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Fabrication of succinic acid-γ-Fe_2O_3 nano core–shells

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ABSTRACT

Core–shell nano-structures were synthesized by adsorbing succinic acid on γ-Fe_2O_3 nanoparticles (hereafter referred to as core–shell nanoparticles or core–shells). Streptomycin was chosen as a model drug to attach on γ-Fe_2O_3 core–shells. Vibration spectroscopic data confirmed the specific adsorption of organic ligands (i.e., succinic acid or streptomycin) onto γ-Fe_2O_3 via bi-dentate, bi-nuclear complex. Possible molecular configurations between organic ligands and γ-Fe_2O_3 were examined by density functional theory (DFT) using $Fe_6(OH)_{18}(H_2O)_6$ ring cluster. The measured vibration frequencies and bond distances (i.e., Fe—O—Fe, Fe—O_w, and Fe—OH units) of the optimized γ-Fe_2O_3 cluster matched well with the calculations.

1. Introduction

The γ-Fe_2O_3 nanoparticles are extensively examined due to their magnetic properties and wide applications as ferrofluids, recording tapes [1], data storage devices, biomedical work and catalysis [1,2]. The design and fabrication of magnetic nanoparticles with a controllable size and uniform dispersion is important research in materials science. The inherent structure of γ-Fe_2O_3 core–shell nanoparticles makes them very useful in biomedical applications, namely enzymes and protein separation, RNA and DNA purification, magnetic resonance imaging (MRI) and drug delivery. The utilization of iron-based nanoparticles in other scientific areas is also gaining momentum largely due to their environmental benignness [3–8]. The surface of a given nanoparticles is generally tailored with synthetic or natural polymers to improve their stability, reactivity, biocompatibility and floatability. Previously, modifications of surface sites were carried out with various functional agents such as polyethylene, polyethylene glycol, and silica [9,10]. The grafting sites on nanostructures immobilize foreign molecules, and the surface-derived functional groups act reversibly for bio-entities. Carboxylic groups on polymeric surfaces immobilize oligonucleotides and protein via covalent bonding [5]. These surface carboxyl groups can readily be derivatized; hence, they can improve the dispersion of iron oxide nanoparticles by shifting the iso-electric point [11,12].

Streptomycin, one of the oldest antibiotics in the world, is used to control the incidence of tuberculosis (TB). (Chemical structure, Fig. 1-S: support documents). Streptomycin, 1-(4-(4-(3,5-dihydroxy-6-(hydroxymethyl)-4-(methylamino)tetrahydro-2H-pyran-2-yloxy)-5-formyl-5-hydroxy-3-methyl tetra hydrofuran-2-yloxy)-2,5,6-trihydroxycyclohexane-1,3-diyl)diguanidine is an aminoglycosidic antibiotic with three components: streptidine, streptose and N-methyl-L-glucosamine. It is also used in the treatment of infections caused by Gram-negative bacteria. Under alkaline conditions, streptomycin is an effective bactericide against rapidly dividing extracellular *Mycobacterium tuberculosis*. However, the major drawbacks associated with application of this drug are the requirements of parenteral dosing and its toxicity. The use of this drug has also declined due to poor gastrointestinal absorption that precluded effective oral administration. However, streptomycin is one of the most cost-effective ATDs and it is recommended in certain categories of TB patients, e.g., patients showing re-lapse or treatment failure, compulsory withdrawal of ionized and rifampicin, TB meningitis, HIV-infected TB patients receiving protease inhibitors, and certain cases of multi-drug resistant TB [13].

Challenges in developing new drugs not only include identifying novel active compounds but also improving their delivery at the biological level. Most of the active compounds on the market are poorly soluble in water, and it is expected that they will be less soluble in the future [14]. Therefore formulation of poorly water soluble active compounds is an important challenge to be faced. Due to

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Table 1
Surface characterization data of γ-Fe_2O_3 and γ-Fe_2O_3–water interface.

Parameter	Value	Source
pH_{zpc}	8.13	Ref. [12]
pH_{IEP}	8.03	This study
Site density (sites/nm^2)	5.66	This study
Specific surface area (m^2/g)	150	This study
Particle size (nm)	10–20	This study

their inherent environmental benignness, iron derived compounds can be considered as potential substrates for controlled delivery of drugs. Therefore we determined the physico–chemical interactions of streptomycin and γ-Fe_2O_3 nanoparticles by spectroscopic, experimental and theoretical methods. Streptomycin was selected as the model drug. Particular attention was paid to select mild acidity conditions of experimental solutions as required for biological systems. The reactivity of γ-Fe_2O_3 surface sites was quantified by a cluster molecular model based on density functional theory (DFT) [15]. Therefore the chemical data presented here will provide an essential first step to assess the suitability of γ-Fe_2O_3/γ-Fe_2O_3 nano-core shells as a drug carrier under controllable fashion.

The succinic acid-γ-Fe_2O_3 core–shells were synthesized by a co-precipitation method and streptomycin was attached to the surface in methanolic medium. The term "core–shell" was used against "surface coating" due to the following reasons. Core–shells are nanostructures that have a core made of a material coated with another material. When a core material is coated with a polymeric or inorganic layer because the polymeric or inorganic layer would endow hybrid structure with additional function/property on top of the function/property of the core hence synergistically emerged functions can be envisioned [16–18]. Henceforth, the succinic acid coated γ-Fe_2O_3 particles are designated as core–shells or core–shell nanoparticles. All ab initio calculations were performed using a cluster model by DFT to affirm the molecular configurations that resulted from experimental data.

