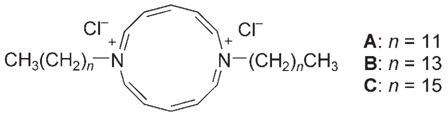
Angewandte Chemie

DOI: 10.1002/ange.200702140

[12]Annulene Gemini Surfactants: Structure and Self-Assembly**

*Lei Shi, Dan Lundberg, Djamaladdin G. Musaev, and Fredric M. Menger**

Enticed by a 2006 report of the first N-substituted diaza[12]annulenes,[1] we shifted the new ring system into the colloidal domain via the long-chain derivatives **A**, **B**, and **C** (Scheme 1). The compounds can be classified as "gemini surfactants" because of their double-chain, double-cation structures.[2–4] In more recent years, particularly after the term "gemini surfactant" had been christened as such,[5] investigation of the compounds has flourished. Both academic and industrial laboratories have sought and found useful members of the family (with potential applications ranging from gene transfection,[6] to oil recovery,[7] styrene polymerization,[8] and the synthesis of mesoporous materials[9]). Inserting a [12]annulene moiety into the gemini format represents an unorthodox approach from which we hoped to learn how a large electronically active core affects self-assembly.



Scheme 1. Structure of [12]annulene gemini surfactants.

Work on the annulene gemini surfactants had origins over and above the general curiosity surrounding most new and interesting molecules. First, we wanted to determine the geometric parameters (planarity, bond-order, etc.) for the non-Hückel ring system—a system that is remarkably stable compared to the ephemeral all-carbon analogue.[10] Second, the annulene core gave us an opportunity to detect by NMR spectroscopy any possible interactions between the head group and the termini of the two hydrocarbon tails. The presence of a "looping disorder" in self-assembled systems has been a contentious issue over the years.[11] Third, a recently installed capability in pulse-gradient-spin-echo NMR (PGSE NMR) spectroscopy allowed us to measure the diffusion constants of the self-assembled structures, and thereby estimate their size and shape, without the use of potentially invasive probes.

A, **B**, and **C** were synthesized by treating *N*-(2,4-dinitrophenyl)pyridinium chloride with long-chain amines.[1] ^{1}H NMR and ^{13}C NMR spectroscopy, high-resolution mass spectrometry (HRMS), and elemental analysis left no doubt as to the structures. For example, the ring moieties showed only three proton signals [$\delta = 8.1$ (4H); 8.5 (2H); and 9.5 ppm (4H)] and three carbon signals [$\delta = 128.6$; 145.1; and 145.5 ppm]. The HR mass spectrum of **A**, for example, gave a mass of 531.44353 (calcd for $[M-\mathrm{Cl}]^+ = 531.44395$).

The first task, after the pure annulene gemini surfactants were in hand, was to obtain the geometry of the *N*-methyl derivative using density functional theory with a large basis set [B3LYP/6-311 + G(2d,p)]. All calculations were performed by using the Gaussian 03 program.[12] The normal mode analysis (1 atm, 298.15 K) confirms that structures **I** and **II** (Figure 1) are the minimum-energy conformers for the *N*-methyl derivative. Conformer **I** was found to be slightly more stable. In contrast, conformer **II** is a few kcal mol^{-1} more favorable than the *N*-hydrogen derivative. Natural population analysis indicated that about half of the total positive charge is borne by the hydrogens on the "spacer" carbons.[13] The analysis also provided a 2s(1.22)2p(4.10) configuration for the N atoms. Steric factors force the two *N*-methyl groups in **I** to point away from each other, a feature that we presume would likewise hold true for our long-chain gemini surfactants.

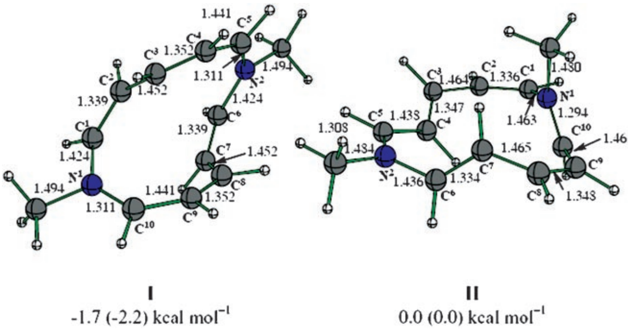


Figure 1. Optimized conformations. Blue: N; gray: C; and white: H. Values in parentheses are derived from PCM computations (see text). Bond lengths (Å) are shown.

