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Planar Mn_4O Cluster Homochiral Metal–Organic Framework for HPLC Separation of Pharmaceutically Important (±)-Ibuprofen Racemate

Reshalaiti Hailili,[†] Li Wang,*[,†] Junzhang Qy,[†] Ruxin Yao,[‡] Xian-Ming Zhang,*[,‡] and Huwei Liu*[,§]

[†]College of Chemistry & Chemical Engineering, Xinjiang Normal University, Urumqi 830054, P. R. China

[‡]School of Chemistry & Material Science, Shanxi Normal University, Linfen 041004, P. R. China

[§]College of Chemistry & Molecular Engineering, Peking University, Beijing 100871, P. R. China

Supporting Information

ABSTRACT: A planar tetracoordinated oxygen containing a homochiral metal–organic framework (MOF) has been synthesized and characterized that can be used as a new chiral stationary phase in high-performance liquid chromatography to efficiently separate racemates such as pharmaceutically important (±)-ibuprofen and (±)-1-phenyl-1,2-ethanediol.

Chiral recognition has become an increasingly significant task in stereochemistry and biologically active compounds as well as the pharmaceutical industry because pure enantiomers may profoundly differ in biological interactions, pharmacology, and toxicity. In many cases, only one of two enantiomers is pharmaceutically active, whereas the other may be inactive or toxic and show unwanted side effects.[1] Taking into account the importance of chiral recognition, tremendous research effort has been devoted to the development of chiral recognition technology including the research and development of chiral recognition materials.[2] Chromatographic techniques based on chiral stationary phases (CSPs) have become an indispensable part of drug discovery for chiral analyses and preparation.[3]

Metal–organic frameworks (MOFs) have potential applications in gas storage, separation, catalysis, and other multifunctional materials[4] because of controllable synthesis, diverse structures, and pore topologies. Emerging chiral MOFs have additional applications in enantioseparation and drug discovery. Recently, some MOFs have already demonstrated great potential as stationary phases (SPs) in both liquid- and gas-phase chromatographic separation.[5,6] However, there are very limited examples showing that chiral MOFs have been used as CSPs for enantioseparation, especially those of important drugs. Ibuprofen, an important nonsteroidal antiinflammatory drug used for relieving pain, helping with fever, and reducing inflammation, has two enantiomers, in which (+)-ibuprofen has been reported to be 160 times more active than its antipode.[7] For improving the selectivity and potency, it is very important to separate the single-enantiomer product of ibuprofen. Although a number of publications have described the resolution of (±)-ibuprofen on different types of CSPs such as amylose and cellulose derivatives, it is rare for SPs showing enantioselectivity and resolution.[8]

In this Communication, we present a planar Mn_4O-based homochiral MOF, $(Me_2NH_2)_2[Mn_4O(D\text{-cam})_4]\cdot(H_2O)_5$ (**1**; D-cam = D-camphorate), that could be used as an efficient CSP for the separation of ibuprofen enantiomers in high-performance liquid chromatography (HPLC). Compound **1** was synthesized from a mixture of $Mn(NO_3)_2\cdot 6H_2O$ and D-camphoric acid in a dimethylformamide–ethanol solution under hydrothermal conditions at 100 °C for 2 days in a yield of 90%. IR spectra, thermogravimetric analysis (TGA), and elemental analysis established the formula (Figures S1 and S2 in the Supporting Information, SI). The bulk purity was confirmed by good agreement between the experimental and calculated X-ray diffraction (XRD) patterns (Figure S3 in the SI).

Single-crystal XRD analysis revealed that compound **1** crystallizes as orthorhombic chiral space group *I*222 (No. 23), featuring a planar tetracoordinated oxygen (ptO) containing a Mn_4O cluster-based homochiral MOF. The asymmetric unit consists of two crystallographically independent Mn atoms, one O atom, and one D-cam ligand in which the C2 and C5 atoms are chiral C atoms (Figure 1).

