Formation of a Macrobicyclic Tris(disulfide) by Molecular Self-Assembly

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Self-assembly is a fundamentally important process employed by nature in the construction of supramolecular biological systems with a minimal expenditure of resources and energy. Extensive effort has been spent in designing components which mimic natural systems by undergoing molecular self-organization through coordination of metals[1] or selective noncovalent interactions such as hydrogen bonding.[2] In contrast, the area of self-assembly with covalent modification is relatively little explored.[3,4] One of the more intriguing examples comes from nature: the thiol−disulfide interchange reaction which is important in stabilizing protein structure by disulfide bridge formation.[4,5] This reaction has potential applications in the self-assembly of robust supramolecular arrays with proof-reading to remove errors by its remarkable ability to effect the reversible formation and cleavage of strong, covalent S−S bonds at room temperature.[6] The ability to control the formation of disulfide bonds can be applied to the design of preorganized monomers which may self-assemble to generate organized entities with interesting architectures and properties. We report herein an enhancement of the thermodynamic stability of a tris(disulfide) dimer by molecular design and the first example of the formation of tris(disulfide) dimer **1** from its trithiol monomer **2** under equilibrium conditions (Scheme 1).

Previous attempts to form a macrocyclic dimeric bis(disulfide) or tris(disulfide) under equilibrium conditions[7] were met with difficulty due to the unfavorable enthalpy term originating in CSSC torsion angle strain. In addition, the thiol groups in the monomer are not preorganized in a geometry that resembles the disulfides in the dimer resulting in an unfavorable entropy change upon dimer formation.

Our approaches in molecular design were to preorganize the starting trithiol into a conformation resembling that of the tris(disulfide) and to eliminate as many rotational degrees of freedom as possible, while allowing the formation of a strain free CSSC dihedral angle of about 90°. We thus designed and synthesized trithiol **2** as shown in Scheme 2. Nonbonded steric effects between adjacent groups on the aromatic ring[8] are expected to force the ethyl groups and the thiol-terminated substituents to lie on opposite sides of the ring. In this conformation, the thiol groups are preorganized into a geometry that resembles the conformation of the monomeric units in dimer **1**. Amide groups which have a lower rotational degree of freedom than alkyl chains are introduced (**7** → **8**) so as to constrain the CH_2SH groups to lie away from the aromatic ring, thereby enabling the formation of disulfide bonds without CSSC angle strain.

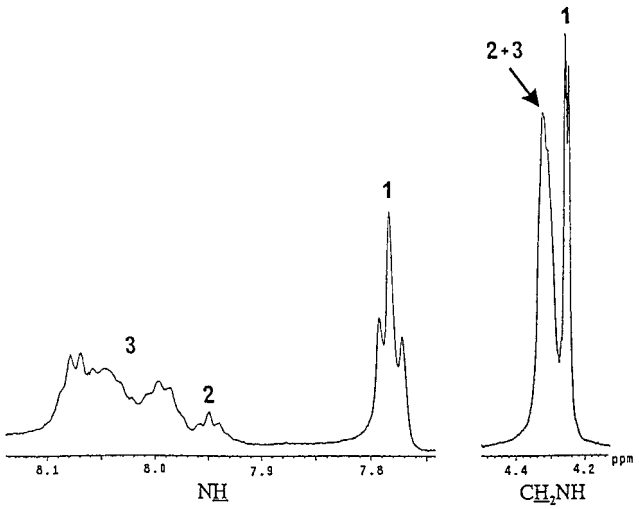

Figure 1. Study of the thiol-disulfide interchange equilibrium (1 mM ME^{ox}) at 298 K among trithiol **2**, dimer **1**, and oligomer **3** in DMSO-d_6 (under argon) by 500 MHz ^{1}H NMR spectroscopy after 17 days.

Under high dilution kinetic conditions, trithiol **2** is oxidized by iodine to tris(disulfide) dimer **1** (in 84% yield after purification). Oligomer **3**, which is insoluble in $CHCl_3$, was isolated as a byproduct in about 10% yield. Evidence for the formation of dimer **1** includes the following: (1) a dimer parent ion peak ([M + H^+]) at *m*/*z* 937.2973 in the HRMS−FAB mass spectrum, and (2) sharp peaks in the ^{1}H NMR spectrum in $CDCl_3$ but no thiol proton peak (a trimer would have shown thiol peaks). In contrast, oligomer **3** showed *no* peak below *m*/*z* 2000 in the HRMS−FAB mass spectrum and *broad* peaks in the ^{1}H NMR spectrum in DMSO-d_6. Dimer **1** is stable in solution up to 50 °C. A 1 mM solution of **1** in DMSO-d_6 showed no change in ^{1}H NMR signals after heating at 50 °C for 6 days.

