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## Thiols and Sulfides as Complexing Agents and Catalysts

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### INTRODUCTION

What if there were no sulfur? Suppose that although sulfur was in its correct place in the periodic system, Nature through some caprice had failed to provide a supply of the element on earth. Imagine - just a few examples, not everything - a chemistry (and world) without the exquisitely active odor components of grapefruit and oranges, the tears brought about by peeled onions, the reek of garlic, the stench of the skunk, sulfuric acid, thiophene, penicillins, cephalosporins, biotin, the biochemically essential methylations brought about by S-adenosyl methionine, the enormous deposits of wurtzite in, for example, the Harz mountains of Germany, the ferridoxins of electron transfer processes.

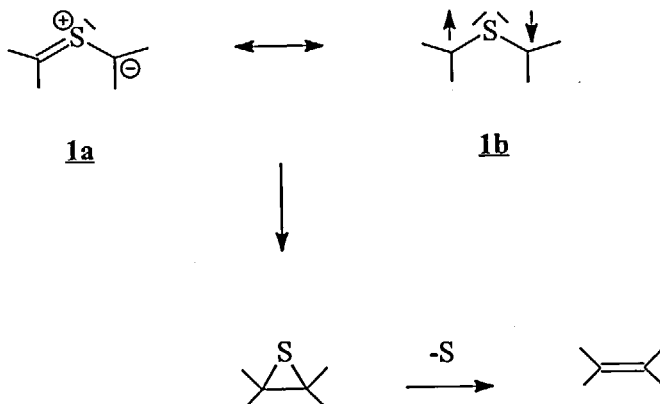
Mankind surely has been aware of sulfur and sulfur compounds since the beginning of human history, this knowledge being one of acute sensation derived from the sense of smell. Think of the stench of hydrogen sulfide from volcanic activity, sulfur containing geologic formations and rotting flesh. Sulfur was burned in religious ceremonies as early as 2000 BC, and its sharp odor and bluish flame were believed to be mystic and purifying. Ulysses employed it, according to Homer, when he returned to Greece, to fumigate his apartment, which also helped dispatch his wife's suitors. Perhaps this mental association of odor and effect lies (unconsciously) at the root of Macbeth's cry of desperation: "What rhubarb, senna or what purgative drug, Would scour these English hence?".<sup>1</sup>

#### 1. Macbeth by W. Shakespeare, Act 5, Scene III

Sulfur finds itself at home both in the worlds of organic and inorganic chemistry and assumes often the cooperative role of team player rather than being a star by itself. A world without sulfur? I doubt it.

The above is an attempt to summarize a little of my own fascination with sulfur. As chemist I first became acquainted with the element during my Ph.D thesis on thiyl radicals derived from thiols.<sup>2</sup> My following encounter was again in the field of radicals (or at least so I thought at that moment) in the form of *diradicals*, but now carbon based, joined by a divalent sulfur atom. What I describe (**1a**) in this uncommon way (and indeed I first thought of these species in this manner) is actually a nicely behaved singlet ground state (**1b**) with little, if any, radical character that falls under the generic classification of a 1,3-dipole in particular a thiocarbonyl ylides as shown in eq. 1.<sup>3</sup>

equation (1)



I note with pleasure that thiocarbonyl ylides continue to have an important role in synthetic strategies, a recent and pertinent example being the synthesis of optically active alkenes that act as molecular switches.<sup>4</sup>

In the present article I will discuss briefly our more recent experiences with sulfur starting with crown ethers that contain sulfur rather than the usual oxygen or nitrogen heteroatoms. This will be only a quick glance, however, and most of the article will deal with various aspects of the interaction between organic thiols and inorganic zinc in liver alcohol dehydrogenase. The ramifications of this work will bring me at the end of the chapter indirectly into catalytically active systems.

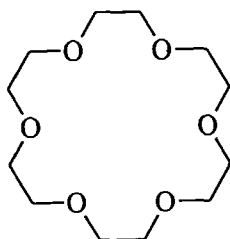
If the reader demands that these divergent topics *must* be held together by a unifying theme, then that is sulfur itself.

