J|A|C|S
COMMUNICATIONS

Published on Web 08/16/2006

Toward the Syntheses of Universal Ligands for Metal Oxide Surfaces: Controlling Surface Functionality through Click Chemistry

Meghann A. White,[†] Jeremiah A. Johnson,[†] Jeffrey T. Koberstein,[‡] and Nicholas J. Turro*[,†,‡]

Department of Chemistry, Columbia University, 3000 Broadway, MC 3157, New York, New York 10027, and Department of Chemical Engineering, Columbia University, 500 West 120th Street, New York, New York 10027

Received June 8, 2006; E-mail: njt3@columbia.edu; jk1191@columbia.edu

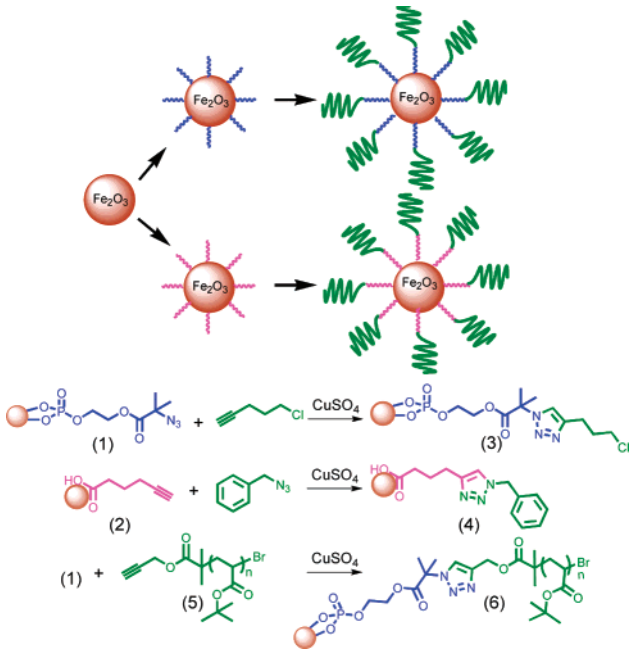
Metal oxide nanoparticles, in particular magnetic metal oxides, have recently attracted a great deal of attention for their potential wide range of applications including use as cellular delivery carriers,[1] magnetic storage media,[2] and MRI contrast agents.[3a,b] In many practical applications, nanoparticle cores must be provided with surface ligands which both prevent aggregation and also provide a handle that conveniently allows functionalization of the final periphery of the system. The harsh conditions generally required for nanoparticle preparation severely limit the use of functionalized ligands during the synthesis. As a result, a common method of functionalizing the nanoparticle surface involves stripping off nonfunctional ligands used for synthesis and then redispersing the particles with functionalized ligands.

In this report we demonstrate a strategy for the synthesis of surface functionalized metal oxide nanoparticles through the design of versatile ligands whose structures include the following features: (1) a robust anchor that can bind generally to a variety of metal oxide surfaces, (2) tailored surface groups that act as spacers or branches from the metal oxide surface, and (3) a general method for covalently attaching a functional perimeter to the spacers through "click" chemistry. Ligands which possess the flexibility and synthetic generality of features 1−3 possess the characteristic of "universal" ligands which allow the construction of a broad range of functionalities for the periphery of nanoparticles with good yields and synthetic facility.

The copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) has received broad attention because of its unique "click" nature: namely, the reaction proceeds with high yields and no byproducts and exhibits functional group orthogonality.[4a−e] As a result, the CuAAC reaction has been employed in a variety of materials synthesis applications including functionalization of polymers and dendrimers,[5a−c] polysaccharides,[6,7] DNA,[8] and a variety of bulk surfaces including gold[9] and silica,[10] as well as gold nanoparticle surfaces.[11] In the design of universal ligands which allow simple and efficient functionalization of nanoparticle-ligand complexes with a desired moeity, we found the CuAAC reaction to be ideal because of its click nature. Herein we demonstrate the potential effectiveness of CuAAC for the modification of γ-Fe_2O_3 nanoparticles with a diverse array of functional species including small molecules and polymers.

In the design of functional ligands for nanoparticle surfaces, one must consider both the binding properties as well as the stability of the ligand and, importantly, prevention of particle aggregation. It has been established that organo-phosphates as well as carboxylates bind strongly to the surface of metal oxides.[12a−g] For our studies we chose ligands containing either a phosphonic acid group or a carboxylic acid group at one terminus, to serve as anchors which can bind strongly to the surface of the γ-Fe_2O_3, and either an azide or alkyne group at the other terminus, providing orthogonal functionality for further chemical modification of the nanoparticle−ligand complex surface. Because organo-phosphates and carboxylates bind well to most metal oxides, this method also has the potential of applying to a range of metal oxide surfaces.

