

## Beyond Crown Ethers: The Chemistry of Macrocyclic Thioethers

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Crown ethers have been extensively studied for their metal ion binding properties. Because oxygen is a hard ligand, complexes of crown ethers with softer metal ions and lower oxidation states are not easily obtained. Replacement of the oxygen atoms with the softer atom sulfur, however, results in macrocycles able to bind soft metal ions and stabilize low oxidation state and low spin [1] metal complexes. Not surprisingly, the chemistry of crown thioethers is sufficiently different from that of their oxygen analogs [2] that there is no good basis of comparison between them.

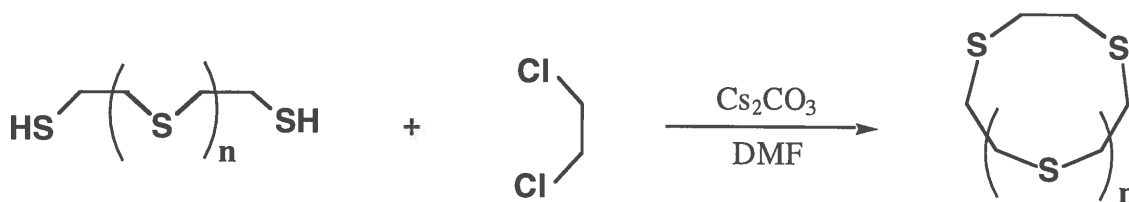
One of the major differences between the two classes of crown ethers is the preferred conformation of the uncomplexed macrocycles. The strong 1,4 sulfur-sulfur repulsions cause the S-C-C-S interactions to adopt an anti conformation, while in crown ethers, the weaker 1,4 oxygen-oxygen repulsions make gauche O-C-C-O conformations more favored [2]. Consequently, lone pairs on the sulfur atoms have a greater tendency to be pointed out of the macrocycle in an exodentate fashion. In order for a metal to be bound inside the macrocycle, one of the lone pairs on each exodentate sulfur atom must be pointed into the ring, requiring an entropically unfavorable reorganization of the molecule. Due to this effect, thiocrown ethers have a tendency to bridge between metal centers in addition to binding single metal ions.

In the uncomplexed macrocycle 14S4 (1,4,8,11-tetrathiacyclotetradecane), all of the sulfur atoms are exodentate (Figure 1b), so significant structural rearrangement must occur before a metal can be bound. The thioether 18S6 (1,4,7,10,13,16-hexathiacyclooctadecane) has two endo and four exo sulfur atoms (Figure 1c). When reorganized for binding, this ligand folds around the metal to encapsulate it in an octahedral geometry. The thioether 9S3 (1,4,7-trithiacyclononane) is an exception because all of the sulfur atoms are in the endodentate conformation in the unbound ligand (Figure 1a) [2]. Although 9S3 can act as a bidentate ligand [3], its conformation makes it ideal for facial coordination, and bis(9S3) metal compounds having octahedral geometries are common.

Because the reorganization required for thiocrown ethers to bind metals reduces their binding affinities, attempts have been made to synthesize thiocrowns pre-organized for coordination. The steric repulsions created by introducing methyl substituents onto the ring carbon atoms can overcome the 1,4 sulfur-sulfur repulsions, and force the macrocycle to adopt an all-endo conformation (Figure 1d) [4]. This increases the metal binding affinity of these ligands. Other substitutions on the carbon backbone, such the addition of as fused cyclohexane rings, can also force the sulfur atoms into endodentate conformations [5, 6].

Crown thioethers have also attracted attention for their ability to stabilize unusual oxidation states of metals. For example, the paramagnetic gold(II) complex  $[\text{Au}(\text{9S3})_2]^{2+}$  has been isolated [7] and the rhodium(II)  $[\text{Rh}(\text{9S3})_2]^{2+}$  complex has been stabilized in solution [8]. The poor donor properties of the crown thioether destabilizes the more highly charged Rh(III) ion, and the forced octahedral coordination of the bis(9S3) complex destabilizes the  $d^8$  Rh(I) complex by inhibiting square planar geometry. Complexation of rhodium by larger thiocrown ethers (10S3, 12S3) raises the redox potentials of the  $\text{Rh}^{3+/2+}$  and  $\text{Rh}^{2+/+}$  couples. This gives rise to the possibility of tuning the redox potentials for metal ion complexes by changing the size of the coordinated thiocrown ether ligand.