A large amount of the work presented here has been published or is in press. Leading references to the original work can be found through the references.

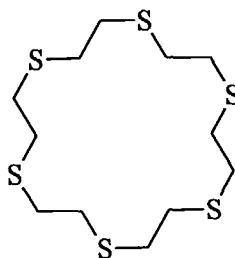
### Thiocrown ethers

Sulfur is not oxygen. That trite truism lies behind, however, why, for example, 18-crown-6 and thio-18-crown-6 differ so greatly in their properties and behaviour.<sup>5</sup> I oversimplify but it is not incorrect to view these two compounds as respectively endodentate and exodentate as pictured.

structures 2 and 3



18-crown-6 (2)

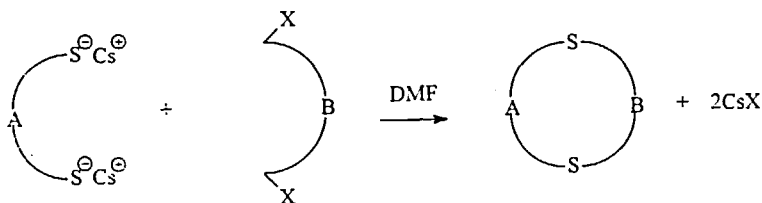


thio-18-crown-6 (3)

This comes about because the unit  $\text{-OCH}_2\text{CH}_2\text{O-}$  tends toward a gauche conformation whereas  $\text{-SCH}_2\text{CH}_2\text{S-}$  tends towards an anti conformation.<sup>6</sup> This causes the heteroatoms to be respectively inside and outside the macrocyclic rings. These effects are reinforced on complexation. The oxa compound 2 complexes ions inside the macrocycle whereas 3 tends (indeed a tendency rather than an absolute rule) to complex heavy metal ions (Ag, Rh, Pd, Ni, etc) on the outside of the macrocyclic ring. The latter process does not profit from cooperativity of bonding and as a result thiocrown ethers tend to be less potent as complexing agents.<sup>7</sup>

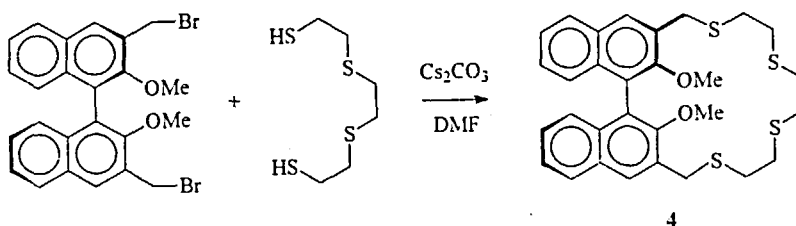
We have learned how to make thiocrown ethers. The most general route is by means of cesium thiolates as indicated in general terms in eq. 2 and as shown for a specific example 4 in eq. 3.<sup>8</sup>

equation (2)



X = halide, OMs, OTs

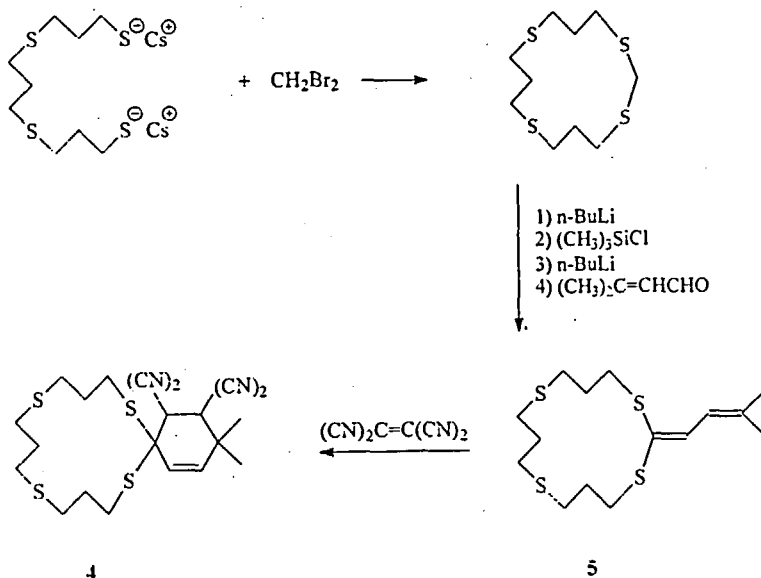
equation (3)



This approach is broadly applicable and we have made numerous thiocrown ethers and have studied their complexing abilities and reactivity.

