Supplementary Information (SI) for Chemical Science.
This journal is © The Royal Society of Chemistry 2025

Electronic Supplementary Information (ESI)

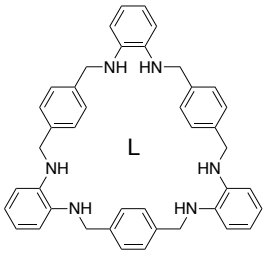
Shape sorting of two distinct amino acid residues at the multiple binding sites of a porous metal-macrocycle framework

Shohei Tashiro,*[a] Kosuke Nakata,[a] Ryunosuke Hayashi[a] and Mitsuhiko Shionoya*[a,b]

[a]*Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

[b]*Research Institute for Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan.*

Materials and methods



MMF-1 crystals were prepared as previously reported using macrocyclic ligand **L** and stored in acetonitrile until use.[1] Other solvents, organic and inorganic reagents are commercially available, and were used without further purification.

Single-crystal X-ray diffraction (ScXRD) analyses were performed using a Rigaku RAXIS-RAPID imaging plate diffractometer with MoKα radiation or a Rigaku XtaLAB P200 diffractometer with MoKα radiation, and the obtained data were analyzed using the Olex2 crystallographic software package[2] except for refinement, which was performed using the SHELXL-2015 program suite.[3] Hydrogen atoms were placed at the calculated positions with the AFIX instructions and refined using a riding model. Several restraints (DFIX, FLAT, RIGU, DELU and ISOR) were applied to MMF-1, bound guests and solvent molecules to avoid the collapse of the structures during the least-squares refinement by the large anisotropic displacement parameters. The large parameters of some parts of MMF-1 originate from structural flexibility with partial disorder, while the parameters of the guest and solvent molecules originate from large thermal vibrations arising from weak noncovalent interactions between the trapped molecules and the interior surface of MMF-1. This leads to some ambiguity in the structure analysis, which are inherent to this system and cannot be avoided. Therefore, in this paper, we do not discuss topics that require high data quality, such as accurate evaluation of guest structures or structure determination of unknown guest compounds. In contrast, it is reasonable to discuss the positions, orientations and intermolecular interactions of guest molecules that show clear electron density, which is sufficient for the conclusion of this study. X-ray structures were displayed using the Mercury[4] or PyMOL[5] programs. The electron density of the guests was displayed using the ShelXle program.[6] To compare the similarity of the host-guest binding modes, Hirshfeld surface analysis was conducted using the CrystalExplorer program (Version 17.5).[7] Note that this analysis considers only host-guest interactions and does not include interactions between the complexes that make up the framework. The intermolecular interaction distances shown in the SI were calculated by the CrystalExplorer program. Conformational analysis of the disordered parts was conducted using the Spartan ‘20 program (Version 1.1.2).

NMR spectroscopic measurements were performed using a Bruker AVANCE 500 spectrometer (500 MHz for ^{1}H), and the chemical shifts were reported in parts per million (ppm).

Details of the crystal structure of MMF-1

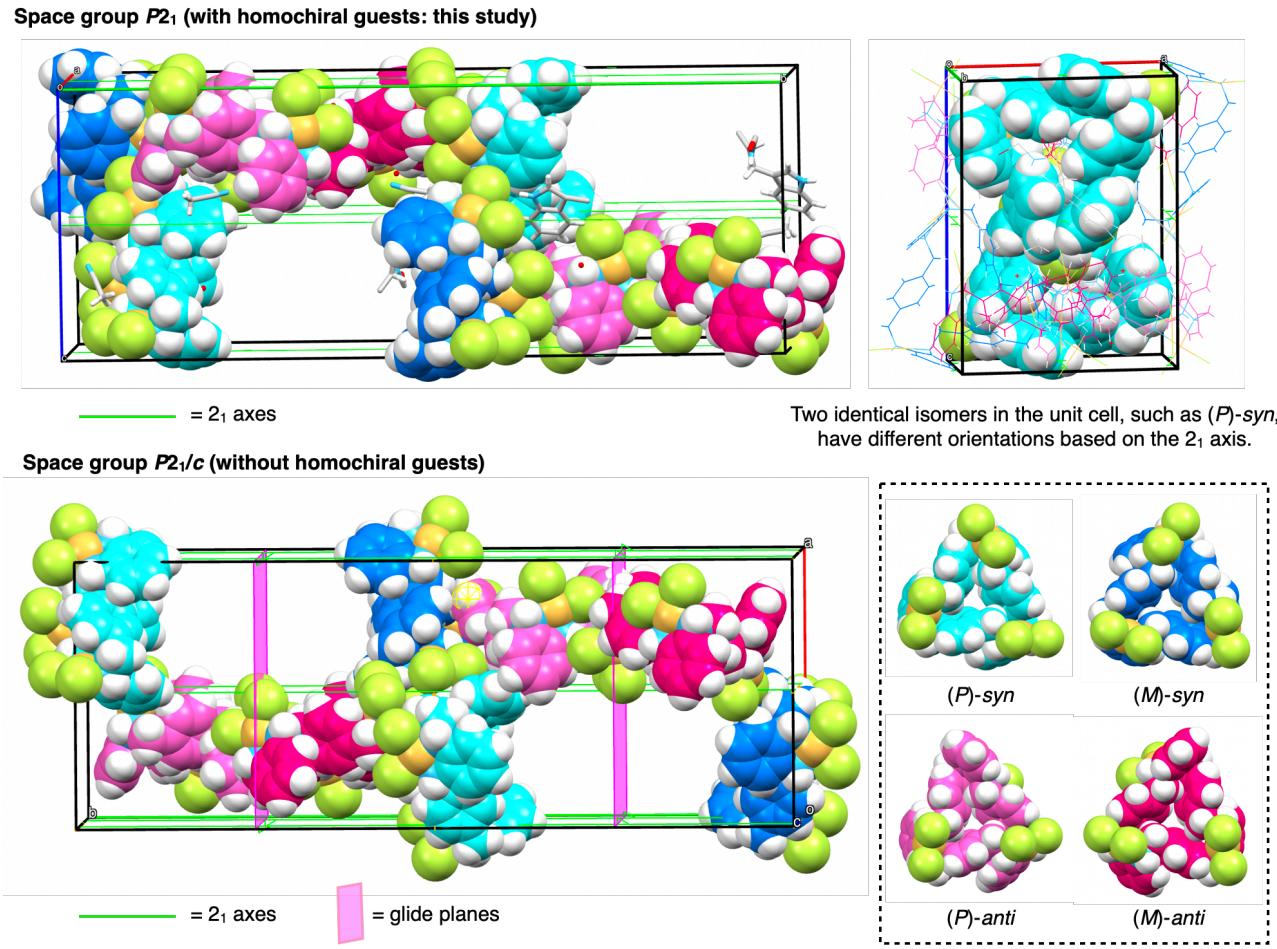


Fig. S1 Arrangement of four stereoisomers of Pd^{II} macrocycles, (*P*)-*syn*, (*M*)-*syn*, (*P*)-*anti* and (*M*)-*anti* (C: light blue, blue, pink and red, respectively), in the unit cell. For more details, see the previous literature.[1]

X-ray crystallographic analysis of amino acid@MMF-1

Z-L-phenylalanine

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-phenylalanine (0.30 M) at room temperature for one day. The crystals were taken out on a glass plate, mixed with a cryoprotectant oil, and then analyzed by single-crystal X-ray diffraction at –180 °C. As a result, the structure of the guest was not observed in the refined crystal structure.

Z-L-tyrosine

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-tyrosine (0.49 M) at room temperature for one day. The crystals were taken out on a glass plate, mixed with a cryoprotectant oil, and then analyzed by single-crystal X-ray diffraction at –180 °C. As a result, the structure of the guest was not observed in the refined crystal structure.

Z-L-tryptophan

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-tryptophan (0.50 M) at room temperature for one day. The crystals were taken out on a glass plate, mixed with a cryoprotectant oil, and then analyzed by single-crystal X-ray diffraction at –180 °C.

Crystal data for $[Pd_3LCl_6]_4\cdot$(Z-L-tryptophan)$_{1.485}\cdot(CH_3CN)_3\cdot(H_2O)_{2.25}$: $C_{190.16}H_{189.64}Cl_{24}N_{29.41}O_{3.18}Pd_{12}$, F_w = 5065.61, crystal dimensions 0.433 × 0.227 × 0.108 mm^3, monoclinic, space group $P2_1$, a = 14.31918(16), b = 51.9317(8), c = 19.4811(2) Å, β = 91.2660(10)°, V = 14483.0(3) Å^3, Z = 2, ρ_{calcd} = 1.162 g cm^{-3}, μ = 0.988 cm^{-1}, T = 93 K, λ(MoKα) = 0.71075 Å, $2\theta_{max}$ = 55.234°, 98802/51423 reflections collected/unique (R_{int} = 0.0277), R_1 = 0.0959 ($I > 2\sigma(I)$), wR_2 = 0.2901 (for all data), GOF = 1.229, largest diff. peak and hole 3.776/–2.661 eÅ^{-3}, Flack parameter = 0.16(4) (refined as an inversion twin). CCDC deposit number 2453192.

