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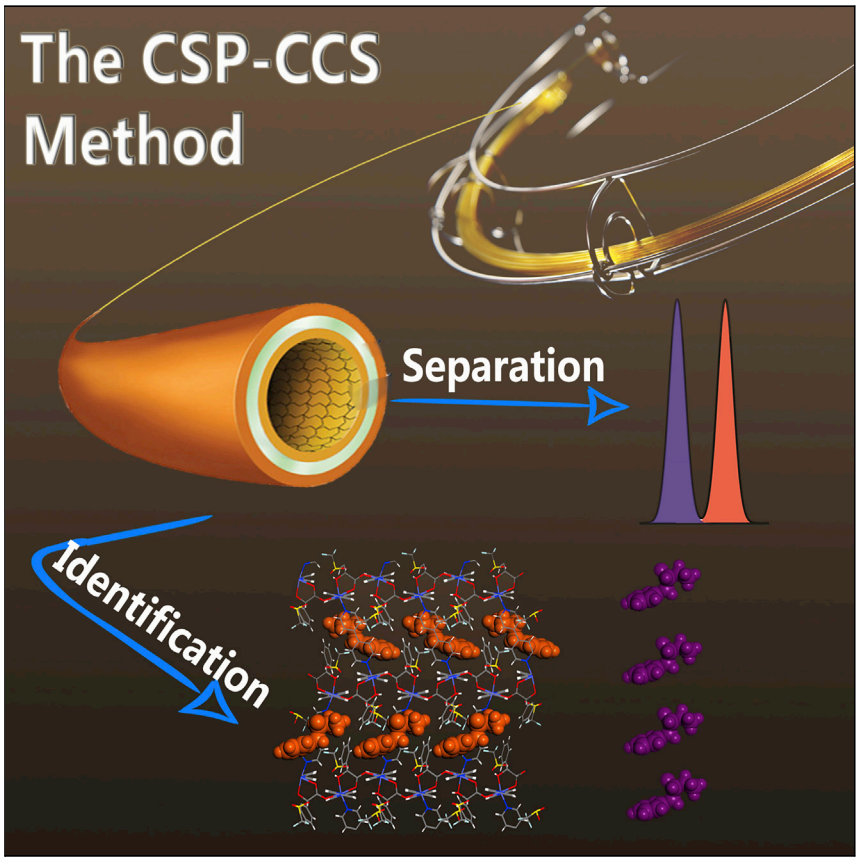

Enantiomeric separation and purification of new chemical entities is an ongoing challenge for synthetic, process, and analytical chemists. The chiral porous material CMOM-3S functions as a chiral crystalline sponge (CCS) for structural determination of either chiral or achiral molecules. Further, CMOM-3S is robust enough to serve as a chiral stationary phase (CSP) for chromatographic separation of enantiomers. A new tool for chiral separation and identification, the CSP-CCS method, is thereby enabled.

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HIGHLIGHTS

Crystal engineering enables the design of a new chiral porous material, CMOM-3S

CMOM-3S functions as both a chiral crystalline sponge and a chiral stationary phase

Practical enantiomer separation and identification are achieved by CMOM-3S

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A Chiral Metal-Organic Material that Enables Enantiomeric Identification and Purification

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SUMMARY

We show that CMOM-3S, a previously unreported porous crystalline metal-organic material that exhibits intrinsic homochirality, serves as a general-purpose chiral crystalline sponge (CCS) and a chiral stationary phase (CSP) for gas chromatography (GC). The properties of CMOM-3S are enabled by nano-sized channels connected to adaptable molecular recognition sites that mimic enzyme-binding sites. Further, CMOM-3S is composed of inexpensive components, facile to prepare, and requires only trace amounts of analyte. When coupled with the thermal and hydrolytic stability of CMOM-3S, these features mean that a coated fused silica capillary column in which CMOM-3S serves as a CSP is both more versatile and more robust than three benchmark commercial columns. That the enantiomer with the longer GC retention time is consistently captured in CCS experiments enables CMOM-3S to serve as a powerful tool to enable both chiral purification and enantiomer identification.

