İSTANBUL TECHNICAL UNIVERSITY ★ INSTITUTE OF SCIENCE AND TECHNOLOGY

SYNTHESIS OF OXAZOLINE SUBSTITUTED NAPHTHOFURANO NAPHTHOFURAN

M.Sc. Thesis by

Chemist and Chemical Engineer Rubabe ŞİNASİ

Department : Chemistry

Programme : Chemistry

Supervisor: Prof. Dr. Naciye TALINLI

JANUARY 2007

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Date of Submission: 25 December 2006

Date of Defence Examination: 29 January 2007

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	Prof. Dr. Ahmet AKAR

JANUARY 2007

İSTANBUL TEKNİK ÜNİVERSİTESİ ★ FEN BİLİMLERİ ENSTİTÜSÜ

OKSAZOLİN SÜBSTİTÜE NAFTOFURANONAFTOFURAN SENTEZİ

Yüksek Lisans Tezi

Kimyager ve Kimya Müh. Rubabe ŞİNASİ

509031231

Tezin Enstitüye Verildiği Tarih : 25 Aralık 2006

Tezin Savunulduğu Tarih : 29 Ocak 2007

Tez Danışmanı : Prof. Dr. Naciye TALINLI

Diğer Jüri Üyeleri: Prof. Dr. Birgül TANTEKİN ERSOLMAZ

Prof. Dr. Ahmet AKAR

OCAK 2007

ACKNOWLEDGEMENT

This Master study has been carried out at Istanbul Technical University, Chemistry Department of the Science & Letter Faculty.
I would like to express my gratitude to my thesis supervisor, Prof. Dr. Naciye TALINLI and co-supervisor Assoc. Prof. Okan SİRKECİOĞLU for offering invaluable help in all possible ways, continuous encouragement and helpful critics throughout this research.
I would also like to thank to my colleagues Volkan KUMBARACI, Duygu ERGÜNEŞ, Murat GÜLÇÜR, and A. Dilek TANRIGÖRÜR for their friendly and helpful attitude during my laboratory works.
Finally, I would like to dedicate this thesis to my mother, father, brother, and friend Hakan HABERDAR for their patience, understanding and moral support during all stages involved in the preparation of this thesis.

Rubabe ŞİNASİ

January 2007

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ABBREVIATIONS

TLC : Thin Layer Chromatography
DMSO : Dimethyl Sulphoxide
DMF : Dimethyl Formamide
GC-Ms : Gas Chromatography-Mass spectroscopy
r.t. : Room Temperature
pm : Picometers
EtOAc : Ethyl acetate

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OKSAZOLİN SÜBSTİTÜE NAFTOFURANONANAFTOFURAN SENTEZİ

ÖZET

En az bir metal-karbon bağı içeren bileşiklerin kimyası olarak tanımlanan organometalik kimya, yirminci yüzyılın ikinci yarısında disiplinler arası yeni bir bilim dalı olarak ortaya çıkmış ve yüzyılın sonuna doğru çok hızlı bir gelişme göstermiştir.

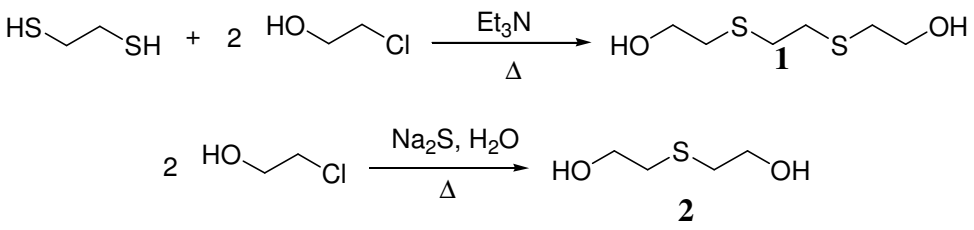
Metal katalizli reaksiyonlarda, özellikle geçiş metali, bileşiği veya organometalik bileşiği katalizör olarak kullanılır. Metal katalizinde ligand, katalizör yapısında veya reaksiyon ortamında katılır. Ligand kullanılarak, reaksiyonun hızı, verimi ve kimyasal seçiciliği kontrol edilebildiği gibi, asimetrik ligand kullanılarak stereoseçicilik de sağlanabilir. Metal katalizli reaksiyonlarda ligandla hızlandırılmış kataliz, laboratuarda ve endüstride çok önemlidir; fakat ligandla yavaşlatılmış kataliz konusunda çok az araştırma yapılmıştır [1].

Bu çalışmada çok dişli ligand karakterinde heteroatom içeren *yeni* halkalı bileşiklerin sentezi amaçlanmıştır. Bu bileşiklerin metal bağlama kabiliyetine sahip olup katalitik aktivite gösterecekleri beklenmektedir. Bu bağlamda iki ana bileşik grubu seçilmiştir: bis-taç eterler ve bis-oksazolinler.

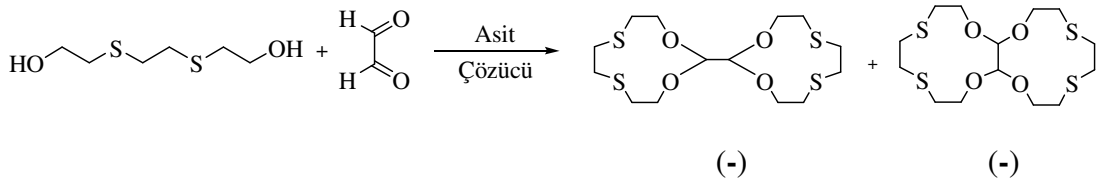
İlk aşamada taç eterler, asetalleşme metodunun kullanılması ile literatürde var olan yöntemlerden farklı olarak daha basit bir şekilde sentezleneceklerdir. Yeni bir yöntem kullanılarak sentezlenecek olan hedef taç eterler de yeni olup literatürde yer almamaktadırlar.

Merkaptanların aldehit ve ketonlara katılması sonucu hemimerkaptal ve tiyoasetal oluşur. Bu reaksiyon aldehit ve ketonların korunması için kullanılabilir. Bu çalışmada glioksal ve malonaldehit gibi 2 karbonil grubu içeren aldehitlerden yola çıkarak, çeşitli tiyol bileşikleri ile asetalleşme reaksiyonu sonucunda, oksijen ve kükürt içeren halkalı bileşikler olan taç eterlerin (crown ether) sentezlenmesi amaçlanmıştır. Taç eterler arasında oluşacak köprüdeki "n" karbon sayısının sandviç etkisi incelenecektir. Taç eter sentezi sırasında halka oluşumunu kolaylaştırmak amacıyla kalıp (template) etkisinden yararlanılacaktır.

Halkalı asetal oluşumu için önce kükürt içeren diyol bileşikleri aşağıda gösterildiği gibi sentezlenmiştir.



Elde edilen bu bileşikler kullanılarak asidik ortamda sırası ile glioksal bisülfit ve malon aldehit gibi 2 karbonil grubu içeren aldehitlerle asetalleşme reaksiyonu yapılmıştır.



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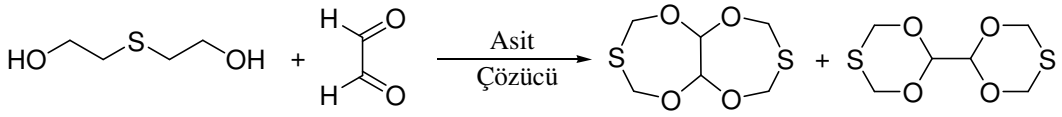

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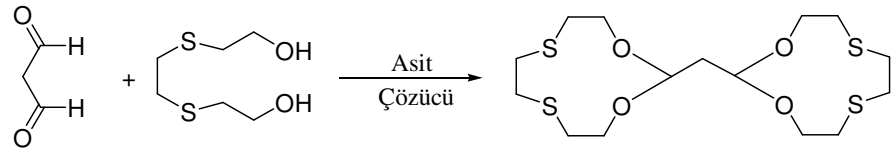
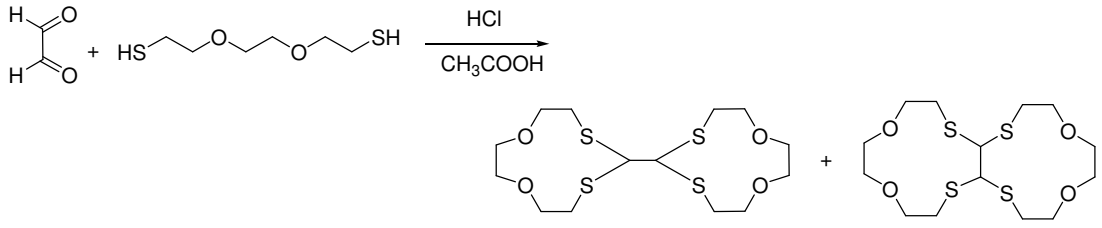
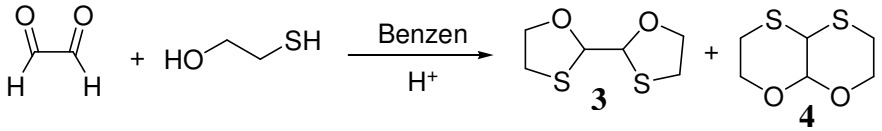


(-)

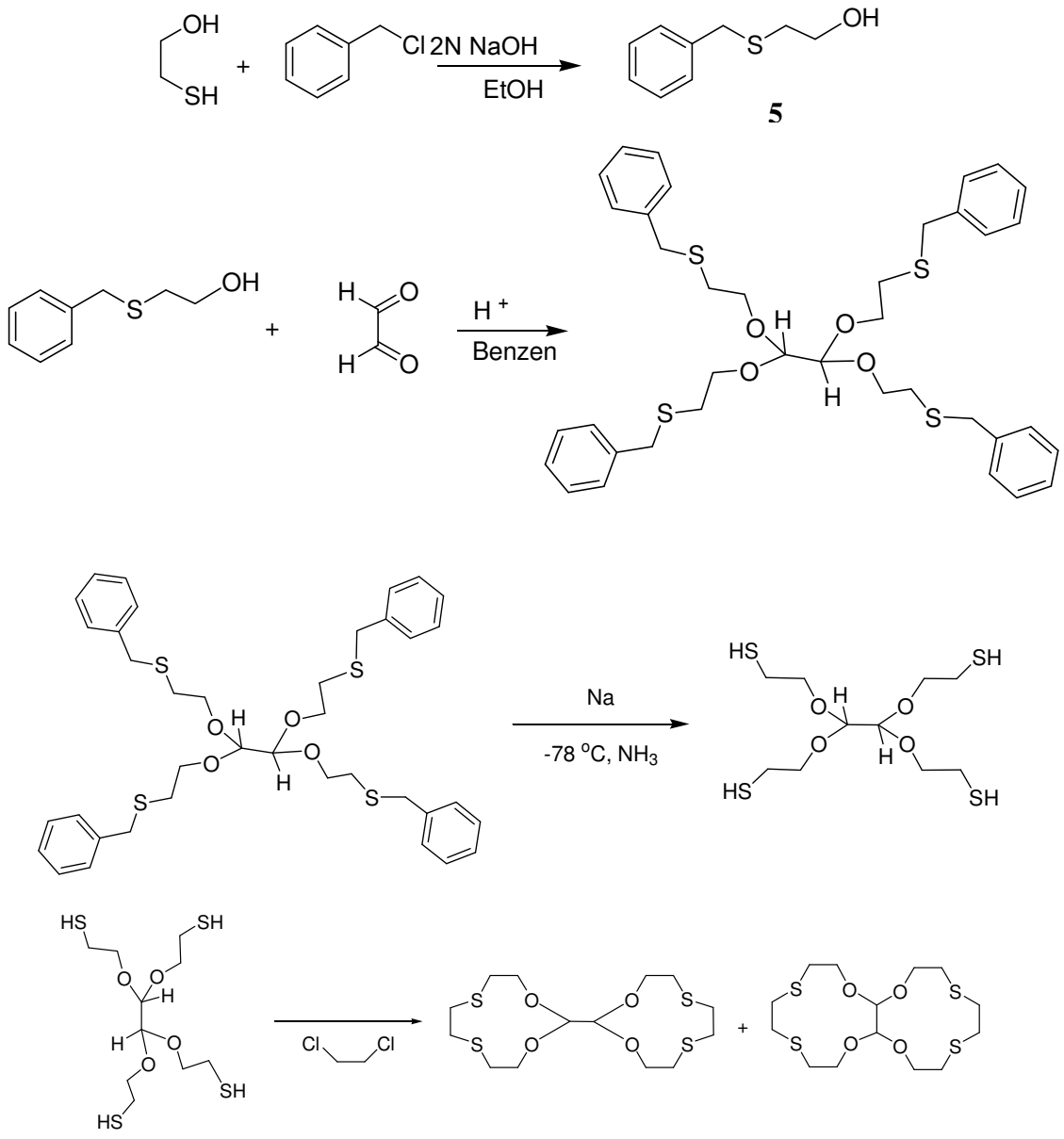
Ancak tüm denemelerde olumsuz sonuçlar elde edilmiştir. Daha önceki çalışmada aynı mekanizma kullanılarak ditiyol bileşikleri kullanılarak asetalleşme reaksiyonu ile istenilen ürünler sentezlenmiştir. Ditiyol bileşikleri ile elde edilen ürünlerin diyol bileşikleri ile elde edilememesinin sebebi, C–S bağlarının C–O bağlarına kıyasla daha kolay kırılabildiğidir.



