June 18, 2009

Formation and Size Tuning of Colloidal Microcapsules via Host-Guest Molecular Recognition at the Liquid-Liquid Interface

D Patra

F Ozdemir

OR Miranda

B Samanta

A Sanyal, et al.

Formation and Size Tuning of Colloidal Microcapsules via Host–Guest Molecular Recognition at the Liquid–Liquid Interface[†]Debabrata Patra,[‡] Firat Ozdemir,[§] Oscar R. Miranda,[‡] Bappaditya Samanta,[‡] Amitav Sanyal,^{*,§} and Vincent M. Rotello^{*,‡}[‡]Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003, and [§]Department of Chemistry, Faculty of Arts and Sciences, Bogazici University, Bebek 34342, Istanbul, Turkey

Received May 2, 2009. Revised Manuscript Received June 1, 2009

Stimuli-responsive colloidal microcapsules have been fabricated at the oil–water interface using molecular recognition between functionalized gold nanoparticles. Water-soluble β -cyclodextrin-capped gold nanoparticles and organo-soluble adamantyl-functionalized gold nanoparticles are self-assembled at the water–toluene interface via specific host–guest molecular interactions to provide robust microcapsules. Multivalent interactions of complementary ligands on the nanoparticle surface provide stability to these capsules. Unlike covalently cross-linked microcapsules, the reversible nature of these bridging interactions can be used to manipulate the size of these capsules via introduction of competing adamantane containing amphiphilic guest molecules. Partial disruption of interfacial cross-linking allows microcapsules to coalesce with each other to form larger capsules.

Introduction

Self-assembled microcapsules have great potential as multifunctional scaffolds for microreactors and carriers for catalysts,¹ enzymes,² and drugs.³ The essential prerequisite for these applications is the fabrication of robust and stable microcapsules. Various types of microcapsules (such as polymeric microcapsules,⁴ vesicles,⁵ and colloidal microcapsules⁶) have been synthesized so far for these applications. Colloidal microcapsules are particularly interesting systems, exhibiting unique features including mechanical stability and tunable permeability,⁷ as well as the ability to integrate the physical properties of their precursor particle building blocks.

The general approach to designing colloidal microcapsules is to use emulsion droplets as a template to self-assemble and cross-

link colloidal particles at the liquid–liquid interface. Recently, significant advances have been made in the area of colloidal microcapsule engineering through covalent cross-linking of the particles.⁸ Molecular recognition mediated self-assembly is an attractive alternative to these covalent strategies, introducing the potential for dynamic systems.⁹ Molecular recognition provides noncovalent coupling between two complementary molecules or functionalized surfaces. The “tailored interactions” between building blocks via molecular recognition along with the “dynamic nature” of the self-assembly process provide a promising tool to create novel functional materials and molecular assemblies.¹⁰

Herein, we report the fabrication of colloidal microcapsules via “host–guest” molecular recognition at the liquid–liquid interface. Specifically, we cross-link β -cyclodextrin (β -CD, “host”) and adamantane (ADA, “guest”) functionalized gold NPs at the oil–water interface to create microcapsules. The size of these microcapsules is tunable via recognition-induced coalescence of the microcapsule by sequential addition of the ADA amphiphile as an external and competing “guest” to the microcapsules.

Experimental Section

Chemicals. Chemicals were obtained from commercial sources and were used as received unless otherwise stated. Milli-Q water with a resistivity greater than 18 M Ω .cm was used in all our experiments. Tetra(ethylene glycol) mono-adamantyl ether and β -CD functionalized Au nanoparticles were synthesized as described before. NMR spectra were recorded on Varian

[†]Part of the “Langmuir 25th Year: Nanoparticles synthesis, properties, and assemblies” special issue.

*E-mail addresses: amitav.sanyal@boun.edu.tr, rotello@chem.umass.edu.

(1) (a) Shchukin, D. G.; Möhwald, H. *Small* **2007**, *3*, 926–943. (b) Buonomenna, M. G.; Figoli, A.; Spezzano, I.; Morelli, R.; Drioli, D. *J. Phys. Chem. B* **2008**, *112*, 11264–11269. (c) Akiyama, R.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594–642.

(2) (a) Zhu, H.; Srivastava, R.; Brown, J. Q.; McShane, M. J. *Bioconjugate Chem.* **2005**, *16*, 1451–1458. (b) Phadtare, S.; Kumar, A.; Vinod, V. P.; Dash, C.; Palaskar, D. V.; Rao, M.; Shukla, P. G.; Sivaram, S.; Sastry, M. *Chem. Mater.* **2003**, *15*, 1944–1949. (c) Alves, C. S.; Yakovlev, S.; Medved, L.; Konstantopoulos, K. *J. Biol. Chem.* **2009**, *284*, 1177–1189.

