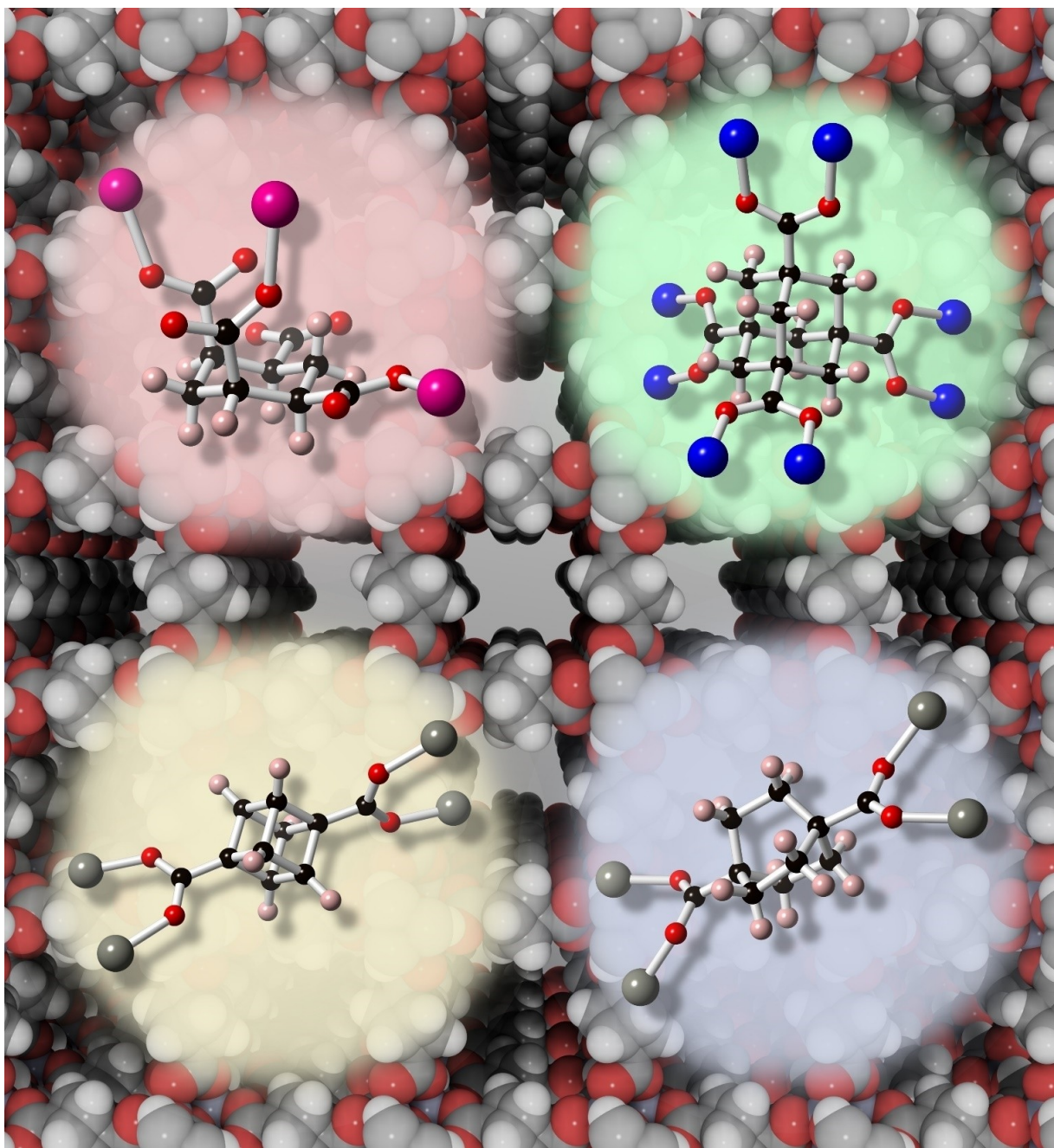


# Cyclic Aliphatic Hydrocarbons as Linkers in Metal-Organic Frameworks: New Frontiers for Ligand Design

Valentyna D. Slyusarchuk,<sup>[a]</sup> Paul E. Kruger,<sup>[b]</sup> and Chris S. Hawes<sup>\*[a]</sup>



In this Minireview we outline the development of cyclic aliphatic moieties as ligands in metal-organic frameworks (MOFs), with a focus on the relationship between ligand design and synthesis and the properties of the subsequent materials. Aliphatic ligands have received considerably less attention than aromatic analogues in MOF chemistry but offer advantages in their unique combinations of geometric and electronic proper-

ties which are unattainable from conventional ligands. Here, we focus on rigid and semi-rigid backbone moieties derived from monocyclic and fused polycyclic aliphatic backbones, including cyclohexane and adamantane, cubane and bicyclo[2.2.2]octane, and discuss the synthetic chemistry of these species along with their potential importance as the next generation of building blocks for microporous materials.

