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Design of functional pores using azaphenalenyl ligands and their application for the structure determination of bioactive molecules

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[Introduction]

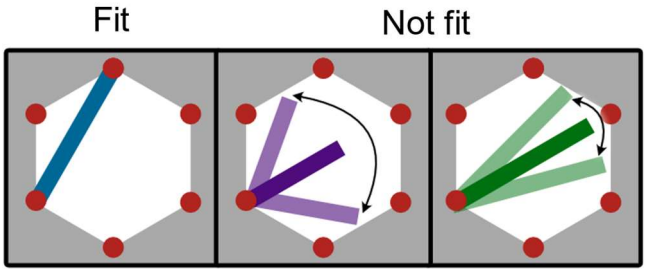

Figure 1 Schematic illustration of the difficulty of designing a universally accommodating PCN

Single crystal X-ray diffraction is one of the most powerful structure elucidation tools, since it can provide critical information regarding three-dimensional atom arrangement and the type of bonding involved, as well as revealing intermolecular interactions and absolute chirality. However, growing crystals of sufficiently large size for structure elucidation can be a daunting task, with a considerable interest in developing alternative techniques. One solution is incorporation into crystalline porous solids. X-ray analysis of compounds encapsulated in the porous materials could reveal a plethora important information about the guest structure and host-guest interactions, as well as monitoring reaction intermediates and detecting metastable species. In particular, structure determination of complex organic molecules has garnered a strong attention since this technique can be applied to non-crystalline solids, oils, and compounds that can only be obtained in trace amounts in what is known as the "crystalline sponge" method. However, to date, only a handful of PCNs have been identified to be compatible for a wide range of substrates since guest capture and stabilization is typically facilitated by a series of finely balanced host-guest interactions, which are difficult to rationally design (Figure 1).

[General Method]

The analysis was performed on a diffractometer equipped in a beamline BL-5A at KEK with a Pilatus3 S6M detector (synchrotron, l = 0.7500 Å, T = 95 K). Powder X-ray diffraction patterns were measured on a Rigaku Miniflex powder diffractometer with D/teX Ultra (1D) detector using Cu Kα radiation at room temperature.

[Result and discussion]

1. Visualization of interactivity of hexaazaphenalenyl (HAP) by single crystal X-ray diffraction

A new 3-pyridyl-substituted derivative of HAP, 3-TPHAP^{-}, was synthesized and characterized. This compound was used as a versatile multi-interactive ligand in the construction of a Co-based coordination network, Co-3TPHAP. The restricted rotation of coordinated pyridyl groups led to a structure with minimized crystallographic disorder. Because of this unique multi-interactive structure, it was possible to assign the pore contents despite its relatively large size. Several guest molecules were encapsulated into Co-3TPHAP. First were the aromatic guests, anthracene and triphenylene. Although they contain large π planes suitable for π–π interactions, no such interaction with the HAP core was observed in either encapsulated structure. In fact,

weaker interactions, including CH−π and weak hydrogen bonds with the network backbone and surrounding solvent molecules, were more prevalent. This behavior was attributed to the unique electronic environment of the pore interior. Second, iodine encapsulation was carried out in different solvents. When ethyl acetate was used, iodine formed two charge transfer complexes with the HAP core. DFT calculations estimated the degree of charge transfer to be ~0.2 electron. The encapsulation from the DMF solution, on the contrary, led to a charge transfer complex with the solvent molecules rather than the network. The presence of these iodine species in both structures was confirmed by UV−vis spectroscopy.

2. Adaptable water networks inside the pore for structure elucidation of bioactive molecules

From the above results, the host-guest crystal structures were shown to contain several solvent molecules in the pore (water, DMF, ethyl acetate), which were highly ordered and could be fully resolved by crystallography. They were interacting with both, the host network, and aromatic guests, forming a kind of solvation shell. From these results, we theorized that the encapsulation process could be additionally mediated by the solvent molecules forming a complex series of host-solvent-guest interactions. The solvent component can be highly malleable and adjust its structure and interactions uniquely for each guest to provide maximum stabilization inside the pore. Such mechanism could considerably enhance capabilities of the crystalline sponge method. To explore this concept further, structure elucidation of several pharmaceutically active compounds was undertaken. These were divided based on their common structural features into artemisinin series, steroid series, and aromatic polycyclic molecules (Figure 2). Moreover, three previously unreported compounds for which crystal structures were not available were also analyzed using this method.