The occupancies of the guest molecules were refined using free variables. The structure of the guests was partially assigned based on the electron density map. For instance, two oxygen atoms of the carboxy group and the benzyloxy moiety of the *N*-protecting group were not observed for the guest trapped on the (*M*)-side, and moieties other than the indole ring and one methylene group could not be assigned for the guest trapped on the (*P*)-side. These missing moieties are considered to be severely disordered in the void due to the lack of strong interactions with the pore surfaces. The existence and the structure of the guests were strongly supported by the electron density map, although some restraints and constraints were applied to the structure.

The occupancies of solvents such as water and acetonitrile were set to 1, 0.75 or 0.5 based on the *Ueq* value. Hydrogen atoms of water molecules could not be located in the difference electron density maps.

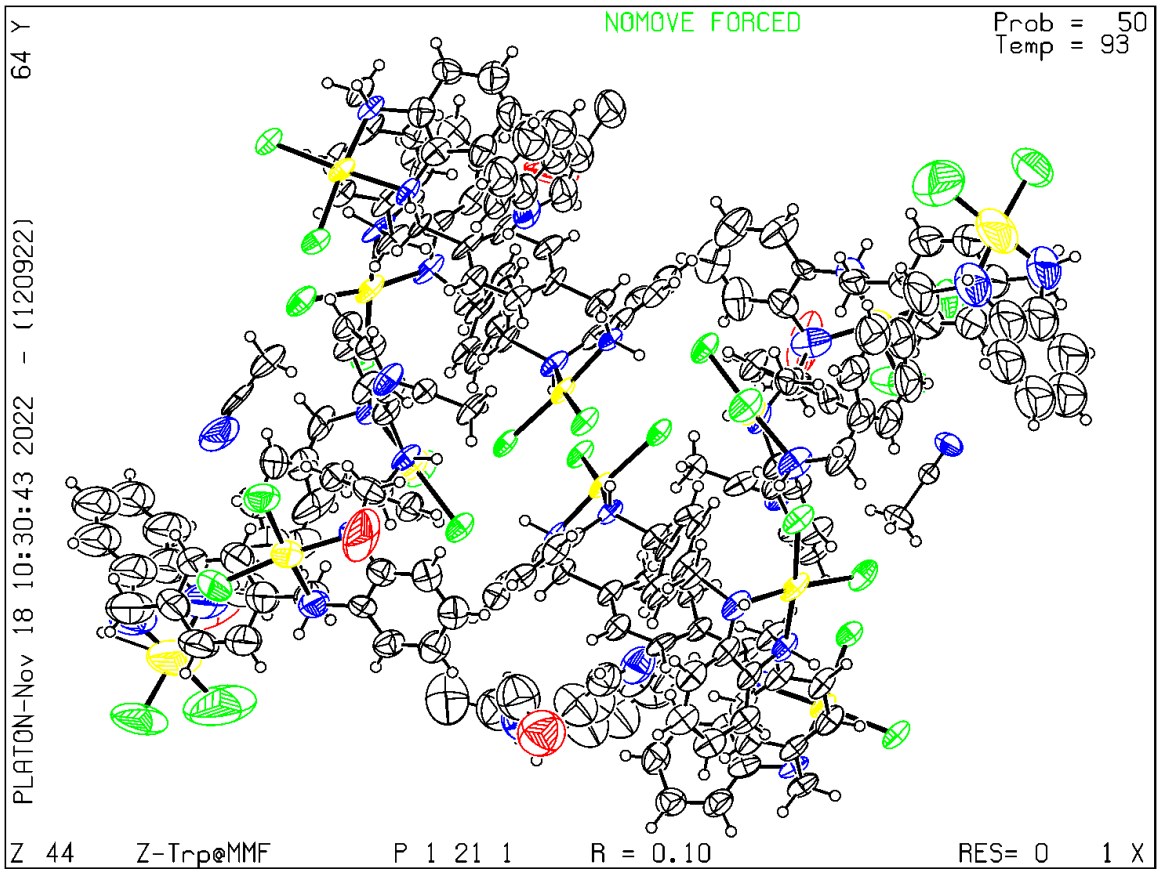


Fig. S2 ORTEP drawing of the asymmetric unit of Z-L-tryptophan@MMF-1 at the 50% probability level. Color: C grey, N blue, O red, Cl green and Pd yellow. Some of the Cl atoms exposed to the pores of MMF-1 have larger anisotropic displacement parameters because they have fewer intermolecular interactions and hydrogen bonds with other Pd^{II} macrocycles.

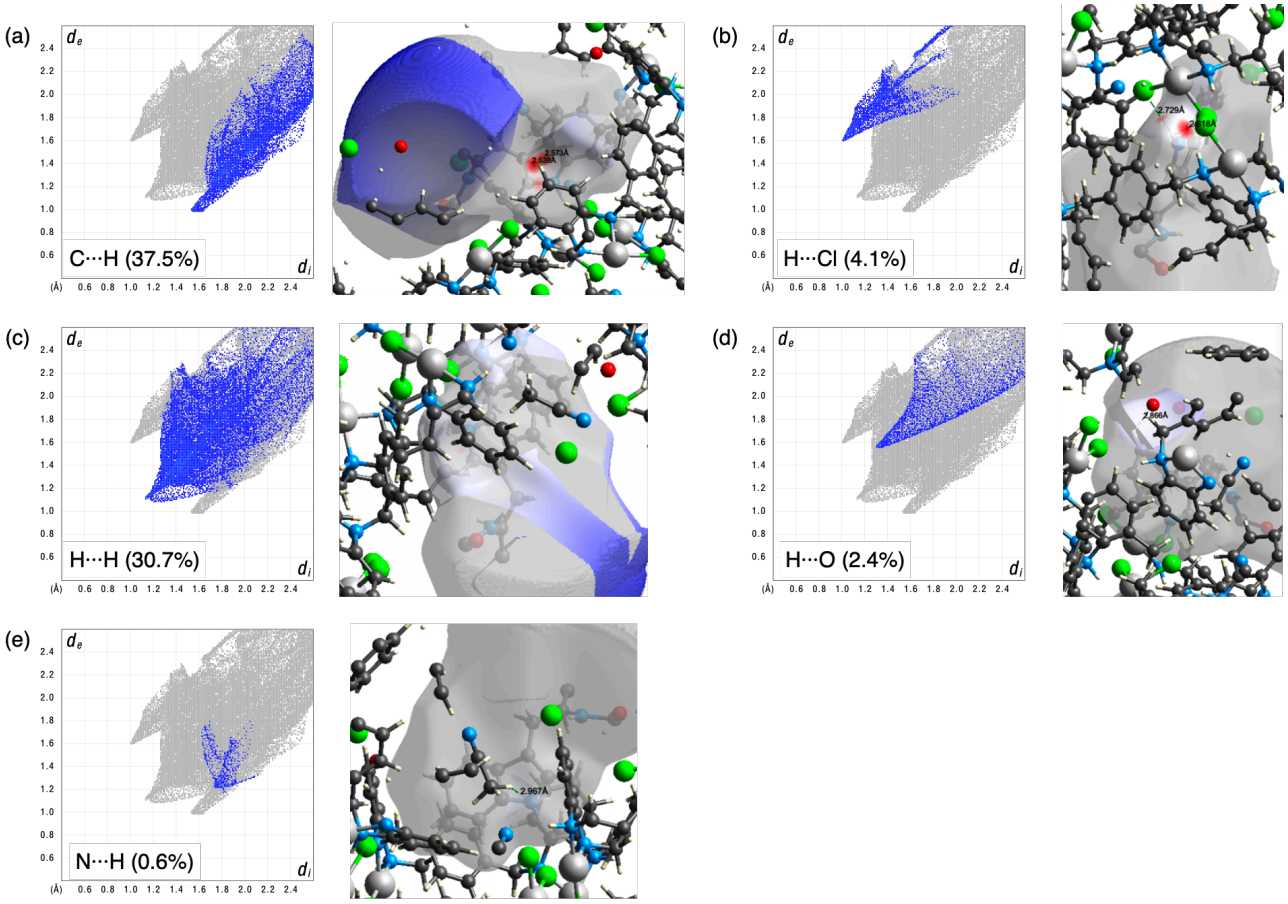


Fig. S3 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*M*)-surface of Z-L-tryptophan@MMF-1 plotted over d_{norm} in the range –0.1778 to 8.0946 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and hydrogen, (b) hydrogen and chlorine, (c) hydrogen and hydrogen, (d) hydrogen and oxygen and (e) nitrogen and hydrogen atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

