Communication

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Chiral Crystalline Sponges for the Absolute Structure Determination of Chiral Guests

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ABSTRACT: Chiral crystalline sponges with a pre-installed chiral reference were synthesized. Based on the known configurations of the chiral reference, the absolute structures of guest compounds absorbed in the pores of the crystalline sponges were reliably determined without crystallization or chemical modification.

Absolute configuration determination is the most important, yet probably the most difficult structure analysis of organic small molecules.[1] Single crystal X-ray analysis is one of the only methods that can directly determine absolute configurations, without any chiral references, by observing the anomalous scattering effect,[1c] commonly from heavy atoms involved in analyte molecules (the Bijvoet method). However, this absolute method is not always practical because of the need to prepare the high quality single crystals of analytes and also for synthetic loads for incorporating heavy atom(s) when the anomalous scattering from the chiral guest is weak.

Crystalline sponge (CS) method is an emerging X-ray technique that does not require sample crystallization.[2,3] This method has been recently utilized to determine the absolute configuration of chiral compounds.[2a,d,4,5] Since heavy (iodine) atoms are already installed in the host framework as ZnI_2 metal nodes, incorporation of heavy atoms to guest analytes is unnecessary. However, to observe effective anomalous scattering from the host, initial achiral space group ($C2/c$) must be altered to a chiral space group ($C2$ or $P2_1$) through efficient chirality transfer from the guest to the host. This requirement limits the method to be applicable only to guests that show strong host-guest interaction with a high site occupancy (normally, > 80%).

To overcome this limitation, we designed here a chiral CS, in which a chiral reference is pre-installed in the host framework. We show that the absolute configuration of the guest is easily and reliably determined by observing the relative configurations of the guest with respect to a chiral reference pre-installed in the chiral CS. Yaghi and co-workers have recently reported a chiral MOF available for the absolute structure determination of post-absorbed chiral guest, but the chirality of the host is unknown and has to be judged from the diffraction data.[5c] Our chiral CS contains a chiral reference of known configuration and the guest configuration can be determined more reliably by simply comparing its *relative* configuration with respect to that of the chiral reference.

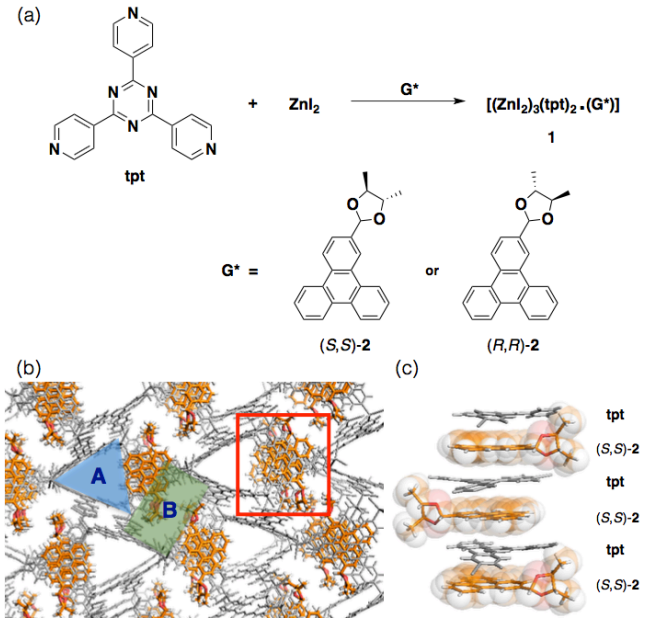

Figure 1. (a) Synthesis of chiral CS **1**. (b) Top view of the X-ray crystal structure of (*S*,*S*)-**1**. The host framework is shown in gray. The chiral reference (*S*,*S*)-**2** (orange) is embedded in the host (gray) through columnar stacking. Solvent molecules are omitted for clarity. (c) Side view of the columnar stacking (inset part of (b)).

