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A facile one pot synthesis of Chiral imprinted nanospheres with hollow and mesoporous structures

Chang-Long Kao^a, Yan-Fu Chen^a, Ping-Chih Huang^b, and Ching-Yun Hsu^b, Chun-Hsiung Kuei^{a*}

Experiment

Reagents

Cetyl trimethylammonium bromide(CTAB), (3-aminopropyl)triethoxysilane (APTES, 99%) and tetraethoxysilane (TEOS, 98%) as the porous structure agents, L-3,4-dihydroxyphenylalanine (L-DOPA, 99%) and D-3,4-dihydroxyphenylalanine (D-DOPA, 99%) as template were purchased from Sigma (USA), NH₄OH(32%), EtOH(99.5%), HCl(37%) and water were purchased from Merck (Germany), while 4-Formylphenylboronic acid(pB, 97%) as functional recognition element was purchased from Alfa Aesar(USA). All the solvents used in this study were not purified before use.

Instrumentations

Ultraviolet-visible (UV-Vis) absorption spectra were recorded using a Hitachi UV-2550 UV-Vis spectrophotometer. FT-IR spectra were measured using Perkin-Elmer 560 FT-IR spectrometer. The fluorescence properties of all samples were recorded by using Hitachi spectrofluorometer. The emission spectra were recorded in the wavelength range of 400-600 nm with an excitation at 254 nm. The slit widths for excitation and emission were 20 nm. ¹³C, Si, H and B solid state NMR spectra were recorded on a Bruker Avance 400 MHz NMR. XRD diffraction data were collected on a Siemens D-5005 X-ray diffractometer using Cu K α radiation. Nitrogen adsorption and desorption isotherm, surface area and median pore diameter were measured using a Micromeritics ASAP 2020 sorptometer. Transmission electron microscopy (TEM) images were acquired using a Hitachi H7500 transmission electron microscope operated at 80 kV. Dynamic light scattering (DLS) was be used to determine the size distribution profile of materials using Nano BT-90.

One-pot Chiral imprinting reaction

Fabrication of L-DOPA or D-DOPA imprinted hollow and mesoporous nanospheres

The L-DOPA or D-DOPA imprinted silica nanospheres (INSs) were synthesized as follows. 3.64 g CTAB (10mmol), 2mL NH₄OH (32%), 0.8 g of L-DOPA or D-DOPA (4 mmol), and 0.5 g of 4-formylphenylboronic acid (4 mmol) were added to a flash bottle and vigorously stirred in 50mL of EtOH. Until solution became homogeneous, 2 mL of APTES (8.5 mmol) was then added to the solution. The optimized time of imprinting process was monitored by fluorescence spectra, ESI Fig. 1. After imprinting process, 10 mL of TEOS (47.6 mmol) and 5mL of water were finally added and reacted for 1 hour. These as-synthesized materials were dried at 80°C in oven for 1 day. The dried materials were dispersed in 50mL EtOH and washed with 15 mL 3 % HCl solution four times (4 hours), followed with 20 mL water four times (4 hours) and 15 mL EtOH (2 hours). Non-imprinted silica nanospheres (NINSs) were synthesized using the same procedure only without a template.

Optimization of Reaction

To investigate and optimize the imprinting synthesized process of INSs, the characteristic fluorescence emission of 4-formylphenylboronic acid (~ 470 nm) was monitored every 10 minutes. When the difference of fluorescence intensity increased to its maximum value, the following reactions were continued. Fluorescence spectra (ESI Fig. 1) show that the difference of fluorescence intensity increased to its maximum value at 1.5 hours, which was chosen as the reaction time.

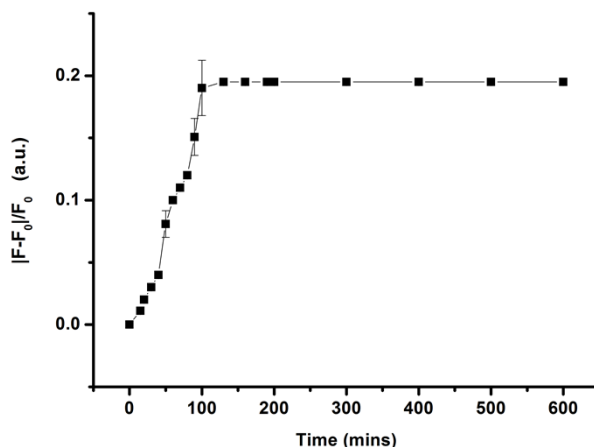


Fig. 1 Fluorescence spectrum during the reaction

Static, kinetic, specific binding and *in vitro* controlled release tests

Static and kinetic binding tests were evaluated by the procedure as shown in references.¹ The *in vitro* controlled release test was evaluated by the procedure as shown in references.^{2a ~ 2c}

The binding isotherm of L-DOPA to INs and NINs was studied in the 0 to 4 mM range of initial concentration of L-DOPA, which shown in the isotherm binding vs L-DOPA concentration (Fig. 4 in the manuscript). In the static binding test, INs or NINs (10 mg) were suspended in an aqueous solution of L-DOPA (4 mM, 10 mL) and briefly ultrasonically dispersed. The suspensions were allowed to stand for 24 hours. Each sample was collected and evaluated by measuring the quantity of residual L-DOPA or by monitoring the fluorescence intensity of pB.

