Functionalized MOF nanocomposites for dispersive solid phase extraction and enantioselective capture of chiral drug intermediates

Xue Ma [a,1], Xiaohua Zhou [a,1], Ajuan Yu [a,*], Wuduo Zhao [b], Wenfen Zhang [a], Shusheng Zhang [b,*], Linlin Wei [c], Debra J. Cook [c], Anirban Roy [c]

[a] College of Chemistry and Molecular Engineering, Key Laboratory of Molecular Sensing and Harmful Substances Detection Technology, Zhengzhou University, Kexue Avenue 100, Zhengzhou, Henan 450001, PR China
[b] Center of Advanced Analysis and Computational Science, Key Laboratory of Molecular Sensing and Harmful Substances Detection Technology, Zhengzhou University, Kexue Avenue 100, Zhengzhou, Henan 450001, PR China
[c] Anasys Instruments Corporation, 325 Chapala Street, Santa Barbara, CA 93101, USA

A B S T R A C T

The facile preparation, characterization and application of a novel magnetic graphene oxide- metal organic framework $[Zn_2(D\text{-}Cam)_2(4, 4'\text{-}bpy)]_n$ (MGO-ZnCB) as a sorbent for fast, simple and enantioselective capture of chiral drug intermediates are presented in this paper. The MGO-ZnCB nanocomposite, developed by encapsulating MGO nanoparticles into the homochiral metal organic framework of ZnCB, can integrate the advantages from each component endowing the hybrids with improved synergystic effects. The enantioselective performance of MGO-ZnCB was evaluated by dispersive magnetic nanoparticle solid phase extraction (d-MNSPE) of 1, 1'-bi-2-naphthol (BN) and 2, 2'-furoin (Furoin) racemic solutions. Due to the excellent dispersive capability, high stability, relatively larger saturation magnetization and distinct enrichment capacity of MGO-ZnCB, the d-MNSPE method provids good enantioselective separation of these compounds with enantiomeric excess (ee) values as high as 74.8% and 57.4%, respectively. The entire process with BN or Furoin can be completed within 3 min or less. After washing with methanol, the host MGO-ZnCB can be easily recycled and reused six times without any apparent loss of performance. Furthermore, the adsorbed BN and Furoin in nanodomains of the MGO-ZnCB composite were directly investigated for the first time by atomic force microscopy-infrared (AFM-IR) technique.

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1. Introduction

Separation of enantiomers has become an increasingly significant task in synthetic chemistry, particularly in the preparation of biologically active compounds, especially drugs [1–5], because pure enantiomers may profoundly differ in biological interactions, pharmacology and toxicity when compared to the corresponding racemates. In many cases, the opposite enantiomers show unwanted side effects or even toxic effects [6–8]. Preparation of enantiomerically pure compounds is extremely important, and it is still a major challenge because of the identical physical and chemical properties of enantiomers in the achiral environment. There is therefore a critical need in the chemical and pharmaceutical fields

to develop a new generation of chiral materials with superior enantioseparative capabilities [9,10].

Metal-organic frameworks (MOFs) built from metal nodes and multitopic organic linkers have received considerable attention recently because of their myriad potential applications in gas storage, catalysis, separation, and sensing [11–17]. A current effort is focused on the development of MOF materials for the recognition and separation of chiral molecules following the judicious incorporation of enantipure building blocks into the porous framework [18–27]. Enantioseparation by MOF materials is attributed to interactions between the framework and individual racemic agents, such as hydrogen-bonding [28,29] and a homochiral environment in the pores [29]. Under normal conditions, the size, shape, chirality and chemical environment of pores are essential for enantioselective sorbent, as they dictate which enantiomer can penetrate the pores as well as the affinity of the enantiomer that is adsorbed within the pores. In recent years, chiral metal-organic assemblies have been used for enantioselective adsorption and separation, and some of these exhibit good to excellent performance [21,22]. How-

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* Corresponding authors.
  E-mail addresses: yuajuan@zzu.edu.cn (A. Yu), zsszz@126.com (S. Zhang).
  [1] These authors contributed equally and should be considered as co-first authors.

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ever, to date, only very limited small chiral enantiomers have been successfully separated on chiral MOFs. The tested chiral MOFs were only the tip of the iceberg and many recently-reported chiral MOFs have not been tested.

As a class of advanced two-dimensional materials, graphene oxide (GO) has attracted intensive interest due to its mechanical and chemical stability, ultrahigh surface area and unique electrical properties [30,31]. It is intriguing to mingle the porous homochiral MOFs as chiral selectors with graphene nanosheets to efficiently screen enantiomers for drug enantioseparations. Nanocomposites containing MOFs, developed by encapsulating GO nanoparticles into MOFs, can integrate the advantages from each component and endow the hybrids with improved synergystic effects. It is expected that distorted graphene sheets will contribute to the enhancement of dispersive interactions, whereas the chiral MOF component will contribute to the expansion of the pore space, in which the enantiomorph can be captured. Surface functionalization of MOFs would significantly ameliorate the dispersibility of graphene in solution and, due to the intrinsic chiral topology properties of MOFs and their high surface area, the reversible affinity between chiral active sites and enantiomers would contribute further to the enantiomer enrichment [32–34]. The unique surface properties and large surface area of graphene composites not only provide affinity sites for interaction with targets but also improve the adsorption forces and the ability of the MOF layer to retain enantiomorphs [35]. Therefore, it is desirable to construct a dense arrangement of atoms to form an accessible porous framework of graphite oxide-chiral MOF composite to provide enantioselectivity. However, achieving fast and simple separation of enantioseparation based on GO-MOF remains a great challenge.