INTRODUCTION

Whereas natural processes can exhibit exquisite discrimination over chirality, the same cannot be said in general about synthetic, process, and analytical chemistry. In 1848,[1] Pasteur kick-started the field of stereochemistry when he reported that crystallization of racemic compounds can afford spontaneous resolution (racemic conglomerates), but this remains the exception rather than the norm. Today, enantiomeric separation and identification matters to technologies as diverse as pharmaceuticals, agrochemicals, flavorings, fragrances, and asymmetric synthesis. However, chiral identification remains a scientific and technological challenge, particularly for new chemical entities (NCEs). The state of the art for separation of enantiomers, chiral chromatography, is based upon the use of chiral stationary phases (CSPs), which require enantiomerically pure reference standards for enantiomer identification.[2] Other techniques such as mass spectrometry and infrared/UV-visible spectroscopy are likewise limited. Here, we reveal that CMOM-3S, a porous crystalline metal-organic material (MOM),[3–5] is the first homochiral MOM that serves as both a general-purpose chiral crystalline sponge[6] (CCS) and a CSP for gas chromatography (GC). CMOM-3S thereby enables CSP and CCS to work synergistically to enable enantiomer purification and identification. This CSP-CCS method requires no reference standard and only trace amounts of analyte (Figure 1).

Chiral separations represent one of the most difficult of preparative and analytical separations because enantiomers have identical physical and chemical properties and most separation methods tend to rely on differences in boiling points or

The Bigger Picture

Enantiomeric identification of new chemical entities (NCEs) and natural products represents an analytical challenge that has an impact on technologies as diverse as pharmaceuticals, agrochemicals, flavorings, and fragrances. Currently, assays to identify enantiomers involve comparison with reference standards, which are unavailable for NCEs. Here, we detail a protocol for chiral discrimination that eliminates the need for enantiomerically pure reference standards and requires only trace amounts of analyte. A thermally and hydrolytically robust homochiral metal-organic material, CMOM-3S, enables chromatographic separations and single-crystal X-ray diffraction to work synergistically because it is stable enough to serve as a chiral stationary phase and its recognition sites are specific enough to act as a homochiral crystalline sponge.

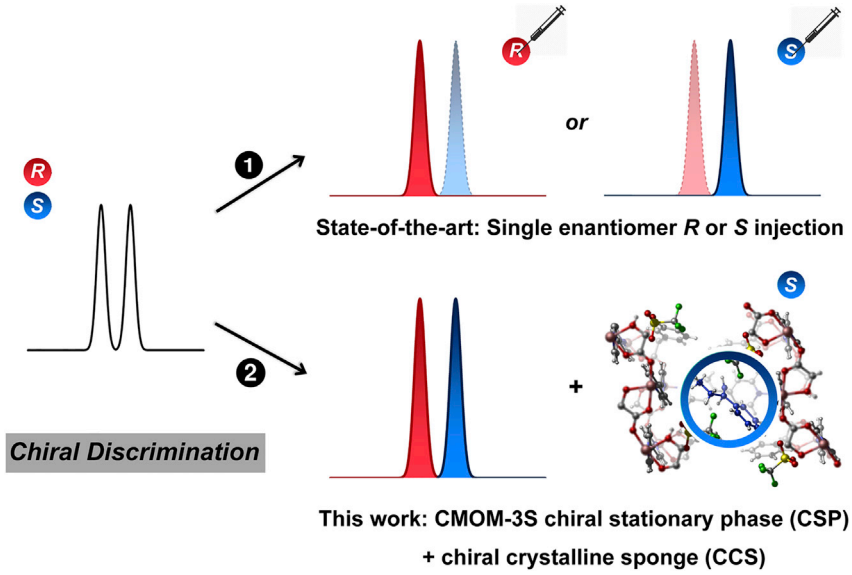

Figure 1. Chiral Separation and Identification by the CSP-CCS Method

Enantiomers can be routinely separated by chromatography, but identification of the absolute configuration of each enantiomer requires an enantiopure reference standard in an additional experiment (method 1). In method 2, a homochiral metal-organic material, CMOM-3S, is used as both a chiral stationary phase for separation and a chiral crystalline sponge for structure determination, eliminating the need for a reference standard.