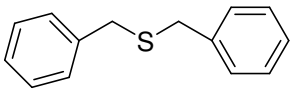
Bu sonucu onaylamak için benzer asetalleşme reaksiyonu 2-merkaptoetanol ve glioksal bisülfit ile denendi ve beklenen ürünler elde edilmiştir.



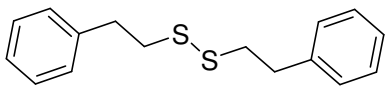
İstenen ürünleri elde etmek için diol yerine bir tane –OH grubu içeren bileşik kullanılarak glioksal bisülfit ve malon aldehit ile asetalleşme reaksiyonu sonunda tetraasetalik bileşikler sentezlenmesi için 2-merkaptoetanol'ün tiyol ucu benzil klorür ile bazik ortamda korunmuştur. Asetalleşme reaksiyonu gerçekleştikten sonra, –SH grubundaki koruma kaldırılıp, 1,2-dikloroetan ile halka kapatma reaksiyonu gerçekleştirilecektir.



Ancak glioksal bisülfit ile gerçekleştirilen asetalleşme reaksiyonundan istenen ürün yerine ağırlıklı olarak *dibenzilsülfan* elde edilmiştir.



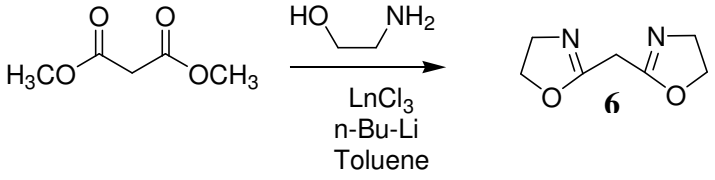
Aynı deneme malon aldehitle de denendi, istenen ürün yerine ağırlıklı olarak *[(benzilditiyo)metil]benzen* elde edildi.

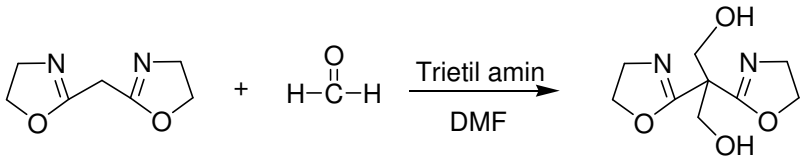


Sentezlemesi amaçlanan bileşiklerden olumsuz sonuçlar alınınca, çalışmanın ikinci kısmı olan bis-oksazolinlere geçilmiştir. Sentezlenecek olan bis-oksazolinler de yeni olup literatürde yer almamaktadırlar. Bu bileşik gurubu da taç eterler gibi metal

bağlama karakterindedirler. Bis-oksazolinler sentezlendikten sonra değişik metallerle oluşturdukları ligandların katalitik aktivite gösterip göstermedikleri incelenecektir. Bis-oksazolinlerin sentezi alifatik zincir veya aromatik halkaya bağlı olarak hedeflenmiştir. Bu bileşiklerin çok dişli ligand oluşturma olasılıklarının yanı sıra yeni bileşiklerin sentezlenmesine yardımcı olma yetenekleri de vardır.

Alifatik zincire bağlı olan oksazolin sentezi için aşağıda gösterilen adımlar gerçekleştirilmiştir. Bunun için dimetil malonat, etanol amin ile $LnCl_3$ katalizörlüğünde sentezlenmiştir.





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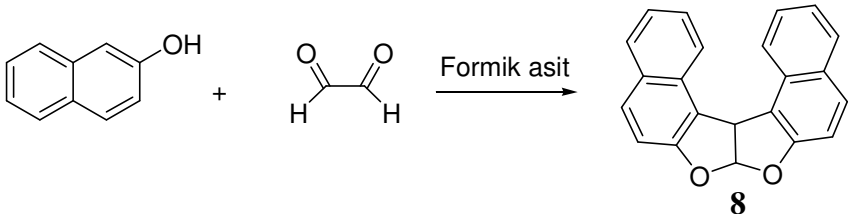
Aromatik halkaya bağlı oksazolin sentezi için naftofuranofuran halkası kullanılmıştır. Bunun için gerekli sentez aşamaları aşağıda gösterilmektedir.



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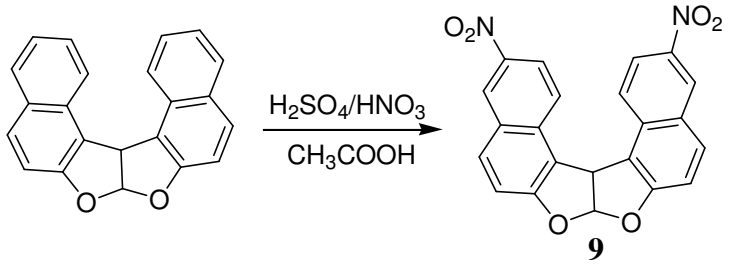

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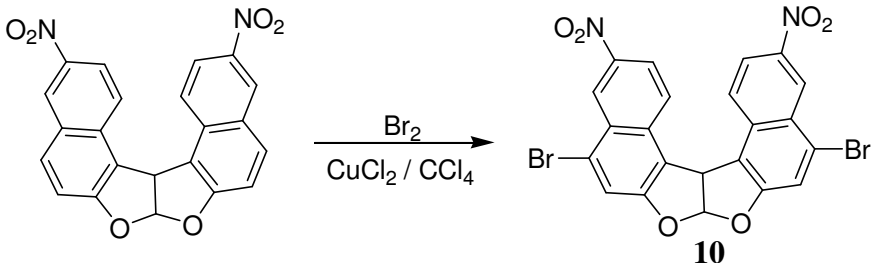

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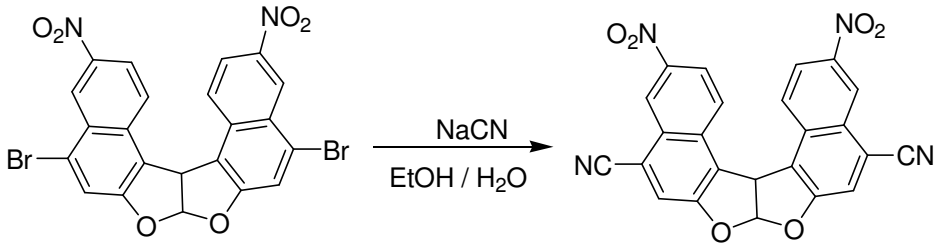
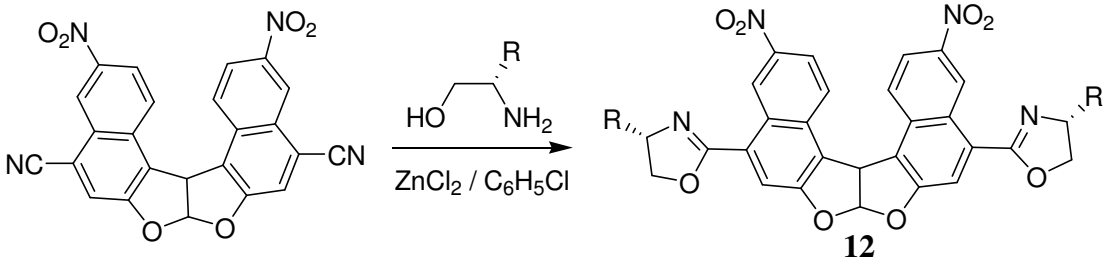

O2N
NO2
Br
Br
O
O
NaCN
EtOH / H2O
O2N
NO2
NC
CN
O
O

11


O2N
NO2
NC
CN
O
O
R
HO
NH2
ZnCl2 / C6H5Cl
O2N
NO2
R
N
O
N
R
O
O
O

12

R = H, -C_6H_5

SYNTHESIS OF OXAZOLINE SUBSTITUTED NAPHTHOFURANO NAPHTHOFURAN

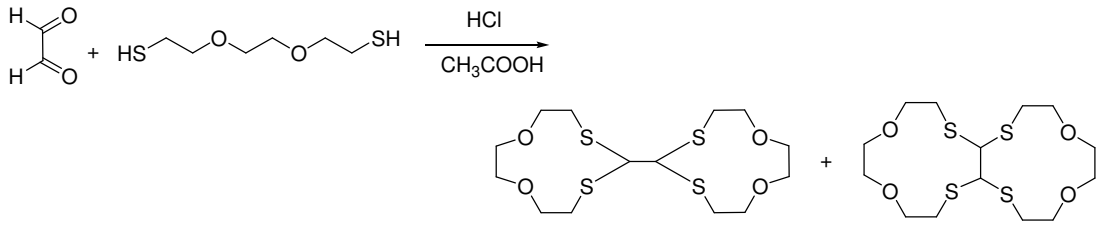
SUMMARY

The main objective of this research project has been the development and exploration of novel, supramolecular catalyst systems that are formed by the assembly of several components using non-covalent interactions. The supramolecular strategy involves the multicomponent assembly of a transition metal catalyst and various building blocks into a new supramolecular catalyst system [1].

For the preparation of these assembled catalysts, selective metal-ligand interactions have been used that control the coordination geometry around the catalytically active metal center and the final shape of the supramolecular catalyst system. Suitable homogeneous transition metal catalysts in combination with properly chosen molecular building blocks led to assembled catalyst systems that improve catalytic properties such as activity and selectivity.

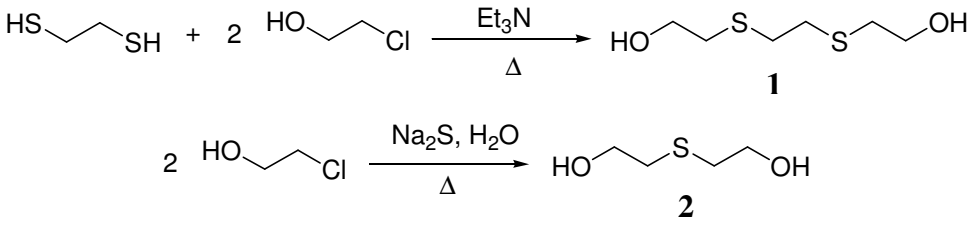
The aim of this project is to synthesize *novel* cyclic compounds containing heteroatoms that act as polydentate ligands and have the ability of both binding metals and the catalytic activity. Two main groups of compounds have been chosen as polydentate ligand compounds: bis-crown ethers and bis-oxazolines.

For the first step of this study we began with synthesizing of different and novel crown ethers containing both oxygen and sulfur atoms together. Crown ethers are generally synthesized using Williamson ether synthesize by forcing of high dilution or template effect methods. The reactions carry out with treatment of the diols and dihalide derivatives in the presence of a base. However, different from the above-mentioned method, bis-crown ethers were prepared by the thioacetalization reaction in the previous study. In that study, glyoxal bisulfite reacted with dithiol in the presence of acid catalyst and two types of crown ethers were produced.

