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Pore Chemistry of Metal–Organic Frameworks

Zhe Ji, Haoze Wang, Stefano Canossa, Stefan Wuttke,* and Omar M. Yaghi**

The pores in metal–organic frameworks (MOFs) can be functionalized by placing chemical entities along the backbone and within the backbone. This chemistry is enabled by the architectural, thermal, and chemical robustness of the frameworks and the ability to characterize them by many diffraction and spectroscopic techniques. The pore chemistry of MOFs is articulated in terms of site isolation, coupling, and cooperation and relate that to their functions in guest recognition, catalysis, ion and electron transport, energy transfer, pore-dynamic modulation, and interface construction. It is envisioned that the ultimate control of pore chemistry requires arranging functionalities into defined sequences and developing techniques for reading and writing such sequences within the pores.

1. Introduction

Many molecules of life perform their functions by using well-crafted pores, such as enzyme pockets for catalysis, transmembrane channels for ion transport, and ligand-binding protein cavities for signaling. Common to these porous constructs is high density of functional groups decorating the internal surface of pores that are arranged in specific ways. The concave shapes of such pores maximize the possible number of interactions an incoming guest is subjected to, while at the same time leaving an opening for access by guests. The intricate pore structure created by nature leads to catalysts of special activity and specificity, membranes of exceptional selectivity for ion passage, and protein interaction networks of high fidelity. For those interested in making synthetic structures with the hope of incorporating these properties, the question becomes how we combine nature's sophistication with the robustness needed for functional synthetic materials to operate under a diversity of conditions.

Inorganic porous solids, such as crystalline zeolite and amorphous carbon, despite their importance, lack the chemical handle to allow for their precise functionalization, and in the case of carbon, the crystalline order needed to permit their definitive characterization. Although supramolecular assemblages are attractive objects for creating molecular porosity, they do not lend themselves to chemical modifications postsynthesis since their overall structure is fundamentally transformed so as to preclude the use of their pores. This problem is being addressed by the development of reticular chemistry,[1] especially through metal–organic frameworks (MOFs),[2] where multimetallic nodes are linked by strong bonds to organic struts to give crystalline, extended porous frameworks. These frameworks can be viewed as each having a repeating architectural backbone serving as the scaffold, supporting an interior pore environment into which diverse chemical functionalities could be introduced. Framework structures of this kind serve as versatile platforms for functionalization chemistry to be performed in their interior with the same precision typically practiced in molecular chemistry. This is further enabled by the fact that: a) The strong bonds making up the backbone of the framework impart the robustness needed for chemical modifications to be performed postsynthetically without losing the integrity of the structure or the pores, b) frameworks with pores of sufficiently large size can be designed to allow access to their interior by various guests and reagents to harness their pore chemistry, c) rich organic and inorganic chemistry can be applied in the

Dr. Z. Ji, H. Wang, Prof. O. M. Yaghi
Department of Chemistry
University of California–Berkeley
Berkeley, CA 94720, USA
E-mail: zheji@berkeley.edu; yaghi@berkeley.edu
Dr. Z. Ji, H. Wang, Prof. O. M. Yaghi
Materials Sciences Division
Lawrence Berkeley National Laboratory
Berkeley, CA 94720, USA
Dr. Z. Ji, H. Wang, Prof. O. M. Yaghi
Kavli Energy NanoSciences Institute at Berkeley
Berkeley, CA 94720, USA
Dr. Z. Ji, H. Wang, Prof. O. M. Yaghi
Berkeley Global Science Institute
Berkeley, CA 94720, USA
Dr. S. Canossa
EMAT
University of Antwerp
Groenenborgerlaan 171, Antwerp 2020, Belgium
Prof. S. Wuttke
BCMaterials
Basque Center for Materials
UPV/EHU Science Park
Leioa 48940, Spain
E-mail: stefan.wuttke@bcmaterials.net
Prof. S. Wuttke
Ikerbasque
Basque Foundation for Science
Bilbao 48013, Spain
Prof. O. M. Yaghi
UC Berkeley-KACST Joint Center of Excellence for Nanomaterials for Clean Energy Applications
King Abdulaziz City for Science and Technology
Riyadh 11442, Saudi Arabia
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functionalization and modification of the pores, and d) persistent crystallinity of these frameworks vastly facilitates their characterization before and after pore functionalization.

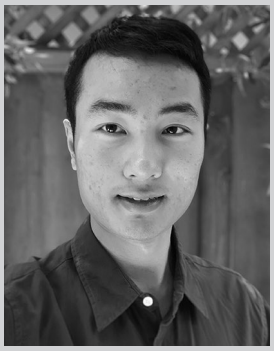
The functionalization chemistry of MOFs discussed in this contribution targets the modification of pores to achieve new framework properties. We consider, for example, new bond formation, exchange of counterions, and encapsulation of nanoparticles, as a process of functionalization. Some of these involve complex multistep chemical reactions or simple removal of solvent from the pores. We articulate the functionalization of MOFs based on the following criteria: a) being an unnecessary outcome of reticulation; b) not leading to structure collapse when replaced or removed; c) being deliberately installed in either presynthetic or postsynthetic manner; d) leading to a specific function. In all cases, the functionalization of MOFs designs the chemical environment of their pores, where every moiety is positioned, manipulated, and addressed for crafting a well-defined, high performing machinery—designed pore chemistry.

Pore chemistry addresses the precise control over the position and spatial arrangement of the installed functionalities guided by the framework backbone. The separation of functionalities across the backbone make these chemical sites isolated and function in parallel, while placing functionalities in neighboring positions within a pore introduces functionality–functionality coupling behavior, dependent on their relative orientation and distance. When functionalities of different chemical identities are distributed over the entire pore space, this heterogeneity in distribution, electron density, and geometrical shapes creates a "forest" covering the internal surface of framework backbone, where diverse chemical synergies may emerge. By tracing the trajectory of a guest molecule, which travels across framework interior and thereby passes through consecutive pores, the varying environment experienced by this molecule constitutes a chemical sequence of high dimensionality.

In this contribution, we focus on this pore chemistry and describe the installation of functionalities for achieving different configurations in positioning, including site isolation, coupling, and cooperation. This is furthered by a brief introduction to frameworks' backbone construction and functionalization chemistry, which provides guidance to the precise control of functionality positioning. Finally, we specify the wide-ranging functions achieved by tuning pore environment, including catalysis, gas adsorption and separation, electron and ion conductivity, and many other processes, with an emphasis on the physical nature underpinning these applications and how site-specific properties are utilized. We note that this review is meant to be illustrative of the rich pore chemistry that can result from chemical modifications rather than provide comprehensive treatment of this topic.

2. Pore-Functionalization Strategies

One practical example that can be useful in developing pore chemistry is to install chloro(triphenylphosphine)gold(I) in the hexagonal channel of IRMOF-74-II[3] (**Figure 1**a). The motivation to pin down this catalytic unit on the internal surface of MOF pore is to enhance its catalytic cyclability. The immobilization of the metal complex can efficiently prevent its degradation, which is favored in solution where the free motion of the metal-phosphine intermediates leads to the generation of



Zhe Ji obtained his Ph.D. at UC Berkeley in the group of Prof. Omar M. Yaghi. After completing his bachelor's degree at Tsinghua University with Prof. Gaoquan Shi, he moved to Berkeley to pursue his doctorate in chemistry, focusing on the design and synthesis of reticular materials. His research interest lies in bringing a high level of complexity and functionality to framework structures, through efforts in connecting metal-sulfur clusters, sequencing metals in multivariate systems, and building framework–bacteria interfaces. He is now a postdoc at Stanford University in the group of Prof. Steven G. Boxer.

Stefan Wuttke created the research group "wuttkegroup for science," initially hosted at the Institute of Physical Chemistry at the University of Munich (LMU, Germany). Currently, he is an Ikerbasque Professor at the Basque Center for Materials, Applications and Nanostructures (BCMaterials, Spain). His research is focused on developing methodologies to read and write chemical information from and onto the backbone of hybrid framework materials. In addition, his research interests also include the acquisition of a fundamental understanding of the chemical and physical processes involved in their synthesis and functionalization.

Omar M. Yaghi received his Ph.D. from the University of Illinois-Urbana (1990) and studied as a postdoctoral fellow at Harvard University. He is currently the James and Neeltje Tretter Professor of Chemistry, University of California, Berkeley, and a senior faculty scientist at Lawrence Berkeley National Laboratory. His research encompasses stitching together organic and inorganic molecules by strong bonds to make crystalline extended porous structures, such as MOFs, ZIFs, and COFs. He named this field reticular chemistry.

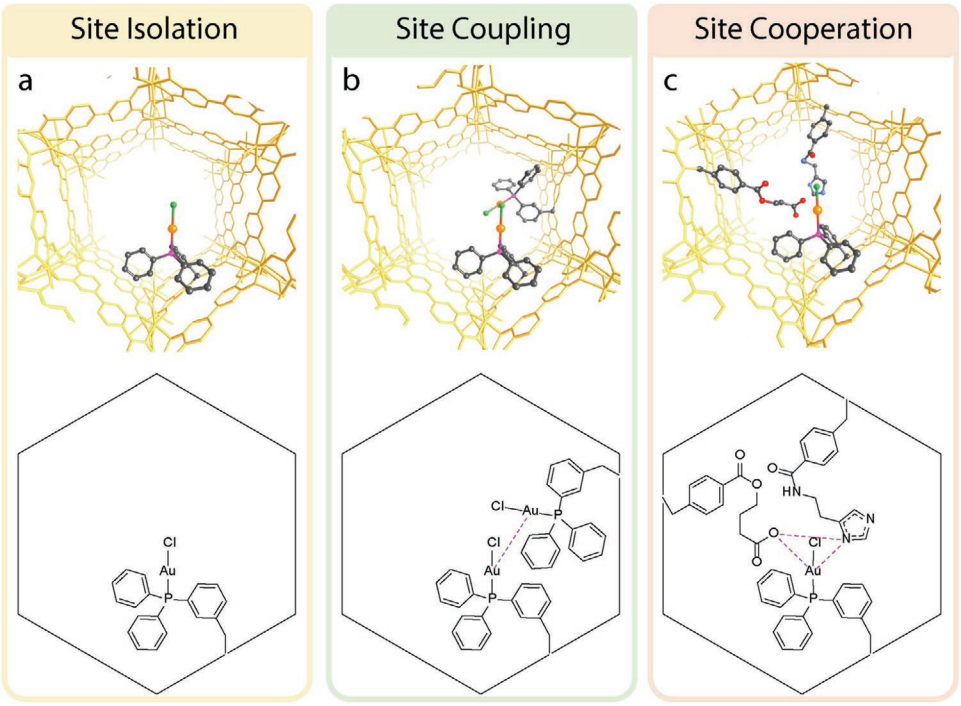


Figure 1. Pore functionalization strategies illustrated by the installation of chloro(triphenylphosphine)gold(I) in the hexagonal channel of IRMOF-74-II. a–c) The metal-phosphine complexes are appended onto the MOF backbone, being isolated, coupled, or cooperative with organic functionalities in close proximity. The backbone of IRMOF-74-II is presented in yellow sticks. The functionalities are illustrated in the ball-and-stick model. Color code: Au, orange; Cl, green; P, magenta; C, gray; O, red; N, blue. H atoms are omitted for clarity. The magenta dashed lines in the molecular structures indicate intermolecular interactions between functionalities.

metal particles through disproportionation reactions.[4] Therefore, the metal complexes appended onto framework backbone become isolated from each other and each single unit can perform independently—*site isolation*. An additional advantage of using MOFs as the immobile phase is that their highly porous nature allows for the facile transport of substrates for accessing the active centers.

The site isolation strategy leads to separation of the desired functionalities, while maintaining their presence in sufficient quantities owing to the repetitive arrangement of pores in MOF structures. An ideal result of such functionalization therefore is to uniformly spread this metal complex over the whole internal surface of IRMOF-74-II. When its density continues to increase, inevitably two molecules will sit in proximity of each other and their chemical interactions become possible (Figure 1b). In this case, the electrostatic interactions between two complexes enforce significant charge redistribution, or they form a gold–gold interaction when their distance is appropriate.[5] The installed functionalities thus are no longer isolated but instead generate a new chemical environment or new chemical species. The two neighboring gold centers can potentially activate a single substrate at the same time, resulting in breaking strong bonds within that substrate. For this reason, functionalities belonging to the same type are sometimes intentionally placed at neighboring sites and we term this functionalization strategy as *site coupling*.

Inspired by metalloenzymes in nature, it becomes interesting to install distinct functionalities, especially organic ones in the primary or the secondary coordination spheres of the gold-phosphine complex. It is envisioned that carboxylate and imidazolate, for instance, can tune the reactivity of this metal complex by either direct coordination or electrostatic interactions (Figure 1c). In general, the use of multiple kinds of functionalities for achieving a property that cannot be accessed by a single functionality can be described by the term *site cooperation*. The molecular definitiveness and the architectural robustness of the MOF structure make the framework backbone a scaffold for the precise positioning of functionalities at designed locations and orientations. The rich functionalization chemistry of MOFs further provides a large design space with high chemical diversity. These two aspects are detailed in Sections 4 and 5. Reticular chemistry distinguishes itself from polymer chemistry in the fact that variation and manipulation of functional groups has negligible structural impact on the backbone. This independency prevents the limitation in functionalities that a given framework can bear, and provides access to a large library of pore chemistry.