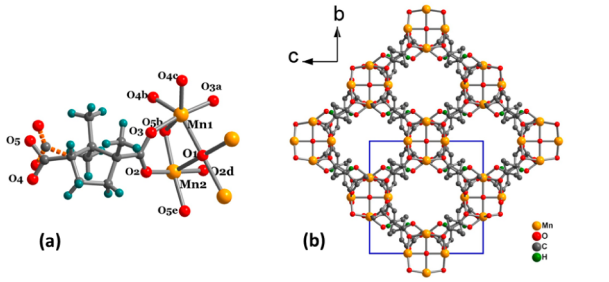

Figure 1. View of (a) the coordination environments of Mn atoms showing the planar tetracoordinated O1 atom and (b) the Mn_4O cluster-based body-centered-cubic framework of $[Mn_4O(D\text{-cam})_4]^{2-}$ showing 1D channels along the *a*-axis direction.

The O1, Mn1, and Mn2 atoms localize at special positions. One of the two carboxylates from D-cam is disordered. The O1 atom has a symmetry of 222 (Wyckoff letter 2c), being a ptO. After considering dual disorder of O5 atoms, the Mn1 atom is hexacoordinated and shows 2 symmetry (Wyckoff letter 4h), coordinated by the O1 atom and five O atoms from four

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carboxylates. The Mn1−O1 bond of 2.381(2) Å is a little longer than other Mn1−O bonds [2.064(6)−2.33(2) Å]. The Mn2 atom has 2 symmetry with the different Wyckoff letter 4i and shows a highly distorted square-pyramidal geometry, coordinated by the O1 atom and four O atoms from four carboxylates. The Mn2−O1 distance is 2.274(2) Å, a little shorter than the Mn1−O1 distance. Four Mn atoms and one O1 atom form a tetranuclear Mn_4O cluster with Mn···Mn distances of 3.293(2) and 4.759(2) Å, in which *cis*- and *trans*-Mn−O−Mn angles are exactly 90 and 180°, respectively. The secondary building units are $Mn_4O(CO_2)_8$ units. Each Mn_4O cluster is linked to its eight neighbors via eight D-cam groups to form an eight-connected body-centered-cubic (bcu) anionic framework with 1D channels formulated as $[Mn_4O(D\text{-cam})_4]^{2-}$. The topology is bcu with a Schläfli symbol of $4^{24}6^4$. The channels are filled by the solvent and Me_2NH_2 cations. As can be seen, the 1D channels along the *a*-axis direction have small square windows sized at ca. 4.8 Å × 4.8 Å (Figures 1b and S7 in the SI).

The most remarkable feature of this structure is ptO in the Mn_4O cluster. The factors stabilizing the ptO in **1** were investigated by all-electron density functional theory computations of a closely related S_4 model $[Mn_4O(OH)_4(HCO_2)_4(HCN)_4]^{2-}$ by the *DMol*[3] program. The most important occupied molecular orbitals of the resulting model complex include σ-bonding molecular orbitals involving 3d valence orbitals of two Mn atoms and the p_xp_y atomic orbitals of the ptO (Figure 2).

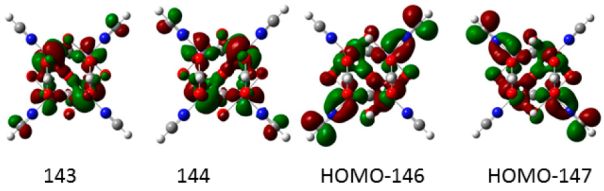

Figure 2. Important molecular orbitals for stabilization of the ptO atom.

Nitrogen, oxygen, and hydrogen sorption experiments have been performed to investigate the pore properties. As shown in Figure S4 in the SI, **1** has a small oxygen gas uptake of 31.34 $cm^3\ g^{-1}$ and negligible sorption amounts for hydrogen and nitrogen gases. The corresponding Langmuir surface area for oxygen gas is 44.72 $m^2\ g^{-1}$. The gas adsorption capacity of **1** is lower than those of the best MOFs but confirms permanent porosity.[9] To estimate the possibility of **1** as a CSP in HPLC, the stability has been investigated by TGA and powder XRD (PXRD; Figures S2 and S3 in the SI).