Chiral CS, $[(ZnI_2)_3(tpt)_2\bullet(\mathbf{G^*})]_n$ (**1**: tpt = 2,4,6-tris(4-pyridyl)-1,3,5-triazine; **G*** = (*S*,*S*)-**2** or (*R*,*R*)-**2**), was prepared by the "plug-in" synthesis, in which a variety of functional groups can be embedded within the host network by the plug-in of functionalized triphenylenes (Figure 1a).[6] Layer diffusion of a methanol solution of ZnI_2 into a $PhNO_2$/MeOH solution of tpt ligand and (*S*,*S*)-**2** gave yellow needle-like crystals formulated as $\{[(ZnI_2)_3(tpt)_2\bullet(S,S)\text{-}\mathbf{2}]\bullet(PhNO_2)_5\bullet(MeOH)\}_n$ in 34% yield. Nitrobenzene that fills the pores was completely replaced with less coordinating solvents such as cyclohexane or *n*-hexane for facilitating the subsequent guest soaking.[2c] The solvent-exchanged CS, (*S*,*S*)-**1**, was fully characterized by elemental analysis, IR, and X-ray diffraction study (See the Supporting Information; SI). The structure of (*S*,*S*)-**1** was solved in the non-centrosymmetric $P2_12_12_1$ space group. (*S*,*S*)-**1** has two types of 1D channels: triangular and

rectangular channels (pores **A** and **B** in Figure 1b). In a similar fashion, enantiomeric (*R*,*R*)-**1** was also synthesized as yellow needles in 37% yield.

Dimethyl L-(+)-tartrate (**3**) was included into the pores of (*S*,*S*)-**1** by soaking a single crystal (0.12×0.19×0.20 mm^3) of (*S*,*S*)-**1** in a cyclohexane (45 μL)/CH_2Cl_2 (5 μL) solution of **3** (10 μg). After slow evaporation of the solvent at 50 ºC over 2 d, the resulting inclusion complex (*S*,*S*)-**1**•**3** was subjected to single crystal X-ray analysis. The crystal structure revealed four guest **3** molecules, one of which was trapped in pores **A** with 100% occupancy. Based on the known stereochemistry of the chiral reference (*S*,*S*)-**2**, the absolute configuration of (+)-**3** was confirmed to be 2*R*,3*R* (Figure 2). It is worth noting that, in this case, the absolute configuration of (2*R*,3*R*)-**3** was also confirmed from the anomalous scattering (Flack parameter (Parsons) = 0.024(4)).

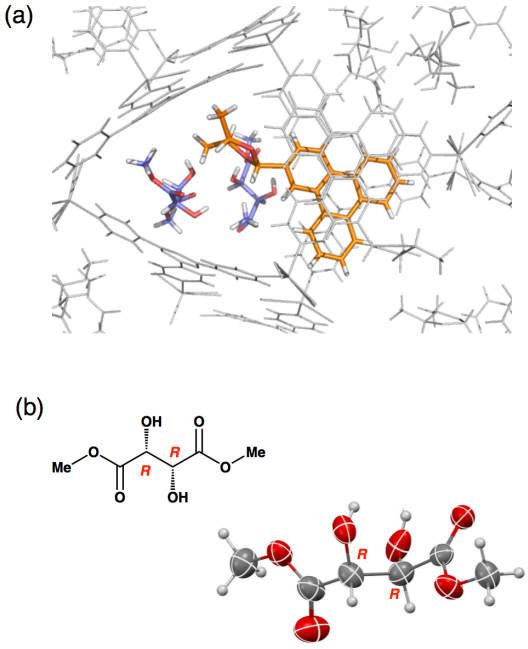

Figure 2. (a) X-ray structure of (*S*,*S*)-**1**•(2*R*,3*R*)-**3**. The analyte (2*R*,3*R*)-**3** and the chiral reference, (*S*,*S*)-**1**, plugged in the host framework are highlighted in color. (b) ORTEP drawing of (2*R*,3*R*)-**3**. Thermal ellipsoids are shown at the 50% probability level. Its *R*,*R* configuration was confirmed by comparing the relative configuration to the chiral reference, (*S*,*S*)-**1**.

