Research Article

Superparamagnetic Ironoxide Nanoparticles via 
Ligand Exchange Reactions: Organic 1,2-Diols as 
Versatile Building Blocks for Surface Engineering

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A method for the preparation of ligand-covered superparamagnetic iron oxide nanoparticles via exchange reactions is described. 1,2-diol-ligands are used to provide a stable binding of the terminally modified organic ligands onto the surface of $\gamma$-Fe$_2$O$_3$-nanoparticles ($r \sim 4$ nm). The 1,2-diol-ligands are equipped with variable terminal functional groups (i.e., hydrogen bonding moieties, azido- bromo-, fluorescent moieties) and can be easily prepared via osmium tetroxide-catalyzed 1,2-dihydroxylation reactions of the corresponding terminal alkenes. Starting from octylamine-covered $\gamma$-Fe$_2$O$_3$-nanoparticles, ligand exchange was effected at 50°C over 24–48 hours, whereupon complete ligand exchange is taking place as proven by thermogravimetric (TGA)- and IR-spectroscopic measurements. A detailed kinetic analysis of the ligand exchange reaction was performed via TGA analysis, demonstrating a complete ligand exchange after 24 hours. The method offers a simple approach for the generation of various $\gamma$-Fe$_2$O$_3$-nanoparticles with functional organic shells in a one-step procedure.

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1. INTRODUCTION

Magnetic iron oxide nanoparticles have gained increased interest during the past decade, mostly due to their superparamagnetic property present at small particle sizes [1, 2]. Thus below a critical size of $\sim 40$ nm, the formation of Weiss domains is no longer possible, leading to the formation of singular magnetic domains and thus the physicochemical phenomenon of superparamagnetism. With the advent of this discovery, numerous exploitations have gained advantage of this effect, mostly due to the inability of superparamagnetic nanoparticles to self-aggregate, thus preventing large agglomerate formation. Applications such as drug and gene delivery [3, 4], magnetic resonance imaging [5], hyperthermia [6–8], and magnetofection [9–11] have demonstrated the wide applicability of superparamagnetic nanoparticles in vivo and in vitro.

A critical issue for the use of these nanoparticles is represented by engineering the surface of the nanoparticles with organic ligands, thus allowing the incorporation, selective recognition, or specific guidance of such nanoparticles. Based on various approaches, a large number of different organic ligands have been described, including ligands such as polymeric [12–14], peptidic [15, 16], protein ligands [17–19], or small organic molecules such as fluorescent dyes [20, 21], biotine [22], drugs, and others [23, 24]. Critical for the achievement of a sufficient stability between the surface of the nanoparticles and the corresponding ligands is the choice of either a multivalent adsorption site (usually present between polymeric ligands and the surface of the iron-oxide nanoparticles) or the use of a specific functional group, binding tightly to the surface of the iron oxide nanoparticles. Inorganic shells, such as silicon dioxide [25–29] have been used extensively as an intermediate shell between the iron-oxide core and the organic ligands, usually binding via terminal aminoligands incorporated on the surface of the silica shell. When purely organic ligands are directly bound to the surface of the iron oxide nanoparticles, carboxylate ligands [30, 31], sulfonates and thiols [32, 33], phosphates and phosphonates [34], as well as aminoligands [35] are
used. Recently, Boal et al. [36] have introduced the use of 1,3-diol-ligands for achieving a tight binding of various organic ligands on the iron oxide nanoparticle surface. 1,3-diols were found superior as ligands in comparison to pure alcoholic substrates, since binding constants of the latter are not sufficient in order to achieve sufficient binding stability.

In the present publication, we report on the use of 1,2-diol-ligands instead of 1,3-diol-ligands for the binding of various ligands to the surface of superparamagnetic iron oxide nanoparticles (see Figure 1) via ligand exchange reactions. In contrast to 1,3-diols, 1,2-diols can be generated easily from the corresponding terminal alkenes via an osmium tetroxide-mediated dihydroxylation reaction, thus achieving a broad spectrum of substrates at the end of the ligand. The binding of various ligands with fluorescent and supramolecular properties onto the surface of the iron oxide nanoparticles together with the kinetic progress of the ligand exchange reaction is reported, allowing a simple and efficient functionalization of the iron oxide nanoparticles.

