Supporting information – Cross-linked polystyrene shells grown on iron oxide nanoparticles via surface-grafted AGET-ATRP in microemulsion

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S1. Experimental section

Synthesis of 11-(2-bromoisobutyrate)-undecyl-1-phosphonic acid (BiB-UDPA)

The ATRP-initiator-ligand BiB-UDPA was synthesized in five steps similarly to the synthetic route reported by Minet et al.\(^1\) with some modifications, giving the product with an overall yield of 59.9 %.

Scheme S1. Route for the synthesis of BiB-UDPA in five steps.

11-Bromo-1-(tetrahydropyranloxy)undecane (1). In a 100 mL round-bottom flask equipped with a stirring bar, 5.0 g 11-bromo-1-undecanol (19.9 mmol) were dissolved in 50 mL 2-methoxy-2-methylpropane and 5 mL 3,4-dihydro-2H-pyran (54.8 mmol) were added. After stirring for 5 minutes, 34 mg of \(p\)-toluenesulfonic acid monohydrate (0.18 mmol) were added and the reaction was stirred at room temperature overnight. Afterwards, the organic phase was washed two times with 30 mL \(\text{Na}_2\text{CO}_3\)-solution (1 mol/L) and one time with 30 mL water. The organic phase was dried over MgSO\(_4\), filtered and the solvent was evaporated under reduced pressure giving 6.7 g of 1 as a yellowish liquid (19.9 mmol, 100 %).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), \(\delta\), ppm): 4.57 (t, 1H), 3.90-3.83 (m, 1H), 3.76-3.68 (dt, 1H), 3.53-3.50 (m, 1H), 3.42-3.34 (m, 3H), 1.90-1.23 (m, 24H).
$^{13}$C-NMR (300 MHz, CDCl$_3$, δ, ppm): 98.99, 67.82, 62.50, 34.19, 32.98, 30.94, 29.89, 29.67, 29.61, 29.60, 29.55, 28.90, 28.31, 26.37, 25.66, 19.86.

ESI-MS (m/z): 357.139 (M+Na)$^+$

$\textit{11-(Diethylphosphonyl)-1-(2-tetrahydropyranyloxy)undecane (2).}$ 6.5 g of 1 (19.4 mmol) were loaded in a glass microwave vessel with a snap-cap and 8 mL of triethylphosphite (46.7 mmol) were added. The reaction was heated under stirring to 165 °C (200 W) for 1 h (CEM Discover SP). During reaction a pressure of 1.6 bar evolved. After cooling to room temperature unreacted triethylphosphite and the byproduct diethyl ethylphosphonate were removed at 1 x 10$^{-3}$ mbar and 60 °C. The product was isolated as a colorless liquid with a yield of 6.9 g (17.6 mmol, 90.7 %). NMR-Spectra revealed some cleavage of the THP-ether. Corresponding signals are marked with *$^\star$.\\

$^1$H-NMR (300 MHz, CDCl$_3$, δ, ppm): 4.56 (t, 1H), 4.15-4.00 (m, 4H), 3.90-3.82 (m, 1H), 3.75-3.67 (dt, 1H), 3.62* (t), 3.52-3.45 (m, 1H), 3.41-3.33 (m, 1H), 1.88-1.20 (m, 30H).

$^{13}$C-NMR (300 MHz, CDCl$_3$, δ, ppm): 98.94, 67.78, 62.44, 61.51, 61.45, 30.88, 29.84, 29.63, 29.61, 29.56, 29.45, 29.18, 26.32, 25.60, 22.51, 17.95, 16.59, 16.52.

ESI-MS (m/z): 309.223 (M-THP+H)$^+$

$\textit{11-(Diethylphosphonyl)undecanol (3).}$ The de-protection of the hydroxyl group was performed by stirring 2 and Amberlyst® 15H in Methanol at 45 °C for 4 h. After cooling to room temperature, the solution was filtered and the solvent was removed under reduced pressure. The crude product was dissolved in hexane at 70 °C and precipitated by cooling to room temperature. The procedure was repeated giving 4.8 g (15.6 mmol, 89 %) of (3).