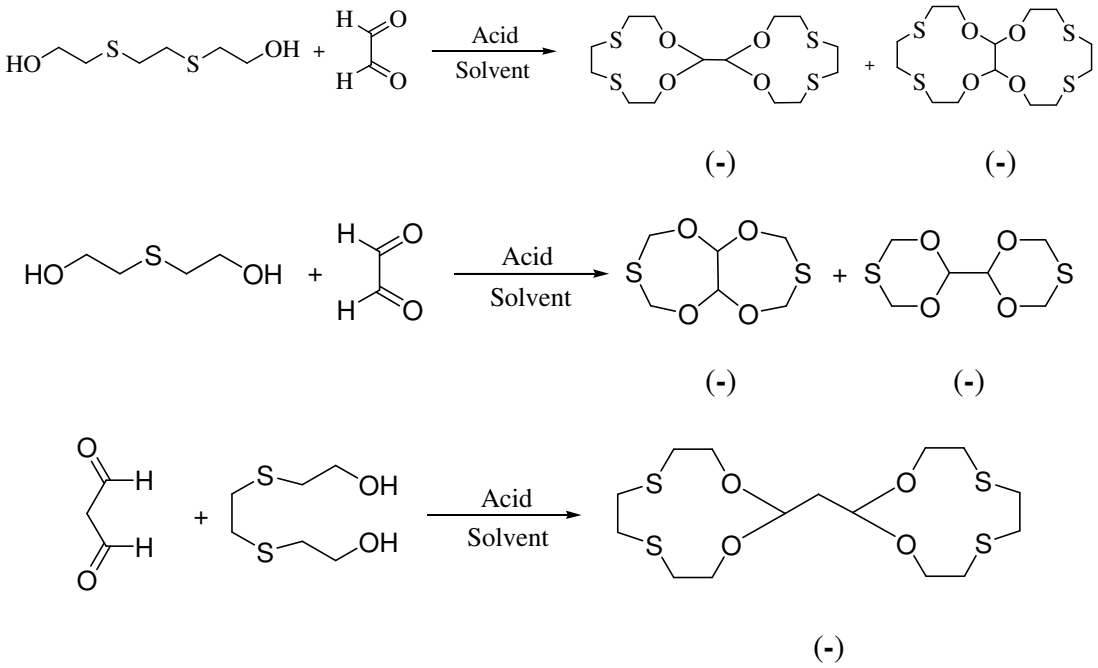


In this study bis-crown ethers were targeted to synthesize by using acetalization reaction that is a new synthesizing method for crown ethers. For this aim mercaptanes and different types of thiol compounds would be reacted with dialdehyde compounds as glyoxal bisulfite and malonaldehyde in an equilibrium process to yield compounds as acetals. This reaction can be used to protect the carbonyl group of aldehydes and ketons. The sandwich effect of two rings that connected with a bridge of “n” number of carbon atoms in one molecule crown ether will be investigated.

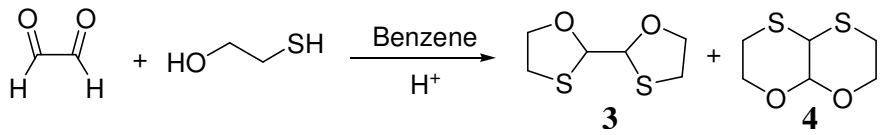
To synthesize cyclic acetals, sulfur-containing diols were synthesized.



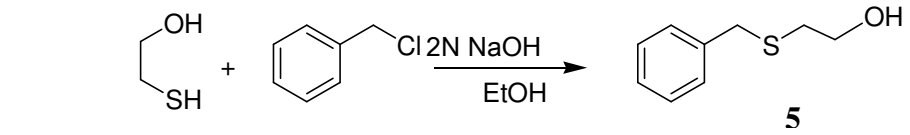
The expected acetalization reactions of **1** and **2** with glyoxal bisulfite and malon aldehyde are as the following reactions. However, the reactions failed and any of the products did not form.



The reason why the reactions, which occurred with dithiol compounds did not succeed with diols is that the C–S bonds can easily break when compared to C–O bonds. In order to confirm this result, similar acetalization reaction was tried with 2-mercaptoethanol and glyoxal, and expected products were obtained.



To achieve desired products another synthesizing method was tried. According to the new method, tetraacetalic compounds will be prepared from dicarbonyl compounds and S-protected thioalcohols. After deprotection reaction free –SH groups will be obtained, then ring closure will be realized with 1,2-dichloroethane as formulated below.



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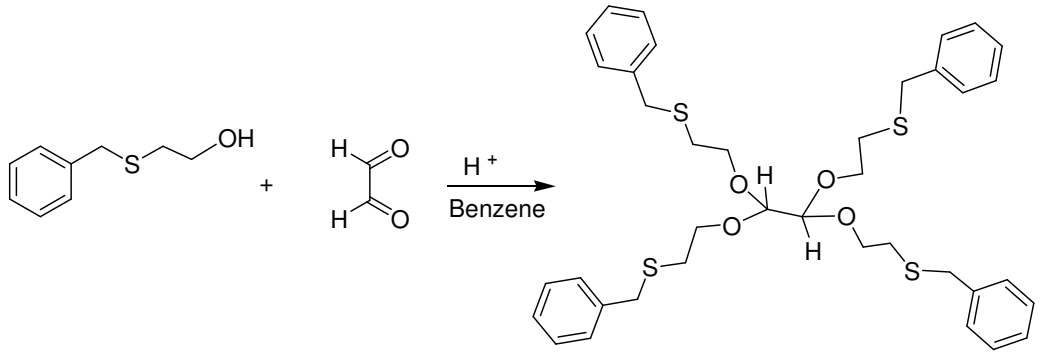
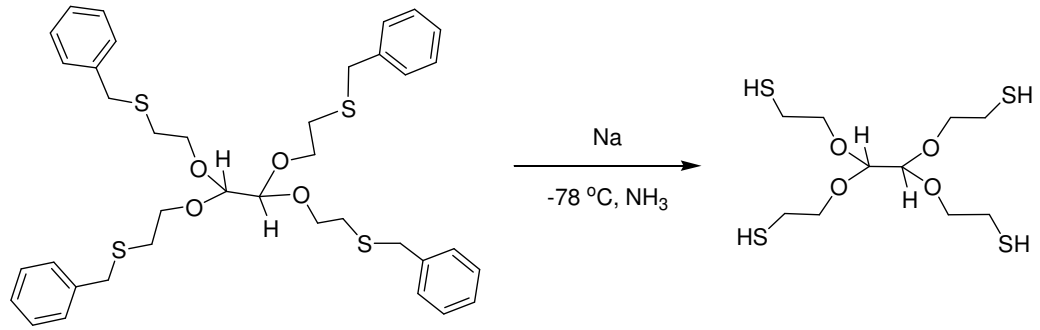
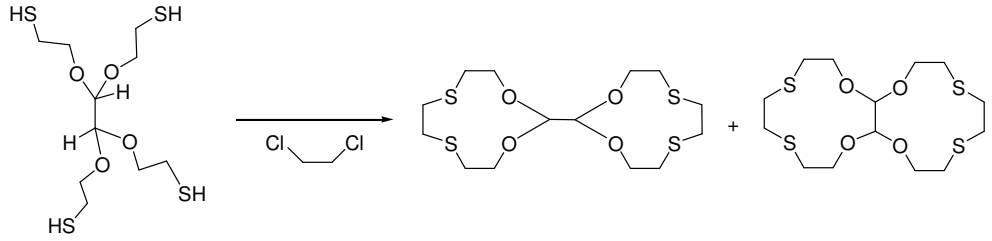
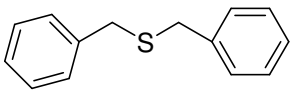


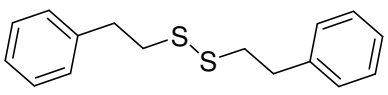




Unfortunately, instead of desired product predominantly another product, *dibenzylsulfane*, produced which is shown below.

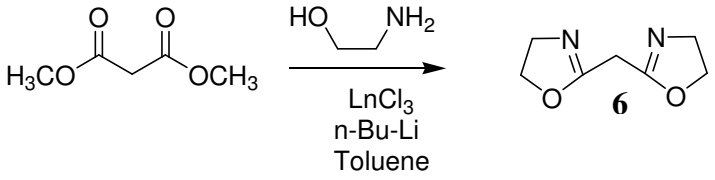


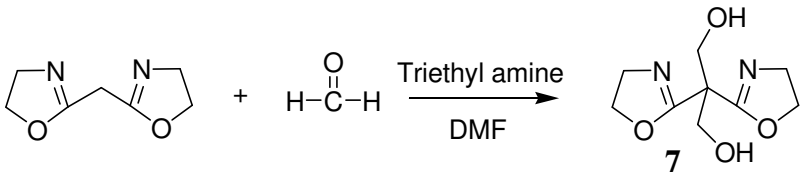
The same acetalization reaction was tried with malonaldehyde. Again instead of desired product predominantly obtained another product: *[(benzyldithio)methyl]-benzene*, which is shown below.



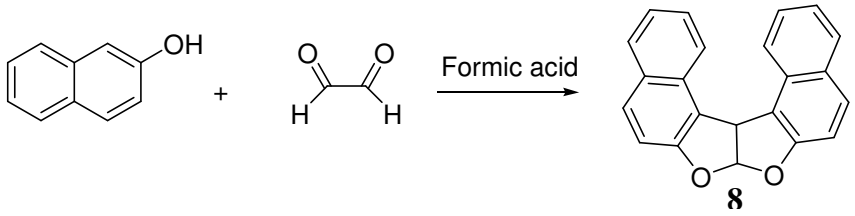
The results of the reactions were not in accordance with the expectations. So the work is continued with the second part: synthesis of bis-oxazolines. The targeted bis-

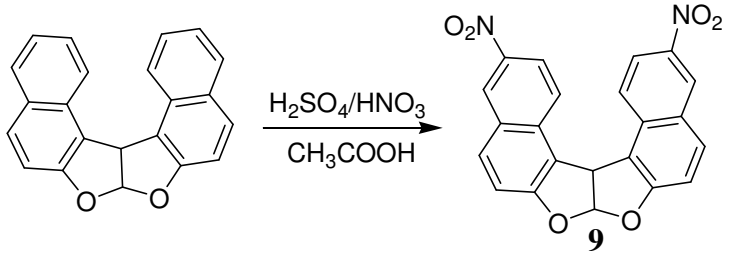
oxazoline compounds attached to aliphatic chain were synthesized from the reaction of malon ester, ethanolamine, n-Bu-Li as base, and $LnCl_3$ as catalyst.

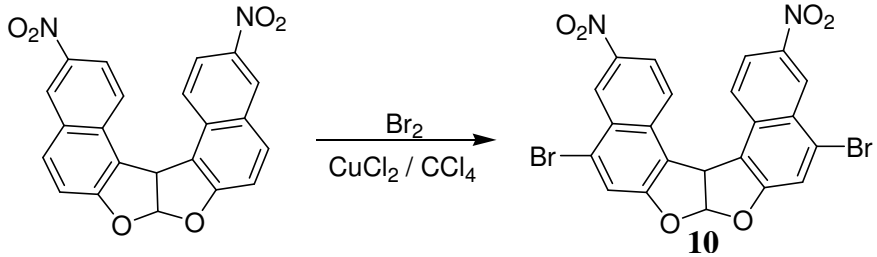


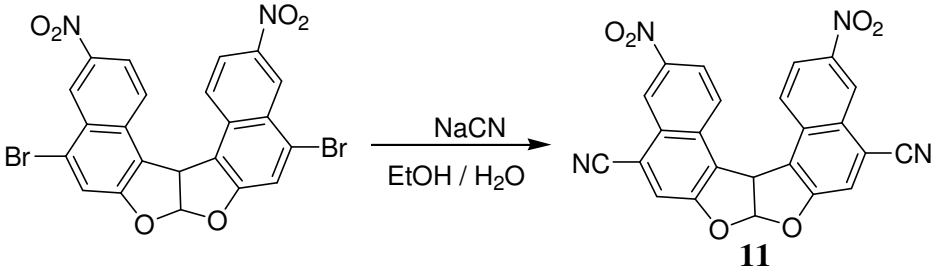


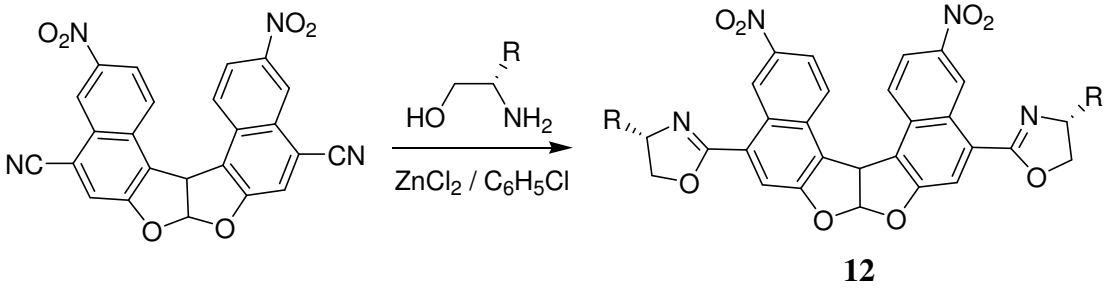
To obtain oxazoline rings as a part of aromatic ring, we worked with naphthofuranonaphthofuran obtained from β-naphthol and glyoxal in the presence of formic acid. Steps of synthesizing bis-oxazoline rings as a part of aromatic ring is summarized below.











12

R = H, -C_6H_5

1. INTRODUCTION

The metal-ion and host-guest chemistry of macrocyclic ligands has developed rapidly over recent years and now impinges on wide areas of both chemistry and biochemistry [2]. The great promise of organometallic chemistry lay in the ability to isolate and then utilize novel organic fragments bonded to a transition metal center [3].

It would be difficult to exaggerate the importance of catalysts, since almost nine-tenths of the chemicals manufactured throughout the world involve the use of catalysts at some stage in the manufacturing process. Yet for all its importance and longevity, the first reported conscious use of catalysts was by Berzelius in 1835. Catalyst users are faced with a bewildering variety of data, concepts, and theories, having little apparent order or organization [4].

