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Isothiouronium-based amphiphilic gold nanoparticles with a colorimetric response to hydrophobic anions in water: a new strategy for fluoride ion detection in the presence of a phenylboronic acid

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Abstract

Gold nanoparticles modified with isothiouronium-derived amphiphile units **1** were prepared by the reduction of $AuCl_4^-$ $(n\text{-}C_8H_{17})_4N^+$ with $NaBH_4$ in the presence of bis(5-(*N*-(2-(2-methoxyethoxy)ethyl)-*N*-methyl-*S*-isothiouronio)pentyl) disulfide **2**. The obtained nanoparticles **1** showed a selective coloration for hydrophobic anions in water, possibly due to an anion exchange and subsequent aggregation. On the basis of this observation, the detection of F^- in water has been achieved using 3-nitrophenylboronic acid as a mediator at pH 5.5, thereby providing a new strategy for the design of a F^- sensory system.

Keywords: Isothiouronium unit; Gold nanoparticle; Colorimetric response; Hydrophobic anion; Fluoride ion

Isothiouronium units, which are synthetic intermediates for the conversion of alkyl halides to the corresponding thiols,[1] possess the following intriguing properties as a functional group: (1) similarity with the guanidyl group; (2) high acidity of the NH group; and (3) high synthetic susceptibility. Due to the combination of the Lewis acidity and synthetic versatility, isothiouronium units can serve as not only anion-binding units in artificial receptors[2] but also cationic detergents in pharmaceutical chemistry.[3] Recently, by exploiting the specific interaction of isothiouronium ion pendants with an oxoanion guest, the supramolecular functionalization of a water-dispersible nanotubular graphite assembly was successfully attained.[4] Our ongoing program to develop anion-detectable fluorescence sensors has led to the use of the isothiouronium unit as a suitable anion-binding site.[5] Further, we fabricated an isothiouronium-organized monolayer for the selective interaction of anions at the air–water interface and proposed that the assembled structure could be feasible for the detection of oxoanions in water.[6] A nanometer-sized monolayer-protected gold cluster provides an efficient alternative for the abovementioned organization.[7] The unique optical properties due to the surface plasmon band[8] allowed us to develop isothiouronium-coated gold nanoparticles as colorimetric sensors for anions in aqueous MeOH solution.[9] In this Letter, newly synthesized nanoparticles **1** are described, wherein the amphiphilic monolayer on the nanoparticle surface comprises not only a hydrocarbon chain close to the gold surface to provide a tightly packed protection for the nanoparticle but also the oxoethylene-appended isothiouronium

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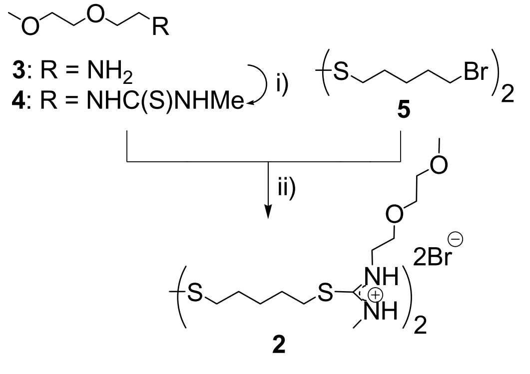
unit to impart sufficient stability to the nanoparticles in water. As described below in detail, we observed that highly dispersed **1** in water display the selective colorimetric detection of hydrophobic anion such as PF_6^-. Although a number of synthetic hosts that can recognize anion species have been reported so far,[10] examples for specific detection for hydrophobic anions are still rare. In this regard, previously reported polythiophenes[11] and gold nanoparticles[12] employed cationic *imidazolium* units for detecting the anion. We report for the first time isothiouronium-based systems that are capable of providing a colorimetric response to hydrophobic anions. Further, as an interesting approach using the abovementioned property, we investigated whether the presence of 3-nitrophenylboronic acid (NPBA) induces a color change upon the addition of F^- to an acidic solution containing **1**. A new strategy for the detection of F^- in water is proposed here.

