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Synthesis of in situ functionalized iron oxide nanoparticles presenting alkyne groups via a continuous process using near-critical and supercritical water

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ABSTRACT

The preparation of iron oxide nanoparticle dispersions of varying properties (e.g. color, crystal structure, particle size distribution) in a continuous hydrothermal pilot plant operating under near-critical and supercritical conditions with the aim of producing in situ functionalized nanoparticles suitable for secondary functionalization via *click* chemistry is reported. The effect of varying the mixing setup, reaction temperature and the starting material (iron salt) in the presence of different carboxylic acids on the resulting nanoparticle dispersions was investigated. The stability of the *clickable* ligands in the harsh hydrothermal environment was also tested and the *clickability* of the functionalized particles was demonstrated by means of XPS and fluorescence measurements after model *click* reactions.

1. Introduction

Near-critical and supercritical water is a suitable medium for the synthesis of in situ functionalized metal oxide nanoparticles. The synthesis has been demonstrated in both batch and continuous processes, providing further control of particle formation regarding size, morphology and surface chemistry as compared to the supercritical hydrothermal synthesis of non-functionalized particles (e.g. [1–12]). Particles synthesized with a stable surface modifier layer often show narrow size distributions and can be transferred into nonpolar organic solvents where they frequently exhibit a very good dispersibility [2].

Using a batch-type approach, the synthesis and morphology control of e.g. surface functionalized Fe_2O_3, AlOOH, CeO_2, Co_3O_4, nanoscale yttrium aluminium garnet particles (YAG), and hafnium oxide (HfO_2) have been demonstrated [2–6]. The organic molecules used for functionalization are mainly C6 to C12 hydrocarbons presenting one functional group such as aldehyde, primary amine, carboxyl or hydroxyl. The optimum conditions for the surface modification have been found to differ among the modifiers and metal oxides. Often the presence of the organic capping agent does not alter the crystal structure but greatly alters the surface morphology and surface charge of nanoparticles by altering nucleation and crystal growth. Furthermore, the size of the particles can be influenced by varying the molar ratio of modifier to starting material [1].

In addition to organic molecules bearing one functional group, also bifunctional molecules have been used as modifiers [7–9]. For example, ZrO_2 nanoparticles have been synthesized in the presence of various carboxylic acids with or without a second functional group at the opposite end [7]. Togashi et al. [9] reported the one-pot synthesis of in situ functionalized Fe_3O_4

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nanoparticle clusters in which the nanoparticles were interlinked by 3,4-dihydroxycinnamic acid. These results are especially relevant for biomedical applications because superparamagnetism enables the clusters to be dispersed in water while allowing manipulation by an external magnetic field. Furthermore, the modification of the particle surface with COOH groups allows the conjugation of biomolecules such as proteins, DNA and pharmaceuticals.

Nanoparticle synthesis in the presence of monofunctional (e.g. indium tin oxide (ITO)/hexanoic acid [10]) and bifunctional ligands (e.g. CeO_2/hexanedioic acid leading to octahedral nanoassemblies of interlinked particles [8]), and polymers (e.g. iron oxide/polyvinyl alcohol, leading to polymer-embedded particles [11]) has also been carried out in a continuous process. In contrast to batch processes where the metal salts are heated together with the organic modifiers, there are more choices available to experimenters in continuous hydrothermal processes. For example, the organic modifiers may pass the reactor together with the metal oxide precursor solutions (e.g. [10]) or be added directly after the reaction section (e.g. [13]).

We have recently shown that it is possible to use a continuous hydrothermal process to produce functionalized metal oxide nanoparticles with terminal groups suitable for further modification by means of *click* chemistry [14]. *Click* reactions are defined to be simple, efficient and applicable in diverse modular approaches without the formation of significant side products [15]. Originally conceived for pharmaceutical research, these characteristics make *click* chemistry also a promising tool in colloidal science [16] and, increasingly, in chemical and biological engineering [17].

In the work reported herein, we explored the effect of different process variables—namely the use of different mixing setups with varying temperature, iron salts, and organic modifiers—on the properties of the resulting in situ functionalized nanoparticle dispersions. There are reasons to expect that changes in these variables will result in measurable changes in the product dispersions, namely:

- It is known that the use of different iron salts can lead to different structures of the iron oxide nanoparticles. In turn, this can influence the reactivity of the particle surface—an important aspect for in situ functionalization.
- Given that organic capping agents affect particle formation, growth and stability, it appears reasonable that the chain length of the modifiers—which in turn affects e.g. diffusion time to the surface and the ability to stabilize the particles via steric interactions—may noticeably affect the properties of the resulting dispersions.
- In terms of particle formation and growth, it could make a substantial difference whether the organic modifiers are already present when the compressed cold iron salt solution is rapidly heated to the reaction conditions or the organic modifiers are added afterwards.
- The reaction temperature not only affects particle formation and growth via the properties of the near-critical or supercritical water but can also influence the reaction medium through the partial thermal decomposition of the added organic modifiers. For this reason, the stability of the added carboxylic acids under near-critical and supercritical conditions was also studied in the absence of the iron salts.