$^1$H-NMR (300 MHz, CDCl$_3$, δ, ppm): 4.08-3.95 (m, 4H), 3.56 (t, 2H), 1.88-1.43 (m, 8H), 1.35-1.16 (m, 20H).

$^{13}$C-NMR (300 MHz, CDCl$_3$, δ, ppm): 63.13, 61.57, 32.92, 29.64, 29.56, 29.51, 29.43, 25.85, 24.88, 22.53, 16.65.

ESI-MS (m/z): 309.230 (M+H)$^+$, 331.201 (M+Na)$^+$

$\textit{11-(2-Bromoisobutyrate)-undecyl-1-diethylphosphonate (4).}$ 608.1 mg (2 mmol) of 3 and 1.2 mL triethylamine (8.7 mmol) were dispersed in 10 mL dry THF. Under stirring in an ice bath, 0.6 mL of 2-bromoisobutyryl bromide (4.9 mmol) was added and the reaction was
further stirred for 2.5 h. The reaction mixture was diluted with 15 mL 2-methoxy-2-methylpropane and washed twice with 10 mL 1 M HCl aq. and twice with 10 mL water. The organic phase was separated, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel; eluent: hexane:ethyl acetate = 1:9) giving 680.9 mg (1.5 mmol, 75 %) of (4) as a slightly yellow liquid.

\(^1\)H-NMR (300 MHz, CDCl₃, δ, ppm): 4.16 (t, 2H), 4.13-4.02 (m, 4H), 1.92 (s, 6H), 1.77-1.50 (m, 6H), 1.43-1.20 (m, 20H).

\(^1\)H-NMR (300 MHz, CDCl₃, δ, ppm): 4.16 (t, 2H), 4.13-4.02 (m, 4H), 1.92 (s, 6H), 1.77-1.50 (m, 6H), 1.43-1.20 (m, 20H).

\(^1\)H-NMR (300 MHz, CDCl₃, δ, ppm): 171.87, 66.28, 61.52, 56.15, 30.92, 29.58, 29.56, 29.46, 29.28, 29.22, 29.21, 28.47, 25.90, 24.89, 22.53, 16.62.

ESI-MS (m/z): 457.174 (M+H)\(^+\), 479.156 (M+Na)\(^+\)

\(11\)-(2-Bromoisobutyrate)-undecyl-1-phosphonic acid (5) (BiB-UDPA). 911.0 mg (1.992 mmol) of 4 were dissolved in 10 mL dichloromethane and 660 µL (5.0 mmol) of bromotrimethylsilane were added. The solution was stirred for 2.5 h before it was quenched by adding 10 mL acetone/water 4:1 (v/v). After stirring for another 30 minutes all volatile substances were removed under reduced pressure. The crude product was purified by recrystallization from ether giving 790.9 mg (1.971 mmol, 98.9 %) white powder.

\(^1\)H-NMR (300 MHz, CDCl₃, δ, ppm): 8.90 (s, b, 2H), 4.16 (t, 2H), 1.93 (s, 6H), 1.82-1.53 (m, 6H), 1.44-1.22 (m, 14H).

\(^1\)H-NMR (300 MHz, CDCl₃, δ, ppm): 171.89, 66.30, 56.15, 30.95, 29.63, 29.60, 29.52, 29.33, 29.23, 28.50, 25.94.