2. EXPERIMENTAL SECTION

2.1. General procedures

Sodium azide (NaN₃) was from Acros and Cu(I)Br (99%) from Fluka. All chemicals were used directly without any further purification. Tetrahydrofuran (THF), diethyl ether, and toluene were dried by distillation over sodium and purified. Tetrhydrofuran (THF), diethyl ether, and benzophenone, dimethylformamide (DMF) over CaH₂, and methanol over magnesium. NMR spectra were obtained with a 200 MHz Bruker AC200 spectrometer and a 400 MHz Bruker Advance DRX 400 MHz. Chloroform (CDCl₃) and dimethylsulfoxide (DMSO-d₆) were used as solvents, tetramethylsilane (TMS) as internal standard. Photoluminescence spectra were recorded on a Perkin-Elmer luminescent spectrometer LS 50 B correlator software.

2.2. Synthesis

2.2.1. Preparation of the 1,2-diol-ligands 1a–1f by osmium-tetroxide catalyzed dihydroxylation reaction of terminal olefines 2a–2f

The corresponding olefin was suspended in the denoted amount of Ar-bubbled solvent. NMO·H₂O (N-methylmorpholine-N-oxide monohydrate) was added in the specified amount. The solution was stirred at room temperature until all reagents were dissolved. During agitation, the solution was bubbled with argon. Now catalytic amounts (one granule) of OsO₄ were added in Ar counterflow. The solution turned immediately yellow after the addition. The reaction mixture was stirred at room temperature until TLC indicates full conversion, which in all cases occurred after 1 hour. Since OsO₄ is a very strong oxidizing agent it has to be decomposed before workup. Therefore 50 mL of an aqueous 10 w% NaHSO₃ solution were added. The reaction mixture turned violet and a precipitate occurred, which was filtered. Phases were transferred into a separation funnel and separated. The organic layer was washed twice with water and dried with brine and Na₂SO₄. Solvents were removed under reduced pressure.

2.2.2. Data for the ligands 1a–1f

5-(10,11-dihydroxyundecyl)-5-ethylpyrimidine-2,4,6-trione 1a

The alkene 2a (3 g, 9.73 mmol), NMO·H₂O (3 g, 21.90-mmol), and OsO₄ were suspended in 50 mL dichloromethane and treated according to the general dihydroxylation procedure described above. The crude product was purified by silica gel chromatography (EE/hexane = 3/1) yielding in 1a as a colorless oil (3 g, 90%). Rf = 0.48 (EE/hexane = 3/1).¹H-NMR (200 MHz, DMSO-d₆) δ (ppm) = 11.57 (s, 2H), 4.40 (m, 2H), 3.26 (m, 2H), 1.83 (t, 4H) 1.39–1.23 (m, 16H), 0.77 (t, 3H). ¹³C-NMR (50 MHz, DMSO-d₆) δ (ppm) = 174.12, 150.86, 72.06, 66.97, 56.71, 38.91, 34.38, 32.66, 30.26, 30.02, 29.84, 29.59, 26.16, 25.46.

2.2.3. 11-Azidoundecane-1,2-diol 1b

Starting from the alkene 2b (520 mg, 2.66 mmol), NMO·H₂O (730 mg, 5.32 mmol) and OsO₄ according to the general dihydroxylation procedure described above, 1b (586 mg, 96%) was obtained as colorless oil after purification by silica gel chromatography (EE/hexane = 1/1). Rf = 0.30 (EE/hexane = 1/1).

¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 4.80 (broad s, 2H), 3.57 (d, 2H), 3.38 (m, 1H), 3.24 (t, 2H), 1.59 (m, 2H), 1.29 (m, 14H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 72.22, 66.60, 51.32, 32.93, 29.53, 29.32, 29.02, 28.69, 26.57, 25.50.