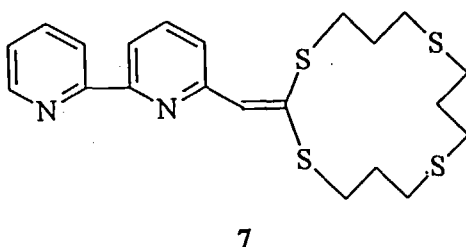
An interesting way, not available to oxa- and azacrown ethers, to achieve functionalization of the periphery of the macrocyclic chain is via the Peterson olefination reaction using a thioketal; the well-studied reactions of 1,3-dithiane are the model for how to do this.<sup>9</sup> An example of the synthesis of diene 5 followed by a Diels-Alder reaction to provide 6 is shown in eq. 4. Compound 7 is an interesting two site complexing agent.

equation (4)



Compounds with nonlinear optical properties can be prepared as two site complexing agents.

structure 7

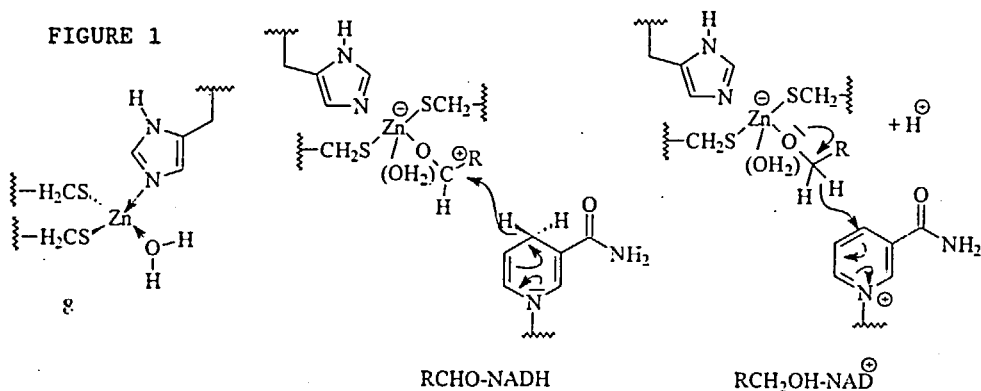


### Models for liver alcohol dehydrogenase

The preorganization intrinsic to a macrocyclic system has undisputed use to achieve encapsulation of a particular guest ion or molecule. The synthetic price must be paid, however. The use of non-macrocyclic systems can be simpler and in many cases equally effective.

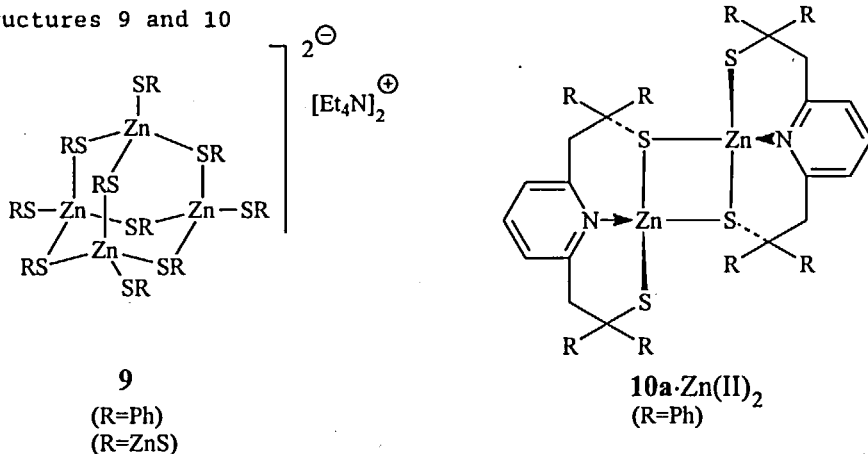
This can be illustrated with the catalytically active metal center of liver alcohol dehydrogenase (8). The center is well known to involve in the resting state a Zn(II) ion coordinated to two cysteine residues, the imidazole of a histidine and a water molecule. This is illustrated in Fig. 1 together with the basic elements of the reactions catalyzed by liver alcohol dehydrogenase, namely oxidation of an alcohol to an aldehyde (ketone) or the reverse reduction of the aldehyde (or ketone). The catalytic center behaves amphoterically.<sup>10</sup>

