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# DEVELOPMENT OF BIOCOMPATIBLE SMALL-MOLECULE SPACERS AS METAL OXIDE NANOPARTICLES' STABILIZING AGENTS

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## Introduction

Development and study of the magnetic nanoparticles for biological and clinical applications remains one of the challenging research areas in chemistry and materials science. The performance of these particles as, for example, drug delivery, MRI, hyperthermia or cell tracking agents, depends on their magnetic susceptibility. Their ability to form stable aqueous colloids, the mobility, and diffusion properties in biological media, rely on organic coating, which is usually composed of hydrophilic biocompatible polymers such as dextrans or poly(ethylene glycol)s. Some areas of biomedical imaging, labeling and delivery application can benefit from magnetic nanoparticles with higher mobility and penetration, stronger interaction with fluids and tissues, and that can be easily conjugated to biological molecules. The idea of this work was to develop a non-polymeric organic coating of an adjustable size, which might offer a simpler way to obtaining particles with these properties.

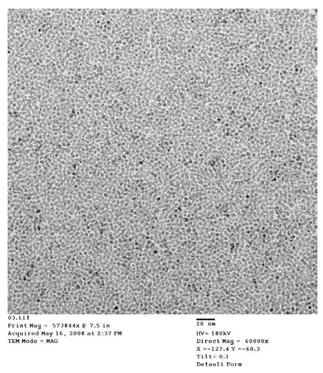
## Materials and methods

Magnetite nanoparticles (3.2-7.5 nm) were obtained in surfactant-free colloidal form by high-temperature hydrolysis of iron(II,III) chelated alkoxides in homogeneous diethylene glycol solutions.

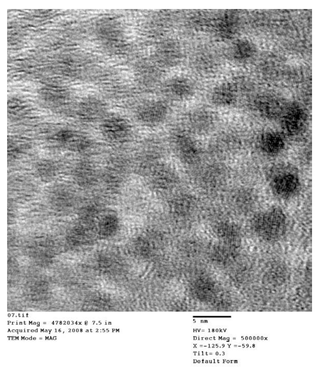
$[Fe(Hdeg)_2] + 2[Fe(Hdeg)deg] + 4H_2O \rightarrow Fe_3O_4 + 6H_2deg$

The products of syntheses readily form aqueous colloids which were characterized by the Dynamic Light Scattering (DLS) and zeta-potential methods; isolated nanopowders were characterized by X-ray diffractometry, TEM, combustion analysis FT-IR spectrometry and magnetic measurements.

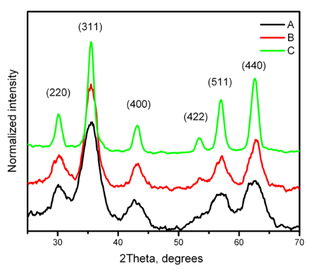
**Large-area TEM image of 4 nm $Fe_3O_4$ particles. Scale bar = 20 nm**



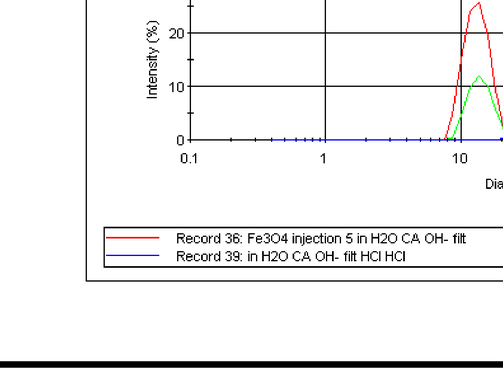
**High resolution TEM image of 4 nm $Fe_3O_4$ particles. Scale bar = 5 nm**



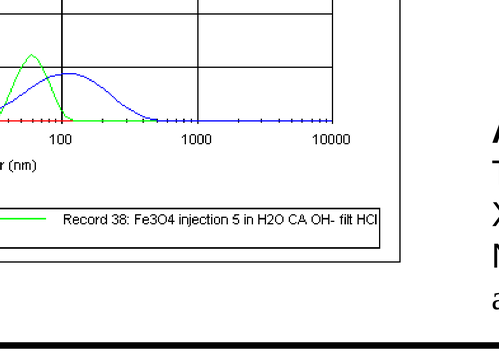
**X-ray diffractogram of 3.2, 4.8 and 7.5 nm magnetite nanoparticles**




**Magnetization vs temperature for 4.8 nm magnetite nanoparticles (B = 50 Oe)**




**Magnetization vs field for 4.8 nm magnetite nanoparticles**




Surface chemistry studies were done by addition of the calculated amount of organic ligands followed by precipitation and transferring adducts into aqueous systems. Acid-base titrations were accompanied by Dynamic Light Scattering and electrokinetic mobility measurements using Malvern Zetasizer Nano ZS instrument.

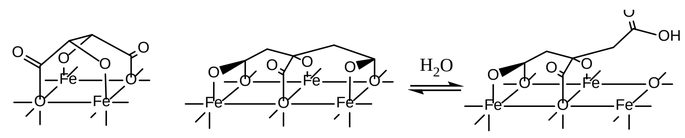
The DLS spectra of magnetite citrate colloid obtained at different pH decreasing in order: Red > Green > Blue
Titration with acid or base gives the reversible results.




In order to identify small organic molecules which would strongly bind to the surface of iron oxide nanocrystals and efficiently stabilize their aqueous colloids, we studied reactions of maghemite nanoparticles with citric, tartaric and malic acids. The reactions were monitored by the Dynamic Light Scattering (DLS) and zeta-potential measurements. The results are summarized in the table below which shows the pH values representing substantial aggregation and de-aggregation events during titration of aqueous $Fe_2O_3$ colloids with 0.01M HCl and 0.01M NaOH. The reference peak* appears at 7-9 nm in the DLS spectra; pH↑ represents titration with base; pH↓ represents titration with acid.

