Covalent Chemistry beyond Molecules

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ABSTRACT: Linking molecular building units by covalent bonds to make crystalline extended structures has given rise to metal—organic frameworks (MOFs) and covalent organic frameworks (COFs), thus bringing the precision and versatility of covalent chemistry beyond discrete molecules to extended structures. The key advance in this regard has been the development of strategies to overcome the "crystallization problem", which is usually encountered when attempting to link molecular building units into covalent solids. Currently, numerous MOFs and COFs are made as crystalline materials in which the large size of the constituent units provides for open frameworks. The molecular units thus reticulated become part of a new environment where they have (a) lower degrees of freedom because they are fixed into position within the framework; (b) well-defined spatial arrangements where their properties are influenced by the intricacies of the pores; and (c) ordered patterns onto which functional groups can be covalently attached to produce chemical complexity. The notion of covalent chemistry beyond molecules is further strengthened by the fact that covalent reactions can be carried out on such frameworks, with full retention of their crystallinity and porosity. MOFs are exemplars of how this chemistry has led to porosity with designed metrics and functionality, chemically-rich sequences of information within their frameworks, and well-defined mesoscopic constructs in which nanoMOFs enclose inorganic nanocrystals and give them new levels of spatial definition, stability, and functionality.

INTRODUCTION

The covalent chemistry of organic and inorganic molecules has long been the practice of chemists and at the heart of many important advances in science. The building-up and modification of organic molecules by covalent bonds to make pharmaceuticals, chemicals, and polymers have fundamentally changed our way of life. Similarly, covalent synthesis of inorganic complexes has led to useful catalysts capable of high activity and selectivity. The precision and versatility with which covalent chemistry on such molecules is practiced have not been translated to either the buildup of extended structures or their modification. This is until the invention of metal—organic frameworks (MOFs)[1−3] and covalent organic frameworks (COFs),[4] where molecular building units are covalently linked to make porous crystals of extended structures. These structures can also be modified by covalent chemistry through post-synthetic modification (PSM) without losing their long-range order.[5−7] In essence, MOF and COF chemistry has taken covalent chemistry beyond molecules to build up crystals of covalently linked extended structures and to carry out reactions on such crystals as if they are discrete molecules. The ability to reticulate molecular building units into frameworks[8,9] not only allows chemistry to be done in a precise manner on those units but also positions and confines them in a new chemical environment otherwise not possible in solution or in the molecular crystals of the unlinked constituents. Here, we highlight how this covalent chemistry practiced beyond molecules has led to (a) linking of building units into covalent crystals by combining organic and inorganic constituents to make MOFs and organic units to make COFs, both as robust materials with ultrahigh porosity; (b) covalent chemistry done by performing PSMs on MOF crystals, which maintain their order throughout the process and therefore provide means of designing the interior of MOFs; (c) emergent behavior resulting from mixing of functionalities within the pores of MOFs that have specific spatial, metric, and compositional characteristics; and (d) MOFs with sequences of chemical functionality running along their pores that are apportioned and compartmentalized on the molecular and nanolevels to make mesoscopic constructs.

COVALENTLY LINKING MOLECULES INTO EXTENDED STRUCTURES

A covalent bond is a chemical bond made by sharing electrons between atoms.[10] Organic synthesis of molecules takes full advantage of the directionality of covalent bonds to build-up elaborate chemical structures using step-by-step reactions, as exemplified by the original synthesis of vitamin B_{12}.[11,12]

In contrast, building-up a covalent extended structure is essentially a one-step synthesis leading to an insoluble product. Thus, the synthetic procedure has to be carefully designed to yield a well-defined material. If covalent chemistry beyond molecules is to be carried out with the same precision as that done for organic and inorganic molecules, the products have to be crystalline so that they are easily characterized. Furthermore, their crystallinity must be maintained even after they have been subjected to PSMs. Both of these challenges have been addressed for MOFs and COFs.

The "crystallization problem" encountered is usually magnified when linking molecular building units by increasingly stronger bonds (Figure 1).[8,13−15] For example, it is relatively easy to make crystals in which weak interactions hold the
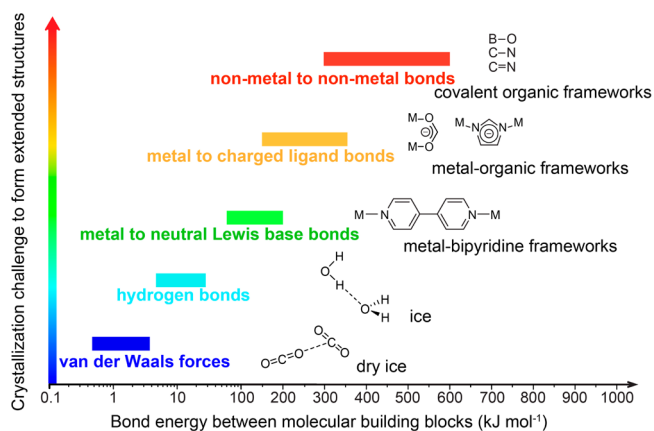
Figure 1. Increasing bond energy of linkages between molecular building blocks leads to increased difficulty in obtaining their corresponding crystalline extended structures.

molecules together such as van der Waals forces in dry ice and hydrogen bonding in ice, not withstanding are some cases where lower symmetry and/or flexible molecules are difficult to organize as molecular crystals. Even crystals of metal-bipyridine-type structures are easy to obtain because of the

weak bonding between the metal and the neutral Lewis base linker (Figure 1). However, crystallizing extended structures in which metal to charged ligand bonds and nonmetal to nonmetal bonds are employed is relatively more difficult as the case previously experienced for MOFs and COFs (Figure 1). The success in the synthesis of MOF and COF materials as crystals (Figure 2),[2,4,16−24] which are held together by strong bonds, vastly expands the realm of covalent chemistry to include extended and nanosized structures, as discussed below.