3. The Conceptual Basis for Functionality Positioning

3.1. Site Isolation

Framework backbones are treated as a pin board onto which functionality moieties are appended (**Figure 2**). The resulting chemically modified frameworks thus inherit the properties of discrete molecules bearing the same functional groups. This strategy bridges the gap between homogenous and

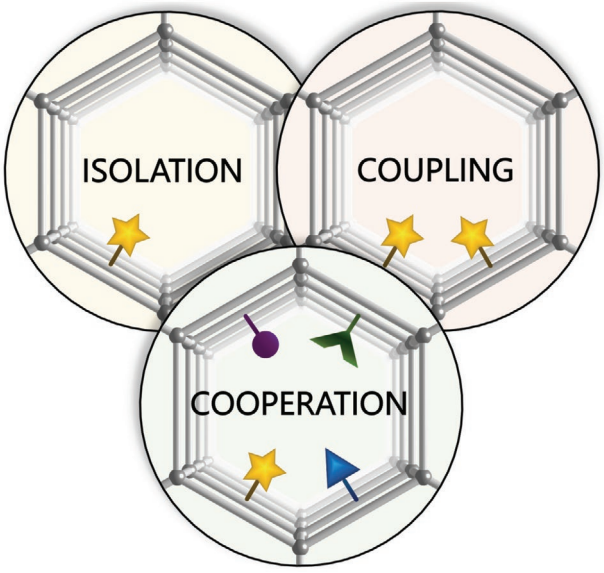


Figure 2. Three pore-functionalization strategies for positioning functionalities onto framework backbone that can be classified as isolation, coupling, and cooperation. The MOF backbones are presented in gray and the functionalities are shown in colorful objects.

heterogeneous systems by loading molecules such as catalysts and dyes onto solids. Compared with other matrix materials, MOFs provide high porosities, enabling the attachment of numerous functional units and having them exposed to an extensive internal surface poised to interact with incoming guests. One advantage of pinning functional groups onto frameworks is that small molecules that tend to cluster in solution and thus lose their functionality can be fixed to a backbone, resulting in their permanent spatial separation.[4] Pinning molecules onto frameworks additionally facilitates recycling, as laborious procedures such as column chromatography are replaced by simple washing techniques. Through site isolation, species that are incompatible with each other can now be combined into one pot given that they are compartmentalized into different pores.[6] In such system, cascade catalysis can take place sequentially in distinct domains, where the product of one reaction serves as the precursor for another. The exchange of mass and energy between domains within a single crystal provides access to a sophisticated system that is driven out of equilibrium, self-maintaining, and responsive to environmental stress.

3.2. Site Coupling

The presynthesized framework backbone can serve as a scaffold for placing multiple functional groups (of the same type) in adjacent positions to accomplish a common task (coupled behaviors, Figure 2). Functionalities that are far apart across the backbone ("moving" across the backbone from one site to the other through chemical bonds), can be brought close in 3D space. This principle is exemplified by the structure of sulfated MOF-808.[7] If one goes from the terminal O atom of one chelating SO_4 group to that of another neighboring SO_4, the shortest path through chemical bonds is 23.34 Å in length, encompassing two metal-containing building units, one organic linker, and 14 bonds in total, while the Euclidean distance between these two O atoms is in fact only 2.57 Å. The alignment of functionalities into close positions, guided by framework backbone, can be designed and implemented with atomic precision. This geometrical control enables concerted performance that cannot be accessed by one functionality alone.

A homocoupling reaction can be accelerated by bringing functionalities that are amenable to this reaction in proximity.[8] When these moieties are preorganized in a reaction-ready configuration, the entropy loss in passing through the transition state can be reduced. Compared with dispersing such molecules in solution, anchoring in vicinity onto a framework scaffold significantly increases their local effective concentration, further driving the reaction forward.[5] Other than catalysis, using the principle of site coupling imparts through-space interactions between the arranged chemical species, thus leading to, for instance, facile electron hopping over a short distance. When these functionalities can interact with a single guest molecule from its multiple sites, the multivalent interaction can enhance the host–guest affinity. It is envisioned that fast transport of guest molecules across framework pores can be enabled if there exist multiple binding sites arranged in a compact configuration and bridged by shallow energy wells.

3.3. Site Cooperation

The third strategy entails the synergistic effect by functionalities of varying types (Figure 2). The concept of decorating a variety of multiple functionalities onto an otherwise periodic backbone is not too dissimilar from how nature arranges nucleobases along the phosphate-sugar scaffold of DNA, or how residues are propped up on polypeptide scaffold enclosing an enzyme pocket. Typically, building synthetic structures by mixing multiple precursors results in phase separation. However, this is not the case in reticular chemistry, where an ordered backbone serves as a robust platform that allows for variation in functionalization. One way of building systems with cooperative functions and rich information is to install functionalities of different types on the symmetric related positions within a pore and among pores, a strategy we termed multivariate chemistry.[9] Multivariate chemistry can be performed by using organic linkers with the same geometrical parameters and linking groups, but different appended substituents. This was demonstrated by the incorporation of up to eight distinct linkers bearing different functional groups into a single crystal of MOF-5.

Multivariate functionalization is carried out through using judiciously chosen combinations of functionalities for achieving their desired spatial arrangement, typically driven by free energy minimization during synthesis. It is noted that multivariate frameworks are still an outcome of design: A plan is made and followed by synthetic efforts, which may or may not result in what was targeted at the outset, but it represents a useful step in understanding what the next step should be toward achieving the targeted design. Such iterative method allows multivariate systems to evolve into optimized structures and thus are distinguished from other chemical architectures where such flexibility is absent. These architectures may have limited choices of placing functionalities (e.g., using only

symmetric unrelated positions with a pore of framework), and human bias imposed onto an all-predetermined design can constrain the search away from global optima.

Cooperation can also take place between functionalities that are connected to linkers coexisting in a crystal yet not symmetrically related, e.g., a three-connected linker and a two-connected linker in MOF-210.[10] This strategy can also be facilitated by installing metal species and organic functionalities that are close in their positions and function cooperatively, or even effected by interacting a building unit with the surrounding framework scaffold. For example, the conformational restrictions imposed by the framework backbone can tune the photophysical behavior of a confined chromophore.[11] In all of these cases, functionalities of different type are positioned in 3D space and cooperate through the heterogeneous chemical environment created by them.

In contrast to site coupling, site cooperation extends the scope of functionalities that can work together in the pore of a framework. As such, reticular chemistry offers the platform to generate a wide array of multicomponent structures by varying the composition, ratio, and arrangement of functional groups on the backbone. In this way, the resulting multicomponent system can outperform the simple linear sum of its constituents and may very well display synergistic effects. To accommodate the varying surface electrostatics of guest molecules, combining multiple functionalities, each providing unique geometry and charge configuration, enables building of a binding pocket with shape and charge complementary to those of the guest. When using multiple functionalities for binding the transition state of a substrate, the activation barrier can be significantly lowered by the cumulative contribution from every binding site. Functionalities that are not involved in direct chemical bonding can also play an important role by modulating electric field, gating the entry of substrate, or aligning substrate in specific orientations.

4. Construction of MOF Backbone

When larger derivatives of the gold-phosphine complex are involved in pore functionalization, they will require the use of MOFs with correspondingly larger pore sizes. The expanded form of the framework should not only accommodate bulky functionalities but also keep their distances the same as those between the less bulky counterparts so that to achieve a constant coupling effect. On the other hand, designers may want to place the neighboring functionalities at different distances and orientations in order to investigate how the geometrical parameters can determine their coupling/cooperation behavior. This may require a framework scaffold of a completely different structure type. Overall, a fine control over the relative position of functionalities requires the global structural control in framework backbone construction. By leveraging methodologies and tools of molecular synthesis, reticular chemists significantly enrich the synthetic pool by bringing the sophistication of covalent chemistry from discrete molecules to extended structures. To achieve this, the building-unit approach has been applied to build frameworks, by which the connectivity, size, and shape of molecular building units predetermine the geometry of the targeted structures.

Two general strategies for reticular design are being practiced (**Figure 3**): retro-synthetic and de novo. In the retrosynthetic strategy, a structure type of a specific topology is identified and used as blueprint. It is then deconstructed into its fundamental geometrical units, and these units are matched to the corresponding molecular building blocks. In contrast, in the de novo strategy, judiciously chosen molecular building blocks are linked together to explore unknown topological outcomes. By using the geometrical, chemical, and compositional features of inorganic building units to direct their linking, this strategy has been heavily applied to extend the structure scope of reticular chemistry.

4.1. Retro-Synthetic Reticular Design

This is performed by using four sequential steps (Figure 3a). i) A target topology (**pcu**) is chosen as the blueprint for the construction of the desired framework. ii) The chosen topology is then deconstructed into its underlying geometric units (octahedra and lines) by breaking edges between vertices. Without altering the connectivity of these geometrical units, the lengths, angles, and dihedral angles can be varied to target specific structural features (e.g., longer lines for larger pores). iii) Molecular equivalents of the geometric units that are synthetically accessible are then identified. These molecules serve as building blocks for the construction of the target framework. It is crucial that during this process the size, shape, and connectivity of the building units remain unchanged to ensure that the linkages exclusively form at the predetermined positions. Molecules constructed from aromatic rings are prevalent in use as linkers of MOFs, and metal clusters with rigid coordination spheres serve as metal-containing building units. In this case, we choose $Zn_4O(-CO_2)_6$, benzenedicarboxylate (BDC), and p-terphenyl-4,4′-dicarboxylate (TPDC) to fulfill the geometrical requirements.[2a,12] iv) Finally, the chemical nature of the linkage connecting metal-containing clusters and linkers here is identified as carboxylate. Other options of linkages are exemplified by the coordination chemistries of sulfonate, phosphonate, catecholate, diamino, disulfido, imidazolate, pyrazolate, and triazolate moieties.[13]

4.2. De Novo Reticular Design

The vast unknown space of framework topologies can be explored by tailoring inorganic building units, organic linkers, and their linkage chemistries. In this context, the $Zn_4O(-CO_2)_6$ was used to connect with the trigonal organic linker (4,4′,4″-benzene-1,3,5-triyl-tribenzoate, BTB) and a net (**qom**) was discovered instead of the expected highly symmetric one (**pyr**) being produced (Figure 3b). To make other MOFs of distinct nets, combinations of organic linkers of mixed connectivity were used for linking the same tetra-zinc units. When 2,6-naphthalenedicarboxylate (NDC) and biphenyl-4,4′-dicarboxylate (BPDC) are combined with BTB and 4,4′,4″-(benzene-1,3,5-triyl-tris(ethyne-2,1-diyl))tribenzoate (BTE), respectively, two new highly porous structures (MOF-205 and MOF-210) were discovered.[10] In contrast to organic linkers that serve as preformed building blocks

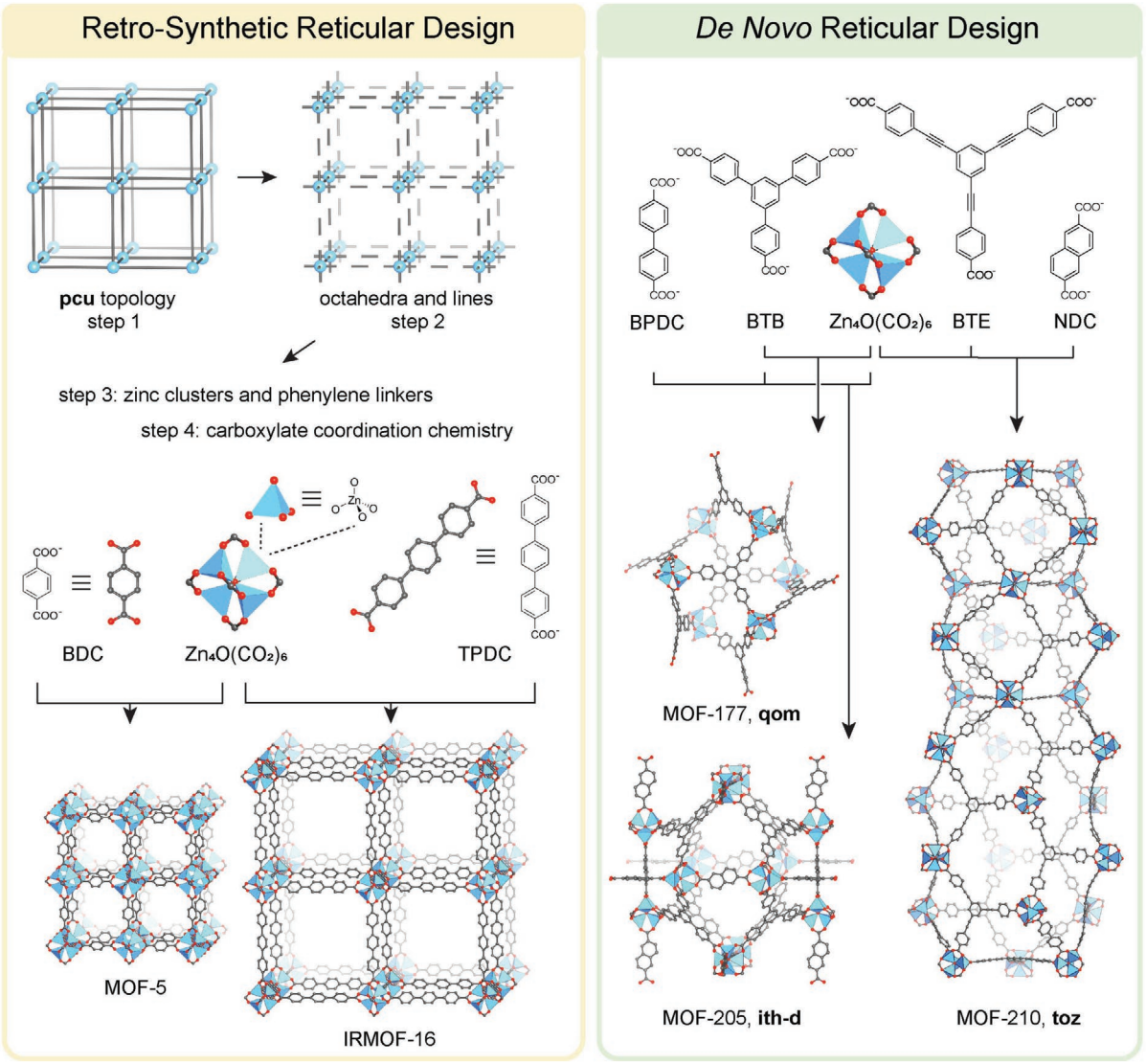


Figure 3. Retro-synthetic reticular design and de novo reticular design. In retro-synthetic reticular design, a target structure type is defined and then specified into chemical details. De novo reticular design, on the other hand, starts with judiciously chosen building units and addresses their linking into unknown structure types. Color code: Zn, blue; O, red; C, gray. H atoms are omitted for clarity.

which remain intact during the reticulation process, the inorganic building units are produced in situ and can vary in their shape and connectivity depending on the specific linkage chemistry. The design and discovery of MOF-910 epitomizes this approach; the choice of a heterotritopic linker bearing three distinct types of functional group (benzoate, semiquinonate, and 2-pyridone) facilitates the formation of helical rod metal-containing building units rather than the common straight ones.[14]

5. Methods for Functionalization of the Pores

When the relative position of the gold-phosphine complexes and the type of framework backbone have been chosen, the next step is to specify the functionalization chemistry that is used for installing this species onto the framework scaffold. The synthesis and functionalization of MOFs represent two distinct stages of the construction. Although this distinction holds at a conceptual level, real functionalization approaches do not necessarily involve a modification of an already assembled framework. Indeed, functionalities are often present as native groups carried by the building units as part of MOF formation. To classify these two kinds of approaches, presynthetic functionalization refers to the modification of the building block that is performed prior to the framework synthesis. Postsynthetic functionalization pertains to modification reactions conducted on an already formed MOF.