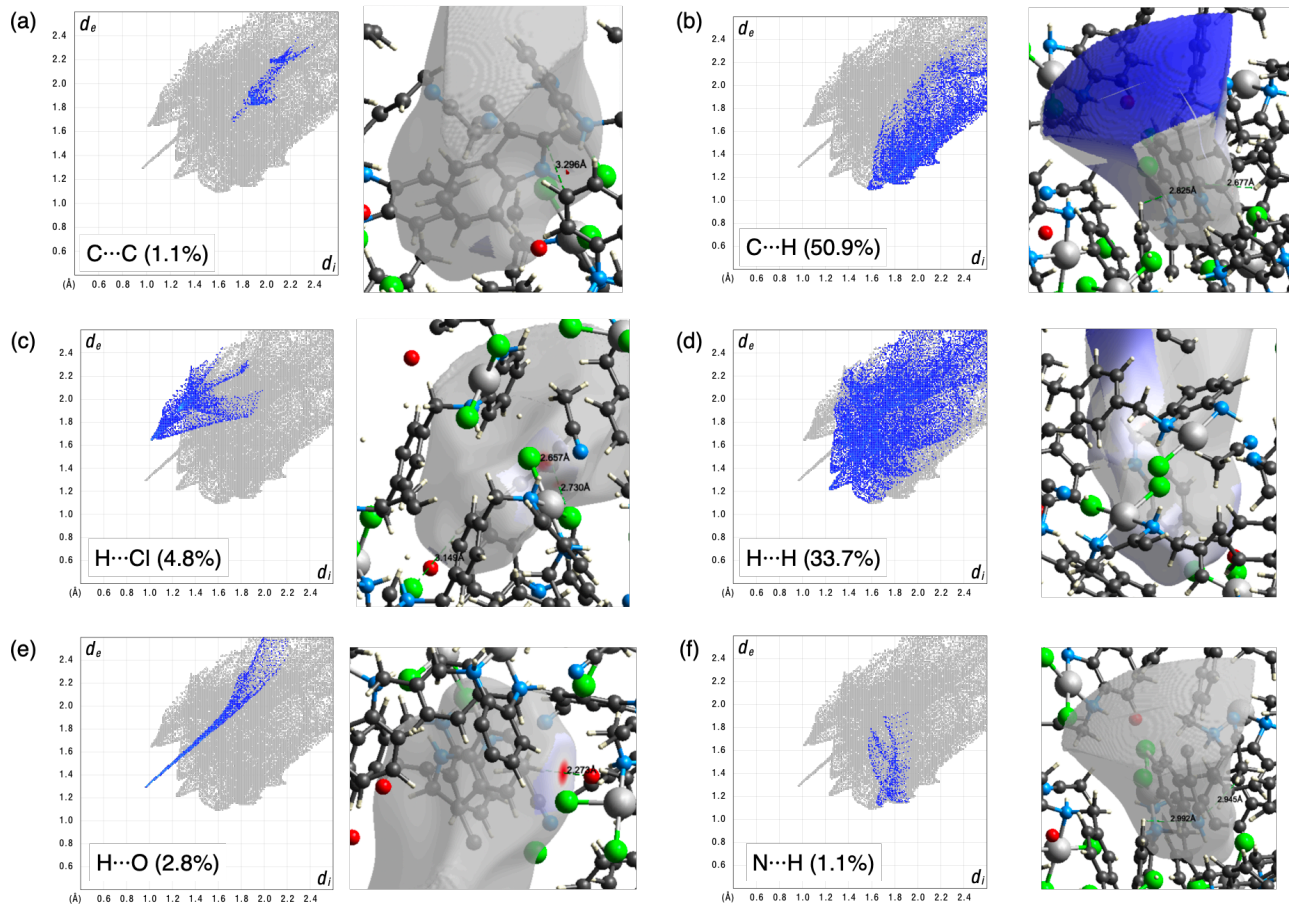


Fig. S4 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*P*)-surface of Z-L-tryptophan@MMF-1 plotted over d_{norm} in the range –0.2499 to 6.8261 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and carbon, (b) carbon and hydrogen, (c) hydrogen and chlorine, (d) hydrogen and hydrogen, (e) hydrogen and oxygen and (f) nitrogen and hydrogen atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

Some of the $PdCl_2$ moieties exposed in the pore exhibit larger anisotropic displacement parameters due to fewer intermolecular interactions and hydrogen bonds with other Pd^{II} macrocycles. The larger residual density on the heavy atoms may be due to the same reason and/or to anomalous dispersion effects. Therefore, the large anisotropic displacement parameters in this part are inherent to the structure and unavoidable. To verify this analysis, a supplementary structural analysis was performed in which the part with large anisotropic displacement parameters was modeled as disordered structures. The results did not change the conclusions, confirming the validity of the original analysis. CCDC deposit number 2255578.

Furthermore, the large unit cell of this structure is consistent with the measured diffraction peaks shown in the Fig. S5.

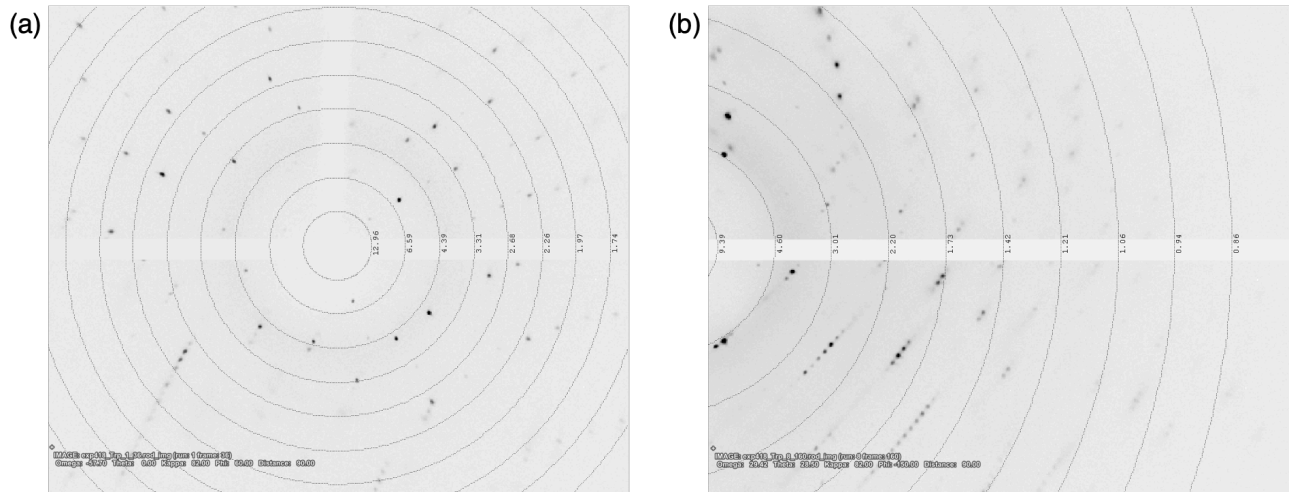


Fig. S5 Diffraction peaks at (a) lower and (b) higher angle regions. The close and continuous diffraction peaks are consistent with the existence of the large unit cell.

Z-L-tryptophan and Z-L-serine

MMF-1 crystals were soaked in a mixed acetonitrile solution of Z-L-tryptophan (0.95 M) and Z-L-serine (0.30 M) at room temperature for 5 days. The crystals were taken out on a glass plate, mixed with a cryoprotectant oil, and then analyzed by single-crystal X-ray diffraction at –180 °C.

Crystal data for $[Pd_3LCl_6]_4 \cdot (Z\text{-L-tryptophan})_{0.878} \cdot (Z\text{-L-serine})_{1.122} \cdot (CH_3CN)_{5.126} \cdot (H_2O)_{2.998}$: $C_{200.14}H_{203.01}Cl_{24}N_{31.63}O_{10.62}Pd_{12}$, F_w = 5349.03, crystal dimensions 0.42 × 0.24 × 0.06 mm^3, monoclinic, space group $P2_1$, a = 14.3191(3), b = 52.5328(10), c = 19.6294(4) Å, β = 91.2340(10)°, V = 14762.3(5) Å^3, Z = 2, ρ_{calcd} = 1.203 g cm^{-3}, μ = 0.975 cm^{-1}, T = 93 K, λ(MoKα) = 0.71075 Å, $2\theta_{max}$ = 54.972°, 143503/66960 reflections collected/unique (R_{int} = 0.0455), R_1 = 0.0702 ($I > 2\sigma(I)$), wR_2 = 0.2229 (for all data), GOF = 1.031, largest diff. peak and hole 2.683/–2.667 eÅ^{-3}, Flack parameter = 0.17(4) (refined as an inversion twin). CCDC deposit number 2255579.

