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ARTICLE

The growing importance of crystalline molecular flasks and the crystalline sponge method

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This article showcases recent advancements made using crystalline molecular flasks and the widening list of prospective applications for the crystalline sponge method. This expansion has coincided with an increasing number of materials termed crystalline sponges, and a report of a predictive means of identifying candidates from crystallographic databases. The crystalline sponge method's primary application has been determination of absolute configuration, and this has evolved from the analysis of carefully chosen planar aromats to more diverse identification of natural products, biological metabolites, and analysis of volatile chemical components. However with time-resolved X-ray crystallography providing arguably the most informative atomic scale insights of dynamic chemical processes, this application of the crystalline sponge method may soon eclipse structural determination in terms of importance.

1. Introduction

The crystalline sponge method[1] grew from the triad of rapid advancements in single-crystal X-ray crystallography, an explosion in interest surrounding porous materials, and exploitation of the dynamic nature of solid-state materials. Central to the crystalline sponge method is a porous framework material, termed a crystalline molecular flask (CMF), which could be classed as either a metal-organic framework (MOF),[2] or porous coordination polymer (PCP).[3] A characteristic of CMFs that sets them apart from the majority of MOFs/PCPs is a high tolerance for structural deformation in the solid-state that occurs without loss of single crystallinity, a property that enhances their ability to uptake guest molecules with a high likelihood of ordering.

Most topical CMFs make use of the trigonal linker 2,4,6-tris(4-pyridyl)-1,3,5-triazine (tpt), coupled with a zinc halide metal salt. Specifically, dynamic behavior in the form of swelling and shrinking of the crystalline lattice was reported for the framework $[(ZnI_2)_3(tpt)_2] \cdot 6C_6H_5NO_2$ (**1**) (Fig. 1) in response to the gain or loss of nitrobenzene molecules with no loss in crystallinity.[4] Flexibility in terms of solvent exchange was additionally observed, laying the foundation for evaluation of more complicated guests. Both of these attributes allowed a key early innovation, solvent exchange of the synthesis solvents for non-polar cyclohexane, to occur without crystal degradation. This had the practical advantage of promoting high guest loadings while eliminating highly toxic nitrobenzene from the material. Other CMFs also showed promise, including a solvated
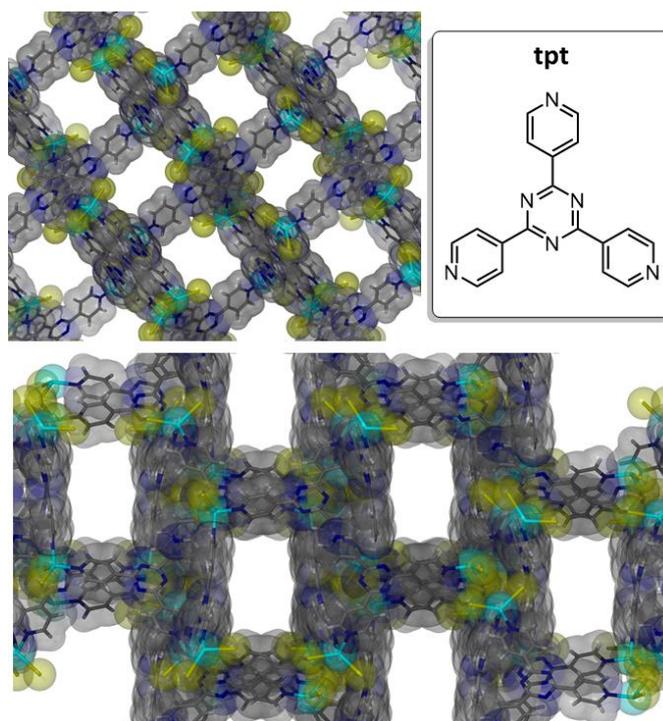

Fig. 1 *Top left:* CMF **1** viewed down the crystallographic *b* axis showing one channel architecture. *Top right*: The structure of the ligand tpt. *Bottom*: Second pore type viewed down the crystallographic [101] direction.

cobalt analogue, $[(Co(NCS)_2)_3(tpt)_4]$,[1b] and several analogous open-framework materials.[5]

Reviews of CMFs draw parallels between discrete cage complexes of tpt (*e.g.* Pd_6tpt_4 type cages) and **1**, owing to similarities in cavity dimensionality, and the ability to host and characterise guests and chemical reactions.[6] Looking further back, links to some founding work in the field of MOFs can be

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found in the form of a mixed ligand species containing tpt and cyanide ligands that was found to capture 'nanodroplets' of up to 20 solvent molecules.[7] Unlike **1**, these early MOF systems were rigid, and had discrete void spaces owing to cyanide linkers sealing the pore apertures.

