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COMMUNICATION

Engineering a Homochiral Metal–Organic Framework Based on Amino Acid for Enantioselective Separation

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A chiral metal–organic framework possessing an open amphiphilic channel is constructed from a dicarboxylate ligand derived from amino acid and is shown to be an efficient and recyclable chiral solid adsorbent, which is capable of separating racemic secondary alcohols, epoxides, and ibuprofen with very high enantioselectivity.

Selective separation of enantiomers has drawn great attention in pharmaceutical industries because the individual enantiomers of a chiral substance often exhibit different physiological effects and pharmacological actions in a living organism.[1] The separation of enantiomers remains to be a challenge because they may feature identical physical and chemical properties in an achiral environment. Although chromatography based on enantioselective adsorbents such as cyclodextrins and polysaccharides is viewed as a powerful approach for separating enantiomers.[2] The uncertain structures, poor stability, high cost, and narrow versatility have limited their wide applications to some extent.[3] Therefore, it is imperative to develop a new generation of chiral materials to overcome the shortcomings.

Metal–organic frameworks (MOFs) are a novel class of porous crystalline materials which are built from metal nodes and organic ligands.[4] Because the pore environment and functionality can be rationally designed according to desired properties, MOFs have become promising candidates for many applications including gas storage, sensing, catalysis and separation.[5] In particular, the judicious incorporation of enantiopure building blocks would confer the resulting chiral MOFs with tunable pore sizes and functionalities, which offers unique opportunities to develop novel chiral selectors aiming for target separations.[6] During the past decades, some examples of separating enantiomers (such as racemic alcohols, amines, sulfoxides, etc.) by using chiral MOFs have been reported, but only a few exhibit excellent separation performance.[7] In addition, currently the synthesis of versatile chiral selectors bearing designed recognition sites remain to be a challenge.

Herein, we present the synthesis of a new chiral MOF constructed from an amino-acid-derived ligand. Owing to the intrinsic chirality and open amphiphilic channel, this MOF can act as a solid chiral adsorbent and feature excellent capability to separate a variety of chiral aromatic alcohols, epoxides, and ibuprofen with enantioselectivity up to 99.9%.

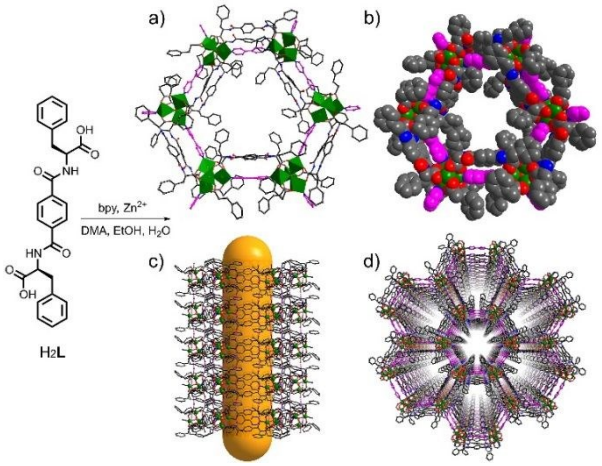

Fig 1. Synthesis of chiral MOF, **1**, and view of its structure: a) the connection of Zn_4O clusters with **L** ligands and 4,4'-bipyridine (bpy) molecules generating a hexagonal window on the ab plane. (green, Zn; grey, C; blue, N; red, O; bpy is highlight as purple for clarity); b) illustration of the space-filling model of the open window along the c-axis; c) the 1D nanotube highlighted as yellow stick generated from the interlayer hydrogen-bonding along the b-axis; d) the packing of the 3D supramolecular structure of **1**.

The enantiopure ligand with C_2 symmetry, (R)-/(S)-H_2**L**, was readily synthesized through the condensation of the terephthaloyl chloride and (R)-/(S)-phenylalanine methyl ester, followed by hydrolysis with a ca. 93% yield. H_2**L** was further characterized by ^{1}H NMR, ESI-MS, IR spectra (Fig. S1 and S2). Reaction of H_2**L**, $Zn(OAc)_2{\cdot}2H_2O$ and 4,4'-bipyridine (bpy) (in a 1:2:1 molar ratio) in a mixture of DMA, EtOH and water at 80 °C for 24 h afforded colorless crystals in a good yield of 75%. The products are stable in air as well as solvents such as CH_2Cl_2,

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MeCN and acetone. Based on single-crystal X-ray diffraction (XRD), thermogravimetric analysis (TGA), and IR spectra, the chemical formula of the MOF can be depicted as $[(Zn_4O)_2(\mathbf{L})_6(bpy)_3]$ (**1**).

