Waals and π interactions, yet they are labile enough to allow for structural reconfiguration of the resulting coordination complexes, which is important for reversible sol-gel transitions, while still tending to lead to the formation of a single thermodynamically favored product.⁴⁸ Post-assembly inclusion of cages into gels may be carried out through metal-ligand exchange involving labile, externally directed metal sites on the cages in order to avoid cage disassembly during sol-gel transitions.

A notable example in which such a strategy has been employed was reported by Furukawa and coworkers. This work focused on a cuboctahedral metal-organic polyhedron based on a dirhodium paddlewheel motif, which contains labile rhodium sites in axial positions.³⁹ These sites enable polymerization through ligand exchange with ditopic imidazole linkers, which can coordinate to these metal sites and thus facilitate gelation (Figure 2B).

A similar method of employing metal-ligand junctions has been used by Zhang and coworkers, who first synthesized a Ag_4L_2 cage that contains labile and thus reactive silver sites. These sites were subjected to further functionalization with ditopic bridging ligands (disphosphines, dipyridines, or diamines), which coordinate to silver. In the presence of a suitable solvent mixture, these assemblies were found to gel.

Work by Schmitt and coworkers found that the kinetic lability of ligands bound to manganese(III) can be exploited to form self-assembled cage-containing gels.⁴⁹ A

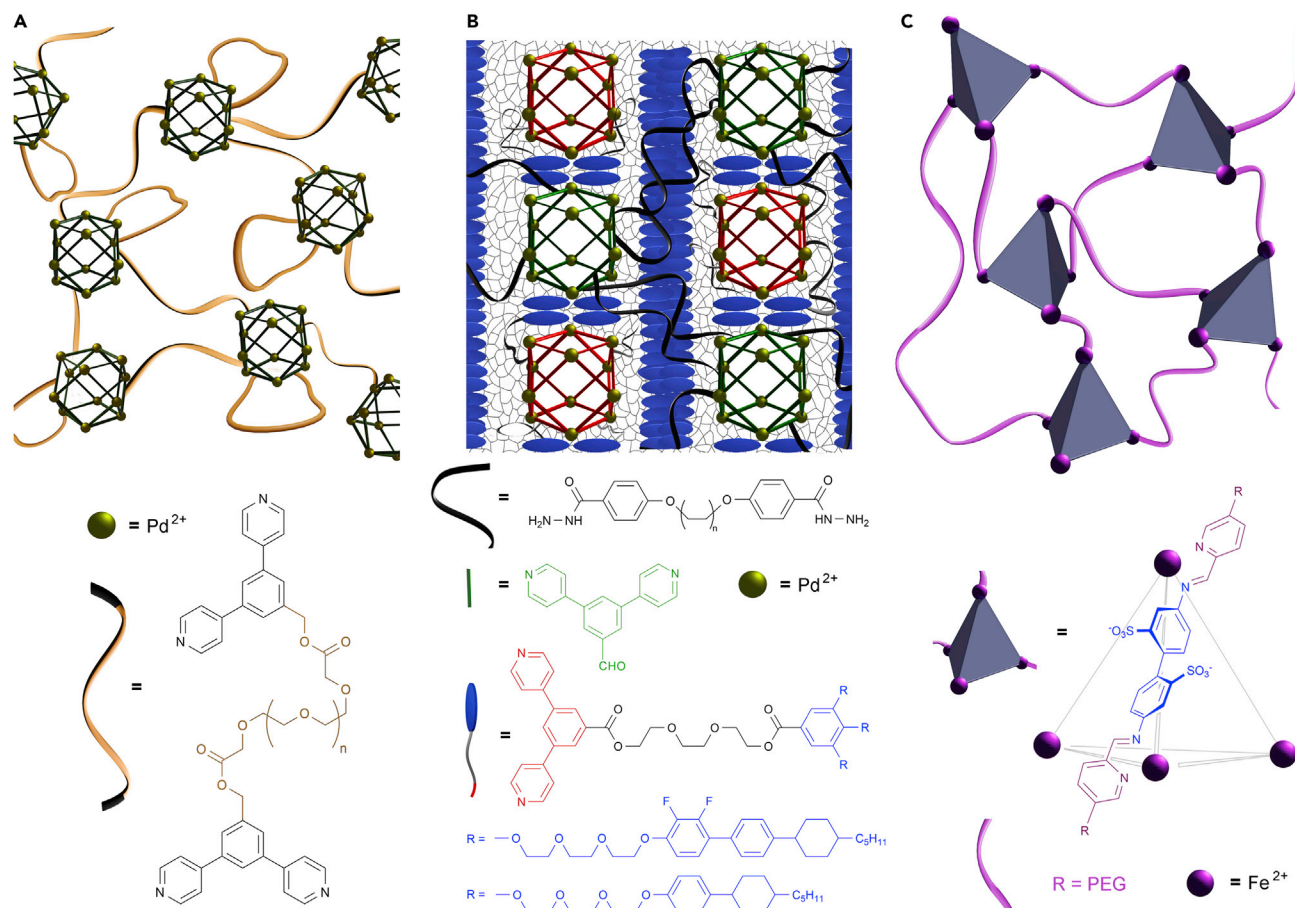


Figure 4. Examples of covalently linked gels containing MOCs

(A) Closed form of the gel containing Pd^{II}₁₂L₂₄ cages cross-linked by a PEG-containing ligand.⁴¹

