Communication

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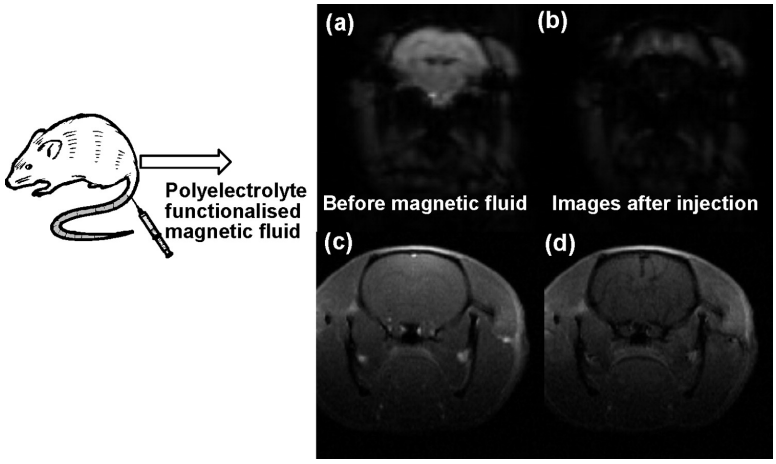
J. Am. Chem. Soc., **2008**, 130 (13), 4214-4215 • DOI: 10.1021/ja710172z



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Published on Web 03/11/2008

Linear Assemblies of Magnetic Nanoparticles as MRI Contrast Agents

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Magnetic nanomaterials represent one of the most exciting areas in nanotechnology, in particular for magnetic memory devices and in biomedical research.[1] Magnetic particles have been envisaged as drug delivery agents which can be localized in the body at a site of interest using an external magnetic field.[2] When exposed to an alternating magnetic field, magnetic nanoparticles can serve as powerful heat sources destroying tumor cells, which opens up great possibilities in hyperthermic cancer treatment.[3] Furthermore, stable aqueous dispersions of small superparamagnetic nanoparticles have been utilized as contrast agents for magnetic resonance imaging (MRI).[4,5] MRI contrast agents act to improve image quality by reducing the relaxation times and hence altering the NMR signal intensity of the water in body tissues containing the agent.

To date most applications of magnetic nanoparticles have focused on spherical primary nanoparticles or nanoparticle assemblies with aspect ratios close to 1, while the use of magnetic nanowires and linear assemblies of magnetic nanoparticles is quite limited. However, quasi one-dimensional magnetic entities have the potential to open up new applications in biomedicine, as their high aspect ratio results in a much larger dipole moment allowing their manipulation with lower magnetic field strengths.[6] Flexible long chains of magnetic particles could also be of importance across a wide range of applied materials technologies. Therefore, an investigation of assembly of magnetic colloidal particles in linear chain-like structures by a magnetic field presents a great interest. Polymers are frequently used as stabilizers and cross-linking agents in the preparation of magnetic nanoparticle assemblies.[7,8] For example, controlled clustering of magnetic particles using cationic-neutral block copolymers was used to prepare magnetic fluids with improved contrast for MRI.[8] Linear chains of magnetite nanoparticles have also been prepared by using a magnetic field induced self-assembly of citrate stabilized magnetite and poly(2-vinyl *N*-methylpyridinium iodide) as a template.[9]

Previously, we reported the use of denatured Herring DNA as a stabilizer for the formation of ordered nanowires of magnetite nanoparticles.[10] These nanowire assemblies also formed a stable aqueous magnetic fluid which gave high relaxivity, the relaxation rate enhancement, per mmol of Fe, at low field. Here we report a new facile *in situ* fabrication of linear, chain-like assemblies of magnetic nanoparticles and show the potential use of these as contrast agents by measuring the MR response in live rats.

Polysodium-4-styrene sulfonate (PSSS) has been used in this work to produce stable magnetic nanoparticle suspensions in water. Briefly, an aliquot of polyelectrolyte solution was added to a predetermined volume of iron solution under argon. The Fe/PSSS ratio could be altered to produce a library of magnetic fluids with different contrast properties. Three composites were prepared, with a range of Fe/monomer ratios of 1:2 (PSSS-Mag1), 3:1 (PSSS-Mag2), and 6:1 (PSSS-Mag3) (see Supporting Information for full experimental details and characterization). The negatively charged polyelectrolyte acts as both a stabilizer, where the positively charged iron ions can accumulate before particle precipitation, and as a template for nanowire formation once the particles are formed. The particles were precipitated with ammonia, and the resulting black material was washed five times with Millipore water (20 mL). The final, fifth washing was found to be a pH neutral, stable, aqueous suspension, which was used in further TEM and MRI (PSSS-Mag1) experiments. Once fully dried, the magnetic material cannot be redispersed to form a stable suspension in water.