5.1. Presynthetic Functionalization

One advantage of pinning functional groups onto frameworks presynthetically is that the incorporation of functionalities

is ensured by their presence on the building blocks,[15] thus eliminating complications linked to functionalization reactions' yield and kinetics. Even challenging reactions can be used for functionalization as the small-molecule product can be purified. This strategy effectively avoids the lack in quantitative control sometimes present in postsynthetic functionalization. It is noted that the ratio of each functionality present in the synthesized framework may differ from that in the reaction mixture, since every building block's reactivity is influenced by the appended functional groups.

5.2. Postsynthetic Functionalization

In order to attach functionalities to the backbone, the synthetic approach known as postsynthetic functionalization has been implemented to complement presynthetic synthesis.[16] One advantage of reticular chemistry is that the functionalization of frameworks can be performed in the same way as the functionalization of discrete building units. The molecular nature of frameworks enables a rich chemistry of postsynthetic functionalization to take place on the periodic scaffold, either by exchange of its constituents or by introducing new moieties at reactive sites.

5.3. Covalent Attachment of Functional Units

Functionalization by formation of covalent bonds is by far the most explored approach to integrate non-native chemical groups into MOFs (**Figure 4**a).[17] One of its main advantages is the stability of the attachment of the introduced functionalities and the possibility to employ a vast library of chemical reactions to identify the most suitable one according to the stability of the material. The covalent bond formation approach is based on the presence of reactive sites in the framework. The most commonly used reactive groups for such transformations include amine,[18] aldehyde,[19] azide,[20] and unsaturated coordination sites.[21] MOFs without any reactive sites are particularly challenging in this respect. Interesting examples are the use of the inorganic cluster as an anchoring point for chemical bond formation[22] or even the aromatic linker as modification point to introduce functional groups (e.g., nitro group) that can be further functionalized.[23]

5.4. Exchange of Building Units

Through linker exchange, the original organic linkers in the crystallized frameworks can be substituted by others that possess different functional groups (Figure 4a).[24] This process is enabled by the dynamic nature of the linkage, during which the incoming linker traverses the framework structures by diffusion and competes with the built-in linkers through continuously forming and breaking coordination bonds. Performing linker exchange allows for the incorporation of linker molecules that are incompatible with synthetic conditions used for the formation of the MOF. Transmetalation occurs when metal cations in the as-synthesized framework are replaced postsynthetically by different metal species.[25] In so doing, the incorporated metal cations are forced into the coordination environment of their predecessors, which may be energetically unfavorable when in solution.

5.5. Functionality Addition at Structural Defects

Another possibility of pore functionalization is to take advantage of the lack of components within the backbone, i.e., the presence of structural defects. The occurrence of these defects implies the presence of linker-terminated or node-terminated sites. As the reactivity of such exposed moieties has not been expressed during the MOF's synthesis, these sites are available for postsynthetic functionalization reactions and can be decorated with chemical groups of interest (Figure 4a). The most studied functionalization of a defect until now focused on missing linker defects in UiO-66. Its framework can be engineered to have short monocarboxylate "capping" species replacing the terephthalate linkers to obtain missing linker defects available for functionalization.[26] Most importantly, these defective sites have also been introduced on purpose and used to incorporate different linkers by "sequential linker installation."[27]

5.6. Use of Intermolecular Interactions in Creating Functionality

Despite being intrinsically weaker, intermolecular interactions have the unique advantage of offering a much higher cooperativity (Figure 4b). While the number of bonds that a given atom can establish is limited by its valence in the state it is found, molecules and ions can be designed to allow manifold cooperative interactions with complementary species, which can result in very high binding energies. This possibility allows for the design of reversible functionalization reactions, so that the functional groups can be removed or substituted with minor damage or alteration to the framework itself, and likely with quantitative yields. Intermolecular interactions include π–π stacking between organic linkers and guest molecules.[28] Coulombic interactions can be established between charged framework backbone and counterions residing in the pore.[29] The presence of hydrogen bond donors or acceptors in MOF backbone can recognize the matching partners with relatively high affinity.[30]

5.7. Introduction of Mechanical Interlocking in the Backbone

One last approach is mechanical interlocking of molecules within the backbone, where chemical bonds are not responsible for the installation of a novel functionality (Figure 4c). In this category, the force which keeps the introduced species in their location is the simple interatomic impenetrability that comes into play when a species is nested in a cavity due to steric hindrance or "tied" to part of the framework by its own structure. An interesting difference of this type of docking compared to the first two functionalization methods is that the introduced species maintain a much higher mobility and, in certain conditions, can slide or rotate about the framework backbone and

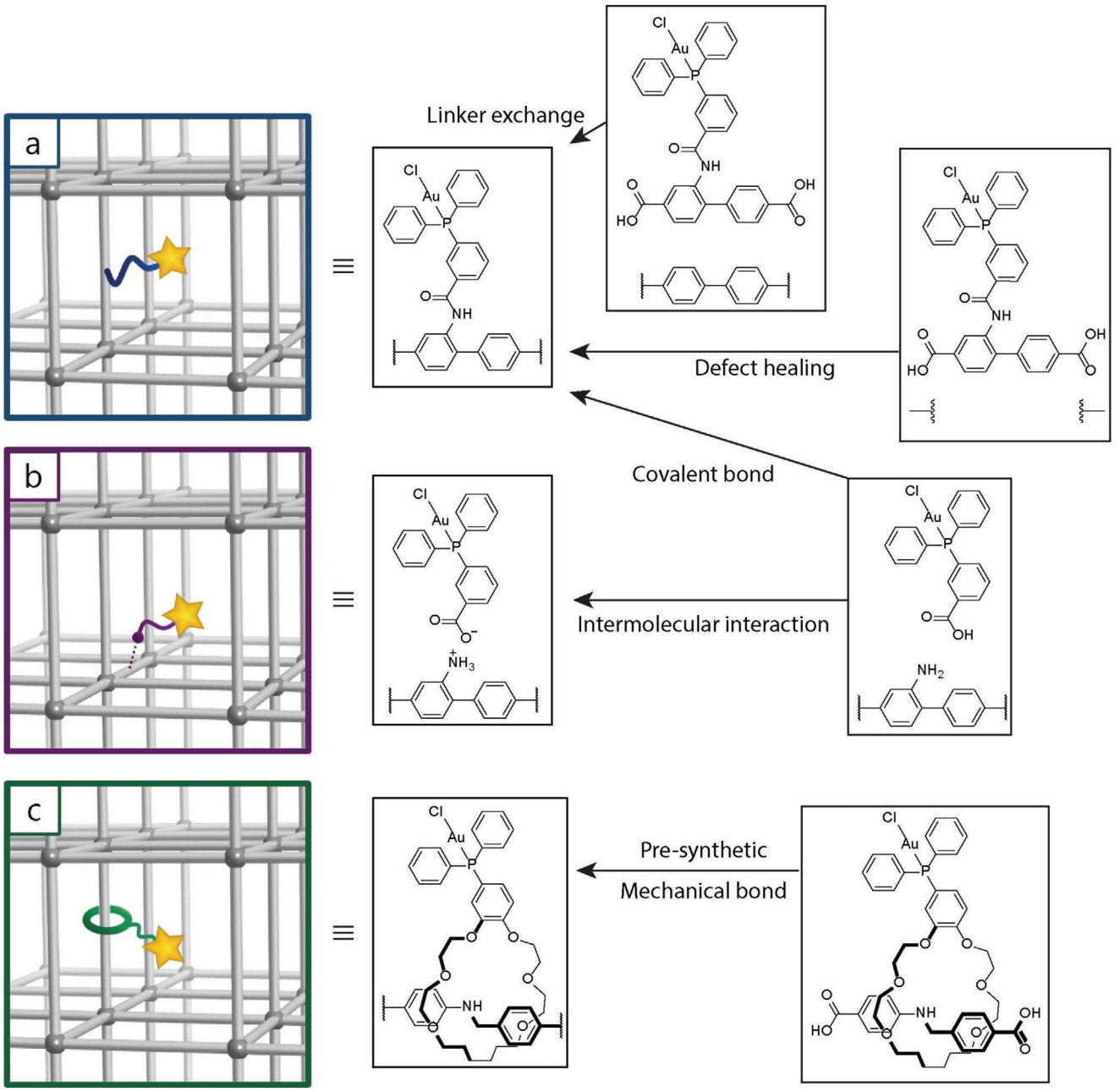


Figure 4. The chemistry of functionalizing a MOF in **pcu** net with chloro(triphenylphosphine)gold(I). a) Covalent attachment can be achieved by grafting functionalites to the reactive moieties on the backbone though the formation of amide. Alternatively, linker molecules bearing the gold-phosphine complex can postsynthetically replace the native ones or occupy missing-linker defects. b) Intermolecular interaction can be used for the adsorption of negatively charged gold-phosphine complex to the positively charged backbone. c) Mechanical interlocking attaches the gold-phosphine complex to the linker molecule permanently. Such functionalized linkers can be used for MOF synthesis and thus bring this functionality to the MOF backbone in a presynthetic manner. The backbone of the MOF is illustrated in gray. The target gold–phosphine functionality is represented as a yellow star. Its attachments to the backbone in the form of a covalent bond, intermolecular interactions, and mechanical interlocking are drawn in blue, purple, and green.

adopt different orientations or positions. This lowers the spatial constraints of the functionalization sites and endows the pore with a unique type of functional group dynamics, where it can be taken advantage of to tune guest permeation or reaction kinetics by dynamically mitigating the pore accessibility. Impressive examples are a molecular shuttle (an interlocked macrocyclic ring is able to move back and forth between two recognition sites) interlocked with MOF backbone,[31] a catenated strut in a catenated MOF,[32] and macrocyclic wheels[33] (i.e., crown ethers). The future development of such "robust dynamics"[34] can transfer precisely designed molecular dynamics to solid state.

6. Pore Chemistry and Its Applications

6.1. Guest Binding with High Specificity and Affinity

Proteins carry out molecular recognition by using their evolved binding pocket to discriminate guest molecules of diverse structures with high selectivity and affinity. The strong host–guest binding packages over all the interactions between an array of amino acid residues appended on the peptide scaffold and all the regions of the substrate exposed to the pocket. The rich chemical diversity of functional groups attached to the amino acids ensures that every region of varying electrostatics and geometries across substrate surface is precisely addressed and thus energetically stabilized. The cooperation and the precise spatial alignment of the pocket functionalities provide insights into the design of artificial pores for guest binding. In this regard, MOFs provide a versatile platform for building binding sites with structural complexity approaching to that of protein pockets. The molecule-level definitiveness of functionalities along with the flexibility in choosing their chemical nature and spatial positions create binding sites of desired energy. A strong binding is beneficial for the adsorption of guest at a low concentration (or relative pressure), while it may complicate desorption, and therefore an optimized binding energy should be targeted. Here, framework pores can be specifically functionalized to meet the demand of a particular application setting. In the following content, we discuss the use of different functionalization strategies—site isolation, site coupling, and site cooperation—to accommodate different guest species (**Figure 5**).

6.1.1. Guest Capture on Isolated Sites

Compared to traditional adsorbent materials, being able to anchor accessible polar functional groups (e.g., Lewis bases) in high density makes MOFs promising candidates for CO_2 separation. Each of these binding sites can interact with CO_2 independently, and give rise to excellent CO_2 adsorption capacity and selectivity over other gases, such as N_2, CH_4, and H_2O. In an attempt to incorporate Lewis base moieties into MOFs, an amine-functionalized terephenylene linker was utilized to build IRMOF-74-III-CH_2NH_2 (Figure 5a).[35] With the presence of amine groups, CO_2 was chemisorbed to form carbamic acid and ammonium carbamate under dry and wet conditions, respectively. Recently, this effort has been continued by increasing the density of amino groups in the same MOF structure. Two primary alkylamine functionalities were covalently tethered to each linker of IRMOF-74-III.[36] Compared with its monoamine counterpart, IRMOF-74-III-$(CH_2NH_2)_2$ collected 2.33 times the amount of CO_2 per gram of material in a low pressure range (<100 Torr), indicative of the effectiveness for site isolating functional groups having strong binding affinity within framework pores.

MOFs also show promise in water adsorption, owing to their structural diversity and functionalization tunability for adjusting pore size and hydrophilicity, parameters that are crucial for their water-sorption performance. The chemical type of functional groups strongly affects hydrophilicity of the pores, and thus the position of inflection point α in water sorption isotherm. For studying this effect, the pristine benzenedicarboxylate (BDC) linker in MIL-101(Cr) was functionalized with −COOH (**1**) (Figure 5b), −NHCOCHCHCOOH (**2**), $-NH_2$ (**3**), $-NHCH_2CH_2CH_2SO_3H$ (**4**), $-NHCONHCH_3$ (**5**), and $-NO_2$ (**6**).[37] Water adsorption isotherms of these MOFs revealed that the introduction of hydrophilic functional moieties (**1**, **2**, **3**, and **4**) shift α to lower pressures, while hydrophobic functional group **5** shifts α to a higher pressure compared with that of the original MIL-101(Cr). The shift caused by hydroneutral moiety **6** on α is negligible as expected.

