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Synthesis and properties of disulfide-bond containing eight-membered rings

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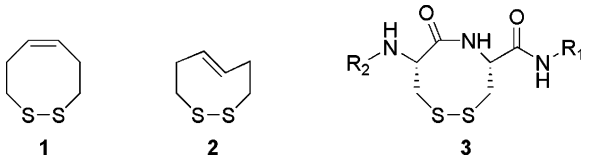
Abstract—The cyclocystine ring structure (CRS, **3**), which results from a disulfide-bond between adjacent cysteine residues, is a rare motif in protein structures and is functionally important to those few proteins that posses it. This letter will focus on the construction of CRS mimics and the determination of their respective redox potentials.

A disulfide-bond between adjacent cysteine residues (**3**, Fig. 1) is a very rare occurrence in protein structures. Currently, 32 out of ca. ~28,000 proteins structurally identified in the Brookhaven Protein Data Bank (PDB) carry this unique motif.[1] In every case the amide bond of the CRS is reported to be in a strained *trans* geometry with an average ω value of 171°.[1] Peptide bonds prefer a *trans* conformation with a torsion angle of 180° so that the nitrogen lone-pair can have maximal delocalization into the π-system, while minimizing steric repulsions from peptidyl side-chains. However, the small ring nature of the eight-membered CRS allows for multiple amide conformations to be energetically feasible. The amide bond could adopt a *cis* conformation, which still allows for delocalization of the nitrogen lone-pair, but would cause the main peptidyl-chain to have a kink in it. A 'strained' *trans* conformation allows the main chain to remain relatively unaltered, but still allows for partial delocalization of the nitrogen lone-pair into the π-system. Our model studies show that a torsion angle of 180° is not allowed for a CRS due to its inability to form the disulfide-bond. Hence, the nitrogen lone-pair must come slightly out of phase with the π-system to allow disulfide-bond formation.



1 2 3

Figure 1. Small molecule mimics of CRS.

A reasonable model for a CRS is cyclooctene. Energetically, the *cis* isomer is more stable than the *trans* as a result of the ring strain required to incorporate a *trans* double bond. This ring strain is demonstrated by the higher $\Delta H_{\text{Hydrogenation}}$ of *trans*-cyclooctene (34.4 kcal/mol) compared to the *cis* isomer (23.0 kcal/mol).[2] If the cyclooctene analogy is applied to the eight-membered CRS, one might expect *cis* amide geometry to predominate. This is not what has been observed experimentally in the PDB. Investigations into proteins that carry the CRS reveal that this motif is important for activity.[3] The central focus of this study is to assess how CRS conformation affects the redox potential of the disulfide-bond. Our central hypothesis is that a CRS with a *cis* peptide bond should be much more reducing (low redox potential) than a CRS with a *trans* peptide bond.

In order to test this hypothesis, *cis* and *trans* substrates were constructed in both oxidized (**1** and **2**) and reduced forms (**10** and **13**). Both systems have a central bond (*cis*/*trans*-olefin) with restricted geometry that mimics the 0° and 180° amide conformations of a *cis* and *trans* CRS. The synthesis of these compounds has not been reported previously, though the theoretical value for the redox potential of **1** has been calculated.[4]

Retrosynthetically, dithiocines **1** and **2** are available upon intramolecular oxidation of the appropriate

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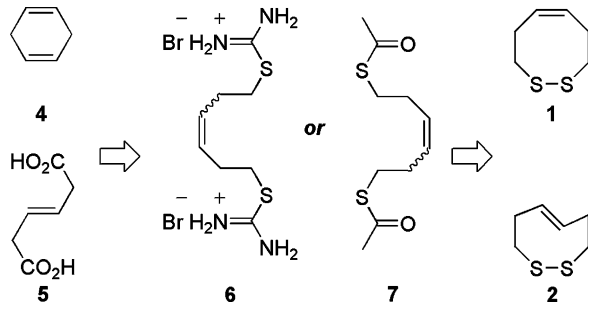


Figure 2. Retrosynthesis of dithiocines.

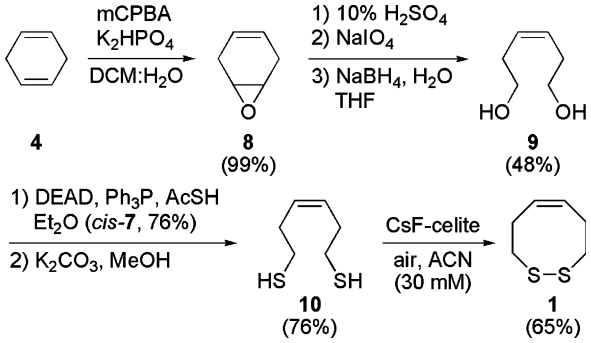
dithiol precursor. Originally the dithiol substrates were to be constructed via dithioureic salt **6**. However, while the synthesis of **6** was non-problematic, the harsh conditions necessary for the generation of the dithiol led to significant by-product formation.[5] This led to the use of dithioester **7** as the intermediary target, which could undergo saponification easily (Fig. 2).[6]

