

## **Porous organic cages: soluble, modular, molecular pores**

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**Preface.** Porosity is a rare property for molecular materials but, surprisingly, porous solids built from discrete organic cage molecules have emerged as a versatile functional materials platform. From modest beginnings fewer than 10 years ago, there are now organic cage solids with surface areas that can rival extended metal-organic frameworks. Unlike network polymers and frameworks, these cages are synthesized first and then assembled in the solid state in a separate step. This offers solution processing options that are not available for insoluble frameworks. In this Review, we highlight examples of porous organic cages and focus on the unique features that set them apart, such as their molecular solubility and their increased tendency to exhibit polymorphism.

### **Introduction**

To be porous in the conventional sense, a material must have permanent, interconnected voids that are permeable to gases or to liquids. Porous materials such as terracotta, charcoal, and dried plant husks have been used for millennia for filtration, purification, and cooling. More recently, porous barrier materials were used to separate uranium isotopes by gaseous diffusion in the Manhattan Project, and porous zeolites are central to processes such as petrochemical cracking, ion-exchange, and the separation and extraction of gases and solvents<sup>1</sup>. More specifically, zeolites have an annual global market of several million tons, and have made a huge impact on society.

Other types of porous solid have also entered the scene in the past two decades, such as metal-organic frameworks (MOFs) or porous coordination polymers (PCPs)<sup>2-5</sup>, covalent organic frameworks (COFs)<sup>6</sup>, and new classes of amorphous porous organic polymers<sup>7,8</sup>. What unifies these structurally diverse materials is that they are all extended single molecules – that is, insoluble frameworks or networks linked together by strong covalent or coordinative bonds<sup>8,9</sup>. Indeed, it is hard to construct porous materials from discrete, small molecules because they tend to pack closely in the solid state to maximise attractive intermolecular interactions. It is hence rare to encounter molecular crystals with open channels or with lattice voids that are stable to the removal of guests, such as solvent<sup>10</sup>. Nevertheless, a growing number of ‘porous molecules’ have been reported recently. In particular, porous organic cage molecules have been discovered with porosity levels in some cases that rival extended porous frameworks.

‘Porous molecules’<sup>11-14</sup> can be defined as molecules that can pack in the solid state to produce pores. This may result from the molecule having a rigid, ‘awkward’ structure that is incapable of packing efficiently, or because it has directional intermolecular interactions, such as hydrogen bonding, that direct it to crystallize in an energetically preferred, low density form. In such cases the porosity is ‘extrinsic’—that is, between neighbouring molecules—rather than in the molecular itself. A different strategy is to build an intrinsic cavity into the molecule. For example, porous cages are molecules with permanent voids inside a rigid structure and windows that allow access to these voids. Although macrocycles and cage-like compounds have been known for some time, porous organic cages are a relatively new type of porous material, and they have some intriguing differences with respect to

extended porous frameworks, such as solution processability. Since the early development of porous organic cages<sup>11</sup>, the scope for these materials has broadened rapidly, both in terms of properties and applications<sup>15-22</sup>. It is now timely to reassess porous organic cages, not as a new area but as a more mature field. In this Review, we focus on selected cage materials and attempt to draw out learning points for readers new to this field. We also discuss the unique features of porous cages, such as their molecular solubility, their tendency to show polymorphism, and the scope for modular cocrystallisation. Our intent is to summarize the key features that set these porous cages apart from extended frameworks and to highlight both the pros and cons of these interesting materials.

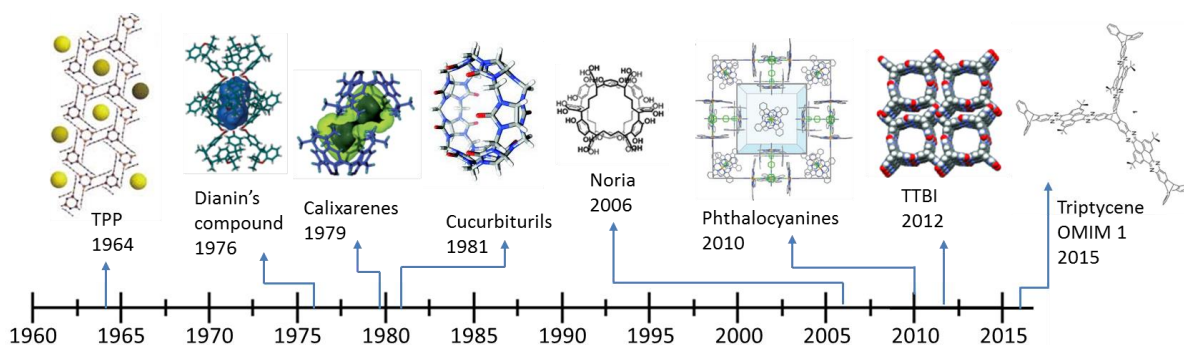
## A historical viewpoint

In 1976, Richard M. Barrer and Vivien H. Shanson reported that a small organic molecule, Dianin's compound (FIG. 1), had properties that were reminiscent of a porous solid<sup>23-25</sup>. This compound was already known to form inclusion complexes when crystallized from solution, but they showed that it could also adsorb gases in its pure, solid form. They concluded that this molecule was behaving like an "organic zeolite", and that its gas adsorption properties could be attributed to its porous, crystalline molecular lattice. Barrer and Shanson also made the prescient observation that: "The framework of the host structure is however less rigid than that of a zeolite and guest molecules can penetrate into the cavities, even though wide windows giving access to these cavities do not exist." As numerous later studies showed, this is often a defining feature of porous molecular solids, where the sub-units in the lattice are held together by relatively weak interactions such as van der Waals forces or hydrogen bonds, rather than the strong, covalent, ionic, or coordinative bonds that define most extended porous frameworks. Hence, porous molecular solids are often quite flexible, and this allows guest molecules to pass from one cavity to another, even if the windows appear too small for this. This was described by Barbour as 'porosity without pores'<sup>10</sup>.

Since the seminal study by Barrer and Shanson, other extrinsically porous molecules have been discovered where the porosity is a function of intermolecular voids. Calixarenes are cup-shaped organic molecules, and their rigid shape often leads to voids in the solid state and the adsorption of gases or other guests<sup>26-33</sup>. Similarly, Noria<sup>34,35</sup> is a paddle-wheel shaped molecule that can also form porous structures, even in the amorphous state. Certain macrocycles pack to give porous, solvent-free phases<sup>36-40</sup>, although most do not and it can require special strategies to maintain porosity. For example, phthalocyanines can be linked to form dimers and hence prevent collapse of the porous crystal structure during desolvation (FIG. 1a)<sup>41</sup>, and porous macrocyclic diynes can topochemically polymerize in the solid state to give covalent conjugated polydiacetylenes<sup>42</sup> that maintained permanent porosity, as evidenced by their type I gas adsorption isotherms with CO<sub>2</sub>. Some molecules are extrinsically porous because of their awkward shape, such as molecular stars<sup>43</sup> and propellers and other paddlewheels<sup>44-47</sup>. These have also been referred to as "organic molecules of intrinsic microporosity", or OMIMs<sup>44,48</sup>. Other systems rely on directional interactions, rather than just shape or bulk, often to form a honeycomb-like pore systems<sup>49</sup>. A prototypical example of this is tris(*o*-phenylenedioxy)cyclophosphazene<sup>50-52</sup> (FIG. 1). Directionally-bonded extrinsically porous materials have been referred to by some teams as hydrogen-bonded organic frameworks (HOFs)<sup>53-57</sup>. The most notable example so far is triptycenetrisbenzimidazolone (TTBI; FIG. 1), which shows a remarkable Brunauer-Emmett-Teller (BET) surface area of 2796 m<sup>2</sup> g<sup>-1</sup><sup>58</sup>.

