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Invited review paper

Design of functionalized nanoparticles for the applications in nanobiotechnology

Kazuo Tanaka, Yoshiki Chujo *

Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

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ABSTRACT

We review the design and synthesis of functionalized nanoparticles for the application in nanobiotechnology. Initially, the modification of the superparamagnetic iron oxide (SPIO) for contrast agents is described. The series of biomolecule-responsive contrast agents are introduced. Next, silica nanoparticle-based probes in ^{19}F NMR are explained. By employing the silica nanoparticles as a signal quencher for NMR signals, the quantitative analysis of the enzymatic activities was accomplished. The design concepts and the results are explained. We also mention the regulation of the cluster formation of gold nanoparticles. Significant changes in optical properties before and after the assembly are presented. Finally, the typical synthetic procedures are also described in the latter part.

Contents

1. Introduction

Nanoparticles have attracted attention as a scaffold to obtain smart biomaterials because of several advantages: Firstly, the biodistribution of the nanoparticles can be modulated by changing the size of the particles. For example, as we presented in this paper, silica-based nanoparticles are versatile materials for designing functional bioprobes and the vesicles for drug delivery because of

* Corresponding author. Tel.: +81 75 383 2604; fax: +81 75 383 2605.
E-mail address: chujo@chujo.synchem.kyoto-u.ac.jp (Y. Chujo).

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their high stability and the flexibility in the modification. Because various size and surface-modified silica nanoparticles can be readily prepared, we can deliver drugs or other bioactive materials to the target sites by loading onto the nanoparticles with the size effects on the distribution. In particular, nanoparticles in the range of 20–400 nm in diameter show tumor-selective integration known as the enhanced permeability and retention (EPR) effect [1–7]. Therefore, the site-specific delivery can be realized based on the preprogrammed designs. Secondly, the local concentrations of the loaded drugs can be readily enhanced. In the case of the drugs with small molecular weights, the drug concentrations could be lowered by the diffusion. On the other hand, since the nanoparticles have better retention ability than those of small molecules, it is relatively easy to keep the local concentration to receive enough drug efficiency. In addition, if the nanoparticle can slowly release the loaded drugs, the sustained release system can be readily realized. Thirdly, the diverse properties can be obtained not only originated from the intrinsic properties of the component elements or the surface modification but also from the nanosized effects of the particles. For example, the nanoparticles composed of ferromagnetic iron oxide show similar behaviors, called superparamagnetism, to the paramagnetic materials such as no hysteresis and no residual magnetization [8,9]. These materials are used as a conventional contrast agent in magnetic resonance imaging (MRI). In the case of gold nanoparticles, the absorption bands in the visible region can be observed. Various kinds of biosensors have been invented based on the gold nanoparticles. The nanoparticles composed of semiconductor materials called as quantum dots show various emission colors depended on their diameters [10–13]. Based on these characteristics derived from the size effects, unique optical bioprobes have been developed. In this review, we survey the functionalized nanoparticles for the application in nanobiotechnology. Our recent studies on the development of bioprobes or bio-related materials with the series of nanoparticles composed of iron oxide, silica and gold are mainly introduced. The typical synthetic procedures are also described in the latter part.

2. Superparamagnetic iron oxide

2.1. MR sensors for biomolecules

Initially, we present the superparamagnetic iron oxide (SPIO)-based contrast agents in magnetic resonance imaging (MRI). MRI is one of the powerful and conventional diagnostic tools in modern clinical medicine for the 3D visualization inside vital bodies with high resolution. In particular, by using contrast agents, sensitivity and specificity in the detection can be extensively improved. The SPIOs are magnetite crystals with several nanometer sizes [8,9]. In the magnetic fields, SPIOs can accelerate the proton transverse relaxation of water tissue in aqueous media and consequently provide hypointense (dark) contrast in magnetic resonance images on T_2 and T_2^*-weighted sequences. SPIO-based contrast agents are already commercially available and used at the clinical stages. Moreover, various techniques using SPIOs such as the cell labeling [14–18], biosensors [19–22], and in vivo imaging [23–26] with MRI have been developed. Thus, the SPIO-based contrast agents can be a suitable platform for designing the advanced imaging probes. In this part, the regulations of the magnetism by modulating the aggregation/dispersion of the SPIO particles and their applications for biosensors in MRI are presented.

By the formation of assembly, the magnetism of SPIOs can be enhanced, resulting in much darker contrasts in the MR images. Based on these phenomena, various kinds of biosensors have been prepared with the modified SPIOs [19–22]. We also have aimed to develop the biomolecule-responsive SPIOs. Particularly, the surface modified-SPIOs were prepared for detecting the bio-significant molecules and environmental factors such as protein, gene, and pH.

We designed the surface modification of SPIOs for realizing the target-responsive cluster formation with the variety of biomolecules [27]. Fig. 1 outlines the system of the modified SPIOs. We initially synthesized the biotin-presenting SPIOs to form the cluster in the presence of an avidin protein. As shown in Fig. 2a, the precipitation was confirmed by the naked eyes immediately after adding avidin to the solution containing the biotin-presenting SPIOs. From the DLS measurements, the increase of the observed hydrodynamic radius (r_H) of the biotin-presenting SPIOs (19.5 ± 5.2 nm) to be 51.2 ± 22.4 nm was monitored by adding the 2000-times diluted avidin solution. Consequently, we showed this system can represent the highly-sensitive protein sensor by the naked eyes with the minimum detection limit of 10 fmol of avidin with the biotin-presenting SPIOs.

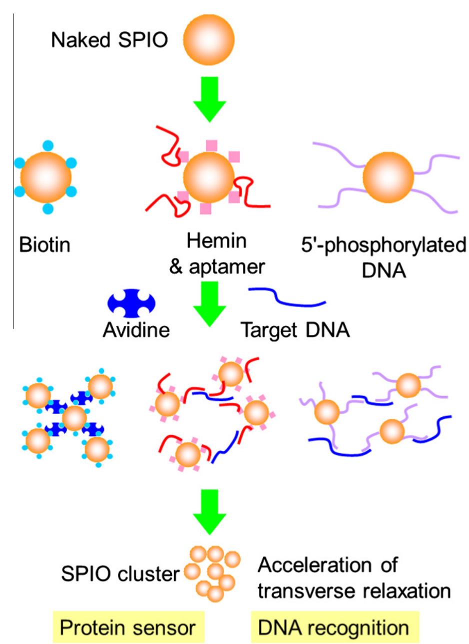

Fig. 1. Schematic illustrations for the biomolecule-triggered cluster formations of the modified SPIOs.

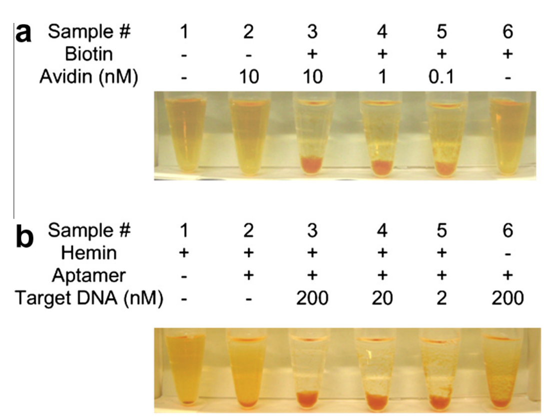

Fig. 2. The cluster formation of (a) the biotin-presenting and (b) the hemin-aptamer DNA complex-modified SPIOs by the addition of each target molecule in the buffer. All images were taken after 15 min standing (+: added to the samples).