Cite this: New J. Chem., 2012, 36, 819-822

A Ag⁺-selective "off-on" probe based on a naphthalimide derivative[†]

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Received (in Victoria, Australia) 21st November 2011, Accepted 29th December 2011 DOI: 10.1039/c2nj20974h

A new naphthalimide-based derivative L bearing an S-benzyldithiocarbazate moiety was synthesized as an "off-on" probe for Ag⁺. The new probe has high binding selectivity for Ag⁺ in water media with a detection limit of Ag⁺ down to 270 nM. Based on the Ag⁺-induced inhibition of a PET process and restriction of C=N rotation, the coordination mode of 1:1 between L and Ag⁺ was proposed.

Introduction

The silver ion (Ag^+) plays a very important role in many industrial processes and in biology. However, a major problem is the subsequent pollution and harm to the environment and humans because of its frequent use. Excessive Ag⁺ intake can lead to the long-term accumulation of insoluble precipitates in the skin and eyes.¹ Accordingly, the recognition and sensing of Ag^+ has been an especially active research area.²

The traditional analytical methods used for the detection of this ion include various instrumental techniques such as atomic absorption, plasma emission spectroscopy and anodic stripping voltammetric as well as potentiometric methods based on ion selective electrodes.³ However, the direct use of these techniques is restricted owing to the interference caused by matrix elements and the lack of certified references for extreme trace levels of metals in different materials. Therefore, reliable and efficient analytical methods are required for the detection of Ag⁺ at low levels in a wide variety of biological and environmental matrices.

Fluorescent probes are powerful tools for monitoring biologically relevant species in vitro/in vivo, because of their simplicity and high sensitivity,⁴ so the development of fluorescent and colorimetric probes for the detection of Ag⁺ has attracted significant attention. So far, probes reported for Ag⁺ have been classified according to their structures as cyclic N, O, S-donor crown ethers based probes,5 acyclic N, O, S-donor crown ethers based probes,⁶ excimer based probes,⁷ Ag⁺ $-\pi$ interaction utilizing probes,⁸ porphyrin or phthalocyanine based probes,⁹ reaction based probes and probes based on polymers, quantum dots, nanoparticles, DNAs or oligonucleotides.¹⁰ Although considerable efforts have been devoted to the development of fluorescent probes specific for Ag⁺, probes with a fluorescent enhancement technique for Ag⁺ still remain rare.

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Scheme 1 Synthesis route of L.

Due to excellent photophysical properties, the naphthalimide derivatives have been extensively applied to the design of colorimetric and fluorescent probes. The photophysical properties can be easily fine tuned through judicious structural design either by the aromatic "naphthalene" moiety itself, or at the "N-imide site", to make their absorption and fluorescence emission spectra lie within the UV and visible regions.¹¹ In general, compounds containing acyclic C=N bonds show weak fluorescence, while compounds bearing cyclic C=N bonds through blocking the C=N isomerization are significantly fluorescent. Therefore, it is reasonable to amplify fluorescence upon binding metal ions to an elaborately designed molecular framework containing the acvclic C=N bond.^{6a,12,13} With this in mind, we can reasonably expect that the C=N isomerization may also be inhibited by Ag⁺ complexation to the recognition moiety linked to the fluorophore. Furthermore, an S-benzyldithiocarbazate motif with S and N donor atoms established high affinity for thio- or aminophilic metal ions such as Ag⁺. Therefore, it is anticipated that a selective fluorescence "turn-on" probe for Ag⁺ can be established with a naphthalimide derivative L. The synthesis route of probe L is shown in Scheme 1. The structures of L were characterized by NMR and MS spectra (Fig. S1-S3, ESI⁺).

Experimental

Reagents and instruments

All reagents and solvents are of analytical grade and used without further purification. The metal ions employed are

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[†] Electronic supplementary information (ESI) available: Experimental details and spectra of probe L. See DOI: 10.1039/c2nj20974h

NaCl, AgNO₃, MgCl₂· $6H_2O$, PbCl₂, CaCl₂· $2H_2O$, FeCl₃· $6H_2O$, CrCl₃· $6H_2O$, CdCl₂, Zn(NO₃)₂· $6H_2O$, CoCl₂· $6H_2O$, MnCl₂· $4H_2O$, CuCl₂· $2H_2O$, HgCl₂, NiCl₂· $6H_2O$, respectively.

Fluorescence emission spectra were obtained on a HORIBA Fluoromax-4 spectrofluorometer. UV-vis spectra were obtained on a Beckman DU-800 spectrophotometer (USA). Nuclear magnetic resonance (NMR) spectra were measured with a Bruker AVIII-500 spectrometer and chemical shifts were given in ppm from tetramethylsilane (TMS). Mass (MS) spectra were recorded on a Thermo TSQ Quantum Access Agilent 1100.

