Solvent Induced Enantioselectivity Reversal in a Chiral Metal Organic Framework

Benjamin Slater[1,2], **Matthew R. Hill**[2,3], **and Bradley P. Ladewig**[1,4] ✉

[1]Barrer Centre, Department of Chemical Engineering, Imperial College London, London SW7 2AZ, United Kingdom
[2]CSIRO, Private Bag 10, Clayton South MDC, Victoria 3169, Australia
[3]Monash Centre for Membrane Innovation, Department of Chemical Engineering, Monash University, Clayton, VIC 3800, Australia
[4]Institute for Micro Process Engineering (IMVT), Herman-von-Helmholtz-Platz 1, Karlsruhe Institute of Technology, 76344 Eggenstein-Leopoldshafen, Germany

Solvent induced enantioselectivity reversal is a rarely reported phenomenon in porous homochiral materials. Similar behaviour has been studied in chiral HPLC, where minor mobile phase modifications can induce elution order reversal. We report the first instance of solvent-induced enantioselectivity reversal for homochiral MOF ZnBLD, highlighting the complex enantioselectivity behaviour.

Metal organic framework | Adsorption | Enantioselective | Enantioselectivity reversal

Correspondence: ***bradley.ladewig@kit.edu***

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 crystallise 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 $[Zn_2(bdc)(L\text{-lactate})(dmf)](DMF)$ (bdc = 1,4-benzenedicarboxylate), (dmf = *N,N*-dimethylformamide) (14). ZnBLD has been shown to enantioselectively adsorb one enantiomer from a racemic mixture such as chiral sulfoxides and alcohols (14, 18).

The enantioselective properties of ZnBLD and other chiral MOFs can be exploited for chiral separation applications. These materials can be engineered to allow lower energy separation processes towards 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 towards industrial processes. However, conditions affecting the chiral separation process in chiral MOFs are rarely studied, overlooked or sometimes appear to be randomly chosen, giving little to no mechanistic separation detail.

In chiral chromatography, enantiomer elution order reversal is a phenomena observed in high performance liquid chromatography (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 (19). Later, solvent induced enantioselectivity reversal was also reported. Unlike temperature induced elution order reversal which can be accounted for with 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 (BINOL) 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 (20). 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 chromatography 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 (21).

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 (22). Similarly, Peng and co-workers reported large changes in the enantioseparation (but no solvent dependent enantioselectivity) of 1-phenylethylamine in the presence of other solvents, ranging from 10 ee% in chloroform to 88.5 ee% in methanol (23).

In this report, through varying the solvent in the adsorption phase of the enantioseparation process, we observe significant changes in the enantioseparation behaviour of ZnBLD towards racemic 1-phenylethanol, 2-butanol and limonene. We further assess the solvent dependant enantioselectivity with enantiopure loading experiments and highlight the complex separation behaviour of metal organic frameworks. To the best of our knowledge, this is the first report of solvent induced enantioselectivity reversal for a chiral metal organic framework.

In order to investigate the effect that solvents have on the enantiomeric excess and loading, chiral separation and loading experiments were conducted by soaking ZnBLD crystals in 1:1 mixtures of chiral racemic mixtures: solvents, the loaded crystals were then digested for nuclear magnetic

resonance (NMR) spectroscopy to determine the loading, or loaded crystals were desorbed in dichloromethane and some supernatant was removed and analysed by chiral gas chromatography to determine the enantiomeric excess (ee%).

Our results show large and unprecedented variations in the enantiomeric excess and loading ability when different solvents are present in the adsorption phase of the chiral separation process.