ESI-MS (m/z): 401.110 (M+H)\(^+\), 423.091 (M+Na)\(^+\)

Synthesis of \(N,N\)-bis(2-pyridylmethyl) octadecylamine (BPMODA)

\[ \text{Scheme S2. Synthesis of BPMODA.} \]
BPMODA was synthesized following the procedure published by Menger and Lee.\textsuperscript{2} 5.2 g (31.5 mmol) (2-chloromethyl)pyridine hydrochloride were dissolved in 53 mL ultrapure H\textsubscript{2}O. The solution was immersed in an ice bath and 50 mL of an aqueous solution of NaOH in ultrapure H\textsubscript{2}O (630 mmol/L) were slowly added from a dropping funnel. 4.3 g (15.9 mmol) 1-octadecylamine dissolved in 100 mL THF were added to the solution. The mixture was allowed to warm to room temperature and again 50 mL of the NaOH solution (630 mmol/L) were added from the dropping funnel over a period of 4 h. During the addition the mixture was heated to 50 °C and further stirred for 48 h. After cooling to room temperature 50 mL of a NaOH solution (4 mol/L) were added, followed by extraction with 300 mL dichloromethane. The organic phase was neutralized with Amberlite IR-120 H-form, dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. The solid residue was purified using column chromatography on silica gel (dichloromethane:methanol:triethylamine = 92:7:1) giving a light brown solid after evaporation of the solvent.

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, δ, ppm): 8.51 (d, 2H), 7.68-7.60 (m, 4H), 7.15 (t, 2H), 3.87 (s, broad, 4H), 2.58 (s, broad, 2H), 1.57 (s, broad, 2H), 1.35-1.1 (m, 30H), 0.87 (t, 3H).

\textsuperscript{13}C-NMR (300 MHz, CDCl\textsubscript{3}, δ, ppm): 159.80, 149.08, 136.45, 123.11, 122.03, 60.50, 54.55, 32.04, 29.82, 29.78, 29.74, 29.71, 29.56, 29.48, 27.40, 27.05, 22.81, 14.23.

ESI-MS (m/z): 452.4002 (M+H\textsuperscript{+}), 468.3951 ([M-Ox]+H\textsuperscript{+}).

S2. Size-distribution of the used iron oxide Nanoparticles

Figure S1. TEM image of SPIONs used in this study (left). Size-distribution of the particles, obtained from evaluation of 1283 particles from various images at different positions of the sample (right).
S3. FTIR-spectra of modified iron oxide nanoparticles

![FTIR Spectra](image)

**Figure S2.** FTIR-Spectra of iron oxide nanoparticles covered with oleic acid (black) and modified with BiB-UDPA (red).

S4. Calculation of grafting-density of ligand molecules

From the TG measurement the mass fractions of the organic and inorganic phases are obtained. With the inorganic mass fraction $w_{IO}$ the overall surface area of the nanoparticles can be calculated as follows.

\[ A_{\text{total}} = 4\pi r^2 \cdot N \]  \hspace{1cm} (1)

The number of particles $N_{NP}$ can be calculated from the ratio of the total volume of iron oxide $V_{IO}$ and the volume of one nanoparticle $V_{NP}$, using the inorganic mass fraction $w_{IO}$ and the density of bulk magnetite $\rho_{IO}$ of 5.2 g/cm$^3$.

\[ N_{NP} = \frac{V_{IO}}{V_{NP}} = \frac{w_{IO}/\rho_{IO}}{\frac{4}{3}\pi r^3} = \frac{3w_{IO}}{4\pi\rho_{IO}r^3} \]  \hspace{1cm} (2)

From the organic mass fraction $w_{lig}$ the total number of ligand molecules can be calculated with the molar mass of a ligand molecule $M$ and Avogadros constant $N_A$.

\[ N_{lig} = n \cdot N_A = \frac{w_{lig}}{M} N_A \]  \hspace{1cm} (3)

The grafting-density is obtained from the ratio of ligand molecules per surface area.
S7

\[ g.d. = \frac{N_{\text{lig}}}{A_{\text{total}}} = \frac{w_{\text{lig}}N_A\rho_{\text{IO}}r}{3Mw_{\text{IO}}} \]  

(4)

S5. Elemental analysis of modified iron oxide nanoparticles

The results from the elemental analysis for iron, phosphorous, carbon and hydrogen are shown in table S1. Additionally, the amounts of bromine and oxygen were calculated. For bromine one atom per phosphorous atom was assumed. Then oxygen was assumed to be the remainder, while it was differentiated between oxygen originating from the ligand molecule or the iron oxide core particle. For oleic acid two oxygen atoms per 18 carbon atoms were assumed. For BiB-UDPA five oxygen atoms per phosphorous atom were assumed.