Kinetic binding show the diffusion speed of the binding amounts of L-DOPA with different incubated binding times for INs and NINs, which were shown in Fig. 5(manuscript). The specific binding test and kinetic binding test were evaluated by HPLC analysis. ¹ The specific binding was evaluated by the loading the INs or NINs in an aqueous solution of L-DOPA or L-tyrosine (4 mM, 10 mL). In the kinetic binding test, INs and NINs were added to a solution of L-DOPA in water (100 mM, 50 mL). All filtrates were concentrated and dried before HPLC analysis. Imprinting factor was also calculated by HPLC analysis.

The *in vitro* controlled release tests were followed by the procedure shown in references.^{2a ~ 2c} Two parallel experiments for INs and NNINs were performed. Firstly, INs and NINs particles (10 mg) loaded with L-DOPA, were dispersed in flasks containing various solutions (10 mL) such as phosphate buffer solution (pH 6.0, 7.4 and 9.0) at 25.0°C in a water bath under magnetic stirring (100 rpm). Samples (2 mL) were drawn from the solution at appropriate time intervals to determine the amount of L-DOPA released. Experiments were repeated three times.

Characterization

FT-IR spectrum and solid-state NMR

FT-IR spectra were measured on Spectrum (Perkin Elmer, USA) with the KBr pellet method to characterize INSs (L-DOPA imprinted nanospheres), as-synthesized INSs (INSsAs) and NINSs (non-imprinted nanospheres) with the wave numbers from 400 to 4000 cm^{-1} (ESI Fig. 2).

For INSsAs and INSs, the C=N double bond (imine group or Schiff base) was formed formation direct condensation reaction between the amine group of APTES and the aldehyde group of pB after the self-assembly process. The C=N double bond formation was monitored by observing the decreasing peak of C=O stretching at 1681 cm^{-1} , and increasing peak of the C=N double bond at 1639 cm^{-1} for INSs, at 1655 cm^{-1} for INSsAs, as shown in the FTIR spectra (ESI Fig. 2). C=O stretching band at 1681 cm^{-1} was showed in NINSs which could come from the nonreactive 4-formylphenylboronic acid. The FTIR spectrum also shows a B-phenyl stretching mode at 1406 cm^{-1} and a B-phenyl stretching mode at 1351 cm^{-1} , which may be the overlap of broad modes of silane about 1071 cm^{-1} . This peak is also present in the FTIR spectra of NINSs. A broad O-H stretching mode about 3400 cm^{-1} imply of some hydrolysis. C-H stretching bands show at 2918 cm^{-1} , 2851 cm^{-1} for INSs and NINSs, 2924 cm^{-1} , 2850 cm^{-1} for INSsAs. N-H stretching bands show at 3422 cm^{-1} for INSs, 3400 cm^{-1} for INSsAs, and 3434 cm^{-1} for NINSs.

Solid-state NMR results confirm the C=N double bond (ESI Fig. 3 ^{13}C solid-state NMR). In Fig.3, the peaks at 9.4, 21.2, and 42.9 ppm were assigned to propyl carbons bonded to Si of APTES. The peaks of phenyl carbons appear around 140 ppm. The peaks imine groups appear around 160 ppm. The peak at 132 ppm was assigned to the carbon in the phenyl bonded to imine groups.