Single-crystal X-ray diffraction data analysis confirms that **1** is a porous 2D MOF (Fig. 1), which crystallizes in the chiral trigonal $P32_1$ space group with one-sixth of one formula unit in the asymmetric unit cell. Of the two crystallographically identified Zn ions, Zn1 ion (with occupancy of 1/3), locating in a distorted tetrahedral coordination polytope, is coordinated with one μ_3-O atom and three carboxylate O atoms of three **L** ligands, while Zn2 ion (with occupancy of 1) exists in a distorted trigonal bipyramid polytope and connects with one μ_3-O atom, one pyridyl N atom from bpy and three carboxylate O atoms of three **L** ligands. All of the lengths of Zn-O and Zn-N are within the normal range as previous reports (Table S1).[8] The basic building block of **1**, therefore, is a tetrameric $[Zn_4O(O_2C)_6]$ unit with a C_3 axis passing through Zn1 centre. Each **L** acts as a tetradentate ligand binding with four Zn ions from two Zn_4O clusters, while each tetranuclear Zn_4O cluster can be viewed as a 3-connected node linked by six **L**, affording a 2D network on *ab* plane. The network is further strengthened by the coordination of bpy with Zn1 ions on adjacent Zn_4O clusters (Fig. 1a). Besides, the intermolecular hydrogen bonding (N-H···O = 2.92-3.03 Å) between the amide groups of two adjacent layers direct the packing of the networks along the *b*-axis, leading to a 3D supramolecular structure featuring 1D channels with the largest diameter around 1.5 nm (Fig. 1b-d). What's more, the chiral nanotubular channel in **1** deploys a manifold of functionalized sites, such as hydrophilic amide groups and hydrophobic benzene rings pointing inward, providing an ideal platform to modulate the interactions of the framework with chiral guests for recognition and discrimination of enantiomers.

The consistence of the observed powder XRD patterns and simulated ones demonstrates the phase purity of the bulk sample of **1** (Fig. S3). TGA showed that the framework remained thermally stable up to ~320 °C (Fig. S4). The circular dichroism (CD) spectra of (*R*)- and (*S*)-**1**, which are produced from the two opposite enantiomers of H_2**L** respectively, are mirrored versions of each other, confirming their enantiomeric nature (Fig. S5). The void space in the framework of **1**, which is accessible for guest molecules, occupies about 36.2% of total space calculated by PLATON program. The porosity of **1** can be further proved by dye adsorption tests, which showed that **1** could adsorb 1.41 methylene blue (MB, ~1.25 nm × 0.50 nm × 0.38 nm in size) per formula unit (Fig. S6).

The presence of chiral amphiphilic channel in **1** prompts the exploration of enantiosorption and separation of chiral alcohols because enantiopure alcohols are important intermediates in the pharmaceutical industry.[9] During the initial enantioselective separation, 1-phenylethanol was selected as a model substrate to optimize conditions. After screening the separation conditions including solvents and concentrations (Table S3), we found that 50 mg (S)-**1** immersed in a vial containing 5 mL acetone and 10 mg 1-phenylethanol for 24 h, followed with washing and extraction procedure, which can afford 99.8% ee for the (S)-enantiomer. The result was confirmed by comparing the retention time with that of the standard sample. When (R)-**1** was synthesized following the same procedure as (S)-**1** and used as the adsorbent, (R)-enantiomer of 1-phenylethanol with 99.9% ee was obtained (Fig. S7), indicating that the chiral nature of the included guest molecule is determined by the chirality of the host framework. Besides, the kinetic study indicated that the adsorption of (S)-**1** to 1-phenylethanol reach adsorption equilibrium in 5 h, generating a host-guest complex with a ratio of ca. 3:5 ((S)-**1**: 1-phenylethanol)(Fig. S8).

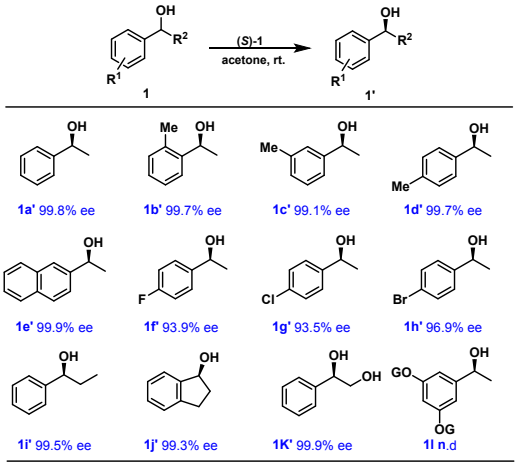

Fig 2. Enantiosorption of (S)-1 towards 1-phenylethanol and its derivatives (for the bulky substrate 1**l**, G = 4-(tert-butyl) benzyl).