General procedure for spectroscopic measurements

A stock solution of L (0.5 mM) was prepared in DMSO. To 5 mL glass tubes, 0.10 mL L (0.5 mM) and a proper amount of Ag^+ stock solution (1.0 mM) were added subsequently and then diluted with ethanol–water (8:2, v/v, pH 6.5, 50 mM HEPES). The resulting solution was mixed thoroughly. For all measurements, excitation and emission slit widths were 5 nm, excitation wavelength was 370 nm.

Synthesis of probe L

Compounds 1 and 3 were synthesized following the reported method.¹³ Compound 2 was obtained according to our previous work.¹⁴

Compound L: under N₂ gas, compound 2 (582 mg, 1.5 mmol) and compound 3 (375 mg, 1.8 mmol) were dissolved in ethanol (50 mL). The reaction solution was refluxed for 6 h and stirred. The precipitate so obtained was filtrated and washed with ethanol three times. The crude product was purified by recrystallization from ethanol to give light yellow L (626 mg, 75%). ¹Η NMR (δ: ppm, DMSO-d₆): 13.38 (s, 1H, OH), 10.63 (s, 1H, NH), 8.57 (s, 1H, ArH), 8.55-8.56 (d, 1H, ArH), 8.54 (s, 1H, ArH), 8.41-8.43 (d, 1H, ArH), 7.87-7.90 (t, 1H, ArH), 7.76-7.78 (d, 1H, ArH), 7.43 (d, 1H, ArH), 7.41 (s, 1H, ArH), 7.31-7.34 (m, 2H, ArH), 7.25-7.28 (t, 1H, ArH), 7.20–7.22 (d, 1H, ArH), 6.75–6.77 (d, 1H, ArH), 6.71-6.72 (d, 1H, ArH), 4.49 (s, 2H, CH₂), 4.02-4.05 (t, 3H, CH₂), 1.58–1.64 (m, 2H, CH₂), 1.32–1.39 (m, 2H, CH₂), 1.05–1.08 (t, 3H, CH₃). ¹³C NMR (δ : ppm, DMSO- d_6): 195.91 (C=S), 163.83, 163.19 (C=O), 159.35, 158.63, 158.05 (ArC), 143.99 (C=N), 137.23, 132.94, 131.96, 129.70, 129.42, 129.34, 128.96, 128.53, 127.80, 127.70, 124.05, 122.72, 117.56, 117.02, 113.44, 111.87, 107.65 (ArC), 56.50, 30.13, 20.27, 19.02, 14.18. MS (ESI) 586.12 [M]⁻, 1136.45 [2M]⁻.

Results and discussion

Photophysical properties of L

L shows a broad absorption band (Fig. 1) at λ_{max} 368 nm in the absorption spectrum, which is due to an intraligand $\pi - \pi^*$ transition. When excited at 370 nm ($\varepsilon = 25\,000$ L cm⁻¹ mol⁻¹), it exhibits a weak fluorescence emission band at λ_{max} 523 nm (Fig. 3(a)). The band is typical of an excited state intramolecular proton transfer (ESIPT) phenomenon. The band has low intensity because of quenching due to a photoinduced electron transfer (PET) mechanism, which comes into play due to the



Fig. 1 Absorption spectrum of 10 μ M of L at pH 6.5 in the ethanol–water solution (8:2, v/v, 50 mM HEPES).

availability of the lone pairs of N of the -C = N group and O of the OH group, which cause quenching.^{6a}

Effects of pH on L and L with Ag⁺

The pH response of the new probe L to Ag^+ was first investigated as depicted in Fig. 2. The results revealed that the fluorescence of the free L was insensitive to pH in the range of 4.0–8.0. However, in the presence of the Ag^+ , there was an obvious fluorescence off–on change of L in the pH range from 4.0 to 8.0. Probe L showed the highest fluorescence response toward the Ag^+ under pH 4.0–6.5, and pH 6.5 was chosen as an optimum experimental condition in that L could work with very low background fluorescence.

Fluorescent signaling of Ag⁺

The fluorescence spectra of L in the presence of different metal ions in ethanol–water solution (8:2, v/v, 50 mM HEPES, pH 6.5) were then recorded (Fig. 3a). The probe itself exhibits a weak fluorescence emission band at λ_{max} 523 nm as expected upon excitation at λ_{max} 370 nm. It is because of the efficient photoinduced electron transfer (PET) quenching, which comess from the availability of the lone pairs of N of the C=N group,



Fig. 2 Influences of pH on the fluorescence spectra of L (10 μ M) and L (10 μ M) plus Ag⁺ (50 μ M) in the ethanol–water solution (8 : 2, v/v). The pH was modulated by adding 1 M HCl or 1 M NaOH in HEPES buffers.