FIGURE 1



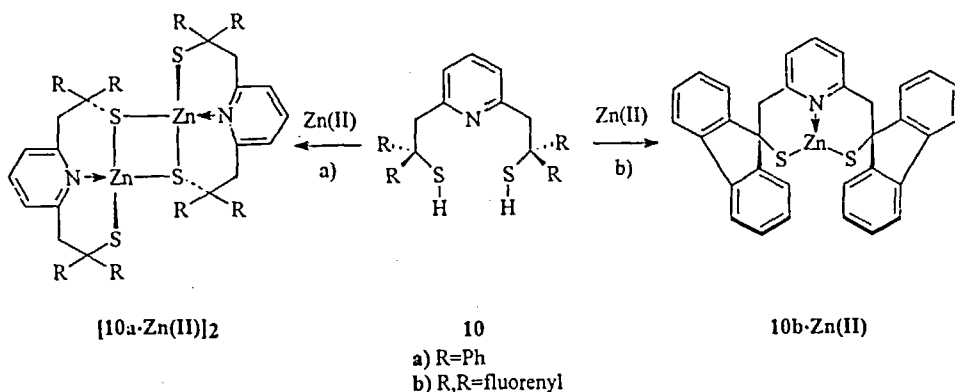
The past several years we have been interested in constructing model compounds in which this coordination at Zn(II) is present. This is a challenge. Zinc thiolates are not monomeric; they tend to oligomerize to structures like 9 or [10a·Zn(II)]<sub>2</sub>. The thiolate bridges between two Zn(II) ions and the dimeric structures that are formed can oligomerize further.

structures 9 and 10



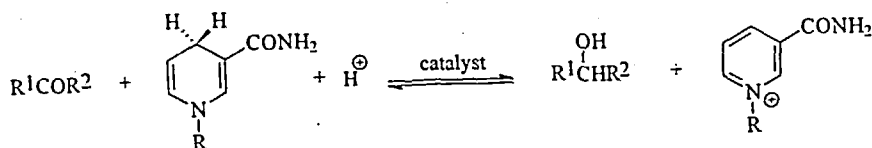
An example of some years ago of how to obtain a monomeric zinc thiolate is provided in eq. 5.<sup>11</sup> The formation of the dimer  $[10a \cdot Zn(II)]_2$

equation (5)



is stopped on introduction of the very bulky fluorenyl groups; monomer  $10b \cdot Zn(II)$  is formed. Unfortunately the  $Zn(II)$  ion in  $10b \cdot Zn(II)$  is so protected that apparently nothing can reach it; we have seen no catalytic activity with this complex, our hope being to mimic the redox reactions summarized in eq. 6.

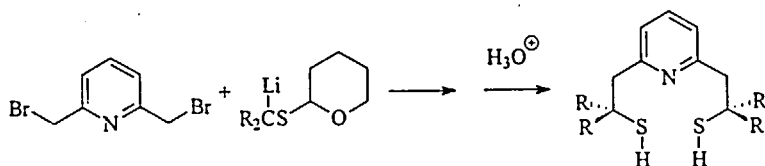
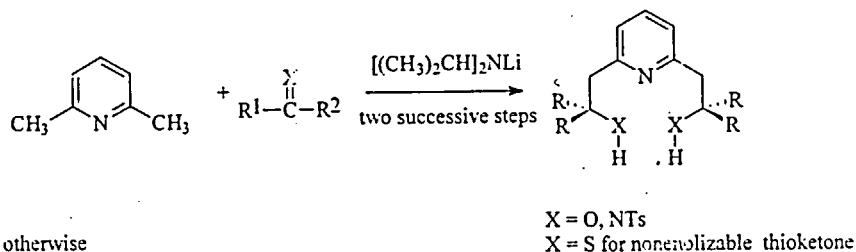
equation (6)



The synthesis of ligands like  $10a,b$ , which we refer to by the trivial name "pyridine dithiol", requires some comment. In recent months we have concentrated on the synthesis of such compounds and we are now able to prepare these materials pretty much at will although the yields are not always as good as we would like.<sup>12</sup> Not only the dithiols but the diols and diamines are available by the synthetic approaches summarized in eq. 7. Far less work has been done on the reactions and reactivity.