Recently CMF chemistry has begun to diversify, including materials other than those comprised of zinc halide nodes and tpt linkers. The drive for this expansion has been two-fold. First there have been obstacles to widespread application of the crystal sponge method, such as variable crystal quality, as well as a synthesis that often results in multiple crystalline morphologies of varying robustness.[8] Refinements to the original method have been made that virtually eliminate these problems,[9] however some inherent limitations have persisted, such as poor framework stability in polar solvents, and a narrow pore aperture cross-section of 8 x 5 Å[2,5,10] Consequently, development of new CMFs with water stability have been undertaken that bear no relation to **1**.[10] Furthermore, a recent method to identify new CMF candidates from the Cambridge Structural Database promises to greatly expand upon this.[11] Similarly, re-evaluating older materials that exhibit porosity from the perspective of guest-hosting ability may yield even more canditates.[12] Primarily, this review will focus on results provided by the founding frameworks **1**, however readers should be mindful that CMF chemistry is evolving rapidly.

2. Determination of absolute configuration

The primary application of the crystalline sponge method has been determination of absolute configuration of small molecules, chiral or otherwise. The instigating publication that triggered widespread interest in this topic was a 2013 *Nature* report describing CMF-enabled visualisation of the chiral natural products santonin, the major components of a polymethoxyflavone mixture, and Miyakosyne A.[1b] Reception towards this paper was initially somewhat muted after it was found that the chiral assignment of the latter molecule was partly incorrect, leading to a corrigendum. However multiple refinements to the crystalline sponge method,[8] coupled with a proliferation of examples served to restore any lost confidence in the technique.

Recent years have seen a wide variety of natural products and small molecule organic species with challenging chiral structures characterised using the crystalline sponge method. Molecules with chiral quaternary carbons, including lactones, indoles and an azetidine species (Fig. 2).[13] The method was practically applied to revise the absolute structure of a pair of natural products, cycloelatanene A and B, which were isolable only as oils in trace quantities.[14] Initial structural reports[15] made using COSY, HMBC and NOE NMR analyses had misassigned a single stereocentre of the spiro[5.5]undecene scaffold, which was later clearly visualised by the crystalline sponge method. Similarly, the functional group assignment of the absolute structure of fuliginone was amended by the substitution of a phenyl ring for an alcohol.[16] These examples built on previous reports in which supplementary crystallographic information
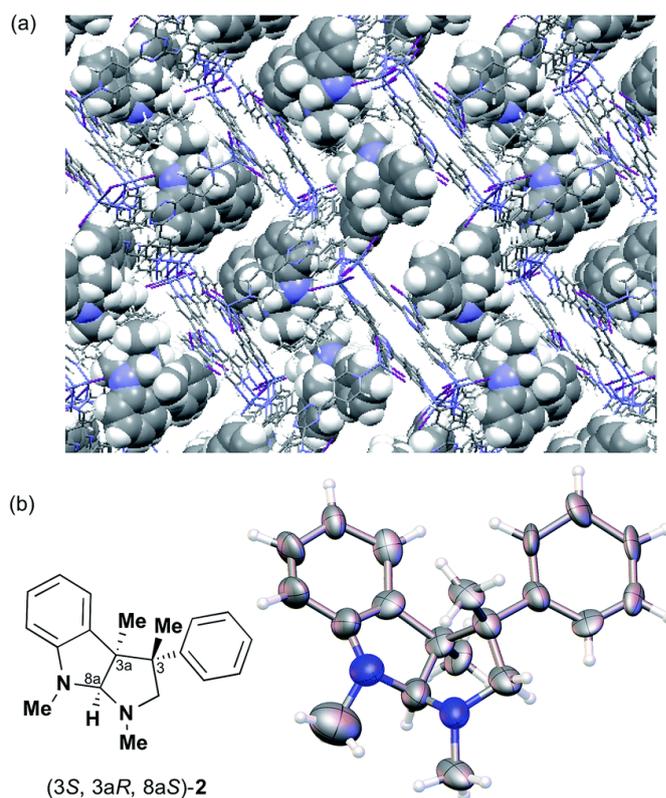
(a)

(b)

(3*S*, 3a*R*, 8a*S*)-**2**

Fig. 2 Example of a pyrrolidinoindoline species exhibiting quaternary carbon chirality that has been determined using the crystalline sponge method.[13] Published by The Royal Society of Chemistry.

was provided in the investigations of astellifadiene[17] and elatenyne,[18] two natural products from a fungus and marine sponge, respectively.