For the synthesis of the capping agent, a disulfide with ethylene glycol-appended isothiouronium units at the terminal positions **2** was targeted; the starting material, 2-(2-methoxyethoxy)ethylamine **3**,[13] was allowed to react with MeNCS to afford the corresponding thiourea **4** in 75% yield. This was followed by the reaction with disulfide **5**[9] to afford the desired **2**[14] in 53% yield (Scheme 1).



Scheme 1. Reagents and conditions: (i) MeNCS, MeOH, rt, 75%; (ii) dry EtOH, 70 °C, under Ar, 53%.

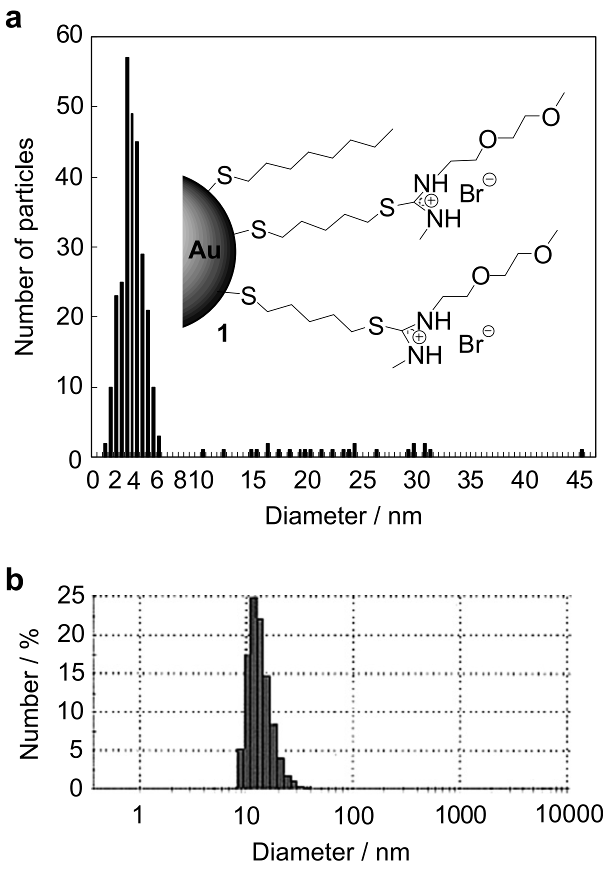


Fig. 1. (a) Histogram of the Au core diameter measured from the TEM image for **1**. (b) The histogram of the nanoparticle diameter measured from DLS for **1**.

The obtained **2** was then used to prepare Au nanoparticles **1** by the following method: **2** (0.536 mmol) and 1-octanethiol (1.06 mmol) were added to a toluene solution of $AuCl_4^-$ $(n\text{-}C_8H_{17})_4N^+$ generated in situ by treating an aqueous solution of $HAuCl_4$ (2.04 mmol) with *n*-tetraoctylammonium bromide (2.15 mmol). The reaction mixture was then treated with $NaBH_4$ (6.56 mmol) to obtain the targeted nanoparticles **1**. A FT-IR measurement of **1**, which showed the vibration bands due to the isothiouronium unit (3418, 1621, 1519, 1106 cm^{-1}), confirmed that **1** was capped by ligands with the isothiouronium units. We attempted to obtain the average Au core diameter by performing transmission electron microscopy (TEM) measurements; Figure 1a shows the size distribution histogram of 299 nanoparticles, 92% of which had an average diameter of 3.8 nm with a standard deviation of 0.82. However, we observed that a small amount of larger-size particles (>10 nm) were also produced. Under the synthetic conditions where [Au]/[thiol ligand] = 1, particles with an average radius of 3.8 nm were mainly formed, which may utilize almost all the available thiols because of their relatively large surface area. Further, a small amount of $AuCl_4^-$ may be transferred from the aqueous phase to the toluene phase due to the amphiphilic property of the ethylene glycol-appended isothiouronium ligand, possibly occurring to grow into insufficiently protected Au clusters that eventually aggregate to form large particles. We also examined the size distribution of the particles in water by means of dynamic light scattering (DLS) with a He–Ne laser (633 nm, 4.0 mW) as the excitation source; the results suggest that well-isolated particles with an average diameter of 35.4 nm exist in water (Fig. 1b). The value of the average diameter, which is considerably larger than that of the core, can be explained on the basis of the hydrated ethylene glycol chain on the coated ligand as well as a partial aggregation. Comparing these two values, we decided that the obtained particles can be regarded to be spherical and the average diameter to be (5.4 ± 3.0) nm from the analysis of the histogram of 299 particles, which is shown in Figure 1a. From the value, we determined an average number of 4800 gold atom/core of 5.4 nm diameter according to Leff's model.[15] Further, elemental analyses (C, 17.28; H, 3.48; N, 3.33; S. 8.00; Au, 57.62) allow us to calculate the average ratio of Au atoms to thiol ligands as 2.25. Thus, the number of ligand molecules attached to one Au particle is approximately 2100 ([isothiouronium unit]/[1-octanethiol] = 11). The ξ potential of the particle was estimated to be 37.1 mV, indicating that the surface was cationic.