Table S1. Results from elemental analysis

<table>
<thead>
<tr>
<th>Element</th>
<th>Content [wt%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPIONs@OA</td>
</tr>
<tr>
<td>Fe</td>
<td>62.59</td>
</tr>
<tr>
<td>P</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>9.51</td>
</tr>
<tr>
<td>H</td>
<td>1.53</td>
</tr>
<tr>
<td>Br</td>
<td>0</td>
</tr>
<tr>
<td>O_{lig}</td>
<td>1.41</td>
</tr>
<tr>
<td>O_{core}</td>
<td>24.96</td>
</tr>
</tbody>
</table>

Based on these values, the molar ratio of iron and oxygen inside the core nanoparticles was calculated. This calculation returned an iron/oxygen ratio of 2.87/4 for oleic acid stabilized particles and 3.12/4 for BiB-UDPA modified particles, both being close to the expected ratio of 3/4 for magnetite.

The organic content of the samples was further calculated from the sum of all contributing atoms (P, C, H, Br, and O_{lig}). For the native oleic acid stabilized iron oxide particles an organic content of 12.45 wt% was calculated. For the BiB-UDPA modified nanoparticles an organic content of 20.37 wt% was obtained.
Furthermore, the grafting-density of phosphorous per surface area was calculated for the modified particles. First, the number of iron atoms per nanoparticle $N_{Fe}$ was calculated from the volume ratio of one nanoparticle and the volume of the magnetite unit cell ($5.92 \times 10^{-28} \text{ m}^3$), multiplied by the number (24) of iron atoms per unit cell.

$$N_{Fe} = 24 \cdot \frac{V_{NP}}{V_{UC}} = 24 \cdot \frac{4}{3 \pi r^3}$$

(5)

With this, the number of particles in a sample of a fictive mass and their total surface area can be calculated following equation (1). Separately, the number of phosphorous atoms in the sample can be calculated and put into relation with the total surface area to obtain the phosphorous grafting density of 3.7 atoms/nm$^2$.

In a last step the composition of the ligand shell was calculated from the C/P ratio of 21.2 carbon atoms per phosphorous atom. The number of carbon atoms in a sample of fictive mass is the sum from 15 carbon atoms per BiB-UDPA molecule or phosphorous atom and 18 carbon atoms per molecule of oleic acid. As the number of phosphorous atoms in the sample is known from elemental analysis, the composition can be calculated from equation (6).

$$n_C = 15n_P + 18n_{OA}$$

(6)

From this a composition of the ligand shell of 75 mol% BiB-UDPA and 25 mol% oleic acid can be calculated.
S6. Size-distributions measured by DLS

Figure S3. Size-distributions measured by DLS for different amounts of monomer ((a) 70 µL, (b) 140 µL, (c) 280 µL). The different colors represent the distributions weighted by intensity (red), volume (blue) and number (yellow).
Figure S4. Size-distributions measured by DLS for different degrees of cross-linking ((a) 50 %, (b) 33 %, (c) 25 %, (d) 10 %, (e) 0 %). In all reactions 140 µL of the corresponding monomer mixture were used. The different colors represent the distributions weighted by intensity (red), volume (blue) and number (yellow).
Figure S5. Summary of DLS results for different degrees of cross-linking. The upper diagram shows the development of z-average (■), intensity mean (●), volume mean (▲) and number mean (▼) with increasing degree of cross-linking. In contrast to the variation of the amount of monomer, no clear trend is visible. The lower diagram shows the unchanged index of polydispersity (PdI) for all three reactions.

