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Application of a chiral metal–organic framework in enantioselective separation†

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A modular approach for the synthesis of highly ordered porous and chiral auxiliary (Evans auxiliary) decorated metal–organic frameworks is developed. Our synthesis strategy, which uses known porous structures as model materials for incorporation of chirality *via* linker modification, can provide access to a wide range of porous materials suitable for enantioselective separation and catalysis. Chiral analogues of UMCM-1 have been synthesized and investigated for the enantioseparation of chiral compounds in the liquid phase and first promising results are reported.

Metal–organic frameworks (MOFs) are highly porous, crystalline coordination polymers generated from metal atoms or clusters as "nodes" and organic linkers as nodal "connectors".[1] Following their recent development, MOFs have found several attractive applications, including gas separation, gas storage and selective catalysis.[2] Among others, the properties and utilities of the MOFs depend on their pore size and shape, the interior and exterior surfaces, and the functional groups employed. Intriguingly, the properties of the MOFs can be easily modified, but minor changes in the synthetic process, linker or the metal often lead to the dramatic changes in their structure and properties.[3]

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Whereas various porous materials including zeolites, activated carbon, silica gel and various polymer resins have been shown to be useful stationary phases in gas chromatography,[4] liquid chromatography[5] and electrochromatography, MOFs are far less explored. Recently, it has been shown that MOFs are able to separate mixtures of compounds in small volumes.[6] Because of their defined architectures, accessible volumes, pore size *etc.*, these porous solids can be used as a promising stationary phase for the separation of organic compounds. Moreover, examples of *in situ* incorporation of chiral auxiliaries into MOF building blocks followed by their subsequent utilization in the enantioseparation are rare and to the best of our knowledge no high performance liquid chromatography (HPLC) enantioseparation by chiral porous MOFs has been reported so far.

One possible way to form chiral materials is utilizing privileged chiral ligands like BINOL or BINAP in the construction of MOFs.[7] Thereby, amorphous solids are generally obtained and control of the resulting topology and porosity is difficult.[7,8] An alternative strategy is the attachment of chiral auxiliaries to well-known linkers, either by postsynthetic modification[9] or by starting from auxiliary substituted linkers in the first place. In the latter case, the synthesis of MOFs with desired chemical interactions, topology, and pore sizes seems to be within reach.[3a]

Herein we report the synthesis, structural characterization, and separation performance of chiral modified UMCM-1 structure (Chir-UMCM-1). UMCM-1 ($Zn_4O(BTB)_{4/3}(BDC)$) was discovered by Matzger *et al.* and is a high surface area mesoporous MOF which consists of 1,4-benzenedicarboxylate (BDC) and benzene-1,3,5-tribenzoate (BTB) linkers.[10] In the Chir-UMCM-1 reported here, the BDC linker was replaced with chiral auxiliary substituted BDC (ChirBDC).

For the ChirBDC linker synthesis, 2-bromoterephthalic acid was converted into dimethyl 2-bromoterephthalate. This was coupled with enantiopure chiral (*S*)-oxazolidinone (Evans auxiliary)[11] in the presence of CuI, K_2CO_3 and dimethylethylene diamine in toluene. Chiral auxiliary substituted BDCs were obtained by basic hydrolysis of the corresponding esters (Scheme S1, ESI†). The linkers were used for the synthesis of ChirMOFs.

We modified the ratio of reagents and reaction conditions of the original UMCM-1 synthesis procedure in order to prevent

the formation of chiral MOF-5 analogue or MOF-177 (for more details see ESI†).

Thus, $Zn_4O(BTB)_{4/3}$(*i*Pr-ChirBDC)$(DEF)_{19}(H_2O)_6$ (*i*Pr-Chir-UMCM-1, **1**) and $Zn_4O(BTB)_{4/3}$(Bn-ChirBDC)$(DEF)_{20}(H_2O)_8$ (Bn-ChirUMCM-1, **2**) were obtained as single phase materials (the composition was derived from TGA and elemental analysis).

The powder (Fig. S1, ESI†) and single crystal X-ray diffraction experiments revealed that the compounds are isotypic to UMCM-1. The structures of **1** and **2** were refined in chiral space group $P6_3$ with similar cell parameters.‡ This led to the absence of an inversion center, which is present in UMCM-1 at the center of gravity of the BDC linker. The structures of both compounds consist of Zn_4O^{6+} clusters interconnected into the 3D-network by 4 BTB and 2 substituted BDC linkers. As expected, the framework structure, topology and pore shape of Chir-UMCMs are similar to UMCM-1.[10] Compound **1** exhibits positional disorder of the BDC oxazolidinone substituent over two equally occupied positions, arranged on the same side of the phenyl ring. Refinement of structure **2** shows disorder of the nitrogen atom of the oxazolidinone over four positions. Unfortunately, only the nitrogen atom and not the chiral substituent itself could be located crystallographically. Hence, they were modelled separately for each position using Forcite geometry optimization tool of Material Studio 5.0 (Accelrys Software, Inc., San Diego, CA, USA). It has been shown that in both cases chiral substituents occupy the positions in the trigonal microporous cages (Fig. 1). The successful incorporation of the substituted BDC linker was proven *via* IR, liquid and solid state NMR experiments (see ESI†).