Practically, most of these structural assignments make use of preparative HPLC to isolate nanogram to microgram quantities of pure natural products or metabolites from mixtures.[1b,13-18] However, the crystalline sponge method will also prove exceptionally useful in the field of total synthesis owing to the very small quantities needed during crystal loading, and the ability to recover up to 95% of the analyte.[18]

Maximising data quality obtained from the crystalline sponge method has been approached from multiple perspectives. In terms of X-ray sources, synchrotron radiation is commonly used to obtain the greatest amount of data possible. Specific protocols for the use of synchrotron radiation in conjunction with CMFs have recently been reported.[19] The use of synchrotrons typically provide better resolution data, enable the use of longer detector distances that benefit to the long unit cell axes found in CMFs, as well as dramatically reduce collection times (from days to hours).[19] A general review appeared in 2015 describing the application of crystallographic analysis to ordered guests in open-framework materials that provides an excellent overview in the context of recent examples.[5]

Iterative improvements in the synthetic protocols used to generate CMFs have similarly improved data quality,[8,19] a trend that is likely to continue into the future. Despite the

improvements made to the synthesis of CMFs, careful evaluation of each crystalline crop to choose the most pristine crystals remains essential to achieving high-quality results. The use of an X-ray scanner to provide preliminary diffraction analysis has been used to assist with this problem, which may be an essential investment for research laboratories targeting high throughput CMF chemistry.[18] The use of welled microscope slides to slow evaporation of mother liquor during the crystal selection phase of crystallography, coupled with the use of coating products that limit rapid solvent loss from highly porous single crystals have similarly provided improvements in the quality of diffraction data.

3. Confinement effects

The act of hosting a guest within a CMF may, in some instances, have an observable influence on that material's property. Typically this is due to a steric effect imparted by the framework. Such effects have been observed for several salicylideneanilines when hosted in CMF **1**.[20] Here two aromatic rings linked by conjugation deviate from planarity by 20-30° when hosted in the framework. This imparts photochromic behaviour in the guest, giving rise to a switchable material.

There is a body of evidence that suggests that the CMF confinement effect can be harnessed in some instances to resolve isomeric mixtures, provided that only one isomer can selectively enter the CMF, and interconversion between forms can be triggered externally.[21] Where mixtures require chiral resolution, there is potential to apply CMFs as a chromatographic stationary phase. This has been explored for the $[(Co(NCS)_2)_3(tpt)_4]$ framework (Fig. 3).[22] Separation of the evaluated mixtures, which included planar aromats and organometallic complexes, was likely influenced by degree of permeation in the pores aided by complementary interactions with the electron-withdrawn tpt ligands in the CMF.
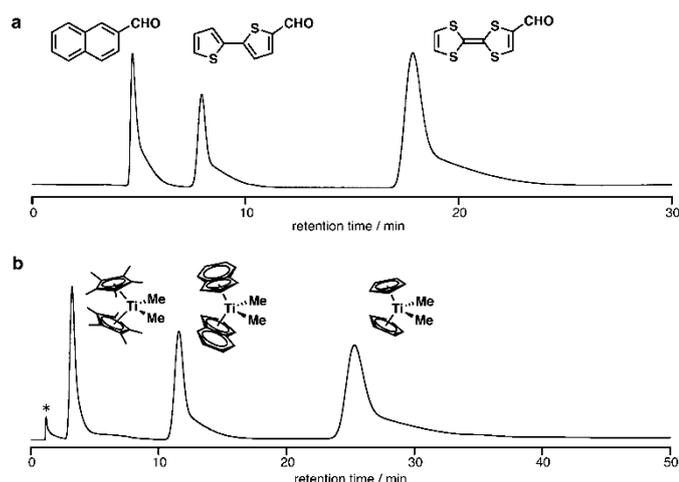

Fig. 3 Loading of a HPLC column with microcrystals of CMF $[(Co(NCS)_2)_3(tpt)_4]$ resulted in separation of two mixtures, one comprised of small-molecule aromatics (*a*) and one comprised of titanocene complexes (*b*). Reprinted with permission from Ref. 22. Copyright 2014 American Chemical Society.