solubilities.[7] Commercial CSPs are typically based upon polymer composites that incorporate component(s) with chiral recognition features such as polysaccharide, β-cyclodextrin, and homochiral amino acids.[2,8,9] Unfortunately, the current generation of CSPs are expensive to manufacture, lack versatility across all types of chiral analytes, and tend to exhibit poor robustness. Chiral MOMs (CMOMs),[10–17] porous organic cages,[18,19] and chiral covalent organic frameworks[20,21] have also been researched for their potential utility as CSPs[21–25] and membranes[26,27] but have not yet been adapted for commercial use. None of these existing classes of CSPs enable enantiomer identification without access to enantiopure reference standards. This is a considerable drawback with respect to natural products or NCEs that are often only available in trace quantities. The concept of "crystalline sponges," pioneered[6] and developed[28] by the group of Fujita and others,[29–31] exploits the crystallinity and porosity of MOMs to offer a new approach to structurally characterize NCEs, especially those hard to crystallize or only available in trace quantities. However, whereas determination of the absolute configuration of an enantiomer included in a crystalline sponge is feasible and homochiral MOMs are long known,[10–17,32] the current generation of crystalline sponges are achiral[6,28–30] or heterochiral (conglomerate)[31] and unsuited for enantiomeric purification. Consequently, there are not yet any materials that facilitate both separation and structural identification of the components of racemates. This matter is addressed herein.

RESULT AND DISCUSSION

CMOM-3S is a variant of $[Co_2(man)_2(bpy)_3](NO_3)_2]$ (man = *S*-mandelate [CMOM-1S] or *R*-mandelate [CMOM-1R]; bpy = 4,4′-bipyridine), an enantiomeric pair of cationic coordination networks that provide insight into the binding sites of chiral guests such as 1-phenyl-1-propanol.[33] That CMOM-1 is inherently modular makes it amenable to crystal engineering.[34] A hydrophobic variant, CMOM-3S, was prepared by layering

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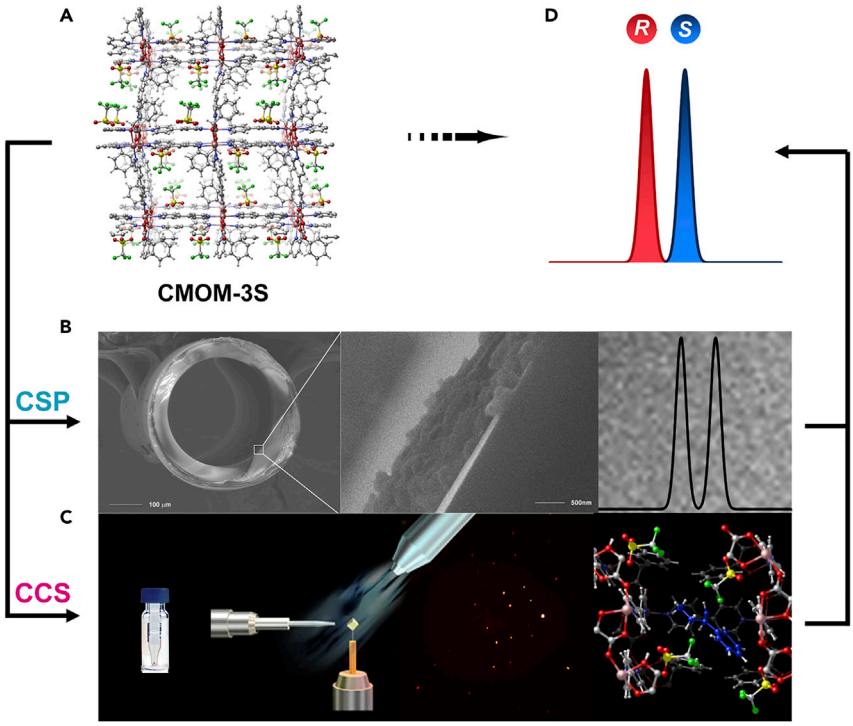

Figure 2. The CSP-CCS Method Enabled by CMOM-3S

(A) The crystal structure of CMOM-3S exhibits 1D channels (C, gray; O, red; N, blue; F, green; S, yellow; H, white; Co, pink; solvent guest molecules are omitted for clarity).