Cage molecules are distinguished from extrinsically porous molecules by their intrinsic cavities. In this regard, there is possible ambiguity for cavitands<sup>59</sup> (container shaped molecules) such as cucurbiturils<sup>60,61</sup> and cryptophanes<sup>62</sup>, which contain an internal void and open windows. Cucurbituril

(FIG. 1), for example, could be viewed as a simple cage consisting of only two windows, and indeed porous cucurbituril phases have been reported<sup>63</sup>. By contrast, cryptophanes, which are molecules consisting of two cyclotribenzylene units connected by bridges of various kinds, tend to lack the shape persistency required to meet our definition of porosity, with some exceptions<sup>64</sup>. Despite the extensive work of Cram<sup>65</sup> and Pedersen<sup>66</sup> and others on all manner of macrocycles, supramolecular guest binding in solution, rather than solid-state porosity, was a more dominant theme in the 1980's and 1990's.

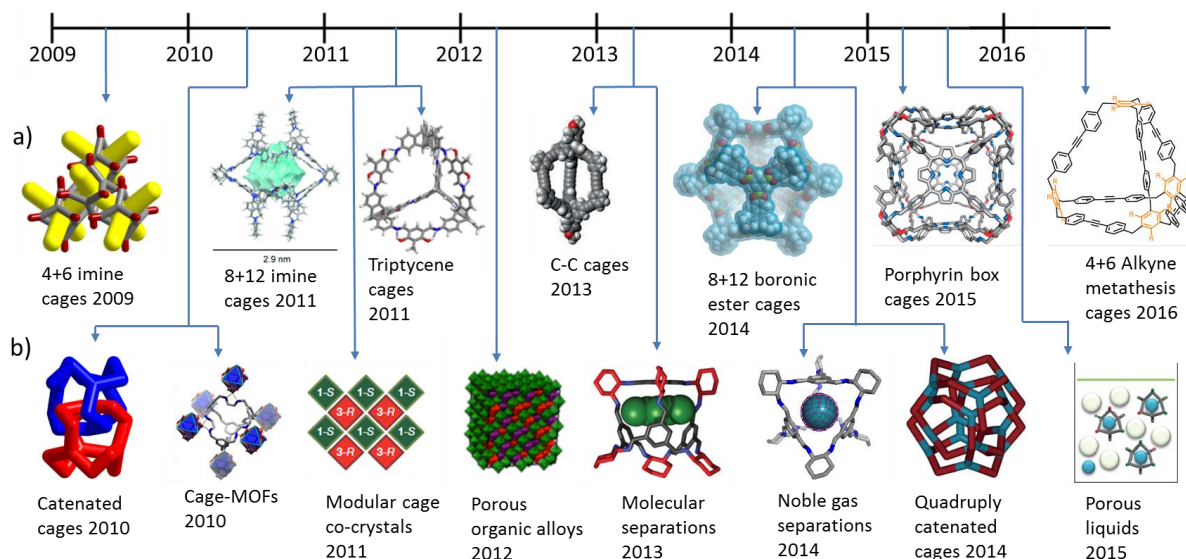


**Figure 1. The development of porous molecules.** a) Porous molecules, from left to right: tris(*o*-phenylenedioxy)cyclophosphazene<sup>50-52</sup>, Dianin's compound<sup>23-25</sup>, calixarenes<sup>26-33</sup>, cucurbiturils<sup>60,61</sup>, Noria<sup>34,35</sup>, phthalocyanines<sup>41</sup>, triptycenetrisbenzimidazolone (TTBI)<sup>58</sup>, and triptycene-based OMIM<sup>44</sup>.

The first demonstration of permanent porosity by gas adsorption for intrinsically porous organic cages, rather than macrocycles, was in 2009, when we described three tetrahedral organic cages formed by the [4+6] cycloimination of trialdehydes with diamines (FIG. 2a)<sup>67</sup> (*c.f.*, first adsorption isotherms for PCPs)<sup>2</sup>. All three cages are based on a three-way triformyl-benzene linker, each with a different two-way diamine linker. A slight modification in the diamine linker led to different packing modes in the solid state for the resulting cages, and hence marked differences in pore connectivity. Further structural analogues reinforced this point<sup>68-70</sup>: changing the cage vertex tends to change the crystal packing and hence the porous properties. In this respect, porous organic cages are unlike isorecticular MOFs, where large families of materials can be produced with the same basic pore topology but with different organic linkers<sup>71,72</sup>. The apparent BET surface areas for these cages (up to  $\sim 1000 \text{ m}^2 \text{ g}^{-1}$ , depending on polymorph and crystallinity) were the highest reported at the time for molecular solids, albeit much lower values than achieved for extended frameworks. This record did not last long: Mastalerz and colleagues soon synthesized porous imine cages, based on triptycene linkers (FIG. 2a)<sup>73-77</sup>, which comprised four three-way and six two-way linkers. As for our smaller cages, the external cage functionalization was found to modify the crystal packing and hence the porosity, but these larger cages<sup>75</sup> gave higher BET surface areas of more than  $2000 \text{ m}^2 \text{ g}^{-1}$ .

Moving away from imine chemistry, Doonan *et al.* reported the first directly C-C bonded porous cage using an irreversible synthesis that directly coupled together two pre-configured hemispheres (FIG. 2a)<sup>78</sup>. The desire for larger-volume cages led to cuboctahedral 8+12 cages (FIG. 2a), again based on reversible imine bonds, but these were found to collapse<sup>79</sup> or decompose<sup>80</sup> upon desolvation: they lacked the rigidity to remain shape persistent. Mastalerz *et al.* overcame this problem and produced the first shape-persistent, porous 8+12 cage (FIG. 2a)<sup>81</sup>. This cage shows the highest surface area reported to date ( $3758 \text{ m}^2 \text{ g}^{-1}$ ) and it can be classed as mesoporous (pores  $> 2 \text{ nm}$ ; its internal pore diameter is  $3.1 \text{ nm}$ )<sup>81</sup>. This study helped to redefine what is possible in terms of porosity with molecules. A disadvantage of this route, however, is the reversible boronate ester chemistry used for

the cage synthesis, which leaves this dramatically porous structure rather unstable to moisture. By contrast, certain imine cages can be stable to boiling water<sup>82</sup>, and other derivatives can even withstand acid or base treatment<sup>83</sup>. Also, the limited solubility of this large 8+12 cage<sup>81</sup> makes it rather hard to process. Kim *et al.* recently reported two ‘porphyrin boxes’<sup>84</sup>: that is, 6+8 imine cages constructed from six four-way pyrene aldehyde linkers and eight three-way amine linkers. These cages have a relatively large internal diameter of 1.7 nm and surface areas up to 1370 m<sup>2</sup> g<sup>-1</sup>. Although less porous than the Mastalerz mesoporous cage<sup>81</sup>, these imine boxes are stable to moisture; a fair compromise.



**Figure 2. The development of porous organic cages.** a) Porous organic cages, from left to right: 4+6 imine cages<sup>67</sup>, 8+12 imine cage<sup>79</sup>, triptycene cages<sup>73-77</sup>, C-C bonded cage<sup>78</sup>, 8+12 boronic ester cages<sup>81</sup>, porphyrin ‘boxes’<sup>84</sup>, and 4+6 alkyne metathesis cages<sup>85</sup>. b) Selected discoveries and practical uses related to porous organic cages, from left to right: Triply-interpenetrated catenated cages<sup>86</sup>, cage-MOFs<sup>87</sup>, cage cocrystals<sup>88</sup>, porous organic alloys<sup>89</sup>, molecular hydrocarbon separations<sup>90</sup>, noble gas separations<sup>91</sup>, quadruply interlocked cages<sup>92</sup>, and porous liquids<sup>93</sup>.

