

# Synthesis of *para*-sulfonatocalix[4]arene-modified silver nanoparticles as colorimetric histidine probes†

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**This Communication reports a novel colorimetric sensor to probe histidine in water based on *para*-sulfonatocalix[4]arene-modified silver nanoparticles; this highly selective sensor allows a rapid quantitative assay of histidine down to a concentration of  $5 \times 10^{-6}$  M, providing a new tool for the direct measurement of histidine.**

Noble metal nanoparticles (NPs), especially of silver and gold, have attracted much attention due to their remarkable optical, electrical and chemical properties.<sup>1–3</sup> In particular, ligand-protected metal NPs have been increasingly explored as analytical tools in many biological fields.<sup>4</sup> The introduction of organic ligands onto NP surfaces provides not only stability to these nanoentities in different solvents, but also desirable surface functionalities.<sup>5</sup> Recently, noble metal NPs modified with macrocyclic molecules have been some of the interesting research topics. For example, Chan and co-workers reported 15-crown-5 functionalized Au NPs for the detection of potassium ions in water.<sup>6</sup> Kaifer and co-workers also synthesized thiolated  $\gamma$ -cyclodextrin-capped Au NPs for the recognition of C<sub>60</sub>.<sup>7</sup> Calixarenes are considered as the third class of host molecules after crown ethers and cyclodextrins, and have demonstrated outstanding complexation activity towards ions, neutral molecules, *etc.*<sup>8</sup> Pochini and co-workers synthesized 1,3-dialkoxycalix[4]arene-modified Au NPs to probe quaternary ammonium cations in CDCl<sub>3</sub>.<sup>9</sup> Unfortunately, an organic medium was required for their analysis, thus restricting tremendously its analytical potential. Therefore, it is a great challenge to construct water soluble noble metal NPs modified with calixarenes.

Water soluble *para*-sulfonatocalix[*n*]arene (*pSC<sub>n</sub>*), which can bind amino acids,<sup>10</sup> has been employed to modify Fe<sub>3</sub>O<sub>4</sub> and Cu<sub>2</sub>O NPs in water.<sup>11,12</sup> Meanwhile, functionalized noble metal NPs have been synthesized to probe various analytes.<sup>13</sup> These findings motivated us to synthesize noble metal NPs modified with *pSC<sub>n</sub>*, which may allow amino acids to be probed in aqueous solution.

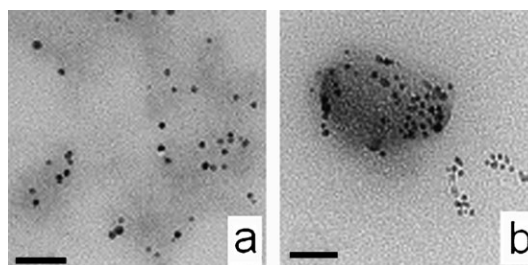
Among the twenty amino acids used as building blocks for proteins, histidine (His) is one of the basic examples due to its aromatic nitrogen-containing heterocyclic imidazole ring and side chain. It is needed for the growth and the repair of tissue,

as well as for maintenance of the myelin sheaths that act as the protector of nerve cells. It is manufactured in sufficient quantities in adults, but children may, at some time, develop a shortage of this important amino acid.<sup>14</sup> For these reasons, several analytical methods have been developed to detect His, such as fluorescence and colorimetry.<sup>15</sup>

In this Communication, we report the synthesis of water soluble *pSC<sub>4</sub>*-modified Ag NPs (*pSC<sub>4</sub>*-Ag NPs) and their application as a novel colorimetric sensor for His.

By reacting silver nitrate with sodium borohydride in the presence of 1.0 equiv. of *pSC<sub>4</sub>* at room temperature for only 5 min, *pSC<sub>4</sub>*-Ag NPs were obtained in water, and characterized by transmission electron microscopy (TEM), FT-IR and UV-vis spectroscopy. A TEM image shows that the modified NPs are highly dispersed and uniform in aqueous solution, with a diameter  $8.0 \pm 1.0$  nm (Fig. 1(a)). Fig. 2 shows the FT-IR spectra of pure *pSC<sub>4</sub>* and Ag NPs modified with *pSC<sub>4</sub>*. Comparing the FT-IR spectra of *pSC<sub>4</sub>* and *pSC<sub>4</sub>*-Ag NPs, significant features can be seen: the peaks for SO<sub>3</sub><sup>−</sup> at 1187 and 1049 cm<sup>−1</sup>, as found in pure *pSC<sub>4</sub>*, are shifted to 1178 and 1036 cm<sup>−1</sup>, respectively, which suggests that the SO<sub>3</sub><sup>−</sup> groups coordinate with the silver atoms on the surface of the Ag NPs. The dramatic differences between the FT-IR spectra, especially for SO<sub>3</sub><sup>−</sup>, indicate that the *pSC<sub>4</sub>* is modified on the Ag NPs. Similar results have been found in Fe<sub>3</sub>O<sub>4</sub> and Cu<sub>2</sub>O NPs modified with *pSC<sub>n</sub>* (*n* = 6, 8), respectively.<sup>11,12</sup>

