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SHORT COMMUNICATION

Solvent-induced enantioselectivity reversal in a chiral metal organic framework

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Solvent-induced enantioselectivity reversal is a rarely reported phenomenon in porous homochiral materials. Similar behavior has been studied in chiral high performance liquid chromatography, where minor modifications to the mobile phase can induce elution order reversal of two enantiomers on a chiral stationary phase column. We report the first instance of solvent-induced enantioselectivity reversal in a homochiral metal organic framework. Further, we highlight the complex enantioselectivity behavior of homochiral metal organic frameworks toward racemic mixtures in the presence of solvents through racemate-solvent enantioselectivity and loading experiments as well as enantiopure-solvent loading experiments. We hypothesize that this interesting selectivity reversal behavior is likely to be observed in other competitive adsorption, nonchiral selective processes involving a solvent.

KEYWORDS
enantioseparation, metal organic framework, selectivity reversal, separation

Metal organic frameworks (MOFs) are an exciting class of porous materials consisting of metal ions or clusters coordinated to organic multivalent ligands to form multi-dimensional structures [1]. MOFs have attractive properties for applications across a wide range of fields from gas separations and storage [2–6], to sensing [7, 8], and controlled release of target molecules [9–11]. Chiral versions of MOFs are widely reported [12, 13], typically containing one or more homochiral ligands. These frameworks usually crystallize in a chiral space group, adopting chiral structures. Chiral frameworks have been widely reported based on a range of homochiral molecules such as lactic acid [9, 14, 15], proline [16], and saccharic acid [17], to name a few. The ZnBLD framework is a homochiral MOF with the formula [Zn_2(bdc)(L-lactate)(DMF)] where bdc = 1,4-benzenedicarboxylate [14]. ZnBLD has been shown to enantioselectively adsorb one enantiomer from a racemic mixture such as chiral sulfoxides and alcohols [14, 18]. A representation of the ZnBLD structure is shown in Supporting Information Figure S1 to aid the reader.

The enantioselective properties of ZnBLD and other chiral MOFs can be exploited for chiral separation applications [19, 20]. These materials can be engineered to allow lower energy separation processes toward enantiopure chemicals from racemic mixtures making them attractive candidates for industrial chiral separation processes. Understanding the chiral separation mechanism is essential for improving the separation efficiency and advancing the separation process toward industrial processes [21]. However, conditions affecting the chiral separation process in chiral MOFs are rarely studied, overlooked, or

Article Related Abbreviations: ee%, enantiomeric excess percentage; PXRD, powder X-ray diffraction

sometimes appear to be randomly chosen, giving little to no mechanistic separation detail.

In chiral chromatography, enantiomer elution order reversal is a phenomenon observed in HPLC, whereby, upon a certain (often subtle) change in the analysis conditions, the elution order of two enantiomers may be reversed. Changes in analysis temperature were first shown to induce elution order reversal and the corresponding equations were reported [22]. Later, solvent-induced enantioselectivity reversal was also reported. Unlike temperature-induced elution order reversal which can be explained with reported equations, the solvents play a much more elusive role in reversing the elution order of the enantiomers. The enantioseparation of 1,1′-bi-2-naphthol was investigated on a polysaccharide-based chiral stationary phase. Upon changing the polar modifier (1.37 M concentration) present in the n-hexane mobile phase from ethanol to 1-propanol, a reversal in elution order and improvement in enantioselectivity was observed [23]. In another study, vibrational circular dichroism coupled with density functional theory calculations were employed to investigate the enantioseparation of two chiral analytes on a cellulose and amylose column under chromatographic conditions. Conformational changes in the amylose stationary phase were reported as being responsible for causing the reversal in elution order for one of the analytes [24].

Solvent-induced enantioselectivity reversal in crystalline porous materials has been previously reported for a leucine-based cage material of the general formula $M_{12}L_{12}$, where the material preferentially adsorbed the (R) enantiomer of 2-methyl-2,4-pentanediol in methanol but the (S) enantiomer in heptane [25]. Similarly, Peng et al. reported large changes in the enantioseparation (but no solvent-dependent enantioselectivity) of 1-phenylethylamine in the presence of other solvents, ranging from 10 ee% (enantiomeric excess) in chloroform to 88.5 ee% in methanol [26].