The $^{13}C\{^1H\}$ cross-polarization (CP) MAS NMR spectra of compounds **1** (*i*Pr-ChirUMCM-1) and **2** (Bn-ChirUMCM-1) were measured at −26 °C (Fig. S19, ESI†). At this temperature, the signals due to the chiral side groups are clearly detectable in contrast to the room temperature spectra (Fig. S19, ESI†). It should be noted that the spectra in general exhibit a pronounced temperature dependence which may be caused by the presence of thermal motions within the relatively flexible framework and/or minor temperature-induced structural changes. Thermal motions lead to decreasing signal intensities in CP spectra. The aforementioned signals due to the chiral side groups are weak at room temperature but become more intense at −26 °C. This behavior indicates the presence of thermal motions especially for the side groups.

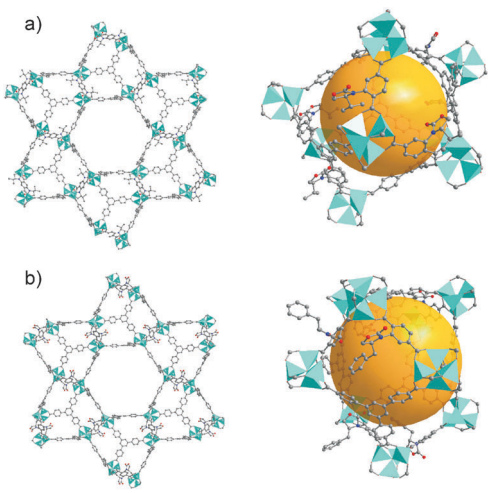

Fig. 1 (a) Structure of *i*Pr-ChirUMCM-1 (**1**). (b) Structure of Bn-ChirUMCM-1 (**2**). Left: view along the *c* axis; Right: micropore containing the chiral fragment (only one position is shown for disordered oxazolidinone groups). Hydrogen atoms are omitted for clarity.

Solvent accessible voids, calculated using PLATON,[12] are 79.4 and 78.2% for compounds **1** and **2**, respectively, which are slightly lower than for non-substituted UMCM-1 (82.8%). The porous chiral framework could be also obtained after solvent removal. The porosity of the activated compounds was verified *via* nitrogen and hydrogen (Fig. S3, ESI†) physisorption experiments. The multipoint BET surface areas calculated from nitrogen physisorption measurements at −196 °C are 3310 m^2g^{-1} for **2** and 3770 m^2g^{-1} for **1**. The pore volumes are 1.78 $cm^3\ g^{-1}$ and 2.03 $cm^3\ g^{-1}$, respectively. The hydrogen adsorption capacities are 1.48 wt% for **1** and 1.21 wt% for **2** at 1 bar and −196 °C.

The Bn-ChirUMCM-1 was tested as the stationary phase for the HPLC column. Particles with spherical shape of less than 100 μm and a narrow particle size distribution are important requirements for a good stationary phase of high performance liquid chromatography. Since the as-synthesized particles are much too large and needle-shaped, they were manually pestled (Fig. S20, ESI†). Fractionation could not be performed, because of the limited amount of the samples. Unfortunately, the crushing process gives a broad particle size and shape distribution (estimated from the SEM image, Fig. S20, ESI†), which seems not to be easily reproducible. Nevertheless, to control the packing quality, the pressure drop of the columns was measured after the packing procedure with a flow of 0.5 ml min^{-1} *n*-heptane at 30 °C. Tests for the stability of the MOF were made by dispersing the Bn-Chir-UMCM-1 in isopropanol. From the XRD (Fig. S2, ESI†) it can be seen that the crystal structure of the material retains. To guarantee the same packing quality, only Bn-ChirUMCM-1 columns are used which have pressure drops between 25 and 30 bar. All other columns have been rejected. For the comparison between the UMCM-1 column and the Bn-ChirUMCM-1 column, a more densely packed unmodified UMCM-1 column with a pressure drop of 70 bar was used.