Scheme 1. General Scheme for Functionalizing the Surface of Iron Oxide Nanoparticles



γ-Fe_2O_3 nanoparticles were synthesized by a previously reported method employing oleic acid as a ligand.[13] XRD and TEM images show that the nanoparticles are crystalline and well dispersed. Within one reaction vessel the nanoparticles vary in size only slightly (<5% rms). The oleic acid was stripped from the particles and exchanged with either the phosphonic acid ligand or 5-hexynoic acid (**1** and **2** in Scheme 1). The particles were then washed with hexanes and methanol for **1** and **2**, respectively, to remove excess ligand followed by dispersion in chloroform. The TEM images of the newly coated nanoparticles indicated that they had not formed aggregates and that their size did not change upon ligand exchange within the limits of TEM accuracy. FTIR spectra of the nanoparticles were compared to those of the free ligands.[14] For **1** there was a very strong absorbance at 2114 cm^{-1} owing to the azide N═N═N antisymmetric stretch, as well as a strong absorbance at 1742 cm^{-1} owing to the C═O stretch of the ester. There was also a series of stretching bands from 1250 to 990 cm^{-1} assigned to the P−O and P−O−Fe stretches of the phosphonic acid group. For **2** there was a very weak absorbance at 2119 cm^{-1} owing to the alkyne as well as a strong absorbance at 1710 cm^{-1} owing to the C═O stretch of the carboxylic acid. It was estimated from thermogravi-

[†] Department of Chemistry.
[‡] Department of Chemical Engineering.

10.1021/ja064041s CCC: $33.50

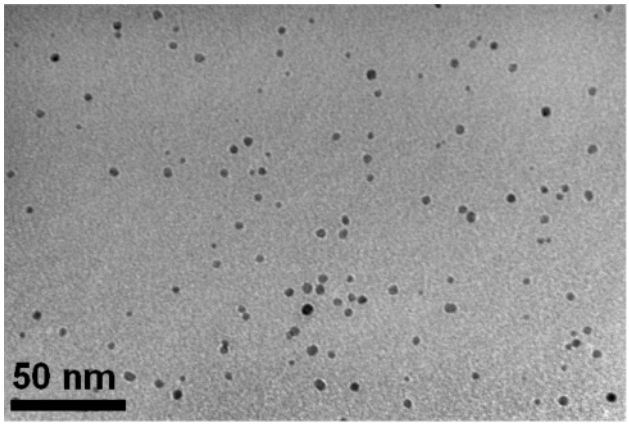


Figure 1. TEM image of γ-Fe_2O_3 nanoparticles that have undergone 1,3-dipolar cycloaddition with poly(*tert*-butylacrylate) (**6** in Scheme 1).

metric analysis (TGA) data that the surface coverage of the particles was ~1 ligand/nm^2 for **1**, and independent of particle size. For **2** we estimated the surface coverage to be ~11 ligands/nm^2.

With **1** and **2** in hand, a CuAAC reaction using the complementary click functional molecule (5-chloropentyne for **1** and benzyl azide for **2**) was performed to prepare **3** and **4** (Scheme 1). The reactions were allowed to proceed overnight, after which time the γ-Fe_2O_3 particles were recovered via extraction with organic solvents. The FTIR spectrum of **3** showed a loss of the N═N═N stretching band, indicating a high yield for the CuAAC reaction, and a peak at 1554 cm^{-1} agreeing with the literature value for a 1,2,3-triazole.[15] The absorbance bands due to the phosphonic acid group (1250−990 cm^{-1}) are still present, implying that the ligand is still attached to the particles and the phosphonate is still intact. The FTIR spectrum of **4** also has a characteristic band at 1551 cm^{-1}, and has no band at 2100 cm^{-1}, indicating conversion of the alkyne group to a triazole. As in previous work using NMR to study surface groups on γ-Fe_2O_3 nanoparticles,[16] very dilute samples of **3** and **4** were examined by ^{1}H NMR. Although the peaks were slightly broadened, the characteristic peak at ~8.0 ppm owing to the triazole proton was clearly present. Both the FTIR and NMR spectra correspond well to those of the control reactions. This spectroscopic evidence, coupled with the TEM image showing dispersed particles, suggests that the 1,3-dipolar cycloaddition was successful and that the particles are stabilized from aggregation by the new ligand system.[14]

To demonstrate that complex functionality could be introduced on the periphery of the nanoparticle surface by the universal ligand strategy, a polymeric ligand was attached to the nanoparticle by CuAAC. An α-acetylene-poly(*tert*-butyl acrylate) (ptBA) polymer (**5**) was prepared by atom transfer radical polymerization (ATRP) of *tert*-butyl acrylate in the presence of an acetylene-functional initiator, CuBr catalyst, *N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine ligand, and toluene solvent. Treatment of **1** with **5** under CuAAC conditions yielded ptBA coated particles (**6**) as shown in Figure 1. On the basis of the estimated surface coverage of **1** on the nanoparticles a 1:1 molar ratio of alkyne to azide was used in the CuAAC reaction. The resultant particles were extracted with organic solvents and then precipitated to remove excess unbound ptBA. The nanoparticles were characterized using TEM, FTIR, and NMR. The FTIR spectrum of the polymer coated particles showed the disappearance of the azide peak at 2114 cm^{-1}, indicating high yield of the CuAAC reaction. The FTIR for the polymer coated particles also contained characteristic peaks due to the ptBA, as well as the peaks ~1100 cm^{-1} due to the phosphonic acid. Furthermore, in the ^{1}H NMR spectrum, the presence of the triazole proton at ~8 ppm was detected.[14] TEM images of the nanoparticles revealed that they were well-dispersed and that no aggregation had occurred (Figure 1). These results demonstrate that the CuAAC reaction successfully coupled **5** to **1** yielding a novel nanoparticle-polymer complex, **6**.