In this report, through varying the solvent in the adsorption phase of the enantioseparation process, we observe significant changes in the enantioseparation behavior of ZnBLD toward racemic 1-phenylethanol, 2-butanol, and limonene. We further study solvent-dependent enantioselectivity through enantiopure loading experiments and highlight the complex separation behavior of metal organic frameworks. To the best of our knowledge, this is the first report of solvent-induced enantioselectivity reversal observed in a chiral MOF.

In order to investigate the effect that solvents have on the ee% and loading, chiral separation and guest loading experiments were conducted by soaking ZnBLD crystals in 1:1 mixtures of chiral racemic mixtures: solvents, the loaded crystals were then dissolved for NMR spectroscopy

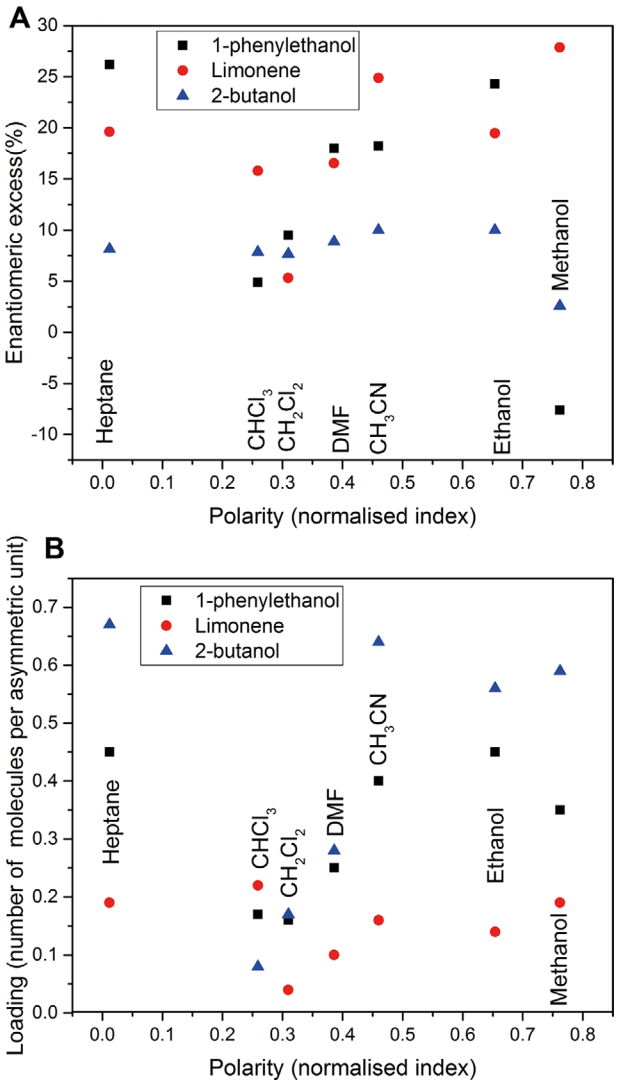

FIGURE 1 (a) Solvent-dependent enantioselectivity from chiral gas chromatography. (b) Loading of ZnBLD with racemic 1-phenylethanol, limonene, and 2-butanol in the presence of other solvents from NMR spectroscopy after digestion

(referred to as digestion) to determine the loading by comparing characteristic integrals of the framework with the guest, or loaded crystals were desorbed in dichloromethane and an aliquot of the supernatant was removed and analyzed by chiral gas chromatography to calculate the ee%, further experimental details and example chromatograms are given in the Supporting Information. Our results show large and unprecedented variations in the ee% and loading of chiral guests when different solvents are present in the adsorption phase of the chiral separation process. Figure 1 displays the enantioseparation and loading of ZnBLD toward the three racemates. The *y*-axes are generated from normalized empirical parameters of solvent polarity from UV-vis absorption spectra [27]. There appear to be some correlations with the ee% and loading with increasing polarity

of the solvent. However, for certain systems the trend is not observed, for example, the heptane enantioseparation systems consistently produce higher enantioseparation and loading than the other low polarity solvents. Most interestingly, the observed ee% was reversed for 1-phenylethanol and significantly reduced for 2-butanol when methanol was present in the adsorption phase but the ee% for the limonene separation was enhanced when compared with the solvent-free neat racemate enantioseparation.