The occupancies of the guest molecules were refined using free variables. Based on the assumption that Z-L-tryptophan and Z-L-serine on the same side cannot coexist sterically, the sum of their occupancies was optimized to be 1. The structure of the guests was partially assigned based on the electron density map. For instance, the phenyl group and the part other than the indole ring were not observed on Z-L-tryptophan trapped on the (*M*)- and (*P*)-sides, respectively. In contrast, the structure of Z-L-serine trapped in both sides was fully assigned. These missing parts are considered to be severely disordered in the void due to the lack of strong interactions with the pore surfaces. On the other hand, the existence and the structure of the guests were strongly supported by the electron density map, although some restraints and constraints were applied to the structure.

The occupancies of solvents such as water and acetonitrile were set to 1, 0.75 or 0.5 based on the *Ueq* value, except for the site occupied by disordered waters and acetonitrile molecules. Hydrogen atoms of water molecules could not be located in the difference electron density maps.

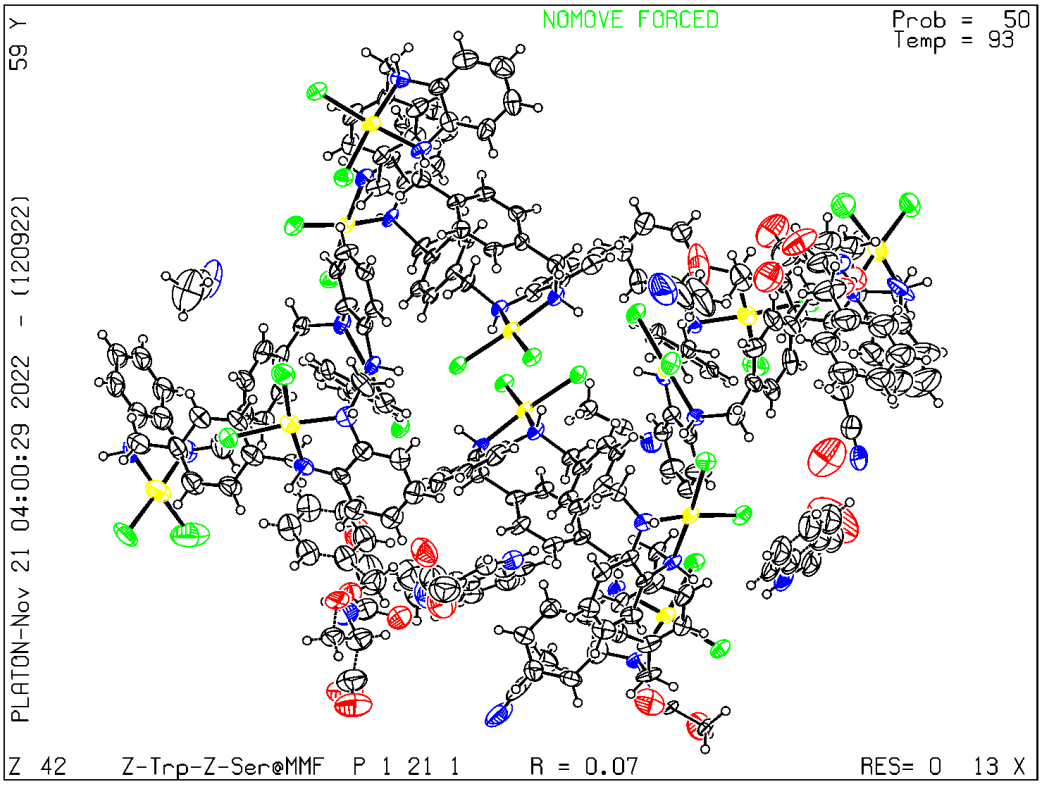


Fig. S6 ORTEP drawing of the asymmetric unit of Z-L-tryptophan/Z-L-serine@MMF-1 at the 50% probability level. Color: C grey, N blue, O red, Cl green and Pd yellow. Some of the Cl atoms exposed to the pores of MMF-1 have larger anisotropic displacement parameters because they have fewer intermolecular interactions and hydrogen bonds with other Pd^{II} macrocycles.

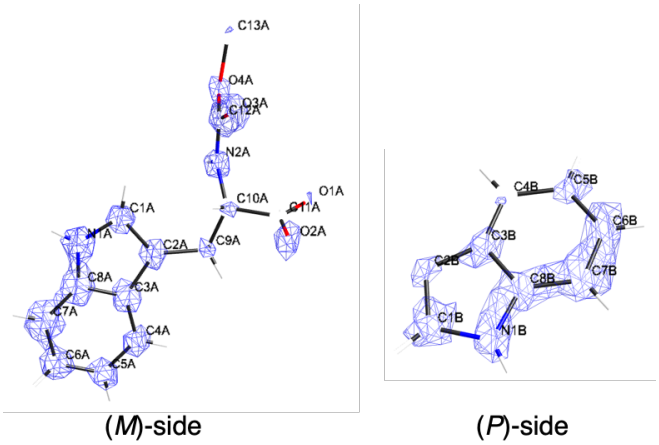


Fig. S7 Electron density maps of Z-L-tryptophan on the (*M*)- and (*P*)-sides of Z-L-tryptophan/Z-L-serine@MMF-1 with contour levels of 0.99σ and 0.81σ, respectively.

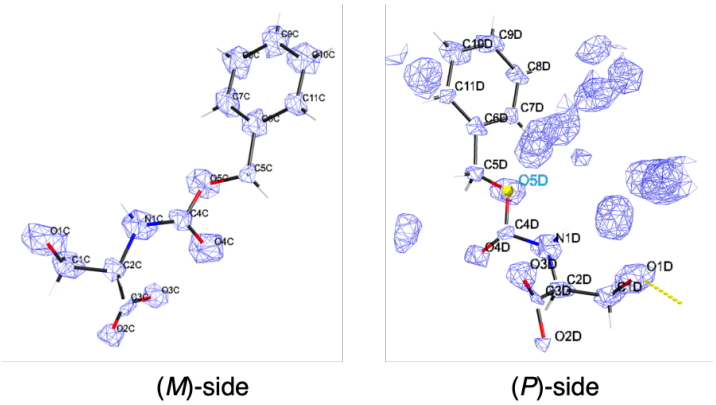


Fig. S8 Electron density maps of Z-L-serine on the (*M*)- and (*P*)-sides of Z-L-tryptophan/Z-L-serine@MMF-1 with contour levels of 0.99σ and 1.23σ, respectively.