## Introduction

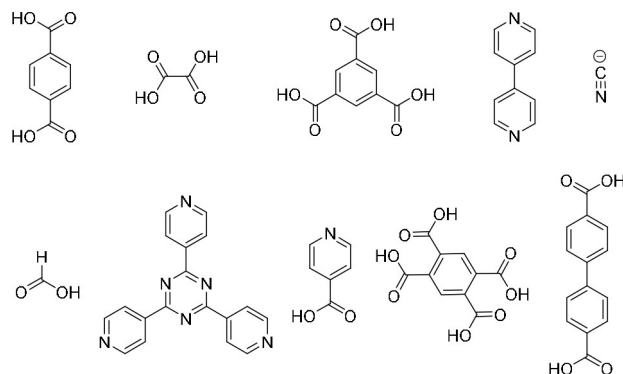
The study of Metal-Organic Frameworks (MOFs) encompasses all aspects of modern chemistry. From their beginnings as structural analogues of inorganic materials and the early studies into their potential for hydrogen storage,<sup>[1]</sup> MOFs have grown into platforms for interdisciplinary study from all branches of chemistry. This is largely due to their modularity: with modern synthetic methods, essentially any known property of organic or inorganic materials can be incorporated into the porous and monodisperse frameworks of these materials.<sup>[2]</sup> While many studies remain focused on gas adsorption and separation,<sup>[3]</sup> catalysis,<sup>[4]</sup> magnetism<sup>[5]</sup> and sensing,<sup>[6]</sup> the modern MOF field is also host to a plethora of much more niche applications.<sup>[7]</sup> In all cases, the combination of tunable metal/ligand character, precise control of microporosity, well-defined host-guest chemistry and advanced characterization methods have proven irresistible.

As the field moves towards a more applications-focused regime, a vital aspect of MOF chemistry which remains prevalent is the necessity of effective ligand design.<sup>[8]</sup> In Robson's seminal report describing the deliberate pursuit of a porous coordination polymer with a specific targeted topology, the design and synthesis of an appropriate organic ligand was essential.<sup>[9]</sup> In that case, the ligand 4,4',4'',4'''-tetracyanotetraphenylmethane was correctly predicted as an extended tetrahedral linker to realize a porous diamondoid topology. Since then, thousands of MOFs (some designed, some serendipitous) have emerged with an abundance of ligand functionalities.<sup>[10]</sup> However, the rate of expansion of the field has outstripped the supply of new ligand classes, and most reported MOFs today make use of only a relatively small group of ligand families.<sup>[11]</sup> Carboxylates remain the most popular coordinating group by a significant margin, followed by pyridines, cyanides and imidazoles, pyrazoles, triazoles and tetrazoles, as more exotic donor groups appear less frequently.<sup>[12]</sup> Even more pronounced,

however, is the dominance of aromatic ligands in MOF chemistry, with some commonly encountered examples shown in Figure 1.<sup>[13]</sup> Ignoring the simpler bridging ligands such as formate, oxalate and cyanide, and bridging oxides or fluorinated anions, it becomes abundantly clear that non-aromatic ligands are an under-represented class of building blocks.

There are several explanations for the dominance of aromatic ligands in MOF chemistry. Rigid aromatic linkers lend structural stability to open framework compounds,<sup>[14]</sup> and polycyclic aromatic ligands can be generally prepared easily through standard metal-catalyzed coupling reactions. Aromatic ligands also offer useful electronic properties, with their extended  $\pi$ -surfaces being implicated as sites for CO<sub>2</sub> adsorption,<sup>[15]</sup> or lending beneficial energy transfer mechanisms for photochemistry.<sup>[16]</sup> Aliphatic ligands on the other hand, tend to suffer from poor structural stability due to the much greater conformational freedom when present as linear alkanes,<sup>[17]</sup> and rigid or polycyclic alkanes are typically much more challenging to prepare with suitable functional groups for metal coordination. Nonetheless, ligands with partially or entirely non-aromatic backbones, such as those represented in Figure 2, have much to offer as unique building blocks within MOFs. Cyclic aliphatic species especially can mimic the levels of rigidity observed in aromatic species, but with additional, unique benefits:

- 1) **3-dimensional structures:** as non-planar scaffolds, cyclic or polycyclic species offer access to useful and unusual node geometries. This approach has already been widely and successfully adopted in the preparation of microporous organic polymers.<sup>[18]</sup>
- 2) **Non-polar backbones:** introducing aliphatic character into pore walls has long been suggested as a mechanism for improving hydrophobicity in water-sensitive MOFs.<sup>[19]</sup>

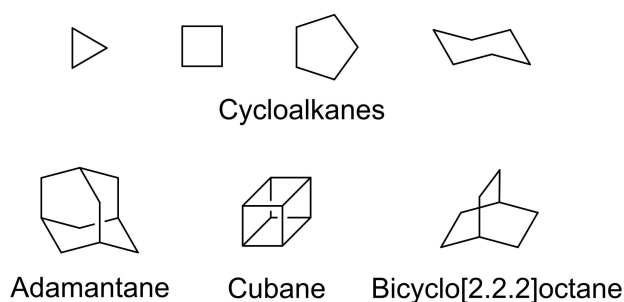


**Figure 1.** The 10 most common linkers in the CoRE MOF 2019-ASR subset.<sup>[13]</sup> Carboxylic acids are represented in their protonated forms for simplicity.

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**Figure 2.** Structures of the cyclic and polycyclic aliphatic cores of interest to this review.