Although there can be no assurance that conformer **I** is maintained when the gemini surfactants self-assemble in water, it is clear that substantial intramolecular chain/chain contact would necessitate major ring distortions. In this regard, polarizable-continuum-model (PCM) calculations show that conformer **I** is further stabilized by 0.5 kcal mol^{-1} relative to conformer **II**. Bond distances, which are interesting

---

[*] L. Shi, Dr. D. Lundberg, Prof. Dr. F. M. Menger
Department of Chemistry
Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6586
E-mail: menger@emory.edu
Dr. D. G. Musaev
Cherry L. Emerson Center for Scientific Computation
Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)

[**] This work was supported by the National Institutes of Health. We thank Dr. Shaoxiong Wu for help with the PGSE NMR experiments.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

in their own right for this non-Hückel conjugated ring system,[14] are also given in Figure 1. The twelve C–N/C–C bonds of **I** alternately shift from shorter ($d_{av} = 1.33$ Å) to longer ($d_{av} = 1.44$ Å), with the former bonds being all cisoid.[15]

Plots of surface tension, conductivity, ^{1}H NMR shifts, and ^{13}C NMR shifts versus gemini concentration show "breaks" corresponding to critical micelle concentrations (CMCs). The surface tension plot for **B** and conductivity plot for **C** shown Figure 2 are typical. CMC values, which are in satisfactory agreement among the different methods, are **A**: 7.7 mM; **B**: 2.0 mM; and **C**: 0.55 mM. These values are much higher than those of conventional gemini surfactants of identical chain lengths (for example, 1 mM for "12–4–12", and 0.009 mM for "16–5–16").[16,17] Indeed, the annulene gemini surfactants have CMC values approaching those of single-chain surfactants (for example, the CMC value of $C_{12}H_{25}N^{+}Me_{3}Br^{-}$, abbreviated "DTAB", is 13 mM).[18] The [12]annulene gemini surfactants clearly encounter difficulties packing within micelles. So-called α parameters (the fraction of dissociated counterions obtained from the ratio of the slopes in the conductivity plots) are all 0.4 for **A**, **B**, and **C** as compared to the more usual 0.20–0.26 for DTAB and conventional gemini surfactants.[19] High α values might be related in part to the positive charge in the annulene head group being distributed over multiple atoms. Inspection of the gemini surfactants by UV spectroscopy (394.5 nm) at concentrations encompassing the CMCs gave no evidence (for example, non-Beer's law behavior) of ring/ring interactions.[13]

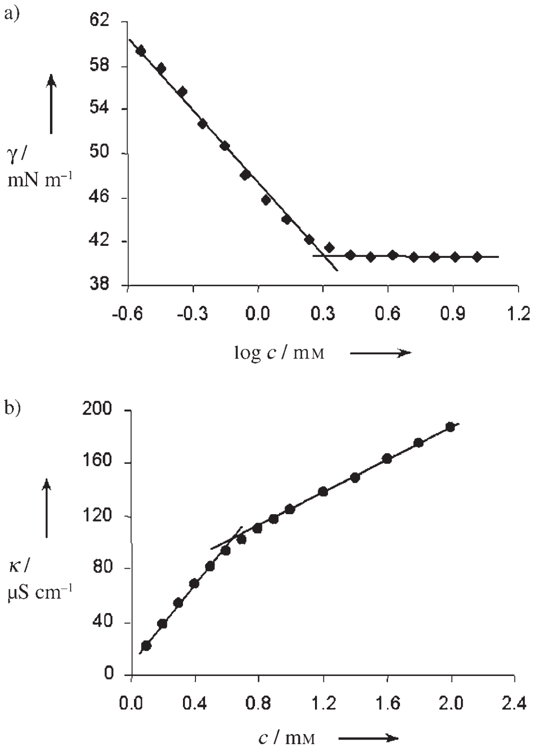


Figure 2. a) Surface tension versus log(concentration) of **B**; b) conductivity versus the concentration of **C**.