■ STRATEGIES FOR ADDRESSING THE "CRYSTALLIZATION PROBLEM"

The crystallization process requires reversible bond formation to allow for self-correction of defects and avoid the formation of amorphous or poorly crystalline products. Elegant examples exist where crystalline covalent extended structures are constructed through single-crystal-to-single-crystal topochemical linking of organic building units by exposure to UV light.[25] This approach is not as widely deployed as that used for MOFs and COFs because it requires meticulous design of the molecular building blocks and their precise positioning in the crystal prior to carrying out the covalent-bond linkage between adjacent molecules.
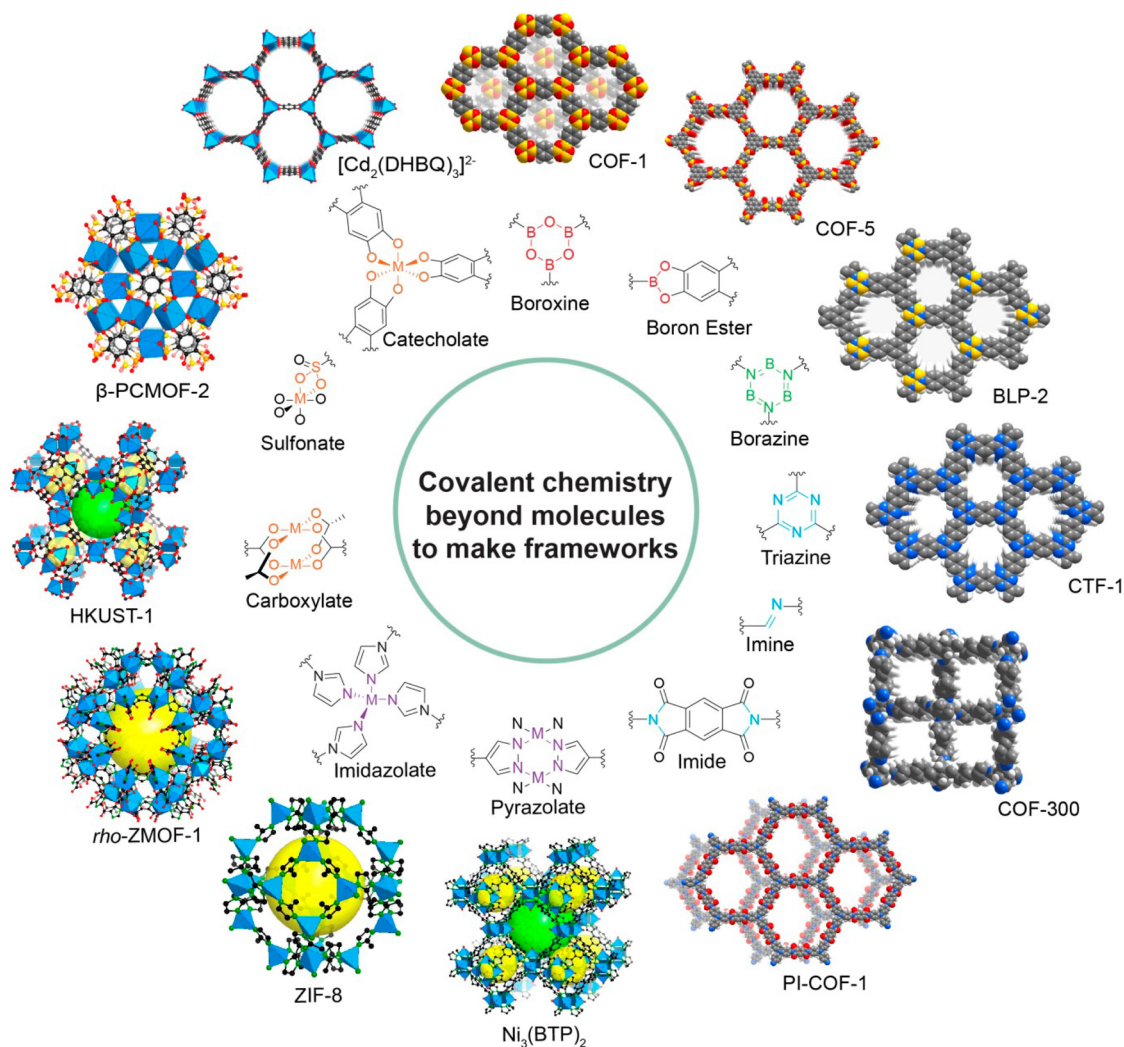
Figure 2. Covalent linkages (inner region) employed in the synthesis of MOFs and COFs (outer region).

In MOF chemistry, the goal of obtaining crystalline solids has been realized largely by slowing down the formation of strong metal−oxygen covalent bonds [M−O bonds, M = Ti(IV), V(III), Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Zr(IV), Ln(III), Al(III), and Mg(II)] between the inorganic and organic building units (termed secondary building units, SBUs) to a point permitting self-correction. Typically, the formation of a MOF requires deprotonation of the organic acid in order to make the metal−oxygen bonds. However, the rate at which this deprotonation process takes place is a critical factor in controlling the crystallization process of the MOF. The key development in making MOF crystals of metal-carboxyl bonds was the use of amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, and N-methyl-2-pyrrolidone.[1,3] Since these solvents are heated in the synthesis of MOFs, they function as sources for the slow release of basic amines,[26] which gradually deprotonate the organic acid and facilitate the formation of covalent bonds between the inorganic and organic SBUs.[1] Large MOF single crystals of millimeter sizes have been reported using these solvents.[27,28] Needless to say, this basic procedure has been employed in the synthesis of the vast majority of MOFs.[29] Recently, other methods involving the use of water as a solvent,[2,30] microwave irradiation,[31] and mechanochemical procedures[32,33] have been developed for MOFs.

It was also shown that highly crystalline MOFs of zirconium, aluminum, chromium, and lanthanide can be obtained by adding modulators;[34−37] these are usually monocarboxylic acids such as formic acid, acetic acid, and benzoic acid. Addition of these modulators along with di- and multitopic carboxylate linkers suppresses the hydrolysis of the metal ions to metal oxides due to their acidity and slows down the crystal growth process to give the control needed for obtaining MOF crystals.