With the optimized separation conditions in hand, the enantioselective adsorption capability of **1** toward a variety of aromatic alcohols was investigated (Fig. 2). First, the alcohols with electron-donating substituents on the aromatic ring give rise to significantly high enantioselectivity, with ee values ranging from 99.1% to 99.9% (1a'-1h'). Second, after introducing electron-withdrawing substituents such as -F, -Cl or -Br, on the *para* position of the benzene ring of 1-phenylethanol, **1** also exhibits high enantioselectivities, with 93.9%, 93.5%, and 96.9% ee values for 1-(4-fluorophenyl)ethanol, 1-(4-chlorophenyl)ethanol, and 1-(4-bromophenyl)ethanol, respectively (1f'-1h'). Finally, when the methyl group of 1-phenylethanol was replaced with the ethyl group, the substrate 1-phenylpropanol was separated by **1** with an enantioselectivity at 99.5%. Besides, in the adsorption of the derivative 1-indanol and 1-phenylethane-1,2-diol, **1** exhibits a high enantioselectivity of 99.3% ee and 99.9% ee, respectively. These results clearly show that **1** represents one of the best chiral adsorbents for the separation of racemic alcohols, which is comparable to some excellent framework adsorbents reported by Cui and co-workers. [10]

Notably, control experiments showed that the optically active ligand H_2**L** itself could not resolve the enantiomers of the tested substrates under the identical conditions. This result indicates that the enantioselective recognition and adsorption process is manipulated by the well-assembled chiral framework. In addition, a more bulky aromatic alcohol substrate (1**l**: ~2.2 nm × 1.0 nm in size) was synthesized and subjected to the identical adsorption condition for 5 h. The ^{1}H NMR result reveals that the relative contents of this bulky substrate and internal standard

did not change after the adsorption experiment (Fig. S9). Such a result indicates that the bulky substrate cannot get access to the chiral channel of **1** due to the size exclusion, which conversely supports that the enantioselective adsorption indeed occurs within the chiral channels for other smaller guest molecules.

The crystal structure of **1** reveals that chiral open channels are periodically decorated by amide groups and benzyl groups of ligands, which are fairly proximity to the chiral guest molecules. Such a delicate arrangement of function groups allows the analytes to interreact with the amphiphilic channel via hydrogen-bonding and π-π stacking interactions, which is crucial for the enantioselective discrimination of small organic molecules.[11] Based upon the results of Monte Carlo simulation performed on **1** and (*R*)-/(*S*)-1-phenylethanol, the adsorbed chiral guest molecules tend to be immobilized near a pocket assembled by flexible benzyl groups, which can mainly be attributed to the π-π stacking between the guest molecules and ligands (Fig. S10-13). Besides, simulation demonstrates that adsorption of (*R*)-1-phenylethanol is more energy favourable than the (*S*)-1-phenylethanol, accounting for the affinity to the (*R*)-isomer.

Moreover, to evaluate the durability of the solid adsorbent, we investigated the recycling capability of **1** in the separation of 1-phenylethanol. Six consecutive separation experiments afforded (S)-1-phenylethanol with 99.8%, 99.3%, 99.5%, 99.9%, 99.5% and 99.8% ee, respectively (Fig.S7). Moreover, the PXRD patterns of the recycled sample revealed that **1** maintained its crystallinity although a slight distortion in structure occurred (Fig. S3). This result suggests an excellent recyclability of **1** in multiple runs for 1-phenylethanol separation.

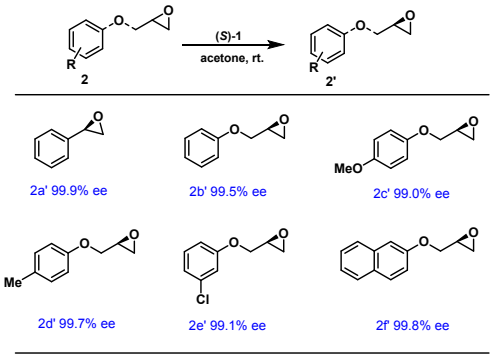

Fig 3. Enantiosorption of (S)-**1** towards styrene oxide and aryl glycidyl ethers.