Fig. 3 (a) Fluorescence spectra of 10 μ M of L in the presence of 50 μ M of various metal ions at pH 6.5 in the ethanol–water solution (8 : 2, v/v, 50 mM HEPES). (b) Fluorescence response of 10 μ M of L to 10 μ M of Ag⁺ or to 50 μ M of other metal ions (the black bar portions) and to the mixture of 50 μ M of other individual metal ions with 10 μ M of Ag⁺ (the gray bar portions).

S of the C=S group and O of the OH group,¹⁵ and rotation of the acyclic C=N bond.¹² However, the fluorescence spectrum of the probe L shows enhancement in the intensity of the signal at 523 nm upon binding with Ag⁺, the increase in the fluorescence intensity can be attributed to the PET process being inhibited upon complexation of the Ag⁺, N of the C=N group, S of the C=S group and O of the OH group, and fluorescence is restored from the off to on signal (about 10 fold), and meanwhile this significantly enhanced fluorescence is somewhat due to the formation of a complex L-Ag⁺ in which the rotation of the acyclic C=N bond is frozen. Among other tested cations, under the identical conditions, only Hg²⁺ caused the ignored fluorescence change. The low background fluorescence of L and the large enhancement in the fluorescence of the Ag⁺-bound form of this probe would make it more advantageous than the reported on-off type fluorescent silver probes in terms of sensitivity and selectivity concerns.

We then examined the fluorescence responses of 10 μ M of L to 1 equiv. of Ag⁺ in the presence of 5 equiv. of other metal ions, respectively. No significant variation in fluorescence intensity is found by comparison with that without other metal ions besides Ag⁺ (Fig. 3b). From the above



Fig. 4 (a) Fluorescence response of 10 μ M of L with various concentrations of Ag⁺. (b) Linear fluorescence intensity (*F*/*F*₀) of L (10 μ M) upon addition of Ag⁺ (0.5–9 μ M).

experimental results, it is suggested that L was a good Ag^+ -specific probe under aqueous conditions.

To learn more about the electronic properties of **L** as a probe for Ag^+ , fluorescence titration was carried out. Fig. 4 illustrates the emission response of probe **L** with increasing Ag^+ concentration. The fluorescence intensity of a 10 μ M solution of **L** at 523 nm enhanced with a slight "red shift" upon the increasing addition of Ag^+ , while the shape of the emission band is not changed. Furthermore, the F/F_0 was well proportional to the amount of Ag^+ (5.0×10^{-7} – 9.0×10^{-6} M) with a good linear correlation (R = 0.999). The detection limit was 270 nM (based on S/N = 3). The result showed that the probe **L** was capable of detecting Ag^+ both qualitatively and quantitatively.

Possible sensing mechanism

The method of continuous variation (Job's method) was used (Fig. 5) to determine the stoichiometry of the L-Ag⁺ complex. As expected, the result indicated a 1:1 stoichiometry of Ag⁺ to **L** in the complex, which was also supported by the Benesi–Hildebrand method (Fig. S4, ESI[†]).¹⁶ The association constant *K* was determined from the slope to be $5.4 \times 10^5 \text{ M}^{-1}$, by plotting the fluorescence intensity $1/(F - F_0)$ against $1/[\text{Ag}^+]$. This *K* value is comparable to the affinities of the reported



Fig. 5 The Job's plot indicating the 1:1 stoichiometry for the L-Ag⁺ complex, the total concentration of L and Ag⁺ was kept fixed at 20 μ M.



Scheme 2 Proposed mode for the L-Ag⁺ complex.

L + Ag

compounds containing a tripodal Schiff-base probe based on an aromatic platform (with a *K* value of $(2.9 \pm 0.1) \times 10^3 \text{ M}^{-1}$),^{6a} and fluorescein-based probe (with a *K* value of $3.5 \times 10^3 \text{ M}^{-1}$).^{6b}

The ¹H NMR experiment was performed to understand the nature of $L-Ag^+$ interactions. The comparison of ¹H NMR spectra of L and L mixed with 1.0 equiv. of Ag^+ is shown in Fig. 6. Apparently, the addition of Ag^+ into the solution of L led to an apparent downfield shift of the signals of –OH and –NH to certain degrees.

On the basis of the above results, the plausible binding mechanism of L in the present system is schematically depicted in Scheme 2. N of the C=N group, S of the C=S group and O of the OH group are engaged in complexation.

Conclusions

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In conclusion, we have developed a new fluorescent probe for Ag^+ to induce enhanced fluorescence change. The fluorogenic probe was selective and sensitive for Ag^+ , capable of detecting the metal ion down to 270 nM. The probe was easily prepared

and found to be stable in both alkaline and acidic solutions. The design strategy and remarkable photophysical properties would help to extend the development of the fluorescent probe for metal ions. Further studies including the design of new analogues of **L** with good solubility in water which enable the practical application of these types of Ag^+ probes will be implemented.

Acknowledgements

This work was financially supported by the Research and Training Foundation of Hainan Medical University (No. HY2010-004) and the National Natural Science Foundation of China (No. 21007087).

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