Docking in Metal-Organic Frameworks

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The use of metal-organic frameworks (MOFs) so far has largely relied on nonspecific binding interactions to host small molecular guests. We used long organic struts (~2 nanometers) incorporating 34- and 36-membered macrocyclic polyethers as recognition modules in the construction of several crystalline primitive cubic frameworks that engage in specific binding in a way not observed in passive, open reticulated geometries. MOF-1001 is capable of docking paraquat dication (PQT2+) guests within the macrocycles in a stereoelectronically controlled fashion. This act of specific complexation yields more than two domains are present, has remained unexplored. Here, we show how molecular recognition components, much used in supramolecular chemistry (9, 10), can be integrated in a modular fashion into struts of MOFs, thereby creating recognition sites into which incoming guests will dock in a highly specific manner with stereoelectronic control. This third architectural domain—the active domain—combines shape, size, and electronic elements in the recognition of incoming guests, and brings order to otherwise highly disordered guests in conventional MOFs. Hence, this chemistry describes a class of MOFs with a level of complexity higher than that of known open reticulated geometries (I).

We used the primitive cubic topology of the archetypical MOF-5 (11), in which benzene struts are joined by Zn4O(CO2)6 cluster junctions, as the target for our design. Initially, we demonstrated the feasibility of using the long 1/4DMBDA (1) to make MOF-1000 (12), which has the MOF-5 topology, albeit quadruply interpenetrated (Fig. 2A). This approach was extended to the more complex struts BPP34C10DA (2) and 1/5DNPPP36C10DA (3), which are known to act as electron-rich receptors for electron-deficient substrates (13), to make the corresponding MOF-1001A, MOF-1001, and MOF-1002 (Fig. 2, B to D). Each of the crown ether receptors in MOF-1001 is accessible, as evidenced by the docking of the paraquat dication (PQT2+) at every one of the receptor sites (see below). In contrast to known MOFs, where the frameworks are used mainly as passive platforms for the adsorption of gases and molecules, MOF-1001 not only has active components in precise recognition sites but also, by virtue of the openness of its structure, allows substrates to diffuse freely from solution, through the pores, and finally dock into these active domains.

Crystals of MOF-1000 (14) (Fig. 2A and Fig. 3A) were obtained by mixing a solution of strut 1 (15) with Zn(NO3)2·4H2O in N,N-diethylformamide under conditions previously used in the synthesis of MOF-5 (5, 11). Its crystal structure displays the same structural topology as does MOF-5. It is found to be four-fold interpenetrated because of the length and slender nature of the strut; the distance between the two carbonate carbon atoms is 19.3 Å. The successful crystallization of MOF-1000 confirmed the practicality of creating MOFs with higher complexity by means of this synthetic protocol.

Struts 2 and 3 respectively contain 34- and 36-membered polyether rings, which have been extensively used (13) as receptors for a wide range of electron-deficient substrates. These struts are ideally suited as molecular recognition modules for making MOFs. Strut 2 was prepared by means of a convergent synthetic approach (14) and was used under conditions similar to those used in the synthesis of MOF-1000 to yield MOF-1001A.
and MOF-1001A is a triply interpenetrating framework (Fig. 2B and Fig. 3B), whereas that of MOF-1001 is the corresponding noninterpenetrating form (Fig. 2C and Fig. 3C); both have the MOF-5-type topology. The existence of MOF-1001A, despite its occasional appearance as a minor product, validates indirectly the high porosity of MOF-1001. The sheer openness of the structure, however, led us to further optimize the reaction conditions to successfully obtain MOF-1001 as a pure phase (14). MOF-1001 has $Fm\overline{3}m$ symmetry.

**Fig. 1.** Classification of the different porous domains in metal-organic frameworks. In the sorting domain, guest molecules are selected according to their size at the orifices of the pores. The entry of $H_2$ (orange) and concomitant exclusion of $CO_2$ (black) and $CH_4$ (purple) reflects the sieve-like action at the entrances to the pores. In the coverage domain, the guest molecules along the walls of the pores are disordered on account of their weak nonspecific interactions with the framework surrounding the pores. By contrast, the active domain has built-in recognition sites that help to maneuver and dock incoming guests in a highly selective and stereoelectronically controlled manner. These recognition sites (red) could be $\pi$-electron–rich and, as such, would seek out $\pi$-electron–deficient substrates (blue).

**Fig. 2.** Ball-and-stick drawings of single-crystal structures of MOF-1000, MOF-1001A, MOF-1001, MOF-1002, and their corresponding organic struts. Strut 1 was used to obtain MOF-1000 (A), which has a four-fold interpenetrating structure with different frameworks shown in four different colors. The crystal structure of MOF-1001A from strut 2 (B) is a triply interpenetrating cubic structure (shown in blue, gold, and gray), with polyethers represented by red balls and wires. (C and D) MOF-1001 from strut 2 (C) and MOF-1002 from strut 3 (D) share an identical cubic framework backbone, and crown ethers are placed precisely throughout the whole framework [$Zn_4O(CO_2)_6$ polyhedra, blue; organic struts, gray; crown ethers, red]. Crown ethers in all the structures were modeled by Cerius$^2$. All hydrogen atoms have been omitted for clarity.
synthesis of MOF-1002 (Fig. 2D and Fig. 3D) with an exceptionally large unit cell parameter \( a = 52.93 \, \text{Å} \).