(3) (a) Allen, T. M.; Cullis, P. R. *Science* **2004**, *303*, 1818–1822. (b) Biju, S. S.; Saisivam, S.; Maria, N. S.; Rajan, G.; Mishra, P. R. *Eur. J. Pharm. Biopharm.* **2004**, *58*(1), 61–67. (c) Langer, R. *Acc. Chem. Res.* **1993**, *26*, 537–542. (d) Meng, F.; Zhong, Z.; Feijen, J. *Biomacromolecules* **2009**, *10*, 197–209.

(4) (a) Cavalieri, F.; Postma, A.; Lee, L.; Caruso, F. *ACS Nano* **2009**, *3*, 234–240. (b) Skirtach, A. G.; Karageorgiev, P.; Bedard, M. F.; Sukhorukov, G. B.; Möhwald, H. *J. Am. Chem. Soc.* **2008**, *130*, 11572–11573. (c) Zhu, Y.; Tong, W.; Gao, C.; Möhwald, H. *Langmuir* **2008**, *24*, 7810–7816. (d) Thibault, R. J.; Galow, T. H.; Turnberg, E. J.; Gray, M.; Hotchkiss, P. J.; Rotello, V. M. *J. Am. Chem. Soc.* **2002**, *124*, 15249–15254.

(5) (a) Uzun, O.; Sanyal, A.; Nakade, H.; Thibault, R. J.; Rotello, V. M. *J. Am. Chem. Soc.* **2004**, *126*(45), 14773–14777. (b) Zhou, Y.; Yan, D. *J. Am. Chem. Soc.* **2005**, *127*, 10468–10469.

(6) (a) Lin, Y.; Skaff, H.; Emrick, T.; Dinsmore, A. D.; Russell, T. P. *Science* **2003**, *299*, 226–229. (b) Duan, H.; Wang, D.; Sobal, N. S.; Giersig, M.; Kurth, D. G.; Möhwald, H. *Nano Lett.* **2005**, *5*, 949–952.

(7) (a) Wang, B.; Wang, M.; Zhang, H.; Sobal, N. S.; Tong, W.; Gao, C.; Wang, Y.; Giersig, M.; Wang, D.; Möhwald, H. *Phys. Chem. Chem. Phys.* **2007**, *9*, 6313–6318. (b) Dinsmore, A. D.; Hsu, M. F.; Nikolaides, M. G.; Marquez, M.; Bausch, A. R.; Weitz, D. A. *Science* **2002**, *298*, 1006–1009.

(8) (a) Arumugam, P.; Patra, D.; Samanta, B.; Agasti, S. S.; Subramani, C.; Rotello, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 10046–10047. (b) Samanta, B.; Patra, D.; Subramani, C.; Ofir, Y.; Yesilbag, G.; Sanyal, A.; Rotello, V. M. *Small* **2009**, *5*, 685–688. (c) Lin, Y.; Skaff, H.; Boeker, A.; Dinsmore, A. D.; Emrick, T.; Russell, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 12690–12691.

(9) Wang, J.; Wang, D.; Sobal, N. S.; Giersig, M.; Jiang, Möhwald, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7963–7966. (b) Wang, H.; Wang, S.; Su, H.; Chen, K. -J.; Armijo, A. L.; Lin, W. -Y.; Wang, Y.; Sun, J.; Kamei, K. -I.; Czernin, J.; Radu, C. G.; Tseng, H. -R. *Angew. Chem., Int. Ed.* **2009**, *48*, 4344–4348.

(10) (a) Shenhar, R.; Rotello, V. M. *Acc. Chem. Res.* **2003**, *36*, 549–561. (b) Storhoff, J. J.; Mirkin, C. A. *Chem. Rev.* **1999**, *99*, 1849–1862.

Scheme 1.^a

^a(a) NP1 and NP2 dispersed in water and toluene, respectively. (b) Fabrication of colloidal microcapsule via recognition mediated cross-linking. (c) Addition of external “guest” ADA-TEG-OH. (d) Disruption of cross-linking and coalescence of the microcapsule into larger size. (e) “Host–guest” recognition between NP1 and ADA-TEG-OH. (f) Competitive “host–guest” recognition between NP1 and ADA-TEG-OH. (g) Structures of the ligands and NPs used for fabrication of microcapsules.

