Chemistry 615: Selected Topics in Inorganic Chemistry

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Review/Proposal

Drug Separations Using Chiral Metal-Organic Frameworks

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Abstract

This Review/Proposal paper will discuss separation techniques, use of chiral stationary phases, and application for delivery and separation of drugs using metal-organic frameworks. Enantioseparation of chiral drugs is an essential topic, as enantiomers generally display different pharmacological and/or toxicological properties, depending on their interaction with the body's metabolic pathway. Metal-organic frameworks (MOFs) can be engineered to exhibit chiral separation. In this paper, a methodology for enhanced enantioselective separation of chiral drugs is proposed after analysis of synthetic methods for inducing homochirality in the metal frameworks from previous literature and discussion on advances in characterization and analysis of enantioselectivity of other racemic drugs. A proposal for drug separation using isoreticular MOFs is discussed with consideration of the synthetic procedure, choice materials, conditions and quantitative analysis influenced by review of this topic.

Introduction

In pharmaceutics, over half of all drugs exhibit chirality or "handedness." Of those, the majority are marketed as a racemic 50:50 mix of their non-superimposable mirrored stereoisomers, also known as enantiomers[1]. Typically, one (eutomer) enantiomer utilizes a different metabolic pathway to make it pharmacologically more active than its (distomer) counterpart[1]. In some cases, one enantiomer displays toxicological properties which may lead to adverse effects within the body.

There exist many examples where having one enantiopure product is ideal in pharmaceutical purposes. Levo-methamphethamine for instance, is a drug with pharmaceutical purposes such as an over-the-counter nasal decongestant whereas Dextro-methamphetamine has similar effects, but is much more potent, addictive, and has a larger tendency for drug abuse. This is an example of a drug that is highly regulated, and prior to distribution for medicinal used, is optically separated.

Selective separation of enantiomers is regarded as a daunting task within stereochemistry as well as for preparation of biologically active compounds such as drugs. Separation of chiral molecules is performed either during stereoselective synthesis or through challenging separation techniques, thus, the process of delivering an enantiopure drug to the market is an essential, yet timely and expensive feat. A simpler mechanism for enantioseparation during the early phases of a drug's discovery could reduce lengthy purification steps and save valuable time and resources to make newer drugs more viable in the market[2].

Porous materials for chiral analysis of drugs and preparation have made an emergence in the form of being utilized in tandem with chiral stationary phases. Choosing the right porous material with high functionality and tunability to be capable of such analysis is of high area of research as of now. Additionally, porous materials have been frequently utilized for various

methods of separation, from gas capture and storage, and now more recently, separation of chiral molecules.

Zeolites are such an example of paragon porous materials with ingrained molecular sieves, high porosity, surface area, and uniform structure. Zeolites are involved in many applications, notably utilizing their large hydrogen uptake and charge uptake, however they lack designability and incorporating zeolites with optical activity and chirality is a challenge in of itself[3]. Other classical adsorbents such as activated carbons similarly lack designability by which their chiral channels can be engineered by size, shape and chemical function.

Metal-organic frameworks (MOFs) show a similar promise to the above materials with their large porosity, structural stability in a variety of solvents, pore tunability but offer a lead in easy designability. Porous MOFs have the added benefit of this extreme functional designability, as one example of new functional engineering is the addition of chiral recognition sites within the channels of the MOFs with a plethora of choice chiral substituents in terms of size, shape, and function while maintaining the MOF's structural chiral integrity once activated. These parameters in chiral ligands can be understood through preferential diffusion of the MOFs once entering the porous channels. One specific stereoisomer may readily diffuse through the chemical environment where the other enantiomer is bound to the chiral recognition sites of the channel. The solution can be simply resolved and the enantiopure product filtered for easy separation.

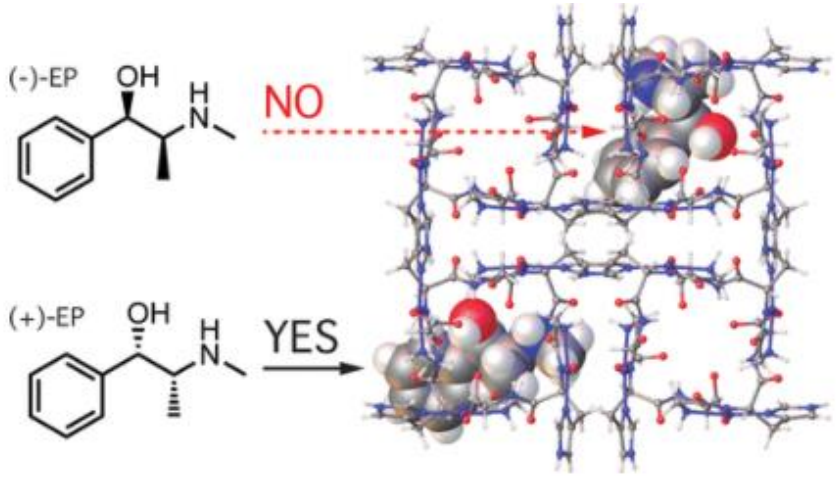

Figure 1: The basis of enantioselectivity in porous materials comes from the chemical environment of the pore channels; preferential binding to one specific stereoisomer from the pore surface allows for diffusion of the other stereoisomer through the pore channel. Reference https://doi.org/10.1021/jacs.7b00280