Since CS **1** is chiral, the two enantiomers of any chiral guests should show different absorption behavior because of their diastereomeric relationship with respect to the chiral reference. Thus, the two enantiomers of menthol (**4**) were subjected to chiral CS analysis.[7] When (–)-**4** was included in (*S*,*S*)-**1**, the guests were observed in both pores **A** and pores **B** by X-ray diffraction study (Figure 3a). Two guest molecules in pores **A** were found in an asymmetric unit with occupancy of 100% and 64%.

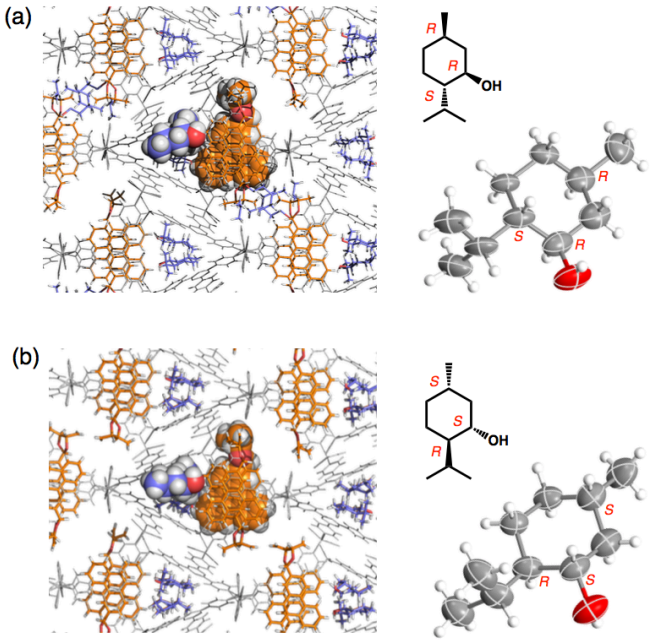

Figure 3. X-ray crystal structures of (a) (*S*,*S*)-**1**•(1*R*,2*S*,5*R*)-**4** and (b) (*S*,*S*)-**1**•(1*S*,2*R*,5*S*)-**4**. Samples for the diffraction study were prepared by the guest soaking of (-)- and (+)-**4** enantiomers with (*S*,*S*)-**1**, respectively. The conformations of the two enantiomers are slightly different because of their diastereomeric relationship to the chiral reference (*S*,*S*)-**1**. Guests are observed both in pores **A** and **B** in (*S*,*S*)-**1**•(1*R*,2*S*,5*R*)-**4** (with 100% and 77% occupancies respectively), whereas they are in only pore **A** in (*S*,*S*)-**1**•(1*S*,2*R*,5*S*)-**4** with 100% occupancy. The guest and the chiral reference are highlighted in color, one pair being presented as space filling model. Thermal ellipsoids are set at the 50% probability level.

One guest engages with a nearby iodine atom in ZnI_2 with an O•••I distance of 3.123 Å. In pores **B**, one slightly disordered guest with occupancy of 77% was observed in close proximity to the dioxolane substituent of (*S*,*S*)-**2** with an O•••O distance of 2.926 Å. By comparing the relative stereochemistry with that of reference (*S*,*S*)-**2**, the absolute configuration of (–)-**4** was clearly determined to be (1*R*,2*S*,5*R*)-**4**. The enantiomeric (+)-**4**, was also included in (*S*,*S*)-**1** but trapped with a slightly different conformation in pores **A** (Figure 3b). Notably, no guest in pores **B**, nor any guest interaction with dioxolane substituent of (*S*,*S*)-**2** was observed with (+)-**4**. The observation of different binding modes in the diastereomeric pairs of (*S*,*S*)-**1**•(–)-**4** and (*S*,*S*)-**1**•(+)-**4** clearly show that the chirality of (–)-**4** and (+)-**4** is discriminated by the chiral pores of **1**. For further confirmation of this chiral discrimination, we analyzed the structure of (+)-**4** with (*R*,*R*)-**1** host (see SI). As expected, (*R*,*R*)-**1**•(+)-**4** revealed the exact mirror-image structure of (*S*,*S*)-**1**•(–)-**4**. In all cases, reasonable Flack parameter values (Parsons) were obtained (< 0.06) and the absolute stereochemistry of the guests was also confirmed by the Bijvoet method.