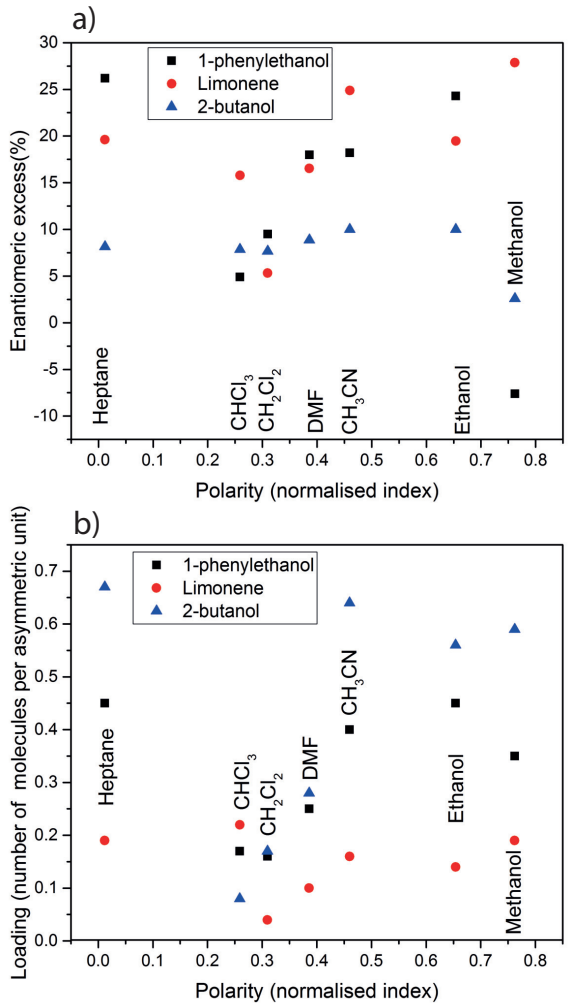

Fig. 1. a) Solvent dependent enantioselectivity b) Loading of ZnBLD with racemic 1-phenylethanol, limonene and 2-butanol in the presence of other solvents.

Figure 1 displays the enantioseparation and loading of ZnBLD towards the three racemates. The *y* axes are generated from normalised experimental data (solvent shifts of adsorption spectra) compared with water (24). There appear to be some correlations with the enantiomeric excess 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 then the other low polarity solvents. Most interestingly, the observed enantiomeric excess was reversed for 1-phenylethanol and significantly reduced for 2-butanol when methanol was present in the adsorption phase but the enantiomeric excess for the corresponding limonene separation was enhanced when compared with the solvent free neat racemate enantioseparation.

Powder X-ray diffraction (PXRD) spectra were recorded for the guest loaded frameworks. Most solvent inclusion complexes did not affect the PXRD pattern. Changes were observed for the methanol and chloroform PXRD spectra, firstly, there is a notable decrease in crystallinity of both samples after exposure to methanol or chloroform, highlighted by the lower signal to noise ratio relative to the other samples. Secondly, there are changes in the peak position at low 2θ, these are highlighted in Figures S2, S3 and S4 (ESI). Thirdly, there is peak broadening and suppression of some of the peaks. 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 (25).

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. Enantiomeric excesses of 21.3 (*S*) $\pm$0.32% and 11.7 (*R*) $\pm$0.58% were observed for 1-phenylethanol and 2-butanol respectively with the same enantiomer in excess as for the as–synthesised ZnBLD. Therefore, we expect that there are competing enantioselective interactions between the ZnBLD framework and each enantiomer of the chiral species and when other solvents are present, some of the dominant enantioselective interactions may be blocked by the solvent, in turn allowing for other less dominant enantiospecific interactions to dominate and reverse the enantioselectivity.

Using the previously reported crystallographic information files (CIF) (18), the void volume was calculated at various probe radii. The results are displayed in Figure S1 (ESI). This shows 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 radii 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 4.27 times higher free volume than the *R* system. Both systems approach zero free volume at 1.4 Å probe radius. We hypothesise that this is 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 ^{1}H digestion NMR spectroscopy after enantiopure loading of the chiral species, 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