Homochiral MOFs have been well researched and show great promise in resolution and adsorption of enantiomers within mixtures, but development in MOFs as a chiral stationary phase and as molecular sieves for enantioseparation is still a growing field, exacerbated by a lack of homochiral, microporous templates available. To understand this, an in-depth analysis of synthesis practice for homochiral MOFs must be examined with respect to their separation abilities of other chiral molecules.

Enantioseparation Techniques and characterization

Chiral Stationary Phases (CSPs)

Emerging chiral MOFs as new types of porous adsorbent materials have great potential as CSPs for chromatographic enantioseparation, due to their large specific surface areas, controllable synthesis and flexibility of their pore sizes[5-9]. Despite this, chiral MOFs for enantioseparation research has primarily focused on selective adsorption and resolution of enantiomers within mixtures of the adsorbents for evaluating their separation performance[10].

Homochiral MOFs typically are utilized as chiral stationary phases (CSPs) to evaluate adsorption either through high-performance liquid chromatography (HPLC) or gas chromatography[38]. Under HPLC, the MOF must exhibit high stability in liquid phase under high pressure. Other methods in obtaining pure enantiomers include supercritical fluid chromatography and capillary electrochromatography. Among these techniques, HPLC holds the title as being the most useful technique, with more than half of all articles pertaining to enantioseparation published within this area[11] and determination of enantiomeric composition. Liquid chromatography using CSPs have proven to be essential within the applications of not only enantiomer separations, but also enantiomeric composition determination[12][13], stereochemistry analysis, pharmokinetics, and other enantioselective studies[14-17]

With limited number of tests involving chiral MOFs SCPs for HPLC enantioselective separation suggests that there are several limitations. For example, peptide-based MOFs are a growing study for such application, however there are few reported in the literature, owing to their poor stability and particle heterogeneity, thus limiting the range of polar mobile phases for HPLC available. Additionally, packing of particles in columns can be more difficult, which may lead to high retention times and low chromatographic performance. Solid phase extraction on the other hand may allow for better chromatographic analysis by avoiding issues with packing. SPE focuses on the separation of enantiomers rather than the quantitative analysis of enantiomer purity in a mixture, and thus is an area of enantioseparative characterization to be researched further.

Ligand Exchange CSPs

Ligand exchange CSPs is one example in which HPLC can be used for enantioseparation. Chiral separation of ofloxacin, a quinolone anti-biotic for ear or eye infection, was studied[18] and found that optimized concentration of ligand, L-isoleucine, in low amounts was able to successfully analyze ofloxacin enantiomers. By using ionic liquid-assisted ligand-exchange chromatography, it was determined that the best separation efficiency and retention was done through chiral amino acid ionic liquids opposed to achiral. Amino acid ionic liquids generally increase enantioselectivity with increasing alkyl chain length of amino acid ions, however, in the case of ionic interactions with imidazolium cations, showed an inverse relation due to an increase steric hindrance that arises from longer chain lengths. An increase steric hindrance due to cations also prevents coordination between amino acids anions and ofloxacin with [BMIM][Leu] showed the best separation as a result.

Molecular Sieving and CSPs

Rather than traditional chromatographic techniques, homochiral MOFs can also be utilized as molecular sieves for enantioseparation.[19] While simple molecular sieving for enantiomeric separation is not typically achieved, MOFs have the benefit of pore tunability to provide chiral environments[20]. An example of such is enantiopure pyridyl-functionalized salen ligand was used in the synthesis of $[ZnLBr]\cdot H_2O\}_n$ to show non-interpenetrated 3D porous frameworks, which was later then used in enantioseparation based on the relative sizes of the chiral channels and the resolved molecules. With the MOF suspended in methanol as CSP, ibuprofen is used to test enantioseparation. As expected, (±)-ibuprofen was successfully resolved and baseline separated on the CSP with hexane/isopropanol (optimized *v/v* = 95:5) as the mobile phase. The high-resolution enantioseparation with a good selectivity factor (α = 2.4) and chromatographic resolution (R_s = 4.1) was achieved only within 6 min. Molecular sieving is shown as main influence in separation, as the MKD of chiral channels of the MOF is around ~9.8 Å and does not exhibit separation with molecules above 9.2 to 9.4 Å. separation of molecules is shown to be most optimal around a critical size around 9.2 to 9.4 Å associated with the packed column.[10]