New cages might be designed in the future to match, or even surpass, the porosity levels obtained in the Mastalerz mesoporous cage<sup>81</sup>, but with higher stability and solubility. Inspiration here could be drawn from the field of metal-organic coordination polyhedra<sup>22,94-96</sup>, where the design principles of ‘emergent behaviour’ introduced by Fujita have allowed spheres with up to 24 metals and 48 ligands to be self-assembled<sup>95</sup>. Indeed, smaller porous metal-organic polyhedra have been already reported<sup>97,98</sup> and exhibit high levels of porosity.

One might wonder, given the rapid recent development of this field (FIG. 2a,b), why porous organic cages were not discovered earlier. At least three technical factors have contributed to this. First, determination of porosity by gas adsorption was once a specialist technique, but this is now much more commonplace in synthetic materials laboratories. Second, our ability to solve crystal structures has advanced enormously since the work of Pedersen and Cram, both in terms of X-ray source intensity (*e.g.*, access to synchrotron facilities) and crystallographic methods to treat problems such as disordered solvent in structures<sup>99-102</sup>. Third, the area of dynamic covalent chemistry<sup>103</sup>, which has been fundamental for most of porous organic cages so far, has matured significantly. However, recent breakthroughs notwithstanding, it should be stressed that porous organic molecules are still rare in comparison with extended porous frameworks. In a recent review of more than 150,000 organic

molecules in the Cambridge Structural Database (CSD)<sup>14</sup>, only 20 or so molecules were found to have pore volumes that exceeded the rather paltry value of  $0.1 \text{ cm}^3 \text{ g}^{-1}$ . Moreover, in the CSD survey no molecular organic materials were found to have pore volumes of  $1.0 \text{ cm}^3 \text{ g}^{-1}$  or more, (calculated from single crystal structures) although the experimental pore volume for one mesoporous cage molecule does exceed that value<sup>81</sup>. By contrast, pore volumes exceeding  $1.0 \text{ cm}^3 \text{ g}^{-1}$  can be achieved routinely for extended frameworks. Although this CSD survey<sup>14</sup> excludes, by definition, molecular materials for which single crystal structures have not been reported, these are rather bleak statistics. Nature really does abhor a vacuum, and stable, low-density molecular solids ( $< 0.8 \text{ g cm}^{-3}$ ) are still rare beasts compared to porous extended frameworks.

## Design of cages and synthetic routes

There are many possible synthetic routes to organic cages, each with benefits and drawbacks, and one must consider both the choice of building blocks, or synthons, and the bond-forming chemistry.

**Choice of synthons:** To make a cage, rather than a linear polymer or a macrocycle, at least one of the synthons must link in more than two directions. Most cages so far are a combination of two-way and three-way linkers, but other combinations are also possible. In general, the geometry of the synthon and, especially, the angles between the linking functionalities will be crucial in defining the cage structure, if a cage is formed. Narrower angles will tend to produce smaller cages, and wider angles larger cages. A good example of this is the emergent behaviour described by Fujita for organometallic cages<sup>95</sup>. Mixtures of two-way and three-way linkers can form 2+3, 4+6, or 8+12 cages, depending on the geometry of the synthons.<sup>104,105</sup> Higher order  $2n+3n$  structures are also possible, in theory, but these may not be entropically favoured. For solid state porosity, it is important that the cage should be rigid enough to prevent collapse of the structure when the solvent is removed.<sup>79</sup> This can be controlled by using aryl linkers and conjugated structures with minimal bond rotation, but even functionality that would be considered 'rigid' for small molecules might be insufficient to prevent collapse in larger cages where cumulative flexibility can be propagated over many bonds<sup>79</sup>.

**Choice of bond-forming chemistry:** Cage syntheses can be divided into two categories:

**Reversible routes:** (FIG. 3). The most prevalent is imine condensation<sup>67-70,76,79,84,88,106-115</sup>, but boronic ester<sup>81,104,116-118</sup> or boroxine<sup>118,119</sup> formation, and dynamic alkyne metathesis<sup>85,120-122</sup> have all been used. There is still much scope to adopt other reversible bond forming chemistries here<sup>123-125</sup>.

**Irreversible routes:** Irreversible linking chemistry is rarer for porous organic cages, but examples include carbon-carbon bond formation through metal catalyst assisted cross coupling<sup>78,126,127</sup>, nucleophilic aromatic substitution<sup>128</sup>, ester condensation<sup>119</sup>, and Azide-alkyne Huisgen cycloaddition<sup>129</sup>.

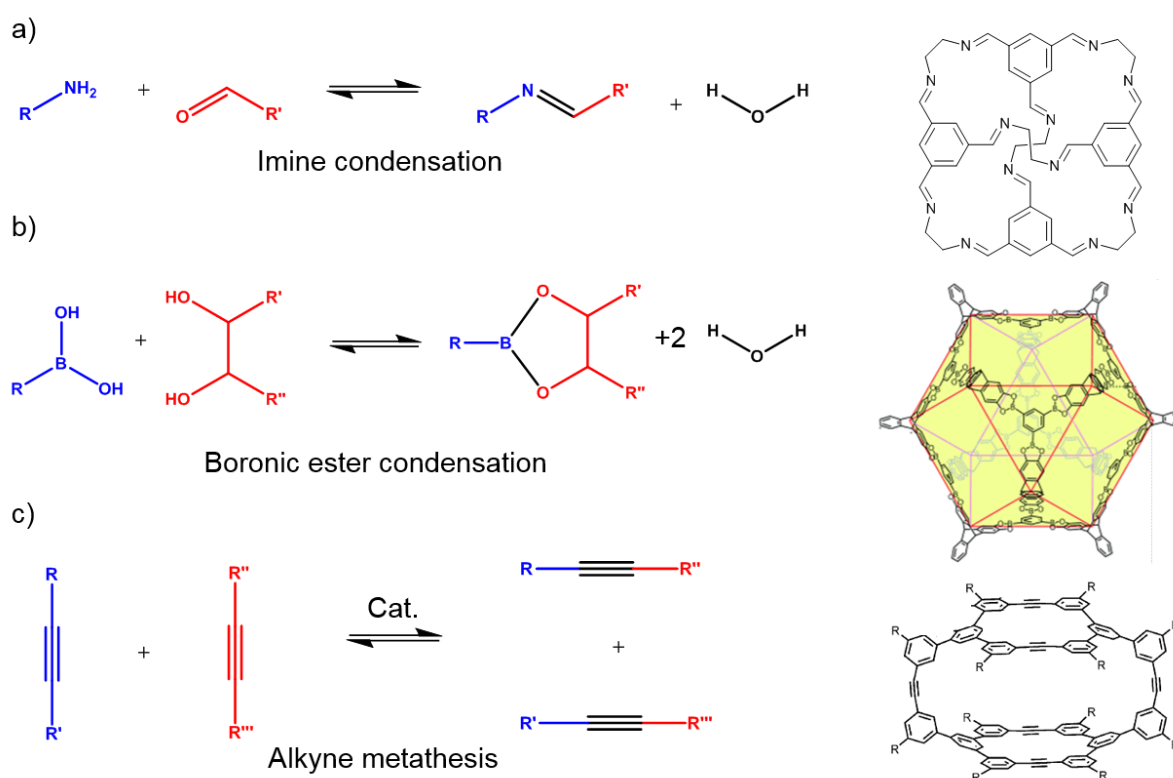
Reversible bond formation allows error correction for the cages to self-assemble as the thermodynamic product. This can give higher yields compared to irreversible carbon-carbon bond formation and avoid purification steps. However, in some cases, reversibility can also lead to the formation of interlocked, catenated cages<sup>86,92,120,130</sup> (though these catenanes can themselves be highly porous<sup>92</sup>). Catenation can occur if there is sufficient space, and the correct geometry, for one or more cages to form through the windows of another. A thermodynamic force for this interlocking to happen may be provided by a favourable interaction between the cages, e.g.  $\pi$ - $\pi$  stacking, and therefore the process can be solvent dependent, i.e. whether the cage-solvent interactions  $>$  cage-cage interactions. The interplay of monomeric cage or catenated cage formation can also be controlled by the addition

of catalysts and the control of crystallisation rate, with increased reversibility and longer times favouring catenation.