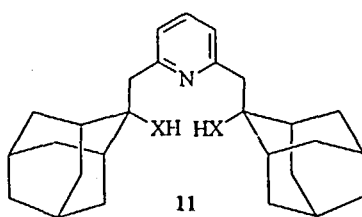


equation (7)

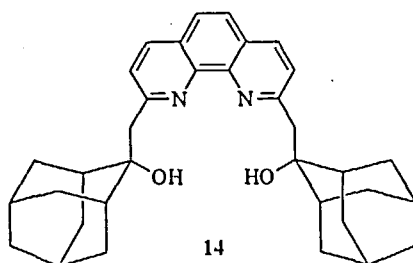
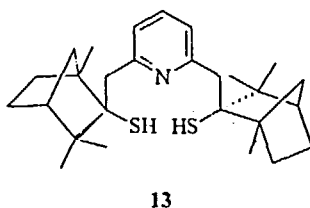
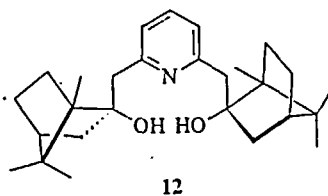


Particularly useful examples (more useful than the fluorenone used for the synthesis of 10b) involve the use of adamantanone derivatives, camphor and (thio)fenchone. This provides entry into bulky achiral structures like 11, and the chiral examples 12 and 13. Although not illustrated "mixed" compounds can be prepared with two different arms. The reaction can readily be extended to phenanthroline as illustrated with compound 14. The corresponding thiol remains to be synthesized.

examples 11 to 14

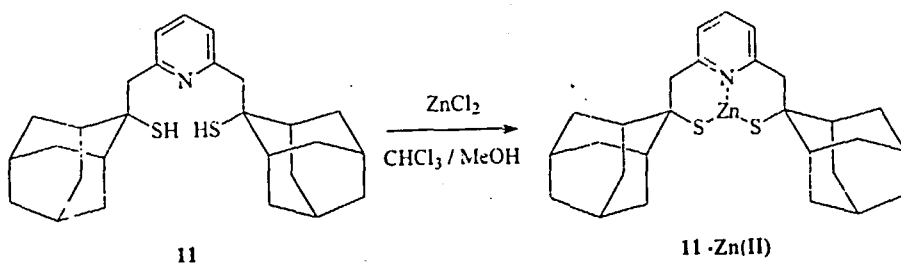


$X = O, S, NTs$



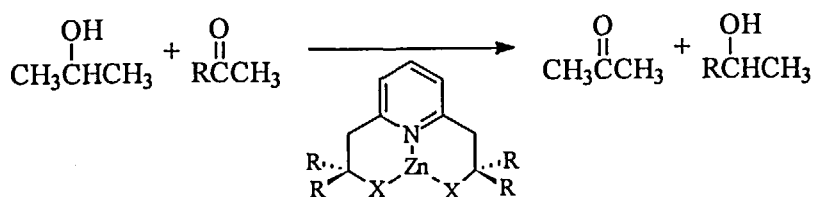
The adamantyl derivative 11 complexes cleanly with  $Zn(II)$  to provide  $11(X=S) \cdot Zn(II)$  as shown in eq. 8.<sup>12b</sup> The crystal

equation (8)