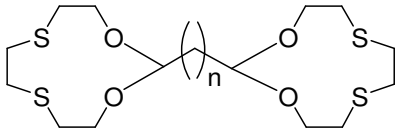
Historically, the first theory of catalysis was developed by Sabatier (1918), who adopted a chemical approach and emphasized the importance of considering the catalyst as part of a chemical system in which a transitory, unstable intermediate was formed on the catalyst surface. This was followed by the geometric theory based mainly on the work of Balandin (1929), who suggested that the activity of a catalyst was determined by the presence on the surface of appropriate multiplets (i.e., groups) of atoms having the correct geometry and lattice spacing to accommodate reactant molecules and facilitate their dissociation [4].

It is generally accepted that the best way of interpreting the differences in the catalytic properties of metals is by considering only the local environment of the active site. The individual surface atom model, which expresses this view, emphasizes the unique properties of each metallic element and draws comparisons with well-established principles in organometallic chemistry [4].

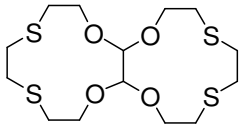
The aim of this project is to synthesize novel cyclic compounds containing heteroatoms that act as polydentate ligands and have the ability of both binding metals and the catalytic activity. Two main groups of compounds have been chosen as polydentate ligand compounds: bis-crown ethers and bis-oxazolines.

The first part of the project is about new type of crown ethers –bis crown ethers– containing both oxygen and sulfur atoms together by using a new method. Crown ethers are generally synthesized using Williamson ether synthesize by forcing of high dilution or template effect methods. The reactions carry out with treatment of the diols and dihalide derivatives in the presence of a base. In this study bis-crown ethers are targeted to synthesize by using acetalization reaction that is a new synthesizing method for crown ethers.

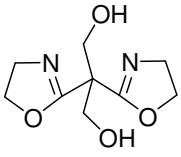
For this aim mercaptanes and different types of thiol compounds would be reacted with dialdehyde compounds as glyoxal bisulfite and malonaldehyde in an equilibrium process to yield compounds as acetals. This reaction can be used to protect the carbonyl group of aldehydes and ketons. The sandwich effect of two rings that connected with a bridge of "n" number of carbon atoms in one molecule crown ether will be investigated. The targeted compounds are shown below.

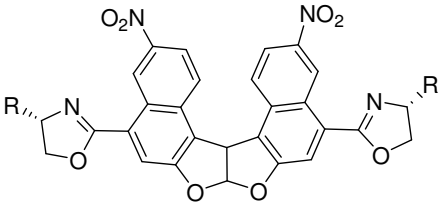


n= 0, 1, 2, 3



The second part of the project is about synthesizing of new type of bis-oxazolines member of both aliphatic chain and aromatic ring. The aim of the synthesizing bis-oxazolines is same as the synthesizing crown ethers: to synthesize novel cyclic compounds containing heteroatoms that act as polydentate ligands and have the ability of both binding metals and the catalytic activity. The targeted bis- oxazoline compounds are given below.





R = H, -C_6H_5

The targeted bis-oxazoline compounds attached to aliphatic chain would be synthesized from the reaction of malon ester, ethanolamine, n-Bu-Li as base, and $LnCl_3$ as catalyst. To obtain oxazoline rings as a part of aromatic ring, naphthofuranonaphthofuran obtained from β-naphthol and glyoxal in the presence of formic acid would be used.

2. LITERATURE REVIEW

Organometallic Compounds: Compounds that contain carbon-metal bonds are called organometallic compounds. The nature of the carbon-metal bond varies widely, ranging from bonds that are essentially ionic to those that are primarily covalent. Whereas the structure of the organic portion of the organometallic compound has some effect on the nature of the carbon-metal bond, the identity of the metal itself is of far greater importance [5,6].

Metal-Catalyst: The production of enantiopure compounds is becoming more and more important in the field of pharmaceuticals, flavors, fragrances, and agrochemical agents; thus, several industrial processes using asymmetric catalytic reactions have been developed. Most of these processes comprise the use of homogeneous catalysts that have the disadvantage of difficult separation and reuse of the expensive catalysts employed [7]. Increasing numbers of effective catalysts (in terms of enantioselectivity, turnover number, and substrate compatibility) have been discovered [8].

Homogeneous catalysis has been responsible for many major recent developments in synthetic organic chemistry. The combined use of organometallic and coordination chemistry has produced a number of new and powerful synthetic methods for important classes of compounds in general and for optically active substances in particular. For this purpose, complexes with optically active ligands have been used, most of them coordinating through phosphorus. More recent developments have highlighted the use of "nitrogen-donors", particularly as they are easily obtained from the "chiral pool. However, the remarkable achievements in this area have been based on an empirical approach [9].

Asymmetric induction with chiral metal-catalysts has been recognized as depending mainly on steric repulsion (i.e. non-bonding interactions) between an active metal-center decorated by chiral ligands and substrates. However, the chemo-, regio- and stereoselectivity in asymmetric catalytic reactions can be determined not only by steric (steric control) but also by electronic properties of the ligand (electronic

control) [10]. The development of methodologies for efficient asymmetric synthesis is one of the most important areas of synthetic organic chemistry [11].

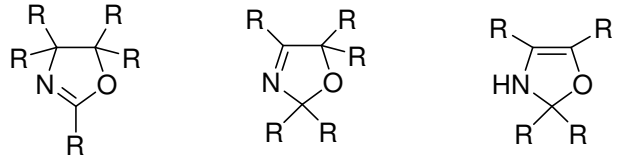
For metal catalyzed reactions, generally a transition metal, a transition metal compound or an organometallic complex is used as a catalyst. A ligand can act either as complexed to the metallic catalyst or as one of the reactants. A ligand has four different modes of operation: (i) to accelerate or decelerate the catalysis, (ii) to control the product yield, (ii) to control chemoselectivity, and (iii) to provide stereocontrol in the case of chiral ligands. The use of ligand accelerated catalysis has become increasingly important for asymmetric synthesis both in laboratory and industrial scale; however, ligand decelerated catalysis has not been investigated in detail [1].

In osmium catalyzed dihydroxylation of alkenes in the presence of nitrogen donor ligands, ligand accelerated or decelerated catalysis can take place as a result of some combination of substrate alkene and ligand. Cu(I) catalyzed C-C and C-heteroatom coupling reactions of Grignard reagents and organolithiums have revealed that reaction yield and chemoselectivity can be controlled by ligand complexed Cu(I) catalysts and one should not use automatically Cu(I), the popular catalyst for coupling, but rather examine several Cu(I) compounds and their complexes to find the optimal one. A research on “ligand controlled catalysis” is offered for optimization of all reaction parameters, i.e. rate, yield, chemo- and stereocontrol in metal and ligand catalyzed reactions [1].

Ligand Catalyst: Metal–ligand complexes can be immobilized by covalent or coordinative linkage or electrostatic attraction via functionalized ligands or by adsorption on porous supports to combine the good activities and selectivities of homogeneous catalysts and the simplicity of recovery and the possibility of reusing the heterogeneous ones [4].

2.1. Oxazolines

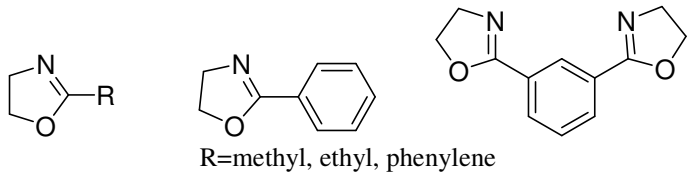
Oxazolines have been known for many years, but only in recent years has the chemical literature shown considerable activity in this field [12]. Oxazolines are five-membered heterocyclic compounds having one double bond and the double bond may be located in one of three different positions. 2-Oxazolines have systematic IUPAC name of 4,5-dihydrooxazoles. It is possible to make the three different groups of oxazolines rings as 2-oxazolines, 3-oxazolines and 4-oxazolines by the position of the double bond segments in the ring.



(2.1)

The 2-oxazoline is the most common in this group. Hydrogen atoms located on the carbon of an alkyl group in the 2 position are active, rather acidic, and are readily replaced with other groups. In addition, the 2-oxazoline ring has two sites in the 4 position and two in the 5 position where reactive groups may be located. Also, the nitrogen of the oxazoline is basic and forms salts with acids and quaternary compounds with alkyl halides. The functionality of oxazolines, the wide variety of derivatives they offer, and their versatility in application started to be recently widely used to synthesize the several functionalized organic compounds.

To date, the 2-alkyl or 2-aryl substituted oxazolines have been studied. One or more oxazoline rings may be covalently bonded to the same organic (R=alkyl or aryl) residue, as shown in Figure 2.1 for phenylene functionalized with one or two oxazoline rings.



R=methyl, ethyl, phenylene

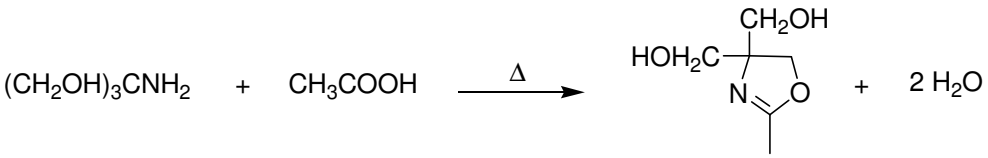
Figure 2.1. Oxazoline and Bis-Oxazoline Structures.

2.1.1. Preparation of Oxazolines

a. From amino alcohols

Oxazolines are prepared in various ways using amino alcohols. Usually the simplest and most inexpensive process involves the reaction of an amino alcohol with a carboxylic acid. The amino alcohol must have the NH_2 and OH groups on adjoining carbon atoms, and the acid may be aliphatic or aromatic. When the amino alcohol is completely substituted on the carbon containing the NH_2 group, the reaction with an acid proceeds smoothly through the amide to the oxazoline with elimination of water. The substituted amino alcohols cyclize readily when heated with carboxylic acids to give high yields to 2-oxazolines. Unsubstituted amino alcohols form amides but cyclize only with difficulty.

Refluxing 2-amino-2-hydroxymethyl-l,3-propanediol in acetic acid until the theoretical water of reaction is removed gives 2-methyl-4,4-bis(hydroxymethyl)-2-oxazoline in high yield. The reaction is illustrated by the following equation [12].

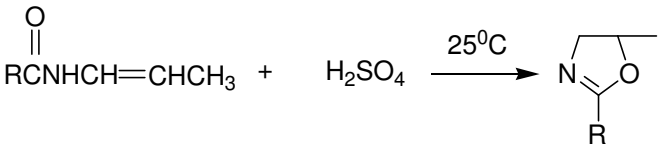


(2.2)

b. From amides

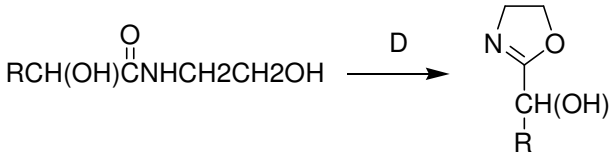
Some amides cyclize with difficulty require the presence of a dehydrating agent and the use of high temperatures. Others go to the oxazoline with only moderate heat and in the absence of dehydrating agents.

The preparation of 2-substituted-5-methyl-2-oxazolines has been accomplished by treating N-(ally1)amides with concentrated H_2SO_4 at below 25°C. The addition of 96% H_2SO_4 to N-allyl-p-toluamide gives 2-(p-tolyl)-5-methyl-2- oxazoline in 50% yield.



(2.3)

The reaction of an a-hydroxy acid with an amino alcohol gives an N-(2-hydroxyethyl) hydroxyamide, which can be converted to a 2-(l-hydroxyalkyl)-2-oxazoline by heating to about 280°C at 3-4 mm in a reactor filled with kaolin.

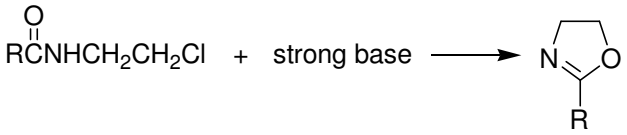


(2.4)

Low yields of 2-oxazoline have been obtained by heating N-(2-hydroxyethyl)formamide to 150-300°C at reduced pressure in the presence of a dehydrating agent such as Al_2O_3. Improved yields are obtained by heating N-(2-hydroxyethy1) amides to 275°C at 200 mm in a reactor filled with $Na_2B_40_7$. The dehydration of N-(2-hydroxyethyl)caproamide gives 2-pentyl-2-Oxazoline [12].

c. From haloamides

Haloamides are converted readily to oxazolines by a strong base and rather slowly by weak base. Preparation of N-(2-halo-l-ethyl)amides in good yield can be accomplished by mixing the halo alcohol or halo olefin with a nitrile at 35°C for 3 hr and then adding Na_2CO_3. The rate of reaction of N-(2-bromoethyl)benzamides with methoxide ion to form 2-oxazolines has been reported.

