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A novel hydroquinidine imprinted microsphere using a chirality-matching N-Acryloyl-L-phenylalanine monomer for recognition of cinchona alkaloids

Qi Zhou[a,b], Jing He[a,b], Youwen Tang[a,b,*], Zhiguang Xu[a,b,**], He Li[a,b], Chengcheng Kang[a,b], Jiabing Jiang[a,b]

[a] *Department of Chemistry, South China Normal University, Guangzhou 510006, China*
[b] *MOE Key Laboratory of Laser Life Science, South China Normal University, Guangzhou 510631, China*

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ABSTRACT

Using a combination of molecular imprinting technology and traditional chiral stationary phases, the synergistic effect between chiral monomer and chiral cavity of molecularly imprinted polymers in stereoselective recognition was investigated. We designed and synthesized an amino acid derivative to be used as a novel chiral functional monomer. Monodisperse molecularly imprinted core–shell microspheres using surface imprinting method on silica gel were prepared with hydroquinidine as the pseudo-template molecule for the resolution of cinchona alkaloids. The results showed a significant synergistic effect in stereoselective recognition, confirming our initial hypothesis. Furthermore, our computational simulation and experiments intensively support the hypothetical chiral recognition mechanism for the imprinted microspheres.

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1. Introduction

Molecular imprinting has been widely used as a bionic technology. Molecularly imprinted polymers (MIPs) are prepared by the copolymerization of functional and cross-linking monomers in the presence of a template molecule. The template is then removed from the resulting polymer matrixes by physical or chemical methods, leaving specific binding cavities that are complementary to the template in size, shape, and functional groups [1]. Molecularly imprinted polymers exhibit high selectivity and affinity towards the target molecule. Due to their outstanding molecular recognition capability and stability, MIPs have been broadly applied in areas such as drug delivery [2–4], solid-phase extraction [5–7], chromatographic separation [8–11], biomimetic sensing [12–14], and mimic enzyme catalysis [15–17].

The selection of suitable functional monomer can effectively improve the affinity and recognition ability of MIPs [18]. Currently, the most commonly used functional monomers are methacrylic acid, acrylamide, and 4-vinyl pyridine. In some studies, novel functional monomers have been synthesized for specific types of research and application. Adil Denizli and coworkers [19] prepared a novel molecularly imprinted adsorbent using methacryloylhistidinedihydrate as a new functional monomer to remove heavy metal ions. The imprinted microbeads showed excellent selectivity and high adsorption capacity for target ions. Ken Hosoya [20] used a chiral monomer, (S)-(−)-N-methacryloyl-1-naphthylethylamine, as chiral functional monomer toward the racemic template, and the MIPs showed chiral discrimination toward N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine. Jiang et al. [21] designed and synthesized a cinchonine derivative to be used for the resolution of ketoprofen. It was used as a single chiral monomer, playing a dual role of functional monomer and cross-linker. Gavioli et al. [22] have used cinchona alkaloid derivative as functional monomer and successfully prepared 3,5-dichlorobenzoyl amino acid imprinted polymers with a high template retention factor and improved stereoselectivity.

Molecularly imprinted polymers have been exploited as chiral stationary phases for many years. Previous studies have used an optically pure enantiomer as a template, followed by selection of a suitable non-chiral functional monomer based on the character of the template. Chiral three-dimensional cavities, which are complementary to the space structure and functional group, are

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* Corresponding author at: MOE Key Laboratory of Laser Life Science, South China Normal University, Guangzhou 510631, China. Tel.: +86 20 39310369.
** Corresponding author at: MOE Key Laboratory of Laser Life Science, South China Normal University, Guangzhou 510631, China.
E-mail address: tanglab@scnu.edu.cn (Y. Tang).

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generated by multi-binding site interactions between monomers and template [23]. The traditional chiral stationary phases in liquid chromatography, such as cellulose, amylose, and cyclodextrin, are used as chiral selectors. It is interesting to investigate that chiral selector combined with common molecular imprinting technique for stereoselective recognition.

Quinine (QN), and its stereoisomer quinidine (QD), are cinchona alkaloids with antimalarial activities. Their relatively rigid structures, bulky groups, and hetero-atom functionalities are factors that allow formation of good molecular imprinting sites [24]. Reversed-phase HPLC using ODS columns in combination with acidic mobile phases is the most widely used method. A review has been reported about the analysis of the cinchona alkaloids by high-performance liquid chromatography by David V. McCalley [25]. Molecularly imprinted polymers for recognition of quinine, quinidine, and their analogues cinchonidine (CD), and cinchonine (CN), have been prepared using methacrylic acid as a functional monomer [26–29]. However, the double bond of cinchona alkaloids might react with crosslinkers by radical copolymerization [30], which inevitably reduces the specific binding sites of resulting MIPs. Column efficiency is often affected by peak broadening and tailing due to binding site heterogeneity partly caused by irregular particles.

Using a combination of molecular imprinting technology (MIT) and traditional chiral stationary phases, MIPs were prepared and the synergistic effect between chiral monomer and chiral cavity in stereoselective recognition was investigated. A chiral functional monomer was designed and synthesized according to the chemical structure of the target molecule. Hydroquinidine, the analogue of quinidine, was selected as the pseudo template molecule, thereby avoiding polymerization of the template. Monodisperse molecularly imprinted microspheres were prepared by surface imprinting method on silica gel. We postulated that multi-binding sites might exist between the chiral monomer and template molecule (Fig. 1), and this assumption was strongly supported by the results of our computational simulation and experiments.