Although crown thioether complexes exhibit such a varied chemistry, study of the properties of these compounds as ligands has been severely hindered by the unavailability of convenient, high-yield syntheses. Not until the mid-1980's were syntheses with yields greater than 30% discovered. Currently, thiocrown ethers are most commonly synthesized by the  $\text{Cs}_2\text{CO}_3$  technique developed by Kellogg and Buter (Figure 2) [9]. The  $\text{CO}_3^{2-}$  ion is able to deprotonate thiols in DMF, but  $\text{Cs}^+$  does not form strong ionic complexes with the resulting thiolates. This makes them very reactive and able to attack electrophiles such as 1,2-dichloroethane [10]. This synthesis provides crown ethers in yields of up to 80% under dilute conditions. More recently, trimethylene-linked thiocrowns have been prepared by catalytic cyclooligomerization of thietane (thiacyclobutane) using a  $\text{Re}_3(\mu\text{-H})_4(\text{CO})_{10}$  catalyst [11]. This is the first catalytic method for synthesizing these compounds, but the yields are modest (~30%) and mixtures of 12S3 and 24S6 are formed.



**Figure 2.** General synthesis of thiocrown ethers using the  $\text{Cs}_2\text{CO}_3$  method.

There has been much interest in functionalizing crown thioethers, especially to increase their solubility in water [12]. To this end, crown thioethers have been synthesized with keto groups [13], hydroxy groups [14], and even chiral groups [15]. Recently, the synthesis of a crown thioether made up of linked thiophene molecules was reported [16]. The quest for pre-organized thiocrown ethers with reactive or water-soluble functional groups will undoubtedly continue as interest in thiocrown ethers as ligands grows.

The largest potential application of crown thioethers is the selective extraction of soft metal ions from low grade ores or mine leach. Thiocrowns 14S4 and 18S6 bind selectively to  $\text{Ag}(\text{I})$ ,  $\text{Cu}(\text{I})$ , and  $\text{Cu}(\text{II})$  [17]. However, due to the necessary structural rearrangement of the ligands before binding, their extraction efficiencies are poorer than those of pre-organized thiocrowns [18]. The thiocrown 14S4 can extract  $\text{Cu}(\text{II})$  synergistically in the presence of an organic-soluble acid [19]. When 14S4 is adsorbed onto acid-functionalized beads in an ion exchange column, a synergistic two-phase separation of  $\text{Cu}(\text{II})$  ions from aqueous solution can be achieved [20]. Because these extraction processes are very dependent upon concentration,

solvent, and counterion, there is hope that some combination of variables exists for the separation of a variety of metal ions, including biologically harmful Pb(II) and Hg(II).

Another area of active research is the use of thiocrown ethers as ligands for  $^{99m}\text{Tc}$  medical imaging agents. With the ability to stabilize low oxidation states and the potential for redox tuning with different-sized thiocrown ligands, thioethers might provide excellent monocationic  $^{99m}\text{Tc}$  heart imaging agents [21]. Several technetium thioether complexes have been synthesized for this purpose [22], and one class is currently undergoing animal testing [23]. The  $[\text{Tc}(\text{9S3})_2]^{2+}$  complex has recently been synthesized [24], and can be reduced reversibly to the corresponding monocation. The same properties of thiocrown ethers might also make them useful as ligands for  $^{186}\text{Re}$  [20], which has been proposed as a possible chemotherapy agent. The  $[\text{Re}(\text{9S3})_2]^{2+}$  complex has been synthesized very recently [25], and it can be reduced to the monocation at a potential which indicates that both the Re(II) and Re(I) species might exist *in vivo*.

Thioethers exhibit a distinctive and complementary chemistry from their oxygen analogs. Their ability to coordinate soft metal ions, stabilize unusual oxidation states, and tune redox potentials of metal complexes make them interesting ligands for a variety of applications. The recent development of high-yield syntheses should lead to wider investigations of the chemistry of these ligands, and will make applications such as metal extraction and technetium radio imaging more economically attractive. The properties and uses of thiocrown ethers as ligands ensure that research in this field will continue.

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