8-2004

Environmentally Responsive Molecular Baskets: Unimolecular Mimics of Both Micelles and Reversed Micelles

Eui-Hyun Ryu
Iowa State University

Yan Zhao
Iowa State University, zhaoy@iastate.edu

Environmentally Responsive Molecular Baskets: Unimolecular Mimics of Both Micelles and Reversed Micelles

Abstract
When four facially amphiphilic cholate derivatives are attached to a tetraaminocalixarene scaffold, the resulting molecule responds to environmental changes by rotation of the cholate units. In polar solvents, the molecule adopts a micellelike conformation with the hydrophilic α-faces of the cholates pointing outward. In nonpolar solvents, it turns inside out, assuming a reversed micellelike conformation with the hydrophobic β-faces pointing outward. Switching between the two conformations is driven by solvophobic interactions and is fully reversible.

Disciplines
Chemistry

Comments
Reprinted (adapted) with permission from *Organic Letters* (2004): 3187, doi:10.1021/ol048679p.

ORGANIC LETTERS

2004
Vol. 6, No. 18
3187−3189

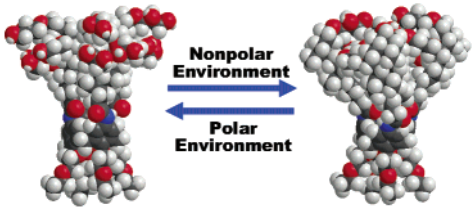
Environmentally Responsive Molecular Baskets: Unimolecular Mimics of Both Micelles and Reversed Micelles

Eui-Hyun Ryu and Yan Zhao*

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111
zhaoy@iastate.edu

Received July 9, 2004

ABSTRACT



When four facially amphiphilic cholate derivatives are attached to a tetraaminocalixarene scaffold, the resulting molecule responds to environmental changes by rotation of the cholate units. In polar solvents, the molecule adopts a micellelike conformation with the hydrophilic α-faces of the cholates pointing outward. In nonpolar solvents, it turns inside out, assuming a reversed micellelike conformation with the hydrophobic β-faces pointing outward. Switching between the two conformations is driven by solvophobic interactions and is fully reversible.

Many peptides and proteins have distinct water-soluble and membrane-bound states.[1] Their ability to adopt radically different conformations in different environments is critical to their functions. Despite much attention to novel amphiphiles in recent years,[2] very few amphiphilic molecules were reported to display well-defined conformational changes according to environmental stimuli.[3] For example, Regen and co-workers designed "molecular umbrellas" that could shield a molecule from incompatible environments and assist translocation of hydrophilic molecules across lipid bilayers.[4] Recently, Moore et al. synthesized phenylacetylene oligomers that fold and unfold in different solvents.[5] We now describe amphiphiles that adopt conformations mimicking normal micelles in polar solvents and reversed micelles in nonpolar ones. Previously reported unimolecular micelles (and reversed micelles) are mostly dendrimers with a hydrophilic exterior and a hydrophobic core (and *vice versa* for reversed micelles).[6] Interchange between the two states is usually prohibited by the fixed arrangement of hydrophilic and hydrophobic moieties.

(1) (a) Kaiser, E. T.; Kézdy, F. J. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1137−1143. (b) Hwang, P. M.; Vogel, H. J. *Biochem. Cell Biol.* **1998**, *76*, 235−246. (c) Hancock, R. E.; Chapple, D. S. *Atimicrob. Agents Chemother.* **1999**, *43*, 1317−1323. (d) Epand, R. M.; Vogel, H. J. *Biochim. Biophys. Acta* **1999**, *1462*, 12−28. (e) Tossi, A.; Sandri, L.; Giangaspero, A. *Biopolymers* **2000**, *55*, 4−30. (f) van't Hof, W.; Veerman, E. C.; Helmerhorst, E. J.; Amerongen, A. V. *Biol. Chem.* **2001**, *382*, 597−619.

(2) (a) Menger, F. M.; Keiper, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1906−1920 and references therein. (b) Velonia, K.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.* **2002**, *124*, 4224−4225. (c) Aoyama, Y. *Chem. Eur. J.* **2004**, *10*, 588−593. (d) Kellermann, M.; Bauer, W., Hirsch, A.; Schade, B.; Ludwig, K.; Böttcher, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2959−2962.

(3) Responsive polymeric amphiphiles exist but often utilize quite different mechanisms. For a recent review, see: *Stimuli-Responsive Water Soluble and Amphiphilic Polymers*; McCormick, C. L., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 2001.

