Host-Guest Driven Ligand Replacement on Monodisperse Inorganic Nanoparticles

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Synthesis of superparamagnetic iron oxide nanoparticles (SPIONs):

Oleic acid (OA) capped superparamagnetic iron oxide nanoparticles (OA-SPIONs) were synthesized via thermal decomposition of iron pentacarbonyl. All materials were used as received without further purifications. In a typical procedure 1 ml of iron pentacarbonyl was quickly injected into a N2-saturated solution of 50 ml dioctyl ether containing certain amount of oleic acid (for example 10 ml to obtain 11 nm SPIONs) at 100°C. The temperature was then gradually raised to 290 °C with a ramp of 3 K/min and held for 1 h. The as-synthesized magnetite nanoparticles were subsequently cooled to room temperature, precipitated with an EIOH and collected with external magnet. The particles were washed 3 times with ethanol and centrifuged at 5000 rpm for 1 minute to remove the large excess of oleic acid and dioctyl ether. The diameter of the resulting highly monodisperse and monocrystalline Fe3O4 particles was calculated by the freeware Pebbles.[2]

Nitrodopamine (NDA):

5 g dopamine hydrochloride (26.36 mmol) and 5.6 g sodium nitrite (81.17 mmol) were dissolved in 150 ml Milli-Q water and cooled in an ice bath. 20 ml of 20% v/v sulfuric acid were added dropwise under vigorous stirring to the cooled solution maintaining a temperature below 10 °C. After complete addition, the reaction mixture was slowly warmed to room temperature and stirred for 12 h. The resulting yellow precipitate was collected by filtration and washed generously with ice-cold water and once with MeOH. NDA was obtained as a bright yellow powder in 60% yield. 1H NMR (300 MHz, DMSO-d6): 3.04 (s, 4H), 6.71 (s, 1H), 7.46 (s, 1H).

Palmitoyl-nitrodopamide (ND-C16, PND):  
PND was synthesized by coupling of NDA (1 eq) with palmitoyl-NHS (1.1 eq) in the presence of N-methylmorpholine (NMM) (2 eq) in dimethylformamide (DMF) (1 mmol of reactant in 3 ml DMF) and purified by solvent extraction (0.1 M HCl and DCM). 1H NMR (300 MHz, DMSO-d6): 0.84 (t, J= 6.4 Hz, 3H), 1.22 (m, 24H), 1.44 (t, J= 6.8 Hz, 2H), 2.00 (t, J= 7.4 Hz, 2H), 2.88 (t, J= 6.9 Hz, 2H), 3.23 (q, J= 6.4 Hz, 2H), 8.88 (s, 1H), 7.47 (s, 1H), 7.84 (t, 1H), 9.80 (br, 1H), 10.32 (br, 1H).

11-mercaptoundecanoyl-nitrodopamide (ND-C11-SH):

NDA-C11-SH was synthesized by coupling of NDA (1 eq) with 11-mercaptoundecanoic acid (1.1 eq) using (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy) dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) (1.1 eq) in the presence of NMM (2 eq) in DMF (1 mmol of reactant in 3 ml DMF) and purified by solvent extraction (0.1 M HCl and DCM). 1H NMR (300 MHz, DMSO-d6): 1.25-1.73 (m, 16H), 2.18 (t, J= 6.3 2Hz, 2H), 2.88 (t, J= 6.8 Hz, 2H), 3.07 (t, 2H), 3.56 (t, J= 6.5, 2H), 6.88 (s, 1H), 7.47 (s, 1H), 7.83 (t, 1H).

11-bromoundecanoyl-nitrodopamide (ND-C11-Br):

NDA-C11-br was synthesized by coupling of NDA (1 eq) with 11-bromoundecanoic acid (1.1 eq) using COMU (1.1 eq) in the presence of NMM (2 eq) in DMF (1 mmol of reactant in 3 ml DMF) and purified by solvent extraction (0.1 M HCl and...
16-hydroxyundecanoyl-nitrodopamide (ND-C16-OH)

NDA-C16-OH was synthesized by coupling of NDA (1 eq) with 16-Hydroxyhexadecanoic acid (1.1 eq) using COMU (1.1 eq) in the presence of NMM (2 eq) in DMF (1 mmol of reactant in 3 ml DMF) and purified by solvent extraction (0.1 M HCl and DCM). $^1$H NMR (300 MHz, DMSO-d$_6$): 1.25-1.46 (m, 16H), 2.00 (t, $J$= 6.3, 2H), 2.18 (t, $J$= 6.5, 2H), 3.51 (t, $J$= 6.6, 2H), 6.88 (s, 1H), 7.47 (s, 1H), 7.83 (t, 1H).