Different strategies are applied in COF chemistry to make crystalline covalent organic solids. Typically, this is achieved by reactions where stoichiometric quantities of a small molecular byproduct such as water are generated. In a closed system, such byproducts of the covalent-bond formation are used to modulate the extent of equilibrium between the product and reactants according to Le Châtelier's principle. For example, water generated from the formation of boroxine anhydride in COF-102 and boronate ester in COF-108 is capable of hydrolyzing and modulating the reversibility of the covalent bonds (B−O and C−O bonds) formed in those COFs.[38] The extra space intentionally left in the closed reactor and the combination of hydrophilic and hydrophobic solvents allow the water formed to be partitioned between the reaction mixture and the headspace. In this way, the formation of the extended structure is driven by the equilibrium between water in the reaction mixture and the headspace. Catalysts, such as acetic acid and hydrochloric acid, which are effective in reversibly controlling reaction rates can be used to accelerate an otherwise slow covalent-bond formation/cleavage, as was illustrated in COFs linked by imine and hydrazone bonds.[18,39−42] Efforts devoted to the crystallization of these extended structures have produced highly crystalline materials and made possible their structural characterization by diffraction techniques (powder and single crystal X-ray, neutron, and electron) and the study of their covalent reaction chemistry.

DESIGN OF POROSITY AND ACCESS TO ENCOMPASSED 3D SPACE

Thus far, we have outlined how building-up covalent extended structures from molecular building units can lead to crystalline MOFs and COFs. The study of these solids by X-ray diffraction techniques revealed not only the strong linkages making up the backbone of the frameworks but also the space encompassed within them.[1] This space is filled with solvent and, in the case of charged frameworks, solvated counterions, which have to be removed and desolvated in order to access the porosity of the material (this process is referred to as "activation") and allow the development of covalent chemistry within the pores.

Early studies on metal−organic materials composed of metal to neutral Lewis base bonds (e.g., bipyridine and nitrile-type) reveal that these frameworks collapse when activated because of their frail architecture.[8] In contrast, MOFs composed of strong covalent linkages such as metal−carboxyl bonds are robust upon removal of the guest solvent molecules and, therefore, were shown to have permanent porosity by gas sorption isotherm measurements.

Proof of permanent porosity was obtained as early as 1998 for MOFs[1] and 2005 for COFs,[4] respectively. This has allowed comparisons to be made between these frameworks and the more traditional porous materials, such as zeolites and related inorganic microporous materials.

It is worth mentioning that activation of MOFs and COFs has been a subject of intense study because of their high porosity and the challenges associated with evacuating large amounts of solvent from the pores. The most reliable activation methods have involved: (a) "solvent-exchange" where the as-synthesized material is immersed in a solvent of less polarity and lower boiling point than the one already in the pores, followed by frequent refreshing and evacuation of that solvent;[43] and (b) 'supercritical CO_2 drying' where liquid CO_2 is used to exchange the solvent in the pores and the system's temperature and pressure are elevated beyond the critical point of CO_2, followed by depressurization to leave behind vacuous pores. The latter method has been proven to be successful for a few cases in which the framework bears large pores but with small pore apertures or has highly hydrophilic pores.[44,45] Presently, these methods are used routinely, thus offering new opportunity for covalently designing the interior of the pores.

The permanent porosity of MOFs has led to unparalleled precision in expanding the pores, designing the pore shape, and the covalent attachment of functional groups to the organic linkers and/or open metal sites within the backbone of MOFs. Thus, in the remainder of this section, we focus on the first two aspects, while the third is discussed in a separate section below. From this point on, we use MOFs as examples because their chemistry is illustrative and, in these respects, far more developed than COFs.

The precision with which covalent chemistry is used to stitch molecular building blocks into extended structures, referred to as reticular chemistry, has made available a diverse class of MOFs in which the pore shape and pore size can be varied nearly at will. For example, isoreticular expansion (expanding the metrics of the framework without changing its underlying topology) has yielded the most porous materials and the largest pore opening in crystals.[46−51] In the cubic HKUST-1 system, the most expanded member, MOF-399, [Cu₃(BBC)₂; BBC = 4,4′,4″-(benzene-1,3,5-triyl-tris(benzene-4,1-diyl))tribenzoate]
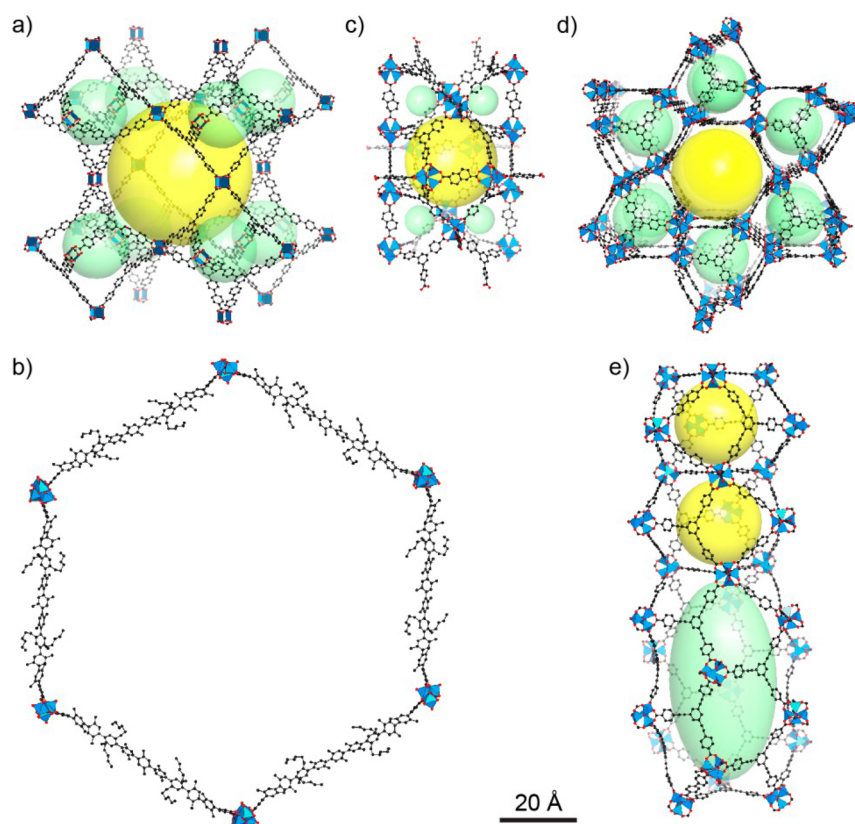
Figure 3. Examples of highly porous MOFs: (a) MOF-399, (b) IRMOF-74-XI, (c) DUT-6 (MOF-205), (d) UMCM-1, and (e) MOF-210. The pores are represented as green and yellow spheres. Atom labeling scheme: M (blue polyhedra, M = Zn, Cu, Mg), C (black), and O (red). All H atoms are omitted for clarity.
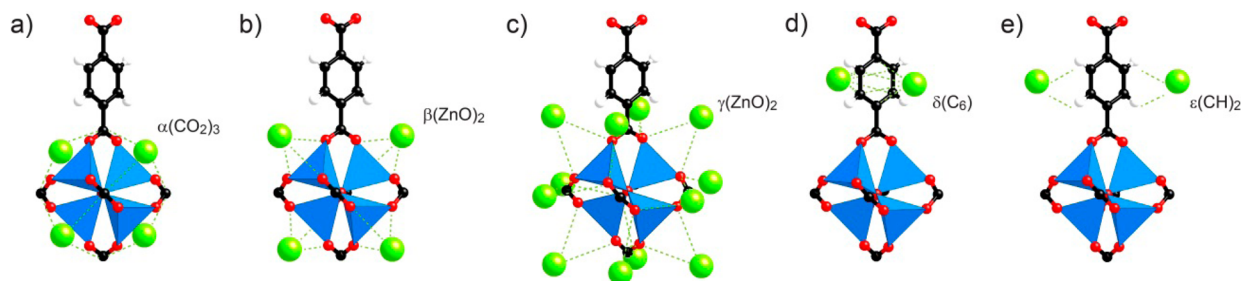
Figure 4. Symmetry-independent adsorption sites partially occupied by Ar atoms at 30 K. These include (a−c) three sites primarily associated with the secondary building unit and those above the (d) face and (e) edges of the linker. The absorption sites are represented as green spheres. Atom labeling scheme: Zn (blue polyhedra), C (black), O (red), and H (white). Adapted with permission from ref 54. Copyright 2005 AAAS.