Although grafting alkyl chains to aromatic linkers is one method of achieving this outcome, doing so comes at a cost to pore volume.<sup>[20]</sup>

- 3) **Fluxional behavior:** Unlike their linear alkane counterparts, where multiple conformations are freely accessible by low-energy bond rotations, the conformational isomerism of cycloalkanes or azacycles gives very distinct ligand geometries separated by relatively large ( $> 30 \text{ kJ mol}^{-1}$ ) energy barriers.<sup>[21]</sup> In instances where multiple stable conformers can be accessed, this provides a pool of multiple ligand geometries in solution which can lead to fascinating structural outcomes (provided the resulting MOFs can retain their structural stability).<sup>[22]</sup>

In pursuing these outcomes, the role of organic synthesis cannot be overlooked. While MOFs derived from commercially available ligands have obvious practical advantages, some of the most important and memorable breakthroughs in MOF chemistry in the last two decades have required bespoke ligand design and synthesis.<sup>[23]</sup> Contemporary advances in synthetic methods have been instrumental in expanding the scope of

potential MOF applications, both in providing new routes to ligand-based functionality and in the ever-expanding field of MOF catalysis as a testbed for new reactivity.<sup>[24]</sup> Likewise, the growth of MOF chemistry as a discipline provides new challenges for synthetic chemistry, both in the laboratory and, in the future, at the process scale.

In this minireview, we outline the origins and recent progress that has been made in cyclic aliphatic ligand design, and the relationship that exists between the design and synthesis of new aliphatic ligands and the structure and function of the resulting MOFs.

## Results and Discussion

### Monocyclic backbones

The use of commercially available aliphatic or olefinic dicarboxylates in MOF chemistry has been widespread, with commercially available malonate, fumarate, adipate, succinate and other linear alkanes or alkene linkers accounting for many of the reported examples.<sup>[25]</sup> Cyclohexane carboxylates have been the most widely studied cyclic aliphatic ligands, with between two and six carboxylic acid groups varying in both position and relative stereochemistry.<sup>[26]</sup> Generally, these species are commercially available and examples of ligand syntheses for cyclohexyl-cored MOF ligands are rare and mostly involve peripheral substitution.<sup>[27]</sup>

The issue of relative stereochemistry in cyclohexane derivatives has provided interesting opportunities for structural engineering in MOFs. Cyclohexane-1,2,4,5-tetracarboxylic acid, for example, is commercially available and can be found as a mixture of up to four non-equivalent isomers. Tong and co-workers, using a recrystallized source of the mutually *cis*, *meso*-



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Paul E. Kruger obtained his PhD from Monash University, Australia and undertook postdoctoral research at Queen's University of Belfast. He was a Lecturer at the University of Dublin, Trinity College, Ireland, and is now a Professor of Chemistry at the University of Canterbury, New Zealand. His research interests touch upon all aspects of supramolecular chemistry through to materials and structural chemistry.

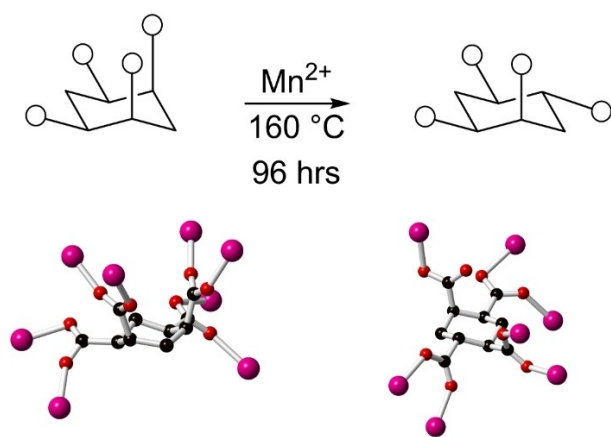


Chris Hawes completed his PhD at the University of Canterbury, New Zealand under the supervision of Prof. Paul Kruger in 2012. He subsequently went on to postdoctoral positions at Monash University, Australia and Trinity College Dublin, Ireland. He was appointed as a Lecturer at Keele University, U.K. in 2017, where his research involves ligand design for the development of new MOFs for carbon capture and chemical sensing applications. It was when working in Paul's laboratory that Chris was first introduced to the opportunities afforded by a ligand design-based approach to structural and metallo-supramolecular chemistry. Since leaving New Zealand, Chris has continued to greatly benefit from Paul's mentorship, and is now working with Valentyna to explore new possibilities in MOF ligand design. This contribution arose from a shared interest in synthesis-driven crystal engineering between Valentyna, Paul and Chris, and a belief that challenges in MOF chemistry may be overcome through materials still yet to be made.

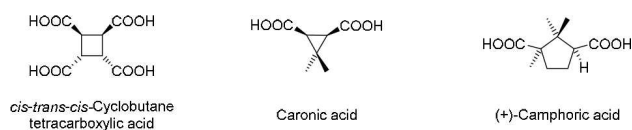


isomer observed partial scrambling to the (racemic) *trans-trans-cis* isomer form under prolonged solvothermal heating at 160 °C in the presence of manganese(II), as shown in Figure 3.<sup>[28]</sup> Since then, several other studies have narrowed the range of synthetic conditions under which 1,2,4,5-cyclohexanetetracarboxylic acid undergoes thermal isomerism in the presence of metal ions, investigating the effect of pH and ancillary ligands to generate permanently porous frameworks with this ligand.<sup>[29]</sup> Similar effects had previously been observed with the hexacarboxylic acid analogue.<sup>[30]</sup>

Other coordinating groups have also been appended to the cyclohexyl skeleton to generate coordination polymers and MOFs benefiting from the structural properties of the flexible cyclic core. 1,2,4,5-Tetrapyriddylicyclohexane ligands (with core hydroxy substituents) have been used in studies of valence tautomerism in coordination polymers,<sup>[31]</sup> and have been formed *in situ* through dehydrogenative coupling of 1,3-bis(4-pyridyl)propane ligands in the presence of copper(II).<sup>[32]</sup> Although generated by a different mechanism, these ligands can be conceptually related to the 1,2,3,4-tetrapyriddylicyclobutane species formed by photocyclization reactions of 1,2-bis(4-pyridyl)ethylene,<sup>[33]</sup> another well-studied mechanism for generating small cyclic alkanes with divergent ligand functionality which has been explored in the solid state by Vittal and others.<sup>[34]</sup> The cyclohexane phosphonates have been another group of aliphatic-cored ligands which have made key contributions to our understanding of the fluxionality inherent in these