Octanoyl-nitrodopamide (ND-C8)

NDA-C8 was synthesized by coupling of NDA (1 eq) with Octanoic acid (1.1 eq) using COMU (1.1 eq) in the presence of NMM (2 eq) in DMF (1 mmol of reactant in 3 ml DMF) and purified by solvent extraction (0.1 M HCl and DCM). $^1$H NMR (300 MHz, DMSO-d$_6$): 0.85 (t, $J$= 6.8 Hz, 3H), 1.22 (m, 24H), 1.44 (t, $J$= 6.7 Hz, 2H), 2.00 (t, $J$= 6.7 Hz, 2H), 2.89 (t, $J$= 7.1 Hz, 2H), 3.24 (q, $J$= 6.3 Hz, 2H), 6.68 (s, 1H), 7.48 (s, 1H), 7.83 (t, $J$= 5.3 Hz, 1H).

Stripping of oleic acid capped SPIONs with sodium halides:

Stripping of OA-capped SPIONs was done using different sodium halides and 15-crown-5. A strong size dependent trend for efficiency of anions to strip OA from SPIONs was observed. SPIONs treated with different salts were collected after 24h of phase transfer and analyzed by thermogravimetric analysis (TGA). As shown in Fig. S1, F$^-$ succeeds to remove completely the deprotonated OA as also confirmed by $^1$H NMR, ATR-FTIR and XPS (see main text). The other halides which are bigger than oxide ions are not able to displace OA from the surface of the SPIONs. The larger the size of the anion, the larger the remaining OA surface coverage found by TGA. Thus, next to F$^-$, Cl$^-$ removed most OA, while a substantially larger amount of residual OA was observed for samples which were treated with Br$^-$ and I$^-$. 

![Fig. S1. TGA data of 11 nm SPIONs collected after 24h stripping using 15-Crown-5 and NaF (blue), NaCl (red), NaBr (green), NaI (black).](image-url)
Sodium halide salts  | NaF  | NaCl  | NaBr  | NaI  
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Remaining mass (%) | 0.03 | 4 | 11 | 11.5  
OA grafting density (molecule/nm²) | 0.006 | 0.84 | 2.50 | 2.63

**Table S1.** The fraction of remaining organic content on particles stripped using 15-Crown-5 and sodium salts of the tabulated anions, calculated from data in Fig. S1. The average surface coverage of OA after stripping is calculated using the total organic content measured by TGA (100 °C – 650 °C), and the surface area of the SPION of core diameter 11 nm determined by TEM.

**Re-grafting of ligands on naked particles**

200 mg of naked particles and 60 mg of palmitoyl-nitrodopamide (PNDA) were added to 12 ml DMF:MeOH (3:1) mixture and sonicated for 12 h under nitrogen atmosphere. MeOH was evaporated with rotavapor and the NPs were subsequently precipitated by adding an excess of acetone to the suspension. Particles were collected via centrifuge at 20000 rpm, re-suspended in acetone, sonicated for 2 min, and centrifuged at 20000 rpm for 30 min to remove excess of ligand. This process was continued until the supernatant became clear. Particles were dispersed in THF and centrifuged at 5000 rpm for 1 min to remove any unmodified particles. Finally, the supernatant was removed by rotavapor and for TGA analysis, particles were dried further under high vacuum (0.05 mbar) for 2 days.

**Fig. S2.** Thermogravimetric analysis of re-grafted SPIONs using various ligands: PNDA on 11-nm SPIONs (green), ND-C8 on 8-nm SPIONs (red), ND-C11-SH on 10-nm SPIONs (black), ND-C11-Br on 10-nm SPIONs (orange), ND-C16-OH (PNDA) on 10-nm SPIONs (blue). The average surface coverage of OA after stripping is calculated using the total organic content measured by TGA (100 °C – 650 °C), and the surface area of the SPIONs determined by TEM.

**Table S2.** Organic mass fraction of re-grafted ligands on SPIONs measured by TGA. The grafting density is calculated from the organic mass fractions using the molecular weight of the ligands and the SPIONs area calculated from TEM.
XPS data of iron oxide nanoparticles

| sample          | C:O ratio (%) stoichiometric | C:O ratio (%) quantification |
|-----------------|-----------------------------|-----------------------------|
| OA-capped NPs   | 90 : 10                     | 89.5 ± 1 : 10.5 ± 1         |

Table S3. XPS elemental analysis of OA-capped SPION, emission angle of 75 °

An excess of OA in these unpurified samples masks the iron oxide cores due to the low penetration depth (1 to 2 nm) of the XPS probe; therefore, an iron signal was not detected. A close agreement between the measured and OA stoichiometric C:O ratios is therefore expected.