(B) A capillary column is coated by CMOM-3S. Shown are SEM images of the CMOM-3S-coated capillary column, the thickness of the CMOM-3S film, and a chromatogram of separated enantiomers.

(C) The process used for determining the molecular structure of the analyte: a single crystal of CMOM-3S is submerged in racemic analyte to facilitate guest inclusion, the crystal is mounted on a diffractometer, SCXRD data are collected on a conventional diffractometer, and the favorable binding site and the absolute structure of the analyte are determined.

(D) CSP and CCS synergistically afford chiral separation and identification.

$Co(OTf)_2 \cdot 6H_2O$ and enantiopure (*S*)-mandelic acid in MeOH above a 1:1 MeOH/1,2-dichlorobenzene (DCB) buffer layered over a 1,2-DCB solution of bpy. CMOM-3S crystallizes in chiral space group $P2_1$ with **bnn** topology (Table S1). Pore chemistry, size, and shape are adaptable to a variety of guests (Table S2) thanks to the mandelate linker and the orientation of the OTf^- counterion. The maximum pore size of the 1D channel, ca. 0.8 × 0.8 nm after subtracting van der Waals radii, is controlled by the length of the bpy linkers (Figure 2A). CMOM-3S, unlike most MOMs,[35,36] is stable to solvent exchange (Figure S1), heat (Figures S2 and S3), and humidity (Figure S1), prompting us to investigate its utility as a both a CSP (Figure 2B) and a CCS (Figure 2C).

CMOM-3S as a CSP

CMOM-3S can be prepared in an efficient one-step method that affords cuboid nanocrystals dimensions of ~500 nm, as revealed by scanning electron microscopy (SEM) (Figure S4). The powder X-ray diffraction (PXRD) pattern of the as-synthesized nanocrystals matches that calculated and measured for single crystals of CMOM-3S. CMOM-3S nanocrystals were loaded onto a capillary column through a dynamic coating process. Figure 2B illustrates an SEM image of the CMOM-3S coating on

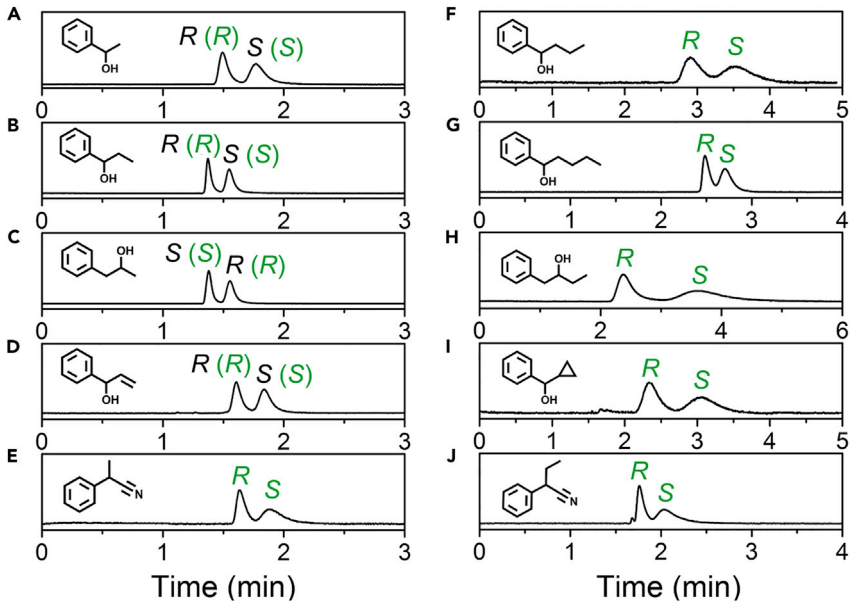

Figure 3. GC Separation of Ten Racemates by a CMOM-3S-Coated Capillary Column (30 m long × 0.32 mm inner diameter)