**Figure 3.** Schematic diagram showing the conversion of the mutually *cis* form of cyclohexane-1,2,4,5-tetracarboxylate to the *trans-trans-cis* form, with circles representing carboxylate groups. Shown below is the coordination geometries of the two forms as their manganese complexes from the X-ray data reported by Tong and co-workers.<sup>[28]</sup> Hydrogen atoms are omitted for clarity.



**Figure 4.** Examples of commercially available cycloalkane polycarboxylic acids with ring sizes smaller than 6 which have been investigated in MOF chemistry.

systems,<sup>[35]</sup> although these are perhaps more often studied as their piperidine or piperazine analogues.<sup>[36]</sup>

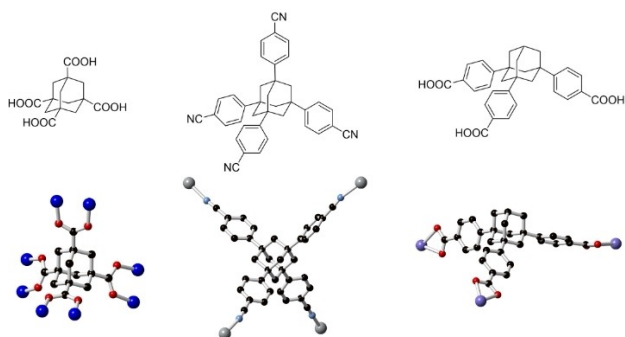
Although the most widely studied, small monocyclic aliphatic ligands used in MOF chemistry are not limited to cyclohexanes; some key MOF ligand examples formed from 3–5 membered rings are shown in Figure 4. Cyclobutane tetracarboxylic acid, for example, tends to act as a divergent polychelating ligand of comparable chemistry to oxalate (itself a well-studied MOF ligand),<sup>[37]</sup> and has been used in several MOF studies, including where the closely bridged metal ions it provides are of interest for molecular magnetism studies.<sup>[38]</sup> Similar to the substituted cyclohexanes, cyclobutane 1,2,3,4-tetracarboxylic acid has also been shown to exhibit *cis-trans* isomerism under a variety of reaction conditions, either at room temperature or under solvothermal heating.<sup>[39]</sup> Although the smaller cycloalkane cyclopropane-1,3,5-tricarboxylic acid is known,<sup>[40]</sup> to our knowledge no MOF structures of this ligand have been reported. However, Bo and co-workers demonstrated the structural properties of a series of 3,3-dimethyl-cyclopropane-1,2-dicarboxylate (caronate) coordination polymers with dipyriddylic co-ligands, showing that MOF structures with the cyclopropane fragment as a building unit are feasible.<sup>[41]</sup> Various discrete palladium(II) and platinum(II) complexes of dicyclopropane polycarboxylate esters have been reported by Hashmi and co-workers,<sup>[42]</sup> although these tend to cyclometallate rather than show bridging coordination modes.<sup>[43]</sup> Sumbly and co-workers have reported several elegant examples of (fully conjugated) hexasubstituted [3]-radialene cores and their silver (I) and copper(I) complexes,<sup>[44]</sup> which demonstrate the potential utility of MOF ligands constructed around 3-membered rings.

Numerous examples of cyclopentane polycarboxylic acid ligands have been reported in the MOF literature,<sup>[45]</sup> and exhibit similar chemistry to their cyclohexane congeners, though the level of geometric variation in their isomeric forms are somewhat less pronounced than in the cyclohexane variants. Camphoric acid is especially useful as a homochiral aliphatic dicarboxylate with a cyclopentane core, which has been widely used to introduce chirality into coordination assemblies.<sup>[46]</sup> Larger monocyclic systems, such as cycloheptane, cyclooctane and cyclodecane, are essentially unknown as core groups in MOF chemistry, most likely owing both to a lack of suitably functionalized starting materials and an anticipated increase in flexibility of these systems as the ring size increases. However, MOF studies with azacyclic analogues such as homopiperazine and substituted TACN, cyclen and cyclam ligands suggest that a wider range of interesting structural outcomes relating to conformational flexibility may result from the larger ring sizes in the pure hydrocarbon analogues.<sup>[47]</sup>

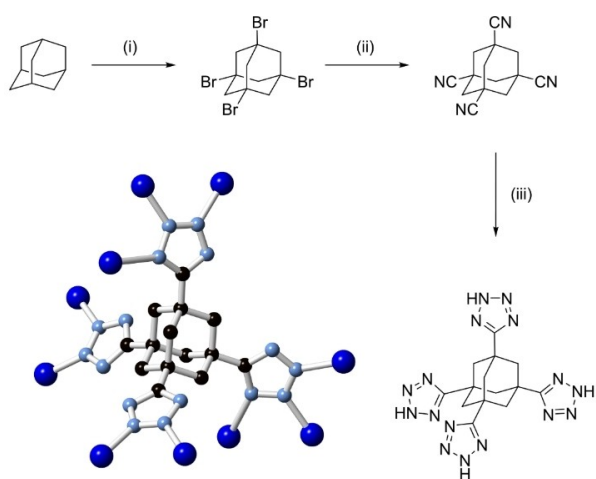
## Adamantane

Adamantane has been a relatively commonly used building unit in network solids, encompassing not only MOFs but also covalent organic frameworks and hydrogen bonded networks.<sup>[48]</sup> It is widely seen as a rigid tetrahedral core unit in its highest symmetry 1,3,5,7-tetrasubstituted form, which

