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Enantioselective sorption of alcohols in a homochiral metal–organic framework†

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Single-crystal X-ray diffraction study reveals the host–guest interactions between a homochiral metal–organic framework and two enantiomers of a chiral alcohol providing the key driving force for the enantioselective sorption of alcohols in the framework.

Metal–organic frameworks (MOFs) or porous coordination polymers (PCPs) are an emerging class of porous materials with rich design possibilities, tunable properties and various applications.[1–5] Enantiopure (homochiral) MOFs are synthesized by polycondensation of inorganic and organic building units, where at least one of them (typically the organic ligand) has to be enantiopure.[6–8] Having a regular structure with uniform pore size, chemical functionality and chiral centers, homochiral MOFs are attractive especially for enantioselective applications, such as sorption,[9–12] separation[13] and catalysis.[14–19] Although the synthesis of homochiral MOFs with desired properties and functions is still challenging, a number of rationally designed homochiral MOFs with tunable structural features have been reported recently.[12,19,20] Despite remarkable progress in the chemistry of homochiral porous materials, there are only a handful of studies of intermolecular interactions between chiral porous frameworks and substrates.[11,12,21] Many useful properties of homochiral MOFs, such as chiral sorption and catalysis, arise from enantioselective recognition based on intermolecular interactions. Apparently, this recognition is attributed to the difference in host–guest interaction between an enantiopure porous framework and two different enantiomers of a chiral molecule. Comprehensive studies of the intermolecular interactions would allow the prediction of the enantioselective properties of a homochiral MOF on one hand, as well as a suitable framework design for the best resolution of a given chiral substrate on the other.

Recently, several groups attempted to simulate optimized geometries of chiral substrates to fit in homochiral frameworks and to calculate their interaction energies.[12,21] According to these reports, the calculated energy difference in intermolecular interactions between a porous framework and different enantiomers varies from 1–5 kJ mol^{-1} to 32 kJ mol^{-1}, depending on host–guest systems. In the latter case, such a difference results in up to 60% enantiomeric excess (ee) in enantioselective sorption, which allows partial or even full separation of a mixture of chiral substrates. However, such quantum mechanical calculations are extremely difficult and time-consuming, which poses a serious drawback for this approach. The interatomic van der Waals forces are known to be the weakest interactions, therefore each small correction, otherwise insignificant, needs to be taken into account as even tiny deviations in energy calculations will strongly affect the result.

A more straightforward approach to study the intermolecular interactions is an *in situ* structural investigation of host–guest complexes, *e.g.* by single-crystal X-ray diffraction techniques. Unfortunately, this approach also has a number of limitations due to incomplete guest exchange or severe disorder of chiral substrate molecules inside a porous coordination framework. To date, there are only a few reports describing the synthesis and X-ray diffraction study of homochiral MOF inclusion compounds with only one enantiomer of a chiral guest molecule.[10,22,23] To the best of our knowledge, there are no comprehensive structural analyses of such host–guest complexes with both enantiomers of a chiral substrate, which is indispensable to understanding the nature of enantioselective discrimination. Here, we present the enantioselective sorption properties of the homochiral MOF $[Zn_2(bdc)(S\text{-lac})(dmf)]$ (**1**) towards chiral alcohol substrates and *in situ* characterization of its host–guest complexes **1**·*R*-PhEtOH and **1**·*S*-PhEtOH by single-crystal X-ray diffraction using synchrotron radiation, and Differential Scanning Calorimetric (DSC) methods (*S*-lac = *L*-(−)-lactate; bdc = 1,4-benzenedicarboxylate; dmf = *N*,*N*′-dimethylformamide; PhEtOH = 1-phenyl-1-ethanol).

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† Electronic supplementary information (ESI) available: Experimental details for sorption experiments, analysis of **1**·guest single crystals. CCDC 847107 (**1**·*R*-PhEtOH) and 847108 (**1**·*S*-PhEtOH). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc16209h

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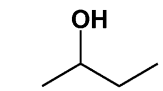
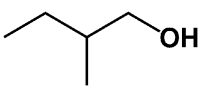
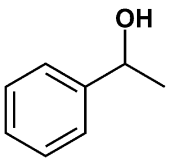
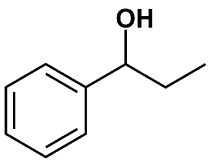
Most interestingly, the O···H–C interactions between substrates and pendant dmf ligands appear to play a critical role in the enantioselective properties of **1**. This is consistent with previous quantum calculations for **1**·PhSOMe complexes, where similar interactions involving dmf ligands were found.[12]