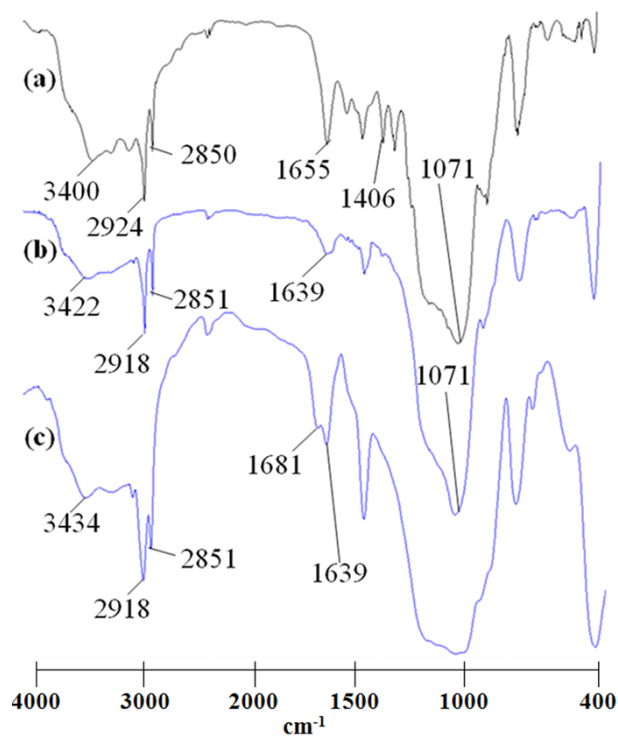


Fig. 2 FTIR spectra of (a) as-synthesized INSs, (b) INSs after extraction, and (c) NINSs.

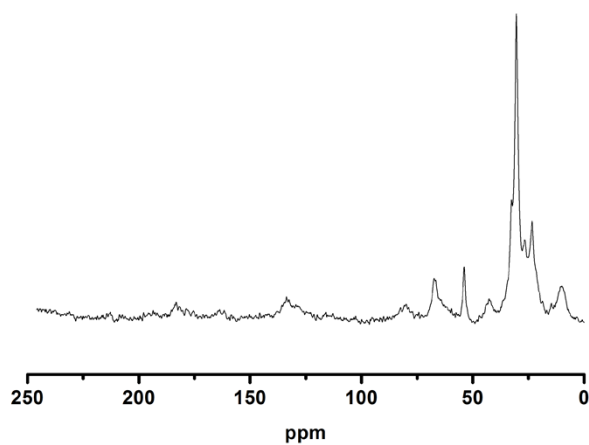


Fig. 3 ^{13}C solid-state NMR of INSs

SAX

INSs and NINSs both show (100) diffraction, which is characteristic of SBA-15 (Fig. 4). Since APTES would disturb the self-assembly of CTAB and precursors, other characteristic peaks indexed to (110) and (200) diffractions are less resolved.³

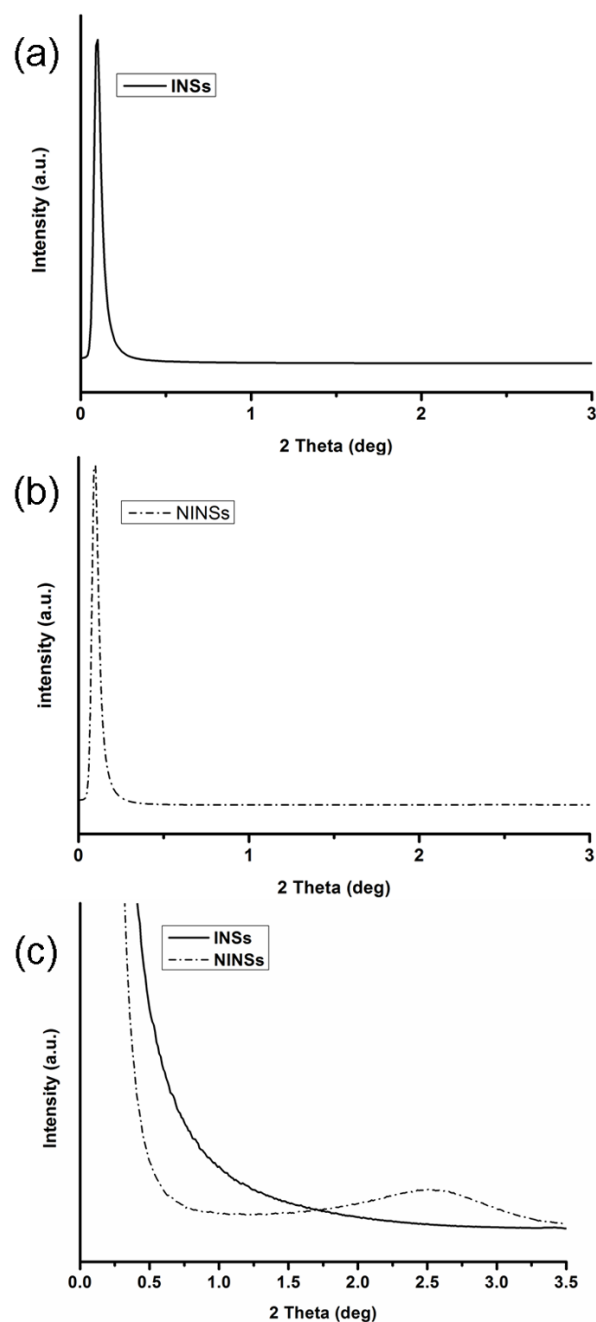


Fig. 4 SAX patterns of (a) INs and (b) NINs (c) zoom in.

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