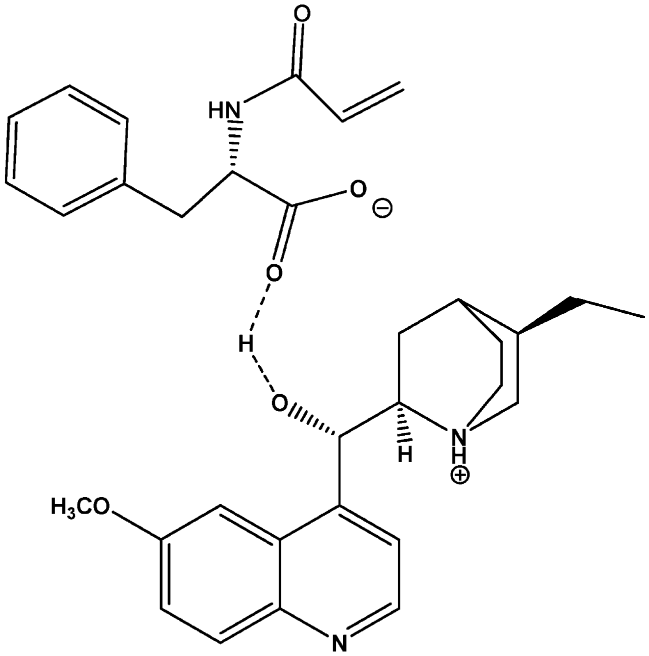

Fig. 1. The pre-arrangement between chiral monomer (a) and hydroquinidine (b).

2. Experimental

2.1. Chemicals and instruments

We made silica particles (diameter about 3 μm) [31] and used them as a support medium for preparation of hydroquinidine imprinted microspheres. Hydroquinidine, quinidine, quinine, cinchonine, and cinchonidine were purchased from Shanghai Ruiyi Medical Technology Co., Ltd. (Shanghai, China). L-Phenylalanine, L-alanine, acryloyl chloride, 3-methacryloyloxypropyltrimethoxysilane (MPTS), ethyleneglycol dimethacrylate (EGDMA), and 2,2′-azobisisobutyronitrile (AIBN) were from Alfa Aesar (Tianjin, China). Toluene, trichloromethane, sodium hydroxide, acetic acid, and methanol were from Kermel (Tianjin, China). All chemical reagents were of analytical or HPLC grade.

Fourier transform infrared (FTIR) spectra were recorded using a PE Spectrum One FT-IR Spectrometer from Perkin Elmer (Foster City, CA, USA). NMR spectra were obtained on a Bruker Vector33 400 MHz spectrometer (Bremen, Germany). UV spectra were obtained using a UV-1700 pharmaspec spectrophotometer (Shimadzu, Japan). The morphology of molecularly imprinted microspheres (MIMs) was investigated using a ZEISS Ultra 55 scanning electron microscope (Oberkochen, Germany). Average pore diameter and surface area of the sorbents were measured by nitrogen adsorption with an ASAP2020 Surface Area and Porosity Analyzer of the Micromeritics Company (Norcross City, GA, USA). HPLC utilized a Shimadzu LC-10AD pump, and a Shimadzu SPD-10A UV/Vis detector was obtained from Shimadzu Company (Kyoto, Japan).

2.2. Preparation of hydroquinidine imprinted core–shell microspheres

2.2.1. Silica-based supports

The silica microsphere surface was activated using the previously described method [32]. 10.0 g of silica microspheres were mixed with 250 mL of aqueous solution containing 8 mol/L hydrochloric acid, and refluxed under stirring for 8 h. The solid product was recovered by filtration, washed with distilled water until neutral, and dried under a vacuum at 120 °C for 12 h. 10.0 g of activated silica microspheres were stirred into the solution containing 110 mL dry toluene and 10 mL pyridine, followed by addition of 10 mL MPTS. The suspension was heated at 110 °C for 24 h, under nitrogen protection. The silica microspheres were collected and washed several times successively with toluene, methanol, distilled water, and acetone. Finally, the vinylated silica microspheres were dried under a vacuum at 80 °C for 6 h, and used for immobilization of the polymer. The activation process is shown in Fig. 2a.

2.2.2. Synthesis of chiral monomers

The synthesis of N-Acryloyl-L-phenylalanine was performed following the procedure [33] shown in Fig. 2b. 3.0 g of L-phenylalanine was dissolved in a well-stirred aqueous solution (15 mL) of sodium hydroxide (0.8 g). Acryloyl chloride (1.5 mL) was added drop-wise over a 30 min period. The reaction was kept at a temperature below 0 °C by cooling in an ice bath. Then, the stirred solution was acidified to pH 1 with HCl. The precipitate was filtered and recrystallized from water (yield: 76%). The physical properties of N-Acryloyl-L-phenylalanine were: melting point: 128–129 °C; IR peak (KBr)/cm^{-1}: 3342, 3028, 1713, 1537; ^{1}H NMR (C_2D_6OS), 8.5 (d, 1H), 7.2 (m, 5H), 6.26 (q, 1H), 6.05 (dd, 1H), 5.58 (d, 1H), 4.50 (m, 1H), 3.40 (s, 1H), 3.10 (dd, 1H), 2.89 (m,1H); ESI-MS *m*/*z* calculated for $C_{12}H_{13}NO_3$ (M−1) was 218.93.

N-Acryloyl-L-alanine [34] was synthesized in a similar manner. L-alanine was used instead of L-phenylalanine and the

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