We then extended the methodology to the synthesis of MOF-1002 (Fig. 2D and Fig. 3D) by using the 1,5-dioxynaphthalene-containing strut 3, which was produced by a divergent synthetic route \((14)\). Single-crystal x-ray diffraction studies \((14)\) indicate that MOF-1002 shares an identical cubic backbone with MOF-1001, affording the possibility of such a methodology for building a variety of crystalline structures with long struts capable of molecular recognition.

Calculations of the volumes of open space within the MOF structures confirmed the highly open nature of these crystals (86.9% space unoccupied by MOF-1001 framework atoms, as assessed by a model using the program Cerius \(^2\), version 4.2). The inherent flexibility of the macrocyclic polyether substructure was evident from the single-crystal x-ray analysis of MOF-1001. The bis(methylene)oxy units of the tetraethylene glycol loops in the substructure are found to be highly disordered. Nonetheless, the positions of all the atoms in the inorganic joints and the rigid backbone of the links are unambiguous, as judged by comparison of the resulting bond distances and angles with the model structure \((16)\). On the basis of the overall geometry and stoichiometry of the MOF framework, we can conclude that the crown ether receptors—capable of the complexation behavior required \((17)\) for molecular recognition—are integrated precisely and periodically inside a robust framework. Thus, the extended framework provides the basis for their strategic placement so that they are exposed to the maximum accessibility to guests in three-dimensional space.

To date, a number of reports \((18-20)\) have appeared on the synthesis and structure of hybrid organic-inorganic compounds with macrocycles and mechanically interlocking components. The MOFs presented here combine the precise positioning of the active domains with docking as an expression of molecular recognition. This property was revealed by examining the molecular recognition behavior of the macrocyclic polyethers 2 and 3 as docking sites. When MOF-1001 crystals were introduced into a saturated solution of PQT·2PF \(_6\) in acetone, the crystals immediately turned red, and the color intensified over 60 min \((21)\) (Fig. 4, A to E, and movie S1)—a typical behavior for this binding event that indicates charge-transfer interactions \((22)\) between PQT \(^{2+}\) and crown ether rings. This observation points to the formation of MOF-1001 pseudorotaxanes \((23)\) by threading of PQT \(^{2+}\) through the middle of the crown ether. The reversibility of such a process was evidenced by the reappearance of the original light yellow color upon rinsing with acetone, where 60% of PQT \(^{2+}\) could be removed after rinsing MOF-1001 pseudorotaxanes \((2.8 \, \text{mg}) four times with 1 ml every 30 min \((14)\). The complexed MOF-1001 maintained the original high crystallinity of the parent framework, as confirmed by coincident powder x-ray diffraction patterns.

Further evidence of complexation was obtained by examining the \(^1\)H nuclear magnetic resonance (NMR) spectrum of the MOF-1001 pseudorotaxanes after dissolution in DCl \((14)\). Integration of the peaks appearing at 7.96 ppm (d, 4H, Ar-H) in 2, \( j = 8.5 \, \text{Hz} \) (Fig. 4F) and 4.60 ppm (s, 6H, N-CH \(_3\) in PQT \(^{2+}\) showed the expected ratio of strut 2 and PQT \(^{2+}\), indicating that the docking phenomenon of PQT \(^{2+}\) does indeed take place at every crown ether ring throughout the whole MOF framework (fig. S10). Solid-state \(^{15}\)N NMR spectroscopy—a technique that is highly sensitive to the environment of the nitrogen \((^{15}\text{N})\) in PQT \(^{2+}\)—provided further evidence for docking in MOF-1001. Isotope-labeled PQT \(^{2+}\) \((14)\) with 25% abundance of \(^{15}\)N was used to make the MOF-1001 pseudorotaxanes, and the resulting solid was examined by \(^{15}\)N cross-polarization magic angle spinning (CP/MAS) spectroscopy \((24)\). The spectrum of the uncomplexed PQT \(^{2+}\) has a \(^{15}\)N signal centered on 207.2 ppm, whereas the spectrum of PQT \(^{2+}\) bound within the crown ether rings in MOF-1001 shows an upfield shift to 204.6 ppm for the \(^{15}\)N resonance resulting from docking into the macrocyclic polyether units of the struts (Fig. 4G).