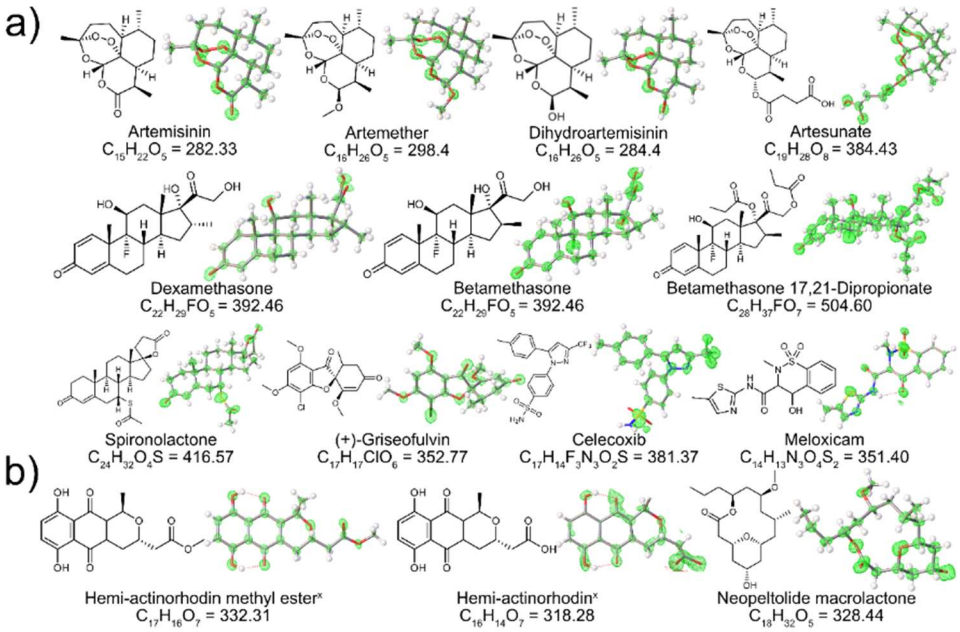

Figure 2 Electron density maps (2Fo - Fc) for elucidated structures of bioactive guest compounds inside the PCN. a) commercially available compounds and b) newly reported compounds. Compounds marked with x were racemic mixtures.

The single crystal analysis revealed that the incorporated guests were surrounded by hydrogen-bonded water networks and clusters inside the pores, which uniquely adapted depending on each molecule, providing clearly defined crystallographic sites. As a result, the guest structures could be determined with high resolution, and limited number of constraints and restraints. The calculations of host-solvent-guest structures showed that the

guests were primarily interacting with the PCN through weak dispersion interaction. Comparatively, the coordination and hydrogen bonds contributed less to the overall stabilization energy, however they provided highly directional point interactions, thus helping to align the guests inside the pore leading to crystal structures with atomic-level resolution.

3. Synthesis of novel C_3 symmetric triazaphenalenyl based ligands

Increased interactivity allowed the structural analysis to be performed on a wider range of molecules. To further explore the arrangements of interactive sites, a new C_3 symmetric triazaphenalenyl (TAP) moiety was developed as a core for the ligand design. TAP has moderate electron-donating ability and is expected to participate in donor-acceptor interactions with guest compounds helping them align along the pore surface. The TAP core can be obtained by a cyclotrimerization reaction followed by an ester hydrolysis to give the HCTAP derivative. After that, the unsubstituted TAP and TCTAP analogues were synthesized from HCTAP by a two-step decarboxylation reaction. Finally, CITAP was prepared through the anhydride of HCTAP followed by condensation with amines.

[Conclusion]

In summary, a wide range of guests was analyzed by the crystalline sponge method using Co-3TPHAP as a host. This network was suitable for guest encapsulation screening in a wide range of solvents. The novel encapsulation mechanism utilizing adaptable water networks presents a significant advancement in precise and rapid elucidation of molecular structures. Additionally, a new family of ligands with promising interacting capabilities was synthesized and is currently being employed for the synthesis of new PCNs.