provides the next smallest rigid tetrahedral carbon core beyond tetrasubstituted methane. Mono, di and tri-substituted forms have also been employed where other connectivities have been sought.<sup>[49]</sup> Representative examples of adamantyl-containing ligands are shown in Figure 5. Direct arylation at the bridgehead carbon atoms of adamantane can be achieved under Friedel-Crafts conditions,<sup>[50]</sup> and a range of tetraaryl derivatives have been prepared by this or related methods.<sup>[51]</sup> Adamantane can be brominated under similar conditions to give mono, di, tri and tetrabromo derivatives, with selectivity gained by varying the presence and activity of Lewis acidic catalysts.<sup>[52]</sup> However, nucleophilic approaches to substitution of these bridgehead-functionalised species do not necessarily proceed cleanly. Instead, efficient tetracyanation of 1,3,5,7-tetrabromo-adamantane only proceeds under UV irradiation, via an  $S_{RN}1$  mechanism.<sup>[53]</sup> The tetracyano species can then undergo alkaline hydrolysis to adamantane 1,3,5,7-tetracarboxylic acid, a



**Figure 5.** Representative examples of adamantane derivatives which have been employed in MOF chemistry, showing (L-R) adamantane-1,3,5,7-tetracarboxylic acid, 1,3,5,7-tetrakis(4-cyanophenyl)adamantane, and 1,3,5,7-tris(4-carboxyphenyl)adamantane. Shown below are examples of the coordination chemistry of each derivative from the reports by Yaghi and co-workers (copper(II), left),<sup>[54]</sup> Hanton and co-workers (silver(I), middle),<sup>[55]</sup> and Boldog, Janiak and co-workers (cadmium(II), right).<sup>[56]</sup> In all cases, hydrogen atoms and any crystallographic disorder are omitted for clarity.



**Scheme 1.** The synthesis of 1,3,5,7-tetrakis(tetrazol-5-yl)adamantane reported by Boldog, Janiak and co-workers,<sup>[57]</sup> and its coordination chemistry with copper(II) as a polyconnected building unit in the resulting gismondine MOF. Hydrogen atoms are omitted for clarity. Reagents and conditions: (i)  $Br_2/AlCl_3$ , reflux; (ii)  $NaCN$ ,  $h\nu$ , DMSO; (iii)  $NaN_3$ ,  $ZnCl_2$ , DMF, reflux.

copper(II) MOF of which was reported by Yaghi in 2000 as an early example of open metal sites in a rigid open framework material.<sup>[54]</sup> Due to the synthetic challenges of adamantane substitution, the majority of adamantyl-derived ligands observed in the MOF literature to date have been derived from bridgehead-arylated species, the tetracyano precursor, or the commercially-available carboxylates.

In one representative example shown in Scheme 1, Boldog and co-workers prepared 1,3,5,7-tetrakis(tetrazol-5-yl)adamantane from the unsubstituted hydrocarbon over three steps.<sup>[57]</sup> The synthesis proceeded through tetra-bromination, photochemical cyanation and formation of the 1H-tetrazole in a “click”-type [1,3]-dipolar cycloaddition with sodium azide. In this example, reaction of the tetrahedral tetrakis-tetrazolate ligand with copper(II) or cadmium(II) chloride gave porous 3-dimensional structures with the zeolitic gismondine (**gis**) topology. Here, the tetrahedral adamantane group acted as a regular tetrahedral node while the metal-tetrazolate clusters formed a second flattened tetrahedral SBU. Only the copper example could be fully evacuated following solvent exchange, but exhibited a two-step nitrogen adsorption isotherm which the authors ascribe to a gating effect most likely involving flexibility in the metal cluster nodes, as opposed to the rigid aliphatic backbone.

Adamantyl ligands derived from tetraphenyladamantane cores are more widely studied (although in those cases, the aliphatic core comprises a relatively small percentage of their total surface area), and are widely used as large tetrahedral bridging units. Hanton and co-workers reported an elegant example of silver(I) coordination networks derived from 1,3,5,7-tetrakis(4-cyanophenyl)adamantane, which was prepared through iodination and cyanation of tetraphenyladamantane.<sup>[55]</sup> In this study, both diamondoid (**dia**) and the elusive lower symmetry lonsdaleite (**lon**) topology were observed from equivalent starting materials. A kinetic solvent effect was implicated, where **lon** networks were favored in nitromethane-rich mixtures while the slower formation of the **dia** equivalents occurred later, in mixtures containing more water. Furthermore, the authors reported nanoindentation results for both networks which show that, while both displayed plastic deformations under applied force, the diamondoid net was consistently harder than the lonsdaleite form.