The magnetic nanocomposites have been characterized using TEM, NMR, X-ray diffraction, FTIR, and Raman spectroscopy. FTIR studies confirm the presence of polyelectrolyte in these materials, with stretches corresponding to aromatic C−C bonds, CH_2 bonds, sulfonate bonds, and aromatic C−H bonds noted. Stretches at 580 cm^{-1} are attributed to Fe−O stretches, while shoulders on this peak, at 631 cm^{-1}, should be a stretch for an Fe−O−S bond (see Supporting Information). XRD patterns and Raman spectra were also obtained (see Supporting Information). TEM images were taken of 5 μL drops of each fluid dried in the presence of an external 0.5 T magnetic field (Figure 1). The primary particle size varies from 7 ± 1 nm (PSSS-Mag1), to 10 ± 1 nm (PSSS-Mag2), to 11 ± 1 nm for the higher ratio sample (PSSS-Mag3). When dried in the earth's field, the nanocomposites appear aggregated showing linear necklace- or chain-like structures (Figure 1a). On application of an external magnetic field, the structures were rearranged into parallel linear arrays or "nanowires" (Figure 1b-d), where neighboring particles are cross-linked by polyelectrolyte molecules due to the interpenetration of the polymer shells.[7] The nanowire width also changes on increasing Fe:PSSS ratios; for example, the widths increase from 670 nm for PSSS-Mag1 to 1.5 μm for PSSS-Mag2. The average hydrodynamic size of PSSS-Mag1 was measured at 298 K by photon correlation spectroscopy (PCS) and was found to be 136 nm, with a polydispersity index (PDI) of 0.21, while for PSSS-Mag2 the values were 203 nm and 0.19 respectively. Extended exposure of these samples in solution to magnetic fields, up to 1.8 T, did not alter these values. PCS results demonstrate that for our suspensions the alignment does not result in any nonreversible aggregation of the nanowires.

We also studied the suspensions using field-cycling NMR; at 37 °C a significant reduction in the relaxation times was observed at all fields. The molar spin−lattice relaxation rate enhancement r_1 (units of s^{-1} mM^{-1} of Fe) was measured as 22.5 and 7.2 s^{-1} mM^{-1}, at 9 and 59 MHz, respectively. As expected[11] for samples where the hydrodynamic size of the assemblies is significantly greater than the superparamagnetic core size, the r_1/r_2 ratio was found to be 0.17 and 0.08 at these two fields, respectively. The r_1 values were always independent of the polarization field used. This demonstrates that field-induced alignment does not alter the suspensions relaxation properties.

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10.1021/ja710172z CCC: $40.75

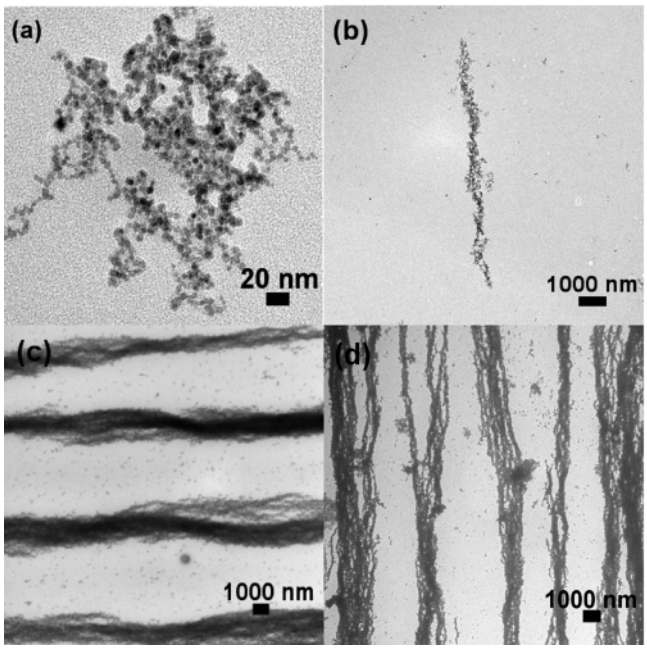

Figure 1. TEM images of (a) PSSS-Mag1 sample dried without magnetic field and (b) PSSS-Mag1, (c) PSSS-Mag2, and (d) PSSS-Mag3 samples upon drying in a 0.5 T magnetic field.