(Figure 3a), bears a pore of the same shape but 16 times larger in volume than that of the smallest member HKUST-1, $[Cu_3(BTC)_2$; BTC = benzene-1,3,5-tricarboxylate].[47] In the hexagonal MOF-74 system, $[Mg_2(DOT)$; DOT = dioxidoterephthalate], the organic linker with one phenylene unit was expanded to have 11 phenylene units resulting in a pore aperture of 98 Å in diameter for the corresponding IRMOF-74-XI (Figure 3b).[51] Modulation of the pore shape is achieved either by changing the combination of SBU geometry or by varying the linker length ratio. For example, linking the $Zn_4O(-COO)_6$ SBU with mixed dicarboxylates and tricarboxylates of different length ratios gives (a) two types of cages (dodecahedral and tetrahedral cages of 2.5 × 3.0 nm and 0.5 × 0.5 nm in size) in DUT-6 [MOF-205, $Zn_4O(NDC)(BTB)_{4/3}$, NDC = naphthalene-2,6-dicarboxylate, BTB = benzene-1,3,5-tribenzoate] (Figure 3c);[46,52] (b) 1.4 × 1.7 nm

cages and 2.7 × 3.2 nm mesoscale 1D channels in UMCM-1, $[Zn_4O(BDC)(BTB)_{4/3}$; BDC = benzene-1,4-dicarboxylate] (Figure 3d);[53] and (c) three different types of cages (2.7 × 4.8 nm, 2.0 × 2.0 nm, and 0.6 × 0.6 nm) in MOF-210, $\{Zn_4O(BPDC)(BTE)_{4/3}$; BPDC = biphenyl-4,4′-dicarboxylate, BTE = 4,4′,4″-[benzene-1,3,5-triyl-tris(ethyne-2,1-diyl)]-tribenzoate} (Figure 3e).[46]

■ ADDRESSABLE RETICULAR MOLECULES

On a fundamental level, the ability to make MOF structures permanently porous has given access to molecules within the confines of an extended structure. From the forgoing discussion, this would not be possible without the covalent chemistry being developed beyond molecules. Indeed, all atoms [with the exception of a central atom which might reside within an inorganic SBU as the O in $Zn_4O(-COO)_6$] that make up the
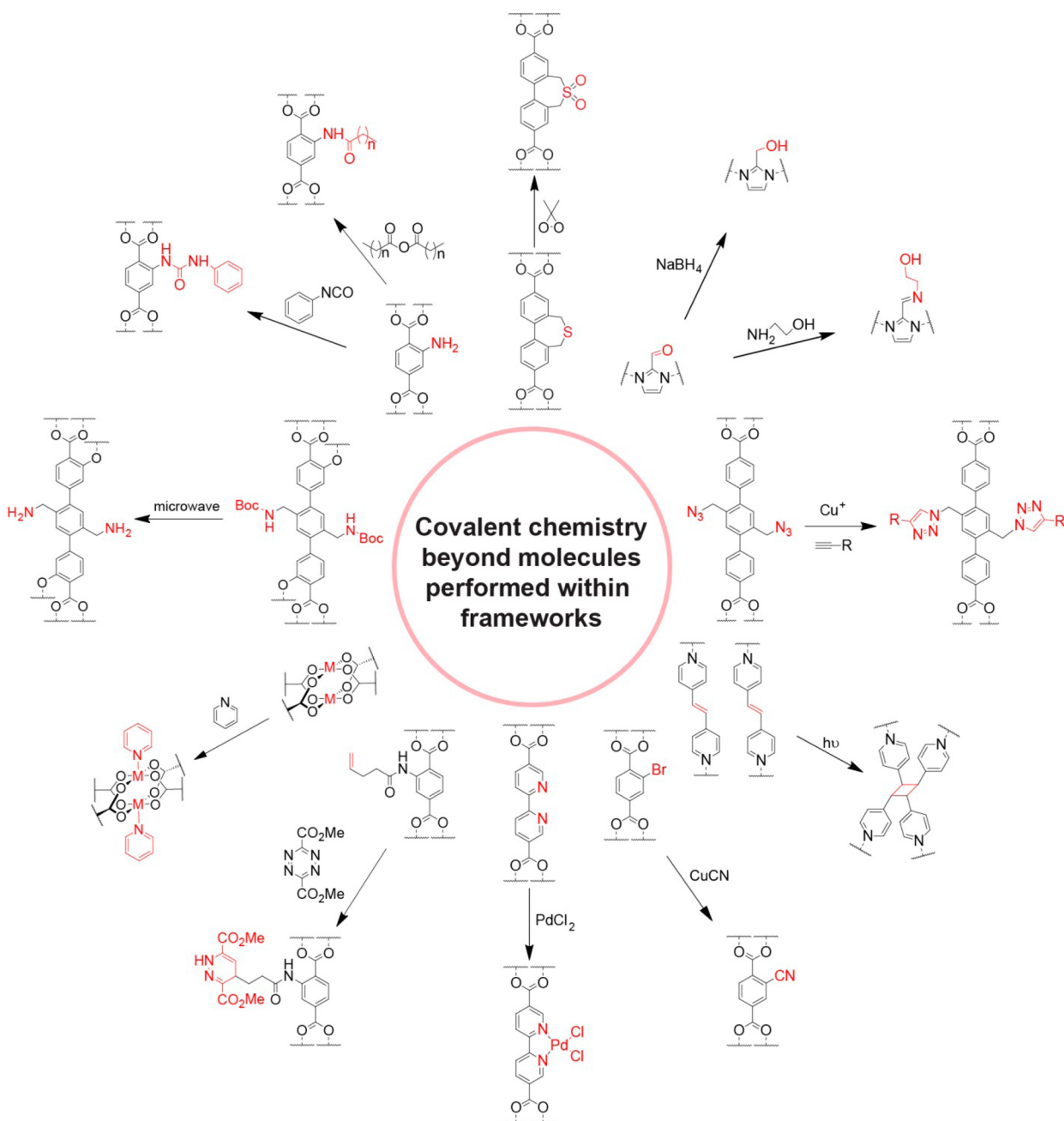
Figure 5. Covalent chemistry employed to modify MOF crystals as discrete molecules.[103]