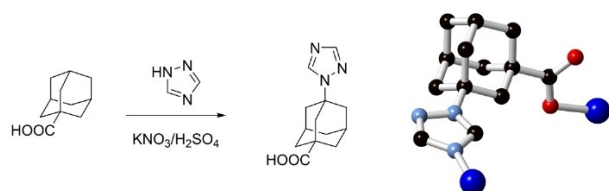
Various di- and tri-substituted adamantane derivatives have also been employed (in both MOF synthesis and other crystal engineering endeavors) for cases where non-tetrahedral linking geometries were desirable.<sup>[56]</sup> Generally, these progress through similar synthetic pathways to the equivalent tetrasubstituted analogues described above. However, one interesting example was recently reported by Popatov and co-workers involving the synthesis of hetero-ditopic adamantane ligands containing both carboxylate and azole functionality.<sup>[58]</sup> Mixed-ligand approaches to ligand design, particularly those combining carboxylate and heterocyclic functionality, have been widely studied for their potential to improve the stability of the coordination sphere.<sup>[59]</sup> In this case, the authors prepare a family of azole-carboxylate ligands by direct N-alkylation of triazoles and tetrazoles with 1-adamantanecarboxylic acid in  $H_2SO_4/KNO_3$ , as

shown in Scheme 2. Although permanent porosity was not demonstrated in this work, these ligands impose considerably more aliphatic character as a fraction of their surface areas compared to the polyaryl-substituted adamantanes, and may see greater use in applications directed towards hydrophobicity.

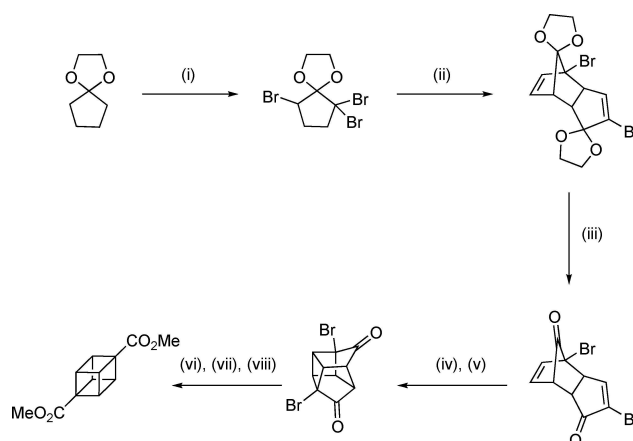
### 2.3 Cubane, Bicyclo[2.2.2]octane and Other Polycyclics

Being much less commonly encountered in synthetic chemistry and with much fewer commercially available starting points, the incorporation of other polycyclic aliphatic compounds as bridging functionalities in MOFs has been limited thus far. One noteworthy example to emerge recently has been the cubane moiety. Although first prepared by Eaton and Cole in 1964, cubane has recently been attracting attention in medicinal chemistry as a non-aromatic isostere to benzene,<sup>[60]</sup> due in part to the advent of improved and scalable synthetic routes. In MOF chemistry, cubane similarly offers a close relationship to benzene, and as such, the as-yet only examples of cubane-containing MOFs have employed cubane-1,4-dicarboxylic acid as an isostere to the ubiquitous 1,4-benzenedicarboxylic acid. The first reported use of this compound as a bridging ligand was by Cotton and co-workers in 2001, as part of a study preparing a series of discrete molecular square complexes.<sup>[61]</sup> This was soon followed by Yaghi and co-workers in 2002,<sup>[62]</sup> who reported a cubane dicarboxylate-containing coordination polymer as part of a wider study involving the synthesis of square-grid type zinc paddlewheel networks. These were subsequently elaborated on by Földes *et al.*, who studied the structural and thermal properties of a related solvate.<sup>[63]</sup> In those instances, the ligand was sourced commercially, although retail sources of cubane-1,4-dicarboxylic acid remain prohibitively expensive for large-scale studies.

Recently, the ligand has been prepared in the optimized kilogram scale batch process reported by Tsanaktsidis and co-workers.<sup>[64]</sup> This method, shown in Scheme 3, successfully scales elements from the previous reports of both Eaton and Chapman.<sup>[65]</sup> Starting from cyclopentanone ethylene ketal, the synthesis proceeds through bromination and Diels-Alder dimerization, followed by a photocyclization step and Favorskii ring contraction to give the cubane dicarboxylate as the disodium salt. In the scaled process, following acidification to precipitate the dicarboxylic acid the substrate is converted to the dimethyl



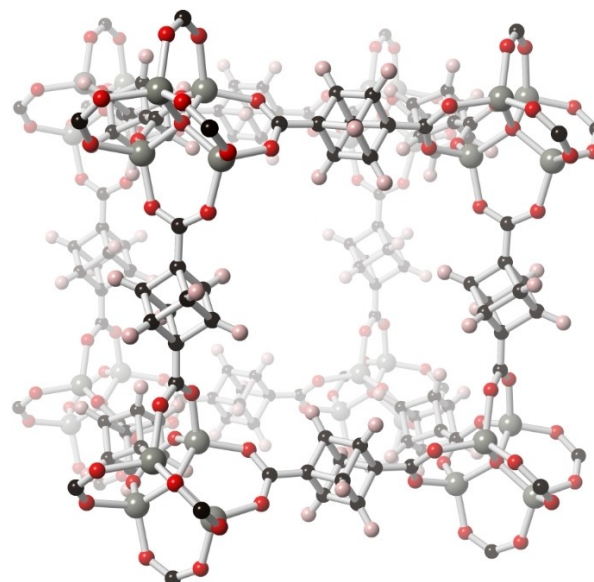
**Scheme 2.** Representative synthesis of a heteroditopic adamantane-based ligand by Potapov and co-workers,<sup>[58]</sup> and its resulting coordination chemistry in the presence of copper(II). Hydrogen atoms are omitted for clarity.