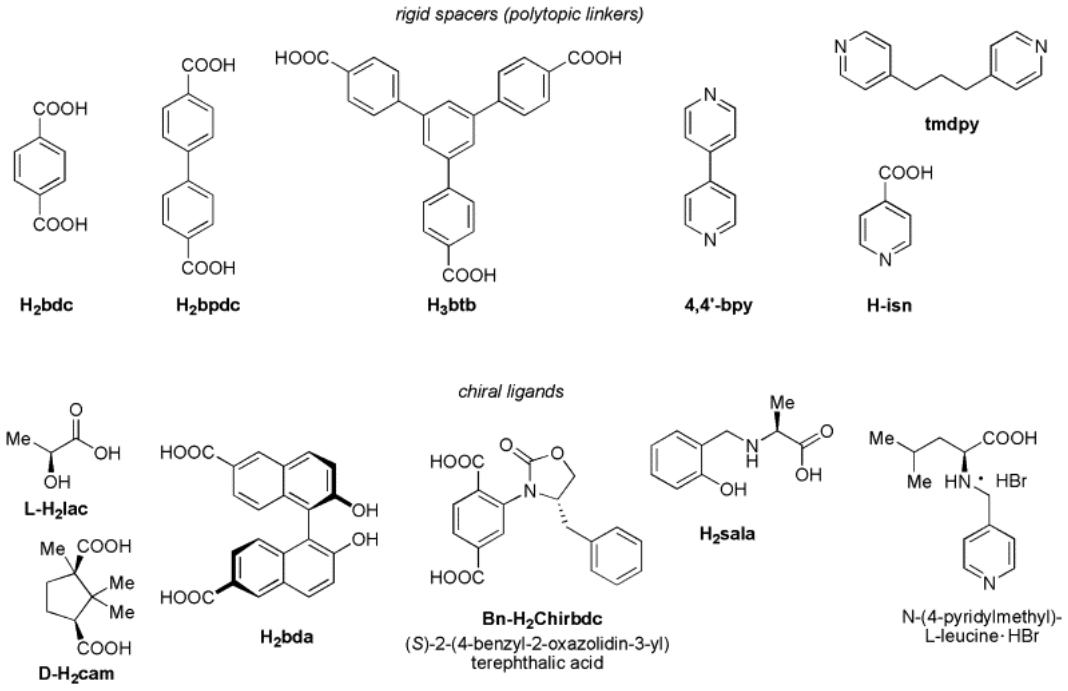

Figure 2. Polytopic linkers and chiral ligands contained in homochiral MOF-based CSPs. Most homochiral MOFs used in CSPs for chromatographic applications use organic bridging ligands such as the ones shown. Taken from https://doi.org/10.1016/j.chroma.2014.06.064,

Synthesis techniques of homochiral MOFs:

This section introduces a few examples of how homochiral, porous forms have been performed in the literature[21]. In general, chirality within MOFs occurs if the organic linker molecules bound to the frameworks are chiral. Homochiral MOFs arise when all crystals of a bulk sample are considered the same chirality[21]. There is a benefit in synthesizing and utilizing such porous structures, as their chiral functionality can be ingrained within open channels of the pore apertures. These chiral recognition sites play an important hand in enantioselective separations of racemic molecules. Typical synthesis of the homochiral MOF consists of the metal, organic chiral ligand, and a rigid spacer molecule to induce a robust structure and permanent porosity. In the case of homochiral MOFs, the synthesis pathways can be deduced to the following approaches:

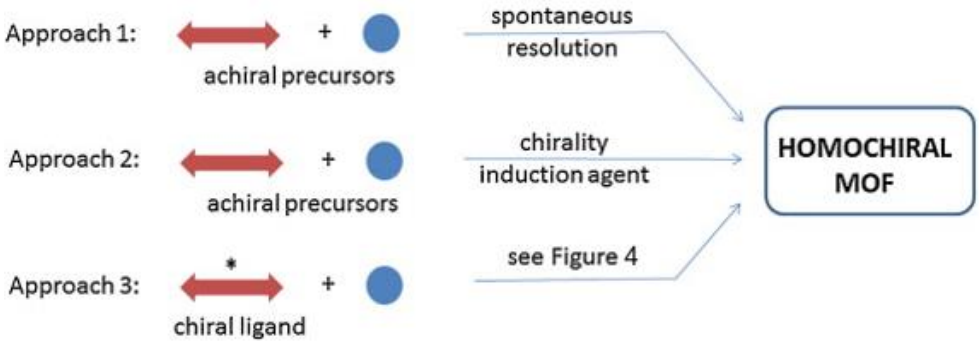

Figure 3: Adapted from https://doi.org/10.1016/j.chroma.2014.06.064 shows 3 approaches typically performed in achieving a homochiral MOFs

