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Dimeric Molecular Capsules under Redox Control

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The design and self-assembly of molecular capsules is a very active topic of research in modern chemistry.[1] A well-established methodology for the assembly of these supramolecular structures relies on the formation of kinetically stable, hydrogen-bonded dimers between two calix[4]arenes, each functionalized with four urea groups on its upper rim.[2] The groups of Rebek and Böhmer have independently shown that two molecules of tetraphenylurea calix[4]arenes (similar to **1**, but with different aliphatic chains in the lower rim) interact head-to-head to form a robust seam of hydrogen bonds between the four urea groups in each of the calixarene upper rims, giving rise to a dimer with S_8 symmetry. In this work, we demonstrate that the functionalization of the urea groups with redox-active, terminal ferrocenyl residues gives rise to calixarene hosts (compound **2**) that can also form kinetically stable dimers (molecular capsules). However, the reversible oxidation of the ferrocene groups induces the destabilization of the dimers and their redox-controlled dissociation.

The preparation of calixarenes **1**, **2**, **4**, and **5** followed established methodology (see Supporting Information for details). Compound **2** was synthesized using the reaction of the corresponding tetraamino calix[4]arene[3] with ferrocene acyl azide. This reagent was prepared by treatment of ferrocene carboxylic acid with diphenyl phosphoryl azide in dry dichloromethane. The ^{1}H NMR spectrum of **2** in CDCl$_3$ only shows the characteristic peak patterns expected for the kinetically stable head-to-head dimer (Figure 1B). For instance, the spectrum shows two doublets (7.54 and 5.95 ppm) for the calixarene aromatic protons, with the typical meta coupling constant of 2.1 Hz. These two signals have their origin on the different microenvironments created by the "locked" urea groups since one of the aromatic protons faces the N–H urea protons and the other faces the carbonyl group. Interestingly, the ferrocene protons on the cyclopentadienyl ring attached to the urea also split [5.19 and 4.05 ppm for the adjacent protons (labeled "e" in Figure 1) and 4.55 and 4.05 ppm for the "f" protons], revealing the overall rigidity of the structure. Addition of 5% DMSO-d_6 to this solution disrupts the hydrogen bonding and leads to a completely different spectrum that corresponds to monomeric **2** (Figure 1A). These data provide unequivocal evidence for the formation of kinetically stable dimers (molecular capsules) by compound **2** in CDCl$_3$ solution. Clearly, the functionalization of the upper rim ureas with terminal ferrocenyl residues does not alter the self-assembly properties of these calix[4]arenes.

^{1}H NMR spectroscopic experiments indicate that **2** is present as a dimer in CDCl$_3$/CD$_3$CN (10:3, v/v), while larger ratios of CD$_3$CN in the solution lead to dimer dissociation. Thus, the electrochemical behavior of **2** was investigated in CHCl$_3$/CH$_3$CN (10:1, v/v) solution containing 0.2 M tetrabutylammonium hexafluorophosphate (supporting electrolyte). Cyclic voltammetry of 1.0 mM **2** in this solvent system reveals a single wave at a half-wave potential of +0.28 V versus Ag/AgCl that corresponds to the one-electron oxidation of the four ferrocene groups in each calixarene
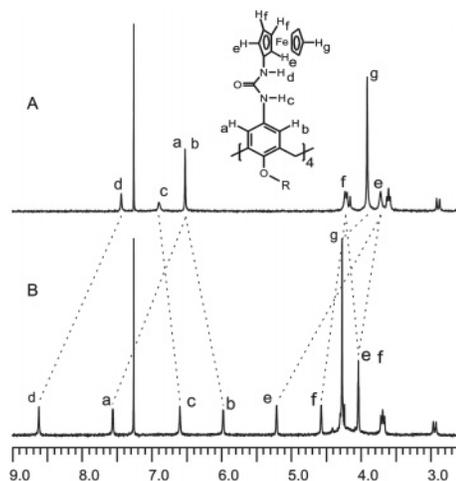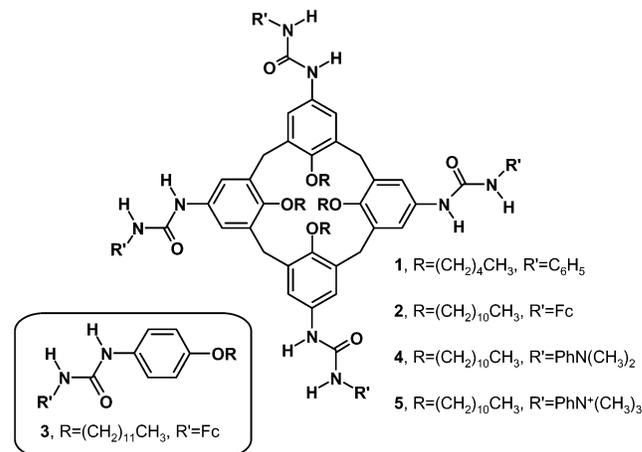

Figure 1. Partial ^{1}H NMR spectra (300 MHz) of **2** in (A) CDCl$_3$ and 5% DMSO-d_6 solution and (B) in pure CDCl$_3$.

Chart 1. Structures of the Tetraurea Calix[4]arenes Used in This Work. In Compound **2**, Fc Stands for $-(C_5H_4)Fe(C_5H_5)$.