Unlike CO_2 and H_2O, H_2 storage in MOFs remains an outstanding challenge due to the difficulty in polarizing H_2 molecules to create attractive interactions. To approach this problem, open metal sites of relatively strong affinity to H_2 becomes a promising target. The axial positions of the paddle-wheel type $[Cu_2(\text{-}CO_2)_4]$ building unit are originally occupied by coordinating solvent molecules. These can be removed by evacuation without compromising the integrity of the framework structure, thus leading to the formation of open metal sites. In this regard, a wide variety of MOFs with open metal sites have been synthesized for optimizing H_2 uptake. In 2005, MOF-505 synthesized from Cu(II) paddle-wheel secondary building units and 3,3′,5,5′-biphenyltetracarboxylate was for the first time studied for H_2 storage using open metal sites (Figure 5c).[38] In the presence of open metal sites, MOF-505 adsorbed at the time an exceptional 2.47 wt% H_2 at 750 Torr and 77 K.

Incorporating foreign cations into frameworks as additional binding sites provides another useful tool to enhance H_2 uptake. In the structure of the MOF Mn-BTT, the positively charged counterions residing in the pore were postsynthetically exchanged with transition metal-ions (i.e., Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}).[39] The newly introduced metal-ions served as effective binding sites, possibly by forming coordination bonds with H_2, and exhibited improved H_2 capacity.

Immobilization of open metal sites within MOFs also helps selectively extract gas molecules from their mixtures. Early efforts achieved preferable adsorption of CO_2 against methane and the separation of harmful gases with MOF-74 replete with open metal sites.[40] The separation of light hydrocarbons is also of great interest. Featuring a high density of open Fe(II) coordination sites, Fe_2(dobdc) exhibited excellent performance for the separation of C_2H_4/CH_4 and C_3H_6/C_3H_8 mixtures (Figure 5d).[41] The strong affinity for unsaturated hydrocarbons with respect to saturated ones was evidenced by the initial steep rise in the isotherms. Additionally, the uptake of these gases at 1 bar approached stoichiometric quantity, suggesting that every Fe(II) site adsorbs one gas molecule. Neutron powder diffraction experiments indicated that these unsaturated hydrocarbons display side-on binding mode, with Fe−C distances varying in the range of 2.42(2)–2.60(2) Å. These distances are much shorter than those in the case of C_2H_6 and CH_4 (≈3 Å), suggesting stronger interactions between MOFs and unsaturated hydrocarbons. The C_2H_4/CH_4 and C_3H_6/C_3H_8 permeation selectivities were calculated to sit in the range of 13–20 and 14–16, respectively.

Purifying ethylene from ethane contamination is of industrial importance and requires an abnormal binding site that favors saturated hydrocarbon against unsaturated ones. Inspired by natural metalloenzymes and synthetic catalysts

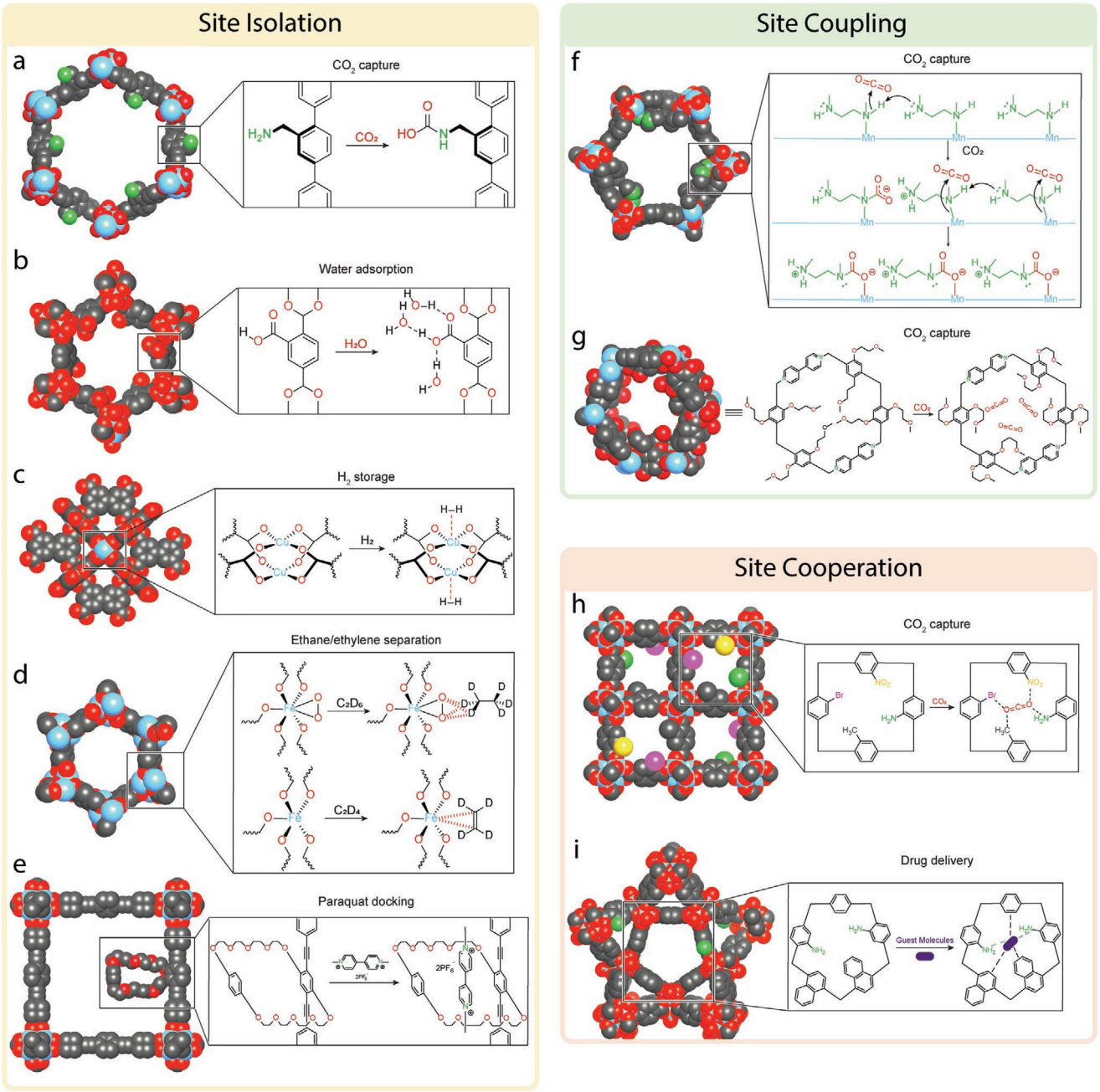


Figure 5. Site-specific functionalization of pores for guest binding. Through site isolation, functionalities work independently: a) the amine group for CO_2 capture; b) the carboxylate group for water adsorption; c) the open metal sites for H_2 storage and d) ethane/ethylene separation; and e) the macrocyclic crown ether for paraquat docking. Through site coupling, functionalities of the same type bind to guests in collaborative ways: f,g) diamine and alkyl ethers gate the adsorption of CO_2. h) Through site cooperation, functionalities of different types bind to guests in collaborative ways: mixing methyl, amine, bromo, and nitro groups in one framework for CO_2 capture, outperforming the sum of every homogeneous component; i) mixing amine and benzene groups for tuning drug release rate. Color code: metal, blue; C, gray; O, red; N, green; Br, magenta. In (h), the nitro groups are represented by yellow spheres for clarity. H atoms are omitted for clarity.

for C(sp3)—H activation, an Fe(III)-peroxo sites in the MOF $[Fe_2(O_2)dobdc]$ was created to preferentially bind ethane over ethylene (Figure 5d).[42] The adsorption measurement showed that $Fe_2(O_2)dobdc$ not only has a relatively high ethane uptake but also exhibits the highest ethane/ethylene selectivity among all porous materials.

Other than binding gas molecules, MOFs can also be functionalized to capture specific species from its solution using their docking sites. Macrocyclic crown ethers which act as electron-rich receptors can specifically recognize electron-deficient substrates and yield corresponding pseudorotaxane complexes. By incorporating 34- and 36-membered macrocyclic polyethers

in the construction of organic linkers, MOF-1001, MOF-1001A, and MOF-1002 are capable of capturing paraquat cations in a stereoelectronically controlled fashion (Figure 5e).[43] Every one of these receptors is accessible for docking paraquat cations, as evidenced by X-ray diffraction and by solid- and solution-phase NMR spectroscopic studies.

6.1.2. Carbon Dioxide Capture through Site Coupling

In the context of MOF-based CO_2 adsorption, step-shaped isotherm is favorable for realizing a large working capacity operated under a narrow window of pressure swing. This has been achieved by the coordinative functionalization of open metal sites with diamines and the resulting coupling behavior between two adjacent amine sites (Figure 5f).[44] For each diamine molecule, one end is bonded to unsaturated metal centers and the other end is dangling in the channel for CO_2 adsorption. Spectroscopic, diffraction, and computational studies showed that the sharp adsorption step is attributed to a unique coupling mechanism, involving the insertion of CO_2 into metal–amine bond by forming ammonium carbonate chains. In addition, the position of the step in the adsorption isotherm can be altered by the change of temperature, the type of metal species, and the structure of appended diamines.

When pores of the framework are modified with alkyl ether chains, the resulting MOF can display novel profiles of guest molecule binding and separation, owing to the coupling effect between side chains in the pore. For example, methoxyethoxy groups on organic linkers interact with each other to form a closed molecular gate that prevents nitrogen molecules from entering the pore (Figure 5g).[45] As a result, the uptake of CO_2 at 273 K and 1 bar is ≈500 times higher than that of N_2, which can be attributed to the larger polarizability of CO_2 which leads to a stronger interaction with the methoxyethoxy groups for opening the gate.

6.1.3. Gas Separations by Site Cooperation in Multicomponent Frameworks

Multivariate MOFs, which are constructed by multiple organic linkers with the same geometrical parameters and linking groups, but different appended substituents provide the opportunity to enable site cooperation for guest binding. In 2010, up to eight organic linkers with distinct functionalities have been successfully incorporated into MOF-5.[9] The arrangement of these linkers and the cooperative effects between specific combinations of functionalities made the multivariate system outperform the simple linear sum of its discrete components. Particularly multivariate MOF-5-EHI, composed of three distinct linkers, displayed up to 400% better selectivity for CO_2 over CO than pristine MOF-5 (Figure 5h).

The design of multivariate MOFs permits the variation in the composition and ratio of functional groups without changing the underlying topology. The cooperation among functional sites with varying ratios generates a series of continuum energy states that can be used to tune the release rate of guest in a precise manner and over a wide range. Multivariate MIL-101(Fe) constructed by BDC linkers with distinct functional groups (−H, $-NH_2$, and $-C_4H_4$) were used to demonstrate this principle (Figure 5i).[46] Three guest molecules (ibuprofen, rhodamine B, and doxorubicin) were incorporated into this series of MOFs and their release rates were found finely tuned by varying the ratio of functional groups. Particularly, the time of release for doxorubicin can be programmed from 17 to 29 d. Additionally, the corelease of multiple guest molecules (rhodamine/ibuprofen and doxorubicin/ibuprofen) was accomplished by adjusting the ratio of the paired-up functional groups in the MOFs. The obtained continuum in coding energy levels holds potential in using multivariate MOFs for drug delivery systems with predictable guest release kinetics. The power of this site-cooperative approach cannot be realized by a physical mixture of discrete linkers.

6.2. Catalysis

Guest molecules residing in the pore can be activated for lowering their energetic barrier to make new bonds. Such catalytic processes rely on the interaction between the substrate and the active site, which stabilizes the transition state and steer the catalytic transformation towards specific products, thereby providing reaction acceleration and selectivity. A strong framework–guest interaction gives an additional enhancement to substrate selectivity, when foreign molecules other than the target one that can participate in side reactions, are prevented from staying at the active site for a time window sufficient for entering the reaction coordinate. Fostering a pore environment that favors the binding of the ground state of substrate does not necessarily undermine the reduction in activation energy, as long as the chemical bond to be broken is less stabilized than the molecule as a whole. Nevertheless, the major function of active sites is still transition state stabilization and the strategies in building such sites within framework pores are detailed in the following sections.

6.2.1. Isolated Active Sites

The most common practice in building active sites within framework pores is to install a single chemical moiety that significantly lowers the activation energy. Open metal sites are capable of this task through their facile coordination with substrate, acting as Lewis acid centers for accepting electrons from substrates. These open metal sites can be readily produced from the synthesis of many framework structures. Following the first mentioning of open metal sites,[47] crystal structure of open metal sites was for the first time reported for MOF-12.[48] In these cases, the linkage of metal nodes only uses partial coordination sites, leaving the remaining ones occupied by dangling solvent molecules. The removal of these solvent molecules through evacuation thus creates open metal sites suitable for catalysis. This is contrasted to the low-coordination metal complexes where bulky ligands for protection from decomposition are needed. Open metal sites in MOFs have low steric hindrance for incoming substrates than their homogenous analogues, as the energy deficit in stabilizing open