400 MHz spectrometer. Elemental analysis results were obtained on a FlashEA 1112 CHNS analyzer.

Synthesis of ADA-Disulfide Ligand. To a solution of tetraethylene glycol mono-adamantyl ether¹¹ (205 mg, 0.63 mmol) and thioctic acid (103 mg, 0.50 mmol) in dry CH₂Cl₂ (5 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC, 105 mg, 0.55 mmol) and 4-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol). The reaction mixture was allowed to stir under argon overnight. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography (40% EtOAc in hexane) to afford the ADA ligand as a yellow oil (196 mg, yield 76%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 4.20 (2H, t), 3.67 (2H, t), 3.63 (8H, s), 3.56 (5H, m),

Figure 1. Optical microscopy image of (a) colloidal microcapsule; (b) fluorescence microscopy image of dye-encapsulated microcapsule; (c) low-resolution TEM image of single microcapsule; (d) high-resolution TEM image of the microcapsule wall. The concentration of NP1 and NP2 used for microcapsule fabrication was 0.4 μ M.

3.12 (2H, m), 2.43 (1H, m), 2.33 (2H, t), 2.11 (3H, s), 1.88 (1H, m), 1.72 (6H, s), 1.63 (10H, m), 1.44 (2H, m). ¹³C NMR (400 MHz, CDCl₃) δ (ppm): 173.43, 72.23, 71.27, 70.63, 70.58, 70.57, 70.55, 69.15, 63.46, 59.23, 56.30, 41.45, 40.19, 38.46, 36.44, 34.57, 33.92, 30.48, 28.71, 24.59. Anal. Calcd for C₂₆H₄₄O₆S₂: C, 60.43; H, 8.58; S, 12.41. Found: C, 60.61; H, 8.62; S, 12.37.

Ligand Exchange Reaction. Reduction of ADA-disulfide to ADA-dithiol was performed before place exchange reaction.¹² In the next step, dodecanethiol-coated Au NPs (10 mg) were dissolved in 5 mL of CH₂Cl₂ and 50 mg of ADA-dithiol was added to the NP solution. Reaction mixture was purged with argon and stirred for 2 days at room temperature in a closed vial. The mixture was precipitated with ethanol and centrifuged. Purification of the NPs was achieved through redispersion in toluene.

Microcapsule Fabrication. In a typical procedure, 300 μ L solution of NP2 (0.4 μ M) in toluene was taken in an Eppendorf tube. In the next step, 10 μ L aqueous solution (11 μ M) of NP1 (final concentration 0.4 μ M) and FITC dextran (fluorescein isothiocyanate functionalized dextran polymer; M_w = 500 000 g mol^{−1}) was added. The heterogeneous mixture was vigorously shaken for 15 s using Amalgamator (blending speed: 4000 rpm). As a result, the solution appeared to be cloudy due to the formation of micro-emulsions. After 10–15 min, emulsions settled at the bottom of the tube and the supernatant liquid was washed several times with toluene prior to characterization.

Microcapsule Characterization. TEM images were acquired on a JEOL 100CX operating at 100 keV. Samples were drop-cast onto a carbon-coated copper grid, dried, and imaged. Both optical and fluorescence microscope images were taken on an Olympus IX51 microscope. For fluorescence images, an excitation wavelength of 470 nm and emission wavelength of >515 nm (green fluorescence) were used.

Results and Discussion

Cyclodextrins (CDs) are well-known molecular hosts capable of including small hydrophobic molecules inside their cavities in aqueous media. In particular, β -CDs have cavities of ~ 7 Å in size and can selectively incorporate ADA molecules (~ 7 Å) inside the hydrophobic cavity via host–guest recognition.¹³ Both CD and ADA functionalized nanoparticles (NPs) can act as

(11) Mulder, A.; Onclin, S.; Peter, M.; Hoogenboom, J.; Beijlvel, H.; ter Maat, J.; Garcia-Parajo, M.; Ravoo, B.; Huskens, J.; van Hulst, N. *Small* **2005**, *1*, 242–253.

(12) Susumu, K.; † Uyeda, H. T.; Medintz, I. L.; Pons, T.; Delehanty, J. B.; Mattoussi, H. *J. Am. Chem. Soc.* **2007**, *129*, 13987–13996.

(13) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743–1754.