Future routes to porous cage formation might involve alternative dynamic chemistries, such as S-S<sup>123,124</sup>, B-N<sup>125</sup>, or O-C-O bonds, or template-assisted routes that improve cage organisation and yield. For example, inspiration could be drawn from large macrocycles that are templated around ‘spokes’, which are subsequently removed<sup>131</sup>.

Irreversible bond formation typically requires multiple steps, greater ‘pre-organisation’ in the synthons and, often, results in lower product yields. However, a significant advantage of irreversible covalent bonds is that they can avoid the chemical stability issues associated with imine and boronic ester cages. An alternative, hybrid route was reported recently that uses dynamic reversible chemistry for the cage formation before locking in the cage structure as a stable amine product<sup>83</sup>. Overall yields for this route are good (67 % over two steps), and the resulting cages are stable in the solid state over a pH range of 2–12. Few crystalline inorganic frameworks, MOFs or COFs are stable over such a broad pH range<sup>132</sup>, although good pH stability is commonplace for amorphous porous organic polymers<sup>7,8</sup>.

All reactions discussed so far are batch processes, but the soluble nature of cages also allows them to be synthesised in continuous flow reactions, either irreversibly to produce C-C bonded cages<sup>133</sup> or using reversible imine condensation.<sup>134</sup> Flow chemistry is attractive both in terms of scale up and safety.



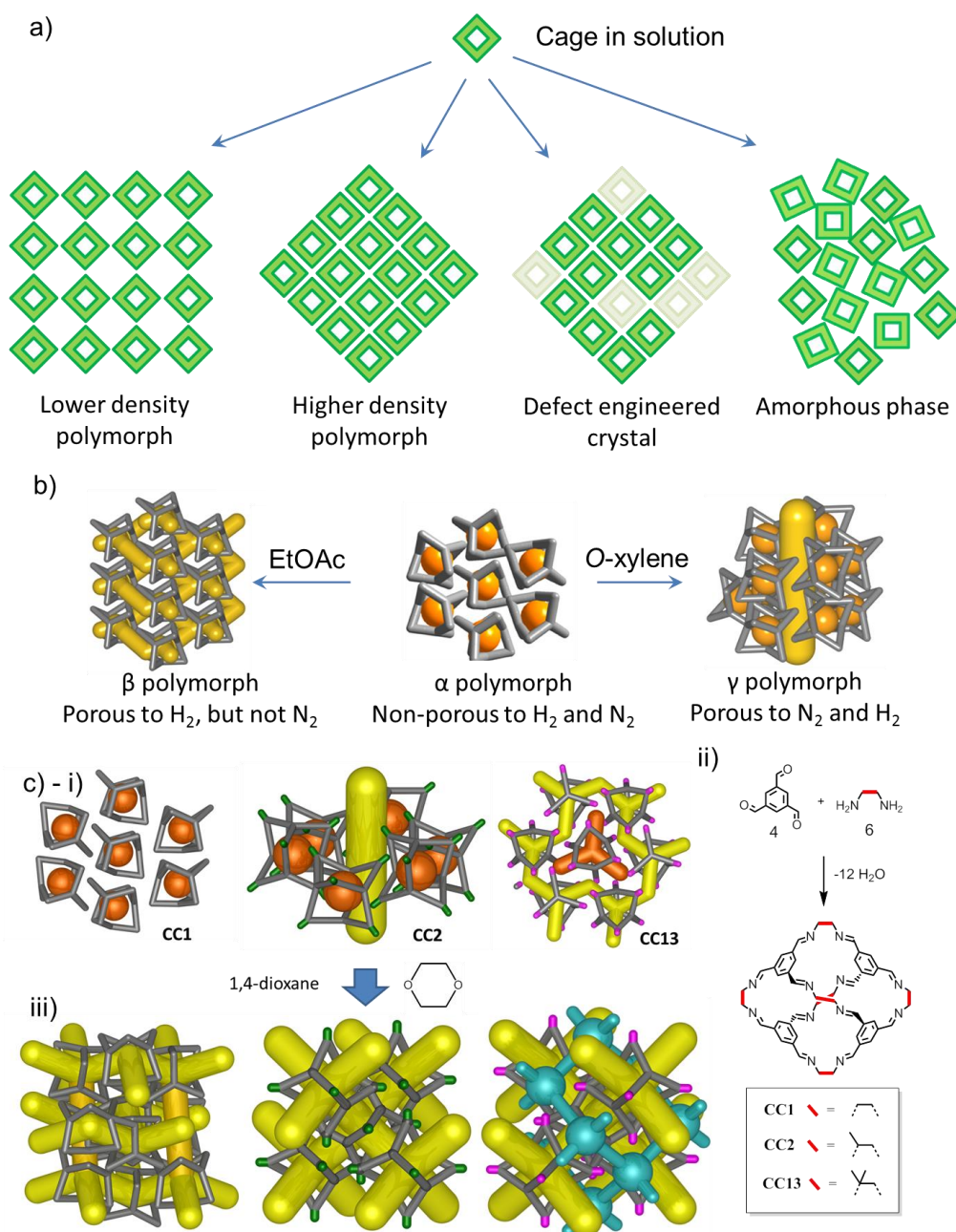
**Figure 3: Reversible synthetic routes used for porous cage formation, with example cages.** a) Imine condensation<sup>67</sup>, b) boronic ester condensation<sup>81</sup>, and c) dynamic alkyne metathesis<sup>122</sup>.

### Polymorphism and crystallinity

Discrete molecules are held together by relatively weak intermolecular forces, and hence cages can crystallise into alternative polymorphs (FIG. 4a), and switch between polymorphs in the solid state<sup>108</sup>. Polymorphism is known for extended frameworks, too, but it is generally more prevalent for porous molecular solids. Favourable interactions between solvent and cage can lower the lattice energy of polymorphs that would otherwise be unlikely to form<sup>69,135,136</sup>; these can then be trapped as a metastable polymorphs after solvent removal. This can be used purposefully to tune the porosity with respect to different gases<sup>108</sup> (FIG. 4b). For example, careful choice of ‘directing solvents’ can be used to control cage packing (FIG. 4c). This strategy recalls isorecticular MOFs<sup>69,135</sup>, in that isostructural series of materials can be obtained by introducing a dominant crystal bonding motif, but in this case by using specific non-covalent interactions involving both cage and solvent rather than metal-organic bonding.