inorganic and organic SBUs are accessible to incoming guests such as gases and organic molecules. This advantage is only possible because the SBUs are stitched through covalent chemistry and thus are suspended in 3D without being solvated as discrete molecules. Additionally, they do not suffer from being inaccessible in the solid state, as would be the case in a closely packed molecular crystal.

Access to each of the atoms in MOFs was revealed by an X-ray diffraction experiment conducted on single crystals of MOF-5 at 30 K.[54] Here, small doses of Ar or N_2 introduced into the already evacuated pores revealed accessible adsorption sites within the pores: the zinc oxide SBU (Figure 4a−c) and the faces and the edges of the phenyl ring of the BDC linkers (Figure 4d,e). This study also served as a benchmark for identifying the origin of the ultrahigh surface areas found in MOFs. Subsequently, adsorption sites for gases, such as

$D_2(H_2)$, CH_4, CO_2, and H_2O, and their behavior in MOFs were identified using a variety of techniques,[55−61] and their interaction strength assessed for a large variety of MOFs. Thus, suspending molecules in 3D space and having access to these molecules by covalently linking them into scaffolds is the best strategy for maximizing access to them as well as for increasing the number of adsorption sites. Other means of increasing adsorption sites involve having multiple interpenetrating frameworks in the crystal.[62,63] It is important to give consideration to the size of substrate to be incorporated in the pores and the most efficient pore size needed from the division of space to maximize its interaction with the framework.

Metal-containing SBUs are strong adsorption sites for gases and can be stronger and more selective if they have open metal sites (also known as unsaturated coordination sites). In the field

of molecular metal complexes, however, this chemistry requires steric hindrance around open metal sites rendering them inaccessible. The covalent chemistry of frameworks helps to address this problem by using strong covalent bonds to fix the metal atoms in a rigid structure and prevent their rearrangement, aggregation, and ligation to them when they are coordinatively unsaturated. This feature greatly facilitates the generation and accessibility of open metal sites in MOFs. In 2000, the first example of open metal sites in MOF was created in MOF-11, [Cu_2(ATC); ATC = adamantane-1,3,5,7-tetracarboxylate], and characterized by single crystal X-ray diffraction experiments.[64] Water molecules bound to copper atoms in $Cu_2(H_2O)_2$(-COO)$_4$ SBUs of the as-synthesized MOFs were readily removed upon heating at 120 °C to generate open coordination sites on four-coordinate coppers in Cu_2(-COO)$_4$ SBUs of the activated MOF-11. Since then open metal sites have been produced in MOFs and used for: (a) enhanced storage capacity of H_2, CH_4, CO_2, and NH_3;[65−68] (b) improved CO_2/N_2 separation;[69] (c) molecular recognition;[70] and (d) Lewis acid catalysis.[71−73]

■ COVALENT CHEMISTRY WITHIN FRAMEWORKS

Covalent chemistry could also be employed to modify MOF crystals as if they were discrete molecules, because the MOF building units retain the same underlying structure and essential chemical reactivity as their molecular counterparts. PSMs involve either organic reactions modifying the organic linkers of the MOF and/or covalent bonding of incoming ligands to open metal sites (Figure 5).[74−83] These modifications are performed orthogonally to the MOF backbone structure. Such chemical reactions are carried out at precise locations within the crystal, and the product remains atomically well-defined (i.e., crystalline). The ability to carry out reactions on extended solids in this manner is possible because of the robustness of the MOF structure due to the strong covalent bonds making up the framework. Furthermore, this chemistry allows functional groups that are not compatible with the MOF synthesis to be incorporated and for the design of a series of MOFs of different functionality using a single synthetic condition. Thus, PSM is a powerful tool to design complexity within MOFs.

PSMs performed on extended solids require reagents to diffuse throughout the crystal. Reactions involving insoluble heterogeneous reagents and catalysts or those producing insoluble byproducts present a challenge to PSMs of MOFs. The candidate reactions for PSM should also be chemically compatible with the MOF backbone. Increasingly, MOFs with unusual stability in aqueous and nonaqueous conditions are being used.[5,84,85] More recently, MOFs stable in acidic and basic media have been reported.[21,30,86] These developments provide plenty of opportunities for PSMs to be used in the development of covalent chemistry beyond molecules.