The redox properties were determined by thiol–disulfide exchange, with the varying concentrations of reduced and oxidized forms monitored by ^{1}H NMR (Fig. 3).[7] Employment of oxidized or reduced butane dithiol ($\mathbf{BDT}_{ox}$ and $\mathbf{BDT}_{red}$, respectively), a species of known redox potential ($E_{0(BDT)}$), allows for the redox potential of the CRS mimics to be determined by Eqs. 1 and 2.

$$K_{ox}^{-1} = K_{red} = [\mathbf{CRS}_{red}][\mathbf{BDT}_{ox}]/[\mathbf{CRS}_{ox}][\mathbf{BDT}_{red}] \quad (1)$$

$$E_0 = E_{0(BDT)} - 0.03\log(K_{ox}) \quad (2)$$

The synthesis of *cis*-dithiocine **1** begins with the epoxidation of 1,4-cyclohexadiene to generate **8** almost quantitatively (Scheme 1).[8] A subsequent one-pot protocol entails diol formation, followed by oxidative ring cleavage and reduction of the intermediate acyclic dial to pro-



Scheme 1. Synthesis of *cis*-dithiocine (**1**).

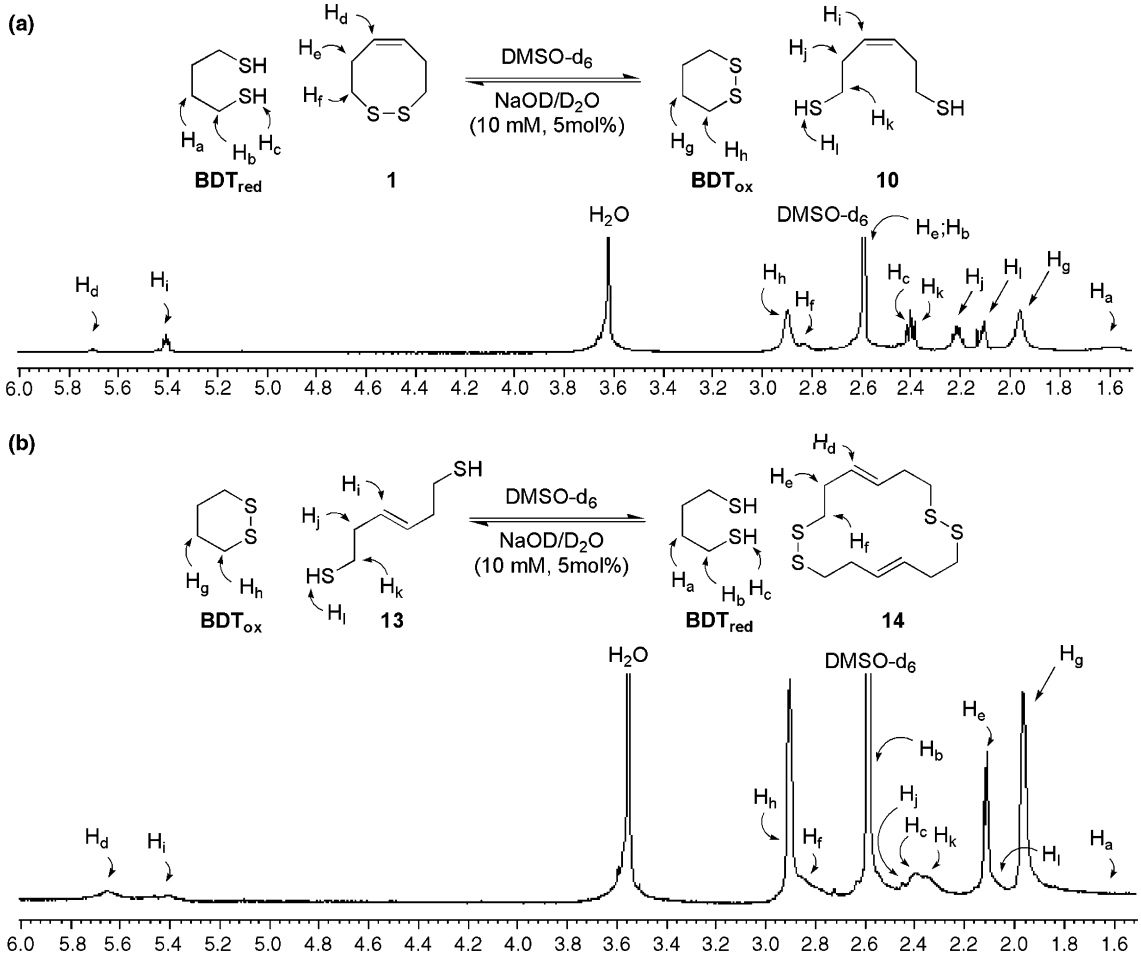


Figure 3. Proton NMR equilibrium redox experiment for *cis*- and *trans*-dithiols.