The enantioselective sorption properties of homochiral framework **1** toward chiral alcohols were studied by immersing as-synthesized **1**·DMF single-crystals in their racemic mixtures, followed by chiral HPLC and/or optical rotation measurements. Typically, it takes 18–24 h to reach equilibrium in enantioselective sorption (see ESI†) even for bulkier substrates. Elemental analysis, NMR spectroscopy, TG and single-crystal X-ray diffraction analysis clearly suggested the complete guest exchange and formation of target host–guest complexes, with one alcohol molecule per formula unit of **1**, with the exception of 1-phenyl-1-propanol, the larger size of which results in a final composition of *ca.* 0.75 guest molecules per formula unit of **1**. We should note that only guest DMF molecules in **1**·DMF are exchanged with alcohol substrates, while the dmf ligands coordinated to the metal–organic framework remain intact. Previous results demonstrated that **1** has great enantioselectivity towards chiral sulfoxides with up to 60% ee for methylphenylsulfoxide.[12] As shown in Table 1, the ee values for different alcohol substrates turned out to be relatively modest with the highest ee of 21% (in favor of *S*-isomer) for racemic PhEtOH.

We investigated the thermal decomposition of both **1**·*S*-PhEtOH and **1**·*R*-PhEtOH by DSC in the temperature range 100–300 °C. The decomposition is associated with the release of coordinated dmf and guest phenylethanol molecules. As expected, both processes are endothermic with a specific heat of 173 or 192 kJ mol^{-1} for **1**·*R*-PhEtOH and **1**·*S*-PhEtOH, respectively (see ESI† for details). Assuming that the desorption of dmf contributed more or less the same amount of enthalpy change to the specific heat for both samples, we can estimate that the interaction between the chiral framework and *S*-PhEtOH is 19 kJ mol^{-1} stronger than that for *R*-PhEtOH. This result is consistent with the theoretical study reported earlier.[12,21]

Table 1 Stereoselective sorption of **1** toward chiral alcohols

Substrate	Formula[c]	ee[d], %
	**1**·Bu	14(*R*)[a]
	**1**·MeBu	7(*R*)[a]
	**1**·PhEtOH	21(*S*)[a]/20(*S*)[b]
	**1**·(PhPrOH)$_{0.75}$	12(*S*)[a]/11(*S*)[b]

[a] Determined by polarimetry. [b] Determined by HPLC. [c] Bu: 2-butanol; MeBu: 2-methyl-1-butanol; PhEtOH: 1-phenyl-1-ethanol; PhPrOH: 1-phenyl-1-propanol. [d] Letters in brackets specify the preferable isomer.

Being a convenient substrate and showing the highest sorption enantioselectivity among the simple alcohols, PhEtOH was chosen as a model guest molecule for a detailed study of the host–guest interactions in the porous channels of zinc(II) lactate terephthalate framework **1**. Also, PhEtOH as well as other alcohol substrates studied here are useful precursors for a number of chiral drugs[24,25] such as salbutamol or epinephrine, the optical isomers of which have different bioactivity[26] and, thus, their purification is highly critical. The single crystals of host–guest complexes **1**·*R*-PhEtOH and **1**·*S*-PhEtOH were prepared by soaking single crystals of as-synthesized **1**·DMF in optically pure *R*- or *S*-PhEtOH, respectively, for 11 days to allow full guest substitution and reach diffusion equilibrium along the channels. The single-crystalline specimens of **1**·*R*-PhEtOH (and **1**·*S*-PhEtOH) were collected and examined by single crystal X-ray diffraction analysis using the synchrotron radiation at Pohang Accelerator Laboratory (PAL).§ The data revealed formation of the desired complexes where guest alcohol molecules *R*-PhEtOH or *S*-PhEtOH occupy the chiral channels of the zinc(II) lactate terephthalate **1** host framework. The inclusion of the guest molecules does not cause any notable distortion in the original host structure of **1**·DMF.[27] Upon inclusion, both *R*- and *S*-PhEtOH occupy similar positions inside the porous channels of **1** (Fig. 1).