The UV-vis spectra of *pSC<sub>4</sub>*-Ag NPs recorded after different reaction times are shown in Fig. 3(a)–(c). An adsorption peak emerges at 394 nm that originates from the surface plasmon absorption of Ag NPs.<sup>16</sup> The spectrum recorded after 5 min has the narrowest full-width-at-half-maximum (fwhm), indicating that the synthesized NPs are monodispersed and uniform. The *pSC<sub>4</sub>*-Ag NPs remain stable for at least one month. To further estimate the stability of the *pSC<sub>4</sub>*-Ag NPs, we compared them with mercaptoacetic acid-modified Ag NPs



**Fig. 1** TEM images of *pSC<sub>4</sub>*-Ag NPs (a) before and (b) after addition of  $10^{-4}$  M His. The scale bars are both 50 nm.

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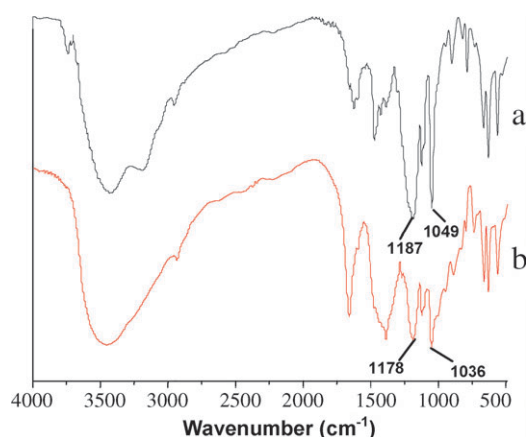


Fig. 2 FT-IR spectra of (a)  $pSC_4$  and (b)  $pSC_4$ -Ag NPs.

(MA-Ag NPs), which were synthesized using quite a long reaction time (7 h) under similar reduction reaction conditions. A MA-Ag NP solution only remained stable for a week (ESI, Fig. S1†). This indicates that  $pSC_4$ -Ag NPs are more stable in aqueous solution due to the macrocyclic effect, which refers to the multidentate macrocyclic ligands modified on the surface of the metal NPs increasing the thermodynamic stability of the NPs compared to open chain ligands.<sup>17</sup>

In order to investigate the molecular recognition ability of  $pSC_4$ -Ag NPs, a variety of amino acids were added to  $pSC_4$ -Ag NP solutions. Fig. 4 displays the color changes and  $R$  values ( $A_{493}/A_{394}$ ) of  $pSC_4$ -Ag NP solutions after the addition of  $10^{-4}$  M solutions of various amino acids. Over 30 min, the solution containing His changed from yellow to red, with a dramatic increase in the absorbance ratio  $A_{493}/A_{394}$ . However, the addition of other amino acids had no effect on the color or adsorption spectrum of  $pSC_4$ -Ag NPs, which indicates that the  $pSC_4$ -Ag NPs responded selectively to His. This response can be attributed to the  $pSC_4$ -Ag NP aggregation induced by His, which is supported by a TEM image (Fig. 1(b)). A schematic of the aggregation process is shown in Fig. 5.  $pSC_4$  possesses an electron-rich cyclic cavity that can fit an imidazole. Therefore,  $pSC_4$  can bind the imidazole and amino residue of His *via* host-guest, electrostatic and cation- $\pi$  interactions. These interactions between a His and two  $pSC_4$ -modified Ag NPs

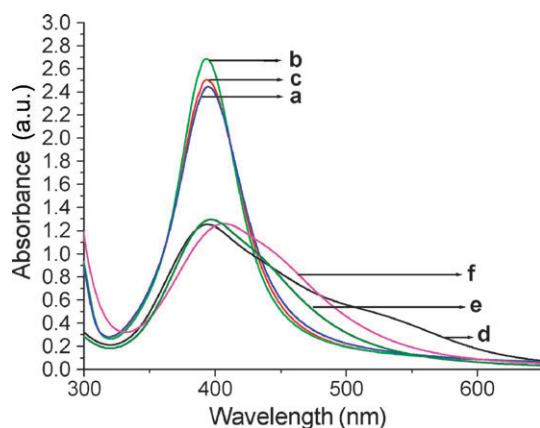


Fig. 3 UV-vis spectra of  $pSC_4$ -Ag NPs recorded after: (a) 1, (b) 5 and (c) 60 min, and MA-Ag NPs recorded after: (d) 4, (e) 7 and (f) 10 h.