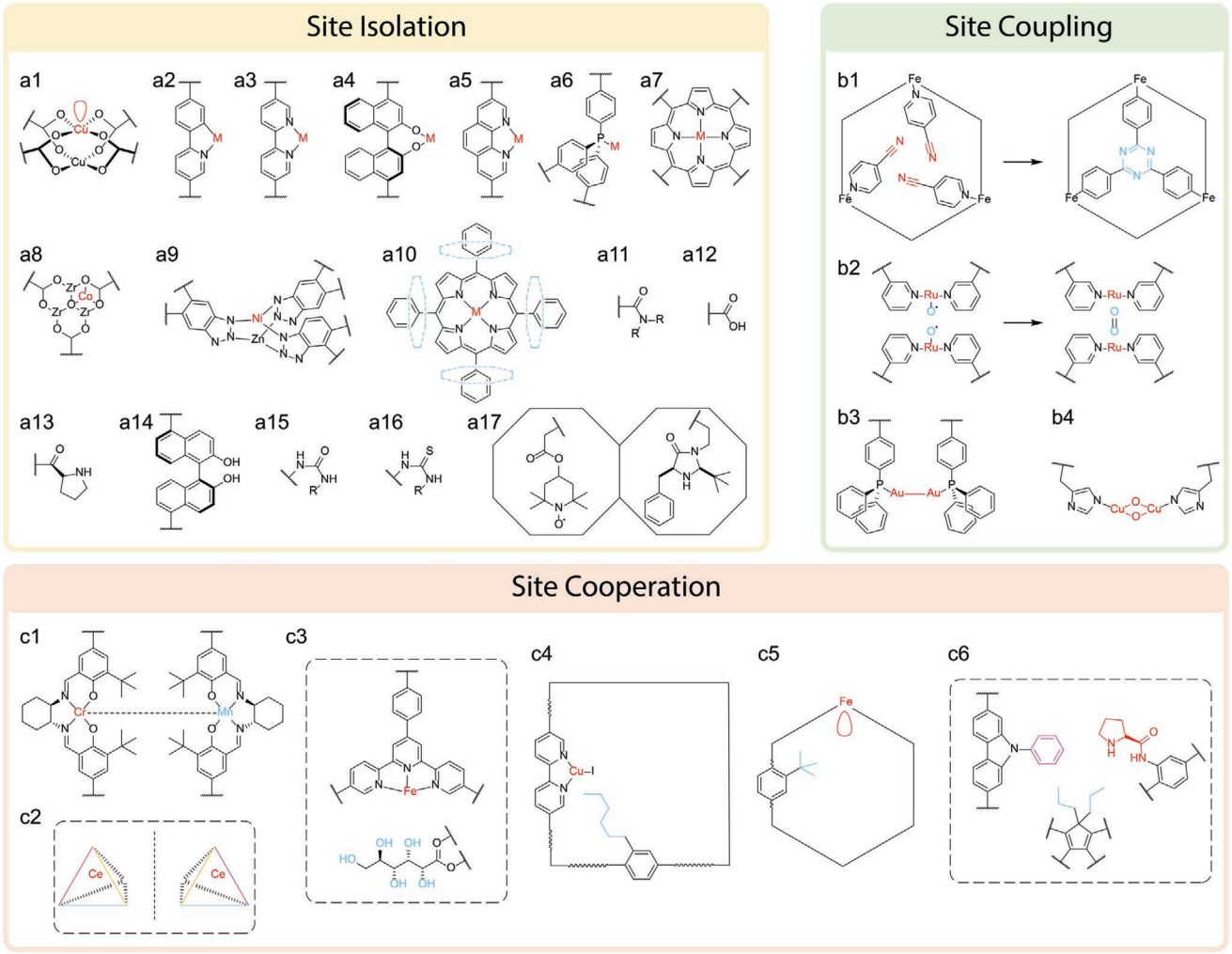


Figure 6. Site-specific functionalization for building active sites. Isolated catalytic units include a1) open metal sites on metal clusters, a2–7) metalated organic linkers, a8,9) extra metals attached to existing metal clusters, a10) a molecular catalyst trapped in the pore, a11–16) organocatalysts appended on framework backbone, and a17) two otherwise incompatible molecular catalysts each compartmented in framework cage catalyzing cascade reactions. Coupled catalytic units include b1) three open metal sites in a triangular shape for preorient substrates for their coupling reactions and b2–4) the neighboring metal species for activating together one substrate. Placing different types of catalytic units in proximity imparts the cooperation between c1) different metallosalens, c2) cerium centers and their chiral backbone, c3–5) metal species and the neighboring organic functional groups, and c6) between different organic moieties.

metal sites has been paid off by the rigid framework backbone. Indeed, the first effort in using open metal sites for catalysis is demonstrated by Cu(II) of HKUST-1 (**Figure 6**a1) in the cyanosilylation of benzaldehyde and the isomerization of terpene derivatives.[49] Further studies explored other open metal sites, such as Mn (II),[50] Cr(III),[51] Fe (II),[52] and Zr (IV),[53] which are isolated across the framework backbone for performing catalysis in high efficiency and stability.

For framework structures that do not have open metal sites on the backbone, foreign catalytic metal species can be installed through functionalization. Organic linkers containing metal docking moieties, such as 2-phenylpyridine (Figure 6a2),[54] 2,2′-bipyridine (Figure 6a3),[54,55] 1,1′-bi-2-naphthol (Figure 6a4),[56] phenanthroline (Figure 6a5),[57] phosphine (Figure 6a6),[4] and porphyrin (Figure 6a7).[58] Inorganic clusters in MOFs have also been used for bonding extra metal species, e.g., bridged through O (Figure 6a8) or N atoms (Figure 6a9) in the cluster.[59] Metal complexes can be encapsulated within the framework pore by Coulombic interaction and trapped due to steric hindrance thus preventing their leakage into solution and the degradative self-dimerization (Figure 6a10).[60] Other than catalytic metal species, organic functionalities that are capable of catalysis have been employed through site isolation. These include amide (Figure 6a11),[61] carboxylic acid (Figure 6a12),[62] proline (Figure 6a13),[63] 1,1′-bi-2-naphthol (Figure 6a14),[64] urea (Figure 6a15),[65] and thiourea (Figure 6a16).[66] When two type of active sites are each isolated within distinct frameworks, but combined into one pot, two intrinsically incompatible catalysts can thus work in parallel for enabling continuous chemical transformations. Such cascade catalysis was demonstrated by site isolation of TEMPO and MacMillan's catalyst in framework cages (Figure 6a17).[6]

6.2.2. Coupled Metal-Ions

Coupling reaction between the moieties that are placed at neighboring sites can be accelerated due to the reduction in entropy loss during passage through the reaction coordinate. While the appropriate geometry necessary for entering the transition state demands a time-consuming sampling through diffusion and rotation of precursor molecules in solution, the preorganization of the reactive precursors guided by framework scaffold confines reaction-ready states in place. This strategy was presented in the framework guided [2 + 2 + 2] cyclotrimerization (Figure 6b1).[67] In the structure of the ground state, three molecules of 4-cyanopyridine are anchored on the backbone of MIL-88B through Fe-pyridine coordination bonds. Their cyano groups are therefore aligned toward the center of the pore in a triangular shape. This constrained geometry enforced by the framework scaffold effects an otherwise sluggish [2 + 2 + 2] cyclotrimerization reaction. A prerequisite for using site coupling for catalysis is to have a reversible bonding between the substrates and the framework, such that the product of the coupling reaction can leave the active site and make room for the entry of substrates for the next turnover. Although product removal becomes energy demanding due to its multivalent bonding with the framework, further efforts in destabilizing product binding by geometric mismatch, for instance, will accomplish a real catalyst.

Other than recruiting substrates in proximity, bringing multiple catalytic species together, for example, metal centers, can lead to significant activation of reaction precursors, exceeding that enabled by a single species alone. This has been observed in encapsulating an otherwise inactive AuCl complex in framework cages for catalyzing intramolecular C—O and C—C bond-forming cyclization reactions.[5] When the AuCl complex densely occupies the pore space to a high local concentrations, up to 1.1 M, the generated Au–Au interactions (Figure 6b3) endow a high reactivity and selectivity, which is inaccessible to homogenous catalysis where catalyst concentration is typically kept in the range of 10^{-3} to 10^{-6} M. The principle of coupling multiple metal centers for catalysis is further presented in the encapsulation of 12 Ru complexes inside a framework cage.[68] These metal centers are placed at close positions for facilitating dinuclear pathway for oxygen bond formation (Figure 6b2), thus enhancing water oxidation rate by two orders of magnitude. In this process, each Ru actives one O atom followed by the coupling of two metal-oxyl radicals. Without framework preorganization, such dinuclear coupling becomes diffusion limited and consequently slow. In another example, bis(μ-oxo) dicopper species are created through their coordination with metal-binding ligands propped up by framework scaffold (Figure 6b4).[69] The structure of MOF-808 was judiciously selected as it possesses the chemical and geometrical parameters allowing two imidazole-containing ligand at neighboring sites to sandwich a dicopper cluster. This construct mimics the active site of methane monooxygenase and is found to display high selectivity for methane oxidation to methanol.

6.2.3. Multicomponent Systems for Synergistic Catalysis

In the scenario of site isolation, we emphasize the predominant component contributing the most to lowering activation barrier. Typically, this is a single chemical moiety that can be recognized and conceptually separated from the rest of the framework pore. However, this does not mean that the surrounding pore environment has no contribution to accelerating reaction rates. Any change in local electrostatic field, arising from charge redistribution or different solvent compositions, results in the variation of activation energy. This inevitably occurs when taking a catalyst from solution to the confined environment of framework pore. The strategy of site isolation applies when the contribution from the pore environment is trivial. For those catalytic sites where pore environment plays a crucial role or is deliberately designed and functionalized for promoting the reaction in parallel with other catalytic units, we term this strategy site cooperation. Site cooperation addresses the cooperation of catalytic partners different in chemical nature, thus extend beyond the scope of site coupling to encompass a wide variety of elements where each contributes substantially to multicomponent catalysis.

Incorporating multiple actives sites for their cooperation can be achieved when distinct metal centers are mixed into one framework. These catalytic species occupy the symmetrically identical positions due to the same connectivity and geometric parameters they assume, but play diverse chemical roles in catalysis. Such multivariate system is embodied by a series of MOF constructed by up to three different chiral metallosalen struts.[70] The twofold interpenetration of the framework backbone brings metallosalen units into proximity (Figure 6c1) and effects their cooperation in catalysis. It was found that the ternary heterogeneity of Co, Mn, and Cr centers displayed higher activities and enantioselectivities than those of the homogeneous mixtures for a variety of asymmetric sequential alkene epoxidation/epoxide ring-opening reactions. A cooperative mechanism was proposed that Cr(salen) serves as a Lewis acid to activate the epoxide, while the adjacent metal centers of other types enhance the nucleophilicity of the other reaction partner.

Catalytic activity of metal centers can be tuned by the structure type of the framework backbone. When a substrate approaches the metal active site, the neighboring framework components impose geometric and electrostatic constraints that can modulate the energy of its reaction pathway. This effect becomes prominent when an asymmetric reaction is carried out in two enantiomeric frameworks that are identical except for being the mirror image with respect to each other. Accordingly, the chirality of the local environment of the metal active site is determined by that of the overarching scaffold and displays enantioselectivity in catalyzing, for instance, cyanosilylation of aldehydes by a cerium chiral MOF (Figure 6c2).[71]

A more versatile strategy to tune the chemical environment of metal catalytic center is to attach functionalities at adjacent positions to the framework scaffold. By modifying a monolayer of MOF with monocarboxylic acids, the local hydrophobicity/hydrophilicity of the neighboring Fe(terpyridine) active site can be finely tuned (Figure 6c3), thus enabling selective photocatalytic oxidation of tetrahydrofuran.[72] The pristine MOF catalyst produces 2-hydroxy tetrahydrofuran as a byproduct. This is due to incomplete oxidation and the premature release of this by product from the active site without further oxidation into the target product butyrolactone. The functionalization with gluconic acid, a molecule of a high affinity to 2-hydroxy

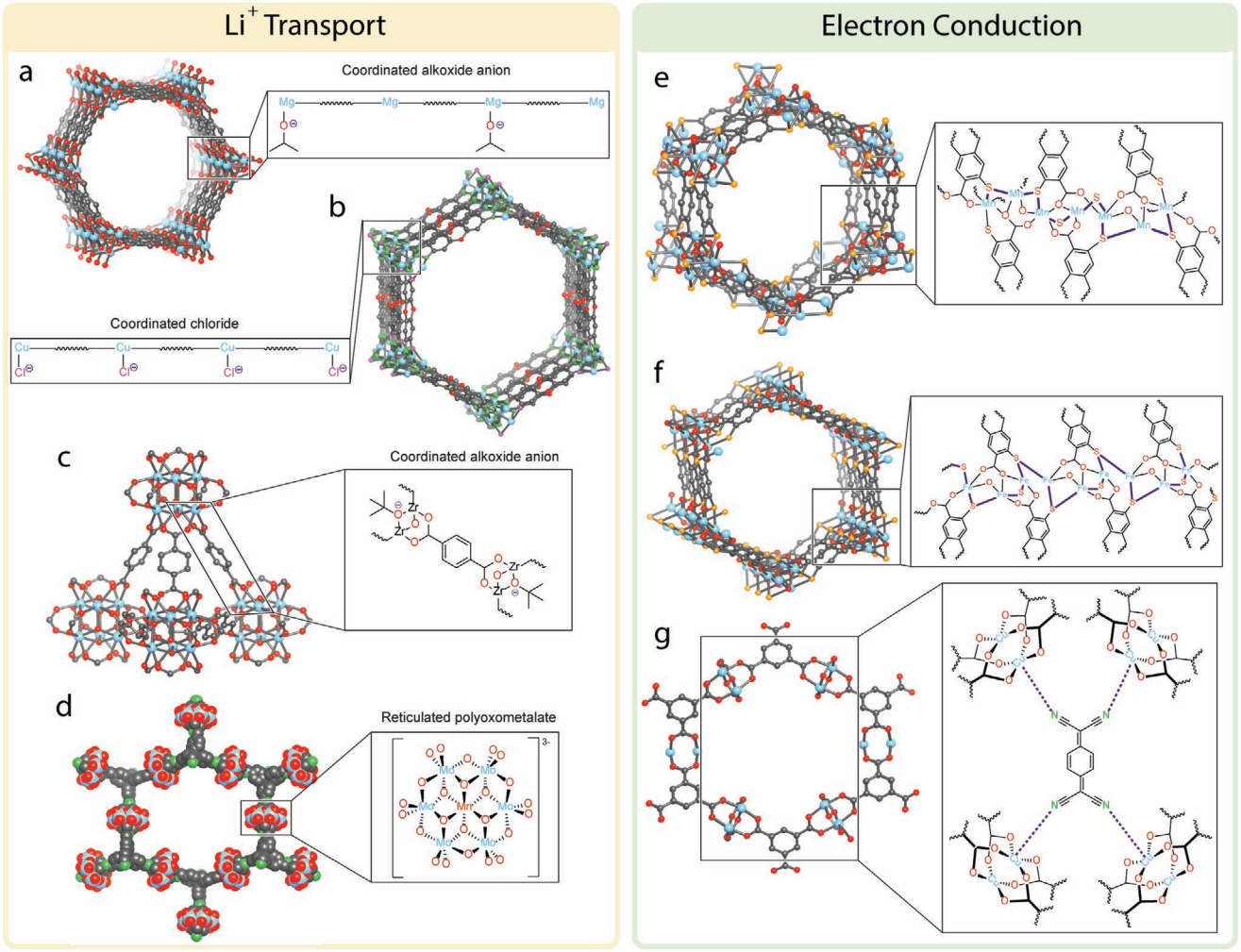


Figure 7. Pore functionalization for constructing ion and electron transport pathways. a,b) For having Li^+ as the only mobile entity, anions are immobilized by coordination to open metal sites of the Mg and Cu rods, c) by ligand substituting on Zr clusters, or d) by the direct reticulation of anionic building units. e,f) To facilitate orbital overlapping, 1D Mn—S and Fe—S chains are crafted; g) framework pore is infiltrated with TCNQ for building a continuous electron transport pathway. Color code: metal, blue; C, gray; O, red; N, green; Cl, magenta; S, orange. The framework structure in (d) is illustrated in the space-filling model for clarity. Other structures are illustrated in ball-and-stick model. H atoms are omitted for clarity.

tetrahydrofuran, promotes its retaining in the hydrophilic environment of the metal center for complete oxidation. In another example, by adopting the strategy of sequential linker installation, each pore of PCN-700 was decorated by a metal center and an organic moiety which are precisely positioned (Figure 6c4).[73] The organic functional group serves as a modulator that can fine-tune the size selectivity of aerobic oxidation of alcohol by discriminating bulky substrates. The tuning of environment around metal site was also demonstrated in MOF-74 (Fe) analogues.[74] By installing nonpolar functional groups near the Fe site (Figure 6c5), a hydrophobic pore environment favors the oxidation of cyclohexane to cyclohexanol against cyclohexanone and an order of magnitude increase in turnover number.