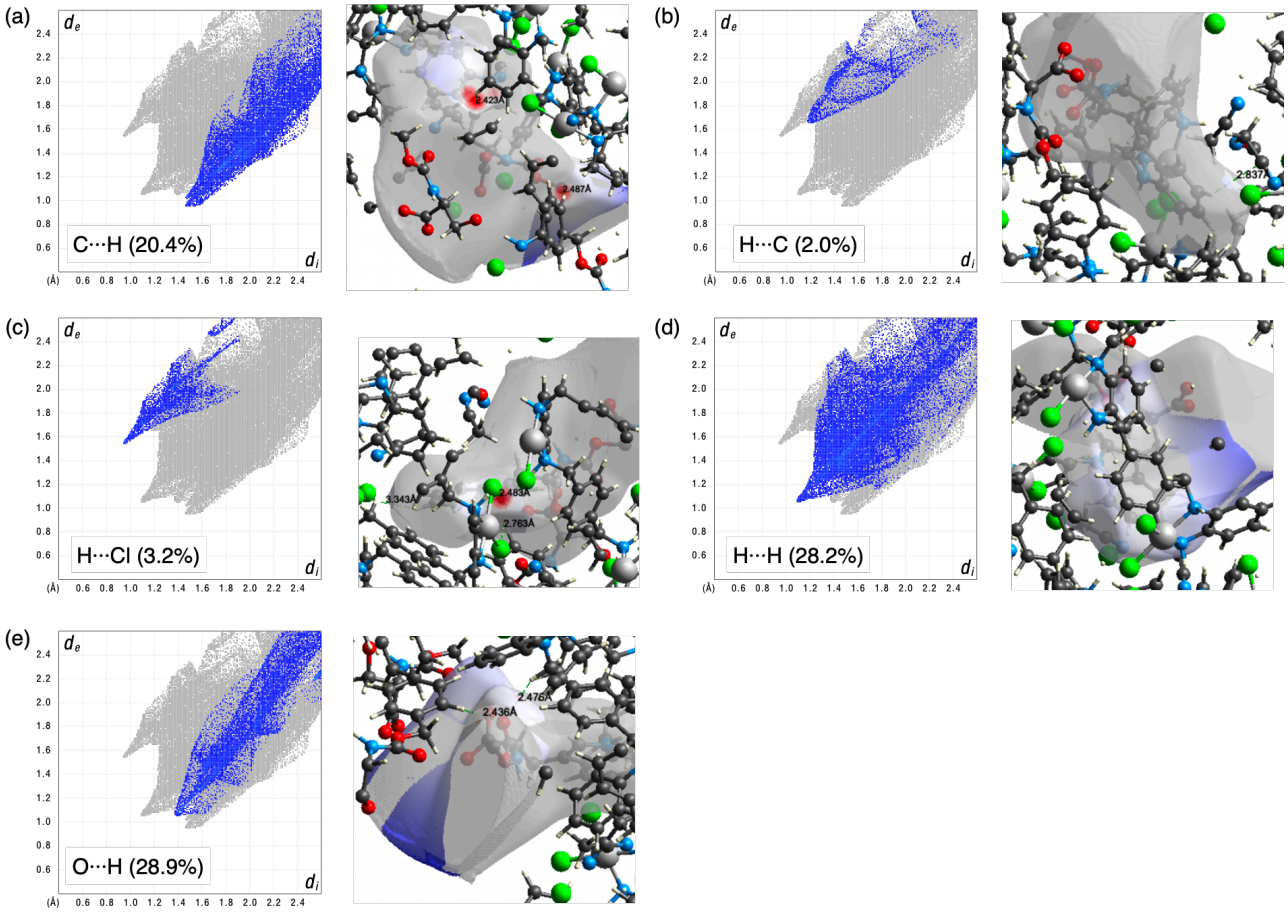


Fig. S9 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*M*)-surface of Z-L-tryptophan/Z-L-serine@MMF-1 plotted over d_{norm} in the range –0.2587 to 6.6571 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and hydrogen, (b) hydrogen and carbon, (c) hydrogen and chlorine, (d) hydrogen and hydrogen and (e) oxygen and hydrogen atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

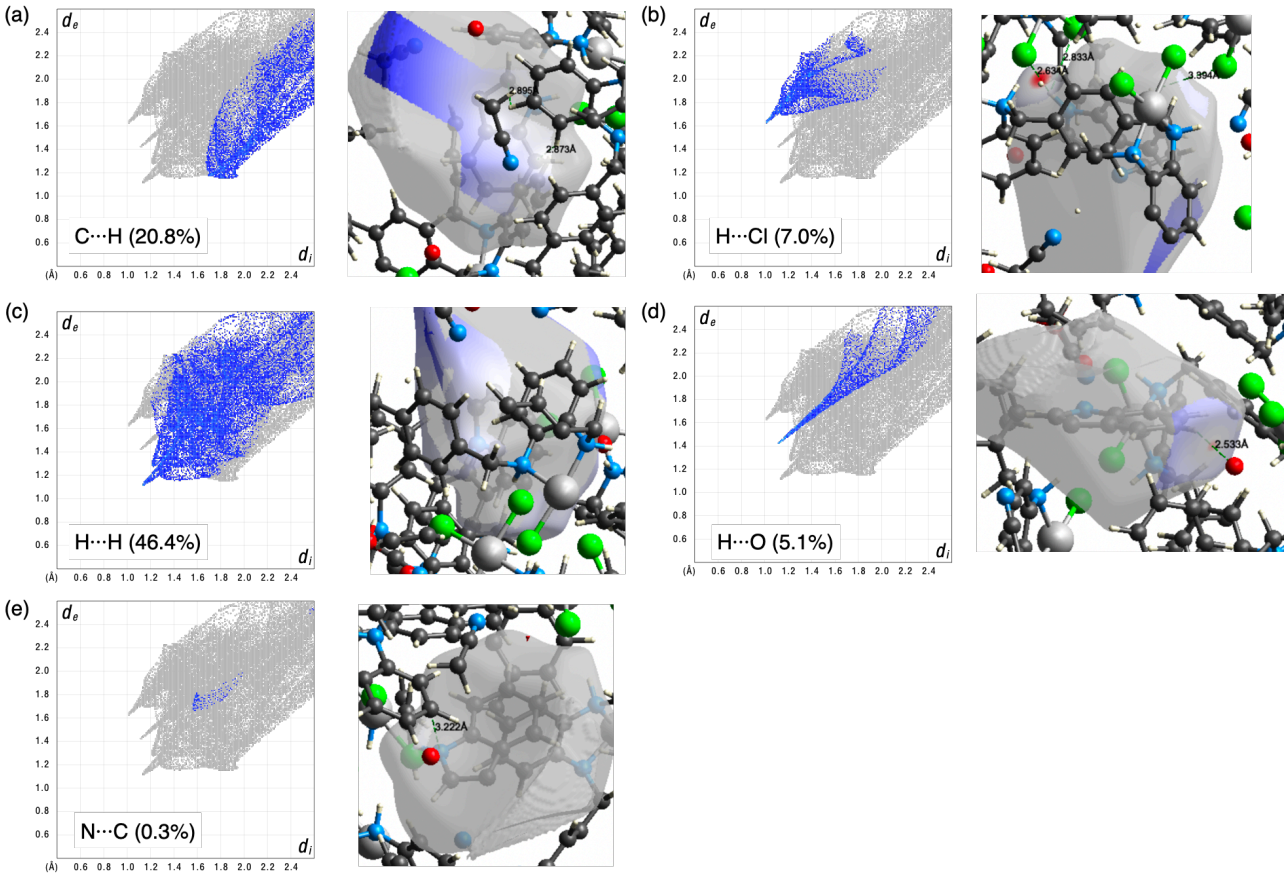


Fig. S10 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*P*)-surface of Z-L-tryptophan/Z-L-serine@MMF-1 plotted over d_{norm} in the range from –0.1456 to 5.9808 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and hydrogen, (b) hydrogen and chlorine, (c) hydrogen and hydrogen, (d) hydrogen and oxygen and (e) nitrogen and carbon atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

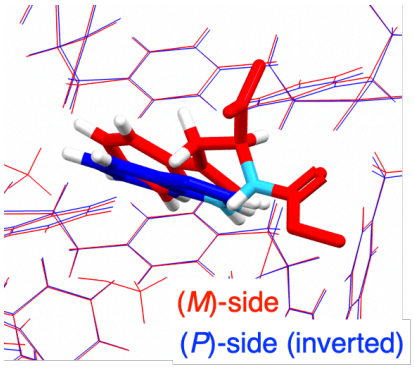
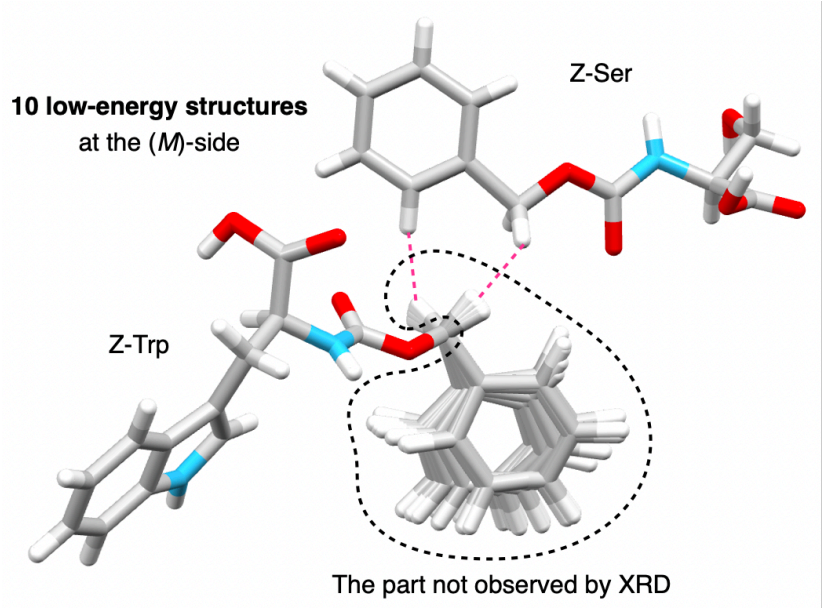


Fig. S11 Superimposed crystal structure of Z-L-tryptophan/Z-L-serine@MMF-1 between Z-L-tryptophan with the (*M*)-side (red) and structurally inverted Z-L-tryptophan with the (*P*)-side (blue).