Confinement effects have also been seen for organometallic species. Ferrocene moieties hosted within CMF **1** and the isomorphous $ZnBr_2$ CMF were found to exhibit higher intensity in the 600-800 nm region by diffuse reflectance spectrum relative to that of the guest alone.[23] It was additionally seen that the rotation exhibited by the ferrocene cyclopentadienyl ligands was less hindered and thus faster when confined within the CMF. This was rationalised in terms of the CMF providing weaker host-guest interactions compared with pure crystalline ferrocene.

Luminescent properties of guests have also been influenced by CMFs. When the dye molecule BODIPY 493/503 was hosted within CMF **1** the $\lambda_{(max)}$ was observed to red-shift by 40 nm concomitant with a drop in luminescent intensity. These effects were attributed to charge-transfer interactions between the guest and tpt ligand of the CMF framework, *i.e.* quenching by exciplex formation.[24] This result mirrored that of a closely related system described as a 'coordination capsule' and possessing many of the same traits as the CMFs described here.[25] Refinement of the chemistry between host and luminescent guest could lead to materials with tuneable wavelength and emission intensity.

4. Dynamic single-crystal reaction studies

Once the ability of CMFs to host and order guest molecules was established, focus began to shift towards monitoring reactive species. Spurred by concurrent interest in post-synthetic modification (PSM) of MOFs and PCPs, the foundations were lain for their application to CMFs.[26] Transfering known PSM reactions to the CMFs scaffold proved successful,[27] taking advantage of the modular behaviour of substituted triphenylene guests.[28] The ability to perform chemical transformations within a pre-formed CMF framework was thus established.

Simultaneously, advancement of time-resolved crystallographic techniques had begun to reveal unprecedented detail of molecular interactions. This typically is achieved by taking crystallographic 'snapshots' of a chemical process with X-ray diffraction experiments. Emergence of this technique was made feasible by advancements in diffraction sources, such as microfocus synchrotron beamlines and X-ray free-electron lasers, which allow a more complete set of chemical process snapshots to be obtained over a given time period. Time-resolved crystallography can reveal bond formation and breakage, changes to bond lengths and unit cell dimensions, conformation changes, isomerisation, as well as other chemical traits.[29] As an example, biological processes can occur on femtosecond (10^{-15} s) timescales, yet with time-resolved crystallography it has been possible to unravel the catalytic cycle of enzymes.[29,30] Suitable crystalline systems for time-resolved crystallography are uncommon, as the molecular processes investigated require freedom to alter conformation. In many crystalline systems this flexibility is absent, however the properties of CMFs are excellently matched to this task.

Changes in chemical conformation or identity may be triggered by an external stimuli, such as temperature, light,

chemical reagent, pressure, magnetic field, etc. Molecular transformations resulting from photoactivation have driven recent progress in this area owing to the potential to achieve high conversion ratios,[31] coupled with relatively minor strain placed on the crystalline lattice when sterically undemanding photoactive ligands (e.g. nitrite, nitric oxide, dimethyl sulfoxide, etc.) are used.[32] There are many examples of external stimuli being applied to CMFs resulting in chemical reactions or changes in guest conformation that were subsequently characterised by X-ray crystallography, many of which were detailed in section 3. The following two subsections emphasise solution–phase and gas–phase chemical reactions with concomitant crystallographic characterisation in CMFs.

Pseudo solution-phase dynamic behaviour

Using the cartridge approach[28] to place an ordered functional group handle suitable for PSM reaction within the CMF pores, simple chemical transformations were initially evaluated. The conversion of an amine to an imine was initially achieved, yielding X-ray visualisation of the initial and final products.[33] This relatively mundane PSM transformation was later enhanced by kinetic trapping and observation of the hemiaminal intermediate in an *in situ* X-ray diffraction experiment (Fig. 4).[34] Provided the kinetics of a reaction are known, and the reaction proceeds within a CMF with crystallographic ordering, the experimenter can selectively halt

an experiment at cryo-temperatures and thereby obtain a snapshot of the reactants at any point.