2.2.4. 11-Bromoundecane-1,2-diol 1c

11-Bromoundecane-1-ene 2c (1 g, 4.29 mmol), NMO·H₂O (1.3 g, 9.43 mmol), and OsO₄ were dissolved in 20 mL dichloromethane and treated according to the general dihydroxylation procedure described above, yielding product 1c as a white solid (1.12 g, 98%). Rf = 0.44 (EE/hexane = 3/1).¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 4.80 (broad s, 2H), 3.57 (d, 2H), 3.38 (m, 1H), 1.81 (m, 2H), 1.41 (m, 2H), 1.29 (m, 12H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 72.22, 66.60, 33.97, 33.02, 32.72, 29.30, 28.66, 28.05, 25.51.
2.2.5. 5-(dimethylamino)-N-(undec-10-enyl)naphthalene-1-sulfonamide 1d

Alkene 2d (400 mg, 1 mmol), NMO·H₂O (275 mg, 2 mmol), and OsO₄ were reacted in 20 mL dichloromethane and treated along the general dihydroxylation procedure described above. The crude product was purified by silica gel chromatography (EE/hexane = 3/1) yielding in 1d as yellow green oil (410 mg, 94%). R_f = 0.23 (EE/hexane = 3/1). ¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 8.54 (d, 1H), 8.27 (m, 2H), 7.55 (m, 2H), 7.19 (d, 1H), 4.71 (broad s, 1H), 3.63 (d, 2H), 3.42 (m, 1H), 2.89 (s, 6H), 2.04 (broad s, 2H), 1.38–1.10 (m, 18H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 134.92, 130.11, 129.70, 129.64, 129.55, 128.20, 123.56, 115.41, 72.26, 66.68, 45.56, 43.32, 33.74, 29.50, 29.26, 29.00, 28.91, 28.84, 26.37.

2.2.6. 5-(10,11-dihydroxyundecanamido)-N¹,N³-bis(6-octanamidopyridin-2-yl)isophthalamide 1e

The alkene 2e (500 mg, 0.64 mmol), NMO·H₂O (176 mg, 1.28 mmol), and OsO₄ were dissolved in 15 mL dichloromethane and treated along the general dihydroxylation procedure described above. No further purification was necessary. Product 1e was obtained as white solid (512 mg, 98%). R_f = 0.31 (EE/hexane = 4/1). ¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 9.34 (s, 1H), 8.93–7.37 (m, 9H), 3.63 (d, 2H), 3.42 (m, 1H), 3.41 (t, 2H), 2.89 (s, 6H), 2.00 (m, 2H), 1.73 (m, 2H), 1.62 (m, 2H), 1.27 (m, 24H), 0.87 (t, 6H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 173.03, 164.72, 156.23, 149.04, 141.07, 137.63, 134.57, 120.65, 120.53, 105.83, 75.44, 70.58 36.11, 33.86, 31.83, 29.69, 29.58, 28.94, 28.65, 28.63, 25.64, 22.73, 14.11.

2.2.7. 4-(1-(tert-butyl(2-methyl-1-phenylpropyl)aminooxy)ethyl)benzyl 10,11-dihydroxyundecanoate 1f

The alkene 2f [37] (450 mg, 0.86 mmol), NMO·H₂O (237 mg, 1.73 mmol), and OsO₄ were dissolved in 20 mL dichloromethane and treated according to the general dihydroxylation procedure described above. No further purification was necessary. Product 1f was obtained as colorless oil (461 mg, 96%). R_f = 0.46 (CHCl₃/MeOH = 20/1). ¹H-NMR (200 MHz, CDCl₃) δ (ppm) = 7.42–7.15 (m, 18H), 4.12–3.16 (m, 10), 2.33 (t, J = 7.5 Hz, 4H), 1.63–1.32 (m, 15H), 2.00 (q, 4H), 1.55 (m, 11H), 1.25 (s, 16H), 1.05 (s, 9H), 0.96 (d, 3J = 6.2 Hz, 3H), 0.77 (s, 9H), 0.55 (d, 3J = 6.4 Hz, 3H), 0.22 (d, 3J = 6.4 Hz, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ (ppm) = 169.08, 146.03, 145.31, 142.22, 142.11, 140.04, 136.44, 135.69, 130.82, 127.56, 126.73, 125.65, 121.37, 121.09, 119.13, 109.52, 109.49, 82.59, 81.68, 71.53,
2.2.8. Preparation of superparamagnetic iron-oxide nanoparticles NP1