Order of stability	Closest H···H (Å)
1st	1.808
2nd	1.854
3rd	1.780
4th	1.871
5th	1.808
6th	1.778
7th	1.780
8th	1.854
9th	1.778
10th	1.865

Fig. S12 Ensemble of 10 low-energy structures generated using the Spartan program. Conformers not observed by XRD were generated and energies calculated using the MMFF force field. The magenta dashed lines indicate the nearest H···H moieties in the structures.

In Fig. S12, all benzyl group conformers not observed by XRD collide with Z-L-serine, which has a nearest neighbor H···H distance of approximately 1.8 Å. Based on previous theoretical calculations and the database searches,[8,9] this is too short for the two residues to coexist; therefore, they are substitutionally disordered.

Z-L-tryptophan and Boc-L-serine

MMF-1 crystals were soaked in a mixed solution of Z-L-tryptophan (0.31 M) and Boc-L-serine (0.51 M) in acetonitrile at room temperature for 2 days. To the mixture acetonitrile (10 μL) containing water (0.6 μL) was added (this operation may not be essential), and then the mixture was kept at room temperature for 3 days. The crystals were taken out on a glass plate, mixed with a cryoprotectant oil, and then analyzed by single-crystal X-ray diffraction at –180 °C.

Crystal data for $[Pd_3LCl_6]_4$·(Z-L-tryptophan)$_{1.278}$·(Boc-L-serine)$_{0.596}$·$(CH_3CN)_{7.026}$·$(H_2O)_{3.153}$: $C_{205.13}H_{211.99}Cl_{24}N_{33.58}O_{8.86}Pd_{12}$, F_w = 5417.02, crystal dimensions 0.45 × 0.26 × 0.05 mm^3, monoclinic, space group $P2_1$, a = 14.3167(3), b = 52.1830(10), c = 19.5516(4) Å, β = 91.1680(10)°, V = 14603.7(5) Å^3, Z = 2, ρ_{calcd} = 1.232 g cm^{-3}, μ = 0.986 cm^{-1}, T = 93 K, λ(MoKα) = 0.71075 Å, $2\theta_{max}$ = 54.97°, 144504/66796 reflections collected/unique (R_{int} = 0.0564), R_1 = 0.0791 ($I > 2\sigma(I)$), wR_2 = 0.2522 (for all data), GOF = 1.031, largest diff. peak and hole 2.088/–1.914 eÅ^{-3}, Flack parameter = 0.20(5) (refined as an inversion twin). CCDC deposit number 2255580.

The occupancies of the guest molecules were refined using free variables. The structure of the guests was partially assigned based on the electron density map. For instance, the part other than the indole ring were not observed on Z-L-tryptophan trapped on the (*P*)-sides. The missing part is considered to be severely disordered in the void due to the lack of strong interactions with the pore surfaces. On the other hand, the existence and the structure of the guests were strongly supported by the electron density map, although some restraints and constraints were applied to the structure.

The occupancies of solvents such as water and acetonitrile were set to 1, 0.75 or 0.5 based on the *Ueq* value, except for some acetonitrile molecules. Hydrogen atoms of water molecules could not be located in the difference electron density maps.

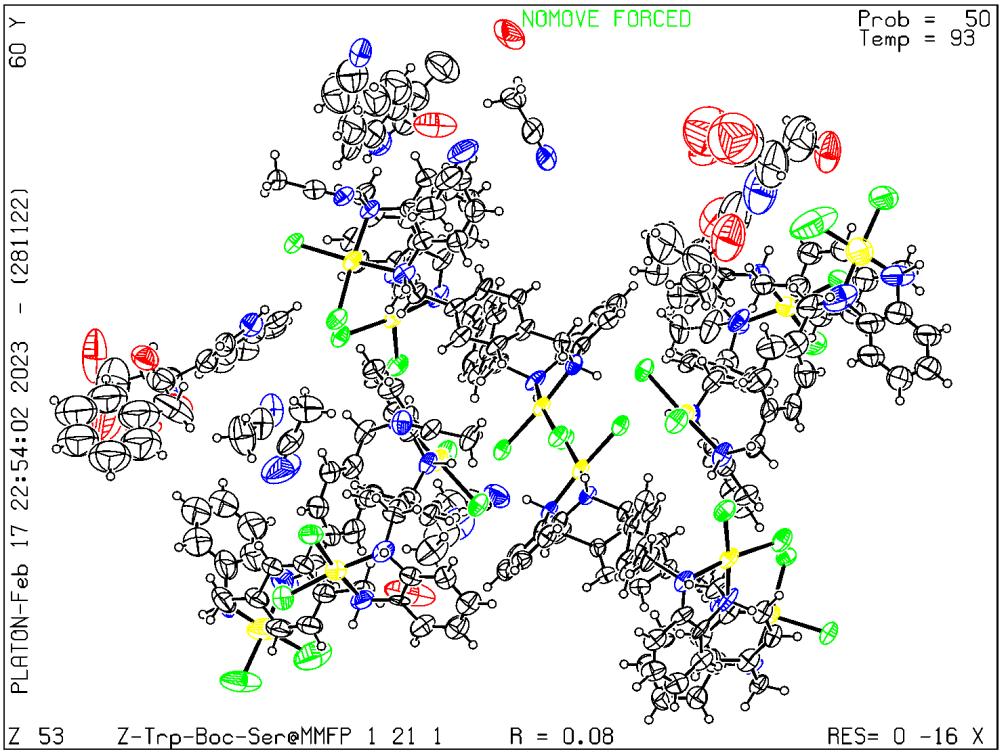


Fig. S13 ORTEP drawing of the asymmetric unit of Z-L-tryptophan/Boc-L-serine@MMF-1 at the 50% probability level. Color: C grey, N blue, O red, Cl green and Pd yellow. Some of the Cl atoms exposed to the pores of MMF-1 have larger anisotropic displacement parameters because they have fewer intermolecular interactions and hydrogen bonds with other Pd^{II} macrocycles.

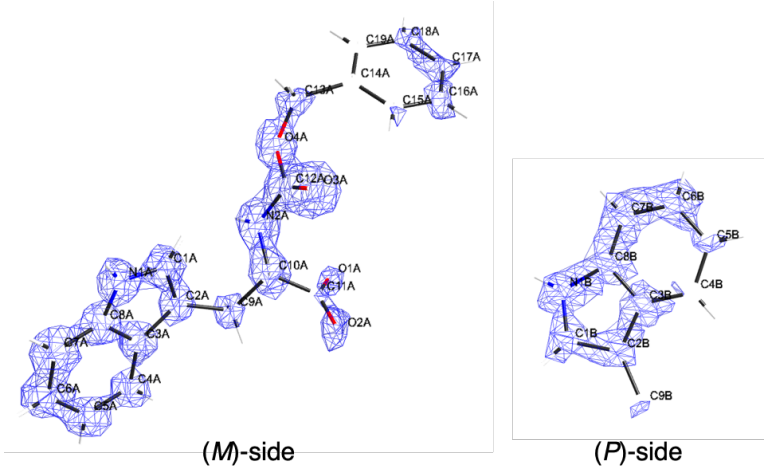


Fig. S14 Electron density maps of Z-L-tryptophan on the (*M*)- and (*P*)-sides of Z-L-tryptophan/Boc-L-serine@MMF-1 with a contour level of 0.81σ.

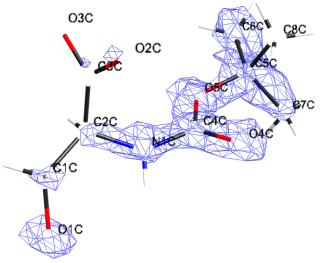


Fig. S15 Electron density maps of Boc-L-serine on the (*P*)-side of Z-L-tryptophan/Boc-L-serine@MMF-1 with a contour level of 0.81σ.