'Click' chemistry has also been evaluated using CMFs, as exemplified by the Huisgen Cycloaddition.[35] The Huisgen reaction between azide and alkene functionalities produces two regioisomeric products, a 1,4- or 1,5-substitued 1,2,3-triazole, based on a range of factors including sterics and electronics. Hosting this reaction within a CMF was found to influence the ratio of the substituted products, likely owing to the sterics of the pore architecture.[36] In the CMFs the azide groups formed a pseudo-component of the framework scaffold, with the alkene component being varied in the pores. An increase in the steric bulk of the alkyne, particularly in the *para* position, resulted in an increase in 1,4-selectivity, with the largest shift towards 1,4-selectivity (as opposed to 1,5-selectivity) imparted by the addition of a *t*-butyl group. This example highlights the possibility of developing catalytic systems tailored to preferentially synthesise regioisomers that are typically disfavoured under normal conditions.

Influence over regioselective behaviour imparted by the CMF scaffold has also been applied to the Diels–Alder reaction.[37] In this example the diene functional group forms a pseudo-component of the scaffold, and a selection of imide dienophiles was introduced into the pores to observe reactivity. Crystal structures showing pre- and post-reaction were
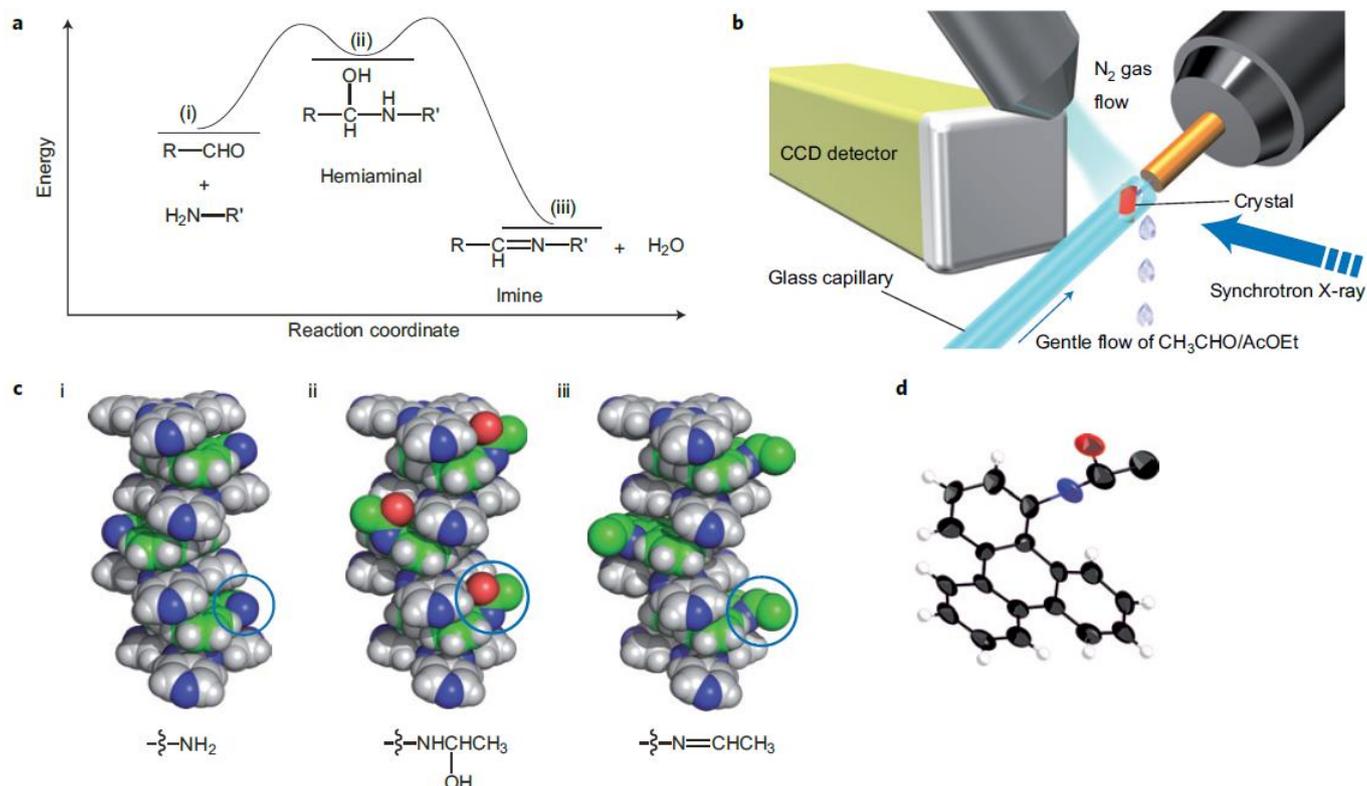