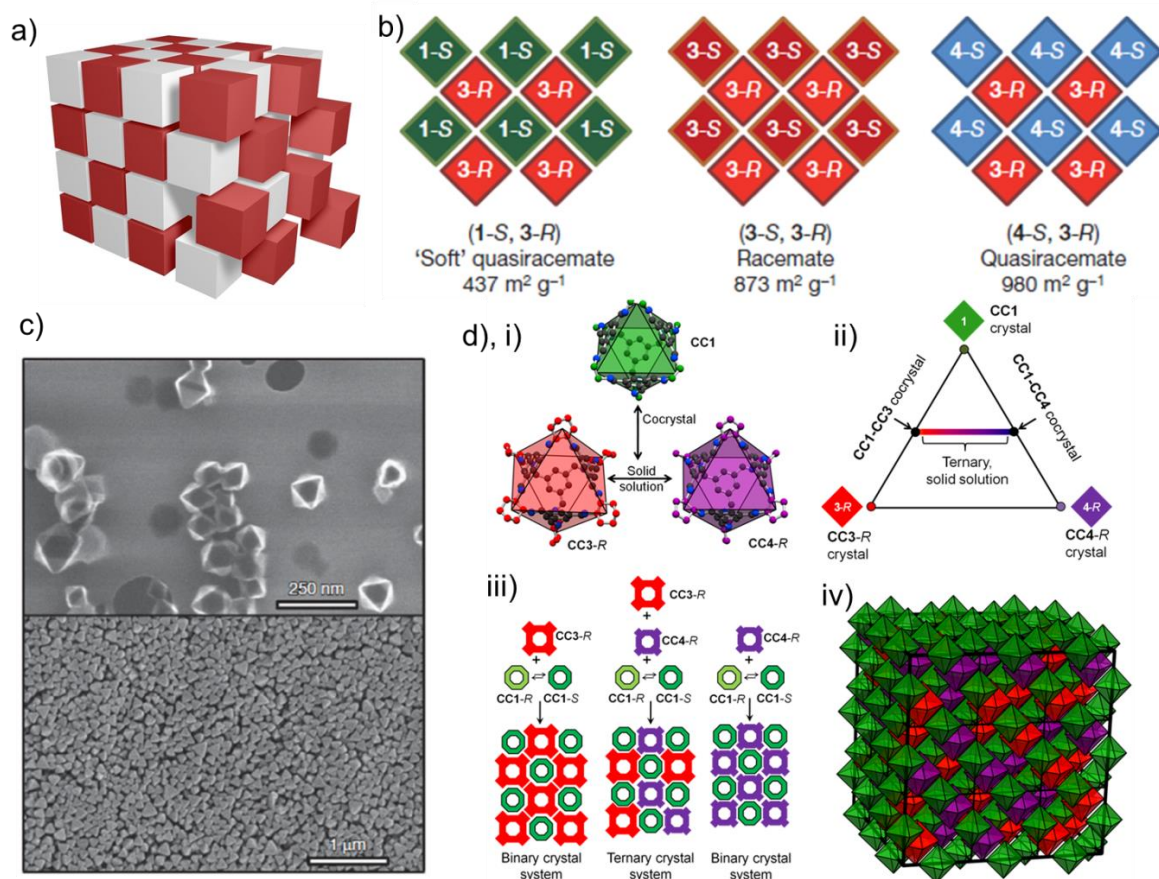
As a result of this sensitivity of the crystal packing to the molecular structure, small changes to the latter can make large differences to physical properties. For example, the addition of a second methyl group to a cage vertex was shown to more than triple the surface area for a cage, from 330 to 1173 m<sup>2</sup> g<sup>-1</sup>, even though the cages were packed in the same basic arrangement for both molecules.<sup>69</sup> This was because the cages were pushed further apart, thereby introducing a second pore channel (FIG. 4c(iii)).

It is also possible to isolate cages in a porous, amorphous state, either by preventing crystallisation through processing (*e.g.*, by freeze-drying)<sup>137,138</sup>, or by ‘scrambling’ cages to create a mixture of structures that frustrates crystallization<sup>107</sup>. Amorphous cages can have either higher<sup>137</sup> or lower porosity<sup>75,138</sup> than their respective crystalline forms. The relative porosity level depends on the pore connectivity and the density of the crystalline phase, and also how closely the cages can pack in the amorphous state. Some cages become totally non-porous upon amorphisation<sup>138</sup>, whereas others can double their surface area with respect to the crystalline phase<sup>107,137,138</sup>. It is important, therefore, that properties such as surface area and pore volume are not assigned to particular organic cage molecules, as one would report, say, a molar mass. The physical properties are a function of the specific polymorph and the level of crystallinity, and crystal defects can play a vital and often overlooked role<sup>69,137</sup>. There are important similarities here with recent studies on defects in MOFs, which help to explain the oft-noted discrepancies between properties derived from ‘ideal’ crystal structures and experimental measurements<sup>139,140</sup>. Cage molecules are perfect systems for investigating ‘defect engineering’ because the synthesis and the crystallisation steps can be separated. Hence, a single batch of cage can be synthesised and fully characterised in solution, before splitting the sample into sub-batches that can be crystallised under different conditions. For example, when a cage material, **CC2-β**, was crystallized both slowly and rapidly, the rapidly-crystallised sample exhibited more than double the surface area, despite both samples showing similar powder diffraction patterns<sup>69</sup>. This highlights the importance of the processing steps for porous organic cages which, unlike for MOFs and COFs, can be separated from the synthesis.



**Figure 4. Controlling solid state porous cage packing.** a) Scheme showing different possible solid state phases for a single molecular cage. b) A cage molecule can be induced to pack into different crystal polymorphs with different gas selectivities by using specific crystallisation solvents<sup>108</sup>. Connected pores are shown in yellow, disconnected pores in orange. c) i) A structurally related series of cages<sup>69</sup> (CC1, CC2, and CC13; molecular structures shown in (ii)), which all pack in different ways. None of these packing modes shows window-to-window pore connectivity. (iii) Use of a directing solvent, 1,4-dioxane, induces all three cages to pack a broadly isostructural window-to-window porous manner. Addition of the second methyl group in CC13 pushes the cages apart, creating a second pore channel (shown in blue, iii), which more than doubles the surface area with respect to CC2.



