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Synthesis of a singly bridged resorcinarene-dimer by Mannich reaction with *N*,*N*′-diethylethylenediamine and formaldehyde: self-inclusion of bridging diazahexamethylene unit in methanol

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Abstract—Mannich reaction of resorcin[4]arene with *N*,*N*′-diethylethylenediamine and formaldehyde produced a singly bridged resorcinarene-dimer bearing sixteen hydroxyl groups at their peripheral positions, which exists in a closed capsular conformation including the diazahexamethylene bridge chain between the two resorcinarene units in CD_3OD.

Calix[4]arenes and resorcin[4]arenes are [1_4]metacyclophane compounds, which can be readily prepared by a one-step procedure without using high dilution conditions.[1] These macrocycles have been used as building blocks for constructing molecular capsules.[2] A family of [1_4]metacyclophane-dimers carrying one intercavity linkage are attractive because the two bowl-shaped subunits arrange in an open-capsule or closed-capsule conformation as shown in Figure 1, and this conformational change may be achieved by varying the solvent polarity or encapsulating smaller molecules.

The synthesis of singly bridged dimers generally requires special precursors.[3] They must be regioselectively functionalized to avoid bridging between two or more subunits. However, a few examples of the direct synthesis of dimers by the reaction of unmodified subunits with bifunctional reagents have been reported.[4] The Mannich reaction of unmodified resorcinarene with ethylenediamine and an excess of formaldehyde yielded a carcerand-type molecule in which two tetrabenzoxazine units are connected by four bridges.[5] We are interested in extending this condensation to obtain a family of singly bridged resorcinarene dimers having sixteen hydroxyl groups.[6] Such dimers might have interesting host properties, since strong electron-donating hydroxyl groups increase the electron density of the cavity. In these systems, cation–π and/or CH–π interactions between the electron-rich aromatic rings and guest molecules play an important role in stabilizing the inclusion complexes.[7] We now report the facile synthesis of a singly bridged resorcin[4]arene dimer via the Mannich reaction of unprotected resorcinarene, *N*,*N*′-diethylethylenediamine and formaldehyde. Furthermore, we discuss its characteristic conformational properties in solution based on ^{1}H NMR spectroscopy.

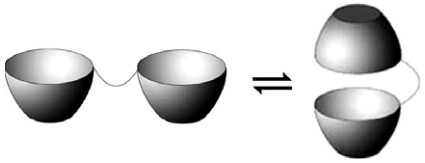

Figure 1. Conformational features in singly bridged resorcin[4]arene dimer.

The condensation of resorcin[4]arene **1**, *N*,*N*′-diethylethylenediamine **2** and formaldehyde in a 1:0.4:0.8 molar ratio was carried out in a 1:1 mixture of methanol and acetic acid at 50 °C for 5 h (Scheme 1). After removal of most of the solvent, the residual material

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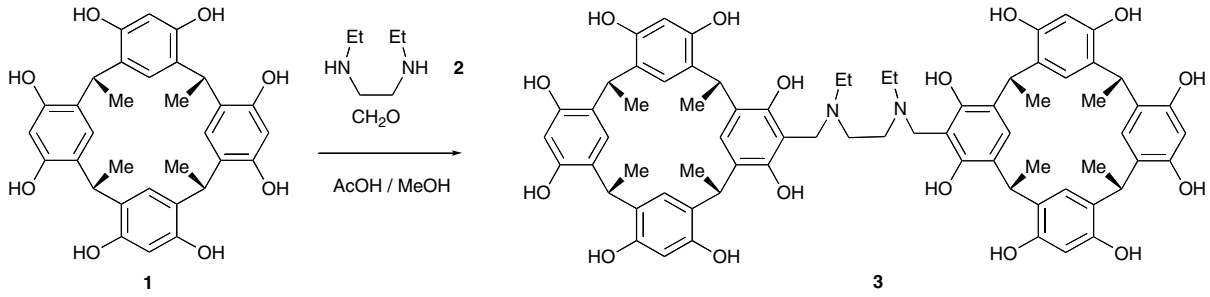