Furthermore, site cooperation can be implemented using solely organic functionalities. The precise spatial arrangement of functional moieties guided by framework scaffold can be used for creating a finely tailored catalytic pocket. A preliminary result shows that mixed functionalities installed in the pores of IRMOF-74-III can mimic the active sites of the enzyme tobacco etch virus endopeptidase.[75] By covalently attaching tripeptides to the organic struts through tandem multistep postsynthetic modification, a complexity of residual groups coded by amino acid sequences as well as guided by the spatial scaffolding of the framework leads to sequence-specific peptide bond cleavage. This work showed the promise of embedding the principle of enzyme machinery into framework design by appending functional groups on an architectural scaffold to create an enclosed pore replete with chemical functionalities. A multicomponent framework MUF-77 provides a platform to place three functionalities in precise locations to circumvent disorder (Figure 6c6).[76] Prolinyl groups known to be catalytically active toward asymmetric aldol reactions were selected as the catalytic unit, along with two other organic groups playing the role of selectivity modulator. The modulator units, even remote from the active site, have a decisive impact on the reaction rate and the obtained enantiomeric excess. The modulated spatial environment

around the proline catalyst can even override its innate stereochemical preference and discriminate between different reaction channels available to a given substrate.[77]

6.3. Functionalities and Pores for Ion and Electron Transport

Moving proton and metal ions across framework pores has been of particular scientific and technological interest. In electrolysis, the collective movement of these ionic species across a membrane, driven by external power, feed the separated half-cell reactions for producing valuable chemicals. On the other hand, ion transport through electrolyte during battery discharge allows the shuttling of electrons along an external circuit, generating electric current on demand. The implementation of solid electrolyte, with framework structures as a promising candidate, eliminates the hazard of housing flammable liquids and provides higher cation transference number (the ratio of the electric current derived from the cation to the total electric current) and mechanical strength. We are not digging into technological specifications, but rather focusing on how pore environments are designed and functionalized to facilitate the transport of Li^+ cation. Our discussion is further briefly extended to electrical conduction in MOFs using similar functionalization strategies.

There are in general two pathways for Li^+ to transport within a framework, either through hopping between sites distributed on the backbone or through pore space in solvated form. In both scenarios, the negative charge should be trapped as much as possible in order to maximize the transference number of Li^+. The immobilized negative charge thus becomes the site of the highest affinity to Li^+ among the whole structure due to Coulombic interaction. Whether the Li^+ is transported in neat or as solvated, these negatively charged sites act as "toll gates" on the highway of Li^+, slowing down its transport by trapping the temporarily bound Li^+ for longer retention time compared with other non-bounding sites along the trajectory. The binding energy of these sites therefore plays a major role in determining cation mobility of the material. The ideal structure features shallow energy wells in high density such that Li^+ can facilely hop from one site to the other in short distances, leading to enhanced transport kinetics. The large number of negative charge supported by a unit volume of framework structure also means that a higher Li^+ concentration can be achieved, further promoting conductivity. Therefore, site coupling has been widely adopted as the functionalization strategy for making a high density of negatively charged hopping sites of minimal binding affinity to Li^+. Anionic functionalities, serving as the hopping sites are expected to locate close to each other and belong to the same type for the formation of an energy landscape of relatively uniform depths.

One way to anchor negative charge in the pore is to coordinate an anionic ligand onto open metal sites. By taking advantage of the coordinatively unsaturated Mg^{2+} sites in MOF-74, the authors add LiOiPr in electrolyte solution for its uptake.[78] The alkoxide anions preferentially bind by coordination, pining themselves on the backbone (**Figure 7**a) while leaving the Li^+ cation more free to move along the channels. In another example, the open Zr^{4+} sites were created by dehydration of the zirconium cluster, a building unit of the MOF UiO-66, and reacted with LiOtBu, consequently occupied by the alkoxide anion (Figure 7c).[79] It was suggested that the negative charge is shielded by the bulky aliphatic group, resulting in a weaker interaction with the charge-balancing Li^+ ion. A MOF capable of reversible phase transition from an anionic phase to a neutral one allows for the coordination of a variety of anions (Figure 7b). Soaking the MOF MIT-20d in LiCl, LiBr, and $LiBF_4$ solution afforded frameworks with different stationary anion, leading to tunable mobility of Li^+ along the framework channel. It was observed that increasing softness of the anion correlated well with increasing Li^+ conductivity.[80]

Conversely, anions can serve as a building unit for framework construction, thus integrated directly into the structure and permanently immobilized. This strategy largely removes the risk of losing the anionic ligand, ensuring a high transference number of Li^+ cation. As long as the integrity of the framework structure is retained, the connected anionic unit remains stationary, which otherwise might release from the open metal sites into the electrolyte when the coordination is not strong enough to prevent the exchange with solvent. This was recently achieved by an intrinsically anionic 3D MOF-688 synthesized by connecting ditopic amino functionalized polyoxometalate with organic linkers through imine condensation (Figure 7d).[29] The cation filling the pore can be exchanged with Li^+ and balanced by the anionic framework. The highly charged Anderson type polyoxometalates and their threefold interpenetration afford a high density of hopping sites distributed among the framework structure. Each negative charge is widely dispersed over the whole polyoxometalate cluster, instead of accumulating at specific atoms, thus exhibiting a low Li^+ binding energy. Indeed, the resulting material displays high ionic conductivity and high Li^+ transference number, making it a competing solid-state electrode, as demonstrated in a prototype lithium metal battery.

For electron conduction, many researchers focus on developing framework backbones as electron transport pathway with high charge mobility. A prefunctionalization strategy turned a previously insulating backbone into a relatively conductive one by replacing the phenol group in the organic linker with the thiophenol group.[81] The resulting Mn_2(DSBDC), a thiolated analogue of MOF-74, features infinite 1D Mn—S chains (Figure 7e) and thus display high charge mobility. A further exchange of the Mn^{2+} building unit with Fe^{2+} (Figure 7f) resulted in a six orders of magnitude higher electrical conductivity, which can be attributed to the loosely bound Fe^{2+} β-spin electrons.[82] In addition, framework scaffolds can template the construction of charge transport pathways using conjugated guest molecules, as exemplified by HKUST-1 infiltrated with tetracyanoquinodimethane (TCNQ).[83] The pores within HKUST-1 were filled with TCNQ molecules anchored to the open Cu^{2+} sites of the backbone (Figure 7g). The formation of a charge transfer complex between Cu^{2+} and TCNQ and their extension into a continuous pathway guided by the framework provide a six orders of magnitude enhancement in electrical conductivity.

6.4. Pores Functionalized for Fluorescence, Light Harvesting, and Energy Transfer

The functionalized pore environment can be used for manipulating the photophysical behavior of an incorporated dye,

leading to its desired performance in photoluminescence, light harvesting, and energy transfer. The reticulation of fluorescent dyes results in the incorporation of a high concentration of luminophores in solid state, leading to strong light emission. Another advantage of using the ordered framework scaffold is that the distance between dye molecules can be well controlled in order to prevent undesired quenching. The fluorescence of a dye molecule can be tuned by the geometric constraint and electric field imposed by the neighboring functional groups appended to the framework backbone, and reciprocally be used as the probe to reveal the distribution of local functionalities and structure defects.

Research using artificially engineered porous scaffold to tune the fluorescence response of chromophores was carried out for biomimicry of green fluorescent protein (GFP).[11] A chromophore with a benzylidene imidazolidinone core was attached by covalent bond to the framework backbone (**Figure 8**a) and exhibited a similar emission profile of GFP, in contrast to its unlinked, nonemissive counterpart. Spectroscopy studies demonstrated that the conformational restrictions imposed on the trapped chromophores by the rigid framework scaffold, which is reminiscent to the β-barrel structure of GFP, suppresses nonradiative pathways. It was envisioned that further tenability of fluorescence response can be achieved by modulating the pore microenvironment.

On the other hand, a fluorescent dye can be employed for probing the local chemical environment when its fluorescence profile can be interpreted as physical metrics for gauging the structural features of the host material. For example, fluorescent dye modified linkers were incorporated into the UiO-67 framework (Figure 8b) and fluorescence lifetime analysis revealed a correlation between fluorescence quenching and the level of local defects, aspects not detectable with standard bulk characterization techniques.[84] The mapping of the spatial arrangement of defects and multivariate functional groups residing in bulk samples as well as single crystals uncovered chemical diversity present in MOF structures, highlighting the potential of fluorescence-based methods in decoding the chemical states of complex porous materials.

An alternative pathway for the dye to be released from the electronic excited state is to relay the energy to neighboring dye molecules. In fact, this energy transfer process is best practiced in the light harvesting complex. A broad range of solar energy can be harvested by an array of antenna pigment molecules due to their nonoverlapping absorption spectra, and shuttled by resonance energy transfer to a reaction center for photosynthesis. The position, orientation, and distribution of pigment molecules are delicately crafted by nature for maximizing the efficiency of the energy transfer in between. The coordination of hundreds of pigment molecules housed by each antenna complex to one reaction center ensures that the total kinetics of light harvesting matches with those of the associated photosynthetic reactions, thereby maximizing the efficiency in transforming the energy from light into that stored in chemicals. The prospect of building such systems in artificial materials drives researchers to position chromophores onto framework backbone.[85] The chemical and spatial precision that can be achieved in functionalizing framework pores allow the design of defined energy transfer pathway, connecting light harvesting units with the downstream charge separation center, charge transfer chains, and finally an active site altogether integrated into a single framework.

The precise arrangement of donor and acceptor chromophores in MOFs makes them an attractive platform for studying long-range energy transfer. The Dexter mechanism plays a dominant role in the case of triplet-triplet energy transfer and is used for describing the energy relay in a MOF containing both Ru and Os complex on the organic linker (Figure 8c).[86] The excited Ru complex exhibits phosphorescence that is otherwise quenched due to energy migration to the Os trapping sites. Luminescence quenching studies in another work indicated that the excited states of Ru complex rapidly migrate over hundreds of nanometer before reaching the MOF–solution interface with efficiency of a near unity.[87]

When energy transfer is based on dipole–dipole interaction between chromophores and thereby the Förster mechanism becomes spin-allowed for transfer longer distances. This is exemplified by MOFs containing porphyrin-based building units (Figure 8d).[88] As the constituent porphyrin units occupy the pillar positions of the pillar-layer structure, the intralayer energy transfer is favored in accordance with the short distance between porphyrin units in lateral direction. Fluorescence quenching experiments and theoretical calculations indicated that the photogenerated exciton migrates over a net distance of up to 45 porphyrin units. The resulting long distance and anisotropic energy transfer provides insight into the rational design of framework structures for guiding directional energy transfer across pores and reaching artificial photocatalytic active sites.