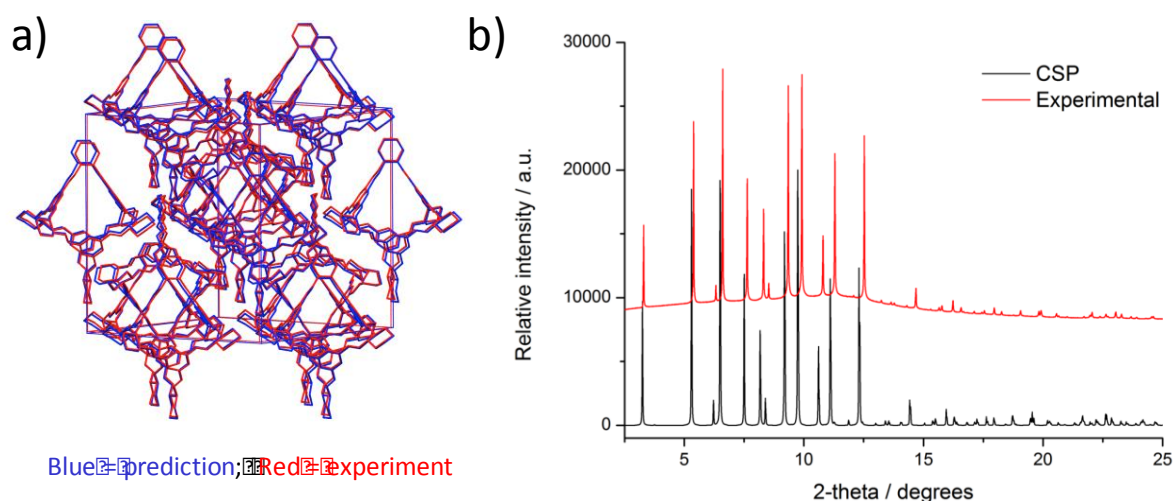


**Figure 5. Modular cocrystallization of porous organic cages.** a) Scheme illustrating molecular cage assembly; b) Cages with opposing chirality can be combined to make binary cocrystals. c) This can be used to produce porous nanocrystals; scale bar shows 250 nm (top), and 1  $\mu\text{m}$  (bottom). d) Scheme for a ternary cage cocrystal. (i) Structures of the three cage modules, **CC1**, **CC3-R** and **CC4-R**, which form the ternary cocrystal; (ii) These three modules form a solid solution. (iii) The chirality of flexible, racemic **CC1** is resolved by cocrystallization with **CC3-R** and **CC4-R**, such that all **CC1** cages in the tercrystal have *S* chirality. (iv) Scheme showing cubic packing in the porous tercrystal. The **CC1** modules (green) occupy half of the lattice sites; **CC3-R** (red) and **CC4-R** (purple) are disordered over the remaining sites.

### Modular cocrystallisation

Cages are soluble, molecular pores that can be combined in modular ‘mix-and-match’ strategies (FIG. 5a). This was first shown for tetrahedral cages<sup>88,137,141</sup> (FIG. 5b), where there is a favourable interaction between cages of opposite chirality and a markedly lower solubility for the cage racemate. This made it possible to produce porous crystals of controlled size and shape, down to the nanoscale (FIG. 5c)<sup>137,142</sup>, simply by mixing the two enantiomers in solution. The same design strategy can be extended to ternary cage cocrystals with three molecular components (FIG. 5d)<sup>89</sup>, which is analogous to the concept of ‘multivariate’ MOFs<sup>72</sup>. Cages **CC3** and **CC4**, both structurally locked in the *R* configuration, were added to a solution of cage **CC1**, present as a racemate in solution, where it has sufficient flexibility to convert between enantiomers. As the cages crystallise out into the solid state the chirality of **CC1** becomes frozen in the *S* configuration. By varying the molecular composition in these tercrystals, the unit cell dimensions change linearly according to Vegard’s Law (FIG. 5d, iii),

allowing surface area and sorption properties to be fine tuned. This type of solid-solution behaviour is common in inorganic systems, and can be used to tune properties of perovskites<sup>143,144</sup> among other materials, but ‘organic alloys’<sup>145,146</sup> are much rarer and this ternary cage system<sup>89</sup> is the first physically porous organic alloy (FIG. 5d, iv). The cocrystallisation of cages is not limited to cages of the same geometry; for example, a smaller ‘propeller’ shaped cage was crystallised with a larger tetrahedral cage<sup>147,148</sup>. This was done by using the size and geometry of large inter-cage voids in an unstable cage solvate crystal to ‘retro-engineer’ the partner cage that could cocrystallise into this void. Future research is likely to expand this modularity further. By doing so, mixed functionality could be engineered into porous cages; for example, by cocrystallizing cages containing acid functions with cages containing base functions. Guest selectivity might also be improved by cocrystallising one cage that favours binding of a specific guest with second cage chosen for its ability to exclude a competitive guest; that is, by the introduction of ‘gating cages’ into a porous cocrystal or tercrystal.



**Figure 6. Crystal structure prediction (CSP) for porous organic cages.** a) Comparison of the lowest energy crystal structure predicted for CC3-R (blue) from the molecular formula of the cage compared with the experimental single crystal structure (red)<sup>88</sup>. b) The similarity between the powder X-ray diffraction (PXRD) pattern calculated from the CSP data (black) and the experimental PXRD pattern allows computed PXRD data to be used to identify specific, targeted phases; for example, by comparing results from high throughput polymorph screens with CSP-derived libraries of PXRD patterns.

### Computational design

Despite recent progress in controlling crystal structure for porous cages by using chirality and directing solvents (Figs. 4 & 5), there are not yet any true molecular cage analogues of isorecticular MOFs<sup>71,72</sup>, where the lattice energy for the material is dominated by a specific, strong interaction across a broad range of building blocks. Hence, computational methods have much to offer in providing the underpinning design basis for new porous molecular crystals and, indeed, for designing functional organic crystals of any type.

The design of functional porous cage solids for specific applications raises a number of difficult questions. The first consideration is whether a given set of precursors will form a cage molecule at all and, if so, what is the most favourable stoichiometry (*e.g.*, 2+3, 4+6, 8+12)<sup>105,149</sup>. If a cage does form, will it maintain its void cavity or collapse to a denser structure upon solvent removal or exchange,<sup>79,149,150</sup> and how will it pack in the solid state? Finally, what will the physical properties of that porous cage crystal be, for example in terms of its adsorption selectivity? If we want to design new functional porous organic crystals ‘on paper’ (or rather, *in silico*), then we need to have the capability to compute answers to all of these questions<sup>8</sup>.

There are few examples of computing formation energies for cages, but this was done recently for a series of 2+3 and 4+6 cages, where the number of carbons in the alkane diamine chain controls the cage stoichiometry<sup>105</sup>. The experimental preference for cage stoichiometry was reflected clearly in the relative formation energies for the possible 2+3 and 4+6 cage products. *De novo* prediction of crystal structure is still a challenging problem, but crystal structure prediction (CSP) has been used to calculate the most energetically favourable crystal packing for porous organic cages (Figure 6a)<sup>88,136,141</sup>. The size of these molecules pushes the current limits of CSP methods, and hence these structure prediction protocols are still at an early stage of development. The potential power of the approach can be illustrated, though, by comparing powder X-ray diffraction (PXRD) patterns calculated from CSP-derived structures with those obtained by experiment (FIG. 6b). This suggests an exciting approach for identifying new porous phases by matching experimental PXRD patterns against patterns derived from computational CSP structure libraries.

Methods to compute the adsorption properties of porous crystalline materials are somewhat more mature than CSP, and the adsorption selectivity of porous cages has been computed recently,<sup>91,151</sup> drawing on major developments in this area for extended porous frameworks<sup>152-154</sup>. The properties of amorphous cage materials can also be simulated, though the lack of structural information requires amorphous models to first be generated<sup>138,155</sup>, which is considerably more laborious than for crystalline solids.