The first approach prepares homochiral MOFs from achiral components, which may give chiral crystals under spontaneous resolution[34][35]. This is advantageous as achiral components are often more accessible than chiral attachments, however is prone to enantiomorphs[34]. A second approach for homochiral MOFs is synthesized from achiral metal nodes and bridging ligands under chiral influence. A chiral ligand forces a specific chiral topology through the pore channels[30][31]. The third method involves the use of reticular synthesis and chiral bridging ligands to ensure a robust network with chiral features embedded within the framework. This method allows for large flexibility and designability of differing functional groups and features for focused application, along with isostructural topology among MOF extensions. Reticular synthesis is expanded (see Figure 4) in later section, but can be summarized by two routes, where the metal is bound to either enantiopure spacer or to an enantiopure auxiliary to create characteristic framework[21].

Introducing chirality to the framework

Precursors are often the main source of inducing chirality, and so this section expands on approach 3, where an enantiopure auxiliary is directly induced to the framework to create homochiral MOFs. The most common methods to induce chirality in the framework is using organic biomolecules, as they are natural, well studied, and readily available.

Amino acids

Biomolecules are a popular and relatively inexpensive source to induce chirality within structures of the MOFs. Proteogenic amino acids have the benefit of ingrained chirality within their structure, consisting of an alpha carbon bonded to an alpha carboxyl, alpha amino, hydrogen, and unique R group side chain. Many studies utilize amino acids for potential ligands as amino acids are well known for their ability to form coordination polymers with transition metal ions[22].

Past homochiral MOFs have been constructed from enantiopure amino acids, L-tyrosine, L-histidine, L-tryptophan, and L-glutamic acid were demonstrated as suitable CSPs for HPLC separation of hexane/isopropanol and hexane/dichloromethane as mobile phase. They all show good chiral recognition ability towards organic compound where MOF-1 and MOF-6 had better recognition, being able to separate 7 and 8 different organic racemates respectively under different mobile phases compared MOFs 2-5. This being attributed to a singular amino acid being used as bridging ligands to the metal center compared to have two of more amino acids coordinating to the metal center oppose to bridging it.

A benefit that most amino acids have compared to oligopeptides is their water stability due to their polar nature. An example of such is reported with TAMOF-1 (triazole acid metal–organic framework) that utilizes a ligand derived from L-Histidine. Asides from permanent porosity and good stability in water and organic solvents, TAMOF-1 demonstrates the ability to act as CSP to separate chiral drugs[23]. By using a simple racemic solution of (±)-ibuprofen and (±)-thalidomide with the MOF bed in place, molecular sieving and HPLC can quantitatively analyze retention times of each enantiomer. Incredibly, homochiral TAMOF demonstrated enantioselective separation and quantitative yields of 99% of (S)- and 92% (R)-ibuprofen at ee >99% and 78% for (S)- and 96% for (R)-thalidomide at ee >99%. For industry use, TAMOF-1 also has a mechanically stable structure, resulting from its strong metal–nitrogen bonds, providing superior chemical stability and can be synthesized at large scale.

Peptides

Peptides are even more prevalent as means to induce homochirality in MOFs. Peptides have the benefit of inherently featuring chirality because of their amino acid constituents. Additionally, peptides provide robust structure for framework, structural versatility, chemical stability and abundant coordination sites within the MOF[28]. Among this, peptide MOFs are well capable of enantioselective recognition because of chiral pockets decorated within the structure. With a

near limitless array of peptide and amino acid sequences, the guest intermolecular interactions of the MOF structure can be maximized for a specific enantiomer by careful inspection of suitable peptide sequencing[24].

The first example of using MOFs for enantioselective separation of chiral polar drugs comes from a copper 3-dimensional MOF using a tripeptide, Gly-L-His-Gly, that enables selective adsorption of ephedrine enantiomers in a solid phase extraction cartridge[2]. Here, they report the Cu(GHG) MOF capable of separating >50% of (+)-ephedrine from a racemic mixture within 4 min once used as chiral solid phase extraction.

There is a limited spread of knowledge in using peptides as chiral template. While robust and flexible, peptides are substantially more expensive than amino acids, and difficulties in synthesis and experimental control arise due to their general low chemical stability and loss of robustness upon solvent removal[26]. Water byproducts must be considered as hydrolysis of peptide bonds would collapse the structure. True porous and robust peptide-based MOFs are scarce, owing to their aliphatic characteristics. As a result, these structures tend to fold on themselves, inhibiting access to their pore apertures and making them incapable of enantioselective chiral drug separation.[26] Choosing a stable, inexpensive peptide template is a challenge in making peptide-based MOFs more prevalent for industry applications. As of now, research of other suitable peptide MOFs capable of separation is still underway.

