Globular Self-aggregates Formed with a Urea-functionalized Resorcinarene Derivative in Chloroform

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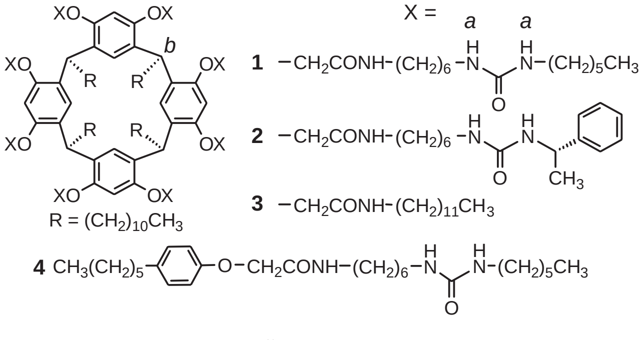
(Received June 30, 2005; CL-050841)

Globular self-aggregates were formed with a resorcinarene derivative having eight *N*,*N*′-dialkylurea side-chains, as confirmed by dynamic light scattering and negative-staining transmission electron microscopy. The resulting aggregates were found to bind anions such as chloride and bromide in chloroform.

Recently, macrocycles such as resorcinarenes and calixarenes endowed with urea-based residues have been extensively studied as self-assembling[1] and self-folding[2] subunits, for the purpose of creating supramolecular structures in organic solvents. Interestingly, Mendoza and co-workers reported that self-assembling dimers of resorcinarenes with cyclic urea residues induced the formation of unique reverse vesicles 0.8–2.2 µm in diameter.[3] On the other hand, we have also shown that chiral macrocycles (**2**) with eight (*R*)- and (*S*)-methylbenzylurea residues on the resorcinarene skeleton form intramolecular hydrogen bonds by bundling the urea residues in a cyclic fashion to give a self-folding molecular cavitand in chloroform as confirmed by CD spectroscopy.[4] The divergently oriented bulky methylbenzyl groups at the termini were aimed to prevent the urea residues from forming intermolecular hydrogen bonds. In addition, anions such as chloride and bromide were entrapped in the cavity.[4] On these grounds, we designed a urea-functionalized resorcinarene **1** having less steric hindrance around the urea termini in order to form a reverse vesicle through intermolecular hydrogen bonding interactions. The urea-functionalized resorcinarene is constructed by introducing eight alkylurea residues onto the macrocyclic skeleton through a short-chain linker, the residues are expected to behave as hosts to the anions. We report here the preparation and the aggregates formation of octaurea **1** in chloroform, as demonstrated by NMR spectroscopic, dynamic light scattering (DLS), X-ray diffraction (XRD), and transmission electron microscopy (TEM) studies.



Scheme 1.

Urea-functionalized resorcinarene **1**[5] (R = undecyl) was prepared in a manner similar to that applied to the synthesis of **2**[4] by using *n*-hexyl isocyanate as an amine-reactive reagent with the octaammonium derivative of resorcinarene (see Supporting Information). A resorcinarene derivative **3**[5] having dodecylamide chains in place of the peripheral *N*,*N*′-dialkylurea moieties of **1** was also synthesized as a reference in order to characterize the hydrogen-bonding feature of the urea groups (Scheme 1). The octaurea compound thus obtained was sufficiently soluble in organic solvents such as $CHCl_3$, CH_2Cl_2, and DMSO under our experimental conditions.

The ^{1}H NMR spectrum of octaurea **1** in DMSO-d_6 showed relatively sharp signals, reflecting the symmetric character of the monomeric state: e.g., urea protons (*a*, 5.73 ppm, half-peak width of 14 Hz), Ar_2CHR methine protons (*b*, 4.64 ppm, 14 Hz), and methylene protons connecting to the urea moiety (2.93 ppm, 12 Hz) (Figure 1a). On the other hand, remarkably broadened ^{1}H NMR signals of urea protons (*a*, 5.1–5.7 ppm) and methylene protons connecting to the urea moiety (3.0–3.2 ppm) were observed in $CDCl_3$ (Figure 1b), suggesting the existence of multiple hydrogen bonding interactions. In both solvents, the signals of methine protons (*b* in Figure 1) of **1** suggested the symmetric, vase-like[6] conformation of the macrocyclic skeleton.