Fig. 4 Crystallographic visualisation of the hemiaminal intermediate in the reaction of an amine guest with an aldehyde. The metastable nature of the hemiaminal intermediate is shown in (*a*), a diagram of the instrumental setup is shown in (*b*), and example X-ray snapshots are shown in (*c*). The hemiaminal is shown in (*d*) with ellipsoid probabilities of 30%. Reprinted with permission from Ref. 34. Copyright 2011 Nature Publishing Group.

obtained, with the former structures showing ideal alignment to promote reaction. This was proven with a greatly increased reaction rate within the CMF relative to a control reaction performed CMF-free and in the solution-state. In addition, the electronically disfavoured regioisomer was preferentially obtained within the CMF, whereas the expected regioisomer was dominant in the control experiment.

The use of CMFs to visualise a chemical process was taken a step further during elucidation of a bromination reaction, whereby an organopalladium species was hosted, then activated, and finally converted to the bromide by reductive elimination.[38] The full reaction sequence occurs upon treating the CMF loaded with a chelated organopalladium guests with *N*-bromosuccinimide dissolved in acetonitrile, with X-ray snapshots taken at T = 0.25, 1, 2, 6, 15 and 24 hours after an initial washing step to eliminate excess material from the pores (Fig. 5). The electron density maps obtained of the CMF pores allowed unambiguous assignment of a square-planar Pd(II) reaction intermediate, as opposed to an octahedral Pd(IV), species. Successful characterisation of this species demonstrated that a Pd(II)/Pd(0) mechanism can account for bromination, even if other mechanisms cannot be discounted in solution studies.

This list of reactions performed within CMFs is not exhaustive. Other reported examples include metallations, oxidations, acetylations, and borations.[39]
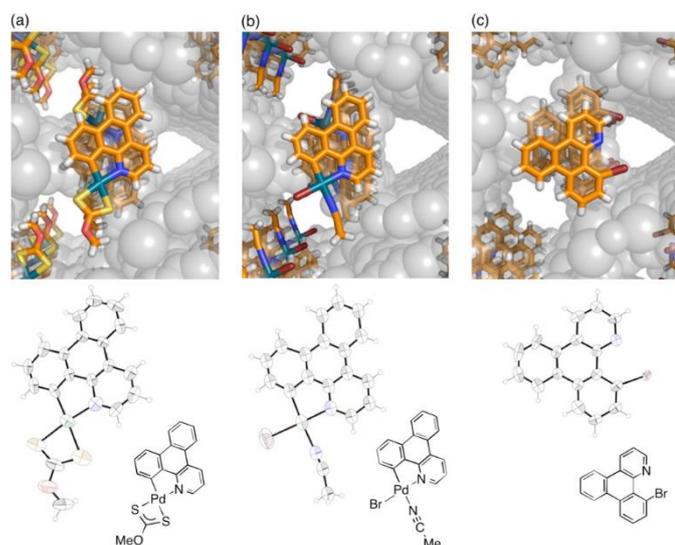

Fig. 5 Crystallographic visualisation of a sequential reaction of an organopalladium guest (*a*, T = 0) with *N*-bromosuccinimide to give an intermediate after acetonitrile washing (*b*, T = 2 h) before completely converting to the brominated product (*c*, T = 24 h). Reprinted with permission from Ref. 38. Copyright 2014 American Chemical Society.

Gas-phase and volatile reagent studies

The use of gas-phase reagents by the crystalline sponge method has arguably received the least attention to date. This is unusual considering that the parent class of materials, MOFs and PCPs, are intrinsically linked with such chemistry.[2,3] Consequently in

terms of new applications that make use of CMFs, this area will likely see a rapid expansion of interest. There have been three main classes of volatile reagent evaluated using the crystalline sponge method, iodine vapour, sulphur vapour and air oxidations.

A recent report exploring iodine uptake by CMF **1** shed light on the reactivity of the framework, as well as the gas loading capacity, from the perspective of developing materials for radioactive iodine sequestration.[40] It was noted that where ordered iodine was observed the molecules were localised and oriented towards the ZnI_2 nodes of the framework by halogen-halogen interactions (Fig. 6). Triiodide formation was found to increase in prevalence with time, and an ultimate iodine loading of almost 65% by weight was recorded, representing one of the highest reports for I_2 uptake known.