Preparation of octylamine-covered nanoparticles was accomplished according to literature [35, 36]. In brief, a solution of iron cupferron complex (780 mg, 1.5 mmol) in octylamine (3.90 g, 27.22 mmol) was alternately evacuated to 10 mbar and aerated with Ar at 60°C. Triocylamine (7.00 g, 18.33 mmol) was treated the same way at 100°C. The degassed octylamine solution was rapidly injected into the triocylamine solution at 30°C. Immediately after the injection, the reaction vessel was moved to a 225°C prewarmed bath and remained there for 30 minutes under vigorous magnetic stirring. After the reaction was accomplished according to literature [35, 36]. In brief, a solution of iron cupferron complex (780 mg, 1.5 mmol) in octylamine (3.90 g, 27.22 mmol) was alternately evacuated to 10 mbar and aerated with Ar at 60°C. Triocylamine (7.00 g, 18.33 mmol) was treated the same way at 100°C. The degassed octylamine solution was rapidly injected into the trioclyamine solution at 30°C. Immediately after the injection, the reaction vessel was moved to a 225°C prewarmed bath and remained there for 30 minutes under vigorous magnetic stirring. After the reaction was stopped by removing the heating source, the particles were allowed to cool to room temperature. They were dissolved in anhydrous toluene, precipitated by the addition of dry methanol, centrifuged, and again dissolved in anhydrous toluene. This washing step was repeated three times. The stabilized particles were stored under Ar-atmosphere in anhydrous toluene. Nanoparticle sizes were determined by DLS and TEM measurements. The stabilized NPs (NP1) stay soluble for several months, indicating that no agglomeration takes place. IR (KBr-pellet) ν (cm⁻¹) 3450 (–OH), 2926 (–CH₃, –CH₂–), 2857 (–CH₃, –CH₂–), 1623 (–NH₂), 1464 (–CH₃, –CH₂–).

2.2.9. Ligand exchange of NP1 leading to NP3a–NP3f

Surface modification reactions were performed according to the general protocol for ligand exchange reactions of Boal et al. [35, 36]. All reaction steps were performed under Ar-atmosphere. 50 mg stabilized NPs (NP1) were dissolved in 30 mL of a 1:1 mixture of CHCl₃ and toluene. A second mixture was prepared consisting of 250 mg of diol-ligand ıa–f in a 1:1 mixture of chloroform and toluene. If the solubility of the ligand in this mixture was too poor—which occurred using ligands ıa, ıd, ıe—the smallest amount of anhydrous isopropanol was added to dissolve the ligand. The ligand solution was added to the nanoparticle solution via a syringe and the reaction mixture was heated up to 50°C under vigorous stirring for 2 days. After ~48 hours, the exchange reaction was finished, resulting in surface modified nanoparticles NP3a–f. The particles were purified by repeated precipitation with dry methanol, centrifugation, and resuspension in anhydrous toluene. Ligand exchange was monitored by FTIR measurements, analyzing the dried modified nanoparticles as KBr-pellets.

NP3a: IR (KBr-pellet) ν (cm⁻¹) 3450 (–OH), 2928 (–CH₃, –CH₂–), 2856 (–CH₃, –CH₂–), 1702 (O=C–NH–C=O, six membered ring), 1450 (–CH₃, –CH₂–), 1300 (–OH). NP3b: IR (KBr-pellet) ν (cm⁻¹) 3420 (–OH), 2920 (–CH₃, –CH₂–), 2848 (–CH₃, –CH₂–), 2094 (–N₃), 1450 (–CH₃, –CH₂–). NP3c: IR (KBr-pellet) ν (cm⁻¹) 3420 (–OH), 2924 (–CH₃, –CH₂–), 2857 (–CH₃, –CH₂–), 1469 (–CH₃, –CH₂–), 775 (–CH₂–Br). NP3d: IR (KBr-pellet) ν (cm⁻¹) 3433 (–OH), 2956 (–CH₃, –CH₂–), 2916 (–CH₃, –CH₂–), 2857 (–CH₃, –CH₂–), 1450 (–CH₃, –CH₂–), 1373 (–SO₂–NH–), 1150 (–SO₂–). NP3e: IR (KBr-pellet) ν (cm⁻¹) 3420 (–OH), 2951 (–CH₃, –CH₂–), 2917 (–CH₃, –CH₂–), 1628 (O=C–NR₂), 1520 (O=C–NR₂), 1450 (–CH₃, –CH₂–). NP3f: IR (KBr-pellet) ν (cm⁻¹) 3431 (–OH), 2920 (–CH₃, –CH₂–), 2848 (–CH₃, –CH₂–), 1740 (–COOR), 1456 (–N–O–), 1260 (–OH), 1030 (2 signals for esters).