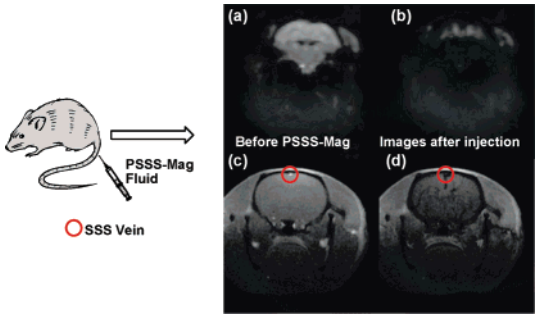

Figure 2. Echo planar image (EPI) of mouse brain (a) before and (b) as PSSS-Mag1 passes through; Fast Low Angle Shot (FLASH) image of mouse brain (c) before and (d) as PSSS-Mag1 passes through.

MR images were obtained for the PSSS-Mag1 sample after injection into live rats (male Wistar rats from Banthan and Kingman, UK) under anesthetic in order to study the effect of our contrast agent on the brain, specifically the hippocampus.[12]

First, a coronal image, positioned at approximately 3.2 mm posterior to the bregma, was obtained using a localizer scan in order to contain a good cross section through the hippocampus. Subsequently, two scans were acquired using the reference image — an Echo Planar Imaging (EPI) scan and a Fast Low Angle Shot (FLASH) scan. For the EPI scan (Figure 2 a, b), the coronal slice was imaged every 0.7 s for a duration of 35 s. Figure 2a shows an image of the brain immediately after injection of PSSS-Mag1 (0.4 mL) in the tail vein. At this time point, none of the bolus has yet reached the brain. Figure 2b shows an image of the brain 11.2 s after injection. There is significant darkening of the image as the bolus has now reached the brain. For the FLASH scan (Figure 2 c, d), the coronal slice was imaged every 0.8 s for a duration of 48.5 s. Figure 2c shows an image of the brain of a second rat immediately after injection of PSSS-Mag1 (0.4 mL), when none of the bolus has yet reached the brain. Figure 2d shows an image of the same brain 13.6 s after injection. Again, a significant darkening of the brain is noted. Using the FLASH scan, the occlusion of the superior sinus sagittalis vein (SSS) can be clearly seen. Before the bolus arrives, the SSS appears white on this T_1-weighted image, and following occlusion of the vein, it appears black as it fills with PSSS-Mag1. A third rat was injected with PSSS-Mag1 (0.4 mL), and no visible signs of any adverse reaction were noted after monitoring for 24 h.

In summary, using a one-step procedure we have prepared magnetic fluids comprised of polyelectrolyte stabilized magnetite nanoparticles. These nanocomposites consist of linear, chain-like assemblies of magnetic nanoparticles, which can be aligned in parallel arrays by an external magnetic field. The new magnetic fluids have demonstrated good biocompatibility and potential for *in vivo* MRI diagnostics. While initial results indicate this contrast agent is quickly cleared from the brain area, further studies are required to determine localization in tissues over time. We believe that 1-D morphology of nanocomposites facilitates their easy passage through the circulatory system. This advantage may allow for some other biological applications of these nanocomposites, e.g., in detecting blocked blood vessels. Further NMR and imaging experiments are ongoing to fully investigate how to tune the relaxivity and r_1/r_2 ratio of the suspensions by varying component concentrations. We think that this approach would allow the preparation of various flexible linear assemblies of magnetic nanoparticles with a number of important potential applications in chemistry, biology, and medicine.

Acknowledgment. The authors wish to thank Dr. Oliviero Gobbo and Christoph Blau for help with MRI imaging. We acknowledge funding support from the SFI RFP scheme.

Supporting Information Available: Experimental details on syntheses and MR procedures, NMR experiments, XRD patterns, TEM images, FTIR and Raman spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Pankhurst, Q. A.; Connolly, J.; Jones, S. K.; Dobson, J. *J. Phys. D: Appl. Phys.* **2003**, *36*, R167. (b) Mornet, S.; Vasseur, S.; Grasset, F.; Duguet, E. *J. Mater. Chem.* **2004**, *14*, 2161. (c) Su, C.-H.; Sheu, H.-S.; Lin, C.-Y.; Huang, C.-C.; Lo, Y.-W.; Pu, Y.-C.; Weng, J.-C.; Shieh, D.-B.; Chen, J.-H.; Yeh, C.-S. *J. Am. Chem. Soc.* **2007**, *129*, 2139. (d) Corr, S. A.; O'Byrne, A.; Gun'ko, Y. K.; Ghosh, S.; Brougham, D. F.; Mitchell, S.; Volkov, Y.; Prina-Mello, A. *Chem. Commun.* **2006**, *43*, 4474.