Furthermore, we applied this method to the absolute configuration analysis of sugar derivative **5**, as sugars are one of the most difficult classes of compounds to be crystallographically analyzed. Empirical configuration

analysis by Mösher method is hardly applied to sugars because of signal overlapping in the NMR analysis. After protecting 2,3- and 4,5-diol groups, D-fructopyranose was subjected to chiral CS analysis with (*S*,*S*)-**1** and its 2*S*,3*S*,4*R*,5*R* configuration was confirmed (Figure 4).

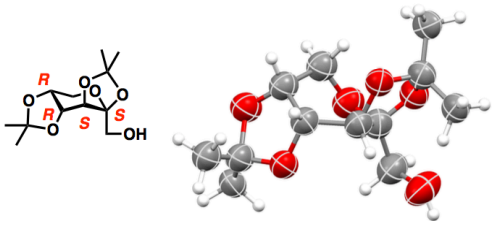

Figure 4. X-ray crystal structure (2*S*,3*S*,4*R*,5*R*)-**5** determined by the chiral CS analysis (occupancy: 54%). Thermal ellipsoids are shown at the 50% probability level.

In combination with chiral HPLC analysis, chiral CS **1** provide a means of chiral LC–SCD (liquid chromatography–single crystal diffraction) analysis for facile and reliable absolute structure determination. A prochiral ketone, phenacyl azide, was reduced to a racemic pair of 2-azido-1-phenylethanol (*rac*-**6**) by $NaBH_4$ reduction. When the crude reaction product, *rac*-**6** (100 μg), was subjected to chiral HPLC analysis, the two enantiomers were separated with retention times of 32.3 and 34.6 min (column: CHIRALPAK IC, solvent: hexane/iPrOH = 99/1, flow rate: 0.5 mL/min at 25 °C). The first and second fractions showed positive and negative CD signals, respectively, at 254 nm (Figure 5a). The first fraction was examined by chiral CS analysis with (*S*,*S*)-**1**. In the asymmetric unit, four guest molecules of **6** were observed, two of which directly interact with (*S*,*S*)-**2** through a hydrogen bond with HO•••O distance of 1.94 and 2.41 Å (Figure 5b). The absolute configuration of the first fraction was thus reliably determined to be *R* (Figure 5c, left). The *S*-configuration for the second fraction was also confirmed by X-ray analysis using (*R*,*R*)-**1** (Figure 5c, right). In a similar way, a racemic pair of 4-bromo-α-methylbenzyl alcohol (*rac*-**7**), obtained from $NaBH_4$ reduction of 4'-bromoacetophenone, was analyzed by chiral HPLC and the first fraction collected (t_{ret} = 58.3 min) was deduced to be (*R*)-**7** using (*S*,*S*)-**1** as the chiral CS and second fraction (t_{ret} = 64.0 min) was assigned to be (*S*)-**7** using (*R*,*R*)-**1** (Figure 5d).

In summary, chiral CS with a pre-installed chiral reference has been developed and successfully used for the determination of the absolute configuration of chiral compounds by comparing the *relative* configurations between the reference and the analyte compound. The only requirement of our method is the concomitant observation of both chiral molecules (the reference and the analyte) in the crystal structure. This represents a great advantage over other commonly used relative methods, such as Mosher's empirical method,[8a-c] co-crystallization method, or sample derivatization with a chiral reference,[8d-e] in which close contact or efficient chiral interaction between the analyte and the reference is essential, yet does not always promise successful determination of the absolute configuration. Because of the crystallization-free protocol, applicability for trace-amount analysis, and, more importantly, high reliability of the relative method relayed to the known configuration of the chiral reference, the present chiral CS is expected to be one of the best tools for absolute configuration determination.

