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Construction of a hydrazone-linked chiral covalent organic framework–silica composite as the stationary phase for high performance liquid chromatography

Kai Zhang[a], Song-Liang Cai[a,*], Yi-Lun Yan[a], Zi-Hao He[a], Hui-Mei Lin[a], Xiao-Ling Huang[a], Sheng-Run Zheng[a], Jun Fan[a], Wei-Guang Zhang[a,b,*]

[a] *School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, PR China*
[b] *Guangdong YanJie Pharmatech Co. Ltd., Guangzhou, 510663, PR China*

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ABSTRACT

Covalent organic frameworks (COFs), as an emerging class of crystalline porous organic polymers, have great potential for applications in chromatographic separation owning to their fascinating crystalline structures and outstanding properties. However, development of COF materials as novel stationary phases in high performance liquid chromatography (HPLC) is just in its infancy. Herein, we report the design and construction of a new hydrazone-linked chiral COF, termed BtaMth COF, from a chiral hydrazide building block (Mth) and present a one-pot synthetic method for the fabrication of BtaMth@SiO$_2$ composite for HPLC separation of isomers. The as-synthesized BtaMth chiral COF displays good crystallinity, high porosity, as well as excellent chemical stability. Meanwhile, the fabricated HPLC column by using BtaMth@SiO$_2$ composite as the new stationary phase exhibits high resolution performances for the separation of positional isomers including nitrotoluene and nitrochlorobenzene, as well as *cis-trans* isomers including beta-cypermethrin and metconazole. Additionally, some effects such as the composition of the mobile phase and column temperature for HPLC separations on the BtaMth@SiO$_2$ packed column also have been studied in detail. The successful applications indicate the great potentials of hydrazone-linked chiral COF–silica composite as novel stationary phase for the efficient HPLC separation.

1. Introduction

Covalent organic frameworks (COFs) are an emerging type of crystalline porous organic polymers with well-defined two-dimensional (2D) or three-dimensional (3D) architectures. These materials are built by the connection of molecular building blocks through strong covalent bonds [1–3]. Such crystalline COFs, in the past decade, have been demonstrated to have various potential applications in the fields of gas storage [4–6], heterogeneous catalysis [7–9], drug delivery [10–12], chemical sensor [13–15], and proton conduction [16–18] due to their outstanding properties such as low density, high surface area, permanent nanoscale porosity, as well as excellent thermal and solvent stability.

In recent years, particular attention has been extended to the application of COFs in the analytical chemistry field such as chromatographic separation [19–24]. Different kinds of COF materials, including a β-ketoenamine-linked COF (TpBD [19]), imine-linked COFs (LZU-1 [20,21] and CTpPa-1 [22]), a hydrazone-linked COF [23], as well as a boronate ester-linked COF (COF-5 [24]), have been successfully utilized as new stationary phases for gas chromatography (GC) or capillary electrochromatography (CEC), and the results indicated that porous crystalline COFs were good candidates to be employed for the separation of homologues, positional isomers, and even racemic compounds. In comparison to the studies performed on GC and CEC separations, the attempts of choosing COFs as stationary phases for high performance liquid chromatography (HPLC) separation have been scarcely reported. This may be due to the fact that if the traditionally prepared COFs particles with various sizes and irregular shapes are packed into the HPLC columns directly, it will lead to some shortcomings such as undesirable peak shapes, low column efficiency and high column back-pressure during the HPLC separation. To overcome these problems, a wise strategy has been recently developed by Yan et al., that is, preparing

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* Corresponding authors at: School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, PR China.
E-mail addresses: songliangcai@m.scnu.edu.cn (S.-L. Cai), wgzhang@scnu.edu.cn (W.-G. Zhang).

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COF-based monolithic columns for HPLC separation by incorporating porous COFs into monolithic materials [25]. Another effective and convenient strategy for enhancing the separation performance of COF-based HPLC columns is probably to fabricate uniform spherical COF–silica composites as novel stationary phases. Nevertheless, studies on application of COF-silica composites in HPLC separation are still extremely rare and definitely necessary to be further investigated [26,27].

On the other hand, the design and preparation of chiral COFs have attracted significant attention because of their promising applications such as asymmetric catalysis and chiral separation [22,28–30]. However, only few chiral COF materials have been documented so far, which mainly may be due to their hard syntheses since porosity, crystallinity, and chiral functionality have to be taken into consideration simultaneously. Herein, we firstly report the design and construction of a new hydrazone-linked chiral COF, termed BtaMth COF (Fig. 1), from a chiral hydrazide building block (Mth) and present a one-pot synthetic method for the fabrication of a BtaMth@SiO_2 composite for HPLC separation of isomers. The as-synthesized BtaMth chiral COF displays good crystallinity, high porosity, as well as robust thermal and chemical stability. At the same time, the obtained HPLC column by using the BtaMth@SiO_2 composite as a new stationary phase exhibits relatively high resolution for the separation of positional isomers including nitrotoluene and nitrochlorobenzene in the reverse-phase mode, as well as *cis-trans* isomers including beta-cypermethrin and metconazole in the normal-phase mode. As far as we know, all the separated isomers in the presented work have not been documented on other COF-based stationary phases by HPLC. These results reveal the potential applications of hydrazone-linked COF–silica composite in both positional isomers and *cis-trans* isomers separations.