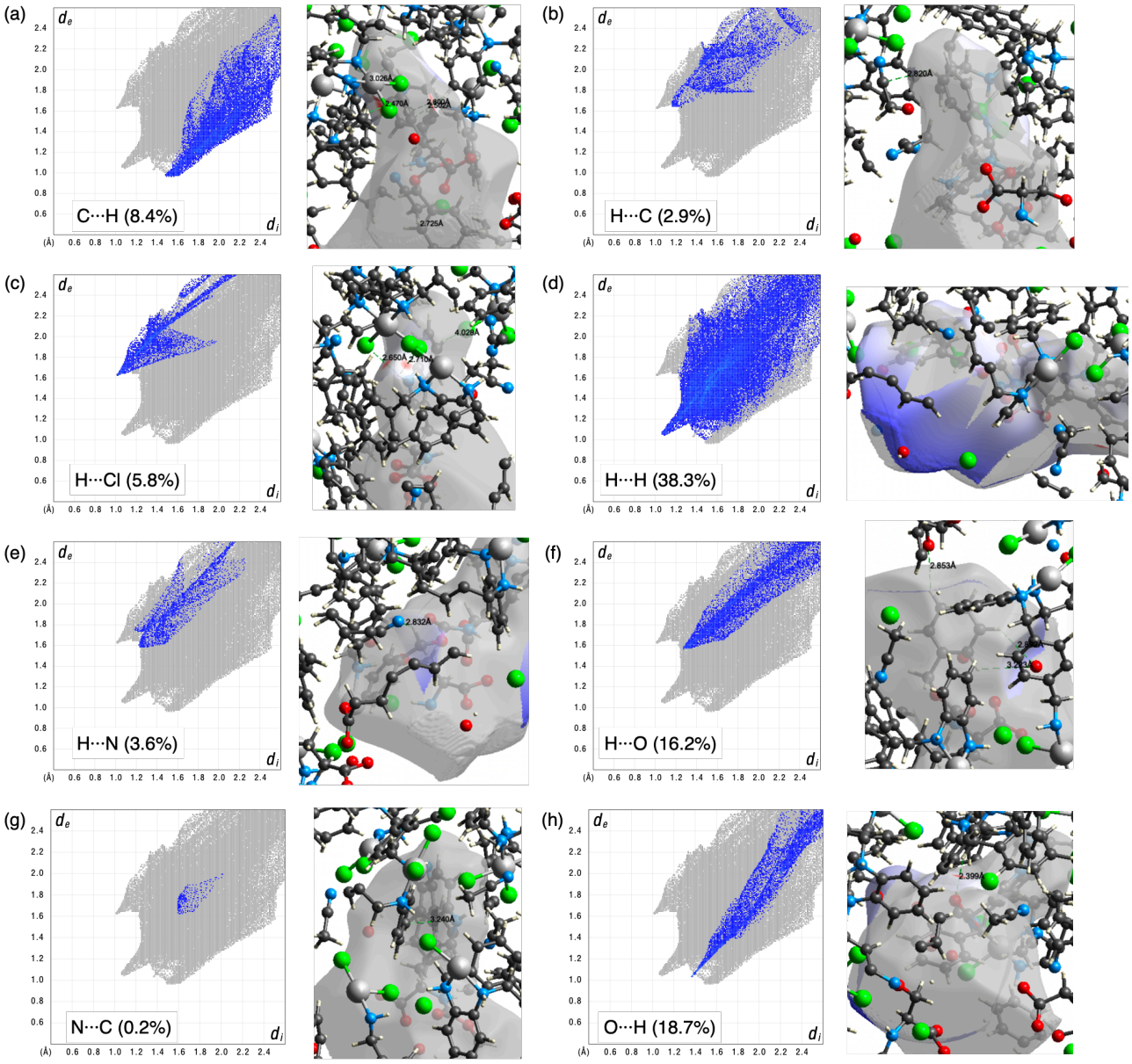


Fig. S16 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*M*)-surface of Z-L-tryptophan/Boc-L-serine@MMF-1 plotted over d_{norm} in the range from –0.2227 to 6.8537 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external

distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and hydrogen, (b) hydrogen and carbon, (c) hydrogen and chlorine, (d) hydrogen and hydrogen, (e) hydrogen and nitrogen, (f) hydrogen and oxygen, (g) nitrogen and carbon and (h) oxygen and hydrogen atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

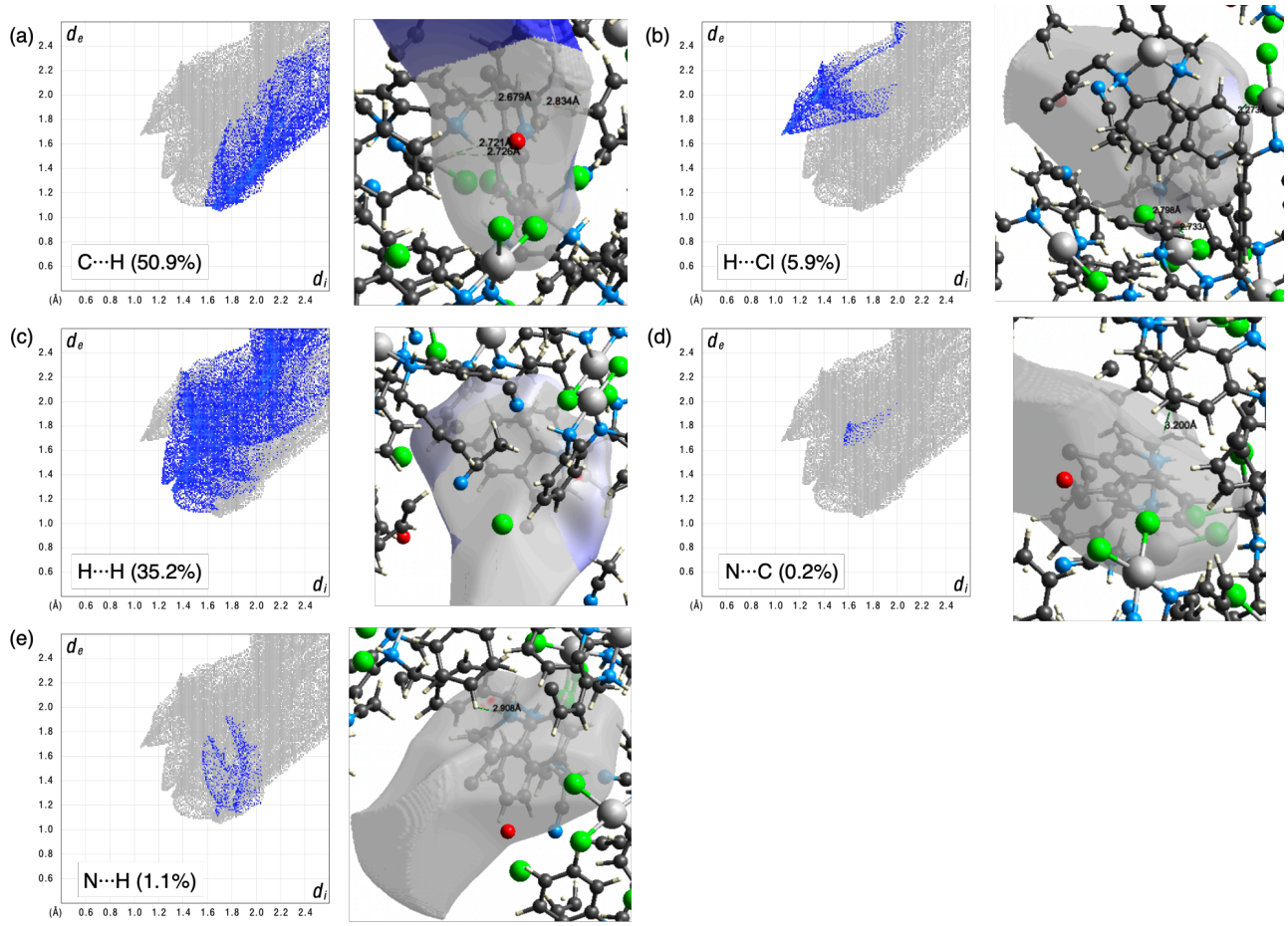


Fig. S17 Three-dimensional Hirshfeld surfaces of Z-L-tryptophan on the (*P*)-surface of Z-L-tryptophan/Boc-L-serine@MMF-1 plotted over d_{norm} in the range from –0.0726 to 6.8301 a.u. and fingerprint plots for the Hirshfeld surface. The percentage values indicate the contribution of the interactions to the Hirshfeld surface, and the d_i and d_e values are the closest internal and external distances (Å) from given points on the Hirshfeld surface. Fingerprint plots between (a) carbon and hydrogen, (b) hydrogen and chlorine, (c) hydrogen and hydrogen, (d) nitrogen and carbon and (e) nitrogen and hydrogen atoms of Z-L-tryptophan and other moieties including MMF-1, respectively.

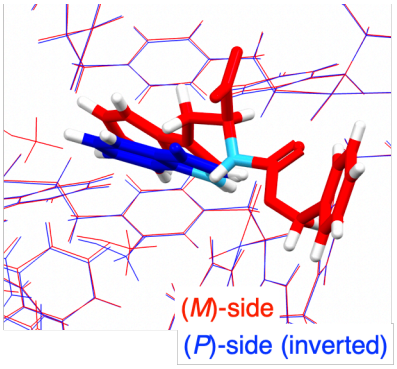


Fig. S18 Superimposed crystal structure of Z-L-tryptophan/Boc-L-serine@MMF-1 between Z-L-tryptophan with the (*M*)-side (red) and structurally inverted Z-L-tryptophan with the (*P*)-side (blue).