**Note on terminology of porosity:**

Three types of porosity can be defined when simulating experimental sorption from crystal structures:

- In **Static porosity** no movement in the structure is needed to rationalise porosity
- In **Dynamic porosity** flexibility in the structure, in the absence of guests, rationalises porosity
- In **Cooperative porosity** a temporary local rearrangement, due to the influence of a guest, is needed to rationalize the observed porosity

**Box 1**

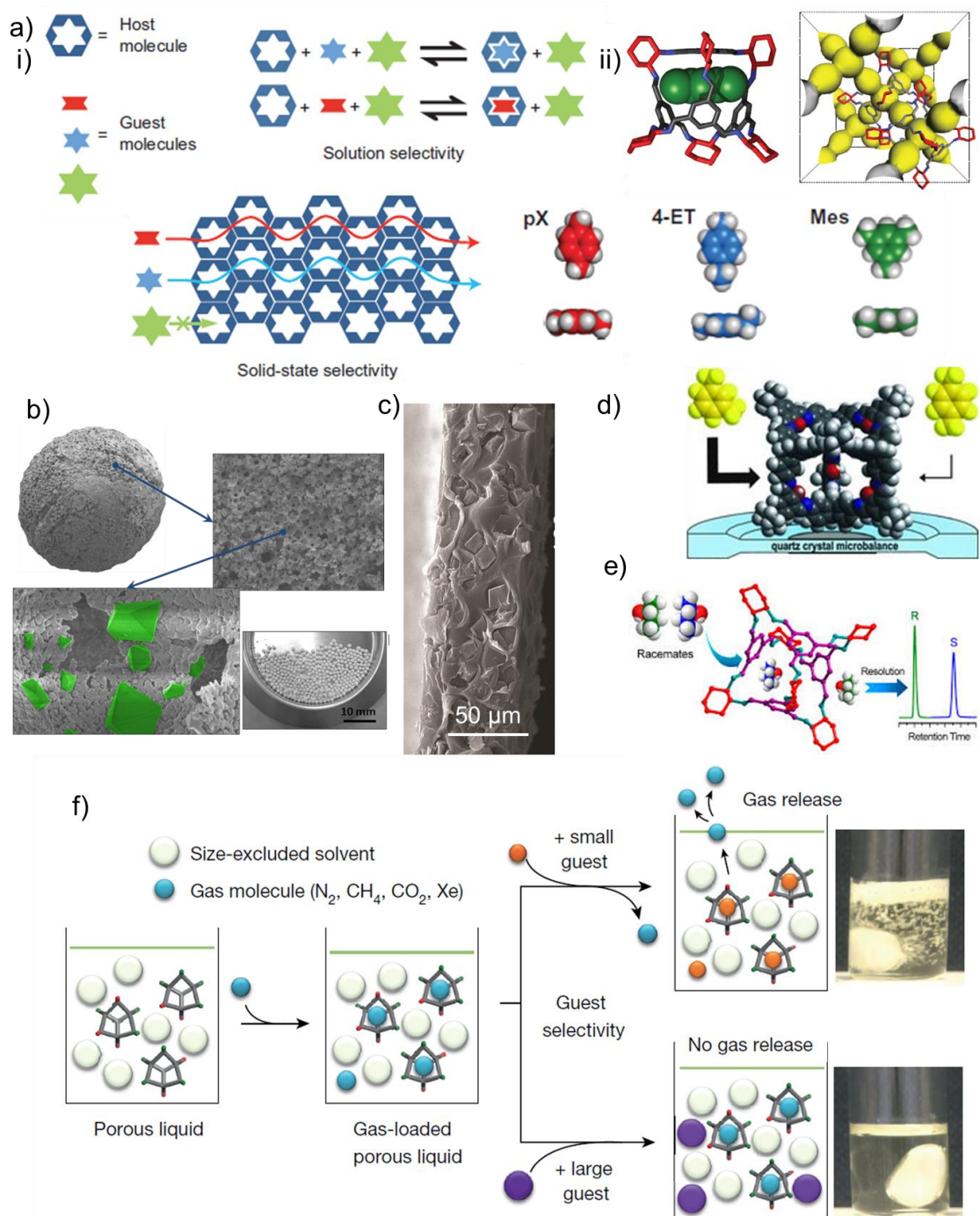
The relative flexibility of porous organic molecules and cages means that it is quite common to find structures that adsorb (or absorb) guests that would otherwise be considered too large for the pores<sup>91,151,156</sup>. Indeed, molecular systems can behave in a ‘porous’ way, albeit often with poor adsorption / desorption kinetics, despite having no permanently connected pores. This has been described, variously, as “porosity without pores”<sup>10</sup>, “sorption in impermeable cages”<sup>157</sup>, and “zero-dimensional porosity”<sup>158</sup>. In a recent study, we classified the different classes of porosity in molecular solids according to the terms given in Box 1<sup>159</sup>. In many cases, computational simulations will be the main tool to understand these dynamic phenomena.

In summary, computation is already an important method for rationalizing porosity in porous organic solids, as it is for extended frameworks. In the future, it will be increasingly useful for the design of new function, coupled with improved methods to predict crystal structure. This *in silico* design approach may be a particular advantage for candidate materials where the preorganized synthons themselves require a substantial time investment in terms of multistep synthesis.

### **Molecular separations using porous organic cages**

The most commonly used proof for permanent porosity in materials is to report the nitrogen adsorption isotherm and, derived from this, the apparent BET surface area. The highest BET surface area reported to date for a porous organic cage<sup>81</sup> is 3758 m<sup>2</sup> g<sup>-1</sup>. This nitrogen BET measurement is largely historical, and a result of the low cost and abundance of nitrogen. It is selective porosity to other gases (*e.g.*, H<sub>2</sub>, CO<sub>2</sub>, CH<sub>4</sub>), or to liquids such as hydrocarbons, that is often of greater practical interest than surface area *per se*<sup>160</sup>.

Cage systems have shown selectivity for gas pairs such as CO<sub>2</sub>/CH<sub>4</sub><sup>74</sup>, CO<sub>2</sub>/N<sub>2</sub><sup>84,106,111,112,161</sup>, H<sub>2</sub>/N<sub>2</sub><sup>138</sup>, and SF<sub>6</sub>/N<sub>2</sub><sup>162</sup>, calculated typically by comparison of single-component isotherms. A particularly nice example of synthetic control is the post-functionalization of cage interiors to modulate gas selectivities.<sup>77</sup> The direct physical separation of chemical feedstocks using porous organic cage crystals packed in a liquid chromatography column was also demonstrated<sup>90</sup>. Cage crystals were shown to separate mesitylene from its structural isomer, 4-ethyltoluene, with perfect specificity for the latter (FIG. 7a). This specificity stemmed from the structure of the intrinsically porous cage molecule, which was itself synthesized from a derivative of mesitylene<sup>67</sup>, suggesting that other cages could be designed specifically to sort particular molecular mixtures. The same organic cage also separates the noble gases xenon and krypton at low concentrations with excellent selectivity, and discriminates between chiral organic molecules<sup>91</sup>. Building on the latter, there were multiple reports recently<sup>163-166</sup> where soluble molecular cages were deposited directly into gas chromatography columns (FIG. 7e). These cage-coated capillary columns showed good selectivity for the separation of a series of organic mixtures and structural isomers, such as *n*-alkanes, *n*-alcohols, and aromatic hydrocarbons, and enhanced resolution for the separation of chiral molecules. Specific adsorption properties can also be built into porous molecular solids. For example, stable, water-tolerant noncovalent organic frameworks based on electron-rich pyrazoles showed a surface area of 1159 m<sup>2</sup> g<sup>-1</sup> and good adsorption properties for both hydrocarbons and ozone-depleting substances such as CFCs and fluorocarbons<sup>167</sup>.



**Figure 7. Selected applications of porous organic cages.** a) (i) Molecules to separate molecules: a discrete host molecule has shape and size selectivity for guest molecules in solution, which translates into solid state selectivity. (ii) The structures of the host cage and the guests, *para*-xylene, 4-ethyltoluene, and mesitylene. b) Micrographs showing the pore structure of macroporous silica beads impregnated with cage crystals (green), and a photograph of the macroscopic beads (bottom right). c) Micrograph of a cross-section of a PIM-1/CC3 composite membrane (weight ratio 10:2) showing porous cage crystals embedded in a porous polymer film. d) Scheme showing how cages deposited on a microbalance can differentiate between analytes. e) Resolution of chiral molecules using cages. f) Porous organic cages dissolved in bulky solvents give rise to porous liquids, which have enhanced, selective solubility for gases such as methane, nitrogen, carbon dioxide, and xenon.