NMR chemical shifts, being weighted averages arising from monomeric and micellar species, are linearly related to the reciprocal of the total surfactant concentration below and above the CMC value. A striking difference was seen between the ^{1}H NMR chemical shift behavior of the terminal methyl groups of **C** and those of DTAB (Figure 3). Whereas a downfield shift of the signals takes place for DTAB upon micellization, **C** shows an upfield shift. The most likely explanation is that the π electrons of the annulene core shield the methyl protons of **C**. This, then, demands transient proximity between the head groups and the mobile chain termini, a result compatible with flexible chains and considerable "chain looping".[11]

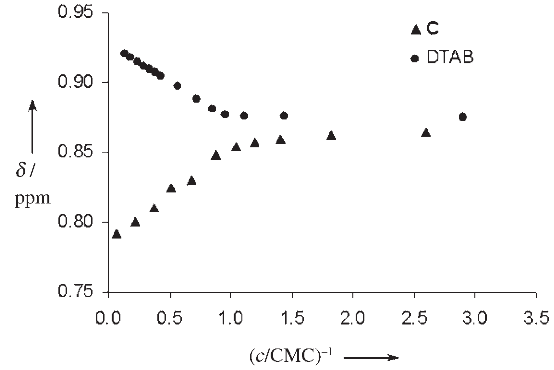


Figure 3. ^{1}H NMR chemical shifts of the terminal methyl groups plotted against the inverse normalized concentrations of **C** and DTAB.

The translational mobility of surfactants in solution diminishes upon formation of aggregates; thus self-diffusion coefficients (D_{obs}) supply important information about the assembly process. D_{obs} values were obtained using a Hahn-echo sequence and the Stejskal–Tanner equation in what is generally termed the PGSE NMR method.[20,21] A plot of D_{obs} versus ([gemini]/CMC)$^{-1}$ is expected to give two straight lines intersecting at unity, and Figure 4 bears this out for gemini **A**. When normalized to adjust for differences in the CMC values, **A** and DTAB have virtually superimposable plots from which we conclude that **A** forms micelles of roughly the same size and spherelike shape (radius ca. 20 Å)[22] as those of DTAB. We surmise that the slight curvature at the CMC for **A** in

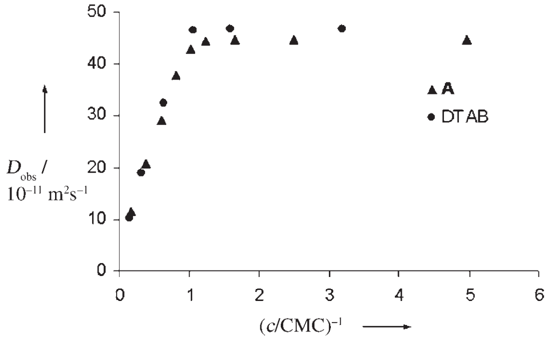


Figure 4. Difffusion coeffecients plotted against the inverse normalized concentrations of **A** and DTAB.

Figure 4 likely arises from a reduced cooperativity in the self-assembly of the gemini surfactant as a consequence, in part, ofthe previously mentioned packing constraints.

To summarize: three gemini surfactants with a non-Hückel diaza[12]annulene core were synthesized and examined by density functional theory, surface tension, conductivity, and UV measurements as well as ^{1}H NMR, ^{13}C NMR, and PGSE NMR spectroscopy. The computations give a minimum-energy conformation in which shorter bonds alternate with longer bonds, and with the two N substituents pointing away from each other. The latter feature renders intramolecular chain/chain contact in self-assemblies difficult. When the gemini surfactants aggregate in water, they form micelles with CMC values that are substantially higher than those of conventional gemini surfactants, a fact that indicates that the annulene molecules encounter packing difficulties. The UV spectra of the gemini surfactants at concentrations encompassing the CMC values show no evidence for ring/ring interactions at the micelle surface. Plots of ^{1}H NMR shifts versus ([gemini]/CMC)$^{-1}$ for the terminal methyl group of the chains suggest the presence of transient proximity between the methyl group and the annulene ring system. Diffusion coefficients from PGSE NMR experiments reveal that the annulene gemini micelles are similar in size and shape to those of simple monochained surfactants.