The following analytes were studied: (A) 1-phenylethanol, (B) 1-phenyl-1-propanol, (C) 1-phenyl-2-propanol, (D) α-vinylbenzyl alcohol, (E) 2-phenylpropanenitrile, (F) 1-phenyl-1-butanol, (G) 1-phenyl-1-pentanol, (H) 1-phenyl-2-butanol, (I) α-cyclopropylbenzyl alcohol, and (J) 2-phenylbutyronitrile. Additional peaks in the chromatograms are attributed to impurities in the as-received samples. Separation conditions are given in Table 1. The absolute configuration of separated enantiomers is confirmed by single-enantiomer reference injection (black) and/or analysis by the CCS method (green). See also Figures S5–S7 for the separation performance of commercial β-DEX 225, Cyclosil B, and Chirasil-L-Val.

the inner wall of the column, which has a thickness of ca. 0.7 μm. The fabricated CMOM-3S-coated capillary column described above was evaluated for its ability to separate racemic mixtures of ten chiral alcohols or nitriles. All ten racemates were separated on the column within 5 min (Figure 3). The chiral separation ability of three benchmark commercial columns was tested against the same racemates: β-DEX 225, Cyclosil B, and Chirasil-L-Val (Figures S5–S7). The optimal separation conditions, separation times of two eluted enantiomers, and resolutions are provided in Table 1. The enantioselectivity of the CMOM-3S-coated column was found to be superior to that of Chirasil-L-Val, with which most of the racemates could not be easily resolved. The resolution values of the racemates were observed to be comparable or better for the CMOM-3S column versus β-DEX 225 and Cyclosil B. Further, the separation time of the racemates on the CMOM-3S-coated column was shorter than with β-DEX 225 and Cyclosil B (e.g., 1.7 versus 13 min for 1-phenyl-2-propanol on β-DEX 225; 4 versus 30 min for 2-phenylpropanenitrile on Cyclosil B). These results demonstrate that CMOM-3S serves as an effective CSP for GC separation of a range of enantiomers. In addition, the durability of the CMOM-3S-coated column was evaluated by studying its performance after 10 months of shelf-life and 1,000 multiple injections. In both instances, there was no loss of performance (Figure S8).

CMOM-3S as a CCS

The supramolecular interactions between the ten analytes and the pores of CMOM-3S were studied by single-crystal X-ray diffraction (SCXRD) after exposing crystals of CMOM-3S to each of the ten racemates. Existing CSPs

Table 1. A Comparison of the Separation Performance of Ten Racemates by a CMOM-3S-Coated Column versus Commercial β-DEX 225, Cyclosil B, and Chirasil L-Val Columns

	CMOM-3S				β-DEX 225				Cyclosil B				Chirasil L-Val			
Analyte	T^a	P^b	t^c	R^d	T^a	P^b	t^c	R^d	T^a	P^b	t^c	R^d	T^a	P^b	t^c	R^d
A	130	150	2.1	1.54	130	150	5.5	1.56	130	150	6.5	1.56	80	100	9.0	1.19
B	150	150	1.7	1.53	120	150	9.7	1.55	150	150	4.6	–[e]	100	125	6.0	1.10
C	150	150	1.7	1.52	110	150	13.0	1.76	130	150	7.2	1.55	150	150	1.7	–[e]
D	140	150	2.1	1.47	120	150	11.0	1.92	140	150	7.5	1.26	100	150	5.0	0.56
E	150	150	2.4	1.45	115	150	13.5	1.53	150	150	4.2	2.28	150	150	1.5	–[e]
F	135	100	4.0	1.51	110	150	20.0	1.61	110	150	30.0	1.31	135	150	4.5	–[e]
G	150	100	3.0	1.42	150	150	8.0	–[e]	150	100	13.5	1.75	100	150	12.0	0.87
H	130	150	5.0	1.52	150	150	6.0	–[e]	130	150	11.0	1.51	80	150	12.0	1.08
I	150	150	3.5	1.57	130	150	15.5	1.73	150	150	9.0	–[e]	100	150	12.0	0.35
J	150	150	2.5	1.42	120	150	14.7	0.45	150	150	5.4	2.22	150	150	2.0	–[e]