6.5. Functionalization for Tuning Pore Dynamics

One advantage of MOFs is the ability to tune the individual building blocks and interactions between them to endow the parent framework with flexibility and dynamics. Conceptually, the term flexibility has been used to describe the change in pore volume, including expansion/shrinkage or opening/closing, triggered by external stimuli. While pore dynamics in a lot of cases result from the constituent metal sites that has a flexible coordination sphere, their responsiveness can be modulated through the functionalization of organic linkers. A library of functionalized BDC (fu-BDC) linkers bearing alkoxy side chains of varying chain lengths dangling from different positions of the benzene core were used as the building unit for constructing pillar-layer MOFs $[Zn_2(\text{fu-BDC})_2(\text{dabco})]_n$ (dabco = 1,4-diazabicyclo[2.2.2]octane).[89] The pristine MOF with unfunctionalized organic linker only exhibited weak dynamic behavior; however, the pore of the functionalized frameworks experienced a drastic and reversible change from wide to narrow upon the insertion and removal of guest molecules (*N*,*N*′-dimethylformaldehyde, CO_2, and ethanol, **Figure 9**a). The framework with relatively hydrophobic pore featuring the bulky butoxy substituent showed the highest phase-transition pressure and a prominent hysteresis. In contrast, the framework modified with the short ethoxy substituent displayed a low phase-transition pressure and a relatively small hysteresis. The different dynamic behaviors of pores are attributed to the

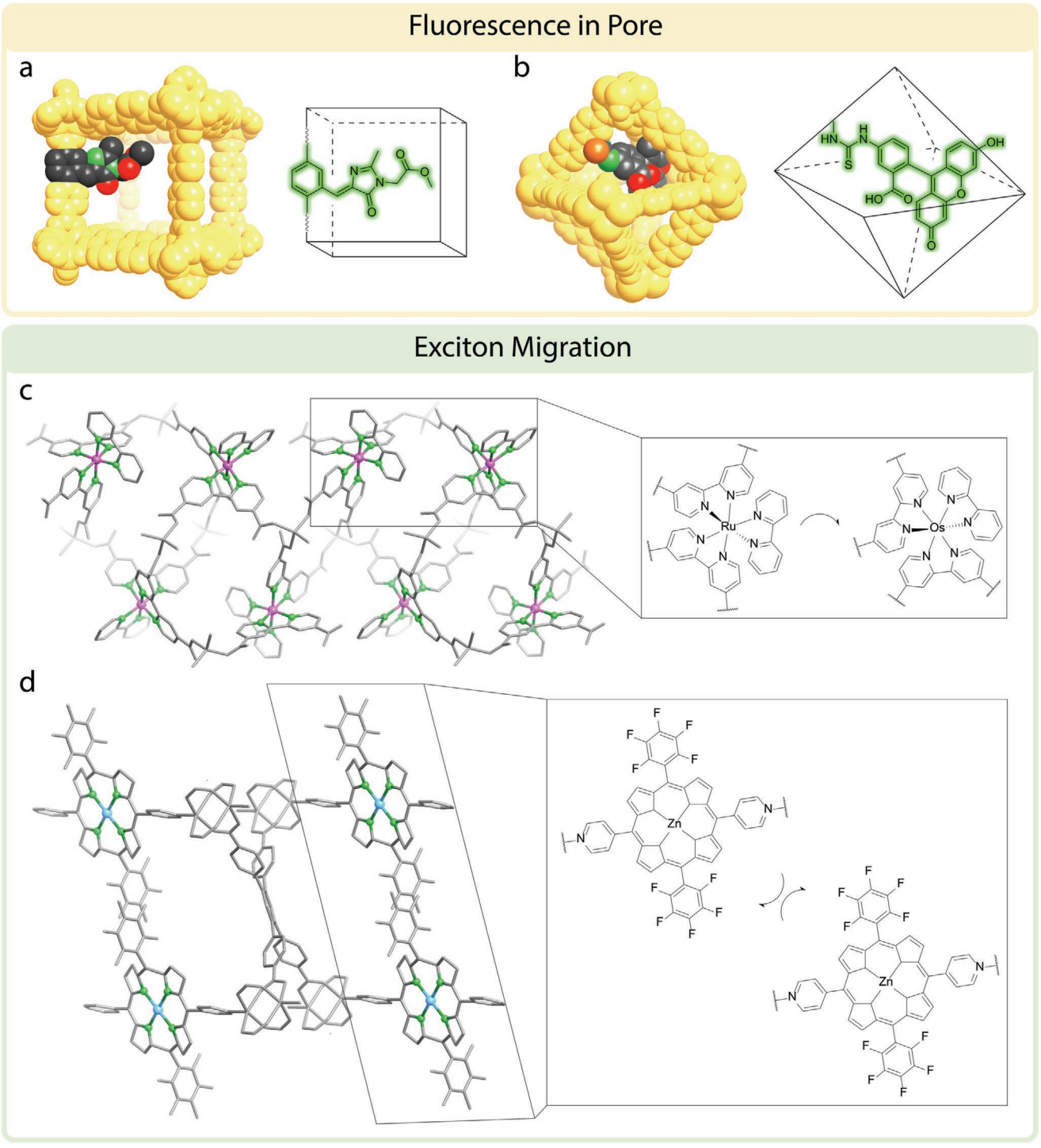


Figure 8. Pore functionalization for facilitating fluorescence and energy transfer. a) A benzylidene imidazolidinone chromophore confined in a cubic pore. b) Fluorescein confined in an octahedron pore containing a missing edge defect. c) Triplet-triplet energy transfer between reticulated Ru and Os complexes through the Dexter mechanism. d) Anisotropic alignment of the reticulated Zn-porphyrin for the Förster energy transfer. Color code: backbone encompassing chromophores, yellow; C, gray; O, red; N, green; S, orange; Ru/Os, magenta; Zn, blue. H atoms are omitted for clarity.

dangling side chains on the fu-BDC linkers that can interact with each other as well as with incoming guest molecules in the pore. This work provides an approach to rationally tailoring the structural dynamics and responsiveness of MOFs.

Another comprehensive study on the influence of functional groups on pore dynamics has been conducted with MIL-53(Al).[90] Five functionalized BDC linkers (substituted with −Cl, −Br, $-CH_3$, $-NO_2$, and $-(OH)_2$, respectively) were

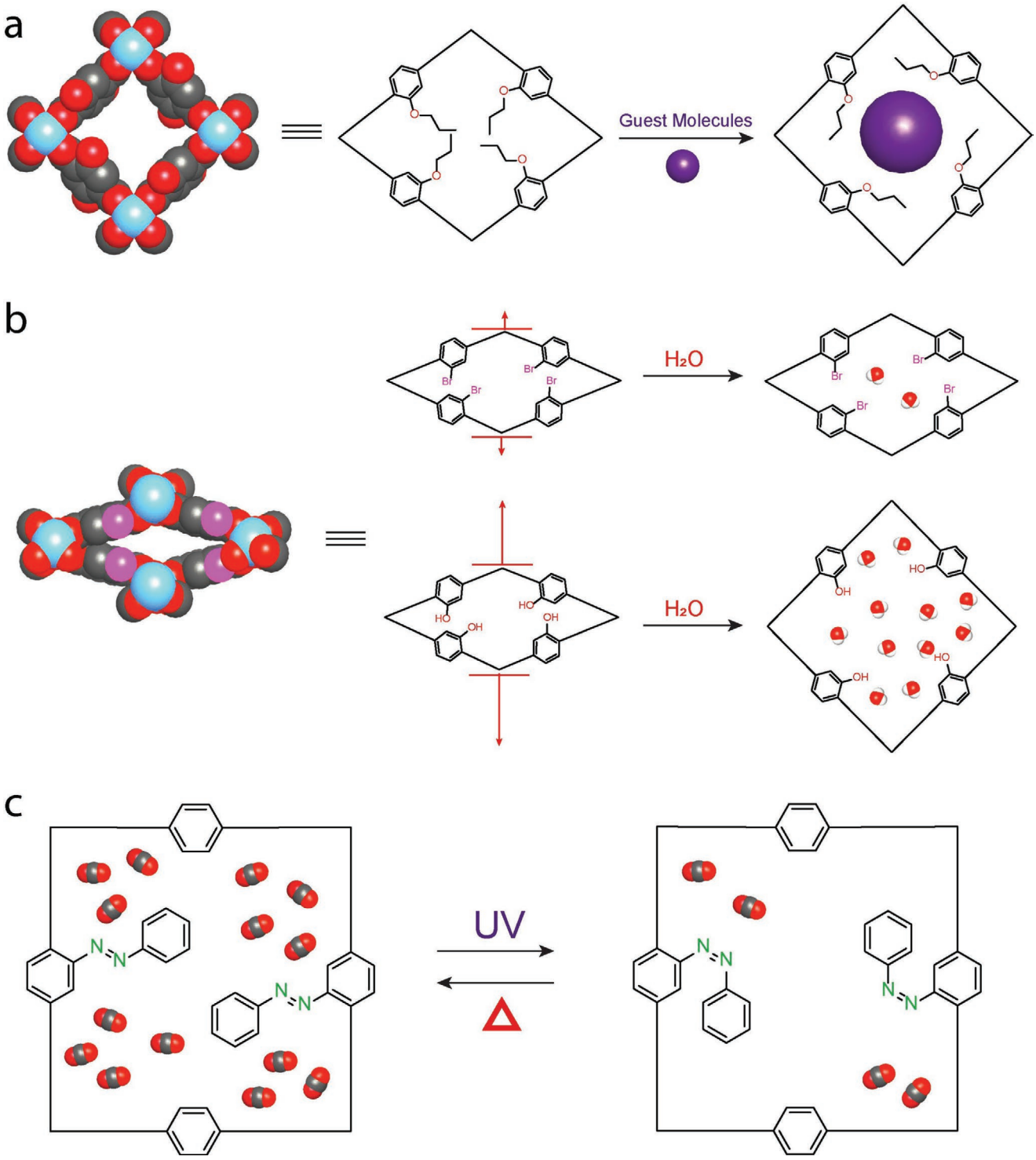


Figure 9. Functionalization for tuning pore dynamics. a) The butoxy groups that can interact with each other and with guest molecules activate the dynamic properties of the pore. b) Hydroxyl groups effect a larger pore-size increase upon water uptake compared with Br groups. c) The photoactive azobenzene can switch between *cis* and *trans* configurations for modulating the uptake of CO_2. Color code: metal, blue; O, red; C, gray; Br, magenta. H atoms are omitted for clarity except for those in water molecules.

incorporated in the structure of MIL-53(Al). The characterization of these MOF analogues indicated that the modification of pore environment with diverse functional groups results in different dynamic behaviors (Figure 9b). The volume of micropore that is H_2O accessible in as-synthesized MIL-53(Al) analogues were measured and the largest value was obtained

from MIL-53(Al)-$(OH)_2$ due to its hydrophilic pore environment. When the pores were filled with N_2, the sequence of pore size became largely reversed: MIL-53(Al)-NO_2 > MIL-53(Al)-Cl = MIL-53(Al)-CH_3 > MIL-53(Al)-Br > MIL-53(Al)-$(OH)_2$. The smaller value obtained from MIL-53(Al)-Br compared with those from MIL-53(Al)-Cl and MIL-53(Al)-CH_3 can be attributed to the larger steric hindrance of −Br group, prohibiting the entry and coverage of N_2. The drastic decrease in micropore volume for MIL-53(Al)-$(OH)_2$ is facilitated by the interactions between −(OH) side chains in the pore when hydrophobic guests can no longer compete for hydrogen bonds.

Besides tuning the flexibility of pores by using differently functionalized organic linkers, dynamic behaviors of the same linker can be induced by external physicochemical stimuli. In order to control the pore dynamics of the framework, a photoactive azobenzene-functionalized BDC linker was chosen for constructing PCN-123, a photoresponsive MOF with tunable CO_2 uptake.[91] This linker can switch its configuration from *trans* to *cis* upon light irradiation and reverse under heat (Figure 9c). The fresh MOF was made from the linker in *trans* configuration, and adsorbed a significant amount of CO_2. UV irradiation triggered the switch of azobenzene configuration, leading to a decreased uptake of CO_2 in accompany with the shrinkage of pore volume. Such phase transformation can be recovered by incubation at ambient conditions for a period of long time or a gentle heating if necessary. Through the control of linker configuration by physicochemical treatment, the pore structure and environment can be adjusted and regulated, and thus modulate its dynamic behavior.

6.6. Molecularly Designed Porous Interfaces

The design of pore chemical environment can be used for tuning the chemophysical properties of a foreign material that is interfaced with MOFs. On the surface of the foreign material, the attached framework structures offer a unique interface distinctive from the typical solid–solid or solid–liquid interface, where either the dense structure (e.g., metal oxide support) does not permit rich chemical modification, or mobile solvent molecules are passively oriented for energy minimizing rather than preorganized for creating specific chemical environments. An architectural scaffold for placing functionalities in the immediate space above the surface atoms of the foreign material allows for a fine-tuning of its performances. The interfacial gap between the two components is segregated into domains by protruding moieties that are involved in attachment. Each domain therefore is consisting of half of the pore contributed by the framework structure and closed by the foreign material on the other side. In this section, we examine the functionalization chemistry in the "half pore" and its role in modulating the behavior of the interfaced foreign material.

In view of attaching inorganic nanoparticles on the surface of MOFs, activity and selectivity of these heterogeneous catalysts are highly dependent on the chemical environment of the half pore. One of widely used strategy for controlling the catalytic performance of inorganic nanoparticles is to tune the type and ratio of functionalities dangling from the organic linkers used for MOF synthesis. Different functional sites in half pore can provide diverse interactions with interfaced nanoparticles for achieving different catalytic performances. Pt nanoparticles were fully encapsulated in UiO-66 (Pt⊂UiO-66) and its derivatives with functionalized organic linkers (bdc-SO_3H, bdc-SO_3^-, bdc-NH_3^+, and bdc-NH_2) and studied for catalytic methylcyclopentane conversion.[92] The chemical environment around Pt nanoparticles can be systematically controlled by incorporating bdc-SO_3H, bdc-SO_3^-, bdc-NH_3^+, and bdc-NH_2 separately (denoted as UiO-66-S, UiO-66-S*, UiO-66-N, and UiO-66-N*) or together (denoted as UiO-66-SN, UiO-66-S*N, and UiO-66-S*N*) in the framework UiO-66 (**Figure 10**a). Pt⊂UiO-66-S showed the highest selectivity of 62.4% for cyclohexane without generating the undesirable acyclic isomers. This catalytic activity was doubled compared with Pt⊂UiO-66, and the enhancement can be attributed to synergistic interplay between Pt nanoparticles and the sulfonic acid in half pore serving as strong acidic sites. In contrast, Pt⊂UiO-66-N exhibited a low selectivity of 10.6% for cyclohexane while displayed enhanced selectivity for the acyclic isomer to 38.6%. When combining two organic functionalities in Pt⊂UiO-66-SN, no cyclohexane was produced and the main product was benzene with a selectivity of 51.7%.

Another way of improving the selectivity of catalysts is to use open metal sites on the interfaced frameworks to exert intermolecular interactions with substrates for discriminating different reaction pathways. These open metal sites usually act as Lewis acid sites which can activate targeted chemical bonds in substrates and thereby lower the energy barrier of the desired chemical transformation. To illustrate this, Pt nanoparticles were sandwiched between an inner core and an outer shell both made of MIL-101 (Fe^{3+} or Cr^{3+}), and used as the catalyst to convert α,β-unsaturated aldehydes toward unsaturated alcohols with high selectivity and efficiency.[93] Although both the C=O and C=C groups are potential hydrogenation targets, the interaction between the C=O bond and the Fe^{3+} or Cr^{3+} unsaturated metal sites (Figure 10b) makes the formation of alcohol products energetically favored. Interestingly, the catalytic activity of Pt nanoparticles interfaced with MIL-101(Fe) was lower than the counterpart interfaced with MIL-101(Cr), while the selectivity was much higher, owing to the interfacial electron-transfer effect. This result shows the possibility to tune the activity and selectivity of catalysts by changing the type of open metal sites inside the half pore.

