BL-5A/ 2024G528

Structural Elucidation of Nucleophilic Compounds through Synergistic Coordination and Hydrogen Bonding in a Metal-Organic Framework

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This study presents the development of a novel metal-organic framework (MOF) denoted as APF-80, suitable for structural analysis of nucleophilic compounds that have traditionally been challenging to analyze using the crystalline sponge method. This framework demonstrated remarkable stability toward nucleophilic molecules, which could be captured inside the pores through a synergistic combination of coordination and hydrogen bonding interactions. APF-80 was successfully applied to determine structures of 12 bioactive molecules, including naturally occurring alkaloids and pharmaceutical compounds. The host-guest interaction modes observed inside the resultant structures were classified into five distinct types. This multimodal capture mechanism enabled precise structural analysis of nucleophilic compounds under mild conditions, expanding the scope of molecules analyzable by the crystalline sponge method.

1 Introduction

Single crystal X-ray diffraction is a powerful tool that can reveal a complete three-dimensional atom arrangement, but it requires sufficiently large single crystals, which can be prohibitively difficult to obtain. The crystalline sponge method was developed to address this challenge by circumventing the crystal growth process entirely and instead relying on encapsulation of the target compound into a porous crystalline matrix [1-3]. This technique promised rapid and reliable structure determination, however, despite more than a decade of research its wider implementation has not been realized. One of the major limitations continues to be the analysis of compounds featuring nucleophilic substituents because they tend to degrade host frameworks [4]. This encompasses many important classes of molecules, such as alkaloids. This work introduces a novel metal-organic framework (MOF) denoted APF-80 (adaptable porous framework), that possesses several structural motifs that allowed it to capture nucleophilic guests and immobilize them inside the pore while maintaining its structural integrity.

2 Experiment

The X-ray analysis was performed on a diffractometer equipped on a synchrotron beamline BL-5A at KEK with a Pilatus3 S6M detector (λ = 0.7500 Å, T = 95 K). XDS software was used for the processing and data reduction. The structures were solved by Dual space methods (SHELXT-2018) and refined by full-matrix least squares calculations on F^2 (SHELXL-2018) using the OLEX2 program package.

3 Results and Discussion

Encapsulation studies were performed on a diverse range of bioactive compounds containing nucleophilic substituents, with a focus on alkaloids, using either pure *n*-heptane or 10 % acetone/*n*-heptane mixture. X-ray diffraction analysis of the resultant crystals revealed 12 structures inside APF-80. The observed electron densities could be unambiguously matched with each atom in the guest molecule, indicating an atomic resolution level analysis (Figure 1).

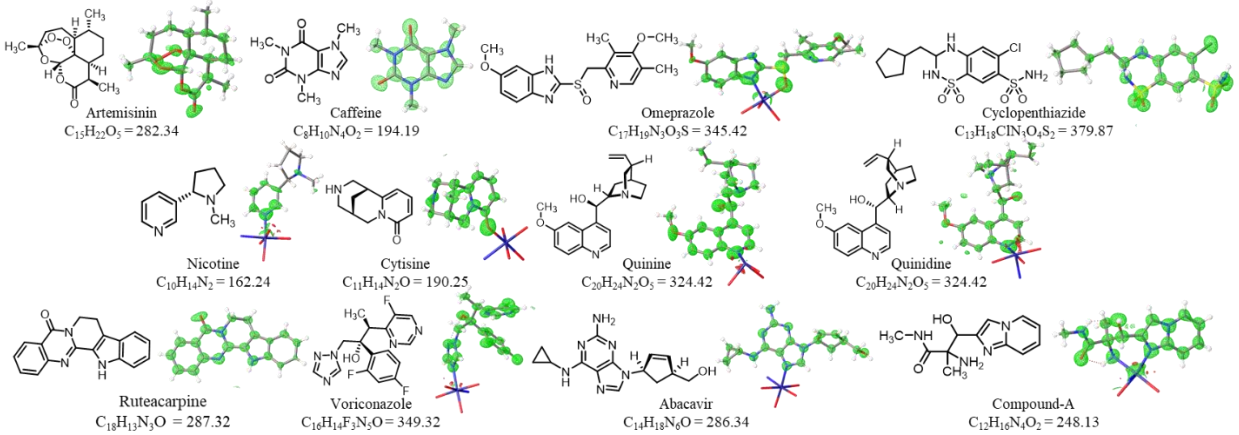

Figure 1. Electron density maps (2Fo – Fc) of elucidated structures of nucleophilic guests encapsulated in APF-80. The corresponding molecular formulas and molar masses (g mol^{-1}) are shown. Omeprazole, cyclopenthiazide and compound-A were encapsulated as racemic mixtures.