(B) Liquid crystal gelation based on the spherical complex Pd^{II}₁₂L₂₄.⁴²

(C) The formation of a polymeric hydrogel network at the same time as Fe^{II}₄L₆ cage assembly.⁴³

manganese-based octahedral cage was first formed, which then acted as a structural building unit for the assembly of the gel structure. Gelation was achieved by subjecting the Mn^{III} sites on the cage to ligand-exchange reactions, whereby the terminal pyridine ligands were replaced by bifunctional 4,4'-bipyridines. These linked the cages together, resulting in gelation if ligand substitution was complete.

Van der Waals and π -stacking interactions

Van der Waals and π -stacking interactions, both of which are weaker than metal-ligand interactions, have also been investigated as possible ways of combining cages into structurally more complex supramolecular gels. To this end, Zhang and co-workers have reported an example of how such a gel can be formed based upon a Fujita-type Pd^{II}₁₂L₂₄ cage.⁴⁰ This spherical cage was decorated with 24 cholesteryl groups, which were found to stack via van der Waals interactions and thus induce cage gelation (Figure 2C).

In a related effort, work by Yang and coworkers has indicated that, in addition to intermolecular Pt \cdots Pt interactions, π -stacking could drive the gelation of an alkynyl-platinum(II) bzimpy-functionalized MOC.⁵⁰ Similarly, Su and coworkers synthesized a Pd^{II}₂L₄ cage, where L corresponded to a bipyridyl-type ligand containing a

diarylethene moiety that underwent photoreversible isomerization between an open and a closed form.⁵¹ The resulting cage displayed a reversible color change upon photoirradiation, in addition to gelation in dimethyl sulfoxide. Gelation in this case was inferred to occur due to hydrophobic and π -stacking interactions. In addition, this work showed that some mechanisms of gelation remain obscure, as other interactions, including those between the cages, or linkers and solvents, or cage counterions, might also play an important role.

Supramolecular gels that embed cages without gel-cage linkages

An exciting area of development consists of the combination of orthogonal supramolecular systems, whereby one is responsible for gelation and the other for the generation of MOCs. This approach presents further challenges related to the stability of each subsystem in the presence of the other. This area thus requires a diverse skill set in orthogonal self-assembling systems, rendering it underexplored. The first study in this direction described the combination of a self-assembling simple tripeptide with two distinct MOCs (Figure 3).³⁷ Each MOC displayed binding of a different guest in acetonitrile. When both hosts were present in the same acetonitrile solution, the selectivity of the two hosts could not lead to a physical separation of the two guests from a mixture. However, the immobilization of the two cages within a gelling tripeptide enabled the formation of different gel layers, each containing a different cage. In this manner, the rapid diffusion of the guest mixture through the gel allowed their selective capture in the corresponding host layer (see Video S1). Cage diffusion through the gel was significantly slower than that of the guests, so as not to interfere with the process of molecular separation. Entrapment of each cage in the gel also increased MOC stability against acid-mediated hydrolysis.

Both MOCs were prepared separately prior to gelation, however. A subsequent investigation might thus address the challenge of designing a truly orthogonal system, whereby all elements self-sort at the same time. Progress in this area could lead to the generation of novel materials for chemical separation through a simple, one-step process.

Gels incorporating cages interconnected by means of covalent bonds

Gels can be formed also by covalent linkages between cage building blocks into networks (Figure 4).⁵² A popular design strategy is based on the use of a pre-formed linker (for instance, based on polyethylene glycol [PEG]) that features a ligand for the MOC at either end of the chain to interconnect the cages in a network (Figure 4A). Alternatively, MOCs may be formed first, and then selectively cross-linked by using reactive sites on the ligands and on the linker (Figure 4B). Further ligand exchange could be used to introduce ligands that are appended with functional moieties that gel or form liquid crystals (Figure 4B). Polymer chains may also be constructed at the same time as the cages, in a subcomponent self-assembly approach (Figure 4C). These approaches all require fine control over the reactivity and gelation ability of the complex mixture of molecules present in the system.