## Exploiting cage solubility

The molecular solubility of organic cages allows processing options that may be hard to mimic with insoluble, extended frameworks; one example is the gas chromatography column method<sup>163-166</sup> outlined above. Cages were also deposited as ‘porous additives’ in macroporous beads<sup>168</sup> using a cocrystallisation strategy (FIG. 7b). Bushell *et al.* showed that cages can be co-dissolved with polymers of intrinsic microporosity (PIMs) and solution cast to create the first organic–organic mixed matrix membrane (MMM)<sup>169</sup> (FIG. 7c). The addition of the porous cage to the polymer membrane was found to substantially enhance permeability while retaining good selectivity for CO<sub>2</sub>/N<sub>2</sub> and CO<sub>2</sub>/CH<sub>4</sub>, as well as providing better resistance towards physical ageing of the membranes. Doonan and colleagues used simulations to investigate a related series of possible cage-based MMMs for the separation of industrially relevant gas mixtures<sup>155</sup>. They found that the gas transport properties in these materials could exceed the polymer upper bound for separations, indicating that cages have exciting potential for clean energy applications. Free standing amorphous cage films can also be used for gas separations, without any PIM matrix, although in this case, ageing effects were pronounced<sup>170</sup>. Thin, solution cast porous cage films were also deposited on quartz crystal microbalances and shown to function as sensors for small molecule analytes (FIG. 7d)<sup>171,172</sup>. Cage solubility in common solvents has also allowed them to be used as components in the synthesis of macromolecular porous materials such as cage polymers<sup>173</sup> and cage MOFs<sup>87</sup>. Finally, molecular, soluble cages have recently allowed us to prepare intrinsically porous liquids<sup>93,174-177</sup> (FIG. 7f). The first generation of these materials was based on concentrated solutions of organic cages in bulky solvents that are too large to enter the cage pores, although one could also envisage single-component porous liquids comprising a low-melting point cage without any additional solvent.

There are situations, of course, where cage solubility would be a strong disadvantage, such as stationary phases for liquid chromatography that dissolve in the eluent. As such, porous organic cages may prove complementary to other porous solids for specific applications. For example, single-phase, solution-processable organic–organic MMM’s<sup>169</sup> and porous cage liquids<sup>93</sup> have no real analogues from the world of extended porous frameworks.

## Practical advice for researchers entering this field

The significant number porous organic cages reported recently might give the impression that almost any combination of diamines and trialdehydes is likely to produce a porous solid (*e.g.*, FIG. 3a). This is not the case. The first challenge is to produce a molecular cage. Even with dynamic covalent chemistry, synthons can form a disordered, crosslinked polymer—for example, as a kinetic product—that is insoluble and hence removed from the equilibrium. High dilution synthesis<sup>178</sup> or careful tuning of conditions in flow reactors<sup>134</sup> can be used to maximize the yield of the target cage. The addition of acid or other catalysts for imine formation is a standard tactic for increasing reversibility<sup>103</sup>. However, a cage with a large, empty void may not, in fact, be the thermodynamic product, and too much reversibility can lead to denser molecular structures, such as catenated cages<sup>86,92,122</sup>. Hence, a compromise may be needed to induce the ‘right’ level of error correction in the reaction. Catenated products can often be detected by broadening, splitting, and pronounced shifts in solution NMR peaks, even if the catenated product is a minor side product, or hard to detect by mass spectrometry.

It is also important to rule out the possibility of amorphous, insoluble polymeric side products, which will be invisible to solution NMR spectroscopy and (probably) undetected by X-ray diffraction. It is therefore good practice to re-dissolve and filter cage products to remove any potential polymeric by-

product. This is particularly true for cages that have low solubility, and where the volume of solvent needed with respect to the solid can make it hard to distinguish between true solutions and dispersions. Electron microscopy is also useful for the detection of polymeric side products, and for establishing phase purity. Single crystal diffraction is, of course, a vital tool, but it is essential that this is coupled with powder X-ray diffraction to ensure that bulk samples are phase pure. If gas adsorption results are to be compared against predictions based on the crystal structure, then powder diffraction should always be performed post-adsorption to assess whether the activation process or the exposure to the gas has caused any change in structure or loss of crystallinity.

Lastly, preparing a shape-persistent organic cage does not ensure porosity, which is a function of both the molecular shape stability and the stability of the extended crystal packing. Most molecular crystals that contain channels or voids, including most organic cages and macrocycles, are unstable to solvent removal. In a few, rare cases where the cage packing is particularly robust (*e.g.*, **CC3-R**)<sup>137</sup>, porous solids can be isolated irrespective of what the solvent is, or how quickly it is removed. For many materials, though, the way that the solvent is removed—the ‘activation’ step—will be crucial to retaining porosity, as for many MOFs. Hence, we suggest that solvent exchange protocols (*e.g.*, from high polarity solvent to low polarity, low-boiling solvents)<sup>58</sup> or techniques such as supercritical drying<sup>179</sup> might be attempted before declaring a molecule to be non-porous.

## Conclusions and future directions

Our aim here was to highlight the current ‘state-of-the-art’ for porous organic cages, and the ways in which these soluble molecular pores differ from insoluble porous frameworks and networks. Switchable polymorphism and solution-processability might be considered both a blessing and a curse, depending on the target application, but these features do at least open up new possibilities, such as simple solution processing and ‘porous liquids’.

A basic difference with MOFs and PCPs, of course, is that organic cages do not contain any metals. This is also true for COFs, but with a few exceptions<sup>180,181</sup>, the degree of extended long-range order in COFs has been lower than that attainable for MOFs, probably due to lower reversibility and therefore reduced error correction in COF synthesis. Where highly ordered single-crystal COFs have been realised, the networks have been heavily interpenetrated<sup>180,181</sup>, severely limiting the porosity. This can also be an issue with molecular HOFs<sup>182</sup>. Porous organic cages provide a potential solution to this problem: large cavity organic pores can be synthesised and then crystallised in a modular way to give low-density, highly ordered structures based on light elements, without any catenation. Large, high-quality single crystals are routinely achieved for porous organic cages, and this may be useful for applications outside of gas adsorption where extended long-range order is important.

Several challenges remain for organic cages. Increased synthetic diversity, both in linker architecture and coupling chemistry, is needed to expand the library of potential structures and functions. As has already happened for MOFs and COFs, this might move the applications of these materials beyond gas adsorption and molecular separations. There is also a need for new design strategies, other than chiral recognition<sup>88,89,183</sup> (which bears the obvious disadvantage of cost), to allow cages of different geometries to be cocrystallised in a modular, predictable way. Porous cage liquids<sup>93</sup> are a new development which, uniquely, combine the properties of fluidity and permanent porosity; these materials could offer distinct technological advantages, but there is first a lot to learn about the basic physicochemical properties of these systems. It might even be possible to conceive a mesoporous

liquid with pores of 2 nm or larger, although this is synthetically challenging, and it may be difficult to combine cage size with the high solubility needed to have a high density of pores cavities in the liquid. The computational design of cages has potential to be a powerful tool, but further development is needed, not least to reduce the computational expense of the crystal structure prediction methods and to deal with the question of solvent templating. Another intriguing target is the synthesis of mesoporous cages,<sup>81</sup> or perhaps even extrinsically mesoporous molecular frameworks, that can accommodate larger guests but that also have more stable bonding chemistry and higher solubility. In conclusion, there has been a dramatic evolution in porous molecular solids over the last decade and this has provided a number of surprises, such as mesoporous molecular solids and porous liquids. We see an exciting future for these unique materials.

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