In conclusion, ligand exchange on γ-Fe_2O_3 nanoparticles was performed with two types of ligands: (1) phosphonic acid-azide and (2) carboxylic acid-alkyne. The resultant particles were submitted to CuAAC reactions with organic substrates, the products of which were well-dispersed in a range of solvents, a property which is dependent upon the ligand of choice. These results establish a "universal ligand" approach for the surface functionalization of γ-Fe_2O_3 nanoparticles and demonstrate that the nanoparticles can be dispersed in a variety of media by control of the ligand. Not only is this method applicable to iron oxide nanoparticles, but it is also presumably applicable to any other metal oxide surface (nanoparticle or bulk).

Acknowledgment. Funding for this work was provided by the National Science Foundation (NSF) under Grant No. IGERT-02-21589 and No. NSF-04-15516. Facilities were provided by Columbia University's Materials Research Science and Engineering Center (MRSEC) under NSF Grant No. DMR-0214363.

Supporting Information Available: Detailed experimental procedures as well as control experiments and spectroscopic data; complete ref 5c. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Xu, Z. P.; Zeng, Q. H.; Lu, G. Q.; Yu A. B. *Chem. Eng. Sci.* **2006**, *61*, 1027−1040.
(2) Huber, D. L. *Small* **2005**, *1*, 482−501.
(3) (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*, 12387−12391. (b) Song, H. T.; Choi, J. S.; Huh, Y. M.; Kim, S.; Jun, Y. W.; Suh, J. S.; Cheon, J. *J. Am. Chem. Soc*. **2005**, *127*, 9992−9993.
(4) (a) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210−2215. (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279. (c) Li, Z. M.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143−3146. (d) Kolb, H. C.; Sharpless, K. B.; *Drug Discovery Today* **2003**, *8*, 1128−1137. (e) Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.
(5) (a) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200−1205. (b) Helms, B.; Mynar, J. L.; Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020−15021. (c) for complete list of references see Supporting Information.
(6) Liebert, T.; Hansch, C.; Heinze, T. *Macromol. Rapid Commun.* **2006**, *27*, 208−213.
(7) Punna, S.; Kaltgrad, E.; Finn, M. G. *Bioconjugate Chem.* **2005**, *16*, 1536−1541.
(8) Seo, T. S.; Li Z.; Ruparel, H.; Ju J. *J. Org. Chem.* **2003**, *68*, 609−612.
(9) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051−1053.
(10) Lummerstorfer, T.; Hoffmann, H. *J. Phys. Chem. B* **2004**, *108*, 3963−3966.
(11) Fleming, D. A.; Thode, C. J.; Williams, M. E. *Chem. Mater.* **2006**, *18*, 2327−2334.
(12) (a) Mutin, P. H.; Guerrero, G.; Vioux, A. *J. Mater. Chem.* **2005**, *15*, 3761−3768. (b) Matsuno, R.; Yamamoto, K.; Otsuka, H.; Takahara, A. *Macromolecules* **2004**, *37*, 2203−2209. (c) Song, Y. N.; Zavalij P. Y.; Chernova, N. A.; Suzuku, M.; Whittingham, M. S. *J. Solid State Chem.* **2003**, *175*, 63−71. (d) Kreller, D. I.; Gibson, G.; Novak, W.; van Loon, G. W.; Horton, J. H. *Colloids Surf., A* **2003**, *212*, 249−264. (e) Kreller, D. I.; Gibson, G.; van Loon, G. W.; Horton, J. H. *J. Colloid Interface Sci.* **2002**, *254*, 205−213. (f) Sahoo, Y.; Pizem, H.; Fried, T; Golodnitsky, D.; Burstein, L.; Sukenik, C. N.; Markovich, G. *Langmuir* **2001**, *17*, 7907−7911. (g) Hofer, R.; Textor, M.; Spencer, N. D. *Langmuir* **2001**, *17*, 4014−4020.
(13) Yin, M.; Willis, A.; Redl, F.; Turro, N. J.; O'Brien, S. P. *J. Mater. Res.* **2004**, *19*, 1208−1215.
(14) See Supporting Information for further details.
(15) Billes, F.; Endredi, H.; Keresztury, G. *J. Mol. Struct.* **2000**, *530*, 183−200.
(16) Willis, A. L.; Turro, N. J.; O'Brien, S. *Chem. Mater.* **2005**, *17*, 5970−5975.

JA064041S