1, R=(CH$_2$)$_4$CH$_3$, R'=C$_6$H$_5$

2, R=(CH$_2$)$_{10}$CH$_3$, R'=Fc

4, R=(CH$_2$)$_{10}$CH$_3$, R'=PhN(CH$_3$)$_2$

5, R=(CH$_2$)$_{10}$CH$_3$, R'=PhN$^+$(CH$_3$)$_3$

3, R=(CH$_2$)$_{11}$CH$_3$, R'=Fc

(Figure 2). The voltammetric data reveal that the ferrocene residues behave as independent redox centers, undergoing oxidation at very similar potentials and exhibiting undetectable electronic communication among them. On the other hand, the shape of the voltammetric wave observed in these experiments departs from that expected for a perfectly reversible electrochemical oxidation process. Specifically, the anodic and cathodic peak currents are dissimilar, and distortions due to the low solubility of the oxidized form may also affect the voltammetric behavior. For comparison, the cyclic voltammogram of the model ferrocenyl–urea compound **3** shows the reversible oxidation of the ferrocene residue at a half-wave potential of +0.31 V (Supporting Information).

Upon oxidation, calixarene **2** contains four paramagnetic ferrocenium units that broaden and shift considerably the ^{1}H NMR
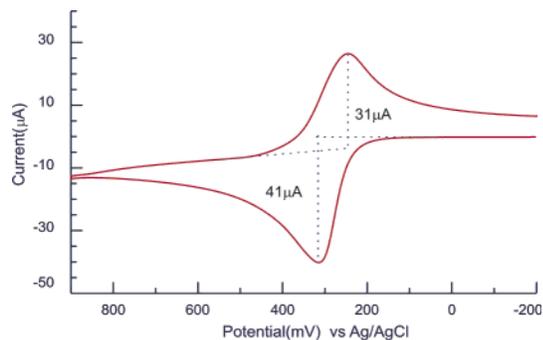
Figure 2. Cyclic voltammetric behavior on a glassy carbon electrode (0.071 cm^2) of a CHCl$_3$/CH$_3$CN (10:1, v/v) solution containing 1.0 mM **2** and 0.2 M TBAPF$_6$. Scan rate = 0.1 V/s.

signals of the nearby protons in this molecule. However, the lower rim aliphatic protons are clearly observed and can be utilized to determine the diffusion coefficient (D_o) of oxidized **2** using PGSE NMR techniques.[4] After oxidation with trifluoroacetic acid (TFA), we measured a value of 7.5×10^{-6} cm^2/s in pure CDCl$_3$ for **2**$^{4+}$, while the same experiment with reduced **2** yielded a value of 3.8×10^{-6} cm^2/s. The 2-fold increase of the D_o values upon oxidation of the ferrocene groups constitutes very strong evidence for the oxidation-induced dissociation of the dimer.

FT-IR spectroscopy also proved very useful for monitoring dimerization in the oxidized state. For instance, the carbonyl region of the FT-IR spectrum of a 2.8 mM **2** solution in CHCl$_3$ shows the amide I peak (C=O stretch) at 1657 cm^{-1}, which is consistent with its involvement in hydrogen bonding. Oxidation of **2** with TFA leads to extensive changes in this spectral region, with the main peaks observed at 1783 and 1698 cm^{-1} (Supporting Information). These peak positions strongly suggest that the carbonyl groups are no longer involved in hydrogen bonding interactions. Could electronic effects related to the oxidation of the ferrocene groups be responsible for the frequency shifts observed? We investigated the FT-IR spectra of compound **3** to answer this question. The amide I peak of **3** was observed at 1678 (before oxidation) and 1683 cm^{-1} (after TFA oxidation). Therefore, electronic effects are not responsible for the large frequency shifts observed upon oxidation of **2**. Furthermore, we also investigated the FT-IR spectra of **2** in CHCl$_3$ solution also containing 5% DMSO, which is enough to prevent dimer formation according to our ^{1}H NMR spectroscopic experiments. In this medium, the amide I peak shifted from 1693 to 1698 cm^{-1} upon TFA oxidation, again a ~5 cm^{-1} blue shift consistent with that detected upon oxidation of **3**.

^{1}H NMR spectroscopic data obtained with model compounds **4** and **5** provide additional support for the disruption of the dimeric molecular capsule when positive charges are present on the calixarene upper rim (Supporting Information). Therefore, all our data reveal that the stable dimers of tetraferrocenylurea calix[4]-arene **2** undergo dissociation upon oxidation of the ferrocene groups (Scheme 1). The four positive charges acquired by each calixarene after chemical or electrochemical oxidation give rise to strong electrostatic repulsions between the two oxidized halves of the dimeric molecular capsule. The dimerization equilibrium of **2** may thus be controlled by its oxidation state. As far as we know, this is the first reported example of redox control on the formation of a

Scheme 1. Redox Control on the Dimerization Equilibrium of Tetraferrocenylurea Calix[4]arene **2**
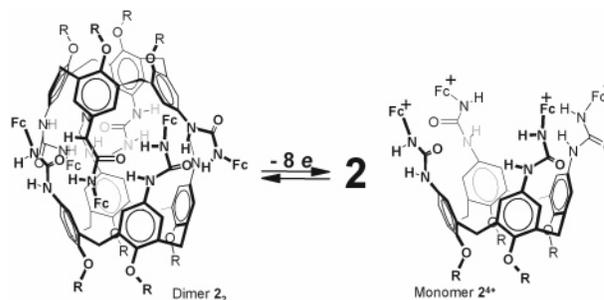
dimeric molecular capsule by two identical redox-active components. We are continuing the investigation of these systems in the hope that they may become useful for controlled drug release and related applications.

Supporting Information Available: Synthetic details, cyclic voltammogram for **3**, FT-IR data for **2** and **3**, and NMR data for model compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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