The obtained particles are well dispersed and red in color in water, and the optical properties show a λ_{max} value of 524 nm ($\varepsilon = 9.8 \times 10^6\ M^{-1}\ cm^{-1}$). It is observed that the particles are considerably stable in water; they do not precipitate within one month. It is well known that nanosized controllable Au nanoparticles with a monolayer-coated surface show aggregation-induced color changes based on the sensitivity of the surface plasmon band.[8] Thus, the exploration of how **1** could exhibit such a phenomenon led us to investigate the colorimetric detection of anions using UV/vis spectroscopy in H_2O with NaCl (300 mM). The addition of carboxylates such as AcO^-, malonates and citrates, and halogen ions except for I^- to the solution induced no change in the plasmon band. A slight change in the absorption was obtained upon the addition of HPO_4^{2-}. We focused on the moderate response obtained upon the addition of I^- to the solution (vide infra) despite its low basicity. This observation led us to investigate whether hydrophobic anions would induce a color change in the solution. As a result, a significant colorimetric change from red to bluish-violet was observed in the case of PF_6^- addition; this indicates a bathochromic shift of 26 nm in the surface plasmon band with an increase in the intensity of extinction ranging from 600 to 700 nm within 4 min (Fig. 2). During the initial stages, the particles were highly dispersed in the solution; time-dependency on the spectral change was monitored in which the intensity of the signal at 550 nm was gradually decreased to precipitate after 2 h. The change in the plasmon band is clearly due to an aggregation with the reduced interparticle distance that was triggered by the added PF_6^-. Indeed, TEM image of the solution in the presence of KPF_6 indicates a macroscopic aggregate structure compared to the KPF_6-free sample (see Supplementary data). To estimate the anion selectivity based on colorimetry, we employed a ratiometric method that is not affected by the sample conditions. The extinction intensities ($E_{525\ nm}$ and $E_{640\ nm}$) at short wavelength (525 nm) and long wavelength (640 nm) were used since they were related to the quantities of the highly dispersed and aggregated species, respectively. Because the plasmon band due to the anion-induced aggregation is time-dependent, the measurements were carried out within 4 min. Figure 3 shows the plots of the ratio ($E_{640\ nm}/E_{525\ nm}$) as a function of incremental concentrations of anions (F^-, Cl^-, Br^-, I^-, AcO^-, HPO_4^{2-}, malonate, citrate, SCN^-, and PF_6^-) in H_2O with NaCl (300 mM). Significant responses to the hydrophobic anions were found to be in following order: $PF_6^- > SCN^- > I^-$; an intense color change was monitored during the addition of 20 mM of PF_6^-. The value of $E_{640\ nm}/E_{525\ nm}$ (0.800) is larger than with the values for other anions under similar conditions by a factor of 2.0 for SCN^-, 2.4 for I^-, and 2.4 for HPO_4^{2-}. These results indicate that strongly hydrated anions do not induce the aggregation, whereas the color change induced by hydrophobic anions can be explained on the basis of the change in their water miscibility via anion exchange on the surface of **1**. Indeed, when PF_6^- (20 mM) was added to the aqueous solution of **1** (1.2×10^{-7} M), an effective phase transfer from the aqueous to the organic (CH_2Cl_2) phase occurred after shaking (see Supplementary data). Subsequently, the organic phase became colored, while the plasmon band in the water phase almost disappeared. Notably, the