(4) (a) Janout, V.; Lanier, M.; Regen, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1573−1574. (b) Janout, V.; Lanier, M.; Regen, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 640−647. (c) Janout, V.; Di Giorgio, C.; Regen, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 2671−2672. (d) Janout, V.; Zhang, L.-h.; Staina, I. V.; Di Giorgio, C.; Regen, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 5401−5406. (e) Janout, V.; Jing, B.; Staina, I. V.; Regen, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4436−4437.

(5) (a) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793−1796. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011.

(6) (a) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003−2004. (b) Tomalia, D. A.; Berry, V.; Hall, M.; Hedstrand, D. M. *Macromolecules* **1987**, *20*, 1164−1167. (c) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1287−1297. (d) Stevelmans, S.; van Hest, J. C. M.; Jansen, J. F. G. A.; van Boxtel, D. A. F. J.; de Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 7398−7399. (e) Gitsov, I.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 3785−3786.

10.1021/ol048679p CCC: $27.50
Published on Web 08/06/2004

For the basic design, we use cholic acid derivatives as the "walls" and a cone-shaped tetraaminocalixarene as the scaffold.[7] The ethoxylethyl groups on the lower rim of calixarene are used for compatibility with both hydrophilic and hydrophobic solvents. Cholic acid is an example of so-called facial amphiphiles.[8] Its α-face is hydrophilic with three hydroxyl groups, whereas the β-face is completely hydrophobic, being all hydrocarbon. Bearing four cholic acid units, molecule **1a** has a total of 12 hydroxyl groups on the hydrophilic faces, and **1b** has 24.

We studied conformational behavior of **1a** and **1b** in a mixture of (deuterated) chloroform and methanol. We postulated that the nonpolar chloroform would favor the α-faces of the amphiphiles and the polar methanol prefers the β-faces. Miscibility of the two solvents allows us to vary the solvent ratios continuously. In the ^{1}H NMR spectra of **1a** in different solvent mixtures (Figure 1), the most noticeable change occurs in the aromatic region. The aromatic protons are equivalent in 60% methanol. However, with either higher or lower percentages of methanol, the two aromatic protons ortho to the amido groups split into two peaks. The two peaks have the same intensity and are coupled by a small coupling constant of 2.4 Hz, which is in the typical range of coupling constant for two meta protons on a phenyl ring.[9] Because secondary aromatic amides are known to adopt trans conformation,[10] we assume that the splitting is a result of hindered rotation of the nitrogen−aryl bonds (vide infra). In contrast, the ^{1}H NMR spectrum of the control compound **2** is completely unchanged in different solvents (see Supporting Information).

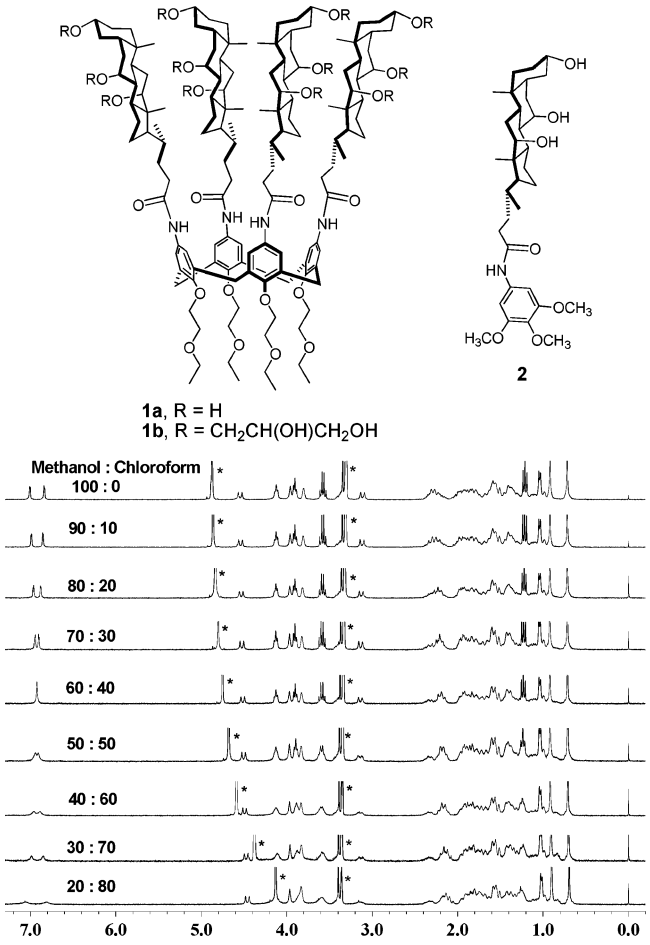


Figure 1. ^{1}H NMR spectra (300 MHz) of **1a** in different ratios of $CD_3OD/CDCl_3$ (v/v) at ambient temperature. The 20%/80% mixture also contains an additional 1% D_2O. Solvent peaks (CD_3OH and CD_2HOD) are marked with an asterisk (*) on the right. The signal at 0 ppm is from added tetramethylsilane (TMS).