Figure S6. Size-distributions measured by DLS for the two different surfactants used during synthesis. Both syntheses were performed under same conditions and only the surfactant was changed. Figure part (a) shows the results for the use of surfactant Brij® O20, which includes a double bond in its hydrophobic residue. Figure part (b) shows that smaller particles are obtained when using Brij® S20 with a fully saturated hydrophobic residue. The different colors represent the distributions weighted by intensity (red), volume (blue) and number (yellow).
S7. Statistical evaluation of different shell-thicknesses

**Figure S7.** Size-distribution of encapsulated iron oxide nanoparticles with 140 µL (a) and 280 µL (b) monomer used during synthesis. The distributions were obtained from TEM by measuring the diameter of the particles over the center point of the iron oxide nanoparticles in different directions, to estimate the mean shell thickness. From the results it can be concluded, that the composite particles formed in the reaction using 280 µL of the monomer (b) do have a slightly larger diameter (2.2 nm), which translates into a mean difference in shell thickness of 1.1 nm.

S8. Calculations on monomer partitioning

In the first step we calculated the expected size of the encapsulated particles based on the assumption, that the monomer is exclusively polymerized on the surface of the iron oxide nanoparticles. To this end, we first calculated the volume \( V_{NP} \) of a single iron oxide nanoparticle and the total number \( N_{NP} \) of nanoparticles in the reaction based on the iron oxide weight fraction \( w_{IO} \) determined from elemental analysis, the overall mass of the used nanoparticles \( m_{NPs} \), and the density of magnetite \( \rho_{IO} \).

\[
V_{NP} = \frac{4}{3} \pi \left( \frac{d}{2} \right)^2 = 1.35 \cdot 10^{-18} \text{ cm}^3 \tag{7}
\]

\[
N_{NP} = \frac{w_{IO} \cdot m_{NPs}}{\rho_{IO} \cdot V_{NP}} = 2.3 \cdot 10^{15} \tag{8}
\]

In the next step, we estimated the expected volume \( V_{\text{composite}} \) and diameter \( d_{\text{composite}} \) of the final core-shell composites by taking into account the ratio of added monomer volume \( V_{\text{monomer}} \) to the number of particles. In the following this is done exemplarily for a monomer volume of 70 µL.
\[ V_{\text{composite}} = V_{NP} + \frac{V_{\text{monomer}}}{N_{NP}} \]  

(9)

\[ d_{\text{composite}} = \frac{\sqrt{6}}{\sqrt{\pi}} \cdot V_{\text{composite}} = 39.5 \text{ nm} \]  

(10)

In our experiments we found the diameter of the final composites to be \(~22\) nm determined from DLS number distribution (see figure S3(a)) when \(70\ \mu\text{L}\) of monomer were used. We explained this with the presence of unbound initiator ligands in “empty” micelles, which do not contain iron oxide nanoparticles, causing the formation of pure polymeric particles, which compete in monomer consumption with the growth of the shells on iron oxide particles.

However, the fraction of monomer, which is lost due to this side reaction, is large. From the obtained diameter of the composites of \(22\) nm we calculated, that the volume \(V_{\text{shells}}\) of the formed shells only corresponds to \(9.7\ \mu\text{L}\) of monomer. In the following, we show that our proposed mechanism is, nevertheless, reasonable. First, we assumed that the pure polymeric particles are of the same size as the composite particles after polymerization. With this and the remaining volume of the added monomer the number \(N_{PP}\) of polymeric particles (PP) can be calculated.

\[ N_{PP} = \frac{V_{\text{monomer}} - V_{\text{shells}}}{V_{PP}} = 1.1 \cdot 10^{16} \]  

(11)

When comparing this value to the number of iron oxide nanoparticles present in the solution, the number of polymeric particles is roughly five times larger. This means that for each iron oxide nanoparticle at least five unbound initiator ligands must be present during phase transfer, which are then solvated in “empty” micelles forming the polymeric particles during polymerization. Based on the grafting-density of \(3.7\) molecules/nm\(^2\) (see section S5), and the surface area of a single nanoparticle, we calculated that roughly \(2200\) initiator molecules per particle are present in the initial solution. Thus, it seems quite reasonable to assume that some unbound initiator molecules per particle are present due to the equilibrium between bound/unbound ligands at the surface or simply a very small excess of unbound ligand molecules.

**References**