A good HPLC SP requires a narrow particle-size distribution and suitable particle shape. The scanning electron microscopy (SEM) image for the as-synthesized sample exhibited a uniform cubic shape with 5−10 μm particle size (Figure S5 in the SI), indicating that **1** could be conveniently used as a CSP in HPLC through control of the reaction conditions without any further crushing process. The composition of the mobile phase can play significant roles in retention, selectivity, and resolution in HPLC. The hexane−isopropyl alcohol system was confirmed to be a suitable mobile phase for enantioseparation on the MOF column, and it is found that the hexane−isopropyl alcohol (96:4, v/v) system as the mobile phase could give a prominent baseline resolution for the separation of (±)-ibuprofen and (±)-1-phenyl-1,2-ethadiol with high resolution. The two corresponding enantioseparation chromatograms are exhibited in Figure 3 and Table 1. For (±)-ibuprofen enantiomers, the

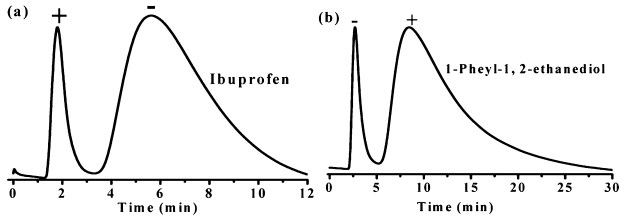

Figure 3. HPLC enantioseparation of (a) (±)-ibuprofen and (b) (±)-1-phenyl-1,2-ethanediol racemates on the column (10 cm length × 4.6 mm i.d.) with hexane−isopropyl alcohol (96:4, v/v) at room temperature with an injection mass of 5 μL at a flow rate of 0.2 mL min^{-1}. The signal of (±)-ibuprofen was monitored at 220 nm, and the signal of (±)-1-phenyl-1,2-ethanediol was monitored at 254 nm.

Table 1. Separation of Racemates in Compound 1

racemate	mobile phase (v/v)	k_1'	α	R_s
(±)-ibuprofen	hexane−isopropyl alcohol (96:4)	0.64	6.48	2.02
(±)-1-phenyl-1,2-ethanediol	hexane−isopropyl alcohol (96:4)	1.45	4.61	1.51

chromatograms show good peaks and baseline or at least 80% valley separation with a good selectivity factor (α = 6.48), anchromatographic resolution (R_s = 2.02) was achieved within only 12 min, and the elution sequence was right-handed and left-handed. The long retention time of (−)-ibuprofen suggests its stronger interaction with the chiral MOF.

The above mobile-phase influence on enantioseparation most probably occurs as a consequence of a distinct competition from solvent adsorption via different forces. In the hexane−isopropyl alcohol system, the MOF adsorbs a sample mainly via a coordination role and hydrogen-bonding forces lead to sample adsorption in a hexane−isopropyl alcohol mobile phase.

To further explore the potential application of **1** for separation of chiral compounds, (±)-ibuprofen was separated under different flow rates on the column MOF (Figure S6 in the SI). As can be seen, the retention factor of (±)-ibuprofen slightly increases with the column pressure. Importantly, the selectivity of (±)-ibuprofen only slightly changes with the flow rate from 0.1 to 0.4 mL min^{-1}, and baseline separation could be achieved within a relatively short time even a high flow rate of 0.4 mL min^{-1}. The results indicate that the column MOF indeed possesses very high enantioseparation ability and is favorable for application in fast analytical enantioseparation.