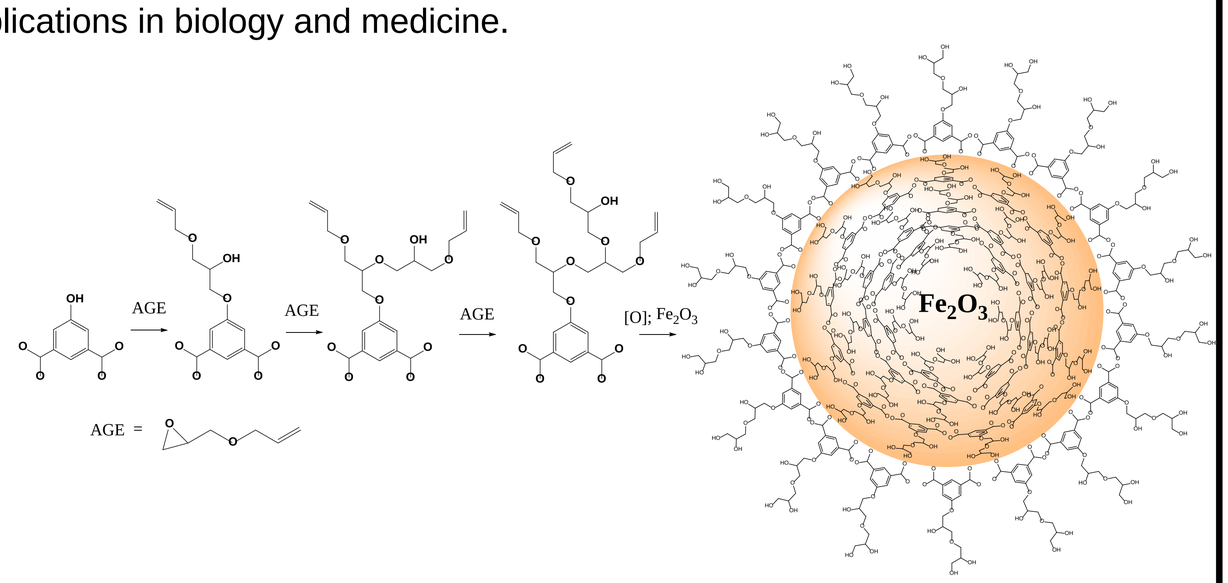
| Changes during titration | Citrate | Tartrate | Malate |
|---|---|---|---|
| The reference peak* intensity turned > 90% (pH↑) | 7.4 | 7.8 | 8.8 |
| The reference peak* intensity is still > 90% (pH↓) | 4.9 | 7.2 | Decomposes |
| The reference peak* intensity turned 0% (pH↓) | 4.5 | 6.9 | Decomposes |
| Isoelectric point | 3.6 | 4.4 | 4.3 |

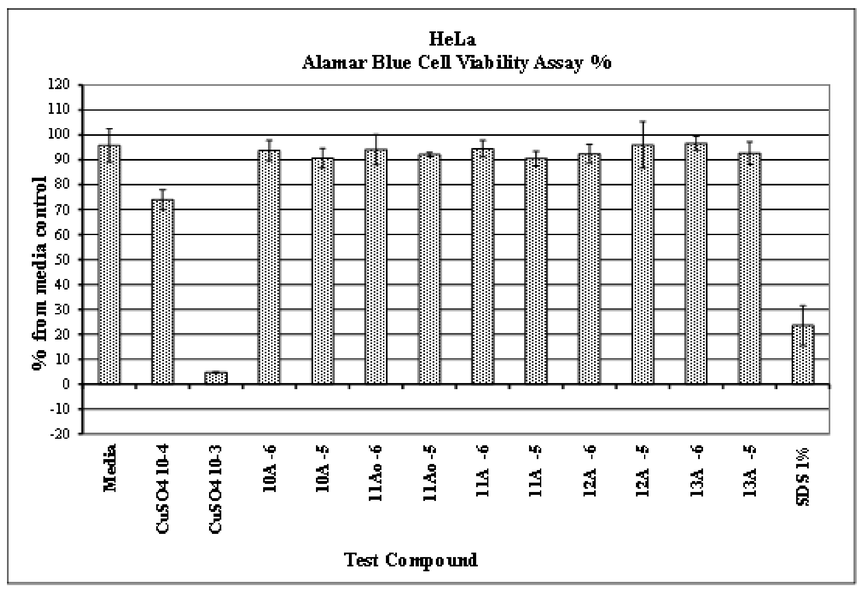
The results revealed that the carboxyl and the adjacent α-OH groups of these acids are involved in coordination with the nanoparticle surface and they are the major contributors to the stability of the resulting adducts against hydrolysis. The proposed binding geometries for tartrate and citrate ligands are shown in the scheme below.




Modification of the ligands' coordinating core by attaching the substituent with variable steric and amphiphilic properties was the next step of our work. Synthesis was performed by a base-catalyzed nucleophilic oxirane ring-opening addition reaction between dimethyl 5-hydroxyisophthalate (as a model) and allyl glycidyl ether, followed by ester hydrolysis. In order to obtain water-soluble capping ligands, oxidation of the allyl double bonds to 1,2-diol was carried out with basic permanganate. Products of organic syntheses after purification were characterized by 1H NMR, 13C and 2D NMR, electrospray MS (acids) and GC-MS (esters)

Cytotoxicity studies showed no reduction in viability after incubation of the synthesized compounds with HeLa cells. The reported method can be extended to the synthesis of O-substituted derivatives of other hydroxyacids of potential applications in biology and medicine.

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