The excellent enantioselectivity, size selectivity and recycling ability of **1** in the separation of racemic aromatic alcohols encouraged us to examine its potential in the separation of chiral epoxides, since enantiopure epoxides constitute an important class of biologically active compounds and therapeutic drugs, such as antibiotics, antifungal drugs, and HIV-protease inhibitors.[12] Under the identical separation condition, styrene oxide and a variety of aryl glycidyl ethers with electron-withdrawing or electron-donating substituents in the aromatic ring were efficiently resolved by the solid adsorbent with enantioselectivity ranging from 99.0% to 99.9% as shown Fig. 3. Moreover, six consecutive separation experiments performed on phenyl glycidyl ether showed that the enantioselectivities were 99.5%, 99.3% 99.4%, 99.6%, 99.6% and 99.4% ee, respectively (Fig. S14). The wider substrate tolerance and impressive enantioselectivity, compared with the recently reported chiral framework materials for separating racemic epoxides,[13] further indicate that **1** is a promising chiral adsorbent. Its excellent separation performance may also originate from the amphiphilic channel, which offers a unique chiral environment for recognition and discrimination of enantiomers of epoxides.

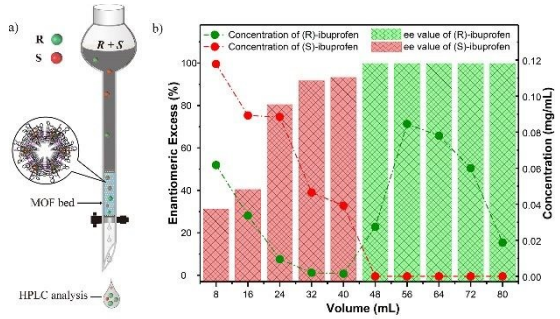

Fig 4. a) Presentative of the enantioseparation of racemic ibuprofen by using glass (S)-**1** column with acetone as the mobile phase; b) Evolution of the enantiomeric excess (Left Y-axis, shown as a column) and the concentration (Right Y-axis, shown as a dot) of each ibuprofen isomer in every 8 mL eluent (red: (S)-ibuprofen, green: (R)-ibuprofen).

After the finding of the excellent enantioselectivity and versatility of **1** in the separation of chiral molecules, we decide to explore its potential as chiral column packing materials for the enantioseparation of drugs. Ibuprofen is selected as a model analyte because (S)- ibuprofen enantiomer exhibits a much stronger inhibitory activity than (R)- ibuprofen when they are used as nonsteroidal anti-inflammatory drug in relieving pain. Moreover, ibuprofen possesses an appropriate molecular size (12.5 × 6.4 × 6.7 Å^3) that fits well to the contour of the open channels. In order to separate racemic ibuprofen, an empty glass column with an inner diameter of ~0.5 cm was set up as shown in Fig. 4a (and Fig. S15), packed with solvent-exchanged crystals of (S)-**1** (360 mg), filled with acetone, and then pressurized under N_2 several times to make the MOF particles packed well. Then, a solution of racemic ibuprofen (6.3 mg, 30 μmol), in which 80 mL acetone served as eluent, ran through the column at near-atmospheric pressure. The resulting eluent at every 8 mL was collected separately and analysed by HPLC. The first 8 mL eluent could afford a 31.2% ee with excessive (S)-enantiomer of ibuprofen, subsequently, the ee value gradually increased until it reached the highest 94% ee at the fifth 8 ml eluent (Fig. S15). After this, enantiopure (R)- ibuprofen (ee up to 99.9%) was obtained in the next 40 mL eluent (Fig. 4b). This result indicates that enantiopure (S)- ibuprofen leaves the column first, due to the preferred interaction of (R)- ibuprofen with (*S*)-**1**, resulting in a slower elution of the (R)- ibuprofen. The separating efficiency of the simple glass column is not as high as commercial HPLC columns, which should be attributed to the large sizes of MOF particles, low MOF loading, and insufficient packing pressure. Nevertheless, the effectiveness of **1** in the separation of racemic drugs, as the MOFs derived from natural

amino acids, made it a promising stationary phase material for practical enantioseparation processes.[14]

The remarkable selectivity of **1** in enantiosorption and separation of chiral molecules has motivated us to obtain the single-crystal structures of the inclusion adducts, which contribute to understanding of the nature of enantioselectivity, but it was unsuccessful due to the poor crystal quality. In this case, the excellent performance of **1** may arise from the combination of chiral channels of appropriate sizes and the amphiphilic inner surface, which is lined up with hydrophilic amide groups and hydrophobic benzyl groups. This combination allows for bioanalogous interaction of the host framework with adsorbate species during the inclusion process.

In conclusion, we present the synthesis and structure of a novel chiral MOF constructed from a C_2 symmetric enantiopure ligand, which is readily available from a natural amino acid. The framework exhibits highly enantioselective abilities to separate a variety of racemic aromatic alcohols, epoxides, and even chiral drug by enantiosorption. Besides, the framework adsorbent can be easily recycled and reused. Further endeavour is aimed at understanding the enantioselective processes of the amino acid-based framework and further studying the potential practical applications in chromatography.

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Conflicts of interest

There are no conflicts to declare.

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