However, the most notable difference is the direction of the OH group of the chiral guests. In the complex **1**·*R*-PhEtOH, the OH group is interacting with the carboxylate oxygen atoms of the framework ($d(O_{1R}\cdots O_{2B})$ = 3.255(4) Å, $d(O_{1R}\cdots O_{4B})$ = 3.342(4) Å) whereas in the complex **1**·*S*-PhEtOH, the OH group is interacting with the carbon atoms of the coordinated dmf ($d(O_{1S}\cdots C_{3D})$ = 3.327(9) Å), which explains the enantioselective sorption of the chiral alcohol in **1**. Although the above-mentioned distances are the shortest contacts between the substrate and host, they are significantly longer than typical hydrogen bond interactions, which indicates that the overall affinity of **1** towards the chiral alcohol is relatively weak and explains the modest enantioselective sorption of the chiral framework. We also note that the coordinated dmf ligands have already been proved to be involved in the enantioselective recognition of chiral sulfoxides by **1**.[12] According to the *ab initio* quantum calculations, the framework

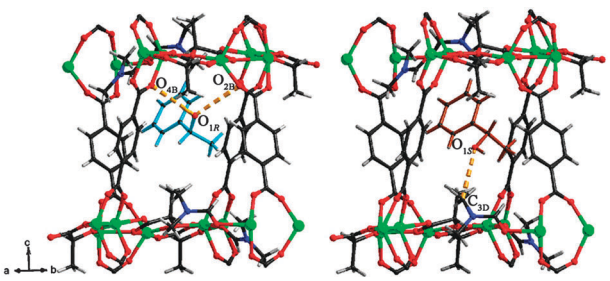


Fig. 1 Structure of host–guest complexes **1**·*R*-PhEtOH (left) and **1**·*S*-PhEtOH (right). C: gray, O: red, N: blue, Zn: green, *R*-PhEtOH: sky-blue, *S*-PhEtOH: brown. Shortest intermolecular interactions are indicated by dashed yellow lines.

1 has higher affinity towards a particular enantiomer, the geometry of which favors the formation of strong C–H···O interactions between dmf and sulfoxide molecules. In our case, similar dmf···guest H-bond interactions appear to be responsible for the enantioselective sorption of **1** in favor of *S*-PhEtOH.

Although the coordinated pendant dmf ligands of **1** do not participate in the formation of the scaffold of the homochiral metal–organic framework, they do play a crucial role in the stereoselective recognition. Such a phenomenon could hardly be predicted *a priori*, but was independently confirmed by theoretical calculations and single-crystal X-ray diffraction study for guest molecules of different nature. This clearly indicates that an in-depth study of host–guest interactions between a porous framework and guest molecules is very important to elucidate the nature of enantioselective recognition. Also, it should provide a clue on how to tweak the porous framework structure to enhance these host–guest interactions for greater enantioselectivity. For example, we believe that the substitution of dmf ligands in **1** with slightly bulkier *N*,*N*′-diethylformamide should shorten the H-bonds and improve the enantioselective discrimination of substrates with different chiral geometries. Such experiments are currently underway.

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Notes and references

§ The diffraction data from single crystals mounted on a loop were collected at 100 K on an ADSC Quantum 210 CCD diffractometer with a synchrotron radiation (λ = 0.80000 Å) at Macromolecular Crystallography Beamline 6B1, Pohang Accelerator Laboratory (PAL), Pohang, Korea. The raw data were processed and scaled using the program HKL2000. The structure was solved by direct methods, and the refinements were carried out with full-matrix least-squares on F^2 with appropriate software implemented in SHELXTL program package. Crystal data for **1**·*R*-PhEtOH. $C_{22}H_{25}NO_9Zn_2$, M = 578.17, orthorhombic, $P2_12_12_1$ (No. 19), a = 10.334(2), b = 11.672(2), c = 20.341(4) Å, V = 2453.5(9) Å^3, Z = 4, T = 100 K, ρ_{calcd} = 1.565 g cm^{-3}, μ(synchrotron) = 2.005 mm^{-1}, 16 254 reflections measured, 5039 unique (R_{int} = 0.0939), R_1 = 0.0479, wR_2 = 0.1324 ($I > 2\sigma(I)$), GOF = 1.136, Flack = 0.058(11). Crystal data for **1**·*S*-PhEtOH. $C_{22}H_{25}NO_9Zn_2$, M = 578.17, orthorhombic, $P2_12_12_1$ (No. 19), a = 10.337(2), b = 11.649(2), c = 20.464(4) Å, V = 2464.2(9) Å^3, Z = 4, T = 100 K, ρ_{calcd} = 1.558 g cm^{-3}, μ(synchrotron) = 1.997 mm^{-1}, 17 272 reflections measured, 5155 unique (R_{int} = 0.0620), R_1 = 0.0481, wR_2 = 0.1318 ($I > 2\sigma(I)$), GOF = 1.019, Flack = 0.006(14). CCDC 847107 (**1**·*R*-PhEtOH) and CCDC 847108 (**1**·*S*-PhEtOH) contain the supplementary crystallographic data for this paper.

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