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Preparation and characterization of dual-template molecularly imprinted monolith with metal ion as pivot

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ABSTRACT

In this work, a method for improving imprinting efficiency of dual-templates molecularly imprinted polymer was developed based on strategy of metal ion as pivot. Two templates, naproxen (NAP) and ketoprofen (KET), were simultaneously imprinted using 4-vinylpyridine (4-VP) as functional monomer and ethylene glycol dimethacrylate (EDMA) as cross-linker with Co^{2+} as pivot. A ternary mixture of dimethyl formamide (DMF)-dimethyl sulfoxide (DMSO)- 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) was used as the porogenic system. The resulting metal ion mediated, dual-templates molecularly imprinted monolith (MDMIM) showed excellent selectivity to the templates and analogues. In contrast to traditionally formulated MIPs made with multi-templates, reduced recognition ability toward targeted analytes on the MDMIM was not found. The structural properties of MDMIM were determined from Fourier transform infrared spectra, mercury intrusion and extrusion experiments and nitrogen adsorption–desorption isotherms. The MDMIM was then tested in the chromatographic mode due to its ability to recognize the templates. The studies of Van't Hoff analysis indicated that the separation of the templates and their analogues on the MDMIM was an enthalpy controlled process. Collectively, metal ion as pivot is demonstrated as an effective method of imprinting dual-templates simultaneously without loss of selectivity.

1. Introduction

Molecular imprinting is a promising way to prepare synthetic polymers featuring receptor or catalytically active sites at a molecular level, which can be created within polymer network via a template synthetic method. After polymerization, the template molecules are removed and the sites left can rebind the targeted molecule highly selectively. Due to their outstanding stability and low cost over bio-antibodies, molecularly imprinted polymers (MIPs) have been applied extensively in different areas such as SPE [1], chromatographic separations [2], sensor [3], drug delivery [4] and artificial antibodies [5].

Most of the researches generally imprints one template (analyte of interest) in the polymer materials with high selectivity. However, the single-template MIPs are not efficient in case of recognition of various targeted analyte simultaneously from complex samples [6–8]. Advantages of the MIPs containing multi-templates imprints are that several different classes

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of compounds can be extracted, separated, assayed, detected, or otherwise analyzed at one time [9]. However, one challenge of the synthetic MIPs made with multi-templates is that they display reduced recognition ability toward targeted analytes. The reduced selectivity was presumably due to the dilution of the number of binding sites per gram of the polymer mixture for each of the templates. In addition, physical mixing the different single-template MIPs was found to provide bad performance versus the MIPs imprinting two analytes in a mixture simultaneously, which may be attributed to blend effect of the molecular recognition properties of the different template materials [10]. In contrast, Sabourin et al. demonstrated that physical mixing the different single-template MIPs was beneficially employed for the simultaneous separation of different stereoisomeric structures [11]. However, the preparation of different single-template MIPs is time-consuming process.

Many efforts were conducted to solve the reduced selectivity of MIPs made with multi-templates. For example, Schweitz et al. reported that the MIPs made with the mixture of templates showed better resolution than the singly imprinted polymers, in which template–template interactions were speculated to be the underlying reason for this increase in the selectivity [12]. Recently, multiple-template MIPs made with a single crosslinking monomer, N, O-bismethacryloyl ethanolamine (NOBE) was found to have better performance versus traditionally imprinted polymers made by crosslinker and functional monomer due to the greater amount of functional monomer available in the NOBE based MIPs for interacting with the templates [13]. However, a general approach to highly selective MIPs containing multi-templates imprints is still lack.

The use of a metallic pivot for self-assembly has been revealed to effectively produce highly specific MIPs [14–23], in which the weak linkage between the functional monomer and template, such as a hydrogen bond or Coulomb force, is replaced by stronger coordination bonding. The stabilization of the functional monomer-template or oligomer-template complex due to a metal ion-mediated self-organized architecture may largely restrain the relative motion of the monomers or oligomer-template. As a result, a higher affinity of the imprint can be achieved using this strategy. Some ions were used as pivot and exploited for selective recognition systems based on MIPs, such as Co^{2+} [14,15], Cu^{2+} [16–18], Ca^{2+} [19], Zn^{2+} [20] and Fe^{3+} [21]. Ketoprofen [22], *R*-mandelic acid [23] and methyl gallate [24] imprinted monoliths have been prepared with the approach by our group.

In view of the facts above, it is intriguing for us to investigate whether the strategy of metallic pivot can be utilized to improve the selectivity of dual-templates molecularly imprinted monolith (MDMIM). Naproxen (NAP) and ketoprofen (KET), non-steroidal anti-inflammatory drugs (NSAIDs) used extensively, were chosen as template, using 4-vinylpyridine (4-VP) as functional monomer, ethylene glycol dimethacrylate (EDMA) as cross-linker. To prepare MIPs in monolithic column form, a ternary mixture composed of ionic liquid, dimethylsulfoxide and dimethyl formamide were used as porogen. Ionic liquid has been employed as green solvents for preparation of MIPs, and not only obtained higher imprinting factor of the MIPs [25], but also achieved monolithic columns with excellent permeability [26]. Dimethylsulfoxide and dimethyl formamide were chosen to solve metal ion and template. The ratio of template to monomer to cross-linker and the type of metal ion on the morphology and selectivity of the MDMIM were investigated in detail. The effects of organic modifier, pH and temperature on the retention for the MDMIM were also studied. In addition, Van't Hoff analysis was applied to study the recognition mechanism.

2. Experimental

2.1. Chemicals and materials

Naproxen (NAP), ketoprofen (KET), ibuprofen (IBU), fenbufen (FBU), fenoprofen (FEP) and flurbiprofen (FLU), were purchased from Dalian Meilun Biology Technology Co., Ltd. (Dalian, China). Ethylene glycol dimethacrylate (EDMA), dimethylsulfoxide-d (DMSO-*d*) and 2,2′-azobisisobutyronitrile (AIBN) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile (ACN, HPLC grade), 4-vinylpyridine (4-VP), methanol, acetic acid, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), ammonium acetate, cobalt acetate, chromium acetate, zinc acetate and nickel acetate were purchased from Kermel Chemical Reagents Development Center (Tianjin. China). 1-Butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) was supplied by Shanghai Chengjie Reagent (Shanghai, China).

2.2. Preparation of MDMIM

In a typical polymerization, a pre-polymerization solution was made with a mixture of template, metal ion, 4-VP, EDMA, DMF, DMSO, [BMIM]BF_4, and AIBN, as shown in Table 1. After sonicated for 15 min, the pre-polymerization mixture was introduced into the stainless steel tube (100 mm × 4.6 mm i.d.). The tube was sealed, and the polymerization was performed in a 60 °C water bath for 24 h. Then the column was connected to an HPLC pump and washed with ACN, acetic acid/methanol (3:7, v/v), and ACN successively to remove unreacted monomer and cross-linker, porogen, template molecule and metal ion.

2.3. Characterization

^{1}H NMR spectra were recorded at a Bruker AVANCE III-400M spectrometer (Bruker BioSpin Group, Swit.) using DMSO-d_6 as solvent. Mercury intrusion and extrusion experiments on the monolithic polymers were performed from vacuum to 60,000 psi using a Quantachrome Instruments Pore Master 60 (Quantachrome Instruments, Boyton Beach, FL, USA).