



Nano-supramolecular complex synthesis: Switch on/off enhanced fluorescence control and molecular release using a simple chemistry reaction



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ABSTRACT

A nanosensor based on β -cyclodextrin (β CD) macrocycles linked to gold nanoparticles for rhodamine B (RhB) sensing was developed applying the metal-enhanced fluorescence effect (MEF). Hence, we have developed many ways to control the distance of supramolecular systems to nanoparticle surface with different bioconjugation strategies in order to optimize signal detection. Different PEG spacer arm lengths were used to cover the nanoparticle surface with molecular spacers. This type of molecular shell is biocompatible, enabling to switch on/off the MEF effect using a dithiane linker by a simple reduction reaction. In the presence of the nanosensor obtained, an increase was observed in RhB fluorescence emission depending on molecular length, that is a characteristic effect of MEF. The major increase measured was 60% compared with RhB emission in buffer at 1 nM level, for a spacer length of 3.58 nm and an 80% increase as compared with that in the presence of β CD. These differences are ascribed to the fact that, in the presence of macrocycle, we can observe a well-known quenching effect that is overcome by the presence of the metallic core. Even at shorter spacer distances, with PEG lengths of 1.2 and 2.17 nm, increases of 25 and 47% respectively allow the analyte detection by the RhB complexation with β CD. The optimal MEF enhancement was measured with the maximal emission signal stabilized after 50 min due to plasmonic effects based on inter nanoparticle interactions. Moreover, the emission increase, in the presence of the metallic core, was accompanied with a diminution in the fluorescence lifetime's decay value averages, characteristic of MEF. This fact shows that the excited state is protected from the non-radiative emission decays enhancing the analytical signal.

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1. Introduction

For the bionanosensor design, we needed to take into account two major parameters: the signal detection recorded; and the recognition system that would allow detecting the target. In the last years, supramolecular chemistry showed many examples developed from dye recognition and quantification using receptors [1]. The most well-known macrocycles in supramolecular chemistry are calixarenes [2] (CA), cucurbiturils [3] (CB) and cyclodextrins [4] (CD). All these receptors have a nanocavity with different organic groups that can interact with the guest included.

In this work we studied the use of cyclodextrins as a recognition supramolecular system, joined to gold nanoparticles for nanosensor developments based on metal enhanced fluorescence (MEF).

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six (α CD), seven (β CD) or eight (γ CD) units of α -D-glucose linked by α -(1,4) bonds. These macrocycles have a nanocavity (internal diameter of 0.7 nm for β CD) which allows them to act as hosts to form inclusion complexes with guest molecules in the solid state or in solution. CDs are interesting microvessels capable of embedding appropriately sized molecules, and the resulting supramolecules can serve as excellent miniature models for enzyme–substrate complexes.

Moreover it is well known that rhodamine B (RhB) interacts strongly with β CD [5,6]. For this reason, and looking for a good target model to evaluate our nano-supramolecular system, we worked with this dye. RhB is an important xanthene dye with a large variety of technical applications, including dye lasers, photosensitizer and quantum counter [7]. The spectroscopic and photophysical properties of RhB have already been extensively studied in different media. Recently, Jian Zhu et al. have studied the mechanisms of interaction between bovine serum albumin nanoparticles with RhB loaded using fluorescence spectroscopy in order to design a drug delivery system [8].

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Metal enhanced fluorescence (MEF) is a plasmonic effect that enhances the emission fluorescence of a substrate placed at a given distance from a metallic surface [9].

The MEF effect depends of the distance of the fluorophore from the metallic surface because the electromagnetic field intensity decays exponentially ($1/r^3$) affecting drastically the fluorophore excitation [10]. For this reason in order to evaluate this parameter there are many studies developed using polymeric spacers such as silica [11]. In these nanoarchitectures, the fluorophore is covalently bonded and the concentration can be controlled for maximal enhancements. These studies are in progress over surfaces [12] and colloidal dispersions [13], depending on the nanoarchitecture design and applications.

In nanosensor developments, there are many studies done with surfaces chemically modified with molecular spacer appending different supramolecular receptors at different distances by different instrumental techniques. But as far as we know there is no reported nanosensor with molecular spacers, based on an on/off MEF switch.

The following examples about molecular spacers used to modify nanoparticle surfaces with cyclodextrins as part of nanosensors coupled with many analytical methodologies could be mentioned. Campina et al. reported gold electrodes modified with 11-amino-1-undecanethiol and di-(*N*-succinimidyl) carbonate for β CD linking [14]. With this surface modification it was possible to shift the oxidation peak at higher potentials compared with those of the free gold surface, showing a good correlation response of hydroquinone with dopamine. A further example involves the fluorescent method developed by Zhang N. et al., based on a novel assembly of gold nanoparticles grafted with β CD monothiolated for the fluorescent probing of cholesterol, using a Förster Resonance Energy Transfer (FRET) control strategy [15]. Another recent case is a quantitative colorimetric method developed using silver nanoparticles modified with thiolated β CD, for organic isomer discrimination [16]. In most design strategies, the use of monothiolated cyclodextrins directly grafted over nanoparticle surfaces was reported. Yet, other studies, including those conducted by Wu et al., were designed with molecular spacers. It was synthesized magnetic nanoparticles grafted with amine- β -cyclodextrin via a novel synthetic route using poly(ethylene glycol) PEG activated as linkers. These nanoparticles were used for dopamine electrochemical detection [17]. The surface properties of magnetic nanoparticles with PEG spacer arms linked were also studied by isothermal titration calorimetry and dynamic light scattering (DLS) methods [18]. Enthalpy–entropy analysis suggested that poly(ethylene glycol) (PEG) modification on particle surface could effectively reduce the interaction between magnetic nanoparticles and plasma proteins, showing that the use of this type of linkers is a particularly good choice for nanosensors likely to be applied to biological media.