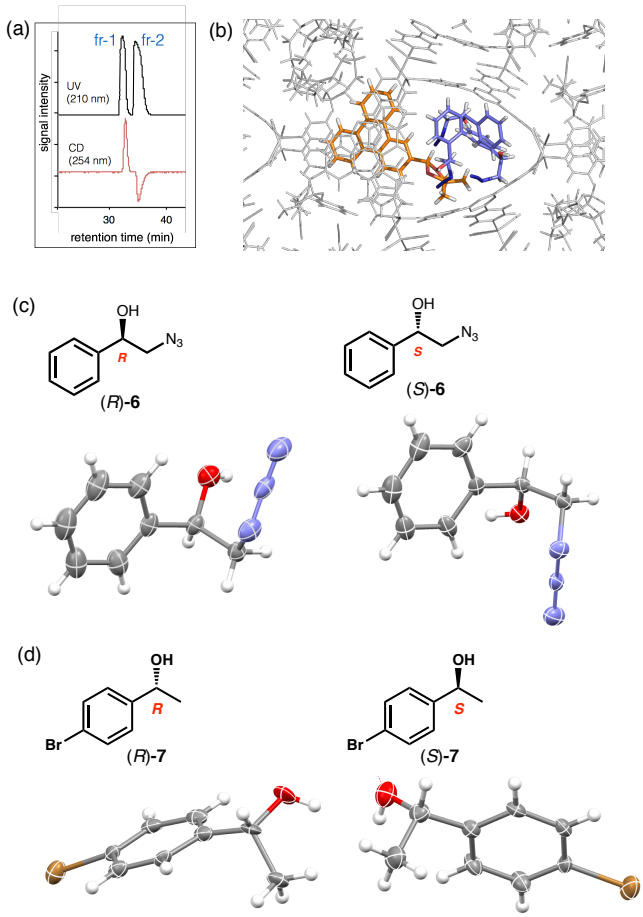

Figure 5. (a) HPLC chromatogram of the racemic pair of **6** (black: UV absorption at 210 nm; red: CD signal at 254 nm). (b) X-ray structure of (*S*,*S*)-**1**•(*R*)-**6**. A sample for the diffraction study was prepared by the guest soaking of the first fraction in the HPLC purification into (*S*,*S*)-**1**. The guest (two molecules) and the chiral reference in one pore are highlighted in color. (c) Left: ORTEP drawing of (*R*)-**6** found in the (*S*,*S*)-**1**•(*R*)-**6** structure (occupancy: 100%); right: ORTEP drawing of (*S*)-**6** found in the (*R*,*R*)-**1**•(*S*)-**6** (occupancy: 94%). (d) Left: ORTEP drawing of (*R*)-**7** found in the (*S*,*S*)-**1**•(*R*)-**7** structure (occupancy: 82%). The analyte (*R*)-**7** was obtained as the first fraction of the chiral HPLC purification; right: ORTEP drawing of (*S*)-**7** found in the (*R*,*R*)-**1**•(*S*)-**7** (occupancy: 86%). The analyte (*S*)-**7** was obtained as the second fraction of the chiral HPLC purification. Thermal ellipsoids are shown at the 50% probability level.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

Materials and methods; experimental procedures and characterizations; X-ray crystallographic data.

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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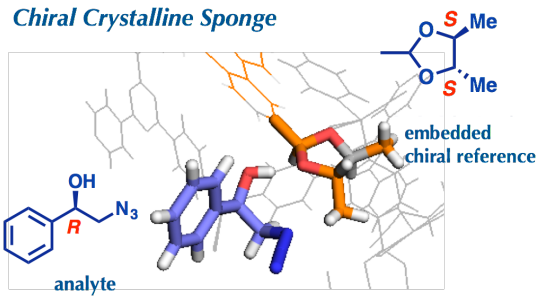
Chiral Crystalline Sponge
S
Me
O
O
S
Me
embedded
chiral reference
OH
N3
R
analyte