Constructing an abiotic–biotic interface between framework structures and living cells in addition provides the access to modulating life with artificial materials. When the anaerobic bacteria *Morella thermoacetica* is uniformly wrapped with a MOF monolayer of nanometer thickness, their inherent susceptibility to O_2 and reactive oxygen species that are inevitably generated on anodes during the artificial photosynthesis was overcome.[94] The cytoprotection is endowed by the MOF-catalyzed decomposition of reactive oxygen species accumulated on the cell surface, with an activity 600 times higher than that of zirconia nanoparticles, thus reducing the death of the strictly anaerobic bacteria by fivefold in air. The artificially enhanced tolerance to O_2 enabled the MOF-wrapped bacteria to continuously produce acetate from CO_2 fixation under oxidative stress. The chemical structure of the MOF–bacteria interface was determined as the coordination of phosphate units dangling from the cell surface to zirconium clusters on the MOF layer

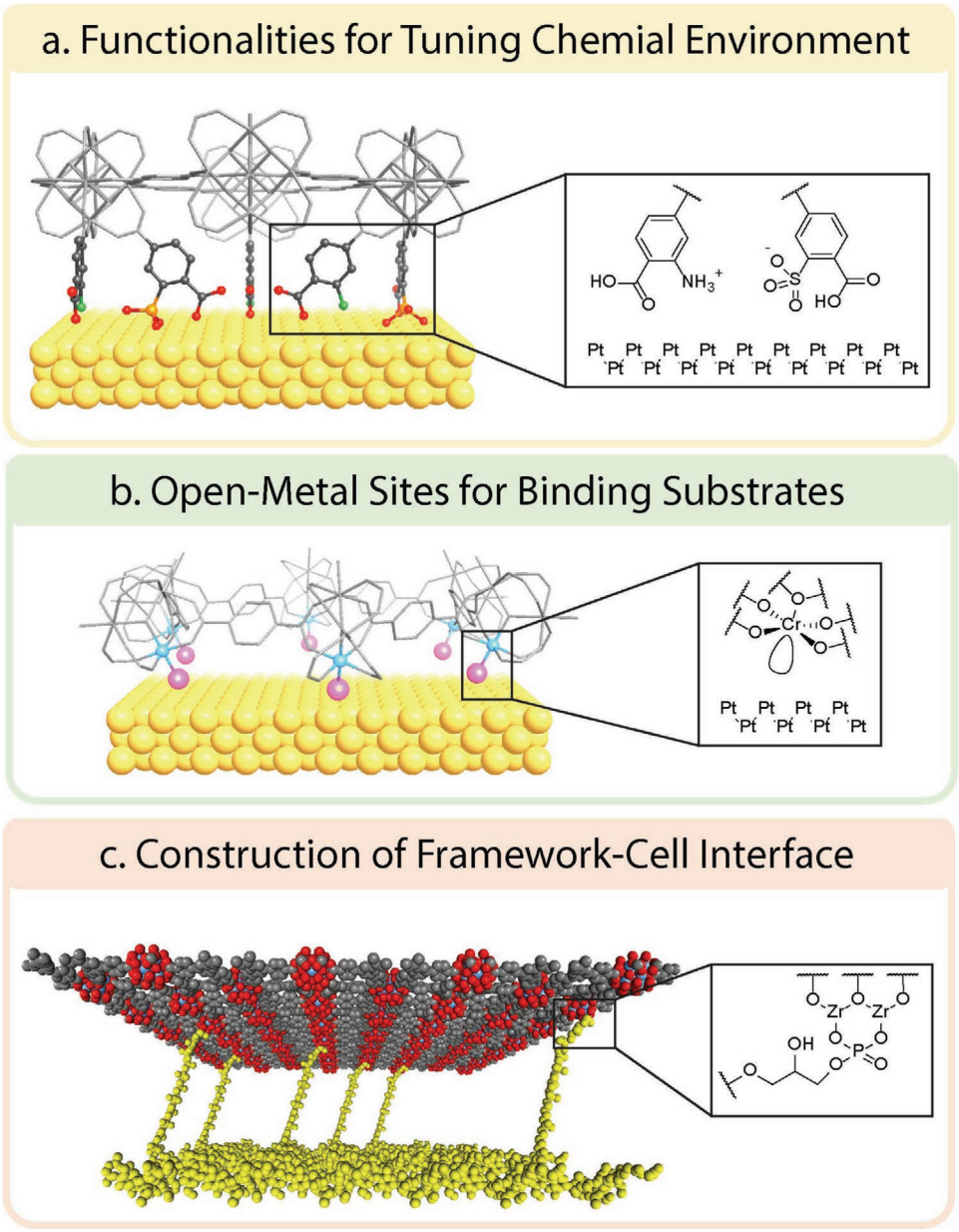


Figure 10. The functionalized, porous interface between frameworks and porous materials. a) Organic functionalities appended on the framework backbone for tuning the environment of catalytic Pt surface. b) Open metal sites for docking substrates in specific orientations with respect to catalytic Pt surface. c) The polymeric phosphate units dangling from the bacterial cell wall coordinate to the unsaturated metal sites of Zr clusters on a MOF monolayer. Color code: metal of interest, blue; O, red; N, green; S orange; other MOF atoms, gray; foreign material, gold. The bound substrate in b is simplified as a purple sphere.

(Figure 10c). The reversibility of the MOF–bacteria bonding gives rise to the dynamic nature of MOF wrapping, allowing for cell elongation and separation without permanently losing the MOF enclosure.

7. Outlook: Writing and Reading Functionality Sequences in MOF Pores

Recent years have witnessed a gradual shift of research interest from site isolation to site coupling and cooperation for addressing challenges that cannot be solved simply by a single functionality. Technological advancement has been accelerated by using multiple functional groups that can cooperate synergistically where the whole outperforms the sum of its parts. This has been a motivation in the field of reticular chemistry for building frameworks with deliberate control over the position, arrangement, and the chemical identity of functional groups inside the pore. Their efforts in anchoring chemical functionalities onto the backbone with atomic spatial resolution exploit the advantage of framework scaffold on precise positioning. Although significant achievements have been made in site coupling and site cooperation, it is noted that the number of types of functionality participating into their collaborative operation is still limited,

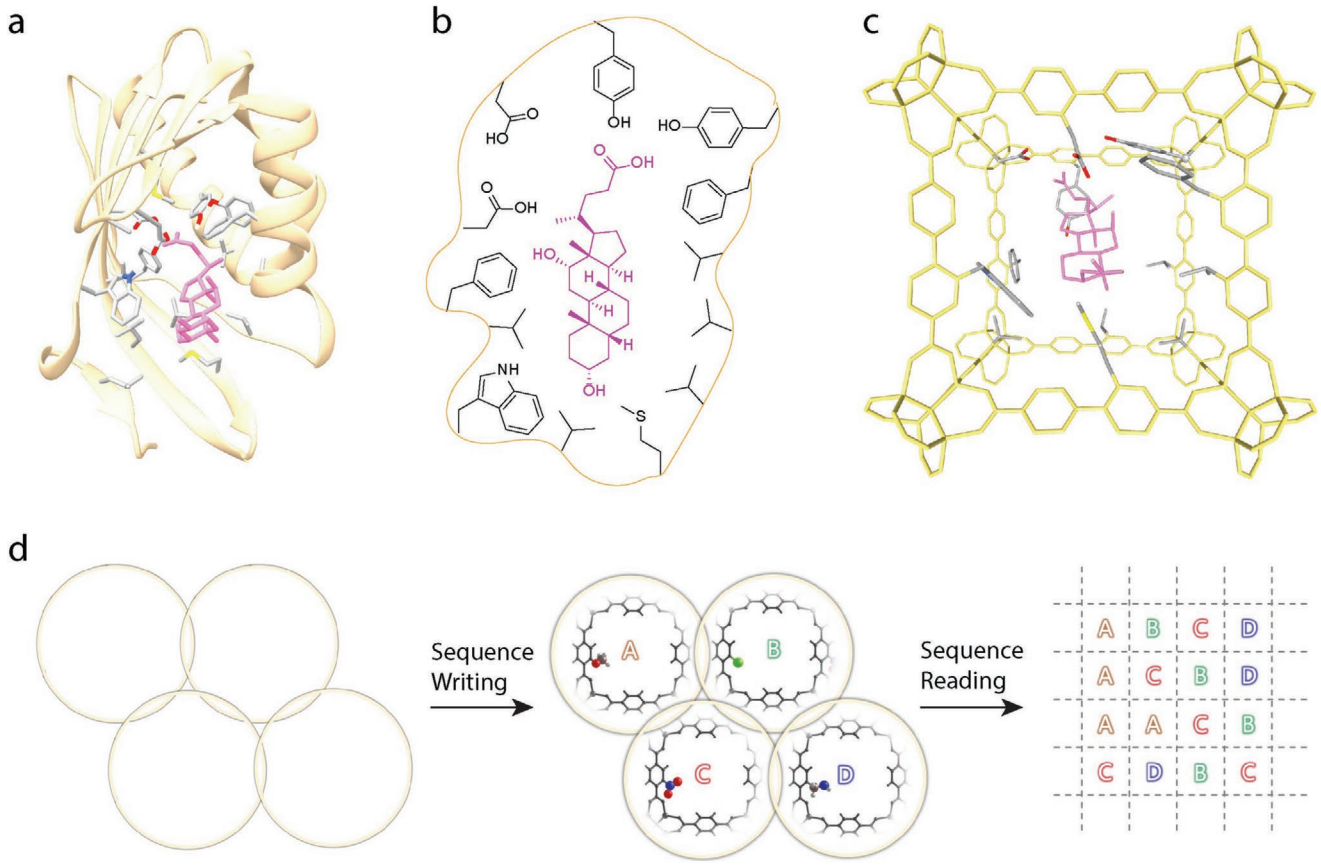


Figure 11. Approaching the structural complexity and sophistication of enzymes by functionalized frameworks. a) The pocket of an enzyme ketosteroid isomerase complexed with a substrate deoxycholic acid (magenta). The polypeptide scaffold is depicted in yellow. Residues involved in substrate interaction are shown. b) The chemical structure of the substrate and the relevant residues. c) Functionalities are installed on the backbone of IRMOF-10 (yellow) for accommodating the binding of deoxycholic acid (magenta). Color code for the residues and functionalities: C, gray; O, red; N, blue; S, yellow. d) Schematic illustration of functionality-sequence writing and reading by using synthetic tools and characterization techniques.

typically varying between 2 and 3, not by the intrinsic attributes of frameworks, but by researchers' will. We envision that the future of pore chemistry lies in combining functionalities within the same pore with higher density, higher chemical variety, and higher positioning precision. Ultimately, these functionalities are arranged into specific sequences spreading over the 3D internal surface of the pore. Such functionality sequence can also propagate along multiple pores and form a channel that is made up by an array of heterogeneous chemical environments.

Appending variable functionalities on rigid backbone resembles the way nature stores genetic information in DNA molecules where the sugar-phosphate backbone acts as the scaffold of double helixes, while the unique arrangement of nucleic bases bound covalently to the backbone encodes the sequence of information that can be passed down to daughter molecules through replication and transcription. An artificial pore replete with chemical functionalities is reminiscent of enzyme pocket where the positioning of amino acid residuals is optimized through evolution for decreasing activation barrier (**Figure 11**). It becomes intriguing to find out whether such functionality sequence can be installed, programmed, and evolved in framework pores. Along these lines, developing methodologies to both write and read this chemical information from and onto architecture backbone allows for the ultimate accomplishment in programing materials on demand. As a result, sequences of functionalities decorating the framework backbone can be programed to create unique pore environments, which are addressable by guest molecules, rich in chemical information, and customizable for targeted applications.

7.1. Writing Sequences

Programing sequence-dependent functions into materials requires the generation of meaningful sequences in frameworks, a field of research that is in its infancy. Preliminary results toward the rational design of multicomponent materials show that a simple change of linker ratio does not necessarily result in a new product. In the structure of MOF-2000, the ratio of the two incorporated linkers remains 2:1 even though this value is varied by an order of magnitude in the starting solution.[95] Advancement in controlling the distribution of functional groups was achieved in multivariate MOF-5, where the choice of combinations of linkers affords distinct patterns of functional group apportionment.[96] In both cases, however, the distribution of functional groups cannot be controlled at the

molecular level, and the obtained patterns of such distribution cannot be tuned independently from the composition of linkers precluding the writing of any arbitrary sequences. The adaptation of solid-state polypeptide synthesis to the construction of metal–organic complex arrays begins to address this challenge by linking constituent metal-containing building blocks in a consecutive way.[97] Alternatively, building units of different types each can be used as the anchoring point for a unique component of the sequence when mixed into a single framework structure.[98] This requires the discovery of multicomponent MOF structures and the number of components determines the length of the sequence that they can constitute. Inspired by how nature replicate information in DNA, potential solution to the sequence writing challenge may take advantage of a template framework that carries preexisting sequences, which can be copied into the functionality sequence of another framework.

7.2. Reading Sequences

Unlike the facility in reading DNA sequences enabled by efficient biochemical technologies, the difficulty in the mapping of spatial distribution of functional groups appended on the ordered framework arise from the fact that characterization techniques synthetic chemists routinely perform rely on the statistical averaging of resonances emanating from the bulk sample. In order to probe the local environment of functional groups, solid-state NMR and molecular dynamic simulation were applied to identify random, alternating, and various cluster forms of the apportionments of organic functional groups.[96] Another work deciphered the arrangement of mixed metals among inorganic building units by measuring X-ray photoelectron spectroscopy.[99] Additionally, fluorescent dyes that can penetrate into the framework and sample along the pore coverage were imaged, and the lifetime analysis revealed the defect distribution and chemical diversity in the crystal.[84] Though these methods show promise, it is noted that the spatial resolution achieved has not been high enough to read the sequence of functionalities at the molecular level. Revolutionary development in finding tools to sequence the channel of frameworks molecule by molecule is highly desired, and we encourage more research efforts in this direction. Both methodological and technological breakthroughs in reading such chemical information with high fidelity will be a revolutionary step toward the sequencing of an increasingly complex pore environment.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

functionality sequencing, metal–organic frameworks, pore chemistry, site cooperation, site coupling

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