[a]Separation temperature (°C).
[b]N_2 pressure (kPa).
[c]Total separation time (min).
[d]Resolution.
[e]Could not be separated. All the separations were performed with optimized conditions.

(e.g., polysaccharides and cyclodextrins)[2] are not amenable to diffraction studies so the precise nature of preferred binding sites in a CSP has not yet been directly observed. That CMOM-3S has an extra-framework cation enables its cavities to adapt to the guest. When coupled with its low-symmetry space group, this adaptability allowed us to directly observe the binding sites of CMOM-3S in high resolution by using a conventional X-ray diffractometer. The absolute configurations of the preferred chiral guest molecules were unambiguously determined and validated for all ten racemates thanks to the anomalous scattering effects of heavy atoms (Co and S). The absolute configuration of the chiral analytes corresponds with the longest retention time, as confirmed by an enantiopure reference standard (Figure 2). The binding preference between CSP and CCS can also be determined without a reference standard. Crystals of CMOM-3S were submerged in racemates as described for the CCS studies, and enantiomer-enriched CMOM-3S crystals were harvested and analyzed with the CMOM-3S column. Figure S9 reveals that the slowest eluent exhibited the higher enantiomeric excess (ee) ratio for all ten racemates. Figure 4 reveals the tight nature of the binding sites for two of the analytes: (*R*, *S*)-1-phenyl-1-propanol ((*R*, *S*)-1P1P) and (*R*, *S*)-1-phenyl-2-propanol ((*R*, *S*)-1P2P). The analytes are located in the channel of CMOM-3S in a similar fashion except for one disordered molecule of 1P2P (Figure 4I), in which the phenyl group and terminal $-CH_3$ moiety of the analyte interacts with the host framework through π···π and C–H···π interactions. Triflate counterions are involved in the formation of C–H···F and O–H···O hydrogen bonding interactions with the analytes, which is presumably a key factor in the observed enantioselectivity. Hirshfeld surface analysis[37,38] of each analyte indicates that the analytes are tightly encapsulated in the chiral channel. A plethora of weak but directional intermolecular forces are therefore responsible for the enantioselectivity toward (*S*)-1P1P and (*R*)-1P2P.

CMOM-3S can serve as a CCS for natural products and biologically active molecules with minute quality. Geraniol and nerol are monoterpenoid isomers present in oils that are used in biosynthesis and as flavors. We exposed a single crystal of CMOM-3S to 20 μL of dichloromethane (DCM) solutions (0.1%, v/v) containing