Reticular synthesis and Chiral Bridging Ligands

Reticular Synthesis focuses on introducing bridging ligands or rigid spacers between characteristic frameworks, affording porous materials. These rigid spacers may be derived from a family of similar spacers, creating a series of isoreticular MOFs with the same structural topology. This approach is by far the most flexible in designability, as it allows the chemist to not only tune the pore size for increased separation but induce functionalities for focused applications. Chirality for example can be introduced in isoreticular MOFs either in the rigid spacers by using chiral ligands or by spatially separating chirality-induced organic-inorganic building units. Separation of molecules and drugs can be done in isoreticular homochiral MOFs through size selectivity within the tunable pore channels of the MOF. Furthermore, stereoselectivity can further separate the racemic drugs entering the pore channel through chemical recognition of chiral sites between the enantiopure drug and chiral channels within the MOF. To the best of my knowledge, there is no research on selective pore size tuning of isoreticular MOFs for drug separation and is a worthy research interest.

Two different routes based on the concept of secondary building units (SBUs) are generally used for the synthesis of such homochiral MOFs,[21] (Figure 3) adapted from approach 2 (see Figure 2): use of a rigid enantiopure spacer to link adjacent metal centers or a preformed achiral secondary building units (SBUs) (route a); a metal ion and a homochiral organic ligand are used to form homochiral SBUs, which in turn, are linked together by rigid spacers to build a network structure (route b).

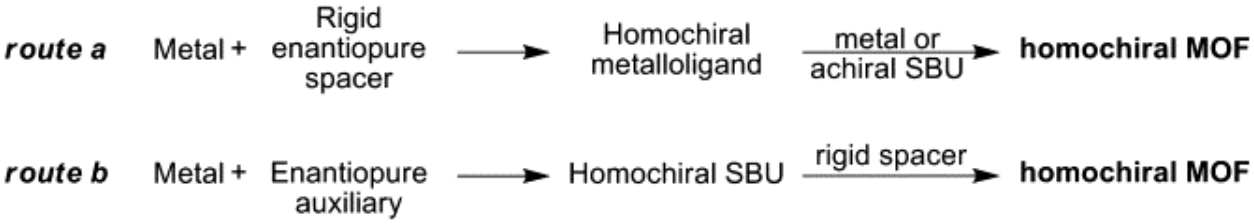

Figure 4 Referenced from https://doi.org/10.1016/j.chroma.2014.06.064. Synthetic route "a" and route "b" are shown for designing reticular MOFs on homochiral SBU

Typical chiral building blocks are derived from tartaric acid and 1,1′-bi-2-naphthol. Common achiral spacers include 4,4-bipyridyl and H2bdc. See Figure 2 for more examples of chiral and achiral spacing components.

A combination of using an organic SBU with reticular synthesis is reported via reticular frameworks for chiral resolution[26]. The use of glycyl-L(S)-glutamate dipeptide is introduced to the cobalt metal framework and spaced judiciously with varying 4-4 bipyridyl (bipy) derived spacers. The result is a family of homochiral MOFs with varying ligand and pore sizes ranging from a reported accessible pore aperture of 115$Å^3$ to 227$Å^3$. Furthermore, these MOFs are stable in Thermogravimetric analysis at 400 dec C.

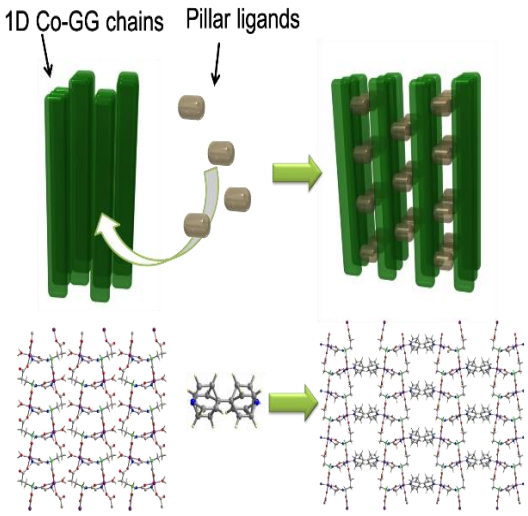

Figure 3. Use of pillar ligands to separate characteristic one-dimensional building units affords for porous structures within the MOF

Here, the MOFs using bpeb with longer ligand extensions can adsorb a larger molecule such as hydrobenzoin compared to those with bipy and azobipy could only enantioselectively adsorb smaller molecules such as glycidol. It is reported that all MOFs enantioselectively separate S-glycidol. Co-L-GGbpeb with its larger pore apertures adsorb mores glycidol at 3.11 $mol_{glycidol}/mol_{MOF}$ compared to 1.13 $mol_{glycidol}/mol_{MOF}$ with Co-L-GGbipy. Interestingly, an inverse relationship between the enantioselective adsorption and total adosorption is reported where Co-L-GGbpeb enantioselective adsorbs S-glycidol over R-glycidol at 37.8±1.0 % compared to 54.1±1.0 % for Co-L-GGbipy. This is hypothesized to be because of the larger pore apertures inducing less affinity as a results of the distance from the chiral pore-wall surface and the molecules. These MOFs show good recyclability, being reusable three times for the same experiment with minimal change in adsorption or separation.