Scheme 1. Synthesis of a singly bridged resorcinarene dimer by the Mannich reaction.

was triturated with cold methanol to leave crude **3**, which was purified by crystallization from hot methanol to produce dimer **3** as an adduct with two molecules of acetic acid in 26% yield.[†] The Mannich reaction of resorcin[4]arenes can be carried out in ethanol–toluene.[8] However, in this solvent system, the reaction with the diamine gave an intractable material. Furthermore, the reaction with piperazine produced a complex mixture from which we could not isolate any distinct product. It is presumed that the formation of the dimer significantly depends on the reaction conditions and the condensation agent.

The structure of dimer **3** was confirmed by elemental analysis, mass spectrometry and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of dimer **3** in CD_3OD at 30 °C (Fig. 2A) shows five singlets at 6.12, 6.28, 7.24, 7.41 and 7.42 ppm in a 1:2:2:1:1 ratio for the aromatic protons, two sets of quartets at 4.49 and 4.50 ppm for the bridging methine protons and two sets of doublets at 1.70 and 1.71 ppm for the methyl protons. These data are in good agreement with C_s symmetrical structure of the monosubstituted resorcinarene **3**.

The chemical shifts of the bridging chain, H_a, H_b, H_c and H_d (see Fig. 2 for labels), are significantly affected by the solvent. In CD_3OD, dimer **3** displayed a triplet at −1.18 ppm and a quartet at 1.04 ppm for the *N*-ethyl groups (H_a and H_b). The central ethylene protons (H_c) and benzyl methylene protons (H_d) appear at 1.71 and 3.47 ppm, respectively. On the other hand, in DMSO-d_6, the ^{1}H NMR spectrum of **3** (Fig. 2B) shows H_a, H_b, H_c and H_d signals at 0.91, 2.40, 2.65 and 3.72 ppm, respectively. The chemical shift differences of those observed in CD_3OD and DMSO-d_6 for H_a, H_b, H_c and H_d are 2.09, 1.36, 0.94 and 0.25 ppm, respectively. These data suggest that, in methanol, the location of the protons of the bridging chain is influenced by the ring current shielding effects of the resorcinarene cavities.

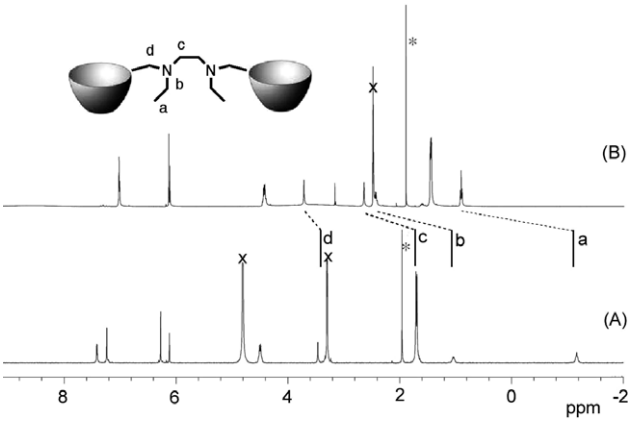


Figure 2. 400 MHz ^{1}H NMR spectra of **3**: measured in (A) CD_3OD; (B) DMSO-d_6. Asterisks (*) and crosses (×) indicate acetic acid and residual solvent protons, respectively.