As an example of the first strategy, Johnson and coworkers have used two isomers of bipyridine ligands attached to a PEG chain in the presence of Pd^{II}, forming spherical Pd^{II}₁₂L₂₄ and paddlewheel Pd^{II}₂L₄ cages (Figure 4A).⁴¹ Cage formation was accompanied by gelation to form polyMOCs gel-1 (with Pd^{II}₁₂L₂₄) and gel-2 (with Pd^{II}₂L₄), respectively. Importantly, it was found that the choice of the isomer of the ligand used in cage assembly could be used to tune the network structure and properties of the gel. Interestingly, gel-1 featured loop defects, which could be substituted with functional ligands without loss of mechanical integrity. These findings thus

demonstrated that the multicomponent metal-ligand system offered a means for tuning the network structure, and thus mechanical properties, through ligand exchange. When the process was carried out in a single step, however, topological defects arose, which could be avoided by the stepwise assembly of large and small MOCs with star block copolymers.⁵³ The choice of MOC size and polymer composition offered a means to control the gel-to-sol transition temperature.

In follow-up work, it was shown that when an analogous ligand containing the dithienylethene moiety was used in gel assembly, the cage could change its shape and size, forming $\text{Pd}^{\text{II}}_3\text{L}_6$ rings and $\text{Pd}^{\text{II}}_{24}\text{L}_{48}$ rhombicuboctahedra upon irradiation with green and UV light, respectively.⁵⁴ As a result, reversible photoswitching between two different gels, *o*-gel (open-form) and *c*-gel (closed-form), was achieved. It was found that the gels exhibited distinct topological states giving rise to different branch functionalities and junction sizes, which may ultimately find use in developing systems for reversible guest uptake and release.

Another type of covalently bound gel was prepared in a collaboration between the groups of Kato and Fujita. This work featured the self-assembly of a well-defined giant spherical liquid-crystalline complex through self-assembly of 24 mesogenic, bis(pyridine) ligands coordinating to 12 Pd^{II} ions.⁴² While the $\text{Pd}^{\text{II}}_{12}\text{L}_{24}$ cage spheres did not spontaneously gel, the addition of a dynamic cross-linker bearing 24 aldehyde groups and PEG-tethered bishydrazide led to the formation of nanostructured gels (Figure 4B).

In 2015, Nitschke and coworkers reported a new class of polymeric hydrogels fabricated from cross-linked MOCs (Figure 4C).⁴³ As they had shown previously, metal-templated imine condensation between suitably chosen aldehyde and amine subcomponents can result in MOC formation. However, when water-soluble PEG moieties were used as bridges in dialdehyde subcomponents, hydrogelation was observed to accompany cage assembly. Thus, a polymeric network rapidly assembled following the mixing of aqueous solutions of a dialdehyde bearing a flexible PEG chain, a linear rigid diamine, a base, and iron(II) sulfate.

PROPERTIES AND APPLICATIONS OF GELS

Properties

The properties of gels directly influence the scope of the applications that these materials can be used for. Stiffness, morphology, and porosity are some of the parameters used to assess the suitability of these materials for specific applications. These characteristics are studied using a variety of techniques.

The mechanical properties of cage-containing gels are studied by rheometry. This technique makes it possible to measure viscoelastic properties, such as storage and shear loss moduli, which can in turn provide valuable information about the structure of the network. Johnson and coworkers have used this technique to calculate the number of loop defects as well as the branch functionality of the polyMOC gels, i.e., the number of branches that originate from a single junction.^{41,54,55} Their research indicated that different ligands could be substituted for defects in polymer gels with large junctions and a relatively high number of loop defects. Their results in turn imply that novel functions could be introduced in this manner, by careful choice of the ligand. Interestingly, the previously discussed example of the gel prepared by Schmitt and coworkers was found to exhibit reversible thixotropic behavior, i.e., upon shaking, the material transformed from a gel to a liquid, which was most likely

the result of interconversion between aggregated nanoparticles and entangled 1D assemblies.³⁹

The study of gel porosity with short-range order by experimental methods remains a challenging task. However, Furukawa and coworkers have made significant steps toward establishing a method for determining the permanent porosity of gels containing cages. This work relies on CO₂ adsorption experiments to compare the porosity of the gel with that of the cage itself. It was found that the surface area of a solid cage sample was 46.01 cm³/g, compared with 68.64 cm³/g in the gel. The difference was inferred to be due to the presence of macropores, which enhanced gas uptake.³⁹

The morphology of gels containing cages has been studied by a combination of techniques, including scanning electron microscopy, transmission electron microscopy, and atomic force microscopy (AFM). These techniques often make it possible to deduce significant structural information about the gel and explain various properties. For instance, AFM was used to study the gel prepared by Haino and coworkers. By measuring the dimensions of various fibers, it was possible to infer their mode of stacking and therefore how host-guest interactions were responsible for the well-developed network structures.⁴⁴

Applications

Smart gels containing MOCs offer great potential for a range of uses. In this section, we review the most promising applications and present proof-of-concept studies that have been reported to date. These examples represent a foundation for materials scientists, chemists, and engineers to build upon to achieve the translation of MOC-based gels from research labs to widespread use in industry.

Guest encapsulation

Smart gels containing MOCs have found broad applications. For instance, they can be used for selective guest encapsulation. A polymeric hydrogel was reported to encapsulate fluorobenzene efficiently, as determined during guest binding studies.⁴³ This gel featured two distinct internal phases—the mesopores within the hydrogel and the inner cavities of the cages—which show selective guest uptake properties and differential release profiles.