Powder X-ray diffraction (PXRD) traces were recorded of the guest-loaded frameworks. Most solvent inclusion complexes did not affect the PXRD trace. Changes were observed for the methanol and chloroform PXRD traces, first, there is a notable decrease in crystallinity of both samples after exposure to methanol or chloroform, highlighted by the lower S/N ratio relative to the other samples. Second, there are changes in the peak position at low 2θ, highlighted in Supporting Information Figures S2–S4. Third, peak broadening and suppression of some of the peaks are observed. It can be concluded that there are some structural changes after exposure to methanol and chloroform, this is also observed when the framework is exposed to 1,2-propanediol as previously reported [28]. However, soaking the framework in methanol for a period of 1 day prior to enantioseparation of neat 1-phenylethanol did not lead to the reversal in enantioselectivity, instead, a minor reduction in the enantioselectivity was observed. ee%s of 21.3 (S) ± 0.32% and 11.7 (R) ± 0.58% were observed for 1-phenylethanol and 2-butanol respectively with the same enantiomer in excess as for as-synthesized ZnBLD. Therefore, we conclude that any methanol-induced structural changes are not responsible for the change in enantioselectivity. Rather, the change in enantioselectivity is caused by competing enantioselective interactions between the ZnBLD framework and each enantiomer of the chiral species, when other solvents are present, some of the dominant enantioselective interactions are blocked by the solvent, allowing for other less dominant enantiospecific interactions to dominate and reverse the enantioselectivity.

Using the previously reported experimentally obtained crystallographic information files [18], the void volume was calculated at various probe radii. These results are displayed in Supporting Information Figure S5, showing that there is a larger accessible free volume around the S-1-phenylethanol guest in the crystal structure of ZnBLD-S-1-phenylethanol than that of the R guest structure. When the probe radius is relatively small, there is no difference in the calculated free volume of the system due to the small probes fitting around the (R) or (S) 1-phenylethanol guests. However, as the probe radius increases, the free volume decreases for both systems but there is a larger decrease in the ZnBLD-R-1-phenylethanol system, at 1.2 Å probe radius, the S-1-phenylethanol system has a 4.27x higher free volume than the R system. Both systems approach 0 $Å^3$ free volume at a 1.4 Å probe radius. This is most likely caused by the different spatial arrangements of each enantiomer in the pore of ZnBLD, with closer interactions between the framework and the (S) enantiomer than the (R). We expected that this simple computational calculation could be used to explain how the loading of each enantiomer changes with different solvents, where there is more accessible space in the (S) enantiomer inclusion complex.

However, the same effect was not observed experimentally from ^1H digestion NMR spectroscopy after enantiopure loading of the chiral species and dissolution of the loaded MOF, where a higher quantity of the (R) enantiomers of limonene and 1-phenylethanol were adsorbed than the (S). This may be caused by the (R) enantiomer systems reaching equilibrium slightly faster due to the lower interaction energy between the (R) enantiomers and the ZnBLD framework. Figure 2 displays the enantiopure loading for the 1-phenylethanol and limonene enantiomers, pure solvent, and the 1:1 solvent: enantiopure loadings of each system studied. When methanol, chloroform, heptane, or acetonitrile are present in the adsorption phase, the adsorption behavior of each enantiomer system is significantly changed. In these systems, all (S) inclusion complexes contain more (S)-limonene or (S)—1-phenylethanol than the (R) enantiomer counterparts. Further, for the chloroform systems, there are some significant differences in the loading of the two enantiomer pair systems. Notably, there is a significant increase in the amount of chloroform present in both 1-phenylethanol enantiomer inclusion complexes compared with the pure chloroform adsorption, indicating that chloroform has a higher affinity to the framework in the presence of the chiral adsorbed species. These data further support our explanation that for the racemates studied, there are competing enantioselective interactions between the homochiral framework and each enantiomer of a chiral species, the presence of other solvents occupy an adsorption site allowing for more favorable interactions with an enantiomer.