This research is important in that it demonstrates that robust MOFs can be designed with functionality and tunable porosity to drive selective adsorption of chiral molecules based on size dependence. While this study demonstrates small molecules such as glycidol and hydrobenzoin

can be separated, the extent of the molecule size has not been fully examined. For instance, pharmaceutical drugs are generally bulkier and many exhibit chirality. Ranging from Dipercaprol ($Å^3$ = 86), a metal chelating agent to Penicillamine ($Å^3$=206) a treatment for Wilson's disease, there is a variety of different sized chiral drugs that can be tested for separation using chiral MOFs.

The design of isoreticular homochiral peptide-based MOFs can be dwelled deeper by using the same ligand extensions but to enantioselectively separate racemic drugs where the enantiomers have different pharmacological effects; where one enantiomer is useful and desired, and the other is either harmful or ineffective and undesired. This proposed research plan will explore ways to utilize robust homochiral MOFs using the ligand extension strategy to enantioselectively separate larger sized drugs. To the best of my knowledge, there is no research utilizing this strategy of reticular synthesis for racemic drug separation using MOFs.

Research Proposal/plan

In this plan, I propose synthetic approach 3 with route "b" for homochiral synthesis of reticular MOFs. I will use enantiopure dipeptide glycyl-L(S)-glutamate (Gly-Glu) with cobalt acetate $Co(OAc)_2*H_2O$ in method described by Stylianou, K. C. et al., to produce one-dimensional Co-L-GG ladder building units[26].

As discussed above, truly robust and porous peptide-based MOFs are scarce in literature due to difficulties accessing pore channels, making them ineffective for most applications, including chiral separation[26]. The proposed synthetic procedure is a simple work around, which utilizes achiral bridging ligands to separate the characteristic ladders. Peptides are good candidates for reticular synthesis as they have abundant metal sites for metal coordination[26][39] and pillar ligands. Here, the Co^{II} center is bound to four oxygens (one from the carbonyl and three from the carboxyl group in the GG peptide), one nitrogen (from terminal amino) and one water molecule. This structure forms one-dimensional ladders with inaccessible void volumes. Use of bipy linker readily replaces the water molecules of Co-L-GG units, affording porosity that can be tuned by ligand extensions of bipy.

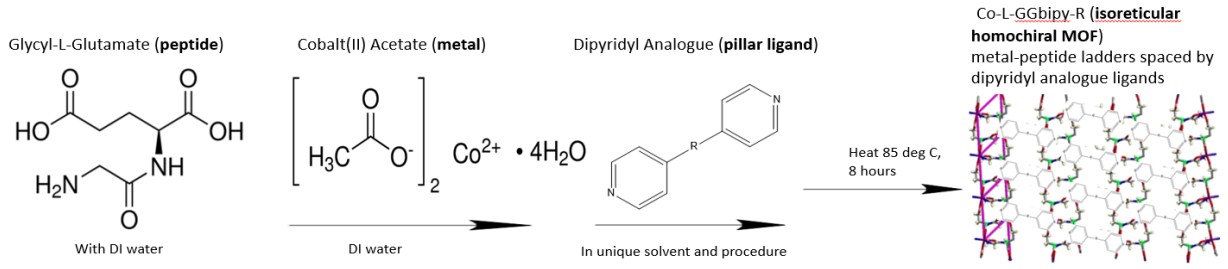

Figure 4: Synthesis procedure for inducing porosity in otherwise, nonporous one-dimensional ladders involve using dipyridyl analogues to spatially separate the homochiral framework.

Reticular synthesis makes the best use of tuning the functionalities and porosity of the materials. To compare impact of pore size in separating larger sized drugs, I report the reticular synthesis of five novel Co-L-GGbipy(R) based MOFs. Longer analogues of bipy were used with varying synthetic procedure including, meso-1,4 di(4-pyridyl) ethanediol (bipyED), 1,2-Di(4-pyridyl)ethane (bipyEth), 1,2-Di(4-pyridyl)ethylene (bipyEthy), 1,4-Di(4-pyridyl)benzene (bipyBZ), and 4,4'-Di(4-pyridyl)biphenyl (bipyBP). Synthetic procedures all involved equimolar amounts Gly-Glu in DI water with $Co(OAc)_2$ solution, and some guest organic solvent heated at 85 deg C for 8 hours. The resulting pink MOF crystals are subsequently vacuum filtered, and air dried overnight.