Figure 2. (a) Size tunability of the colloidal microcapsule at different ADA-TEG-OH concentrations in the presence of stable microspheres, with overall NP1 and NP2 concentrations of 0.4 μM. Representative fluorescence microscopy images of different-sized microcapsules with varying ADA-TEG-OH concentrations (b) 0 mM, (c) 26 mM, (d) 37 mM, and (e) 47 mM.

multisite hosts/guests for molecular recognition,¹⁴ generating supramolecular assemblies.¹⁵ In the present study, we have synthesized hydrophilic β-CD functionalized Au NPs (NP1, size ~3 nm; Scheme 1d) as a functional host according to the literature reported procedure.¹⁶ The guest-functionalized hydrophobic NPs (NP2, size ~6 nm; Scheme 1d) were prepared by ligand exchange reaction of ADA-dithiol with 6 nm Au NPs.¹⁷

(14) (a) Han, C.; Li, H. *Small* **2008**, *4*, 1344–1350. (b) Palaniappan, K.; Hackney, S. A.; Liu, J. *Chem Commun.* **2004**, 2704–2705.

(15) (a) Crespo-Biel, O.; Dordi, B.; Reinhoudt, D. N.; Huskens, J. *J. Am. Chem. Soc.* **2005**, *127*, 7594–7600. (b) Ludden, M. J. W.; Mulder, A.; Tampé, R.; Reinhoudt, D. N.; Huskens, J. *Angew. Chem.* **2007**, *119*, 4182–4185. (c) Liu, J.; Alvarez, J.; Ong, W.; Kaifer, A. E. *Nano Lett.* **2001**, *1*, 57–60. (d) Park, I.; von Recum, H. A.; Jiang, S.; Pun, S. H. *Langmuir* **2006**, *22*, 8478–8484.

Microcapsules were created through standard water-in-oil emulsion methods. As an example, NP2 was dissolved in toluene, and then, an aqueous solution of NP1 and fluorescent dye was added. Vigorous shaking for 15 s resulted in the formation of stable emulsions. The supernatant liquid was washed several times with toluene, and microcapsules were analyzed both by optical and fluorescence microscope (Figure 1a,b). The size of the microcapsules fabricated by this procedure was $18.3 \pm 9.3 \mu\text{m}$. Emulsions formed using the particles separately provided unstable emulsions that rapidly coalesced, whereas cross-linked emulsions are stable for several days. Thus, the formation of stable emulsions (Figure 1a) confirmed sufficient and extended cross-linking between NP1 and NP2 at the oil–water interface via host–guest recognition.

To determine the nanostructure of these droplets, the microcapsules were drop-cast on carbon-coated grids for transmission electron microscope (TEM) analysis. Low-resolution TEM imaging (Figure 1c) depicts the dried capsule structure, whereas high-resolution TEM imaging (Figure 1d) revealed that the capsule is composed of a multilayer of closely packed cross-linked NPs.

An important aspect of host–guest chemistry is that the interactions can be disrupted by competing ligands, a possible means for weakening the assembly and potentially controlling microcapsule size. Size tunability of the colloidal microcapsule (Figure 2a) was demonstrated by sequential addition of an external amphiphilic “guest” ADA-TEG-OH (Scheme 1d) to the microcapsule in toluene. Addition of ADA-TEG-OH to the NP1–NP2 microcapsules interferes with the “host–guest” recognition between NP1 and NP2. As a result, interfacial cross-linking is disrupted and microcapsules coalesce with each other forming larger droplets (Figure 2b–e).

Conclusions

In summary, we have developed a noncovalent approach to fabricating colloidal microcapsule at the liquid–liquid interface based on molecular recognition. The reversible and dynamic nature of the specific recognition process provides a tool for structural manipulation, specially tuning the size of the microcapsules. Further studies aimed at controlling the size and release profile by external stimuli (i.e., temperature, redox potential) are under investigation and will be reported in due course.

Acknowledgment. A.S. would like to thank the financial support from Turkish Academy of Sciences under the TUBA-GEBIP fellowship program. V.R. acknowledges NSF (CHE-0808945, VR), MRSEC facilities, and the Center for Hierarchical Manufacturing (DMI-0531171).

Supporting Information Available: Additional figures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(16) Liu, J.; Ong, W.; Román, E.; Lynn, M. J.; Kaifer, A. E. *Langmuir* **2000**, *16*, 3000–3002.

(17) Teranishi, T.; Hasegawa, S.; Shimizu, T.; Miyake, M. *Adv. Mater.* **2001**, *13*, 1699–1701.