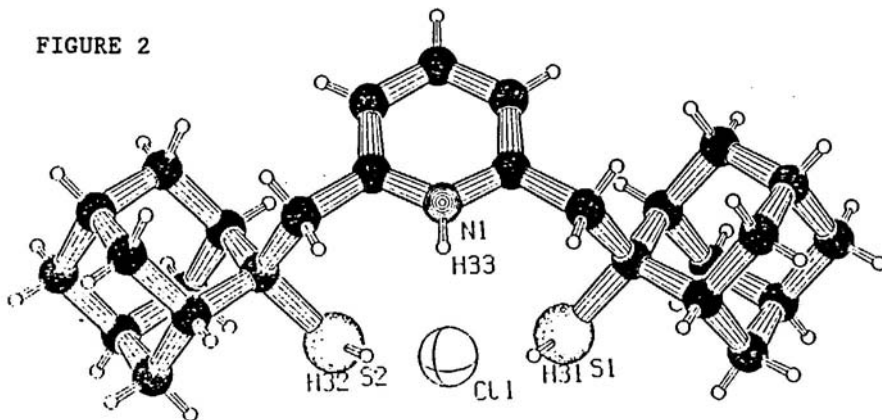
structure of this complex is currently being determined. On the basis of preliminary experiments it appears that  $11(X=S)Zn(II)$  will dimerize but that the dimerization is an equilibrium that lies on the monomer side. Complexation with methanol also seems to occur. This indicates that  $Zn(II)$  in the monomer is accessible and that the monomer does not fall into an irreversible thermodynamic hole of a dimeric structure. We have not yet examined  $11(X=S).Zn(II)$  as a catalyst for reductions of carbonyl compounds by model 1,4-dihydropyridines or reduction of the corresponding pyridinium salts ( $NAD^+$  models) by alcohols. The reactivity of such compounds (the corresponding complex from the pyridine *diol* may be a better candidate) in Meerwein-Ponndorf-Verley reductions remains also to be examined (eq. 9).<sup>13</sup>

equation (9)



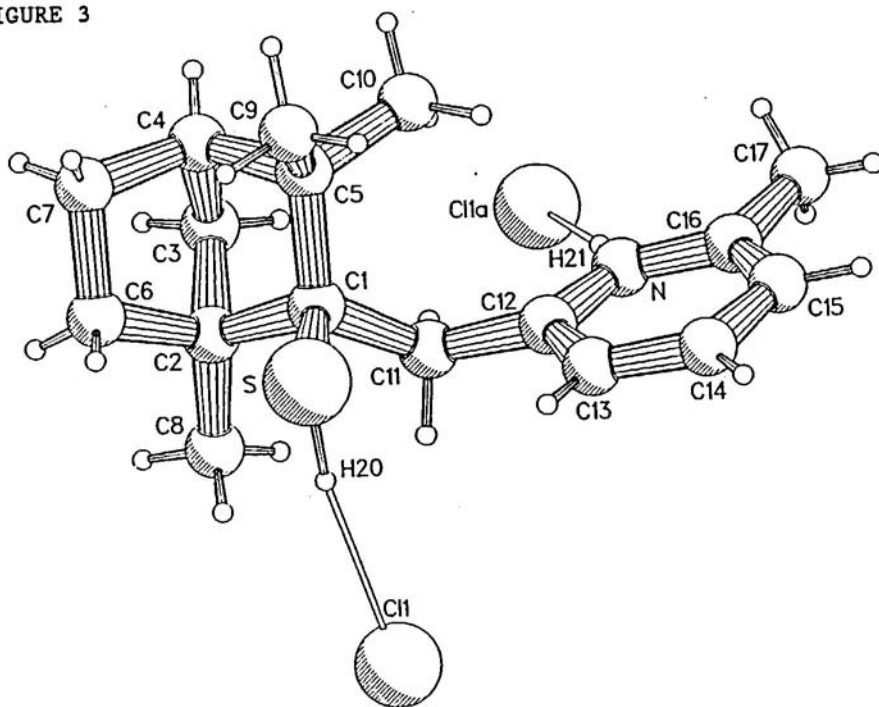
Not unsurprisingly all the pyridine thiol, diol and amine derivatives are avid complexing agents for metal ions. Some of the complexes and their behaviour have been previously described.<sup>14</sup> Acids are also complexed. In Figure 2