The column MOF has excellent chiral recognition ability toward racemates because of the influence of the chiral microenvironment of **1**. Structurally, there are 1D chiral channels along the *a*-axis direction with channels (Figure S7 in the SI) with a solvent accessible volume of 22.6% (the countercation not included) by the *PLATON* program.[10] The counterions Me_2NH_2 are filled in the channels. After the van der Waals radii of Mn^{II} ions are taken, the actual window of the channels is about 4.8 × 4.8 Å. This means that (±)-1-phenyl-1,2-ethanediol and (±)-ibuprofen could not enter into the chiral channels. Therefore, chiral recognition mostly depends on the noncovalent interactions of the analytes with the homochiral surface of **1**. Besides the D-cam groups, planar Mn_4O clusters having 222 symmetry can also provide homochiral environments. As far as noncovalence interactions are concerned, hydrogen-bonding and electrostatic interactions should be dominated. Possibly, the O−H···O hydrogen bonds from (±)-ibuprofen and (±)-1-phenyl-1,2-ethanediol donors and D-cam acceptors and electro-

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static interactions between the framework and analysts contribute to chiral recognition. The PXRD patterns after HPLC measurements were coincident with the as-synthesized solid, confirming maintenance of framework **1** (Figure S4 in the SI).

The grand canonical Monte Carlo technique was used in the simulation of adsorption on (±)-ibuprofen both inside the channel and on the surface. XRD reveals that **1** contains too small channels to accommodate (±)-ibuprofen molecules, which was further confirmed by the initial simulation of a sorption isotherm (Figure S7 in the SI). Then, it is reasonable to think that the mutual interaction of the surface of the framework with (±)-ibuprofen is crucial to adsorption and separation. Theoretically, HPLC successful separation should be the outcome of the collective interaction difference of (±)-ibuprofen on many particles of different crystal faces. The sample of **1** for SPs has 5−10 μm particle-size distribution of different shape, and there is no real information on the crystal surface, which complicates the simulations. Given the complexity of the system, a cleaved supercell 30 × 30 × 30 Å^3 was prepared and universal force-field parameters were used. This model supercell meets the accommodations of (±)-ibuprofen on three main low-indexed crystal faces. We assume that surface (+)-D-cam molecules are coordinated to Mn with one carboxylate and the other carboxylate in the surface ibuprofen molecule points out from the surface and is attached to a proton. These simulations consisted of two ibuprofen molecules of adsorbate with the model framework at fixed loading number. The calculated van der Waals energy for adsorbed (+)- and (−)-ibuprofen is −16.5 and −20.1 kcal mol^{-1}, respectively (Figures 4 and S9 and S10 in the SI), which indicates stronger (−)-ibuprofen and framework interactions, in agreement with the separation results.

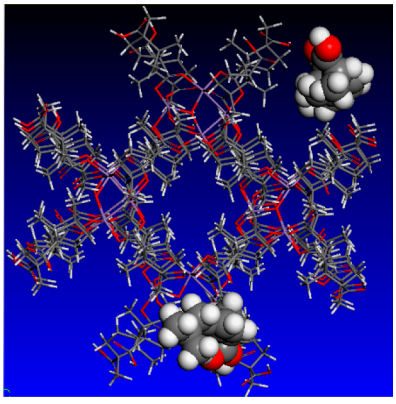

Figure 4. Possible interaction of the (−)-ibuprofen isomer and compound **1** viewed along the *c*-axis direction.

In conclusion, we have reported the first Mn_4O cluster-based 3D homochiral framework with a ptO and enantiopure D-camphoric acid, which was used as a new SP in HPLC. The high-yield synthesis and cheap starting materials indicate practical applications in the future. The activated MOF packed column showed excellent high resolution and good selectivity for chiral compounds including (±)-ibuprofen and (±)-1-phenyl-1,2-ethanediol. The unique features of shape selectivity and multiple active sites provide MOF packed columns a greater potential for HPLC separation. We believe that this work will open a gateway in chiral separation science and broad applications of MOFs in HPLC enantioseparation.

■ ASSOCIATED CONTENT

Supporting Information

Crystal data in CIF format, crystal data and details of data collection and refinement, final coordinates, selected bond distances, bond angles, elemental analysis, IR, a TGA curve, a gas storage curve, SEM images of crystals, HPLC results, and a comparison of PXRD data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wangliresearch@163.com.
*E-mail: zhangxm@dns.sxnu.edu.cn.
*E-mail: hwliu@pku.edu.cn.

Notes

The authors declare no competing financial interest.

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