3. RESULTS AND DISCUSSION

The basic strategy for the surface modification of the iron oxide nanoparticles with various organic ligands is...
shown in Figure 1. Starting from octylamine-covered Fe₂O₃ nanoparticles, a direct ligand exchange reaction with substituted 1,2-diols in organic solvents takes place, using the 1,2-diol-moiety as attachment site for the NP-binding. Critical factors, such as the kinetics of ligand exchange, the quantification of surface coverage are described. Basically, four different types of ligands are described: (a) the supramolecular ligands 1a and 1e, (b) ligands bearing the fluorescent label 1d, (c) the azido- and bromine ligands 1b and 1c, as well as (d) the polymerization initiator 1f.

### 3.1. Preparation of 1,2-diol-ligands 1a–1f

The functionalization of γ-Fe₂O₃ nanoparticles with different targeting ligands asks for the creation of an effective nanoparticle binding site on the corresponding ligand. Therefore, the synthesis of 1,2-diols (1a–1f) (see Scheme 1) was planned and prepared via a non-stereoselective Sharpless dihydroxylation [38]. The reaction was effected by the addition of catalytic amounts of OsO₄ to a mixture of N-methyl-morpholine-N-oxide (NMO) and the corresponding (terminal) alkenes 2a–2f in CH₂Cl₂. Using this methodology, the ligands 1a–1f were prepared in 85–98% yield. ¹H-NMR spectra and ¹³C-NMR-spectra are indicative of the high purity and chemical integrity of the prepared samples.

### 3.2. Preparation of iron oxide nanoparticles

Iron oxide nanoparticles were prepared by use of the thermal decomposition of iron cupferron complex in octylamine and trioctylamine (see Scheme 2) at elevated temperatures, as described by Alivisatos [35] and Boal et al. [36], yielding NP1 \((r = 3.6–4.2 \text{ nm})\), as determined by DLS-measurements) with an octylamine shell around the iron
Figure 5: IR spectra of NP’s 3a–3f. In each spectrum the upper traces are those of the free ligand, the lower traces those of the corresponding NP-bound ligand. (a) NP3a, (b) NP3b, (c) NP3c, (d) NP3d, (e) NP3e, (f) NP3f.

oxide nanoparticles. The stabilized nanoparticles are soluble for several month, indicating the absence of agglomeration effects.

The nanoparticles NP1 were characterized by UV-VIS and fluorescence-spectroscopy (see supplementary available online at doi:10.1155/2008/383020) as well as via TEM, XRD, and IR-spectroscopy (see Figure 2).

TEM measurements (see Figure 2(a)) were performed to prove the size of the synthesized nanoparticles and to determine the shape of the NPs. According to these measurements, γ-Fe$_2$O$_3$ nanoparticles crystallize in a spherical shape with a diameter of 6–15 nm which is in good accordance with DLS results. The determination of the lattice structure of the synthesized nanoparticles was accomplished by powder XRD measurements (see Figure 2(b)). Comparing the resulting reflexes to the patterns of both possible structures revealed that the synthesized nanoparticles crystallize in the γ-Fe$_2$O$_3$-structure. Due to the small size of the nanoparticle in comparison to the bulk material, the reflexes are not as sharp but the angle-2Θ-values fit to the bulk pattern. FTIR spectroscopy was used to determine the chemical nature of the surface bound ligands, for example, octylamine (see Figure 2(c)). The nanoparticle spectrum (bottom) is showing all peaks at the characteristic frequencies, such
as 2926 cm\(^{-1}\), 2857 cm\(^{-1}\) (–CH), and 1623 cm\(^{-1}\) (–NH\(_2\)), but with a slight line broadening and less intensity. This is in good agreement with literature [36], showing the same phenomenon.