Due to a comparable structural topology among isoreticular MOFs, Powder X-Ray Diffraction (PXRD) was used to verify for similar crystallinity (Figure 7). The largest intensity diffraction peaks centered around 5 degrees are the predominant lattice planes in all my MOFs, confirming their structures. It is reasoned that since diffraction plane scattering at a smaller 2θ incidence angle occurred in materials with larger unit cells, by increasing the size of the pillar ligands and, therefore, the unit cells, a diffraction would occur at a smaller 2θ angle. PXRD confirmed this as the intensity peak of the MOF with the longest ligand, bipyBP, had the smallest diffraction angle at 3.62 degrees and the MOF using bipy with the smallest length had the largest diffraction angle at 6.06 degrees

A challenge in gauging MOF performance is finding and operating under conditions that these MOFs will not collapse under. As mentioned, peptide MOFs have poor stability and particle heterogeneity, thus limiting the range of polar mobile phases for HPLC available. Water by-products must be carefully considered for reactions involving Co-L-GGbipy(R) to prevent hydrolysis of peptide bonds. Thermogravimetric Analysis record their thermal stability up to 300°C, and all synthesized MOFs showed solvent stability through PXRD when immersed overnight in liquid methanol, dimethylformamide and tetrahydrofuran.

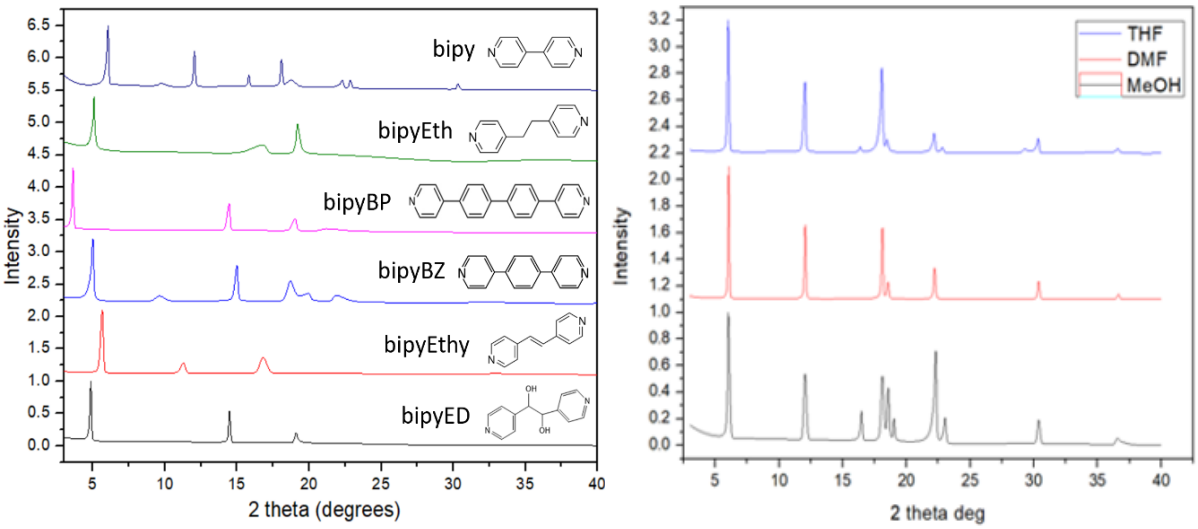

Figure 5: Powder X-ray Diffraction data for isotructural MOFs indicate that MOF structures have been produced. Stability of each MOF is shown under THF, DMF and MeOH solvent

BET isotherms demonstrate type I isotherm, indicating high porosity. Due to the ultra-porous nature of these MOFs, molecular sieving can be applied as the main source for resolution and separation of chiral substances. Glycyl-L(S)-glutamate exhibits chiral recognition sites in the pore channels of the framework and so it is predicted that these sites will preferentially bind to the L(S)-enantiomer of racemic drugs[29]. The use of larger ligands during reticular synthesis is also expected to influence the molecular sieving separation, as Co-L-GGbipy(R) MOFs with larger ligand extensions will have larger pore apertures and can so sieve larger molecules than the MOFs with smaller pores. This size-selection study will be performed by utilizing each MOF to determine resolution of molecules to determine the influence of pore size in separation and optimized to determine the best MOF and pore size for drug separation.