As shown in [Figure 5A](#), guest-release experiments were conducted using gels loaded with two similar molecules, benzene and anisole. Due to the size difference between the two molecules, benzene was found to occupy both the cage cavities and the gel pores, while anisole was located only in the gel pores. Because anisole was too large for the cage cavity, it was released more rapidly than benzene from the gel into an adjacent aqueous phase. Interestingly, furan could serve as a competing guest, and therefore it induced the release of benzene from the gel into the aqueous phase.

This proof-of-principle study showed that selective guest binding and replacement in a MOC is possible also within a gel phase. This concept might be further extended and applied to other guests of industrial relevance, for instance, to assist with the separation of desired small molecules from impurities. Furthermore, guests could include biomolecules, and encapsulation could enable a variety of applications, such as to extend their lifetime, to preserve their integrity, and to control their release. For example, cage encapsulation of a peptide was demonstrated to successfully protect it from enzymatic degradation.⁵⁶ If a gel was to embed a cage hosting a bioactive peptide, this could be then selectively released once it reached the intended biological target, without risking prior degradation, which is a common pitfall for peptide-based therapeutics. Another

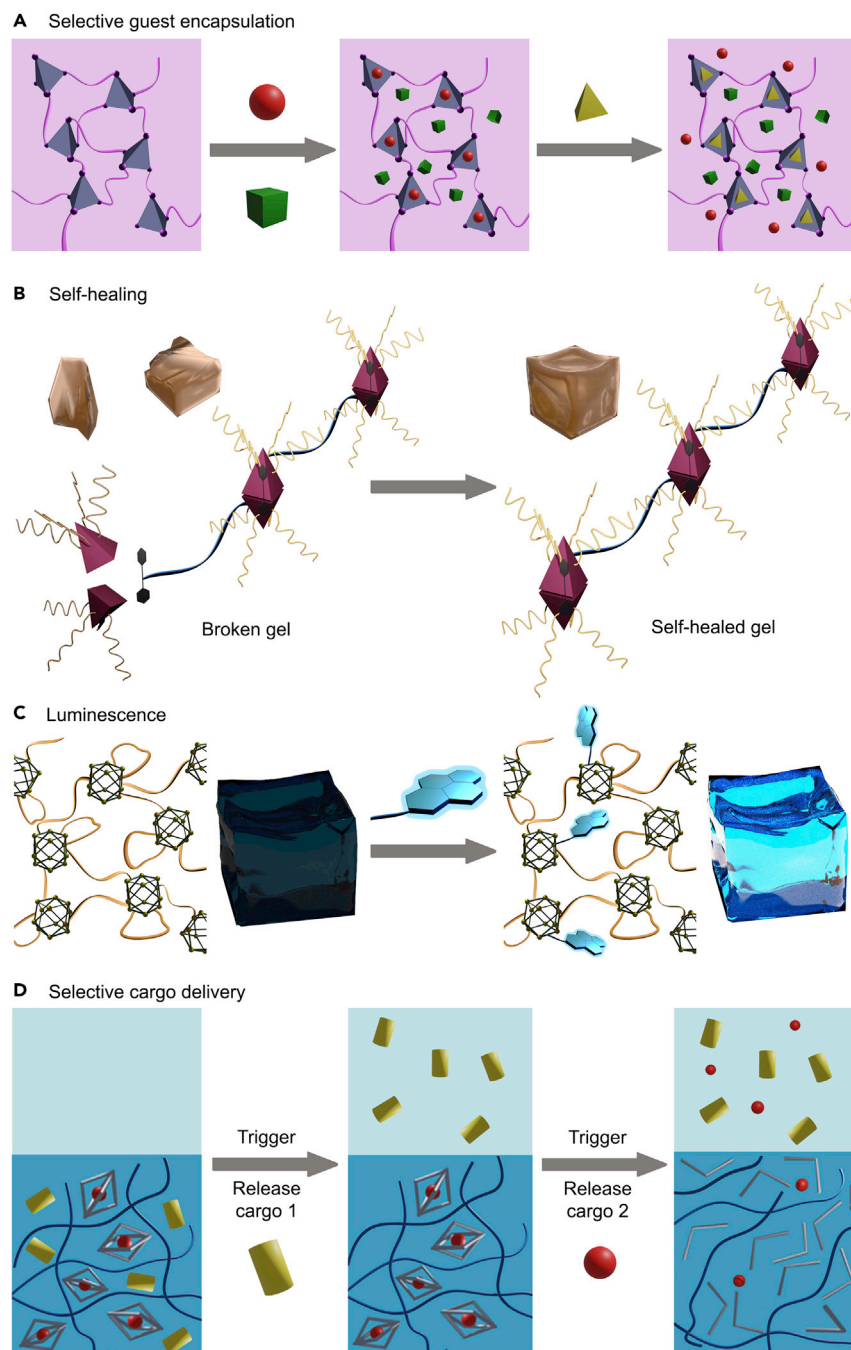


Figure 5. Examples of MOC-gel applications

(A) Multiple-guest-selective capture (red ball, benzene; green cube, anisole; yellow tetrahedron, furan).