An important parameter concerns the surface coverage of the nanoparticles with the organic ligand (octylamine).

In order to generate a value of significance, both a theoretical calculation and an experimental determination via TGA analysis were performed (see Figures 3(a) and 3(b)). According to the literature [36], \(\gamma\)-Fe\(_2\)O\(_3\) crystallizes in a cubic closed-packed structure. In this sphere, each atom has 6 neighbors in plane and 3 in each plane above and below, leading to a sum of 12 neighbor atoms. Referring to DLS measurements, NP1 has an average radius of 3.92 nm, leading to a volume of the particle of \(V_{\text{particle}} = 252.32 \, \text{nm}^3\) and a particle surface of \(S_{\text{particle}} = 193.10 \, \text{nm}^2\). Considering the density of \(\gamma\)-Fe\(_2\)O\(_3\) (\(\rho_{\text{Fe}_2\text{O}_3} = 4.9 \, \text{g/cm}^3\)), the theoretical mass of one particle \(m_{\text{particle}} = 1.24 \times 10^{-18} \, \text{g}\). Taking the surface of one particle \(S_{\text{particle}}\) and the binding area of one ligand \(A_{\text{octylamine}}\) on the nanoparticle surface into account, the amount of surface bound ligands \(n_{\text{octylamine}}\) can be calculated. The binding area of one ligand is assumed as quadratic, therefore, \(A_{\text{octylamine}} = (a_{\text{octylamine}})^2\), where \(a_{\text{octylamine}}\) is the side length of the quadratic binding area of one ligand. Using the molecular weight of the surface bound ligand \((M_{\text{octylamine}} = 129.3 \, \text{g/mol})\), it is now possible to determine the theoretical mass fraction of the surface bound ligands with respect to the total mass of the nanoparticle. Furthermore, paying attention to the molar mass of \(\gamma\)-Fe\(_2\)O\(_3\) \((M_{\text{Fe}_2\text{O}_3} = 159.7 \, \text{g/mol})\) and to the length of the elemental cell of \(\gamma\)-Fe\(_2\)O\(_3\) \((a_{\text{Fe}_2\text{O}_3} = 0.8339 \, \text{nm})\), it is possible to determine the number of \(\gamma\)-Fe\(_2\)O\(_3\)-units per nanoparticle \(n_{\text{Fe}_2\text{O}_3}\) and in the outer shell of the nanoparticle \(n_{\text{outer Fe}_2\text{O}_3}\).

TGA (thermogravimetric analysis) measurements of NP1 were performed to estimate the amount of surface bound ligands. The mass loss of 22.02 w\% indicates that the total mass of a nanoparticle NP1 is composed of 78 w\% iron oxide core and 22 w\% organic stabilizing ligand, thus being in excellent accordance to the calculated value. Therefore, TGA was assumed to represent an excellent tool for the characterization of the amount of surface bound ligand.

### 3.3. Ligand exchange with 1,2-diols

Using the general protocol for ligand exchange reactions according to Boal et al. [36], stabilized NP1 are treated with a 5-fold excess of diol-ligand 1a–f in a 1:1-mixture of CHCl\(_3\) and toluene at 50°C. The reaction finished after 48 hours resulting in surface modified nanoparticles NP3a–f. The particle size was determined by DLS measurements showing no change in particle diameter.

A first hint at a successful ligand exchange was provided by solubility experiments. Thus the solubility of NP3a–f was rather different as compared to the nonmodified nanoparticle (NP1a–d). Whereas NP3a, c, f were completely soluble in common organic nonpolar aprotic solvents, such as CHCl\(_3\) and toluene, NP3a, d, e were only poorly soluble in any of these solvents, presumably due to self aggregation phenomena of the respective multiple hydrogen bonding interaction, now present at their surface due to the ligand exchange reaction. Even ultrasonic irradiation was not able to improve their solubility. NP3a were soluble in dipolar aprotic solvents such as in DMF or THF. This behavior is also visible in TEM measurements, where the formation of aggregates of nanoparticles NP3a is clearly visible (see Figure 4(a)) in comparison to the noninteracting NP3c. XRD measurement still indicates the presence of \(\gamma\)-Fe\(_2\)O\(_3\) after the exchange reaction (see Figure 4(b)).