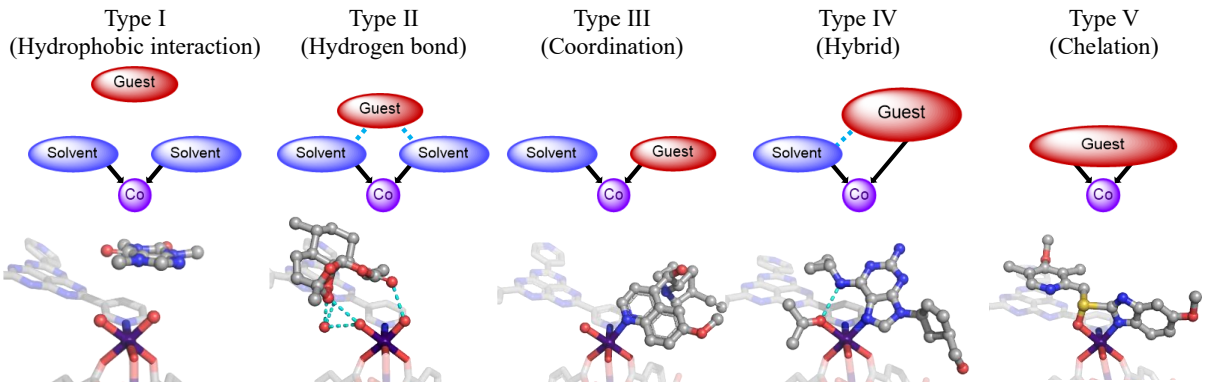

Figure 2. Simplified models of five types of interactions observed between guests and APF-80 (*upper*). Select examples of encapsulated guest structures highlighting each corresponding interaction type: I) caffeine, II) artemisinin, III) quinine, IV) abacavir and V) omeprazole (*lower*). Cyan dash lines represent hydrogen bond contacts. Co – purple, C – grey, O – red, N – blue and S – yellow. Hydrogen atoms were omitted for clarity.

Inspection of the guest structures encapsulated inside APF-80 identified several recurring interaction patterns, which were systematically categorized into five distinct types (Figure 2). Molecules that belong to Type I did not display any strong interactions with the framework backbone or internal solvent molecules, such as hydrogen or coordination bonds. Instead, they were supported entirely by weaker hydrophobic interactions. Due to the weakness of these interactions compared to hydrogen or coordination bonds, the guest sites exhibited very low occupancies and a high degree of disorder appearing as diffuse electron densities that were difficult to model. The remaining four types were defined by the guest interactions with the labile sites on the Co^{2+} dimers of the framework. Type II interaction mode involved guest immobilization exclusively through hydrogen bonding with coordinated water molecules, or the ligand inside APF-80. This type was the most common among the analyzed host-guest structures accounting for 51 % of all sites. This prevalence was attributed to the ability of the surrounding water molecules to generate adaptable hydrogen bonded networks that could effectively capture a wide variety of compounds. Types III, IV and V interaction modes included the formation of coordination bonds between the guest and the Co^{2+} ion. In the case of Type III, the guest acted as a monodentate ligand attaching to one of the labile sites around the metal center. At the same time, the neighboring labile site was occupied by a solvent molecule, such as water or acetone, which existed independently and showed no interactions with the guest. Type IV was structurally similar to Type III, however in this case, the solvent and guest molecules coordinated to the same Co^{2+} center formed a hydrogen bond between each other. This interaction mode can be considered a hybrid of hydrogen bonding and coordination, and offers greater stabilization to encapsulated compounds. In the final interaction type observed inside APF-80, Type V, the guests acted as bidentate ligands binding to the same Co^{2+} center in a chelated manner. The presence of two labile sites in a *cis* configuration enabled the guest capture without compromising the framework structural integrity. This adaptable binding mechanism, utilizing coordination bonding that responds to guest characteristics, represented a defining feature of APF-80.

In previous crystalline sponge reports, guests were typically immobilized inside the pores using a limited range of interactions. For example, in the frameworks that rely on the coordinative alignment strategy [3], only single-point coordination interactions between the guest and the host were observed, which significantly narrowed the scope of analyzable compounds. In contrast, APF-80 exhibited a diverse range of interaction modes with different guest sites, including coordination to Co^{2+} centers, hydrogen bonding with water molecules and the ligand, and hydrophobic interactions. The availability of multiple complementary interactions ensured that at least one highly ordered atomically resolved site could be observed for each encapsulated compound. The framework pore could provide a more favorable arrangement of interaction points for effective capture of various functional groups in the target molecules allowing it to crystallographically resolve a broader range of guest structures.

References

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Research Achievements

1. Academic paper, Nakagawa, T., Wada, Y., Chan, B., Baba, T., Hanaya, K., Koseki, Y., Asano, R., Aoki, K., Usov, P.M. and Kawano, M. Structural Elucidation of Nucleophilic Compounds through Synergistic Coordination and Hydrogen Bonding in a Metal-Organic Framework, *J. Am. Chem. Soc.* **2025**, 147, 32, 29013–29025.
2. Patent, JP2024-30775, Kawano, M., Wada, Y., Nakagawa, T., 2024. 2. 29.

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