(B) Supramolecular graft polymer and properties of self-healing.⁴⁴

(C) Luminescence arising from cross-linker substitution by a pyrene-containing analog.⁴¹

(D) Selective cargo delivery.

potential advantage could be to mask a peptide from other types of biological recognition, such as those leading to the triggering of an undesired immune response or to the shuttling of the peptide off its biological target. However, further research is needed in this direction to verify the biocompatibility of cage components.

Self-healing gels

Some MOC-based gels also showed remarkable self-healing properties. One such example is the gel produced by the groups of Fujita and Kato (Figure 4B), consisting of a giant spherical liquid-crystalline complex. This liquid-crystalline gel self-healed as a result of its dynamic covalent network generated from the aldehyde and hydrazide moieties.⁴² Similarly, the crown-ether-decorated cage reported by Stang and coworkers (Figure 2A) exhibits macroscopically self-healing properties, as the cracked gel could fully recover within several minutes.³⁸ This gel also featured multiple functions, such as fluorescence, stimulus responsiveness, and enhanced stiffness, as well.

The photoswitchable gels prepared by Johnson and coworkers also exhibited self-healing behavior. More specifically, the *o*-gel showed self-healing properties and the *c*-gel did not, due to its slower exchange kinetics (Figure 4A).⁵⁴ The difference between these two gels opened a new avenue for using a single material in applications that require both strength and self-healing, albeit not both at once. In another example, Haino and coworkers constructed a self-healing gel from a polymer-attached MOC with encapsulated polyester guest (Figure 5B).⁴⁴ At the concentration of 45 mM, the gel could heal itself within 10 min.

The area of self-healing materials contains a variety of industrially relevant applications that would benefit from dynamic coatings. For instance, car polishes exist that can self-repair from small scratches, and cage-gels could extend this concept to other use cases that would benefit from a soft coating that is able to keep integrity after being excessively stressed. Alternatively, industry may benefit from flexible surfaces whose motion could otherwise result in irreversible breakage of their coatings. Self-healing gels are also useful in tissue-engineering applications, where they need to accommodate the dynamic nature of living cells. Applications in this direction require the design of biocompatible cages, which could be engineered to direct cell fate toward differentiation or adhesion to the gel upon release of biochemical stimuli and growth factors.

Luminescent materials

The development of novel luminescent materials based on MOCs is an attractive area of research in materials science, as such materials can report, using light, upon their environment or the identity of a guest. For instance, Johnson's gel containing Pd^{II}₁₂L₂₄ cages gave rise to blue fluorescence under the irradiation of long-wavelength UV light when the cross-linker was replaced with its pyrene-containing variant (Figure 5C). Gels based on a Ag^I₄L₂ cage prepared by Zhang and coworkers exhibited aggregation-induced emission with luminescence resulting from the TPE moieties on the ligands.⁵⁷ Remarkably, the gels transformed into luminescent crystals when Cl⁻, Br⁻, or I⁻ was added, which provided a new and convenient way of preparing highly emissive crystalline materials.

The alkynylplatinum(II) bzimpy-functionalized cage synthesized by Yang and coworkers showed an emission color change in different solvent mixtures.⁴⁸ The emission color of the cage solution in a mixture of dimethylformamide and H₂O changed from pale yellow to orange-red with increasing H₂O content. In addition, the solution of the cage spontaneously converted to a transparent gel at ambient temperature. Gels formed from such cages might find applications as luminescent materials in light of the existing emissive cage cross-linkers.⁵⁸

The gels based on cholesteryl moieties and Pd^{II}₁₂L₂₄ cages (Figure 2C) did not exhibit luminescent behavior, but emission was observed when a ligand containing

a TPE moiety was used during the self-assembly process.⁴⁰ This gel was observed to disassemble when strongly coordinating CN^- was introduced, which may be due to the coordination of CN^- to the Pd^{2+} center.

All of these examples demonstrate possible ways to engineer cage-gels with programmable luminescence. A potential future direction could target materials that emit light when cracked, for instance, in industrial contexts where knowledge of material failure is essential. If fluorescence was to follow guest or ligand exchange, the process could offer a direct way to monitor the function of the material, for instance, to see when specific guests are released or trapped for an intended application (e.g., nutrient release, pollutant entrapment, or sensing of analytes).

Cargo release

The gel based on $\text{Pd}^{\text{II}}_2\text{L}_4$ cages and pillar[5]arenes fabricated by Huang and co-workers was found to be able to take up and release certain drug molecules. The MOC gel could selectively encapsulate the drug molecule emodin and the dye methylene blue in its cage cavities and the pores of the gels, respectively. Upon heating and shaking, gel-sol transition took place, and methylene blue was first released from the gel into the aqueous phase (Figure 5D). Subsequently, treatment of the resulting mixture with excess acid led to the destruction of the MOC and the release of emodin. The ability of gels to release different cargoes in a controlled manner may find applications in biology, including the delivery of drugs or biomolecules as mentioned in the previous sections.