While the reasons outlined above appeared compelling, it was not clear a priori whether these changes would be significant. Thus, conducting an exploratory study—which can point the way to fruitful in-depth work—appeared to be a sensible course of action. The ultimate goal is to contribute to the development of a convenient and versatile process for the synthesis of metal oxide nanoparticles with universal and accessible anchors on their surface.

2. Experimental

2.1. Materials

Iron(III) nitrate nonahydrate (99.99%, Aldrich), ammonium iron(III) citrate (purum, 20.5–23.5% Fe basis, Fluka), 5-hexynoic acid (97%, ABCR), hexanoic acid ($\geq$99.5%, Aldrich), 10-undecynoic acid (97%, ABCR, ammonium hydroxide solution (Sigma–Aldrich), benzyl azide (94%, Alfa Aesar), copper(II) sulfate pentahydrate (p.a., Sigma–Aldrich), L(+)-ascorbic acid sodium salt ($\geq$99%, Sigma), ethanol ($\geq$99.9%, Roth), sodium hydroxide (p.a., Roth), and toluene (99.9%, Sigma-Aldrich) were purchased as indicated and used as received. With the exception of the main water stream (heated to near- or supercritical conditions), the deionized water used was further purified to 0.055 $\mu S\,cm^{-1}$ (Elga Purelab Ultra, Viola Company, Analytical grade).

2.2. Continuous hydrothermal particle synthesis

The supercritical hydrothermal synthesis was carried out with a high pressure pilot plant mainly built from standard high pressure components from Sitec-Sieber (Mauer, Switzerland) and Swagelok (B.E.S.T. Fluidsysteme, Karlsruhe, Germany). Refer to Fig. 1a for a flow diagram containing all essential parts and to Fig. 1b for the different mixing setups used. Generally, deionized water with a reduced oxygen content (sparged with nitrogen prior to use) was delivered into the plant with a flow rate of 80 $mL\,min^{-1}$ using two coupled syringe pumps (model 500D, Teledyne Isco, Inc., NE, USA) and heated appropriately using electrical heating blocks in order to obtain a certain reaction temperature after mixing with the cold metal salt stream and/or the stream containing the organic compounds. An aqueous iron salt solution with a concentration of 0.0275 $mol\,L^{-1}$ with a reduced oxygen content (sparged with helium prior to use) was delivered with a flow rate of 20 $mL\,min^{-1}$ into the plant using an HPLC pump (SD1, AlphaCrom OHG, Langenau, Germany) and mixed with the hot compressed water stream. For all mixing setups, commercially available T-type mixers (720.1633, Sitec-Sieber, Maur, Switzerland) were in use to mix the cold streams (solution I and II) with the hot compressed water stream. The inner diameter of these mixing units as well as that of the adjacent high pressure capillaries was 1.6 mm. After passing the reaction zone (consisting of the T-unions and high-pressure capillaries), the stream was cooled to a temperature <298 K with an external water jacket. The residence time from the entry into the second mixing unit (for the mixing setups “salt–organic” and “organic–salt”) or only mixing unit (for mixing setup “mixed”) up to the entry into the cooler was from about 300 ms to 600 ms (calculated on the basis of the density of pure water under the process conditions). Thereafter (with the exception of setup “undecynoic”, see below), the stream was recovered as a particle suspension after passing through a filter unit (pore size approx. 10 μm, Swagelok) and a back pressure regulator (26-1700 Series, Tescom Europe, Selmsdorf, Germany) installed to control the process pressure of 30 MPa.

A summary of the experimental runs performed is given in Table 1. At first, a series of particle syntheses in the absence and presence of hexanoic acid, 5-hexynoic acid or a 1:1 (mol:mol) mixture of these acids was carried out using iron(III) nitrate hexahydrate as starting material and the ‘organic–salt’ setup. For that, 1.38 $mL\,min^{-1}$ hexanoic acid, 1.25 $mL\,min^{-1}$ 5-hexynoic acid, or 1.32 $mL\,min^{-1}$ of the mixture of the acids, respectively, were delivered into the plant using an HPLC pump (PU 2080, Jasco,