Iodine vapour has additionally been harnessed in CMFs to catalyse the cyclisation reaction of a hosted dialkylnaphthalene guest.[41] The reaction was shown to reach completion by ^{1}H-NMR analyses performed on digested single-crystals after 7 days, with intermediate sampling done at 3 and 0.5 days. X-ray diffraction methods were used to identify the likely location of the cyclised product, as well as iodine molecules in the crystalline lattice. This work also identified a secondary reaction in the CMF, whereby oxygen from air was found to sequentially oxidise the cyclised reaction product in an unoptimised yield of 35%.

Oxygen reactivity derived from air in chemical processes was also seen in the 2,2'-azobis(isobutyronitrile) initiated oxidation of vinylic groups crafted into CMF **1**.[42] Oxidation was the sole transformation to occur within the framework, whereas in solution the dominant products were polymeric species formed by polymerisation reactions. It should be noted that in this example the oxygen dissolves in the liquid reaction medium, hence this is not a true gas-phase reaction like the previous examples.

Volatile sulphur species have also been elucidated using a CMF closely related to **1**, with the composition reported as $[ZnI_2(tpt)_3]_n$. Study of a previously uncharacterised sulphur allotrope, S_3, was made possible by encapsulation in the CMF after treatment with vacuum (~70 Pa) at 533 K.[43] This resulted in a colour change in the host framework, and prominent changes to the X-ray powder diffraction pattern. The structure of the framework was solved by *ab initio* X-ray powder diffraction analysis. The structural nature of S_3 was determined spectroscopically,[44] and was consistent with the *ab initio* model generated from the experimental data. This approach to visualising sulphur allotropes was later refined using a new framework comprised of CuI and tetra-4-(4-pyridyl)phenylmethane (tppm).[45] The porous $[(CuI)_2(tppm)]_n$ framework, coupled with a gentler means of generating and transferring sulphur vapour, allowed the first direct crystallographic characterisation of small sulphur allotropes. The identity of the allotrope was found to change with temperature, with metastability of linear S_2 and cyclic S_3 observed at 250 and 300 K, respectively (Fig. 7).
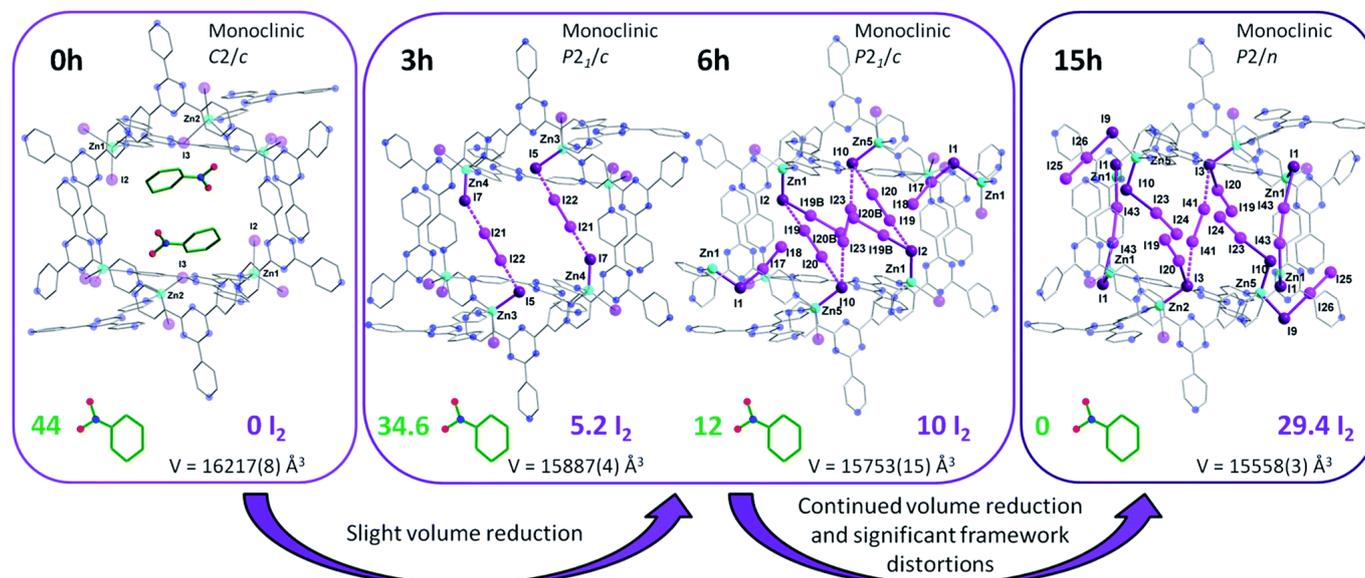
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Fig. 6 Progression of iodine uptake in CMF **1** showing increasing loading up to *ca* 30 iodine molecules with concomitant triiodide formation. Uptake was monitored by X-ray snapshots taken at T = 3 h, 6 h, and 15 h. Iodine uptake was found to occurs with phase changes in the crystal, likely to accommodate the contraction in cell volume that occurs with the loss of the 44 molecules of nitrobenzene from the T = 0 h motif. Reprinted with permission from Ref. 40.
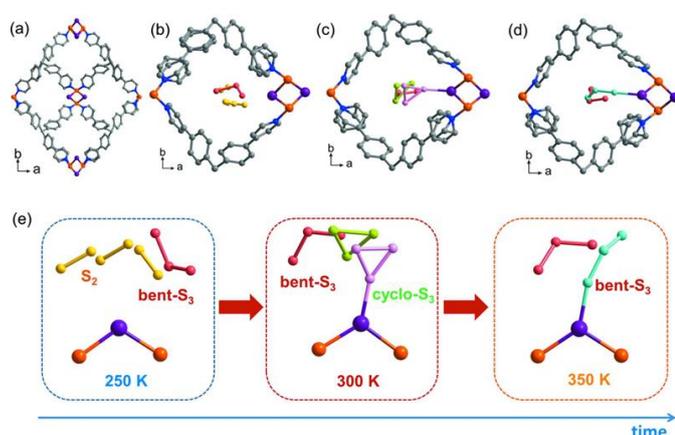