Catalysis

In addition to guest encapsulation, self-healing, liquid crystals, luminescent materials, and drug release, MOC-based gels have also been used in catalysis. Recently, Johnson and coworkers synthesized an elegant $\text{Cu}^{\text{II}}_{24}\text{L}_{24}$ -cross-linked polyMOC c-gel and successfully applied it to the copper-catalyzed alkyne-azide cycloaddition “click” reaction.⁵⁹ A polyMOC c-gel was fabricated from a four-arm PEG star polymer functionalized with *m*-BDC (BDC = benzenedicarboxylate), an *m*-BDC-derivatized coumarin-based ligand, benzophenone, $\text{Cu}^{\text{II}}(\text{OAc})_2$, and ethyl-4-(dimethylamino)benzoate (Figure 6A). The authors found that this polyMOC c-gel could be reversibly switched between Cu^{II} , Cu^{I} , and Cu^0 states through photoreduction or air oxidation (Figure 6B). Upon irradiation with UV light, the c-gel disassembled into a green transparent liquid within 2 h, and the photoexcited coumarin moiety reduced Cu^{II} to Cu^{I} . Further irradiation led to a brown liquid resulting from the formation of Cu^0 nanoparticles. Interestingly, the polyMOC c-gel could be regenerated from either the Cu^{I} or the Cu^0 solution upon exposure to ambient air. To demonstrate the potential utility of the polyMOC c-gel, the authors showed that the “click” reaction between benzyl azide and tetrakis(prop-2-ynyloxymethyl)methane proceeded smoothly in the presence of a catalytic amount of polyMOC c-gel upon UV irradiation, and the desired triazole product was isolated in 85% yield (Figure 6C).

Cages with catalytic properties could thus be used to provide sites where catalytic transformations could take place, acting as nanoreactors embedded within the gel matrix. Products of the reactions would then diffuse into the gel network, endowing it with additional or different properties. Another outcome might be the ability to perform reactions in pre-determined locations in the gel by using the resulting substrates without the need for their prior purification. Previous work has shown that cages can act as catalytic platforms suitable for a range of reactions, including Diels-Alder,⁶⁰ Nazarov cyclization,⁶¹ and hydrolysis.⁶² Therefore, we expect that the field

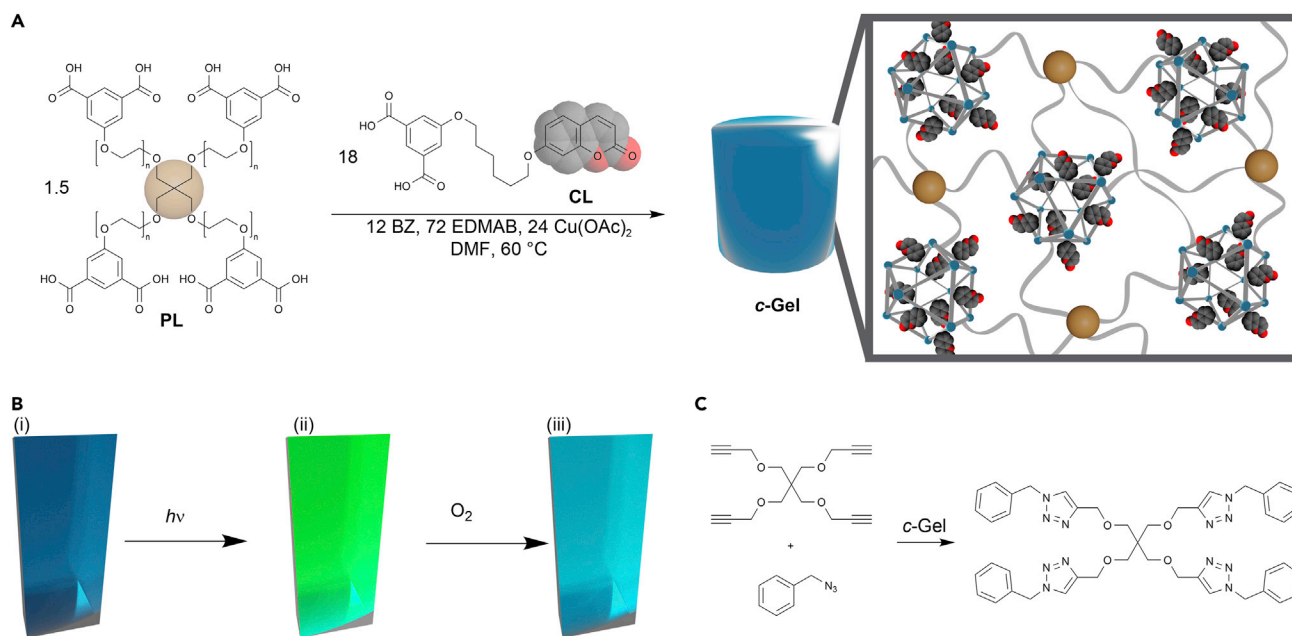


Figure 6. MOC-based gels in catalysis

(A) Synthesis of Cu₂₄L₂₄-cross-linked polyMOC c-gels from *m*-BDC-functionalized PEG star polymers (PL) and coumarin-functionalized *m*-BDC (CL). DMF, dimethylformamide; EDMAB, ethyl-4-(dimethylamino)benzoate.