In conclusion, enantiomer selectivity reversal was observed in MOF ZnBLD toward racemic 1-phenylethanol but the presence of methanol causes an increase in the observed enantioselectivity for the corresponding limonene separation, this phenomenon was only observed when methanol was present in the adsorption phase and not when the MOF was pre-soaked in methanol prior to racemic 1-phenylethanol separation. We explain that homochiral MOF ZnBLD has competing enantioselective interactions with each enantiomer of 1-phenylethanol and

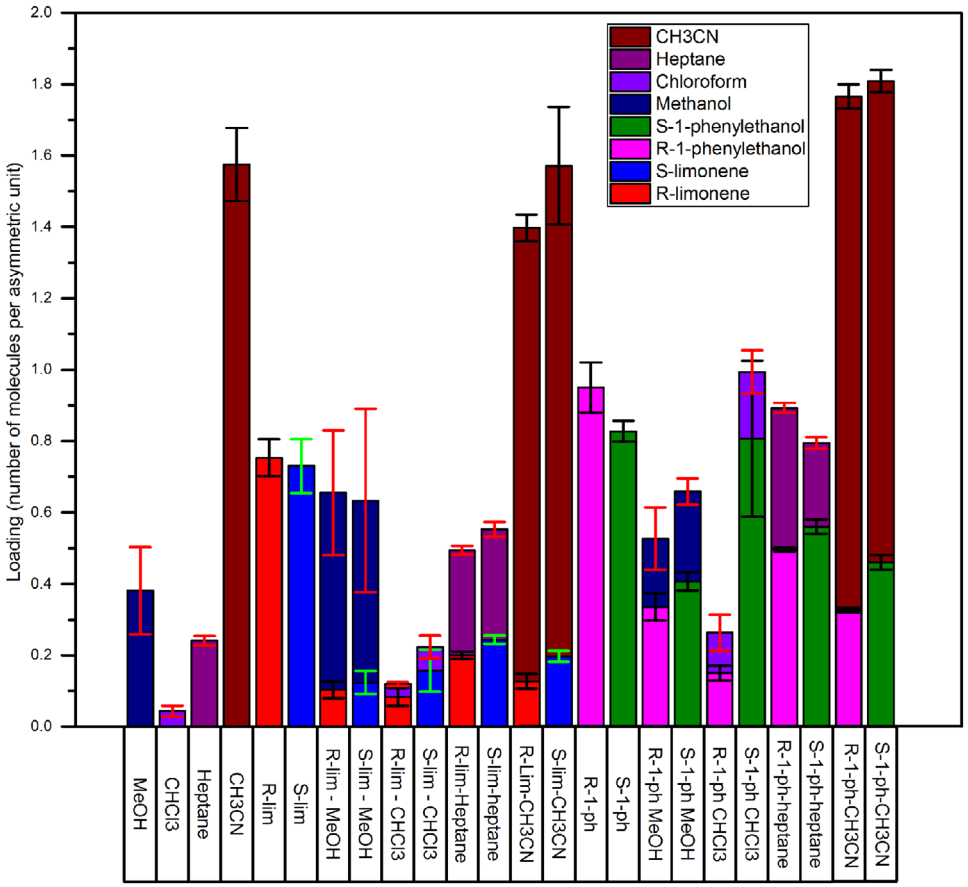

FIGURE 2 Enantiopure loading of the 1-phenylethanol and limonene enantiomers in the presence of other solvents from NMR spectroscopy after digestion. The *y*-axis depicts the guests loaded in that experiment which were either a pure solvent, a pure neat enantiomer of (R) or (S) limonene or 1-phenylethanol, or a pure enantiomer of (R) or (S) limonene or 1-phenylethanol and a solvent in a 1:1 ratio. Each experiment was performed in triplicate

limonene. The presence of methanol in the adsorption phase blocks an enantioselective adsorption site causing other enantioselective interactions to be favored leading to an enantioselectivity reversal or enhancement. We hypothesize that enantiomer selectivity reversal is highly likely to be observed in other chiral framework materials should solvent-dependent loading and separation be investigated as in this study. Further, the influence different solvents have on porous materials like metal organic frameworks are likely to have effects on non-chiral separations and in our opinion should be well studied for all MOF separation processes requiring a solvent. MOFs loaded with enantiomerically pure molecules are excellent matrices to study the chiral interactions between each enantiomer of a guest and the chiral framework species and further study of these systems is encouraged to better understand the chiral separation mechanism.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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