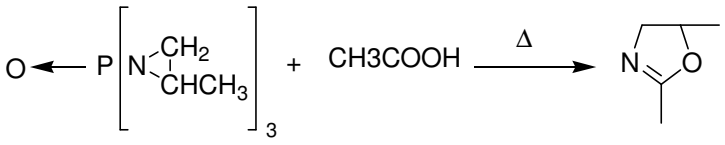


(2.5)

The reaction of N-(2-bromoethyl)phthalimide with warm 30% KOH solution gives about 75 % yield to 2-(o-carboxyphenyl)- 2-oxazoline [12].

d. From aziridines

Refluxing suitable organic acids and aziridinylphosphine oxide in toluene gives mixtures, which can be thermally decomposed to give 2-substituted oxazolines. For example, refluxing acetic acid with tris(2-methyl-laziridiny1) in toluene gives 2,5-dimethyl-2-oxazoline.

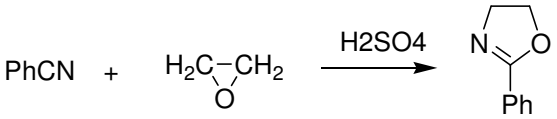


(2.6)

Heating aziridines with an alkali metal iodide at 50-150^{o}C in a solvent gives the corresponding 2-oxazoline by molecular rearrangement. Specifically, ethyl-1-aziridinyl formate with NaI in acetonitrile refluxed for 4 days gives a 47% yield of 2-ethoxy-2-oxazoline [12].

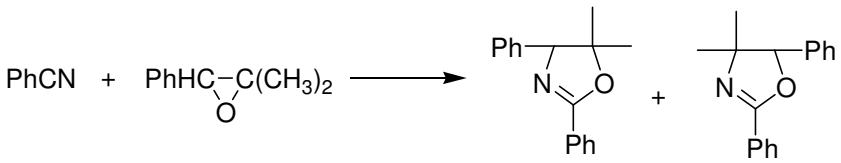
e. From epoxides

The addition of aliphatic epoxides to nitriles in strong acid at low temperature gives 2-oxazolines upon neutralization with NaOH. Benzonitrile in concentrated H_2SO_4 at 0^{o}C treated with ethylene oxide and followed by neutralization with NaOH gives 2-phenyl-2-oxazoline. The reaction is general and can be used for the preparation of a variety of 2-oxazolines [12].



(2.7)

Reaction of 2,2-dimethylstyrene epoxide with benzonitrile in dibutyl ether gives 4,4-dimethyl-2,5-diphenyl-2-oxazoline and 5,5-dimethyl-2,4-diphenyl-2-oxazoline in 2:l ratio as a result of two possible sites of the epoxy ring opening. Since the reaction does not take place when dibutyl ether is omitted, the reaction must proceed through a carbonium ion stabilized by that solvent [12].



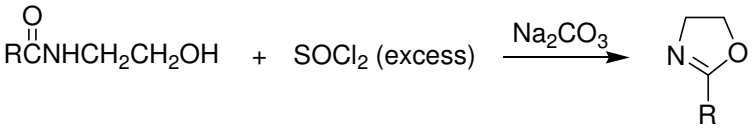
(2.8)

f. From grignard reagents

The reaction of alkyl- and aralkylmagnesium halides on unsaturated azlactones (oxazolones) gives 4-substituted-5-keto-2-oxazolines with the alkyl or aralkyl group from the Grignard reagent adding to the unsaturated spot in the 4 position of the heterocyclic ring. For example, 2-phenyl-4-benzylidene-5-keto-2-oxazoline and anal kylmagnesium halide give 2-phenyl-4-(α-phenyl)alkyl-5-keto-2-oxazoline [12].

g. From reaction of $SOCl_2$ on hydroxyamides

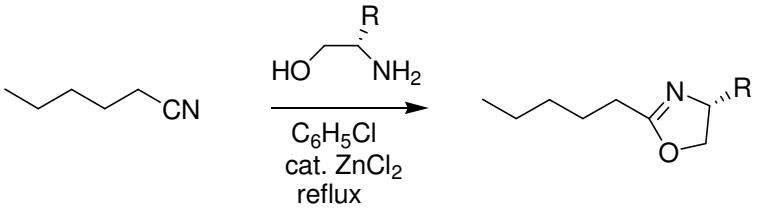
The reaction of $SOCl_2$ with 2-hydroxyalkylamides has been investigated thoroughly. In the cold with a large excess of $SOCl_2$, complex salts are formed. Refluxing with $SOCl_2$ gives about 85% yield to the 2-chloroalkylamide. Heating the chloro derivative in water gives about 80% yield to the amine hydrochloride ester. When the complex salt, formed from the large excess of $SOC1_2$, is decomposed in Na_2CO_3 solution, a yield of about 70% to the oxazoline is obtained [12].



(2.9)

h. From nitriles

Different alkyl, aryl, and thiophene nitrile compounds in the presence of homochiral amino alcohols with catalytic amounts of zinc chloride afford the 2-oxazoline compounds [13].



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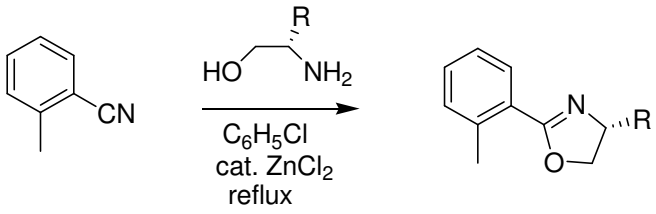

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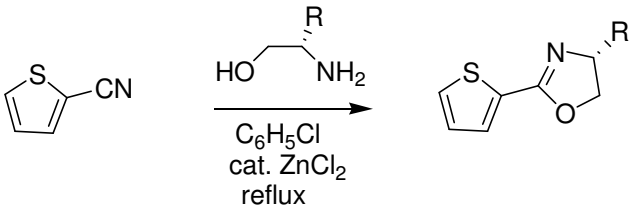
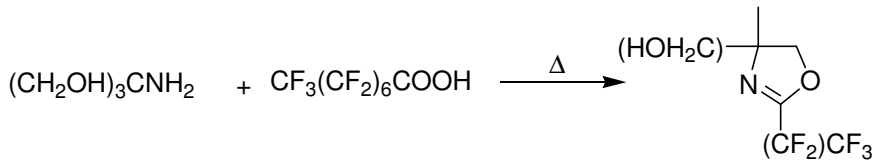


(2.12)

i. Halooxazolines

Heating perfluoroalkylcarboxylic acids with an amino alcohol gives 2-perfluoroalkyl-2-oxazolines in good yields. For example, pentadecafluorooctanoic acid and 2-amino-2-hydroxymethyl-l,3-propanediol gives 2-pentadecafluoroheptyl-4,4-bis-(hydroxymethyl)-2-oxazoline [12].

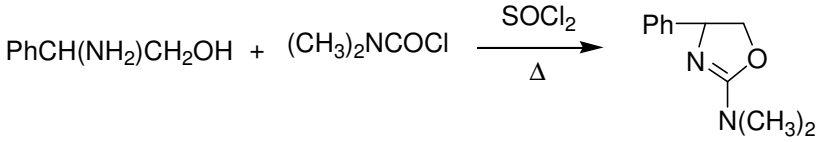


(2.13)

j. Aminooxazolines

Aminooxazolines are of particular interest in therapeutic applications, and this interest has stimulated considerable research in the preparation of a variety of compounds.

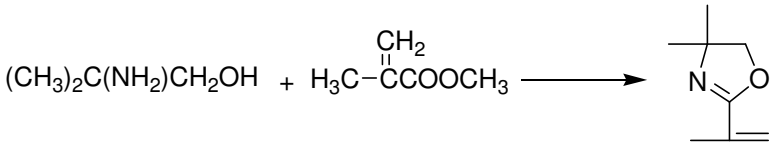
By treating an amino alcohol with ethyl chloroformate and chlorinating with $SOC1_2$, which replaces the hydroxyl group with chlorine substituted 2-amino-2-oxazolines can be prepared. Further treatment with PCl_5 gives 2-chloroalkyl isocyanate. Addition of a primary amine gives a substituted urea which cyclizes to yield a substituted 2-amino-2-oxazoline of the type where R can be α-naphthyl, 2,6-di-methylphenyl, phenyl, and tolyl [12].



(2.14)

k. Vinyloxazolines

Vinyloxazolines have been prepared from the reaction of amino alcohols with acrylic esters. 2-Amino-2-methyl-lpropanol and methyl methacrylate refluxed briefly and then distilled in the presence of aluminum isopropoxide give 2-isopropenyI-4,4-dimethyl-2-oxazoline [12].



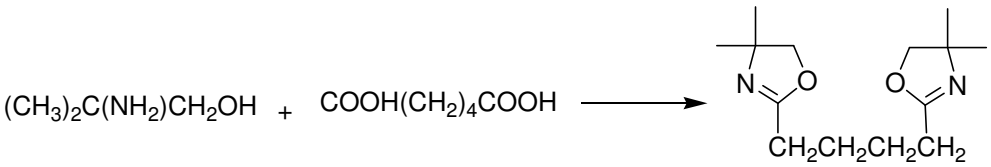
(2.15)

Vinyloxazolines have been prepared by the action of fatty acids on amino alcohols at about 230°C to form an oxazoline that after reaction with formaldehyde can be dehydrated to the vinyl derivative. For example, 2-amino-2-hydroxymethyl-1,3-propanediol and linseed oil fatty acid give an oxazoline, which reacts with formaldehyde and, after dehydration at about 190°C, gives the vinyloxazoline monomer. The vinyl group is located on the α-carbon of the alkyl group attached at the 2 position of the oxazoline ring [12].

l. Bis(oxazo1ines)

Bis(oxazo1ines) are formed from the reaction of dicarboxylic acids and amino alcohols. Adipic acid and 1-amino-2-propanol heated under a nitrogen blanket to about 200°C give a 74% yield of distilled 2,2'-tetramethylenebis(5-methyl-2-oxazoline). A yield of 48% 2,2'-heptamethylenebis(5-methyl-2-oxazoline) has been obtained from the reaction of the same amino alcohol and azelaic acid.

By a similar procedure bis(oxazo1ines) are prepared from 2-amino-2-methyl-1-propanol and dibasic acids. The reaction with adipic acid gave an 84% yield of distilled 2,2'-tetramethylenebis(4,4-dimethyl-2-oxazoline) [12].



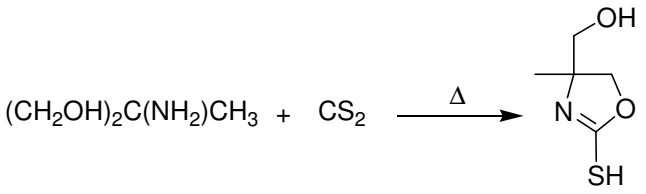
(2.16)

m. Mercaptooxazolines

The action of CS_2 on certain amino alcohols gives good yields of the mercaptooxazoline. For example, CS_2 with 2-amino-2- methyl-l,3-propanediol will give 2-mercapto-4-methyl-4-hydroxymethyl-2-oxazoline. A large excess of CS_2 is required and the reaction mixture is refluxed (ethanol) for several hours.

The use of iodine catalyst with amino alcohols and CS_2 to give mercaptooxazolines has been reported. The reaction between 2-amino-2-methyl-1-propanol and CS_2 gave

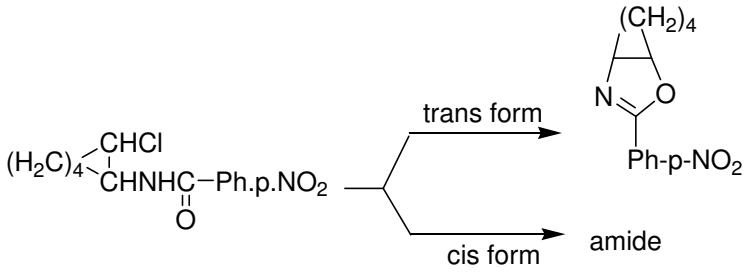
2-mercapto-4,4-dimethyl-2-oxazoline. Also, the action of thiocarbonyl chloride on certain amino alcohols forms 2-mercaptooxazolines [12].



(2.17)

n. Effect of stereochemistry

The effect of stereochemistry has been demonstrated in the reaction of trans- and cis-2-chlorocyclohexylamine. The pnitrobenzamide of the transform could be converted to 2-(p-nitrophenyl)4,5-tetramethylene-2-oxazoline, but the cis form would not cyclize, indicating that the trans form is better oriented for ring closure [12].