(B) Images of c-gels (synthesized from 2 kDa α,ω -azide-terminated PEG and tetrakis-alkyne) after annealing (i), after irradiation with UV light to induce the copper-catalyzed alkyne-azide cycloaddition reaction (ii), and after reoxidation (iii).

(C) PolyMOC c-gels catalyzed the alkyne-azide cycloaddition “click” reaction.

will develop new supramolecular catalytic systems that involve reactions with industrially relevant substrates.

PERSPECTIVES

Porous soft materials composed of gels that incorporate MOCs into their frameworks have attracted considerable attention in recent years. Their potential lies in the premise that the advantages of both cages and gels could be incorporated into a single material, which both would be straightforward to produce and could lead to improved solutions for existing applications. In addition, it is possible that by way of synergy between their MOC and gel components, enhanced and unprecedented properties could be imparted to these gels, enabling advances in different fields. However, we find that new methods for characterizing MOC-based materials are needed to guide their future development. The application of positron annihilation lifetime spectroscopy or neutron scattering in this area of research could enable scientists to study MOCs within gels as discrete entities as well as further characterizing porosity, both of which have so far been done only by indirect methods, such as guest binding. In this section, however, we focus on the potential of more diverse applications of the field, with an eye on the future.

A key potential advantage of coupling MOCs to gels is the presence of dual porosity. Thus, different cargoes might be encapsulated within the gel mesh, and inside the cages, to achieve control over the release kinetics and the resulting interactions. As an example, gels are widely studied for environmental remediation, for instance, to entrap pollutants or confine oil spills.⁶³ The presence of MOCs could add useful features, to monitor the process or control its kinetics. Pollutants could diffuse through the gel and displace an encapsulated fluorophore

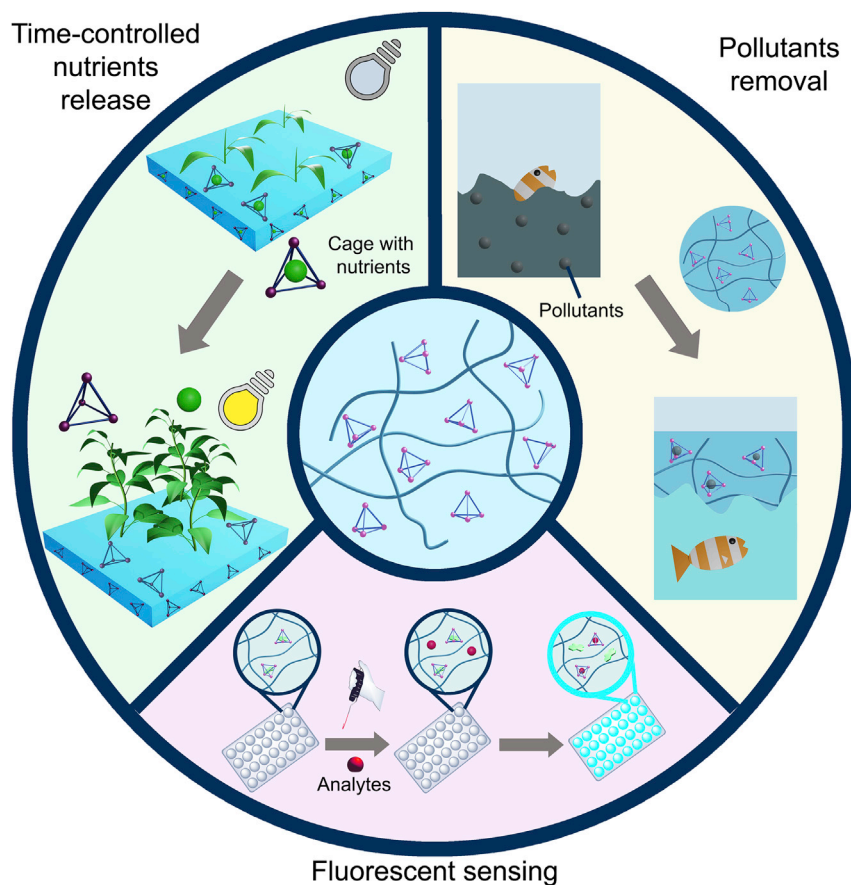


Figure 7. Potential future developments in the area of cage-containing gels could find a variety of applications for the benefit of society

guest (e.g., a polycyclic aromatic hydrocarbon)²¹ from the cage, giving rise to a material that becomes luminescent and making it possible to monitor the efficiency of entrapment of the pollutants. Similarly, an alternative system could be envisaged in which a pollutant instead quenches the fluorescence of a luminescent cage upon binding, as was shown to be possible in the case of Hg^{2+} uptake in a zirconium-based MOC.⁶⁴ Finally, the physical separation of a pollutant inside a cage from the previously polluted liquid could be achieved if the cage were embedded into a solid gel (Figure 7, right section).