In order to fully characterize the surface bound ligands on NP3a–f, FTIR measurements were performed. Figures 5(a)–5(f) show the IR spectra of all synthesized nanoparticles, in each case the upper spectrum shows the unbound ligand, the lower one of the functionalized NPs. Since the binding site of the ligand on the nanoparticle is the electron donating diol group, an OH-signal is always present at \(\sim 3400 \, \text{cm}^{-1}\). Furthermore, characteristic peaks are always present, thus proving the presence of the ligands on the NP-surface. NP3a show a characteristic carbonyl signal at 1702 cm\(^{-1}\), NP3b show a significant azide band at 2094 cm\(^{-1}\). Furthermore, NP3c show a typical band at 1470 cm\(^{-1}\) and in NP3d the band at 1373 cm\(^{-1}\) for the sulfonamide moiety is clearly visible. NP3e and NP3f show a significant band at 1628 cm\(^{-1}\) for the amide and in NP3f a signal at 1456 cm\(^{-1}\) is indicative for the nitrooxide moiety.

Again, as already demonstrated before, TGA (see Figure 6) and DLS results were used for the determination of the number of surface bound ligands, the number of iron centers on the surface, and the ligand binding area. The following nanoparticles were analyzed: NP3a–d and NP3f. The results are compiled in the following table (Table 1).

Comparison of the weight loss gained by TGA measurements and calculations based on the hydrodynamic radius gained by DLS shows an excellent match, thus proving the complete ligand exchange.

### 3.4. Kinetics of the ligand exchange reaction

This is an important point concerning the follow-up of the ligand exchange kinetics during the incubation of the octylamine-covered nanoparticles with the 1,2-diol-ligands.
As described by Boal et al. [36], a time of 48 hours is required for all diol-ligands to effect the efficient exchange reaction, replacing the initial octylamine ligand by the much harder alcohol. However, ligands bearing monovalent
hydroxyl moieties are not stable over a long term, leading to irreversible aggregation of the nanoparticles after the eventual loss of the covering ligand.

We therefore have studied the kinetics of the ligand exchange reaction of NP1 with ligands 1a and 1d (see Figure 7(a)), enabling to follow the ligand exchange via TGA due to the significant increase in weight when compared to the octylamine ligand in NP1. The nanoparticles NP1 were treated under standard ligand exchange conditions with the corresponding diol-ligand (1a and 1d), respectively. Samples of ∼5 mg were taken at different time points (t1 ··· tn), purified by repeated precipitation, and analyzed thermogravimetrically. The weight loss was plotted versus time resulting in the results in Figure 7(b), indicating a saturation law. The final theoretical mass loss was calculated and compared to the values gained by TGA measurements. The calculated values of 16.76 w% of ligand 1d on NP3d are in excellent accordance with the measured value of 16.29 w% (NP3d) elicited by TGA. In case of NP3a, the theoretically calculated mass loss of 13.64 w% fits well the measured value of 14.60 w% determined by TGA. In comparison to the results obtained by parallel FTIR measurements (data not shown), TGA results indicate a complete exchange of octylamine after 24 hours whereas IR results indicate a reaction time of 48 hours.

Therefore, it can be concluded that a complete ligand exchange reaction can be effected within one day of reaction time using a nonpolar reaction medium.

4. CONCLUSION

In summary, we have developed an easy access to the surface modification of γ-Fe2O3 nanoparticles via exchange reaction with 1,2-diols. The generation of the corresponding ligands is simple, since the 1,2-dihydroxylation reaction can be performed in the presence of a multitude of functional groups, as demonstrated with the ligands 1a–1f. Clearly, the method offers the possibility to engineer superparamagnetic iron oxide nanoparticles with a large variety of functional organic ligands, being bound stable to the nanoparticle surface.

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