In all the examples mentioned, the cyclodextrin cavities were used as efficient dye recognition nanocavities and signal modifiers for sensor developments. But, also it is important to mention about the application of CDs in pharmaceuticals and nanomedicine. For example the first experimental therapeutic application with cyclodextrin self-assemblies was developed and applied in humans to provide targeted delivery of RNA [19]. By similar manner, novel quaternary ammonium β -cyclodextrin (QA β CD) nanoparticles as drug delivery carriers for doxorubicin (DOX), a hydrophobic anticancer drug, across the blood brain barrier were developed [20]. For this reason, from the drug delivery point of view, the design and synthesis of new prototypes of supramolecular nanoparticles applied in nanomedicine is also of high interest.

The final goal of this work was to join the supramolecular knowledge to metallic nanoparticles for a nanosensor design based on MEF for nanoimaging and new analytical methodology developments [21]. For this reason, the study of different ways to control the distance of the supramolecular system to the nanoparticle surface with different bioconjugation strategies was required to optimize the effect needed depending on the application. Different PEG spacer arm lengths were

used to cover the nanoparticle surface, thus it is possible to switch on/off the metal-enhanced fluorescence effect (MEF) using a dithiane linker by a simple reduction reaction. These PEG molecular shells are biocompatible and prevent aggregation in cellular media.

2. Experimental

2.1. Apparatus

UV–vis and spectrofluorimetric determinations were carried out in a Varian UV-50 Carry 50 Conc. and a Fluorolog HORIBA JOBIN YVON, respectively. Lifetime measurements were done with a PicoQuant, Fluotime 2000. The pH was measured with a Fisher Scientific Accumet model Excel XL20 at 25.0 ± 0.1 °C. The pH-meter was first calibrated using standard buffers (pH = 4.00; 7.00; and 9.00). An ultrasonic bath (Branson 2510) was used for the dispersion of the reagents. Transmission electron microscopy (TEM) images were taken using a TEM JEM-1230, JEOL with an operating voltage of 200 kV. Data analysis was performed with Origin (Scientific Graph system) version 8.

2.2. Reagents

Water was obtained using a Millipore apparatus. RhB (99% purity, Sigma-Aldrich), β CD (98% purity, Sigma), hydrogen tetrachloroaurate, $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$ (99%, Sigma-Aldrich), citrate sodium tribasic dehydrate (99%, ACS reagent), polyvinyl pyrrolidone 40,000 g/mol (98%, Sigma-Aldrich) and mercaptophenylboronic acid ($\geq 95\%$, Aldrich) were used as received. The spacer arms 3,3'-dithiobis(sulfosuccinimidyl)propionate (DTSSP), and bis-succinimide ester activated PEG (polyethylene glycol) compounds for crosslinking BS(PEG)_n were from Fisher Scientific company. The pH = 7.4 (10 mM) buffer was prepared according to literature procedures (2.3 mM monosodium dihydrogen phosphate and disodium hydrogen phosphate 7.7 mM). All buffer constituents were commercial analytical-grade reagents.

2.3. General procedure

Gold nanoparticles were synthesized by the classical Turkevich method of citrate reduction of HAuCl_4 and were afterward stabilized with PVP 40. The resulting nanoparticles were then redispersed in anhydrous ethanol (mother solution, $[\text{Au NPs}] = 3.88 \cdot 10^{10}$ NPs/mL, diameter = 55.5 nm). This nanoparticle diameter was chosen in order to get an optimal nanoparticle plasmon band to interact with the fluorophore.

After that the surface of the nanoparticles was modified with 3-(aminopropyl)triethoxysilane (APS) to functionalize it with amine groups. Over this surface different spacer lengths of bis-succinimide ester activated PEG (polyethylene glycol) compounds (BS(PEG)) were covalently bonded by stable amide bonds. The spacer arms used were with $n = 5$ (BS (PEG)₅, 2.17 nm) and $n = 9$ (BS (PEG)₉, 3.58 nm). Moreover, we chose a cross-linker with disulfide bonds for cyclodextrin–rhodamine B complex delivery, with 1.2 nm spacer length, called 3,3'-dithiobis(sulfosuccinimidyl)propionate (DTSSP). After DTSSP cyclodextrin linking, we were able to reduce the disulfide covalent bond with a specific reducing agent, DL-1,4-dithiothreitol (DTT) for complex delivery. In general, we called the nanoparticles β CD grafted with different spacers as Au@spacer_n- β CD.

For 5 mL of gold nanoparticles in ethanol, 50 μL of APS was added and allowed to react for 2 h at room temperature. Nanoparticles were centrifugated and washed with ethanol. To confirm the presence of amine sites over the surface, we assayed with a specific reagent used in proteins, 2,4,6-trinitrobenzenesulfonic acid solution (TNBS) measuring an absorbance band at 340 nm [22]. The results were not significantly conclusive, probably due to the low total amine concentration in the nanoparticle solution and the sensitivity of the colorimetric method.

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