Fig. 7 Use of $[(CuI)_2(tppm)]_n$ (*a*) as a CMF to capture and visualise small sulphur allotropes. Initially, at 250 K, only linear S_2 and bent S_3 were observable in the CMF pores (*b*). With increased temperature (300 K) and time, the sulphur exclusively adopts S_3 allotropes, including both cyclic and bent variants (*c*). At higher temperature (350 K) only the bent S_3 allotrope of sulphur is observed. Reprinted with permission from Ref. 45.

In the majority of these examples, the CMF absorbing or interacting with gaseous reagents has an observable effect on the material, be it a change in crystalline colour, crystal size or chemistry of the guest. Such behaviour has a plethora of potential applications. Examples include sequestration materials for gases, sensors for dangerous reagents, and new catalysts for gas-phase reactions. Progress towards developing materials that exhibit these behaviours has already begun. MOFs showing the ability to host and degrade chemical warfare agents have been reported,[46] while a material capable of monitoring iodine vapour uptake holds important applications for forensic science and first responders to clandestine drug laboratories.[47] Essentially any methodology that requires monitoring of a gaseous species, or a process catalysed by such a species, could potentially benefit from this aspect of CMF chemistry.

5. Summary

The crystalline sponge method has matured from an obscure complementary approach to X-ray crystallography, to a diverse strategy capable of characterising a wide range of dynamic molecular processes. The method's usefulness has begun to expand beyond the scope of pseudo-solution state hosted reactions to truly encompass the solid-gas interface. Refinements made to both experimental methodology, and to CMFs themselves, have eliminated many of the initial drawbacks that prevented adoption of these materials to diffraction experiments. In response, the main current application of CMFs, absolute structure configuration, has been

demonstrated for a range of organic and inorganic entities. This has benefitted a growing range of scientific disciplines in areas such as natural product identification, metabolite analysis, and analytical process chemistry.

Innovations that emerge from the less-established applications of CMFs will be of great future interest, such as hosting and elucidating dynamic chemical processes, gas-phase reactions, and imparting unique hosting effects on guests to obtain unique properties. Perfecting the ability to perform hosted X-ray diffraction experiments and circumvent the need to crystallise the guest analyte promises to speed new scientific discoveries.

As new members of the CMF family continue to appear that unlock new frontiers, or negate past limitations, it would seem that the only limitation these materials possess resides with the ingenuity of synthetic chemists, which for now seems far from abating.

Conflict of interest

There are no conflicts to declare.

Acknowledgements

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