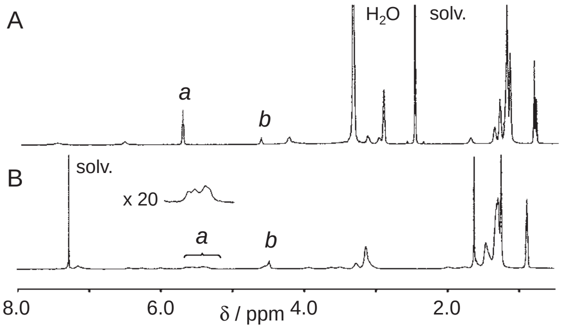


Figure 1. 600 MHz ^{1}H NMR spectra of **1** (1.0 mM) in DMSO-d_6 (A) and $CDCl_3$ (B) at 298 K.

Hydrogen bonding interactions of the urea moieties of **1** in $CDCl_3$ were evaluated by FT-IR measurements and compared with those of a monourea derivative **4**[7] as a component analogue of the octaurea. The absorption frequencies originating from the N–H deformation band and the C=O stretching vibrations of **1** shifted to higher and lower wave numbers ($\delta_{N\text{–}H}$, 1571 and $\nu_{C=O}$, 1638 cm^{-1}), in comparison with those for the reference compound **4** ($\delta_{N\text{–}H}$, 1537 and $\nu_{C=O}$, 1670 cm^{-1}), indicating the

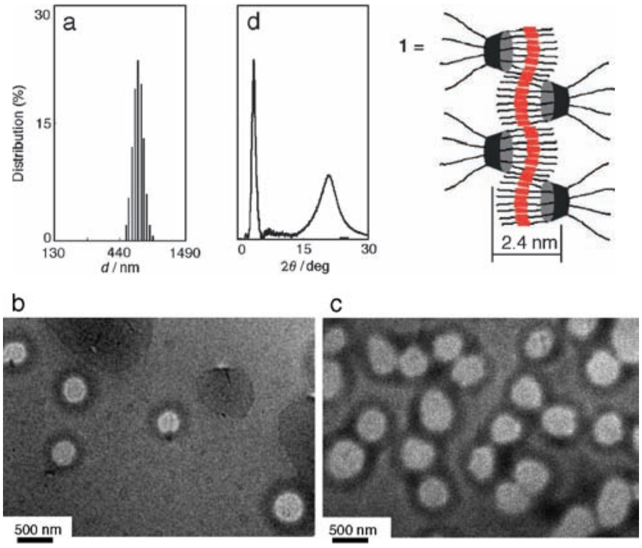


Figure 2. Size distribution of **1** (1.0 mM) in $CHCl_3$ as evaluated by DLS with 50 mW Ar^+ laser at 298 K (a). TEM micrograph of globular self-aggregates formed with **1** in $CDCl_3$ in the absence (b) and presence (c) of $Bu_4N^+Cl^-$ (2 equiv.)(poststained by 5% uranyl acetate solution). X-ray diffraction diagram of a cast film of **1** (d). Illustrative speculation of the layer structure of aggregate from **1** (upper right). Each red rectangle stands for urea residues having hydrogen bonding functionality.

formation of hydrogen bonds[8] for almost all urea and amide residues of **1**. On the other hand, resorcinarene **3**, bearing eight dodecylamide chains, gave 1537 and 1678 cm^{-1} for N–H deformation band and C=O stretching vibrations, respectively, indicating its relatively weak hydrogen bond formation.

DLS measurements in fact revealed that octaurea **1** formed vesicular-size aggregates in $CHCl_3$ with a diameter (d)[9] of 620 ± 100 nm (Figure 2a). A similar aggregation characteristic of **1** was observed in CD_2Cl_2 by identical methods (data not shown). On the other hand, DLS measurements for a DMSO solution of octaurea **1** showed the absence of large aggregates and the presence only of a small one with a d (2.2 ± 0.3 nm), which has good agreement with the molecular size estimated by computer-aided molecular modeling in the unextended conformation (see Supporting Information).