The two aromatic peaks coalesce at higher temperatures. In 65% methanol, the coalescence temperature (t_c) is 50 °C. The rotation barrier is calculated[11] to be $\Delta G^{\ddagger} = 17.0$ kcal/mol with $\Delta\nu = 8.8$ Hz. The barrier increases to $\Delta G^{\ddagger} = 17.7$ kcal/mol ($t_c = 70$ °C, $\Delta\nu = 15.6$ Hz) in 70% methanol, and further to $\Delta G^{\ddagger} > 17.9$ kcal/mol ($t_c > 80$ °C, $\Delta\nu = 28.0$ Hz) in 75% methanol.[12] Upon cooling, the singlet in 60% methanol splits into two peaks. The rotational barrier is $\Delta G^{\ddagger} = 13.8$ kcal/mol ($t_c = 0$ °C, $\Delta\nu = 15.6$ Hz at −40 °C). Clearly, the distance between the two aromatic peaks at ambient temperature is a measure of the rotational barrier around the nitrogen−aryl bonds.

Splitting of the ortho aromatic protons has been found in other amido calixarenes and typically caused by hydrogen bonds that hindered rotation of the nitrogen−aryl bonds.[13] Hydrogen bonds, however, are unlikely to be responsible in the current system. This is because rotation is most hindered when the percentage of methanol (which is a competitive hydrogen bonding solvent) is either high or low but least hindered in the intermediate range.

We propose that **1a** adopts a normal micelle conformation in polar solvents (>60% methanol) and a reversed micelle conformation in nonpolar solvents (<60% methanol). It seems that there is no preference for either face of cholic acid in 60% methanol and rotation of nitrogen−aryl bonds is thus least restricted. In a methanol-rich environment, the solvent prefers the α-faces, causing the hydrophobic β-faces to aggregate intramolecularly.[14] Solvophobic interactions probably constrain the cholate units and result in hindered

(7) For examples of cholic acid-based molecular containers, see: (a) Davis, A. P.; Bonar-Law, R. P.; Sanders, J. K. M. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davis, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Elsevier: Oxford, 1996; Vol. 4, Chapter 7. (b) Ariga, K.; Terasaka, Y.; Sakai, D.; Tsuji, H.; Kikuchi, J.-I. *J. Am. Chem. Soc.* **2000**, *122*, 7835−7836, (c) Yoshino, N.; Satake, A.; Kobuke, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 457−459.

(8) (a) Cheng, Y.; Ho, D. M.; Gottlieb, C. R.; Kahne, D. Bruck, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 7319−7320. (b) Venkatesan, P.; Cheng, Y.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6955−6956. (c) McQuade, D. T.; Barrett, D. G.; Desper, J. M.; Hayashi, R. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 4862−4869.

(9) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. *Organic Structural Spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 1998; p 75.

(10) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517−551.

(11) Reference 9, p 95.

(12) We performed the variable-temperature NMR experiments with sealed tubes but still lost the signals above 80 °C.

(13) (a) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407. (b) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329. (c) Brewster, R. E.; Shuker, S. B. *J. Am. Chem. Soc.* **2002**, *124*, 7902−7903. (d) Corbellini, F.; Costanzo, L. D.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946−9947.

rotation. As the ratio of methanol increases, the micelle-resembling conformer becomes more favorable compared to other conformers with exposed hydrophobic β-faces. Indeed, a progressively larger splitting is seen as methanol is increased from 60 to 100%. Note that our variable-temperature NMR data also suggest that a larger splitting at ambient temperature corresponds to a higher rotation barrier.