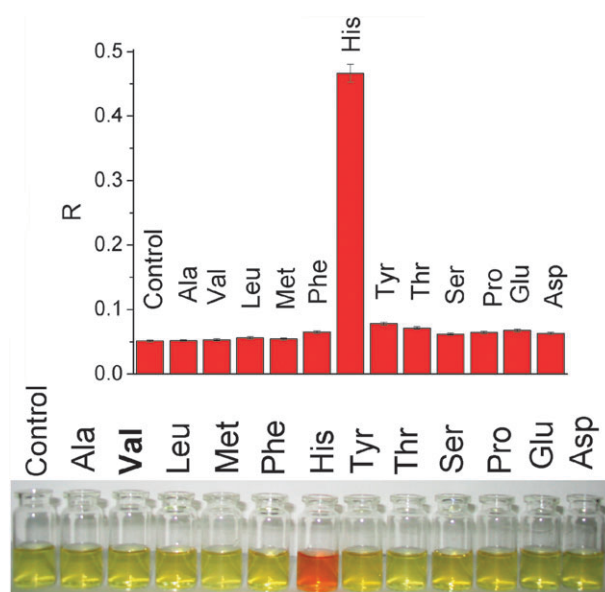


Fig. 4  $R$  ( $A_{493}/A_{394}$ ) (top) and photographic images (bottom) of  $pSC_4$ -Ag NP solutions containing different amino acids. Typically, 1 mL of  $10^{-4}$  M solutions of various amino acids were added to 4 mL  $pSC_4$ -Ag NP solutions, and the combined solutions mixed well for 30 min and then tested.

result in  $pSC_4$ -Ag NPs tending to aggregate more easily than the other amino acids tested.

Fig. 6 indicates the adsorption spectrum changes of  $pSC_4$ -Ag NPs after the addition of different concentrations of His over 30 mins. A linear correlation exists between  $R$  and the logarithm of the His concentration  $C$  over the range of  $5 \times 10^{-6}$ – $10^{-3}$  M. The linear equation is as follows:  $R = 1.825 + (0.334 \times \log[C])$ . The limit of detection ( $3\sigma$ ) for His was  $5 \times 10^{-6}$  M.

In conclusion, water soluble and stable *para*-sulfonatocalix[4]arene-modified Ag NPs were prepared successfully. The modified NPs could be utilized as a novel colorimetric

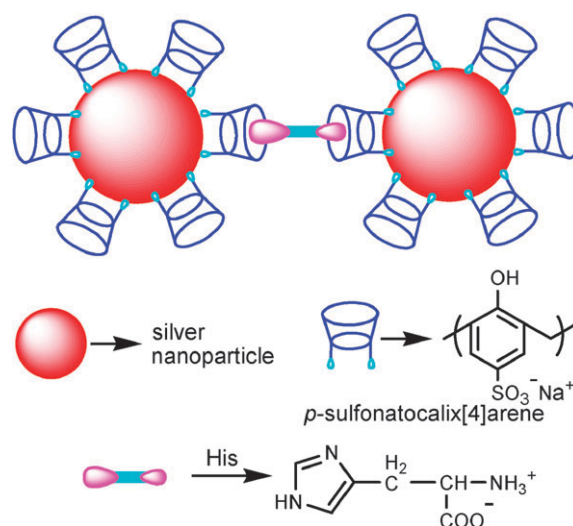
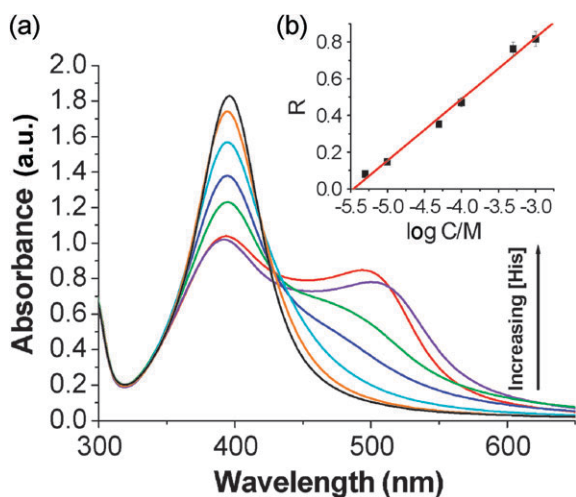


Fig. 5 Schematic representation of the His-induced aggregation of  $pSC_4$ -Ag NPs.



**Fig. 6** (a) The adsorption spectra of  $pSC_4$ -Ag NP solutions with various concentrations of His ( $0$ ,  $5 \times 10^{-6}$ ,  $10^{-5}$ ,  $5 \times 10^{-5}$ ,  $10^{-4}$ ,  $5 \times 10^{-4}$  and  $10^{-3}$  M). (b) The dependence of the  $R$  ( $A_{493}/A_{394}$ ) values of the  $pSC_4$ -Ag NPs on increasing concentrations of His. Typically, 1 mL of various concentrations of His were added to 4 mL  $pSC_4$ -Ag NP solutions. The solutions were then mixed well for 30 min before being tested.

probe for His, which allowed a rapid quantitative assay of His down to a concentration of  $5 \times 10^{-6}$  M.

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