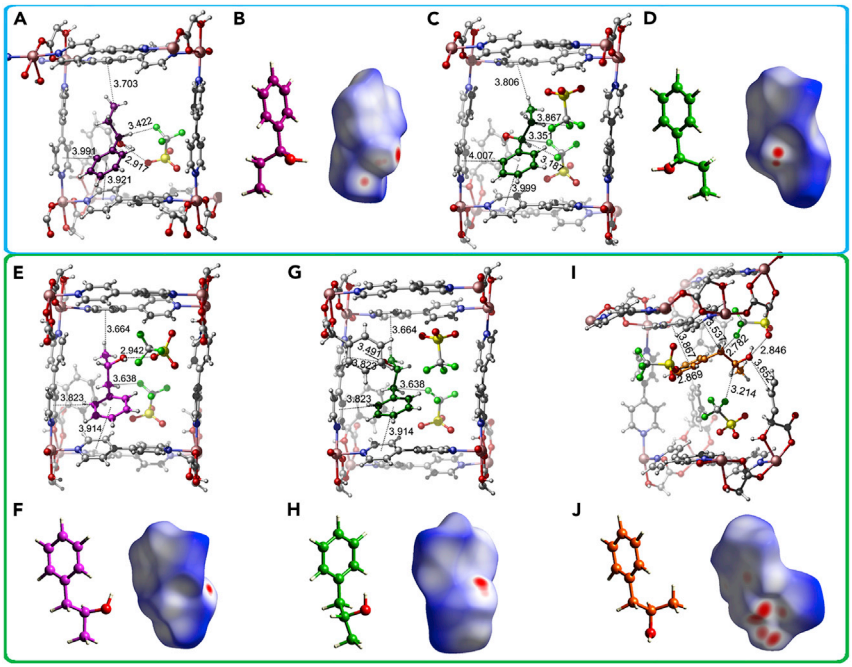

Figure 4. Chiral Binding Sites in CMOM-3S as Determined by SCXRD

The binding sites for 1-phenyl-1-propanol (1P1P, A–D in the blue box) and 1-phenyl-2-propanol (1P2P, E–J in the green box) are sustained by a plethora of intermolecular interactions. Shown are interactions of position-disordered 1P1P molecules (colored magenta and green; A and C) and 1P2P molecules (colored magenta, green, and orange; E, G, and I) in the cavity of CMOM-3S, as well as absolute configuration and corresponding Hirshfeld surface of 1P1P molecules (B and D) and 1P2P molecules (F, H, and J).

17 μg of geraniol or nerol in a 0.3 mL microvial. The screw cap was loosened to enable slow evaporation of CH_2Cl_2 over 2 days. The molecular structures of geraniol and nerol were determined by SCXRD with a conventional X-ray diffractometer as revealed in Figure S10.

The CSP-CCS Method

Whereas CCSs are established for structure identification and MOMs that serve as CSPs are known, the type of synergy between CSPs and CCSs observed here has not been reported previously. CMOM-3S is therefore the first porous material that enables the CSP-CCS method (Figure 2). We attribute its performance to a combination of distinct properties and structural features: (1) CMOM-3S exhibits homochirality with exceptional thermal and hydrolytic stability, which enables fabrication of a robust chiral GC column; (2) the nature of the multiple and directional intermolecular interactions in CMOM-3S creates enzymatic-like binding sites for the accommodation of a range of chiral and achiral guest molecules. The tight stereospecific binding sites are the driving force for chiral recognition and separation; (3) the highly crystalline nature and low-symmetry space group of CMOM-3S enables determination of the absolute configuration of chiral guest molecules and assignment of chirality in the CSP experiments without the need for a reference standard.

To conclude, CMOM-3S is to our knowledge the first porous material that can serve as both a CCS and a CSP. A new reference standard-free method for chiral identification of trace analytes, the CSP-CCS method, is thereby enabled. CMOM-3S demonstrates how CMOMs can address chiral separation challenges that were hitherto

difficult or intractable. We envisage that the CSP-CCS method could be applied to natural product separation, asymmetric synthesis, and drug discovery in future developments.

EXPERIMENTAL PROCEDURES

Synthesis of CMOM-3S Single Crystals

The compound CMOM-3S was synthesized by a procedure analogous to that reported recently. Specifically, a 5 mL methanol solution of 0.4 mmol $Co(CF_3SO_3)_2 \cdot 6H_2O$ (180 mg) and 0.4 mmol enantiopure (*S*)-mandelic acid (60.8 mg) was layered above a 5 mL 1,2-DCB solution of 0.3 mmol bpy (46.8 mg). The buffer solution of 5 mL 1:1 methanol/DCB was layered between the top and the bottom layers to allow slow diffusion for 7 days. Red rectangular prismatic crystals were obtained in ~60% yield. The as-synthesized crystals were exchanged with DCM daily for 5 days to remove DCB. The resultant crystalline samples were stored in neat DCM for all further experiments.