The formation of vesicle-like aggregates in the diameter range of 400–700 nm, in accord with the DLS size, was also observed for a $CHCl_3$ solution of **1** by negative-staining TEM (Figure 2b), even though their internal compartments were not identified clearly. No aggregates were observed by DLS and TEM measurements in the case of compound **3**, strongly suggesting that urea moieties of **1** play key roles in the formation of the aggregates in $CDCl_3$. Bundling structure of **1** was also important for formation of the aggregates, because mono-valent reference **4** gave no aggregates under the experimental conditions, as confirmed by DLS and TEM measurements. Figure 2d shows the XRD diagram for a cast film of **1**. The observed strong high-ordered reflection peak at 1.8° indicates the existence of a well-organized layer structure. The d-spacing is calculated from the Bragg equation to be 25 Å, which is comparable to the length of hydrogen bonded side-chains of **1**, estimated from the CPK space-filling model (see Supporting Information). These results suggest that the side chains around urea residues of **1** were well-assembled and constructed in a layer structure through inter- and intramolecular hydrogen bonding interactions.

As regards the guest-binding of urea-functionalized resorcinarenes, upon addition of tetrabutylammonium chloride (Bu_4N^+ Cl^-) (24 mM) to a solution of **1** (1 mM) in $CDCl_3$ gave a downfield shift ($\Delta\delta = 0.38$ ppm) for NH(urea) protons (see Supporting Information). No induced shifts were detected for the protons of Bu_4N^+. A bromide ion was also bound to the aggregates as confirmed by ^1H NMR spectroscopy in $CDCl_3$ under identical conditions: $\Delta\delta = 0.28$ ppm for NH(urea) protons. The binding constants (K) of **1** toward Cl^- and Br^- were evaluated on the basis of the computer-aided least squares curve fitting methods applied to the NMR data ($K = 480$ and 280 M^{-1}, respectively). On the other hand, compound **3** showed almost no capacity of binding the identical guests ($K < 5\,M^{-1}$). Urea moieties are powerful hydrogen-bond donors, and the functionalized hosts with urea can bind anions through hydrogen bonding and ion–dipole interactions in apolar organic solvents.[4] The present results suggested that anions were accommodated in the polar urea domains of the neutral aggregates. In addition, the formation of aggregates was maintained for **1** in the presence of chloride ions, as confirmed by TEM (Figure 2c) and DLS[10] measurements.

In summary, a resorcinarene derivative having eight *N,N′*-dialkylurea side-chains was found to form globular self-aggregates in chloroform as confirmed by DLS and TEM studies. The polar urea groups of **1** play key roles for the formation of the aggregate as well as the guest-binding toward anions in chloroform. Thus, a promising aspect of future research is to make a reverse vesicle into a nano-sized reaction flask having molecular recognition ability by introducing appropriate catalytic functions. Work is now underway along this line.

References and Notes

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3 There are only a few reports about reverse vesicles of amphiphiles: M. H. K. Ebbing, M.-J. Villa, J.-M. Valpuesta, P. Prados, and J. de Mendoza, *Proc. Natl. Acad. Sci. U.S.A.*, **99**, 4962 (2002).

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5 **1**: Anal. Calcd for $C_{192}H_{344}N_{24}O_{24}\cdot H_2O$: C, 68.04; H, 10.35; N. 9.87%. Found: C, 67.90; H, 10.23; N, 9.89%. MS (FAB) m/z 3374 $(M + 1)^+$. **3**: Anal. Calcd for $C_{184}H_{328}N_8O_{16}\cdot 2H_2O$: C, 75.05; H, 11.36; N, 3.81%. Found: C, 75.18; H, 11.22; N, 3.76%. MS (FAB+) m/z 2952 $(M + K)^+$.

6 It is well known that the resorcinarenes can adopt a vase or a kite conformation, which can be identified by ^1H NMR signals of methine protons: J. R. Moran, J. L. Ericson, E. Dalcanale, J. A. Bryant, C. B. Knobler, and D. J. Cram, *J. Am. Chem. Soc.*, **113**, 5707 (1991).

7 Compound **4** was synthesized in a manner similar to that applied to the synthesis of **1**, by using of 4-*n*-hexyl-phenol in place of a resorcinarene.

8 Kobayashi and Seki reported similar results for the hydrogen bonding formation of urea derivatives by identical methods: T. Kobayashi and T. Seki, *Langmuir*, **19**, 9297 (2003).

9 The d value and size-distribution were calculated by a cumulant analysis on the basis of the assumption of spherical particles, see: a) D. E. Koppel, *J. Chem. Phys.*, **57**, 4814 (1972). b) L. Cao, I. Manners, and M. A. Winnik, *Macromolecules*, **34**, 3353 (2001).

10 The size-distribution of the aggregate was little changed upon addition of Bu_4N^+ Cl^- (24 equiv.).

Published on the web (Advance View) August 13, 2005; DOI 10.1246/cl.2005.1276