2. Materials and methods

2.1. Materials

The iron derived particles were characterized by X-ray diffraction (XRD) and the γ-Fe_2O_3 phase. The surface structure, particle size and morphology of γ-Fe_2O_3 were examined by transmission electron microscopy (TEM). Unless otherwise stated, all chemicals used were either from Aldrich (USA) or FLUKA (Switzerland). The water used was de-ionized-distilled water produced by All-Glass Distillation Unit.

2.2. Synthesis of γ-Fe_2O_3 nanoparticles

The γ-Fe_2O_3 was synthesized by the co-precipitation of Fe (II) and Fe (III) containing solutions in 1 M NaOH as detailed in Ref. [12]. An aqueous iron solution with a molar ratio of Fe (II)/Fe (III) = 0.5 was prepared in 1 M HCl. This solution was titrated with 100 ml 1 M NaOH under vigorous shaking. The reaction was carried out under inert atmosphere in a glove box filled with 99.5% Ar. After the titration was completed the reaction mixture was stirred for 30 min prior to centrifugation at 2500 rpm. The supernatant solution was removed and precipitate was rinsed with distilled water several times to remove the remaining ions. The solid residue was freeze dried and re-dispersed in 500 ml distilled water under sonication. Table 1 showed the basic surface properties of the γ-Fe_2O_3 phase. The black colloid thus obtained was stored for further use.

2.3. Synthesis of succinic acid coated-γ-Fe_2O_3 core–shell nanoparticles

Succinic acid coated γ-Fe_2O_3 nanoparticles were synthesized using the same co-precipitation method. However, in this case, the aqueous solution of iron species was spiked with 0.025 mole succinic acid prior to titration with 1 M NaOH. The colloid suspension thus obtained was centrifuged at 2500 rpm and the precipitate was washed with de-ionized, distilled water several times before drying at 60 °C.

2.4. Synthesis of streptomycin–succinic acid coated γ-Fe_2O_3 nanoparticles

Succinic acid-γ-Fe_2O_3 core–shell nanoparticles (~0.1 g) were mixed in 50 ml methanol solution. A portion of 0.25 g streptomycin was added to the solution and stirred for 12 h. This experiment was conducted under acid different conditions, i.e., pH = 3.0, 7.0 and 11.0. The filtered precipitate was washed with methanol followed by water several times. Finally, the solid residue was dried at 60 °C [19].

2.5. Analytical methods

The pH of the suspensions was determined by a pH sensing electrode (model H 112, Kyoto, Japan) and reference electrode (R 116, Kyoto, Japan) with a potentiometric auto-titrator (AT 400 Kyoto, Japan). The pH_{IEP} of γ-Fe_2O_3 suspensions were measured by electrokinetic mobility (Zeta Meter 4.0, USA). Infrared analyses were carried out using a FTIR spectrometer at 4 cm^{-1} spectral resolution (Nicolet 6700, USA). The γ-Fe_2O_3, different core–shells, succinic acid and streptomycin were mixed separately with spectroscopic grade KBr at 1:6 (w/w) ratio, crushed in agate mortar and pestle to achieve homogeneous mixtures. All spectra were collected at the transmission mode.

2.6. Molecular cluster modeling

The cluster modeling method based on density functional theory (DFT) was used to calculate surface complexes, vibration frequencies and bond lengths. Because of its computational advantages, DFT has evolved as the most important quantum mechanical approach in solid-state geometry optimization [20,21], and it can handle large systems that are intractable by Hartee–Fock methods [22,23]. DFT is based on the fact that the ground-state properties of a molecular system are uniquely defined by the electron density ($\rho(\mathbf{r})$) [15]. In DFT, the energy functional ($E[\rho]$) is written as a sum of four terms [24]:

$$E[\rho(\mathbf{r})] = -\sum_{\mathbf{A}=1}^{M} \int \frac{\mathbf{Z_A}}{|1-\mathbf{R_A}|}\rho(\mathbf{r})dr + \sum_{i=1}^{N}\varphi_i(\mathbf{r})\left(\frac{-\nabla^2}{2}\right)\varphi_i(\mathbf{r})dr + \frac{1}{2}\int\int \frac{\rho\mathbf{r}_1\rho\mathbf{r}_2}{|\mathbf{r}_1-\mathbf{r}_2|}d\mathbf{r}_1 d\mathbf{r}_2 + E_{XC}|\rho(\mathbf{r})|$$

where, $\mathbf{Z_A}$ is the charge on nucleus **A**, **r** is a position vector, $\mathbf{R_A}$ is the position vector of nucleus **A**, *M* is the number of nuclei, *N* is the number of electrons, φ_i is the spatial orbital occupied by the *i*th electron, and $E_{XC}|\rho(\mathbf{r})|$ is the exchange correlation energy functional. The first term on the right-hand side of the equation corresponds to the potential energy due to nucleus–electron interactions, the second term is the kinetic energy for *N* non-interacting electrons, and the third term represents the energy for electron–electron repulsions. Inter-nuclear repulsions are constant and are accounted for separately. The equation serves to define $E_{XC}|\rho(\mathbf{r})|$ as the energy needed to be added to the other terms to reproduce the exact energy of