Thus, shorter retention times on the unmodified UMCM-1 column cannot be caused by an inferior packing quality but must be caused by the linker modification with the chiral auxiliary.

Since the chiral auxiliary group of the Bn-ChirUMCM-1 is a (4*S*)-benzyl-2-oxazolidinone, oxazolidinones were chosen as appropriate analytes in the first attempt. Indeed one can clearly see a selective interaction with the selector, because on the unmodified UMCM-1 column no retention was observed, whereas on the chirally modified UMCM-1 a significant retention occurs. Unfortunately, we could not find an enantio-selective interaction on the chirally modified UMCM-1 (see Table S2, ESI†). Probably, the difference in the free adsorption enthalpies of the enantiomers is too small to observe enantioseparation on that short column. Thus, we decided to choose analytes expecting a stronger interaction with the chiral selector by hydrogen bonding. Therefore, 2-butanol, as a representative of a chiral aliphatic alcohol,

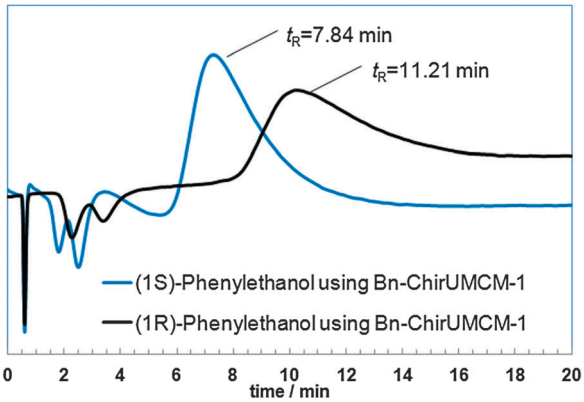

Fig. 2 Chromatogram of 1-phenylethanol enantiomers using Bn-ChirUMCM-1.

and 1-phenylethanol, as a representative of a chiral aromatic alcohol, were tested. Both showed a significant selective interaction with the chiral column compared to the non-modified column (see Table S2, ESI†).

With 1-phenylethanol as an analyte a much stronger interaction with the chiral selector was observed than with 2-butanol. Furthermore, with the 1-phenylethanol enantiomers enantioselective interactions with the chiral selector can be found (see Table S2, ESI†). Fig. 2 depicts the chromatograms of the pure 1-phenylethanol enantiomers measured on the chirally modified Bn-ChirUMCM-1 column (for results on the unmodified UMCM-1 see Fig. S21, ESI†). The selectivity α and the resolution R_S for the enantiomer separation can be calculated as 1.6 and 0.65, respectively. The resolution of less than 1 indicates a significant overlap of the peaks, which is due to their strong tailing. For further optimization of the separation efficiency, the length of the column must be adapted and/or a gradient elution is necessary.

The use of 1-phenylethylamine as a 1-phenylethanol analogue with an amino-function instead of the hydroxyl-function was not successful, because the interactions were too strong already even with the unmodified UMCM-1. The same holds true for the amino acid D,L-alanine.

After around 200 injections the column material was characterized by nitrogen adsorption and PXRD. No significant changes were detected.

In summary, we have prepared and characterized two porous chiral metal–organic frameworks (*i*Pr-ChirUMCM-1 and Bn-ChirUMCM-1). Bn-ChirUMCM-1 was successfully used as the stationary phase for HPLC applications. Namely, 1-phenylethanol as analyte showed both selective and enantioselective interactions with the MOF. The potential for enantioseparation can be clearly seen from the selectivity, which is high enough to reach enantiomer separation. However, the resolution was too low to reach peak separation under the chosen conditions. The results presented herein are promising for the proof of principle and in the future these valuable chiral materials should be useful for the separation of enantiomers in the liquid phase.

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Notes and references

‡ Crystal data for **1**: $C_{50}H_{32}NO_{15}Zn_4$, M = 1148.25, hexagonal, a = 41.459(6), c = 17.561(4) Å, V = 26140(7) Å^3, T = 293 K, space group $P6_3$, Z = 6, 80 884 reflections measured, 28 147 unique (R_{int} = 0.0501). The final R_1 was 0.0532 and wR_2 was 0.1181 (all data). **2**: $C_{54}H_{30}NO_{15}Zn_4$, M = 1194.27, hexagonal, a = 41.414(6), c = 17.637(3) Å, V = 26197(7) Å^3, T = 293 K, space group $P6_3$, Z = 6, 83 244 reflections measured, 28 628 unique (R_{int} = 0.0354). The final R_1 was 0.0533 and wR_2 was 0.1115 (all data).

CCDC 831931 and CCDC 831930 contain the supplementary crystallographic data for **1** and **2**, respectively.

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