FIGURE 2



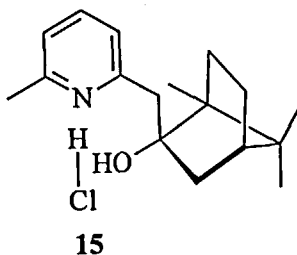
the structure of the HCl complex with 11(X=S) is shown together with that of the previously published complex with the corresponding diol 11(X=O).<sup>12a</sup> Both structures have much in common. The chloride is held fast by hydrogen bonds and the proton of HCl is hydrogen bonded to nitrogen. The HCl bond length in 11(X=S) (within the accuracy of the X-ray structural determination) is 2.19Å and 2.21Å in 11(X=O), consistent with a neutral HCl molecule rather than ionic  $H^+$ ,  $Cl^-$ . On the basis of currently available information we tend towards a covalent HCl molecule encapsulated by the two arms of 11 and 12. At least in the crystal the singly armed derivative 15 (Fig. 3)

FIGURE 3



seems to have a different type of HCl (bond length 2.48Å). Such conclusions must be drawn with caution, however; the HCl lies on a symmetry axis in the doubly armed molecules and this can lead to systematic crystallographic errors in, for example, corrections for thermal movement.

structure 15

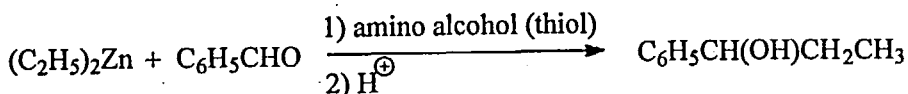


The availability of chiral derivatives like 13 derived from thiofenchone offers the unusual possibility of carrying out asymmetric additions of HCl. We are not aware of any precedent for this. This possibility is actively under investigation (as well as the possibility of carrying out asymmetric addition reactions of other complexed acids). The diol complexes are also being used. Preliminary results are promising; conditions have been worked out to open prochiral epoxides to the chlorohydrins. Moderate enantiomeric excesses are observed; it is not clear at the moment whether the enantiomeric excesses simply are not too high or whether there is competition from decomplexation of HCl followed by an achiral reaction in solution.

We hope that complexes like  $11(X=S).Zn(II)$  will be active in the promotion of hydride transfer reactions like those given in generic terms in Fig. 1. This would be direct mimicking of the action of the catalytically active zinc in liver alcohol dehydrogenase. Unfortunately at the time of writing no experiments in this direction have been carried out. This work has, however, high priority and will soon be undertaken.

Pyridine thiols and diols are also inducers of the addition of diethyl zinc to benzaldehyde (eq. 10).

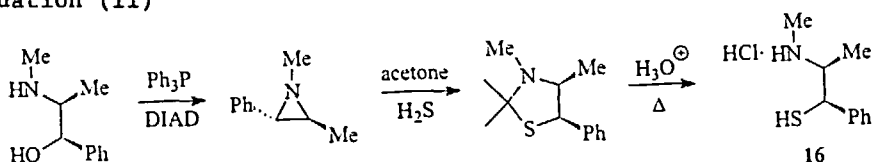
equation (10)



Both the *singly armed* alcohol 15a and thiol 15b are excellent inducers of the addition although only the alcohol leads to high enantiomeric induction. The *doubly armed* derivatives like 12 and 13 are very reactive but, as far as we have been able to ascertain, no 1-phenyl-1-propanol is formed. Clearly the Zn of diethyl zinc is trapped in a complex analogous to 10b.Zn(II) that is incapable of proceeding further as catalyst.