(2) (a) Petri-Fink, A.; Chastellain, M.; Juillerat-Jeannerat, L.; Ferrari, A.; Hofmann, H. *Biomaterials* **2005**, *26*, 2685. (b) Lübbe, A. S.; Alexiou, C.; Bergemann, C. *J. Surg. Res.* **2001**, *95*, 200. (c) Lübbe, A. S.; Bergemann, C.; Brock, J.; McClure, D. G. *J. Magn. Magn. Mater.* **1999**, *194*, 149.

(3) (a) Gordon, R. T.; Hines, J. R.; Gordon, D. *Med. Hypoth.* **1979**, *5*, 83. (b) Babincová, M.; Leszczynska, D.; Sourivong, P.; Babinec, P. *Med. Hypoth.* **2000**, *54*, 177.

(4) (a) Huh, Y.-M.; Jun, Y.-W.; Song, H.-T.; Kim, S.; Choi, J.-S.; Lee, J.-H.; Yoon, S.; Kim, K.-S.; Shin, J.-S.; Suh, J.-S.; Cheon, J. *J. Am. Chem. Soc.* **2005**, *127*, 12387. (b) Weissleder, R.; Elizondo, G.; Wittenberg, J.; Rabito, C. A.; Bengele, H. H.; Josephson, L. *Radiology* **1990**, *175*, 489. (c) Kim, D. K.; Zhang, Y.; Kehr, J.; Klason, T.; Bjelke, B.; Muhammed, M. *J. Magn. Magn. Mater.* **2001**, *225*, 256.

(5) Na, H. B.; Lee, J. H.; An, K.; Park, Y. I.; Park, M.; Lee, A. S.; Nam, D.-H.; Kim, S. T.; Kim, S.-H.; Kim, S.-W.; Lim, K.-H.; Kim, K.-S.; Kim, S.-O.; Hyeon, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5397.

(6) Chen, M.; Sun, L.; Bonevich, J. E.; Reich, D. H.; Chien, C. L.; Searson, P. C. *Appl. Phys. Lett.* **2003**, *82*, 3310.

(7) (a) Philip, J.; Mondain-Monval, O.; Leal-Calderon, F.; Bibette, J. *J. Phys. D: Appl. Phys.* **1997**, *30*, 2798. (b) Furst, E.; Suzuki, C.; Fermigier, M.; Gast, A. *Langmuir* **1998**, *14*, 7334. (c) Biswal, S. L.; Gast, A. P. *Phys. Rev. E* **2003**, *68*, 021402. (d) Goubault, C.; Jop, P.; Baudry, J.; Bertrand, E.; Fermigier, M.; Bibette, J. *Phys. Rev. Lett.* **2003**, *91*, 260802. (e) Goubault, C.; Leal-Calderon, F.; Viovy, J.-L.; Bibette, J. *Langmuir*, **2005**, *21*, 3725. (f) Singh, H.; Laibinis, P. E.; Hatton, T. A. *Nano Lett.* **2005**, *5*, 2149.

(8) Berret, J. F.; Schonbeck, N.; Gazeau, F.; El Kharrat, D.; Sandre, O.; Vacher, A.; Airiau, M. *J. Am. Chem. Soc.* **2006**, *128*, 1755.

(9) Sheparovych, R.; Sahoo, Y.; Motorov, M.; Wang, S. M.; Luo, H.; Prasad, P. N.; Sokolov, I.; Minko, S. *Chem. Mater.* **2006**, *18*, 591.

(10) Byrne, S. J.; Corr, S. A.; Gun'ko, Y. K.; Kelly, J. M.; Brougham, D. F.; Ghosh, S. *Chem. Commun.* **2004**, *22*, 2560.

(11) Roch, A.; Muller, R. N.; Gillis, P. *J. Chem. Phys.* **1999**, *110*, 5403.

(12) (a) Bliss, T. V.; Collingridge, G. L. *Nature* **1993**, *361*, 31. (b) Lynch, M. A. *Physiol. Rev.* **2004**, *84*, 87.

JA710172Z