(2.18)

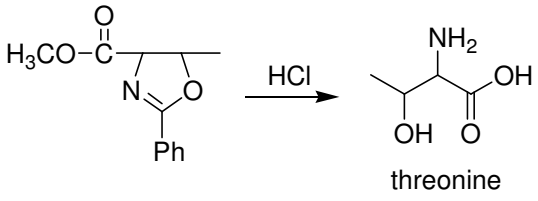
Both cis- and trans-2-aminocyclohexanol form oxazolines when treated with ethyl imidobenzoate. The conversion of cis-2-aminocyclopentanol to oxazoline is easy, but transcyclopentanooxazoline cannot be prepared. Stereochemical studies involving oxazolines indicate that cis-2-aminocyclotetradecanol can be changed to the transform by going through the trans-2-phenyl-4,5-dodecamethylene-2-oxazoline and hydrolyzing back to the amino alcohol using HCl. trans-2-Aminocyclopentadecanol can be obtained in 82% yield from trans-2-phenyl-4,5-tridecamethylene-2-oxazoline [12].

2.1.2. Reactions of Oxazolines

a. Use of acids, anhydrides, methyl esters, and bases

Oxazolines hydrolyze with mineral acids. Advantage is taken of this property to make DL-threonine. 2-Phenyl-5-methyl-4-carbomethoxy-2-oxazoline hydrochloride and dilute HCl give a 70% yield of DL-threonine (α-amino-β-hydroxybutyric acid) When alkaline hydrolysis is used the yield of DL-threonine is only 27%. If the

oxazoline is hydrolyzed by boiling in water, the product is o-benzoyl-DL-threonine methyl ester hydrochloride [12].

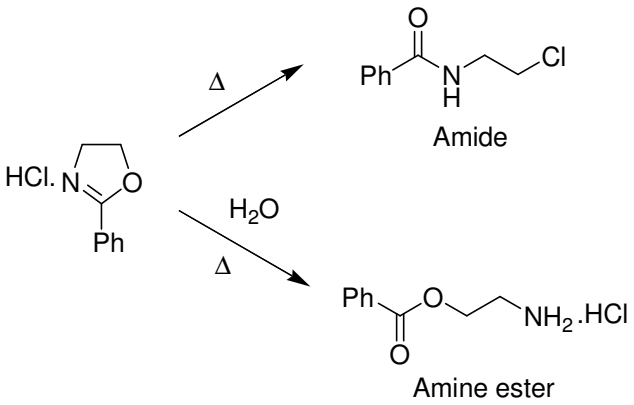


(2.19)

Also, the ethyl ester of DL-trans-2-phenyl-5-methyl-2-oxazoline-4-carboxylic acid will hydrolyze in dilute NaOH solution to give DL-o-benzoylthreonine. Sodium ethoxide has been used to convert methyl cis-L-2-phenyl-5-methyl-2-oxazoline-4-carboxylate into trans-D-2-phenyl-5-methyl-2-oxamethyl-2-oxazoline-4-carboxylic acid.

The D and L forms of cis-2-phenyl-4-carboxy-5-hydroxymethyl-2-oxazoline give α-amino-β, γ-dihydroxybutyric acid when treated with base and hydrolyzed with acid.

2-Phenyl-2-oxazoline hydrochloride will change on heating to give N-(2-chloroethyl) benzamide. The same compound heated in water for only 2 min gives the hydrochloride of 2-aminoethyl benzoate. Rearrangement of the hydrochloride of 2-(p-nitrophenyl)-5-(diethylaminomethyl)-2-oxazoline on a steam bath gives N-(3-diethylamino-2-chloropropyl)-p-nitrobenzamide hydrochloride [12].



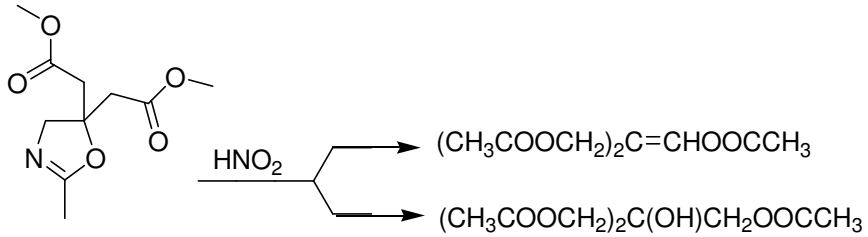
(2.20)

DL-4-Carbohydroxamido-2-phenyl-2-oxazoline in dry dioxane treated with HCl in dry dioxane and heated for a few minutes on a steam bath gives N-(l-carbohydroxamido-2-chloroethy1)benzamide. Treating the oxazoline with dilute NaOH gives the sodium salt of 4-carboxy-2-phenyl-2-oxazoline [12].

Reactions involving the effect of potassium acetate, acetic anhydride, and acetic acid on DL-threo-2-phenyl-4-(phenylhydroxymethyl)-2-oxazoline show that acetic acid is more effective in opening the oxazoline ring. The ring fails to open when treated with potassium acetate-acetic anhydride; instead the acyl derivative forms.

Nitration of the phenyl group of 2-methyl-5-phenyl-2-oxazoline sulfate, to give the p-nitrophenyl derivative, has been accomplished by treatment with HNO_3 at low temperature.

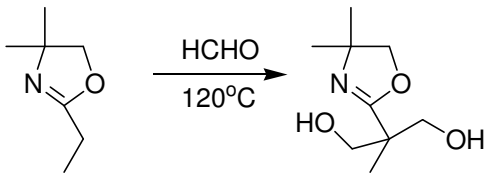
The reaction of HNO_2 (from aqueous HCl and $NaNO_2$) with oxazoline diesters such as 2-methyl-5,5-bis(acetoxymethy1)-2-oxazoline gives triester derivatives, 2,2-bis(acetoxymethyl)-ethenyl acetate and 2,2-bis(acetoxymethyl)-2-hydroxyethyl acetate [12].



(2.21)

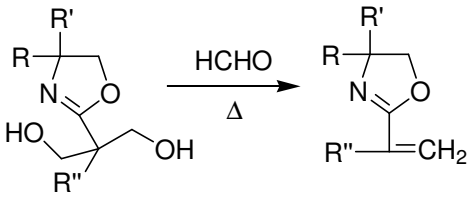
b. Use of aldehydes

The reaction of paraformaldehyde with 2-alkyl-2-oxazoline at about 120°C gives the [bis(hydroxymethyl)alky1]-2-oxazoline condensation product. From 2-ethyl-4,4-dimethyl-2-oxazoline and paraformaldehyde at 120°C the product is 2-[1,1-bis(hydroxymethyl)ethyl]-4,4-dimethyl-2-oxazoline.



(2.22)

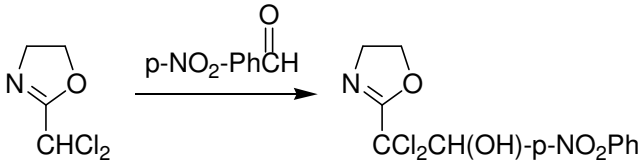
Vinyloxazolines are prepared by the action of paraformaldehyde on 2-alkyl-4,4-substituted-2-oxazolines. The reaction first forms the condensation product, and then at high temperature dehydration occurs to give the vinyl derivative. The products obtained are 2-alkylethenyl-4,4-substituted-2-oxazolines [12].



(2.23)

Benzaldehyde and other aromatic aldehydes react with 2-alkyl-2-oxazolines to form phenylethenyloxazobnes. The reaction of benzaldehyde with 2-methyl-4,4-dimethy1-2-oxazoline gives 2-phenylethenyl-4,4-dimethyl-2-oxazoline. Hydrolysis of the latter gives cinnamic acid in high yield [12].

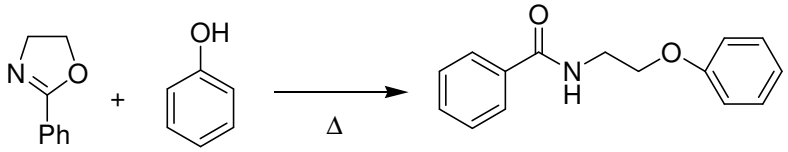
The reaction of 2-dichloromethyl-2-oxazoline with p-nitrobenzaldehyde occurs under mild conditions to give 2-[(p-nitrophenyl)-2-hydroxy-1,1-dichloroethyl]-2-oxazoline.



(2.24)

c. Use of phenols

Substituted 2-oxazolines react with phenol or thiophenol in the absence of water to give ethers, thioethers, and carboxamides. A mixture of 2-phenyl-2-oxazoline and phenol refluxed for 7 hr forms N-[l-(2-phenoxyethyl)]benzamide. 2-Phenyl-2-oxazoline and hydroquinone give 1,4-bis(2-benzamidoethoxy) benzene. The reaction of thiophenol with 2-2-phenyl-2-oxazoline yields the thioether N-(2-phenylthioethy1) benzamide [12].



(2.25)

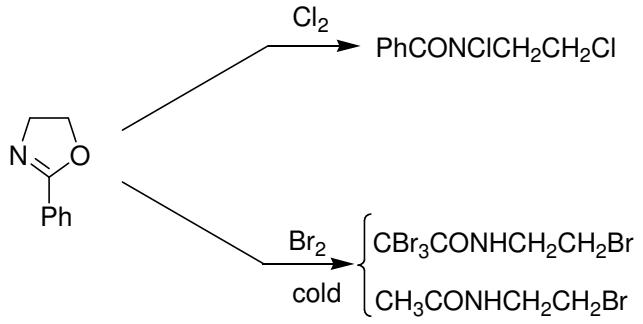
d. Use of halogens, phosgene, and alkyl halides

The reaction of 2-phenyl-2-oxazoline with chlorine goes smoothly with ring opening to form the N-chloramide, N-(2-chloroethyl)-N-chlorobenzamide. The action of bromine on the oxazoline yields N-bromo-2-phenylazolinium bromide. The addition of bromine to 2-alkyl-2-oxazolines in the cold gives a mitxure of N-(2-bromoethyl)tribromoacetamide and N-(2-bromoethyl)acetamide. There is no partial

bromination at the α-carbon. The addition of chlorine to 2-alkyl-2-oxazolines gives partially chlorinated products. 2-(1-Monochloroalkyl)-2-oxazolines can be obtained by using an excess of the oxazoline. With 2-ethyl-2-oxazoline and equal molar amounts of chlorine, mixtures of N-(2-chloroethyl) propionamide, N-(2-chloroethyl)-2-chloropropionamide, and N-(2-chloroethyl)-2,2-dichloropropionamide are obtained [12].

The chlorinated amide can be converted to 2-trichloroalkyl-2-oxazolines by treatment with alkali and further chlorination.

Oxazolines having hydroxymethyl substitution on the ring react with phosgene to form the chloroformoxymethyl derivative. For example, 2-aryl-4-hydroxymethyl-4-methyl-2-oxazoline in chloroform treated with a toluene solution of phosgene gives the 2-aryl-4-(chloroformoxymethyl)-4-methyl-2-oxazoline. This compound can be converted to the corresponding 4-carbamoyl derivative by treatment with NH_3 [12].



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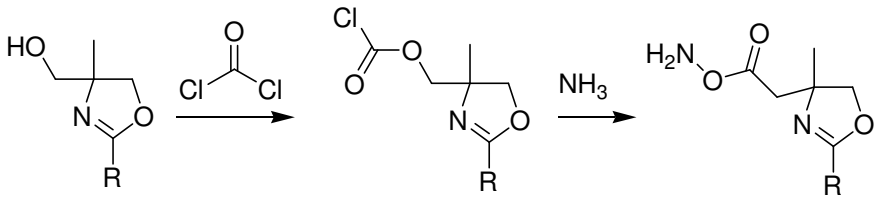
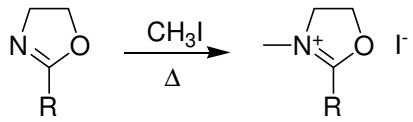


(2.27)

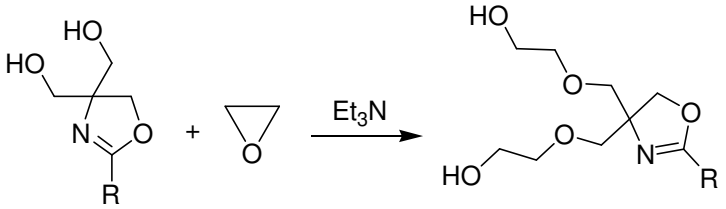
Oxazolines react with alkyl halides to give the corresponding quaternary compound. For example, the oxazolinium salt of 2-cyclohexyl-4,4-dimethyl-2-oxazoline can be prepared by treating the oxazoline with methyl iodide in nitromethane at 70°C. Oxazolinium iodides in methanol, treated with $NaBH_4$ at below 5°C, are reduced to the corresponding oxazolidine. 2-(2-Phenylethyl)-3,4,4-trimethyl-2-oxazolinium iodide gives 2-(2-phenylethyl)-3,4,4-trimethyloxazolidi [12].