**Scheme 3.** The kilogram-scale synthesis of dimethyl cubane-1,4-dicarboxylate by Tsanaktsidis and co-workers.<sup>[64]</sup> Reagents and conditions: (i) Br<sub>2</sub>, 1,4-dioxane, 10 °C – Rt; (ii) NaOH, MeOH, reflux; (iii) 98% H<sub>2</sub>SO<sub>4</sub>, 25 °C; (iv) hv, aq. MeOH/H<sub>2</sub>SO<sub>4</sub>; (v) H<sub>2</sub>O, reflux; (vi) 30% aq. NaOH, reflux; (vii) aq. HCl, < 5 °C; (viii) MeOH, H<sup>+</sup>-Dowex, reflux.

ester for purification, which can be subsequently hydrolyzed to give the pure carboxylic acid.

The first reported use of this cubane dicarboxylate ligand in a 3-dimensional MOF by Macreadie, Batten, Hill and co-workers demonstrated the formation of a **pcu**-type framework,<sup>[66]</sup> named as CUB-5, containing basic zinc acetate nodes and iso-reticular to the well-known MOF-5 (Figure 6).<sup>[67]</sup> The authors found a marginally smaller pore volume in comparison to MOF-5 (0.92 cm<sup>3</sup>g<sup>-1</sup> and 1.20 cm<sup>3</sup>g<sup>-1</sup>, respectively), relating to the greater equatorial steric bulk of the ligand compared to the aromatic isostere. However, the authors observed a substantial



**Figure 6.** Coordination chemistry of cubane dicarboxylate in the crystalline phase in the aliphatic MOF-5 analogue CUB-5.<sup>[66]</sup> The experimental structure is severely disordered through unrestricted rotation of the entire cubane unit: the structure shown above is generated from a single idealised rotamer.

improvement in adsorption of non-polar hydrocarbon adsorbates, particularly benzene, which they ascribe to the additional adsorbent-adsorbate interactions involving the methine groups directed into the pores in CUB-5. This report has recently been followed by another from the same group which incorporates the cubane-1,4-dicarboxylate ligand into several multi-component MOFs with supporting aromatic ligands (again, with the cubane ligand acting as an isostere to benzene-1,4-dicarboxylate).<sup>[68]</sup> In this report, the authors find the additional contouring of the pore environment caused by the more 3-dimensional structure of the ligand backbone leads to a significant increase in cyclohexane adsorption compared to the fully aromatic MOF equivalent.

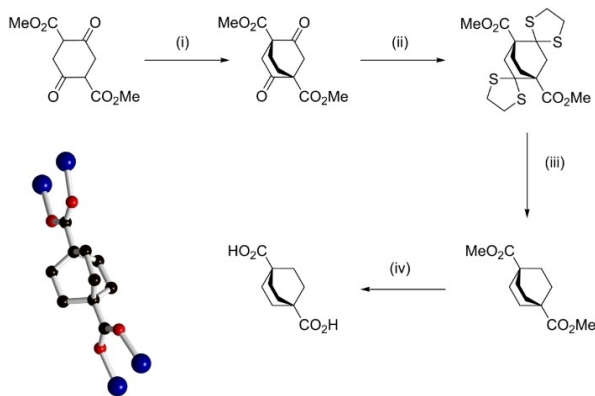
Another example of a compact polycyclic aliphatic hydrocarbon is the bicyclo[2.2.2]octane skeleton. This backbone is most well-known to MOF chemists as its diaza derivative 1,4-diazabicyclo[2.2.2]octane (DABCO),<sup>[69]</sup> a ubiquitous bridging ligand which has also been used to introduce Lewis base character as part of an immobilised frustrated Lewis pair (FLP)<sup>[70]</sup> or for directed N...X halogen bonding interactions.<sup>[71]</sup> The all-carbon analogue has been much less widely studied, presumably due to a lack of commercially available derivatives, although a handful of studies have explored the dicarboxylate derivative. The first such study, by Li and co-workers in 2008,<sup>[72]</sup> reported a 4-step synthesis of bicyclo[2.2.2]octane-1,4-dicarboxylic acid starting from dimethyl 1,4-cyclohexanedione-2,5-dicarboxylate (Scheme 4). In this process, the dione is converted to the bicyclic skeleton by alkylation of the disodium salt with dibromoethane, followed by conversion to the bis-dithiane and reduction, and ester hydrolysis to give the dicarboxylic acid on a multi-gram scale. The ligand was used in this study in combination with DABCO to generate porous MOFs containing nickel(II) or cobalt(II) paddlewheel nodes isostructural to the well-known  $[Zn_2(bdc)_2(DABCO)]$  structure.<sup>[73]</sup> The authors also observe strong hydrocarbon adsorption performance including two-step adsorption profiles for cyclohexane at temperatures up to 70 °C. The authors also note the influence of the

equatorial bulk of the ligand on preventing interpenetration to maintain micropore volume, an observation which has also been noted for the cubane analogue (*vide supra*).<sup>[66]</sup>

More recently, Ballesteros-Garrido and co-workers employed the same ligand in a series of homoleptic MOFs with the aim of generating porous crystalline materials which are optically transparent in the visible and near-UV region,<sup>[74]</sup> and so necessitating the lack of any aromatic character whatsoever in the ligands. In this case, the authors report the use of a similar synthetic procedure to Li and co-workers, except proceeding *via* a semicarbazone for the reduction step in place of the dithiane.<sup>[75]</sup> One MOF generated in this study was subsequently used as a non-absorbing host matrix for pyrene, which showed unusual intermediate behavior in its emission spectrum between that observed in the solid state and in ethanol solution. The Kaskel and Glorius groups have also taken advantage of the bicyclo[2.2.2]octane skeleton by appending chiral secondary amines to bicyclo[2.2.2]octane-1,4-dicarboxylic acid.<sup>[76]</sup> Using this ligand in place of homochiral terephthalic acid derivatives gave a new chiral MOF of sodalite topology (DUT-129).