2. Experimental

2.1. Chemicals and reagents

Spherical silica gel (5 μm, 1000 Å, 300 $m^2 g^{-1}$) was purchased from Fuji Silysia Chemical Ltd. (Aichi, Japan). Syntheses of 3-aminopropylsilica (SiO_2–NH_2) [31] and (*S*)-2-methylbutyl 4-methylbenzenesulfonate [32] were carried out according to the corresponding literature methods. The analytes of nitrochlorobenzene and nitrotoluene were bought from Aladdin Chemistry Co. Ltd. (Shanghai, China), while those of beta-cypermethrin and metconazole were kindly provided from Yingde Greatchem Chemicals Co. Ltd. (Yingde, China). Methanol (MeOH), ethanol (EtOH), 2-propanol (IPA), acetonitrile (ACN), and *n*-hexane (Hex) were of HPLC-grade and used as mobile phases for HPLC separations. All other chemicals were of analytical grade and some of them were dried and purified before used. Stainless steel column tubes were obtained from Jiangsu Hanbon Science and Technology Co. Ltd. (China).

2.2. Instruments

Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured on either a Varian 400 (400 MHz) or a Bruker Avance 500 (500 MHz) with tetramethylsilane (TMS) as internal standard at ambient temperature. The solid-state ^{13}C NMR spectrum was collected on a Bruker AV-400 NMR spectrometer (Bruker, Switzerland) using a standard Bruker magic angle-spinning (MAS) probe with 4-mm (o.d.) zirconia rotors. LC–MS determination was performed on an Agilent LC–MS equipment. Infrared (IR) spectra were determined on a Nicolet FT-IR-170SX spectrophotometer in the range of 4000–400 cm^{-1} by using KBr pellets. Elemental analysis (C, H, and N) was measured on a Perkin-Elmer 240C elemental analyzer. Powder X-ray diffraction (PXRD) measurements were carried out by using a Bruker D8 Advance diffractometer at 40 kV, 40 mA with a Cu-target tube and a graphite monochromator. Thermogravimetric analyses data were acquired on a Perkin-Elmer TGA7 analyzer with a heating rate of 10 °C min^{-1} under air atmosphere. Scanning electron microscopy (SEM) images were recorded on a Maia3 Tescan or a Vega3 Tescan Scanning Electron Microscope at 15.0 kV or 30.0 kV. Nitrogen adsorption-desorption measurement was conducted on a BELSORP-Max gas adsorption instrument. Evaluation of the fabricated column was carried out by employing an HPLC system consisting of a Shimadzu HPLC system SPD-15C, a Shimadzu UV–vis detector, as well as a 7725i injector equipped with a 20 μL sample loop.

2.3. Synthesis of diethyl 2,5-bis((S)-2-methylbutoxy)terephthalate (**1**)

A mixture of (*S*)-2-methylbutyl 4-methylbenzenesulfonate (2.15 g, 9.0 mmol), diethyl 2,5-dihydroxyterephthalate (0.915 g, 3.6 mmol), K_2CO_3 (1.44 g, 10.8 mmol) and DMF (50 mL) was stirred at 100 °C under argon overnight. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Eluent: hexane/EtOAc, 25/1) to yield the desired compound **1** as a light yellow oil (0.980 g, 70% yield). Results of NMR and LC–MS are shown in the Supporting Information.

2.4. Synthesis of (S)-2,5-bis(2-methylbutoxy)terephthalohydrazide (Mth)

A mixture of compound **1** (0.860 g, 2.2 mmol), hydrazine hydrate (0.82 mL, 26.4 mmol), EtOH (30 mL) was heated at 80 °C for 24 h, and then cooled to room temperature. The formed precipitate was collected by filtration and washed with cold EtOH. The crude product was purified by recrystallization from EtOH to offer the chiral building block Mth as white crystals (0.734 g, yield 91%). Results of NMR and LC–MS are shown in the Supporting Information.

2.5. Synthesis of the model compound

A mixture of the Mth (44 mg, 0.12 mmol) and benzaldehyde (26 μL, 0.24 mmol) in MeOH (10 mL) was refluxed for 48 h, during which white solid was precipitated. The solid was isolated by filtration, washed with MeOH, dried at 80 °C under vacuum to yield the model compound as a white solid (65 mg, 88% yield). Results of NMR and LC–MS are given in the Supporting Information.

2.6. Synthesis of the BtaMth COF

A mixture of 1,3,5-benzenetricarboxaldehyde (Bta, 6.5 mg, 0.04 mmol), the chiral building block Mth (22 mg, 0.06 mmol), anhydrous 1,4-dioxane (0.5 mL), and mesitylene (0.5 mL) in a 10 mL vial was stirred for 5 min under argon. A 0.1 mL portion of 3 M acetic acid was added, and the resulting mixture was then bubbled with argon for 15 min. The vial was quickly sealed and heated at 110 °C for 72 h. After cooling to room temperature, the formed precipitate was isolated by filtration, washed with anhydrous THF several times and anhydrous acetone for one time, and dried under vacuum at 120 °C overnight to offer a light yellow solid of chiral BtaMth COF (24.0 mg, yield: 91%). Calcd. for $C_{12}H_{15}N_2O_2$: C, 65.73; H, 6.90; N, 12.78%. Found: C, 62.43; H, 6.87; N, 11.55%. IR (KBr pellet, cm^{-1}): 3287w, 2961w, 2932w, 2876w, 1672s, 1616w, 1526s, 1489m, 1464w, 1412s, 1389w, 1340w, 1300w, 1222s, 1078w,