To test enantioselective separation of a chiral drug, Penicillamine (Pen) is used to analyze the pore size impact for enantioselective adsorption. D-Pen is an intended antiarthritic and is used to treat Wilson's Disease whereas L-Pen is toxic and inhibits the production of vitamin B6. To prepare a chiral gas chromatography (GC),1,000 ppm solutions of both enantiomers are ran to obtain an enantiopure reference. Since Pen would be soluble and Co-L-GG MOFs are stable under a methanol environment, methanol is chosen as the solvent for GC. Single-Crystal XRD on Co-L-GGbipy and Co-L-GGbipyED showed that separation will be possible within accessible pore apertures of 115Å^3 and 179Å^3, respectively. Once solvent conditions are optimized, equimolar amounts of D-pen and L-pen will be mixed into two vials with methanol of ground and

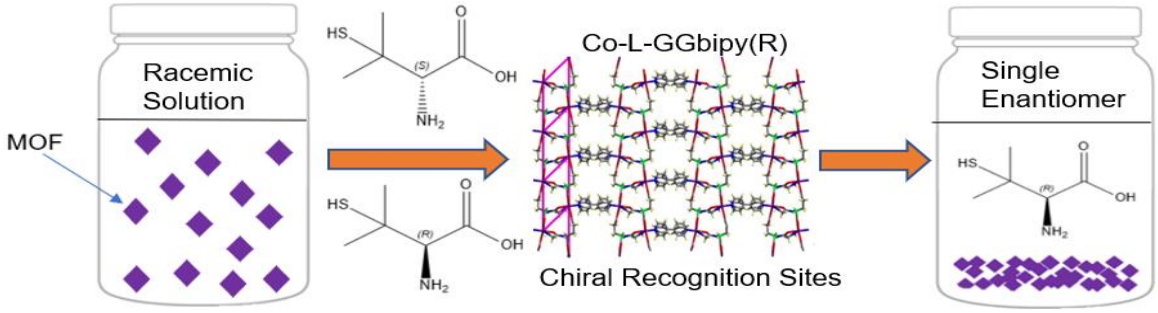

Figure 6: Schematic showing separation of DL-Penicillamine (DL-Pen). Pore diffusion occurs in homochiral Co-L-GGbipy(R) and leaves a single stereoisomer to be collected for chiral gas chromatography.

activated Co-L-GGbipy and Co-L-GGbipyED will be immersed into each racemic DL-Pen solution (20 mg DL-Pen in 0.10 mL methanol) at room temperature for 48 hours (Figure 8). Once filtered and dried with anhydrous methanol to encourage diffusion of the chiral drugs in methanol, the methanoic solution will be analyzed by gas chromatography, mass spectrometry or high-pressure liquid chromatography. With chiral gas chromatography, the data will be compared with the reference to determine the preferential enantioselective adsorption and enantiomeric excess.

Afterwards, each of the remaining isoreticular MOFs will be tested for enantioselective adsorption via the same method with the hope that larger ligand extensions with larger pore apertures will allow for more adsorption of larger drugs. With more robust and diverse ligands to utilize, more applications regarding the separation capabilities of different drugs can be elucidated. For instance, Co-L-GGbipyBZ and Co-L-GGbipyBP MOFs feature pillar ligands with additional aromatic phenyl structures within the pores which, during diffusion, may interact and bind with other aromatic chiral molecules or drugs such as Ibuprofen; further research could use these MOFs to investigate separation efficiency between aromatic and aliphatic chiral drugs.

Co-L-GGbipyED features dual hydroxyl groups as spacers and so investigations around interactions with these functional groups and with certain drugs can also be investigated.

Optimization for each reticular MOF will be performed by altering the ligand and metal ratio, as these parameters seem to have the largest influence on yield for amino acid-based MOFs used in CSPs.[18] With an array of different sized MOFs, optimization will be performed to determine the MOF with critical pore aperture size that has the best total adsorption and enantioselective adsorption of chiral drugs. If an inverse relation is shown as described by Stylianou, K. C. et al.[26],for total and enantioselective adsorption, mixtures of homochiral reticular MOFs can be studied and optimized for best general separation of chiral drugs.

Conclusion:

This research plan proposes a fruitful endeavor in hopes of using a very stable, recyclable, robust family of isoreticular homochiral peptide-based MOFs for separation of chiral drugs.

Six isoreticular homochiral MOFs of varying ligand sizes are prepared and show varying porosity and great stability in methanol, tetrahydrofuran and dimethyl formamide. Investigations for enantioselective separation for racemic drugs Penicillamine, Ibuprofen and 3,4-dihydroxyphenylalanine (DOPA) are underway and if shown to be successful as with the predecessor racemic glycidol and hydrobenzoin, will be the first case of reticular synthesis for pore-size tuning for enhanced enantioselective drug separations. This is especially important for pharmaceutical industries as this will serve as a cost-efficient method of separating undesired enantiomers during synthesis, reducing drug purification steps, and making them more accessible to the public.

Further research will investigate the variety of pillar ligands to extend characteristic framework and explore functionalities with them, such as branch functional groups and aliphatic groups for selectivity of a certain drug. This study and application are believed to be an excellent contender for the American Chemical Society Chemistry of Materials journal and funding for this project will enable a wider selection of diverse, functional ligands and drugs to expand the knowledge of utilizing MOFs for chiral separations.

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