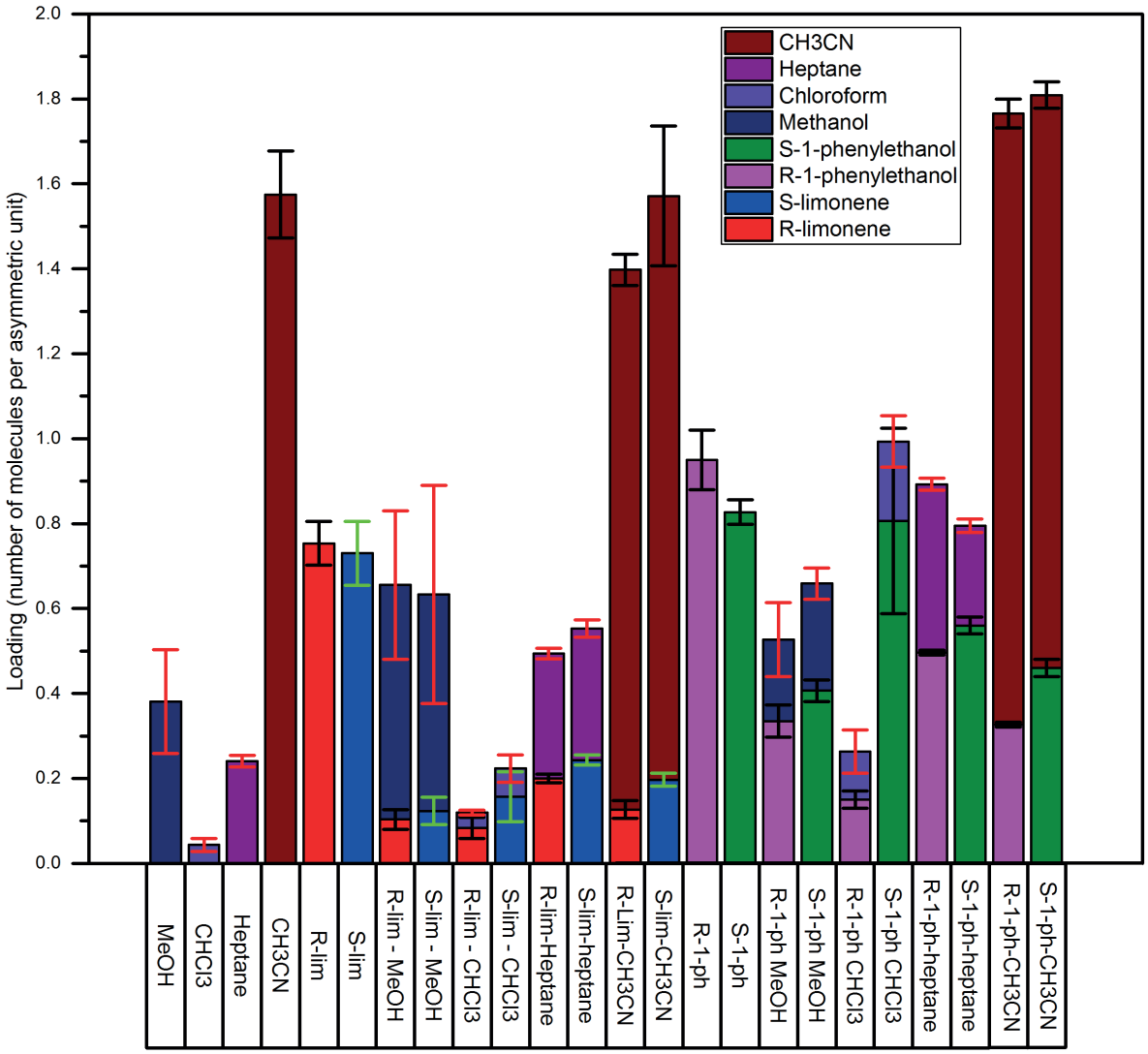

Fig. 2. Enantiopure loading of the 1-phenylethanol and limonene enantiomers in the presence of other solvents.

interaction energy between the (*R*) enantiomers and the Zn-BLD framework. Figure2 displays the enantiopure loading for the 1-phenylethanol and limonene enantiomers as well as the pure solvent loadings and the 1:1 solvent:enantiopure loading of each system studied. When methanol, chloroform, heptane or acetonitrile are present in the adsorption phase, the adsorption behaviour of each enantiomer system is significantly different. 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 difference 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. This data further supports our hypothesis that (for certain racemates) there are competing enantioselective interactions between the homochiral framework and each enantiomer of a chiral species, the presence of other solvents may in turn occupy an adsorption site allowing for more favourable interactions with an enantiomer.

Conclusions

Enantiomer selectivity reversal was observed in MOF Zn-BLD towards racemic 1-phenylethanol but the presence of methanol causes an increase in the observed enantioselectivity for the corresponding racemic 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 seperation. We hypothesise that the homochiral MOF ZnBLD has competing enantioselective interactions with each enantiomer of 1-phenylethanol and limonene. The presence of methanol in the adsorption phase, blocks an enantioselective adsorption site causing other enantioselective interactions to be favoured leading to enantioselectivity reversal or enhancement in the enantioselectivity. We hypothesise that enantiomer selectivity reversal may be observed in other chiral framework materials should the solvent dependant loading

and separation be investigated as in this study. Further, the influence different solvents have on porous materials like metal organic frameworks is 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, allowing the enantioselectivity of these materials to be better tailored for each separation.

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