Finally, light might be used to trigger the conformational change of photoresponsive cage ligands to release guests, which would then diffuse out of the gel with kinetics controlled by the gel phase. Potential cage candidates whose cavities undergo a transformation upon light irradiation have already been reported (see Figure 4A). Active guests (e.g., bioactive molecules, soil nutrients, dyes, etc.) would thus be released only upon suitable illumination (Figure 7, left). Analogously, this concept could find applications in sensing if an analyte was to be selectively detected by entrapment in a cage and consequent release of a fluorophore (Figure 7, bottom section). Research in photoresponsive cage-gels is ongoing, and recently the first example was described that used a photoacid generator to induce cage disassembly, with consequent gel-to-sol transition, upon irradiation of a cage-polymer system.⁶⁵

Molecular separation

Soft materials containing metal-organic frameworks (MOFs) in their structures are attractive for molecular separation because they can be designed so as to possess cavities of various sizes, due to the micropores of the cages and the mesopores of the gels. In addition, by careful choice of organic ligands used for the construction of cages, hydrophobicity and cavity chemical environment could be tuned, thus making it possible to encapsulate only certain types of guest molecules from a mixture.

MOFs are porous solids that have emerged as a promising class of materials, for example, in gas storage.⁶⁶ Certain types of MOFs have already been commercialized. Nonetheless, gels containing cages can offer advantages complementary to those of MOFs. For instance, to be applicable in an industrial setting, MOFs need to be embedded within other solids, whereas the gels described here can be readily incorporated into soft composites, for example, as membranes for molecular separations. In addition, MOFs are relatively brittle, whereas porous soft materials are potentially more moldable. There exist a wide range of environmentally relevant mixtures that are difficult to separate using current technologies and where gels could be used for remediation.⁶⁷ H₂/hydrocarbon separation in the petrochemical industry is a promising application, given that some MOCs have already been shown to selectively take up certain hydrocarbons.

Catalysis

Catalytic cages have to date been employed in the solution phase. The development of cage-containing gels offers new opportunities for heterogeneous catalysis. An advantage of systems described above in this context is the presence of macro- and mesopores within the gel network, which could help the diffusion of substrates to the catalytic cage sites. Reactions may be catalyzed by the cages themselves or by catalysts embedded within the cavities of the cages. Technologies with an even higher level of complexity could be envisaged, where consecutive chemical reactions are allowed to take place, leading to catalytic cascades.

Other applications

Given the cavities of the cages and malleability of gels, the systems presented here could be used to design optimized materials for drug delivery. Wettability of the gels is an important advantage when it comes to biological applications. In addition to optimizing the performance of cage-containing gels for existing applications, they could also be used to tackle novel challenges. For instance, artificial soils to support plant growth could be formed by using hydrogels that contain a small proportion of cages. Compared with currently used materials, these new systems could provide finer-grained control over the structure and facilitate controlled release of pesticides, nutrients, or other plant-relevant compounds (Figure 7). The UN Sustainable Development Goals also justify research in this area.⁶⁸

CONCLUSION AND OUTLOOK

Given the above discussion, further investigation and development of novel and already-existing applications of MOC-based gels are warranted. There is great potential for building upon the current applications, but also for devising new ones that could not previously be imagined. The field has already resulted in the fabrication of gels with tunable mechanical properties. As a next step, we envisage systems consisting of arrays of cages that could change their architectural frameworks within the soft matter matrix. This would enable further fine-tuning of properties of both the cage micropores and the gel mesopores, which could lead to the advent of

attractive applications such as catalytic cascades or chemical separations. Finally, we suspect the future will bring further development of characterization methods for MOC-based gels, which will guide rational design and fabrication of these materials. Clearly, there are many challenges to be addressed for the implementation of these systems for the benefit of society. These include the development of convenient methods for the large-scale production of cages at a reasonable cost, the optimization of cage solubility and stability, and the development of systems that can undergo many cycles of assembly and disassembly in an efficient manner. Finally, the identification of suitable metal-ligand combinations that are environmentally friendly, or biocompatible, depending on the application, will be needed for deployment at the industrial level. Given the high level of interest by different research groups worldwide in cage-gel design, and the rapid progress in this field, we anticipate that soon the diversity of these systems will be expanded to address many of these challenges.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.matt.2021.04.018>.

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AUTHOR CONTRIBUTIONS

All authors contributed to researching and writing this perspective.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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