A major objective of this paper is to present the facile preparation, characterization and application of a novel magnetic graphite oxide-MOF $[Zn_2(D-Cam)_2(4, 4'-bpy)]_n$ (MGO-ZnCB) sorbent for the first time. The appeal of novel nanocomposites such as MGO-ZnCB lies in their integration of several different functionalities into a single structure. They have a number of advantages that distinguish them from other affinity materials that have been reported. First, MGO-ZnCB nanocomposites show excellent dispersive capabilities in solution. Second, due to the unique porous structure of homochiral metal organic frameworks, MGO-ZnCB composites are enantioselective and can capture and extract one enantiomer from a racemic sample while blocking the other ones. Third, their unique magnetic properties would contribute to the rapid and convenient magnetic separation process. A dispersive magnetic nanoparticle solid phase extraction (d-MNSPE) strategy with the fast extraction and elution procedures was designed and optimized for the racemic solution of 1, 1'-bi-2-naphthol (BN) and 2, 2'-furoin (Furoin). MGO-ZnCB with d-MNSPE method showed good performance for enantioselective separation of BN and Furoin with enantiomeric excess (ee) values as high as 74.8% and 57.4%, respectively. The whole process for BN or Furoin can be completed within 3 min or less. After washed with methanol, the host MGO-ZnCB can be readily recycled and reused six times without any apparent loss of performance. Furthermore, an atomic force microscopy-infrared (AFM-IR) technique was employed to measure infrared maps and spectra of the absorbed BN and Furoin at nanoscale.

2. Experimental section

2.1. Materials and chemicals

Graphite powder, hydrogen peroxide, sulfuric acid, hydrochloric acid, potassium permanganate, acetonitrile, ethanol, iron (III) chloride hexahydrate, ethylene glycol, sodium acetate, poly(ethylene glycol), ammonium hydroxide, toluene, N, N-dimethylformamide

(DMF), sodium carbonate and zinc nitrate hexahydrate were purchased from Alfa Aesar. Tetraethyl orthosilicate (TEOS) and 3-aminopropyltriethoxysilane (APTES) were purchased from Aladdin. 4, 4'-Bipyridine, N-hydroxysuccinimide (NHS), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), D-(+)-camphoric acid, 1, 1'-bi-2-naphthol and 2, 2'-furoin were purchased from Energy Chemical. Water was purified with Milli-Q purification equipment.

2.2. Apparatus and methods

The size and surface morphology of the materials were observed on a scanning electron microscope (S-4300 SEM instrument) and Tecnai G^2 F20 microscope (TEM). The energy dispersive X-ray (EDS) analysis of the graphene composites were recorded on a JSM-7001F instrument. The FTIR spectra were obtained from a Nicolet 6700 spectrometer between 4000 and 400 cm^{-1}. A STA 409 PC TGA (Thermogravimetric Analysis) was used to characterize the stability of the prepared materials. X-ray diffraction (XRD) data were collected on an ARL X'TRA diffractometer. A Lake Shore VSM 7307 magnetometer was used to characterize the magnetic properties of the materials. Nitrogen adsorption isotherms of composite materials were recorded on an Autosorb-1 MP gas adsorption instrument. High performance liquid chromatography (HPLC) analysis was carried out with an Agilent HPLC System.The morphology and thermal expansion performance of the materials were collected by AFM-IR measurements carried on a nanoIR2 instrument (Anasys instruments Corp. USA) with a MIRcat QCL laser (Daylight solutions Inc., USA).

2.3. Preparation of $Fe_3O_4@SiO_2-NH_2-GO@ZnCB$ (MGO-ZnCB) composite (Fig. S1)

2.3.1. Fe3O4@SiO2-NH2-GO (MGO)

Monodisperse Fe_3O_4 microspheres were synthesized by a solvothermal method [36], which was followed by coating with silica through a sol-gel process [37]. The silica shell can protect Fe_3O_4 spheres from oxidation and agglomeration. The silica-coated Fe_3O_4 was further functionalized with APTES to obtain $Fe_3O_4@SiO_2-NH_2$. Then, 0.2 g GO with carboxyl synthesized from the Hummers method [38], was chemically bonded onto the 0.5 g amino-functional silica-coated Fe_3O_4 spheres through 0.1 g NHS, 0.2 g EDC with 50 mL DMF to achieve the $Fe_3O_4@SiO_2-NH_2-GO$ (MGO).

2.3.2. MGO-ZnCB

An aliquot of $Fe_3O_4@SiO_2-NH_2-GO$ was added according to the yield of ZnCB using a round-bottom flask in oil-bath with magnetic stirring (Supporting Information). Seven different weight of $Fe_3O_4@SiO_2-NH_2-GO$ (2%, 4%, 7%, 8%, 10%, 12%, 15%) were added into the mixed ultrapure water solution of $Zn(NO_3)_2·6H_2O$ (1.1155 g), Na_2CO_3 (0.265 g), 4, 4'-bipyridine (0.39 g), and D-(+)-camphoric acid (0.5005 g), respectively. The suspensions were sonicated for 30 min, and then heated in oil-bath at 120 °C for 2 days with mechanical agitation. The resulting gray powders produced were collected, washed with ultrapure water and ethanol three times, and dried in a vacuum oven to obtain the MGO-ZnCB composites.

2.4. Typical separation procedure using MGO-ZnCB composite

For extraction of BN, racemic solution of BN dissolved in 10 mL acetonitrile (final concentration 0.015 mg/mL) and 20 mg four different composites, including ZnCB, $Fe_3O_4@SiO_2@ZnCB$, $Fe_3O_4@SiO_2-NH_2@ZnCB$ and MGO-ZnCB (10 wt% of MGO), were mixed in vials, respectively. These four solutions were all first