(2.28)

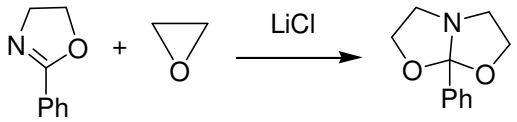
e. Use of epoxides

Epoxides undergo base-catalyzed addition to hydroxymethylsubstituted 2-oxazolines to form hydroxyethyl ethers or polyethers depending on the ratio of epoxide to oxazoline. Ethylene oxide adds to 2-alkyl-4,4-bis(hydroxymethyl)-2-oxazoline in the presence of triethylamine to give 2-alkyl-4,4-bis(2-hydroxyethoxymethyl)-2-oxazoline [12].



(2.29)

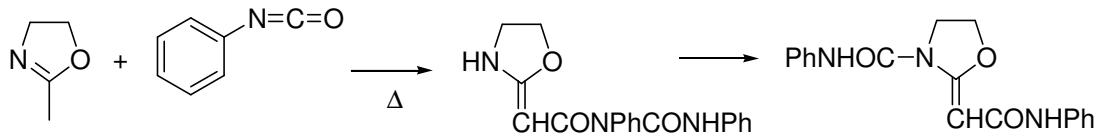
The reaction of an epoxide with 2-oxazolines having no active groups in the 4 and 5 positions and in the presence of LiCl catalyst forms l-aza-4,6-dioxabicyclo[3.3.0]octane. From ethylene oxide and 2-phenyl-2-oxazoline the product is 1-aza-5-phenyl-4,6-dioxabicycl0[3.3.0]octane [12].



(2.30)

f. Use of isocyanates

Phenyl isocyanate reacts with 2-alkyl-2-oxazolines when hydrogens are present on the α-carbon of the 2-substituted group to give either mono- or disubstituted addition products. For example, 2-methyl-2-oxazoline and phenyl isocyanate, in a molar ratio of 1 : 2 and heated under anhydrous conditions for 2 hr at 80°C, give about 80% disubstituted product. One group is attached at the ring nitrogen and one at the 2-methyl group of the oxazoline ring. The product is a disubstituted oxazolidine [12].

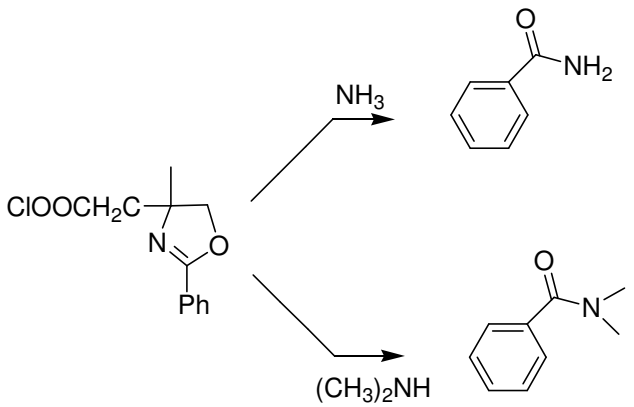


(2.31)

g. Use of amines

Certain amines react with oxazolines in various ways. The methyl ester of 2-(o-carboxyphenyl)-2-oxazoline is obtained from the reaction of the carboxyl group with cyanamide in ether. However, when 2-(o-carboxyphenyl)-2-oxazoline is allowed to react with aniline in ethanol, the product is 2-phenylamino-2-(o-carboxyphenyl) oxazolidine.

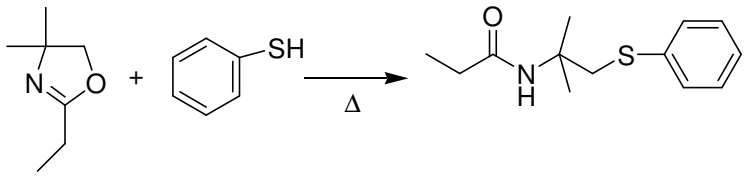
Treatment of 2-aryl-substituted 2-oxazolines with ammonia or methylamine opens the oxazoline ring and forms a benzamide. For example, when substituted oxazolines such as 2-aryl-4-chlorocarboxymethyl-4-methyl-2-oxazolines are treated with ammonia or dimethylamine at about 80^{o}C in a sealed tube with dry dioxane, the main product of the reaction is benzamide or N,N-dimethylbenzamide.



(2.32)

h. Use of aromatic thiols and sulfides

Reaction of aromatic thiols with oxazolines causes ring opening and amide formation, with addition of the thiol to the original oxazoline ring. A mixture of 2-ethyl-4,4-dimethyl-2-oxazoline and thiophenol refluxed for 6 hr gives 98% N-(2-phenylthio-1,1-dimethylethy1)propionamide [12].



(2.33)

The reaction of a thiol with an oxazoline in an organic solvent at 0-100°C gives an intermediate, which upon hydrolysis with HC1 gives 2-aminoalkanethiols. Thiobenzoic acid in pyridine and 2-methyl-4,4-bis(hydroxymethyl)-2-oxazoline yields a mixture which, with HCl hydrolysis, gives about a 70% yield of 2-amino-2-mercapto-l,3-propanediol.

Reaction of a sulfide with 2-oxazolines opens the ring and forms the thioamide derivative. For example, the reaction of $(NH_4)_2S$ with 2-phenyl-2-oxazoline at 30°C gives N-(2-hydroxyethy1)thiobenzamide [12].

i. Oxidation

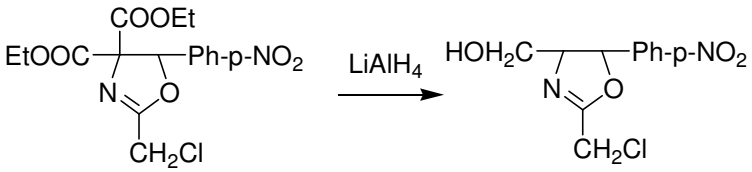
Oxidation of bis(hydroxymethy1)-substituted 2-oxazolines with $KMnO_4$ provides a means for obtaining β-hydroxy-aamino acids. For example, 2-phenyl-4,4-bis(hydroxymethyl)-2-oxazoline (prepared from benzoic acid and 2-amino-2-hydroxymethyl-1,3-propanediol) treated with $KMnO_4$ gives 2-amino-2-hydroxymethylmalonic acid [12].

j. Reduction

Reduction of a carbalkoxy group on the oxazoline ring using $LiAlH_4$ gives the hydroxymethyl group. For example, 2-dichloromethyl-4-carbethoxy-5-(p-nitropheny1)-2-oxazoline has been reduced by this procedure to give 2-dichloromethyl-4-hydroxymethyl-5-(p-nitrophenyl)-2-oxazoline. Wide use has been made of this property in the preparation of chloramphenicol, which can be obtained by hydrolysis of the hydroxymethyloxazoline. Reduction of an ester group on an oxazoline to the hydroxymethyl group has been accomplished also with $NaBH_4$ or KBH_4 in various solvents [12].

The action of hydroxylamine on oxazolines containing a carbalkoxy group on the oxazoline ring will convert that group to a hydroxycarbamoyl group. For example, 2-phenyl-4-carbethoxy-2-oxazole with hydroxylammonium chloride (in hot anhydrous

ethanol and Na) is converted in 88% yield to 2-phenyl-4-hydroxycarbamoyl-2-oxazoline.



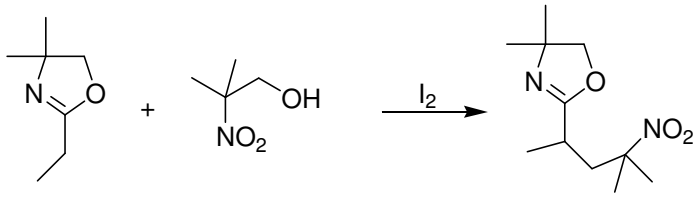
(2.34)

k. Pyrolysis

2-Alkyl- (and aryl-) 4-methyl- (and -4,4-dimethyl-) 2-oxazolines can be pyrolyzed at 500-600°C to give products of the general structure $RCONHCH_2CR'=CH_2$, where R is alkyl or aryl and R' is H or methyl. For example, heating 2-ethyl-4,4-dimethyl-2-oxazoline at 500°C gives N-methallylpropionamide, which can be converted in concentrated H_2SO_4 at 30°C to 2-ethyl-5,5-dimethyl-2-oxazoline. Thermal rearrangement of 2-(o-carboxyphenyl)-2-oxazoline gives N-(2-hydroxyethyl)-phthalimide [12].

l. Use of nitro alcohols

Nitro alcohols react with 2-substituted-2-oxazolines that have an active hydrogen on the α-carbon of the group attached at the 2 position. The action of 2-nitro-2-methyl-1-propanol on 2-ethyl-4,4-dimethyl-2-oxazoline in the presence of iodine gives 2-[1-(1,3-dimethyl-3-nitrobutyl)]-4,4-dimethyl-2-oxazoline [12].



(2.35)

2.1.3. Applications of Oxazolines

a. Protective coatings

Oxazolines are used in large volume in the field of surface coatings. They are used in aqueous systems as emulsifiers or surface-active agents. An effective dispersing agent for metallic aluminum pigment in water-base paints is 2-heptadecenyl-4,4-bis(hydroxymethyl)-2-oxazoline.

Oxazolines, oxazoline esters, and their vinyl derivatives, prepared from long-chain saturated or unsaturated fatty acids and amino alcohols, are useful plasticizers for ethyl cellulose compositions. Films from the plasticized ethyl cellulose are tough, flexible, strong, and clear [12].

Terpolymers containing an oxazoline are useful in coating compositions. For example, styrene, 2-ethylhexyl acrylate, acetic acid, and catalyst in a suitable solvent and then 2-amino-2-hydroxymethyl-1,3-propanediol added give a mixture which can be converted to the oxazoline acrylate structure by heating. The polymer product blended with melamineformaldehyde resin in aromatic solvent and applied on metal and baked gives a film, which is clear, tough, and resistant to alkalies, solvents, and grease [12].

b. Surface active agents

The surface tension of amides, oxazolines, and ester amines derived from the same fatty acids and amino alcohols has been compared. That of an amide is lower than an oxazoline, while the ester amine is much higher.

Oxazolines derived from long-chain fatty acids and amino alcohols have been used to lower the surface tension of mustard gas and the interfacial tension between mustard gas and water [12].

Surface active compositions containing 2-substituted-4,4-substituted-2-oxazolines are used as a lubricant and freeing agent between well-drilling pipes and well solids.

Long-chain 2-alkyl-2-oxazolines are useful for dispersing pigments in transfer or carbon-paper inks. Oxazolines prepared from the reaction of carboxylic phenol-aldehyde resins with amino alcohols are useful in the preparation of deemulsifying agents for water-in-oil emulsions [12].

c. Gasoline and lube oil additives

The addition of substituted oxazolines, such as 2-heptadec-enyl-4,4-bis(hydroxymethyl)-2-oxazoline, to gasoline reduces surface ignition and carburetor fouling and icing.

The reaction products of substituted oxazolines, such as 2-heptadecenyl-4,4-bis(hydroxymethyl)-2-oxazoline, and boric acid give improved carburetor

cleanliness, act as anti-icing agents, and suppress surface ignition when added to gasoline [12].

Reaction products of oxazolines with phosphite diesters have been used as anti-icing and antiknock additives for fuels.

Lubricating greases containing 2-heptyl-4-hydroxymethyl-4-ethyl-2-oxazoline have been used to improve oxidation and corrosion characteristics.

d. Corrosion inhibitors

Oil-soluble oxazolines, in combination with organic phosphates and sulfonate salts, are effective as rust inhibitors when added to oils. The combination of 2-heptadecenyl-4,4-dimethyl-2-oxazoline and dilauryl phosphate with sodium petroleum sulfonate prevents steel from rusting in humid atmosphere or salt water.

Products having excellent inhibiting action on the corrosion of metals may be obtained by treating an oxazoline of the type 2-alkenyl- or 2-alkyl-2-oxazolines with CrO_3 [12].

e. Antifoam agents

Oxazolines are effective antifoam agents and have been used to control foaming during fermentation. The substituted oxazolines having a C_7 to C_{17} group in the 2-position are the most active.

2-Heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline has been used to control foaming during the regeneration of amine solutions, which are used for removal of H_2S and CO_2 from synthesis gas [12].

f. Textile chemicals

A mixture of 2-heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline, mineral oil, neatsfoot oil, and oleic-lactic acid amide is a good lubricating and conditioning agent for yarns and fibers.