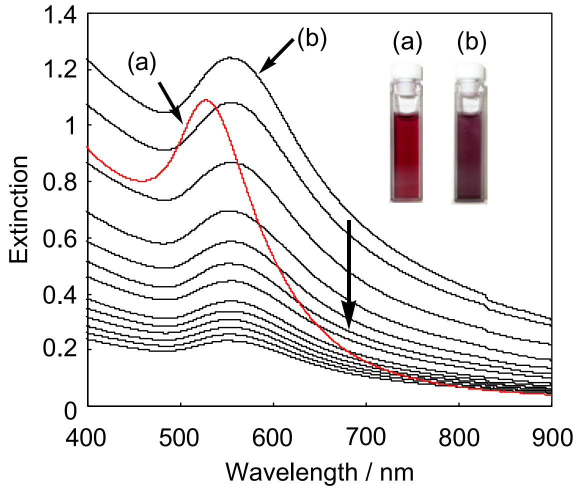


Fig. 2. Time-dependency of UV/vis spectra of **1** (1.2×10^{-7} M) in the presence of KPF_6 (20 mM) in H_2O with NaCl (300 mM) at 25 °C. The red line denotes the spectrum of **1** and the black lines denote the spectra of **1** with KPF_6, which were measured after 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 min.

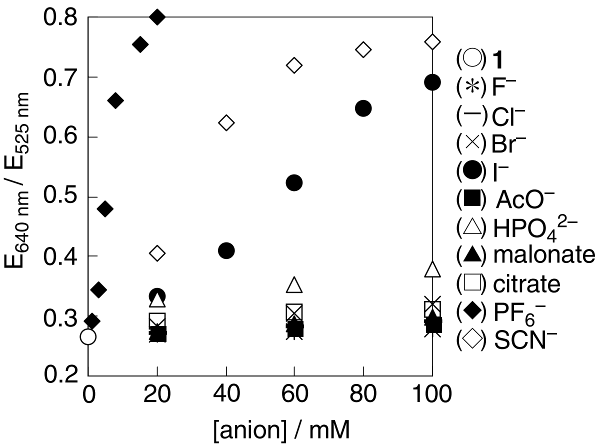


Fig. 3. Changes in the extinction ratio ($E_{640\ nm}/E_{525\ nm}$) upon the addition of an incremental amount of anions as potassium salts into the aqueous solution of **1** (1.2×10^{-7} M) with NaCl (300 mM) at 25 °C. The data were collected within 4 min after mixing **1** with the anions.

transferred particles displayed no signs of aggregation in the organic solution, thereby suggesting that the phase transfer of **1** was achieved.