Over the past few years cationic gemini surfactants have been used in vitro gene transfection investigations.[6,23] Invariably, these gemini surfactants have flexible spacers separating their cationic nitrogen atoms (as do other DNA binders such as spermidine and spermine). How our more rigid annulene gemini surfactants (with an N···N distance of 4.8 Å approximating the $N(CH_2)_3N$ distance in spermidine) behave toward DNA is as not yet known.

Received: May 15, 2007

Keywords: annulenes · density functional calculations · gemini surfactants · micelles · self-assembly

---

[1] I. Yamaguchi, Y. Gobara, M. Sato, *Org. Lett.* **2006**, *8*, 4279.

[2] F. M. Menger, J. S. Keiper, *Angew. Chem.* **2000**, *112*, 1980; *Angew. Chem. Int. Ed.* **2000**, *39*, 1906.

[3] M. J. Rosen, *CHEMTECH* **1993**, *23*, 30.

[4] R. Zana, *Curr. Opin. Colloid Interface Sci.* **1996**, *1*, 566.

[5] F. M. Menger, C. A. Littau, *J. Am. Chem. Soc.* **1991**, *113*, 1451.

[6] A. J. Kirby, P. Camilleri, J. B. F. N. Engberts, M. C. Feiters, R. J. M. Nolte, O. Söderman, M. Bergsma, P. C. Bell, M. L. Fielden, C. L. García Rodríguez, P. Guédat, A. Kremer, C. McGregor, C. Perrin, G. Ronsin, M. C. P. J. van Eijk, *Angew. Chem.* **2003**, *115*, 1486; *Angew. Chem. Int. Ed.* **2003**, *42*, 1448.

[7] H. Chen, L. Han, P. Luo, Z. Ye, *Surf. Sci.* **2004**, *552*, L53.

[8] M. Dreja, B. Tieke, *Langmuir* **1998**, *14*, 800.

[9] M. Benjelloun, P. Van Der Voort, P. Cool, O. Collart, E. F. Vansant, *Phys. Chem. Chem. Phys.* **2001**, *3*, 127.

[10] a) J. F. M. Oth, J.-M. Gilles, G. Schröder, *Tetrahedron Lett.* **1970**, *11*, 61; b) J. F. M. Oth, H. Röttele, G. Schröder, *Tetrahedron Lett.* **1970**, *11*, 67.

[11] F. M. Menger, R. Zana, B. Lindman, *J. Chem. Educ.* **1998**, *75*, 115.

[12] Gaussian 03 (Revision C1): M. J. Frisch et al., see the Supporting Information

[13] See the Supporting Information.

[14] K. B. Wiberg, *Chem. Rev.* **2001**, *101*, 1317.

[15] For optimized geometries of the all-carbon analogue without substituents (tri-*trans*-[12]annulene), see C. Castro, W. L. Karney, M. A. Valencia, C. M. H. Vu, R. P. Pemberton, *J. Am. Chem. Soc.* **2005**, *127*, 9704. In this molecule, where there are no alkyl groups to perturb the conformation, the double bonds alternate *cis* and *trans.*

[16] E. Alami, G. Beinert, P. Marie, R. Zana, *Langmuir* **1993**, *9*, 1465.

[17] F. Devínsky, I. Lacko, F. Bittererová, L. Tomeèková, *J. Colloid Interface Sci.* **1986**, *114*, 314.

[18] S. S. Berr, E. Caponetti, J. S. Johnson, Jr., R. R. M. Jones, L. J. Magid, *J. Phys. Chem.* **1986**, *90*, 5766.

[19] Y. Geng, L. S. Romsted, F. M. Menger, *J. Am. Chem. Soc.* **2006**, *128*, 492.

[20] F. M. Menger, H. Lu, D. Lundberg, *J. Am. Chem. Soc.* **2007**, *129*, 272.

[21] W. S. Price, *Concepts Magn. Reson.* **1997**, *9*, 299; W. S. Price, *Concepts Magn. Reson.* **1998**, *10*, 197.

[22] V. K. Aswal, P. S. Goyal, *Chem. Phys. Lett.* **2003**, *368*, 59.

[23] M. Castro, D. Griffiths, A. Patel, N. Pattrick, C. Kitson, M. Ladlow, *Org. Biomol. Chem.* **2004**, *2*, 2814.