Synthesis of CMOM-3S Nanocrystals

The nanocrystals of CMOM-3S were obtained by the slurry method. Typically, 0.8 mmol $Co(CF_3SO_3)_2 \cdot 6H_2O$ (360 mg) and 0.8 mmol enantiopure (*S*)-mandelic acid (121.6 mg) were stirred in 5 mL of methanol. A solution of 0.6 mmol bpy (93.6 mg) in 5 mL of DCB was added to that solution for 1 day with continuous stirring. The pink nanocrystalline powder was filtrated from the mother solution and washed with DCM (20 mL) ten times. The resultant material was stored in neat DCM for all further experiments.

Fabrication of the CMOM-3S-Coated Capillary Column

A fused silica capillary (30 m long × 0.32 mm inner diameter; Yongnian Optic Fiber Plant, Hebei, China) was pretreated according to the following recipe before dynamic coating: the capillary was washed with 1 M NaOH for 2 hr, ultrapure water for 30 min, 0.1 M HCl for 2 hr, and ultrapure water until the outflow reached pH 7.0.

The capillary was then dried with N_2 at 100°C overnight. CMOM-3S was coated onto the pretreated capillary column via a dynamic coating method. A 3 mL DCM suspension of CMOM-3S (1 mg/mL) was first filled into the capillary column under gas pressure, and then pushed through the column at a constant N_2 pressure of 20 kPa to leave a wet coating layer on the inner wall of the capillary column. After coating, the capillary column was settled for 2 hr for conditioning under N_2. Further conditioning of the capillary column was carried out with a temperature program: 30°C for 10 min, ramp from 30°C to 150°C at a rate of 3°C min^{-1}, and 150°C for 2 hr.

Inclusion of Racemates and Other Guest Molecules in Single Crystals of CMOM-3S

Multiple single crystals of CMOM-3S were submerged in 0.5 mL of neat racemates and other guest molecules at ambient temperature for 5 days. This is the regulated optimal condition according to previous reports[29] for the following reason. By placing multiple crystals in parallel, the probability of selecting a high-quality crystal for SCXRD examination increases. Neat racemates and other guest molecules are used for inclusion of sufficient quantity of guest within the crystal. The equilibrium of preferred enantiomers is reached in guest binding sites after 5 days.

Microgram Scale Inclusion of Geraniol and Nerol

A 20 μL DCM solution of 17 μg of geraniol or nerol was added to a 0.3 mL Qsert low adsorption vial. A single crystal of CMOM-3S was placed at the bottom of the vial

and submerged in the solvent. Then the vial was loosely capped to allow DCM evaporation over 2 days. The crystal was coated in immersion oil for transfer and mounting.

Stability Test

The crystalline sample of desolvated CMOM-3S was exposed to 40°C and 75% relative humidity for 7 days in a desiccator. The condition was achieved with a supersaturated aqueous solution of NaCl maintained at 40°C. After 7 days, the samples were removed from the desiccator and characterized by PXRD.

ACCESSION NUMBERS

Crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre under accession numbers CCDC: 1495053–1495064. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 10 figures, 2 tables, and 12 crystallographic data files and can be found with this article online at http://dx.doi.org/10.1016/j.chempr.2017.07.004.

AUTHOR CONTRIBUTIONS

S.Y.Z. and M.J.Z. conceived and designed the project. S.Y.Z. conducted all synthetic experiments. S.Y.Z. collected and analyzed experimental data including SCXRD data, PXRD data, SEM images, and stability tests. C.X.Y. performed the preparation of the GC column and separation of racemates. C.X.Y., X.P.Y., and S.Y.Z. analyzed the GC data. L.W. revised the SCXRD data. S.Y.Z., W.S., P.C., and M.J.Z. interpreted GC and SCXRD data. S.Y.Z. and M.J.Z. wrote the paper, and all authors contributed to revising the paper.

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