A typical example of PSMs using metal coordination is the metalation of MOF-253, [Al(OH) (BPYDC), BPYDC = 2,2-bipyridine-5,5-dicarboxylate],[79,87,88] where BPYDC molecules linked up with alumina rods are metalated with Cu(II), Ru(II), and Pd(II), rendering the MOF with unusual gas separation and catalytic properties [e.g., Cu(II) metalated MOF-253, Al(OH) (BPYDC)·0.97Cu(BF$_4$)$_2$, shows 4-fold increase of selectivity in N_2/CO_2 separation].[79] Other examples include metalations, with first-row transition metals, of the free-base porphyrin TCPP-H_2 in MOF-545, [$Zr_6O_8(H_2O)_8$(TCPP-H_2)$_2$, TCPP-H_2 = 4,4,4,4‴-(porphyrin-5,10,15,20-tetrayl)-tetrabenzoate], and Al_2(OH)$_2$(TCPP-H_2).[89−91]

Coordinating ligands such as amines and sulfates can bind to metal SBUs containing open metal sites.[2,92−94] These PSMs are facile and have proved to be useful in introducing catalytically active sites and new gas adsorption sites. For example, MOF-808, [Zr_6O_5(OH)$_3$(BTC)$_2$(HCOO)$_5$(H_2O)$_2$], can be treated with sulfuric acid to produce its sulfated analogue, MOF-808–2.5SO$_4$, [Zr_6O_5(OH)$_3$(BTC)$_2$(SO$_4$)$_{2.5}$(H_2O)$_{2.5}$], which shows superacidity.[93] The sulfate groups are covalently bound to the zirconium based SBUs in a spatially well-defined manner as confirmed by single crystal X-ray diffraction.

Modification on the organic linkers has been done using various organic reactions involving click chemistry, imine condensation, amide-bond formation, and functional group deprotection (Figure 5). For example, primary amines can be incorporated in IRMOF-74-III through post-synthetic deprotection.[76] The MOF constructed with linkers bearing tert-butyloxycarbonyl group protected amines was heated at 230 °C in a ternary mixture of solvents under microwave irradiation to deprotect and obtain primary amine groups covalently linked in the pores. These primary amine groups, which are incompatible with the MOF synthesis conditions, enable the MOF to selectively bind CO_2 in the presence of water.[76] Other examples are the PSMs carried out on IRMOF-3, [Zn_4O(BDC-NH_2)$_3$, BDC-NH_2 = 2-aminobenzene-1,4-dicarboxylate], where the amino groups react with alkyl anhydride to form an amide bond and introduce alkyl groups into the MOF.[95] It is shown that with increased length of the alkyl group, the IRMOF-3 becomes more hydrophobic and resilient to moisture.[83]

Metal-binding sites,[96] carboxylic acids,[97] amines,[76] and triazoles[81,98,99] have also been incorporated into the organic linkers of MOFs using similar PSMs. Biomolecules such as amino acids have also been introduced into MOFs by multiple sequential reactions with full preservation of crystallinity. Aniline units in MIL-68-NH_2, [In(OH) (BDC-NH_2)], were coupled with protected proline and alanine using 4-dimethylaminopyridine/PyBroP coupling reagent.[100] Upon deprotection, the free amino acids covalently attached to the organic linkers were obtained. These versatile multiple-step covalent reactions on MOF crystals, just like the synthesis of vitamin B_{12} referred to earlier, take full advantage of the directionality of covalent bonds while operating in 3D extended crystals.

Given the versatility of PSMs and the diversity of MOF structures, which can be modified without losing their crystallinity, we anticipate further growth of this approach to include precisely designed interiors of MOFs to carry out complex catalytic reactions. To illustrate this point, we use IRMOF-74-III as a platform for covalently dangling amino groups inside its 1.5 nm pores. A catalytic MOF can be made by covalently attaching a conventional organometallic catalyst inside the pore using imine condensation (Figure 6). Here, the MOF backbone may be considered as being analogous to the enzyme backbone "propping up" the catalytic active site. The pores of the MOF help control the selection of substrates and products.[101,102]

■ MULTIVARIATE COVALENT CHEMISTRY

As covalent chemistry performed on discrete molecules may give mixtures of products, the same is true when such chemistry is performed on MOFs. However, the "reaction mixture" resulting from PSMs remains as an integral and inseparable part of the MOF structure. Thus, such MOF crystals have both the functionalized and nonfunctionalized linkers in the backbone
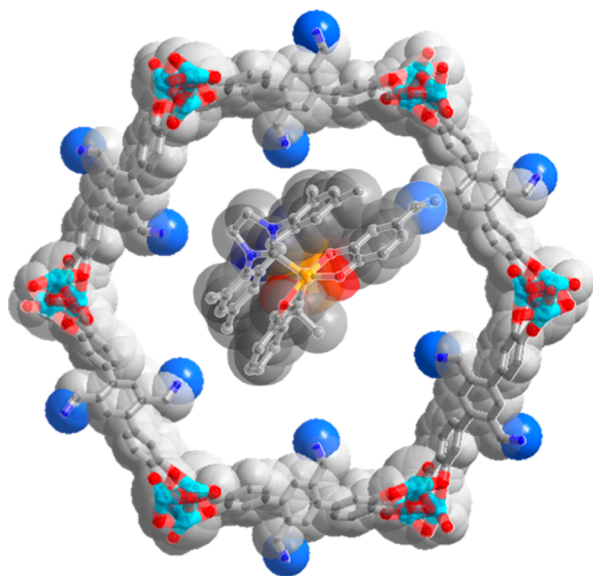
Figure 6. A conceptual example of an organometallic complex covalently linked in a MOF. A derivative of a ruthenium-based olefin metathesis catalyst, [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]catecholato(o-isopropoxyphenylmethylene) ruthenium,[104] is attached to a MOF (IRMOF-74-III) with 1D pore to produce a complex active site. Atom labeling scheme: Mg (light blue), C (gray), N (blue), O (red), and Ru (orange). H atoms are omitted for clarity.