Under equilibrium conditions in the presence of 2-hydroxyethyl disulfide (ME^{ox}), trithiol **2** exists in equilibrium with dimer **1**, oligomer **3**, and unsymmetrical disulfide[9] (Figure 1). Starting from a solution of **2** (1 mM) and ME^{ox} (1 mM) in DMSO-d_6 under argon in a sealed NMR tube, equilibrium was achieved in several weeks.[10] Integration of the NH peaks in the ^{1}H NMR spectrum shows that 30% of the amide hydrogens are present as dimer **1**. Calculations based on 1 mM ME^{ox} indicate that the theoretical amount

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(9) The presence of unsymmetrical disulfide is due to the formation of disulfide bonds between mercaptoethanol and the free thiol ends of monomer **2** and oligomer **3**.
(10) Equilibrium can also be established by mixing mercaptoethanol with a solution of dimer **1** or oligomer **3**.

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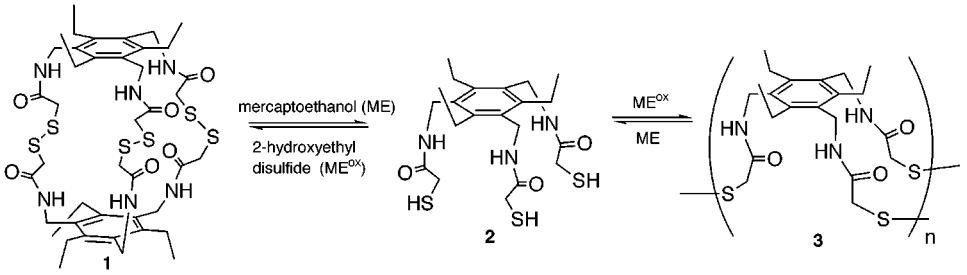
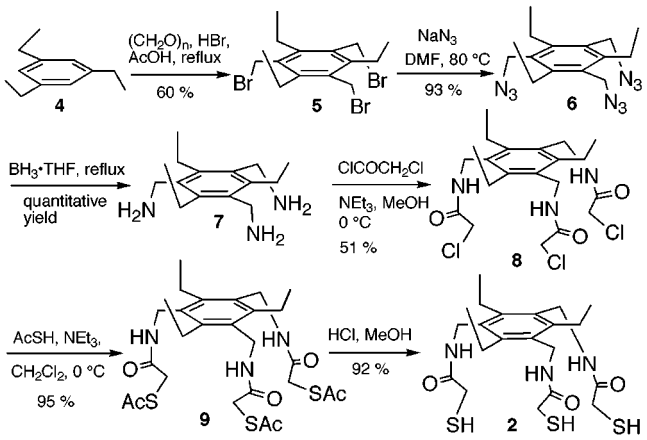
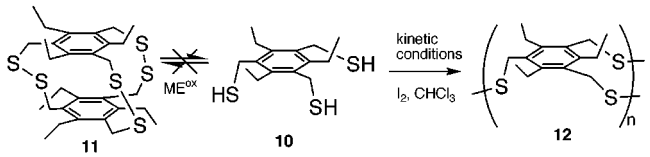
Scheme 1



Scheme 2



Scheme 3



of disulfide bond formation is 66%.[11] Similar studies using 1.5 mM (stoichiometric) and 3 mM (excess) of ME^{ox} result in 27% and 23%, respectively, of the amide hydrogens present as dimer **1**.[12] We could not determine the exact concentration of the oligomer, and therefore its relative stability compared with the dimer because the amount of monomeric units existing as trithiol **2**, oligomer, or unsymmetrical disulfide could not be determined precisely due to overlapping peaks for their NH protons and overlapping peaks for their C*H*$_2$NH protons. In addition, the exact formula of the oligomer is not known. An attempt to determine product percentages with HPLC was unsuccessful because the compounds do not significantly absorb in the UV−vis spectral region.

Trithiol **10** (Scheme 3) was prepared and used as a control to test the effect of CSSC dihedral angle strain on dimer formation. CPK modeling of dimer **11** showed that it is highly strained. The inability to form strain-free CSSC dihedral angles presumably discourages the formation of **11**. Attempts to prepare **11** from trithiol **10** under conditions identical to those used to prepare tris(disulfide) **1** yielded only oligomeric product **12**.

In conclusion, we have demonstrated that by appropriate molecular design it is possible to enhance the stability of a dimeric tris(disulfide) which we have observed in equilibrium with the oligomer. The result is a macrobicyclic capsule having a cavity size large enough to accommodate small guest molecules. We are currently working toward increasing the stability of the self-assembled dimer through hydrogen bonds and/or electrostatic interactions as well as specific guest encapsulation within the cavity.

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Supporting Information Available: Spectroscopic data for compounds **1**−**3**, and experimental procedures for equilibrium studies.

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(11) The total theoretical amount of free thiol ends remaining in monomer **2** and oligomer **3** is 33%.

(12) The decrease in dimer formation is presumably due to competing formation unsymmetrical disulfide. Attempts to minimize unsymmetrical disulfide formation by using cyclic disulfide (e.g. *trans*-1,2-dithiane-4,5-diol) instead of 2-hydroxyethyl disulfide (ME^{ox}) to induce equilibrium were unsuccessful due to the weak oxidative strength of the cyclic disulfide.