Confirmation of guest inclusion in MMF-1 by ^{1}H NMR analysis

Z-L-tryptophan

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-tryptophan (0.50 M) at room temperature for one day. The crystals were collected by filtration, washed with a small amount of acetonitrile, and then dissolved in DMSO-d_6 containing DCl to measure ^{1}H NMR spectroscopy.

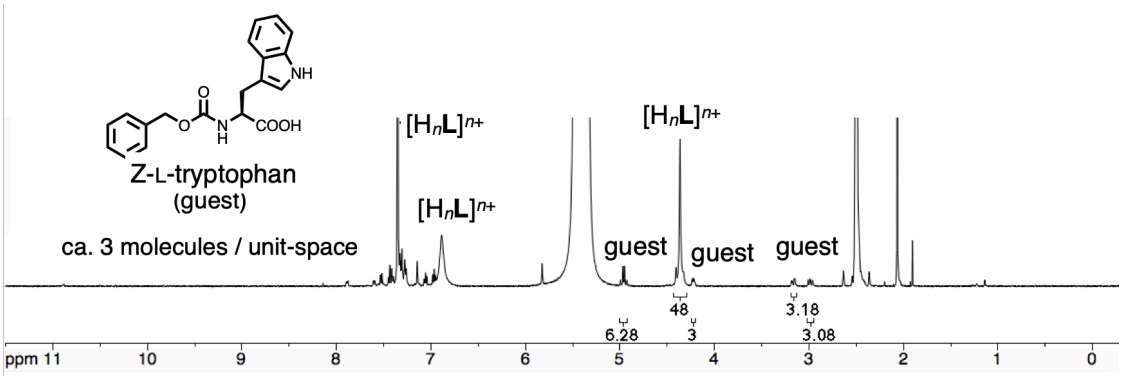


Fig. S19 ^{1}H NMR spectrum (500 MHz, DMSO-d_6, 300 K) of Z-L-tryptophan@MMF-1 after dissolving in DMSO-d_6/DCl.

Z-L-phenylalanine

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-phenylalanine (0.30 M) at room temperature for one day. The crystals were collected by filtration, washed with a small amount of acetonitrile, and then dissolved in DMSO-d_6 containing DCl to measure ^{1}H NMR spectroscopy.

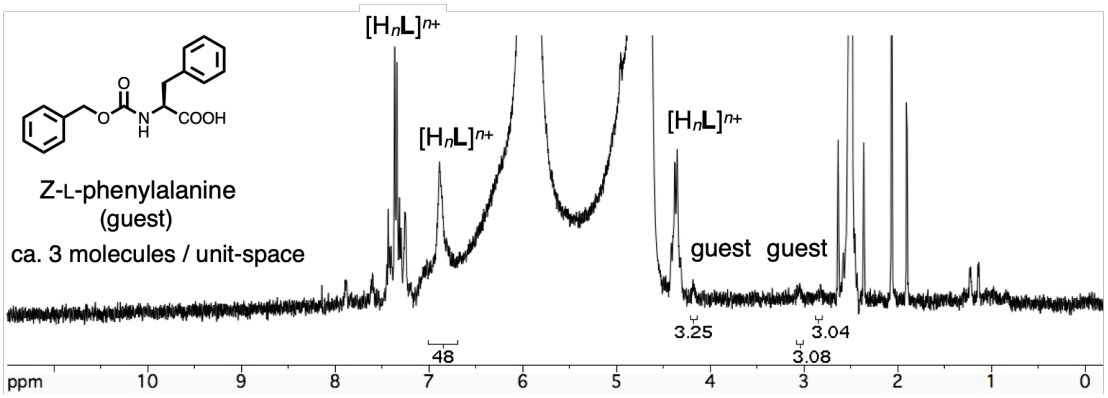


Fig. S20 ^{1}H NMR spectrum (500 MHz, DMSO-d_6, 300 K) of Z-L-phenylalanine@MMF-1 after dissolving in DMSO-d_6/DCl.

Z-L-tyrosine

MMF-1 crystals were soaked in an acetonitrile solution of Z-L-tyrosine (0.49 M) at room temperature for one day. The crystals were collected by filtration, washed with a small amount of acetonitrile, and then dissolved in DMSO-d_6 containing DCl to measure ^{1}H NMR spectroscopy.

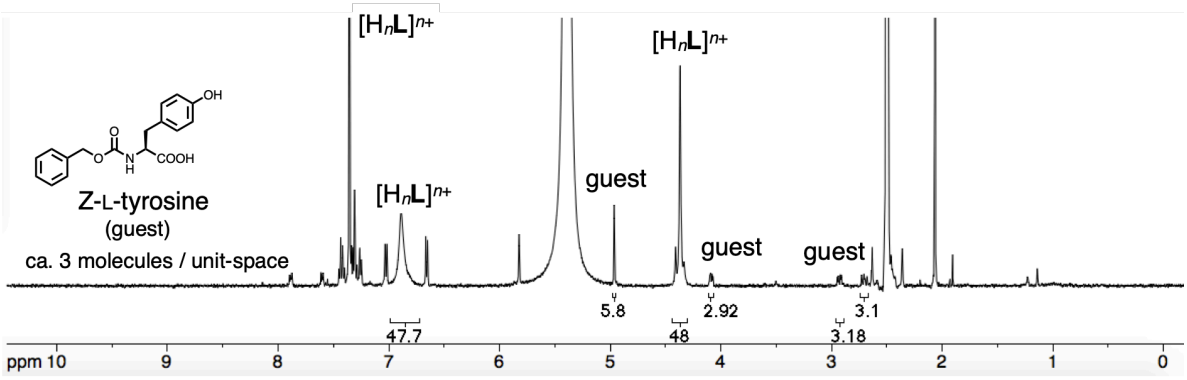


Fig. S21 ^{1}H NMR spectrum (500 MHz, DMSO-d_6, 300 K) of Z-L-tyrosine@MMF-1 after dissolving in DMSO-d_6/DCl.

Selective separation experiment with MMF-1

Procedure

MMF-1 crystals were soaked in a CD_3CN solution containing six amino acids (Z-L-serine, Z-L-tryptophan, Z-L-phenylalanine, Z-L-leucine, Z-L-valine and Z-L-alanine) at equal concentrations (25 mM) at 20 °C for one day. The crystals were collected by filtration, washed with a small amount of CD_3CN, and then re-soaked in CD_3CN for another day to extract the adsorbed guest molecules from the crystals. The extract was analyzed by ^1H NMR spectroscopy.

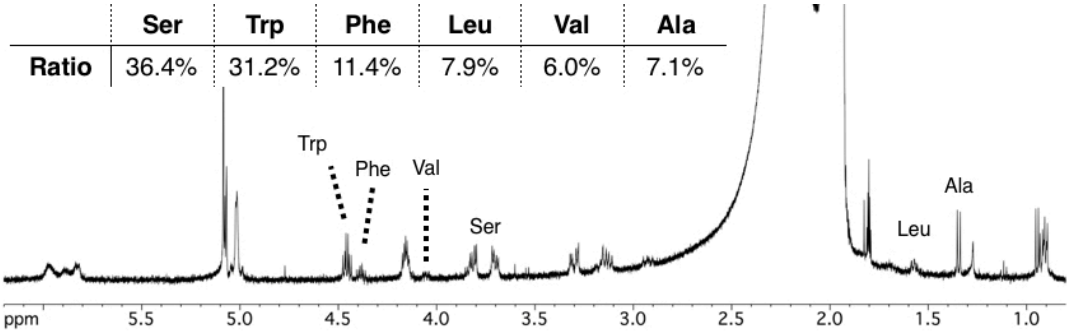


Fig. S22 ^1H NMR spectrum (500 MHz, CD_3CN, 300 K) of the extract from MMF-1 after the selective adsorption experiment.

References

1. S. Tashiro, R. Kubota and M. Shionoya, *J. Am. Chem. Soc.*, 2012, **134**, 2461–2464.
2. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339–341.
3. G. M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3–8.
4. C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. MaCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Cryst.*, 2020, **53**, 226–235.
5. The PyMOL Molecular Graphics System, Version 2.5.2 Schrödinger, LLC.
6. C. B. Hübschle, G. M. Sheldrick and B. Dittrich, *J. Appl. Cryst.*, 2011, **44**, 1281–1284.
7. M. A. Spackman, D. Jayatilaka, *CrystEngComm*, 2009, **11**, 19–32.
8. H. E. Simmons and J. K. Williams, *J. Am. Chem. Soc*., 1964, **86**, 3222–3226.
9. D. Danovich, S. Shaik, F. Neese, J. Echeverría, G. Aullón and S. Alvarez, *J. Chem. Theory Comput.*, 2013, **9**, 1977–1991.