The exact opposite trend is observed when the percentage of methanol drops below 60% and can be explained by solvophobic interactions in the context of reversed micelles. Molecule **1a** is not soluble in chloroform with less than 20% methanol. A small amount of water (ca. 1%), however, can significantly increase the solubility.[15] Such behavior is typical for reversed micelles formed by regular surfactants, which require a small amount of water for stability.[16]

Changes in other areas of the spectra in general are relatively small. Toward the low-polarity end, signals from the calixarene protons, including those from the ethoxyethyl groups (i.e., a triplet at 1.2 ppm and a quartet at 3.6 ppm), become quite broad. The peak broadening is likely caused by intermolecular aggregation. However, if carbon tetrachloride instead of chloroform is used in the solvent mixture, signals become much sharper (see Supporting Information). The behavior is consistent with a reversed-micellelike conformer, which should be more stable in carbon tetrachloride than the more polar chloroform. A more stable conformer has its solvophobic faces better shielded from the solvents and thus has a lower tendency for aggregation. Besides the sharpness of the signals, two other pieces of evidence support that carbon tetrachloride is a better solvent than chloroform for the reversed-micelle conformer. First, at the low-polarity end, splitting between the aromatic protons is larger in methanol/carbon tetrachloride mixtures than in methanol/chloroform mixtures: 0.098 ppm in 40/60 mixture of CD_3OD/CCl_4 vs 0.074 in $CD_3OD/CDCl_3$; 0.156 ppm in 30/70 mixture of CD_3OD/CCl_4 vs 0.135 ppm in $CD_3OD/CDCl_3$. Second, molecule **1a** has greater solubility in methanol/carbon tetrachloride than in methanol/chloroform: only 5% methanol is needed in the former mixture to solubilize **1a**, whereas >20% methanol is required in the latter.

Similar splitting of aromatic protons is found for **1b** in methanol/chloroform mixtures (see Supporting Information). Importantly, **1b** shows consistently higher sensitivity toward solvent changes than **1a**. When the difference in the chemical shifts of the ortho aromatic protons is plotted as a function of solvent ratios (Figure 2a), **1b** gives a similar but steeper curve than **1a**. This is probably due to the larger difference between the solvophobicities of the α- and the β-faces in **1b** than in **1a**. Quite interestingly, the sensitivity enhancement is largest toward the ends of the polarity scales but smallest in the middle, which is again in agreement with the solvophobic mechanism.

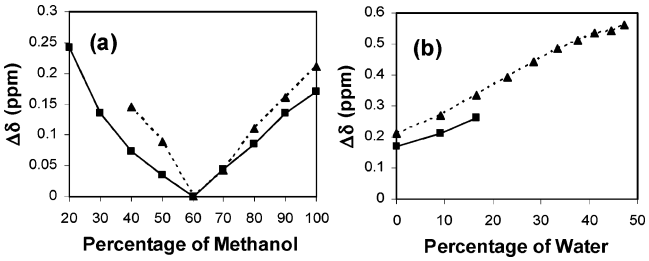


Figure 2. Chemical shift difference ($\Delta\delta$) of the ortho aromatic protons as a function of solvent composition for **1a** (■) and **1b** (▲) (a) in a mixture of (deuterated) methanol and chloroform and (b) in a mixture of (deuterated) water and methanol.

Further evidence for the solvophobically driven conformational change comes from the effect of water in the solvent mixture. The amphiphiles are assumed to adopt normal micelle structures in methanol (vide supra). Addition of water increases the polarity of the environment and is anticipated to further stabilize the micelle conformation. In fact, the distance between the ortho aromatic protons continues to enlarge with higher percentage of water (Figure 2b). Molecule **1a** reaches solubility limits after addition of 20 % water. With increased hydrophilicity, **1b** stays soluble in a nearly 1:1 mixture of CD_3OD and D_2O with a splitting of 0.56 ppm between the two aromatic protons.

In summary, we have designed and synthesized amphiphiles that have basketlike structures. The amphiphiles respond to solvent changes to act like unimolecular micelles in polar environments and unimolecular reversed micelles in nonpolar environments. Switching between the two conformations is driven by solvophobic interactions and is fully reversible. Potential applications of these novel amphiphiles include colloid stabilization, catalysis, and solubilization and transport of agents through incompatible phases.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Iowa State University for support of this research.

Supporting Information Available: Experimental details and NMR spectroscopic data for **1a**,**b** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048679P

(14) ^{1}H NMR study was performed at about 1.5 mM of **1a** or **1b**. The molecules showed intermolecular aggregation at higher concentrations.

(15) Similar effect of water was observed for **1b**.

(16) Fendler, J. H. *Membrane Mimetic Chemsitry*; Wiley: New York, 1982; Chapter 3.