structure. In other words, the MOF interior and its multiple functionalities are of a multivariate nature (MTV-MOFs), where phase purity is preserved while incorporating multiple derivatives of linkers. For example, in the previous case of IRMOF-3 modified with alkyl anhydride, when the conversion of the amino group throughout the material is incomplete,[95] amino and amide groups co-exist to make for mixed linkers in the makeup of the MOF crystal. Here, the amide and amino groups can only reside as attached units to the ordered arrangement of phenyl ring units of the linkers. However, the spatial distribution of the functional groups on the linkers is disordered because they all lie on the same crystallographic position. Thus, the question of how they are spatially arranged in the crystal is both a challenge and an opportunity.[27,105] This can be best understood by conceptually considering the spatial arrangement of the functionalities in MTV-MOFs as a sequence of information, which, in principle, is not very much unlike the sequence of nucleotide units in DNA molecules. In the MOF, these sequences are propagating in 3D and, therefore, are more complicated. The exciting

opportunity is whether it is possible to characterize these functional group sequences and if indeed they could be designed to code for specific properties. A recent observation is encouraging: MTV-MOF-5, $[Zn_4O(BDC-X)_3$, BDC = benzene-1,4-dicarboxylate, and X = -NO$_2$, -(OC$_3$H$_5$)$_2$, and -(OC$_7$H$_7$)$_2$], was directly synthesized and shown to have 4 times better separation of CO$_2$ from CO compared to its best same-link counterpart.[27] Furthermore, it was intriguing to note that the whole performed significantly better than the sum of the parts.

The question of characterizing the functional group sequences is a new one requiring development of physical techniques capable of deciphering them on the atomic level. However, a recent effort to determine the distribution of multiple functionalities in the MTV-MOF revealed that they are not always random. An indication of this was the observation that the ratio of the linkers used in the reaction is not the same as that actually incorporated into the product. This indicates biasing toward a specific linker or set of linkers. Indeed, it was shown by solid-state NMR that mixed linkers are apportioned on the nanoscale throughout the crystal.[105,106] Specifically, for the MTV-MOF-5 binary mixed linker systems: BDC-NO$_2$ and -(OC$_7$H$_7$)$_2$, BDC-NO$_2$ and -(CH$_3$)$_2$, and BDC-NH$_2$ and -(CH$_3$)$_2$, it was found that they are apportioned in an alternating, random, and small clustering motif, respectively (Figure 7).[105]

The MTV approach has also been effective in producing MOFs incorporating linkers into certain topologies not observed when only one kind of linker is used. In the case of MOF-177, $[Zn_4O(BTB)_2]$, nitro group functionalized BTB (BTB-NO$_2$) linkers can be readily incorporated when mixed with BTB linkers, while the BTB-NO$_2$ linker itself, when used alone, does not form MOF-177.[107] In catalytic MOFs, the MTV concept has been used in the dilution of active sites, where "doping" with an active linker into an otherwise inert framework has proved powerful in optimizing catalytic performance.[108]

The MTV-MOF concept intellectually leads to further development of the compartmentalization of space within MOFs. Here, different compartments, which are linked and open to each other, can be functionalized differently so that they perform different functions; a likely scenario since in MTV-MOFs equivalent crystallographic positions can bear different functionalities. One can envision how this could produce multiple compartments spanning many unit cells when the functionalities are apportioned in the crystal. We note that compartments of this kind are possibly intermingling and may very well be able to operate synergistically. This might be the
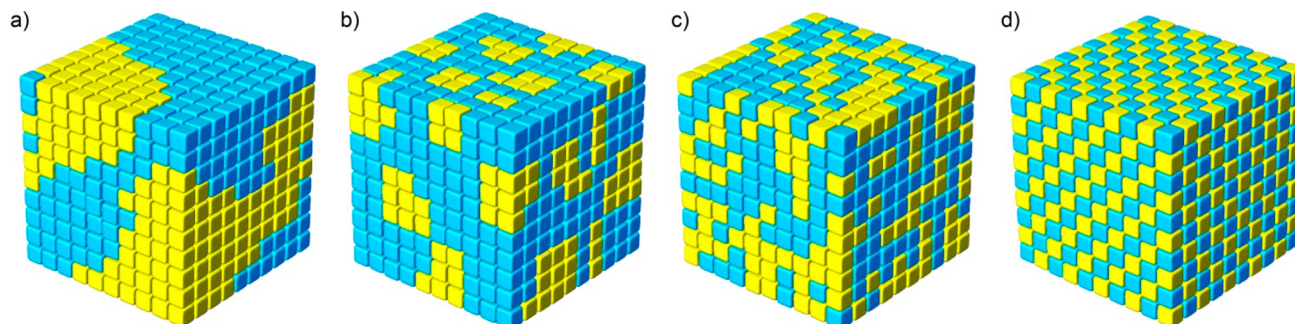
Figure 7. Scenarios of linker apportionment in MTV-MOF materials: (a) large clusters, (b) small clusters, (c) random, and (d) alternating.

reason for the unusual emergent properties observed for MTV-MOFs compared to the physical mixtures of same-linker MOFs.[27,105]

The missing linker defects and their spatial arrangement in MOFs are another aspect of the MTV concept.[109] It is common in zirconium MOFs especially UiO-66, $[Zr_6O_4(OH)_4(BDC)_6]$, that water or acetic acid instead of BDC is coordinating to the zirconium SBUs leading to defective frameworks with improved porosity.[86,110,111] A more elaborate example involves the selective removal of half of the linkers and a quarter of the metal ions in $Zn_4O(PyC)_3$ (PyC = 4-pyrazolecarboxylate) without losing the MOF crystallinity.[112] This process can be reversed with new metal ions and linkers to give new frameworks of the same topology, with preserved crystallinity and ordered distribution of linkers. Additionally, when functional monodentate molecules are incorporated, new functionalities arise without compromising the overall structural integrity and order.[113] In addition to control of defects, a versatile aspect of this concept is the direct exchange of the linker and metal ions in MOFs. Here, a MOF is immersed in a solution containing different linkers or metal ions under mild condition to give a MOF that incorporates these components.[49,114−117] This approach has enabled the incorporation of otherwise incompatible building units into MOFs and often affords MOFs of multivariate composition. In the case of UiO-66, Hf(IV) and Ti(IV) can be incorporated into the SBUs of a MOF by treating the crystals with the corresponding solution of the desired metal ion.[114] All these mixed systems are intrinsically multivariate and subject to the same uncertainties associated with the question of spatial arrangement of functionality and metal atoms.