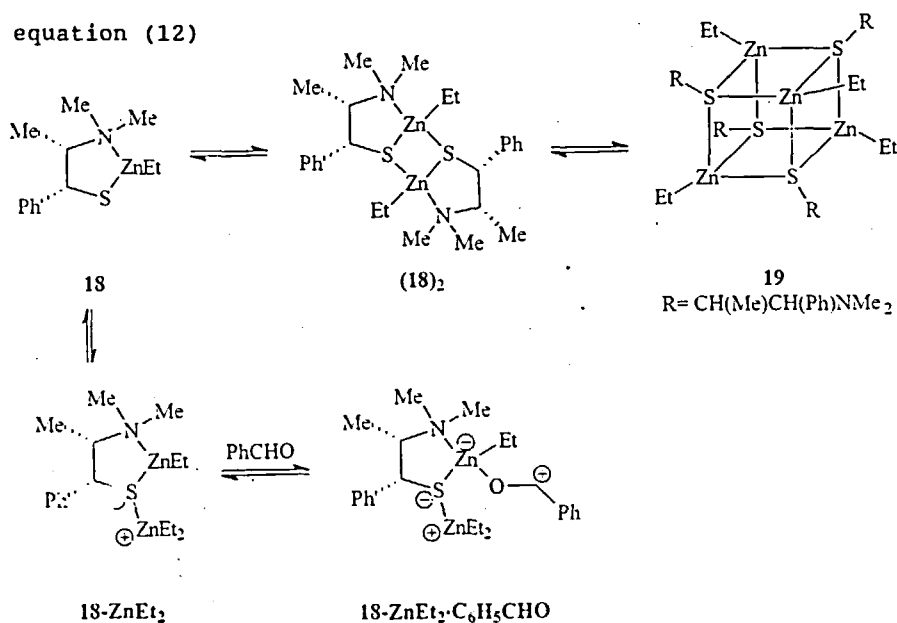
This postulation is based on a reasonable understanding of how pyridine thiols will induce the reaction of eq. 10. In earlier work we prepared ephedrine thiol 16 and pseudoephedrine thiol 17 by the route summarized in eq. 11.

equation (11)



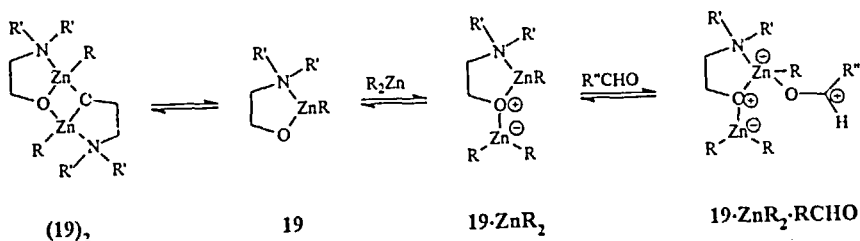
Particularly 16 turned out to be a very good inducer of the addition of  $(C_2H_5)_2Zn$  to benzaldehyde; 1-phenyl-1-propanol is obtained in virtually quantitative yield and 94% e.e.<sup>15</sup>

equation (12)



On the basis of mechanistic studies<sup>16</sup> as well as literature precedent we are quite sure that a catalytic species is the *monomer* 18. This is entirely analogous to the monomeric intermediate formed when amino alcohols are used as inducers (eq. 13).<sup>17</sup> The latter reactions have been

equation (13)



thoroughly examined by Noyori and coworkers. On the basis of osmometric measurements we believe that oligomerization can proceed as far as cubane structure (19); the formation of this species probably lies at the heart of a significant positive nonlinear effect in asymmetric induction that has been observed.<sup>16</sup>

A species like 10b.Zn(II), although monomeric, is apparently not capable of catalytic activity because it is no longer an alkyl zinc. The monomer (18) is still an alkyl zinc and complexes an extra equivalent of dialkyl zinc.

## Conclusions

This overview has sulfur as main theme. The brief mention of thiocrown ethers concentrates mostly on synthesis and neither does justice to the sulfide linkage as a ligand for transition metals nor does it pay enough attention to the *catalytic* potential of many of these metal complexes. Our observations have been that sulfide often can replace phosphine (it coordinates in general less strongly, that is true) and this can be of industrial interest.

Alcohol dehydrogenase provides a central theme for the study of thiol containing ligands. Most of the attention is devoted to Zn(II) as metal and the complexities of (de)aggregation dominate the chemistry. Such phenomena lie also at the heart of the observed catalytic reactivity. Little is said of the attractive prospects of these ligands for the complexation of other metal ions. A broad catalytic chemistry involving such ligands is starting to emerge in our group and our hope is that this will form the basis of future reports.

### Acknowledgement

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