Farha and co-workers have also recently reported a zirconium MOF isorecticular with UiO-66 constructed from bicyclo[2.2.2]octane-1,4-dicarboxylic acid, which they gave the identifier NU-403.<sup>[77]</sup> In that study, the authors found a large degree of missing linker and missing cluster defects in their attempts to generate the MOF in the presence of modulators, and so employed a post-synthetic defect healing approach to prepare the pristine MOF. Similar to the observations from cubane-derived MOFs, here the authors targeted the smaller pore size compared to UiO-66 as a result of the 3-dimensional bulk of the aliphatic ligand backbone, in this instance to enhance Xe/Kr separation. Reduction of the pore size in NU-403 compared to UiO-66 (once the mesoporous defects were eliminated) did indeed give a higher selectivity for Xe over Kr in a 20:80 mixture (9:1, *cf.* 7:1 for UiO-66), which was ascribed to better size matching between adsorbent and adsorbate in the small-pore aliphatic MOF.

Many other polycyclic aliphatic hydrocarbons and their polycarboxylate derivatives are known in organic chemistry, and non-planar structures are becoming increasingly important in drug design and other molecular architectures.<sup>[78]</sup> Popular small-molecule examples include bicyclo[1.1.1]pentane<sup>[79]</sup> and norbornane,<sup>[80]</sup> both of which being capable of extension into oligomers.<sup>[81]</sup> Likewise, flat polycyclic aliphatic systems such as *trans*-decalin and the wide range of known steroid derivatives also qualify as rigid aliphatic groups capable of functionalization through rich and well established synthetic methods, and have already seen use in supramolecular chemistry.<sup>[82]</sup> Given the positive results seen so far in small polycyclic aliphatic species it seems likely that the infiltration of these functional groups into MOF chemistry is only a matter of time.



**Scheme 4.** The synthesis of bicyclo[2.2.2]octane-1,4-dicarboxylic acid reported by Li and co-workers, and its coordination chemistry in the presence of cobalt(II) ions.<sup>[72]</sup> Hydrogen atoms are omitted for clarity. Reagents and conditions: (i) NaH, DME, reflux, then 1,2-dibromoethane, reflux; (ii) 1,2-ethanedithiol,  $BF_3 \cdot Et_2O$ , 0 °C – RT; (iii) Raney-Ni, EtOH, reflux; (iv) NaOH, EtOH/ $H_2O$ , reflux, then HCl.



## Conclusion and Outlook

Following the progression of MOF chemistry toward the applications-based regime, the importance of ligand functionality is still a crucial aspect of the design process. The diversity in MOF geometries/topologies synthesised in recent years reflects on both the supply of new materials and the demand for materials to meet these applications. Given the well-known weaknesses for many MOFs towards hydrolysis, the hydrophobicity of aliphatic linkers has the potential for a huge impact on the hydrolytic stability in the next generation of porous materials. The ligand backbones discussed in this minireview, especially those containing fused rings, offer a bulky hydrophobic group that could prevent the approach of water molecules to the relatively weak metal-carboxylate coordination bonds and therefore prevent subsequent degradation. The water stability of MOFs based on polycyclic aliphatic linkers has not yet been widely and systematically explored through water vapor adsorption measurements or tensiometry, and this is a logical next step in establishing these properties. However, and promisingly, their enhanced affinity for non-polar hydrocarbon adsorbates such as benzene and cyclohexane has already been observed in the two cubane-derived MOFs described above.

By virtue of their 3-dimensional steric profile, cyclic and fused polycyclic aliphatic ligand backbones also offer access to some interesting MOF geometries, which may be inaccessible from planar aromatic ligands. Ligands such as the cyclohexane polycarboxylates, with several stable conformers, provide a handle to access different linker geometries through control of reaction conditions. On the other hand, fused systems provide predictability in linker conformation, and have also been implicated in pore size “contouring”, giving greater orthogonal steric bulk to enhance adsorbate interactions with the pore walls. While such influences have been seen to impact the separation performance of cubane and bicyclo[2.2.2]octane-based MOFs for benzene/cyclohexane and xenon/krypton mixtures, respectively, a wide range of industrially relevant gas separations may benefit from this new approach.

Considering the advancements made so far in employing cyclic aliphatic hydrocarbons in MOF linkers, there remains much work to be done in diversifying these systems. It is well known that anionic nitrogen heterocycles such as pyrazolate and imidazolate offer improved hydrolytic stability in their metal complexes compared to carboxylates, which has been used to great effect in conventional aromatic systems.<sup>[83]</sup> Likewise, core-functionalised linkers containing amine functionality have been widely used to improve CO<sub>2</sub> adsorption properties, and an analogous approach with aliphatic ligands may be even more effective, given the much greater basicity of aliphatic amines compared to anilines.<sup>[84]</sup> Finally, given the rapid expansion of interest in non-planar hydrocarbon scaffolds in drug discovery and the associated advances in synthetic methods for these systems, we expect that such backbones will also grow in importance in the MOF field.

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## Conflict of Interest

The authors declare no conflict of interest.

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