The dimer is isolated as an adduct with two molecules of acetic acid, hence it is believed to exist as an ammonium salt. Therefore, the cation–π and/or CH–π interaction between the bridging chain and resorcinarene cavities is presumed to play a dominant role in the control of the conformation of the dimer since the resorcinarene anions strongly interact with ammonium ions. These interactions may occur in either an intra- or intermolecular fashion. To discriminate between these interactions, we examined the concentration dependence of the chemical shifts of **3** in CD_3OD. Figure 3 shows the high-field region of the ^{1}H NMR spectra of **3** as a function of the concentration. There are small, but clear changes in the chemical shift upon going from 0.27 to 13.5 mM. The upfield shifts of these protons with the decreasing concentration of **3** are not consistent with the intermolecular interaction, ruling out the possibility of the multi-component capsule formation. Thus, we speculate that **3** exists in a closed-capsule type conformation, in which the linkage moiety is included in the enclosed cavity, although the interaction in an intramolecular

[†] *Preparation of dimer* **3**: Resorcin[4]arene **1** (1.06 g, 2.0 mmol) was dissolved in hot methanol (20 ml). The solution was diluted with acetic acid (20 ml) and cooled to ambient temperature. To this were added *N*,*N*′-diethylethylenediamine (0.093 g, 0.8 mmol) and 36% aqueous formaldehyde (0.13 g, 1.6 mmol). The mixture was stirred for 2 h at ambient temperature and at 50 °C for 5 h. The solution was concentrated to one fifth under reduced pressure, and stored at 5 °C for 14 h to give solid material, which was washed with cold methanol to leave pure dimer **3** (380 mg) in 26% yield. mp 250 °C (dec). Anal. Calcd for $C_{72}H_{80}O_{16}N_2\cdot(C_2H_4O_2)_2\cdot(H_2O)_6$: C, 62.62; H, 6.92; N, 1.92. Found: C, 62.72; H, 6.55; N, 1.91. FAB-MS (MNBA) Calcd for $C_{72}H_{80}O_{16}N_2$: 1228.5. Found 1229.5 (M+1). δ_H (400 MHz; CD_3OD; Me_4Si; 30 °C) −1.18 (6H, br t, 6H, *N*-CH_2CH_3), 1.04 (4H, br q, *N*-CH_2CH_3), 1.70 (12H, d, bridge CH_3), 1.71 (12H, d, bridge CH_3), 1.71 (4H, s, CH_2CH_2), 1.96 (s, acetic acid), 3.47 (4H, s, Ar-CH_2–N), 4.49 (4H, q, bridge CH), 4.50 (4H, q, bridge CH), 6.12 (2H, s, ArH), 6.28 (4H, s, ArH), 7.24 (4H, s, ArH), 7.41 (2H, s, ArH), 7.42 (2H, s, ArH).

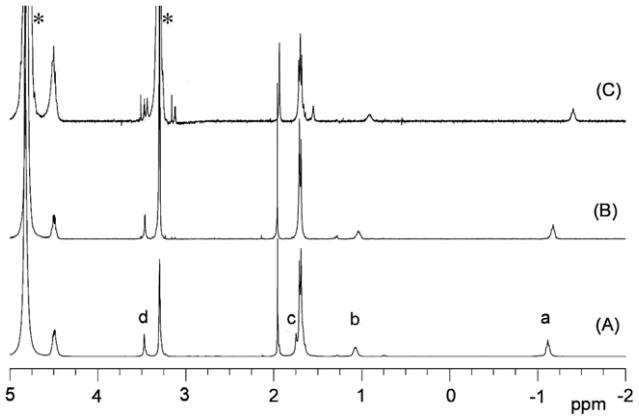


Figure 3. Partial 400 MHz ^{1}H NMR spectra of **3** in CD_3OD at different concentrations: (A) 13.5×10^{-3} M; (B) 2.7×10^{-3} M; (C) 0.27×10^{-3} M. Asterisks indicate residual solvent peaks. Labels for the bridging moiety are the same as in Figure 2.

fashion is usually independent of the concentration.[9] This unexpected concentration dependency may be ascribed to the increase in the degree of association of the hydroxyl groups on the resorcinarene cores by decreasing the concentration. Thus increasing the deprotonation enhances the interaction of the resorcinarene cores with the ammonium function, consequently, resulting in the upfield shift of the protons of the bridging chain. To ascertain whether this phenomenon is attributable to the deprotonation of the hydroxyl groups of the resorcin[4]arene, we examined the effect of the addition of triethylamine on the chemical shifts. When 2.2 equiv of the amine was added, the signals of H_a and H_b shifted upfield by 0.19 and 0.10 ppm, respectively. This phenomenon could be accounted for by the increasing deprotonation of the hydroxyl protons. Therefore, we concluded that the concentration dependency is responsible for the dissociation of the hydroxyl groups of the resorcinarene cores.