The colorimetric response induced by hydrophobic anions on **1** allows us to propose a new design for the sensor system for F^-. As shown in Figure 3, F^- ions never induce a color change in **1** in H_2O because of their high Gibbs hydration energy.[16] However, the use of a phenylboronic acid as a mediator may overcome the difficulty; this is because phenylboronic acid is known to interact with F^- to form trifluoroboronate anions [$Ar–BF_3^-$] in aqueous media.[17] The fluoride ion-appended hydrophobic anion would be feasible for the colorimetric response based on the aggregation of **1**. With this strategy in mind, we measured the UV/vis spectra of **1** in the presence of 3-nitrophenylboronic acid (NPBA) (5 mM) upon the addition of incremental amounts of KF in the MES buffer solution (pH 5.5) (MES = 2-(*N*-morpholino)ethanesulfonic acid). It is important to maintain an acidic condition to avoid the interference of OH^- with NPBA.[17a] As expected, we detected a spectral change by increasing concentration of F^- in the solution (Fig. 4). The control measurements using NPBA-free conditions at pH 5.5 afforded almost no spectral change, even in the presence of excess KF. The ^{11}B NMR spectra of NPBA (5 mM) in an acidic condition (pH 5–6) that is adjusted by the addition of HCl showed a signal at 29.0 ppm, which was indicative of sp^2-boron. The presence of KF (200 mM) in the conditions allowed us to detect new peaks at 12.0 and 4.6 ppm, which is attributable to the formation of tetrahedral fluoride adducts $Ar–B^-(OH)_{3-n}F_n$ ($n = 1–3$). We can infer that the fluoride-inserted boronates with the hydrophobic aromatic ring could induce the aggregation of **1** via an anion exchange process. Currently, the development of colorimetric F^- sensors that are capable of operating in aqueous solutions has become one of the interesting research projects pertaining to the molecular recognition of anions, but it is still in its infancy.[18] Although the preliminary results represented in this study require the improvement of the responsive ability towards F^-, our proposed system using a phenylboronic acid as a mediator has a conceptual novelty with regard to the sensing principle for the detection of F^- in water.

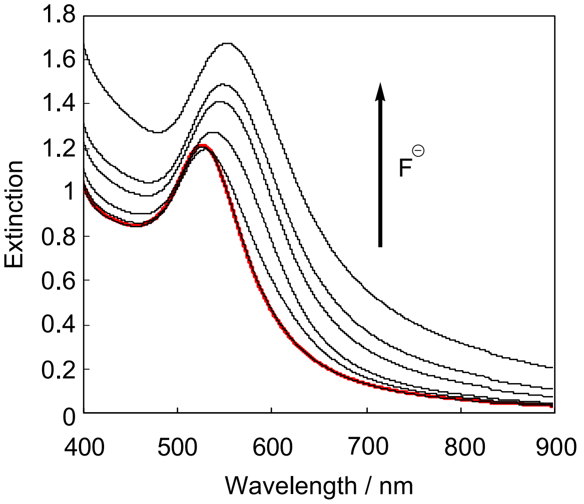


Fig. 4. UV/vis spectra of **1** (1.2×10^{-7} M) in the presence of NPBA (5 mM) upon the addition of incremental amounts of KF in MES buffer solution (300 mM, pH 5.5) at 25 °C; [KF] = 0, 40, 80, 120, 160, 200 and 240 mM. The data were collected within 4 min after mixing **1** with KF.

In conclusion, this Letter describes the newly synthesized amphiphile nanoparticles coated by ethylene glycol-appended isothiouronium units. It shows the colorimetric detection of hydrophobic anions in water through a particle aggregation process based on anion exchange on the surface. This observation allows us to propose a new strategy for the colorimetric detection of F^- in water, that is, the use of NPBA, which interacts with F^- under acidic conditions to provide a fluoride-inserted phenylboronate, serves as a mediator towards this end. An improvement in the system, which aims at a better response to the anion, will be an intriguing research subject.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.120.

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14. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (quint., $J = 6.60$ Hz, 4H, –CH_2–), 1.61–1.68 (m, 8H, –CH_2–), 2.71 (t, $J = 6.88$ Hz, 4H, –CH_2–), 2.96 (d, $J = 4.60$ Hz, 6H, –NH–CH_3), 3.19–3.25 (m, 4H, –CH_2–), 3.25 (s, 6H, –O-CH_3), 3.44 (t, $J = 4.24$ Hz, 4H, –CH_2–), 3.54–3.57 (m, 12H, –CH_2–), 8.94–9.20 (m, 4H, –NH–); FAB MS (*m*/*z*) 667 $[M-Br]^+$, 587 $[M-H-2Br]^+$; Anal. Calcd for $C_{24}H_{52}Br_2N_4O_4S_4 \cdot 0.5$ $CHCl_3$: C, 35.66; H, 6.55; N, 6.93. Found C, 35.75; H, 6.57; N, 7.09.
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