Similar studies carried out on strut 2 were used as a molecular analog for comparison with MOF-1001 complexation experiments. Here, addition of PQT·2PF \(_6\) to an acetone solution of strut 2 led to the formation of a pseudorotaxane, [PQT·2PF \(_6\)]⊂2PF \(_6\). The binding affinity \((K_a = 829 \, \text{M}^{-1})\) (fig. S2) between PQT \(^{2+}\) and strut 2 in solution was obtained from spectrophotometric titrations. Single-crystal x-ray diffraction of the [PQT·2PF \(_6\)]⊂2PF \(_6\) (Fig. 4H) clearly shows the insertion of the \(\pi\)-electron-deficient bipyridinium dication through the middle of the macrocyclic polyether. \(\pi\)-stacking and [C–H···O] interactions are reflected in the interplanar separation of 3.6 Å between the bipyridinium unit of PQT \(^{2+}\) and the hydroquinone rings. The same upfield shift trend in the \(^{15}\)N NMR spectra observed for MOF-1001 pseudorotaxanes was also evident in the \(^{15}\)N NMR spectra of [PQT·2PF \(_6\)]⊂2PF \(_6\) in the solid state \((14)\) (Fig. 4I) as well as in solution (fig. S5). Control experiments were carried out by attempting to introduce PQT·2PF \(_6\) into porous MOF-177 crystals \((25)\), the pore dimensions \((d = 11.8 \, \text{Å})\) of which were expected to allow the free movement of PQT \(^{2+}\) within the pores. We found that fewer than 0.06 PQT \(^{2+}\) molecules per strut of MOF-177 were incorporated in the pores (fig. 4J).
These results clearly show that specific stereoelectronic host-guest interactions, rather than simple diffusion and adsorption, are responsible for the all but quantitative formation of the MOF-1001 pseudorotaxanes.

Fig. 4. X-ray diffraction and solid-state NMR spectroscopic studies on MOF-1001, MOF-1001 pseudorotaxanes, and their molecular analogs. (A to C) MOF-1001 [(A) and (B)] maintained its crystallinity after docking of PQT$^{2+}$, a single crystal–to–single crystal transformation revealed by the x-ray diffraction pattern (C). Dimensions of the cubic crystals varied from 0.05 to 0.45 mm. (D to F) This quantitative threading to form MOF-1001 pseudorotaxanes [(D) and (E)] was confirmed by the 1:1 stoichiometry of PQT$^{2+}$ and strut 2 (F). The crystal structure of MOF-1001 and the simulated MOF-1001 pseudorotaxanes structure are illustrated in ball-and-stick models. (G) This docking phenomenon resulted in the upfield shifts of the $^{15}$N CP/MAS signals (1) relative to free PQT$^{2+}$. (H and I) The molecular pseudorotaxane analog [PQT·2$^{-}$]2PF$_6$ (H) was found to have the same upfield shift trend (I) ($\Delta\delta = 4.9$ ppm). Color code: Zn$_4$(CO$_2$)$_6$ polyhedra, gold; organic struts, gray; crown ethers, red; PQT$^{2+}$, blue. All hydrogen atoms and counterions have been omitted for clarity.
The controlled use of fire was a breakthrough adaptation in human evolution. It first provided heat and light and later allowed the physical properties of materials to be manipulated for the production of ceramics and metals. The analysis of tools at multiple sites shows that the source stone materials were systematically manipulated with fire to improve their flaking properties. Heat treatment predominates among silcrete tools at ~72 thousand years ago (ka) and appears as early as 164 ka at Pinnacle Point, on the south coast of South Africa. Heat treatment demands a significant amount of time and allows the physical properties of materials to be manipulated for the production of ceramics and metals. The analysis of tools at multiple sites shows that the source stone materials were systematically manipulated with fire to improve their flaking properties. Heat treatment predominates among silcrete tools at ~72 thousand years ago (ka) and appears as early as 164 ka at Pinnacle Point, on the south coast of South Africa. Heat treatment demands a sophisticated knowledge of fire and an elevated cognitive ability and appears at roughly the same time as widespread evidence for symbolic behavior.

The MSA contains an evolutionary record consisting of stone tools, lithic technology, and behaviors. The MSA is also known for its early use of fire, which has been dated to ~280 ka at Schöningen, Germany. The use of fire in the MSA is significant because it allowed early humans to manipulate and shape materials, providing them with the ability to create tools and structures.

Fire, in combination with the controlled use of tools, allowed early humans to adapt to changing environments and exploit new resources. The use of fire likely facilitated the development of more sophisticated stone tools, as heat treatment could improve the flaking properties of stone materials. This technology is further supported by the presence of hearths and fire-cracked stone at many MSA sites in South Africa, indicating the use of fire for warmth, cooking, and perhaps symbolic purposes.

The MSA is a key period in human evolution, providing evidence for the appearance of modern human behavior and technology. The MSA marks a significant transition in human adaptation, with the emergence of more complex tool assemblies and evidence for symbolic behavior. This period is crucial for understanding the evolution of human cognition and technology, setting the stage for the later development of modern human behavior and culture.