Finally, we examined the complexation behaviour of **3** with Et_4NBr. Small alkyl ammonium cations have been proven to be good guest candidates for resorcinarene capsules.[10] In methanol, the resorcin[4]arenes are able to form inclusion complexes with various quaternary ammonium cations.[11] In practice, the addition of Et_4NBr resulted in the small downfield shift of the protons of the bridging moiety (Fig. 4). This behaviour indicates the presence of an equilibrium between the self-inclusion capsule and the guest-inclusion capsule in the presence of guest molecules (Scheme 2). Assuming that the chemical shifts of the ethyl group in the guest-inclusion capsule in CD_3OD are equal to those observed in DMSO-d_6, the equilibrium constant for the reaction is calculated to be ca. 7 M^{-1}. This value is much smaller than that of the ethylene-bridged resorcinarene dimer bearing sixteen hydroxyl groups (850 M^{-1}).[6] These data also support the idea that the self-inclusion capsule is a very stable species in methanol.

In conclusion, a 2,5-diazahexamethylene bridged resorcin[4]arene dimer was prepared by the Mannich reaction. In methanol, the dimer exists in closed capsular conformation and includes its bridging chain. The cation–π and/or CH–π interaction between the protonated diazahexamethylene chain and the partially deprotonated resorcinarene cores is the driving force for the formation of the closed capsule, including its bridging chain.

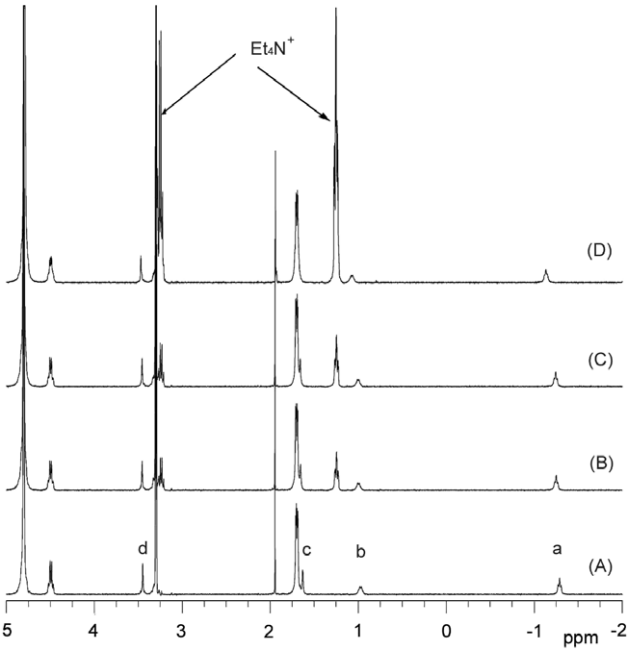
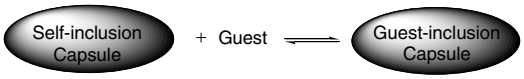


Figure 4. The ^{1}H NMR (400 MHz; CD_3OD) titration experiment of **3** (1.8×10^{-3} M) with Et_4NBr: (A) **3**; (B) **3**/Et_4NBr 1:0.5; (C) **3**/Et_4NBr 1:0.9; (D) **3**/Et_4NBr 1:6.3. Labels for the bridging moiety are the same as in Figure 2.



Scheme 2. An equilibrium between the self-inclusion capsule and the guest-inclusion capsule in the presence of guest molecules.

Further work is now underway to synthesize resorcin[4]arene dimers by the Mannich reaction as well as to study the conformational properties of the dimer under various conditions.

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