■ THE FUNCTIONALIZATION OF NANOPARTICLES WITH MOFS

MOFs, when synthesized in their nanocrystalline form (nanoMOF),[34,118,119] bring the merits of covalent chemistry beyond molecules into the nanometer regime and enrich the library of nanocrystalline materials. It is clear from Table 1 that nanoMOFs have unprecedented versatility compared to inorganic nanocrystals. By enclosing inorganic nanocrystals with nanoMOFs to form mesoscopic constructs,[90,120−134] the versatility of MOF chemistry can be applied to the functionalization of inorganic nanocrystals in a spatially defined manner.

A recent example involved having alumina with controlled thickness conformably coated on surfactant-free silver nanocrystals, which was reacted with $H_4TCPP-H_2$ to form oriented nanocrystalline $Al_2(OH)_2(TCPP-H_2)$ enclosures around the silver nanocrystals (Figure 8a).[90] The MOF enclosures can be regarded as modular functional units, where all the atoms in the MOF can be pinpointed relative to the inorganic interface due to the crystalline nature of the MOF.

Another generalizable approach to synthesize similar constructs requires growing nanoMOF in the presence of inorganic nanocrystals such that they are incorporated within the nanoMOF during the growth process,[120,122,124−128,134] as exemplified by the Pt nanocrystals enclosed in nano-UiO-66 (Figure 8b).[122,125,128,134] This construct displays unusual catalytic properties in hydrogenative conversion of methylcyclopentane, where benzene can be obtained at much lower temperature than that required when using surface supported Pt nanocrystal.[122] When a Pd nanocrystal is enclosed by ZIF-8, $[Zn(2-mIm)_2$, 2-mIm = 2-methylimidazolate], ethylene and

Table 1. Characteristics of nanoMOFs, Inorganic Nanocrystals, And Their Mesoscopic Constructs

nanomaterial	NanoMOF	inorganic nanocrystal	mesoscopic construct
structural order	crystalline (atomically well-defined structure)	crystalline (atomically well-defined structure)	atomically well-defined (with oriented MOF)
covalent modification	covalent modification on well-defined positions	only on surface ligands without determination of the exact position of functionalization	covalent modification at well-defined positions on the MOF enclosure; tuning of the chemical environment and metrics of the inorganic nanocrystal
porosity and pore environment	pores with well-defined interior	typically nonporous	transport to the inorganic nanocrystals is regulated by MOF pores
structural diversity and designability	isoreticular expansion available; inorganic clusters and organic molecules incorporated; multivariate in nature	change of constituents changes the phase of the material; limited to inorganic materials	orthogonally combines the merits of both nanoMOF and inorganic nanocrystal. Tunable synergistic effect arises
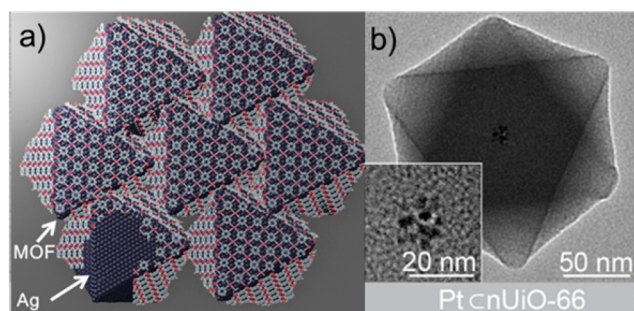
Figure 8. MOFs enclosing inorganic nanocrystals: (a) oriented Al$_2$(OH)$_2$(TCPP-H$_2$) MOF enclosing octahedral silver and (b) UiO-66 enclosing Pt nanocrystal.

cyclohexene can permeate the pores of ZIF-8 to access the Pd nanocrystal and undergo hydrogenation reaction, while the larger cyclooctene substrate is blocked.[135]

Enclosing inorganic nanocrystals with nanoMOFs has opened up new opportunities in the design of nanomaterials because: (a) the functional groups in MOFs are distributed around the inorganic nanocrystals with ordered spatial arrangement;[90] (b) the well-defined pore structure of MOFs controls access of guests and the evolution of products from the inorganic nanocrystals;[135] (c) the robust, crystalline enclosure enhances the stability of nanocrystals and prevents their aggregation;[122] and (d) the functional groups in the MOF tune the chemical environment of the inorganic nanocrystals.[125] Thus, the covalent chemistry beyond molecules practiced on MOFs and extended to nanoMOFs provides a new level of control over the surface structure and reactivity of inorganic nanocrystals.

PROSPECTIVE

Covalent chemistry beyond molecules has created a large class of MOFs and COFs whose robust structure is endowed by strong covalent bonds. This robustness leads to permanent porosity, which is the key to altering the framework backbone to include a diversity of organic and inorganic units. Thus, the outcome of this has been to fix molecules in position within 3D space of MOFs and have the capability of addressing them through PSM, defect control, and ligand or metal exchange, without losing the order of the MOF crystal. By reticulating molecules and carrying out covalent chemistry on them, the molecules become part of a new chemistry that is not attainable when they are used in solution as discrete entities. These aspects give rise to molecules being part of 3D sequences within MOFs, precisely designed cavities capable of unusual selective binding, and metrically and compositionally well-defined environment for catalytically active sites. Future efforts will undoubtedly focus on alignment of molecules in MOFs to facilitate charge and energy transport and on the positioning of dynamic groups in strategic locations within MOFs for complex functions.[136,137] The introduction of multivariation covalently within MTV-MOFs promises to deliver sequence-dependent properties, compartments of different functionality operating synergistically, pores with chemically-rich information, and eventually systems based on well-defined building units and chemistry designed for specific chemical transformations. A future area of development where this new chemistry will make a positive difference is the design of MOFs with exceptional electronic properties;[138−140] an aspect already on the way in the emerging chemistry of COFs[141,142] and mesoscopic constructs of MOFs.[143,144]

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Notes

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