| sample          | C 1s  | O 1s  | F 1s  | Na 1s | Fe 2p | Si 2p |
|-----------------|-------|-------|-------|-------|-------|-------|
| Stripped NPs    | 6 ± 2 % | 33 ± 2% | 24 ± 4% | 12 ± 2% | 3 ± 2% | 21 ± 4% |

Table S4. XPS survey analysis of stripped (naked) SPION, emission angle of 75 °

The low carbon content is consistent with the complete removal of OA and low amounts of contaminant from the preparation of the XPS samples. The iron oxide NP cores are detected (compared to the OA-coated SPION) as the nanoparticles are now stripped naked without an attenuating ligand shell. Although salt is present and Na is a common contaminant, a striking excess of F anions is observed compared to the expected stoichiometric ratio of Na:F from the added salt. This excess is consistent with a picture in which F⁻ now comprises the main anion ligand species compensating the SPION surface ions by ligation.

| sample          | C:O ratio (%) Stoichiometric | C:O ratio (%) Quantification |
|-----------------|-------------------------------|-----------------------------|
| Re-grafted PNDA NPs | 83 : 17                      | 87 ± 2 : 14 ± 3             |

Table S5. XPS elemental analysis of re-grafted PNDA SPION, emission angle of 75 °

After re-grafting, phase transfer and washing, only the ligand coating on the particles is detected due to the low XPS probe penetration depth (1 to 2 nm).

X-ray diffraction measurements

X-ray diffraction (XRD) spectra were recorded for nanoparticles before and after stripping using 15-Crown-5 and NaF, and after re-grafting with PNDA. Powder X-ray diffraction data were collected with a PANalytical multi-purpose diffractometer (MPD) Pro in Bragg-Brentano geometry operating with a Cu (Kα) anode. A PIXCel 3D detector was used. Samples were mounted as loose powders on silicon single crystal sample holders. The diffraction patterns were recorded between 3.5 and 70° (2θ) with 90 s/step and a step size of 0.02°.

The spectra are presented in Fig. S3. Nanoparticles of this size have broad and weak peaks as can be seen for the as-synthesized OA-capped particles. No significant change is observed in the main peak positions of iron oxide between OA-capped nanoparticles (red line), nanoparticles stripped with 15-Crown-5/NaF (black line) and PNDA re-grafted nanoparticles (blue line). Fe₂O₃ and Fe₃O₄ are almost indistinguishable by XRD. We therefore cannot tell if the oxidation state has changed and note that iron oxide nanoparticles synthesized by the heat-up method from oleate precursors inconclusively have been attributed to be both Fe₂O₃ and Fe₃O₄ in the literature. Additional sharp peaks appearing for the stripped particles (black line) can be attributed to NaF crystals present in the stripped sample. The additional sharp peaks for the OA-capped nanoparticles in OA excess most likely originate from oleate complex structures. The large broad peak in the range 2θ = 10°-25° for the OA-capped sample also most likely originates from the OA, since the peak is not observed for iron oxide NPs synthesized by the sol-gel method. These additional features in the OA-capped sample disappear from the spectrum after stripping, which supports the interpretation that they should be attributed to oleate complex structures. The PNDA-grafted nanoparticle spectrum contains only a signal from iron oxide.
Colloidal stability of unmodified and re-grafted iron oxide nanoparticles

**Fig. S3.** XRD spectra recorded for powders of OA-capped nanoparticles in excess OA (red line), nanoparticles stripped with 15-Crown-5/NaF (black line) and PNDA re-grafted nanoparticles (blue line). The blue arrows indicate the peaks that correspond to iron oxide and the black arrows indicate the peaks that correspond to villiaumite (NaF).

**Fig. S4.** DLS of 9.2-nm OA-capped nanoparticles before stripping in toluene (red line) and after re-grafting of PNDA (blue line) measured in THF. The DLS results demonstrate that there is no significant size change of nanoparticles in the dispersion before and after the method of re-grafting has been applied. Nanoparticles that are stripped of the OA shell but not re-grafted with ligand do not produce meaningful DLS data, since they were found to aggregate in all solvents without a protective shell.
Stripping and re-grafting of high-curvature iron oxide nanoparticles

Fig. S5. Thermogravimetric analysis of stripped (black line) and re-grafted SPIONs using PNDA (red line) on 4.2-nm SPIONs. The TGA results correspond to a grafting density of PNDA ligand of 3.2 molecules/\text{nm}^2. The average surface coverage of PNDA after re-grafting is calculated using the total organic content measured by TGA (100 °C – 650 °C), and the surface area of the SPIONs determined by TEM.

Chemical formulas and abbreviations used for ligands

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\text{ND-C16 (PNDA)}
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\text{ND-C11-SH}
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\text{ND-C11-Br}
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\text{ND-C16-OH}
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\text{ND-C8}
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\[
\text{OA}
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References

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