A good textile lubricant having antistatic properties can be prepared using a mixture of 2-alkyl-4,4-dimethyl-2-oxazoline, mineral oil, phoshate ester of lauric acid, and lauryl alcohol. Alkylated or acylated oxazolines in combination with hydroxymethylurea compounds give improved creaseproofing to the ureas and

provide a softening effect on textiles. It also provides improved shrinkage and wears resistance [12].

g. Pharmaceuticals

Substituted 2-oxazolines have been investigated widely for phamaceutical uses. Especially useful as tranquilizing agentsand central nervous system regulators are the substituted 2-amino-2-oxazolines. 2-(l-Naphthylamino)-2-oxazoline, substituted and unsubstituted benzofuranylamino-2-oxazolines, and substituted and unsubstituted 2-(l-indanylamino)-2-oxazolines are among those investigated and found useful.

Also, 2-(9-fluorenylamino)-2-oxazolines and their salts are effective in the same application. N-Substituted 2-amino-2-oxazolines in which the substituted group is benzyl, 1-naphthyl, or 1-naphthylmethyl have been tested in dogs and found to have vasoconstrictive properties [12].

The benzylaminooxazoline has 50 % of the vasoconstrictive action of adrenaline. N-Substituted aminooxazolines in which the substituent is o-tolyl, p-tolyl, 2,6-dimethylphenyl, and 2-methyl-6-chlorophenyl have marked vasoconstrictor action and are superior to cocaine in local anesthetic activity.

Certain oxazolines substituted in the 2 position are competitive inhibitors of acetylcholinesterase. These include 2-amino-2-oxazoline, 2-(1-naphthylamino)-2-oxazoline, and 2-methyl-2-oxazoline [12].

h. Adhesives and binders

Oxazolines having a long-chain unsaturated group with a vinyl group on the a-carbon and attached at the 2 position of the oxazoline ring are useful in combination with other vinyl monomers as binders for fiberboard. Recommended oxazolines include 2-[l-(hexadecenyl)ethenyl]-4,4-dimethyl-2-oxazoline. Long-chain oxazolines, such as 2-heptadecyl-4,4-bis(hydroxymethyl)-2-oxazoline, are effective as antistripping agents in asphalt pavings [12].

Polymerized 2-isopropenyl-2-oxazoline gives improved adhesion of tire cords to rubber compositions. Oxazoline esters of the type 2-alkyl-4-methyl-4-acyloxymethyl-2-oxazoline are good plasticizers prior to vulcanization of butadiene-acrylonitrile rubber. Also, bis(oxazolines), such as 2,2'-tetramethylenebis(4,4-

dimethyl-2-oxazoline), give improved properties when used as vulcanizing agents for rubber [12].

i. Stabilizers for chlorinated hydrocarbons

Chlorinated hydrocarbons may be stabilized against metalinduced decomposition by the addition of a small amount of an oxazoline, such as 2-methyl-2-oxazoline. 2-Ethoxy-2-oxazoline, at 0.02% concentration, is a good stabilizer for trichloroethylene.

Vinyl chloride resins are stabilized by the addition of substituted 2-oxazolines, such as 2-ethyl-4,4-dimethyl-2-oxazoline. The resin is protected from heat degradation when applied on metal surfaces [12].

The presence of a small amount of vinyloxazoline copolymerized with vinyl chloride gives thermal stability to the polymer. Vinyl chloride, vinyl acetate, and 2-isopropenyl-4-ethyl-4-propionyloxymethyl-2-oxazoline give a terpolymer having excellent heat stability when applied on steel surfaces.

j. Protective films in polish formulations

Oxazoline diester waxes prepared from 2-amino-2-hydroxymethyl-1,3-propanediol and saturated fatty acids have been used in polish formulations. In addition to good properties as a protective film, the waxes contribute mildew and fungus resistance, and antistatic and anticorrosive properties [12].

k. Photography

The addition of 2-mercapto-2-oxazolines (or substituted derivatives) to photoinsensitive, image-receptive coatings containing colloidal silver causes the formation of a darker positive image. 2-Mercapto-2-oxazolines are also used in photography as antifoggant development retarders.

Photographic sensitizers have been prepared which contain substituted 2-oxazolines, such as 2,4-dimethyl-4-acetoxymethyl-2-oxazoline [12].

l. Agriculture

A study of phytotoxicity of a series of 2-substituted-4-methyl-4-hydroxymethyl-2-oxazolines has shown that the substitution of one or more OH groups for hydrogen atoms in the methyl group markedly reduces toxicity. Compounds with short-chain alkyl groups in the 2 position are less toxic than those with longer groups in that position. The presence of one or more double bonds in the chain increases toxicity [12].

Aromatic imido esters prepared by treating substituted oxazolines with phthalic or naphthalic anhydrides have been suggested as plant growth regulators. Formulations of 2-ethylthio-2-oxazoline or 2-propargylthio-2-oxazoline are effective in controlling plant-infesting nematodes.

m. Plasticizers

Long-chain oxazolines or ethylene oxide addition products of long-chain oxazolines, such as 2-heptadecenyl-4-methyl-4-hydroxymethyl-2-oxazoline or 2-heptadecenyl-4-methyl-4-hydroxydiethoxymethyl-2-oxazoline, have been used to improve plasticity and extrudability of gelatin dynamite compositions [12].

2.2. Chiral Bis(Oxazoline)–Metal Complexes

The versatility of chiral bis(oxazoline)–metal complexes has been documented in numerous asymmetric syntheses. Particularly notable is the utility of bis(oxazoline)–metal complexes in enantioselective Diels–Alder reactions. Recently, metal complexes of *cis*-1-aminoindan-2-ol derived conformationally constrained bis(oxazoline) ligand (inda-box) have been shown to undergo enantioselective Diels–Alder reactions of cyclopentadiene with various bidentate dienophiles [14].

The advances in asymmetric synthesis have now reached the point that many organic molecules can be prepared with near complete enentioselectivity [15]. Asymmetric catalysis with chiral metal complexes has received considerable attention in recent years, and its contribution to the art of organic synthesis has become of leading importance. In the field of chiral Lewis acid catalysis, the catalyst, in general,

consists of a cation coordinated/bound to an optically active ligand to give a chiral complex with at least one vacant Lewis acid site suitable for coordination and activation of the reagent. To induce a good level of enantioselection, the coordinated reagent should be suitably oriented to favor a selective attack to one specific face. One approach to an easier and less costly route to reduce half the variables required for good face selectivity is the use of a C_2-symmetric chiral ligand. In recent years, C_2-symmetric chiral bis(oxazoline) Ligand-metal complexes have received a great deal of attention through their use in various catalysis process. 4,5-Dihydro-1,3-oxazole ligands (commonly known as 2-oxazolines or simply oxazolines) have been used by many research groups as chiral auxiliaries in transition metal-catalyzed asymmetric organic syntheses. The oxazolines show a number of attractive characteristics: versatility of ligand design, straightforward synthesis of ligands from readily available precursors, and modulation of the chiral centers, which are located near the donor atoms [16].

The box ligands quickly became widely adopted bidentate ligands for their easy and flexible synthesis and for the excellent enantioselectivity induced first in two very useful reactions, and later in a large variety of other reactions. The communications also anticipated the usual protocol of research in box chemistry: (a) synthesis of the ligand following a sequence that, for a long time, would become a standard (reaction of dialky malonyl dichloride with an optically active 1,2-amino alcohol, conversion of the bis-hydroxyamide to the corresponding bis-chloroamide, and ring closure under basic conditions); (b) preparation of the chiral catalyst by reaction of the box ligand with an inorganic salt (CuOTf and $FeCl_2/I_2$); (c) testing of the chiral Lewis acid complex as a catalyst for asymmetric induction in the reaction; (d) proposal of a reacting intermediate in which the reagent is coordinated to the chiral Lewis acid-box complex to rationalize the stereochemical outcome of the catalytic process [2,17].

The oxazoline ligands used in asymmetric synthesis are generally polydentate ligands containing one or more oxazoline fragments. The chelation effect is related to the constrictions imposed by the coordination to the metal complex, so that only one stereogenic center lies near the coordination sphere. This favors strong asymmetric induction in the catalytic reaction. The arrangement also allows the modulation of ligand substituents, depending on the specific asymmetric process, thereby improving its enantioselectivity. The modification of

the chelate ring size is another means of optimizing the inductive effect at the metal center. Furthermore, combinations of soft and hard donor groups are used in designing highly active bidentate ligands. This furnishes their directing capacity with an electronic factor [17].

As the number of catalytic applications of oxazolines to organic processes has increased, the mechanism of these reactions and the characterization of precursors and intermediate metal species have also been studied.

Although the oxazoline cycle was first prepared in 1884, it is only in the last two decades that the ligands containing oxazoline groups have been extensively applied, principally in asymmetric catalytic processes.

In the case of chiral oxazolines, their stereocenter lies very near the metal sphere in the catalytic species, upon chelate N-coordination of the ligand to the metal atom. In spite of the two Csp^3 at positions 4 and 5 (Figure 2.2), the oxazoline cycle is nearly planar (the torsion angles 5–1–2–3 and 4–3–2–1 are 4.21 and 2.48°, respectively). However, it is less planar than the unsaturated oxazole cycle, because of the sp^2 hybridization of 4 and 5carbon atoms [17].

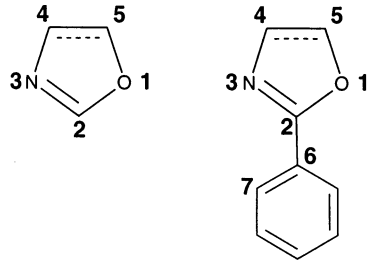
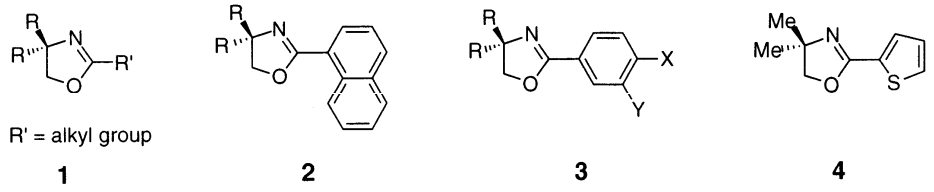


Figure 2.2. 4,5-Dihydro-1,3-oxazoles (Single Bond Between 4 and 5 Carbon Atoms) and 1,3-Oxazoles (Double Bond Between 4 and 5 Carbon Atoms).

2.2.1. Metal Transition Complexes

a. Monodentate oxazoline ligands

Coordination complexes with the oxazoline ligands N shown in Eq. 2.36 acting as monodentate were prepared.



(2.36)

The reaction of metal salts with monodentate type 1 oxazoline ligands is straightforward and leads to the preparation of the corresponding coordination compounds. Hexacoordinate $[TiX_4(1)_2]$ compounds were prepared by reaction of 1 with TiX_4 (X=Br, Cl).

Regioselectivity studies of the cyclopalladation of naphthyl and phenyl oxazolines showed that the reaction of ligands 2 and 3 with Li_2PdCl_4 gives the $[PdCl_2(N)_2]$ coordination complexes instead of the 3-palladated complex (Figure 2.3), although high yields of cyclometalated complexes are formed when $Pd(AcO)_2$ is employed.

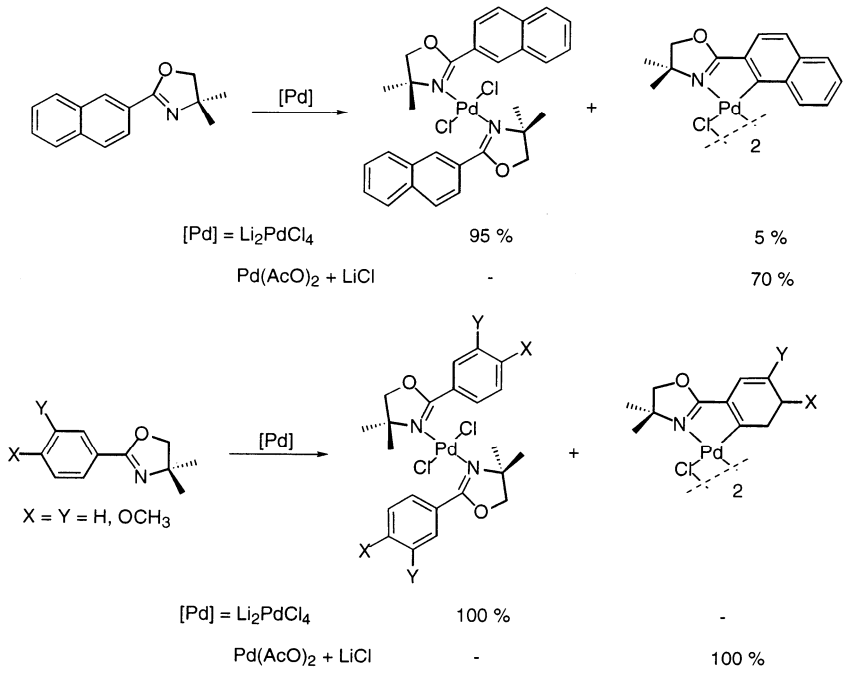


Figure 2.3. Coordination Complexes of Naphthyl and Phenyl Oxazolines.

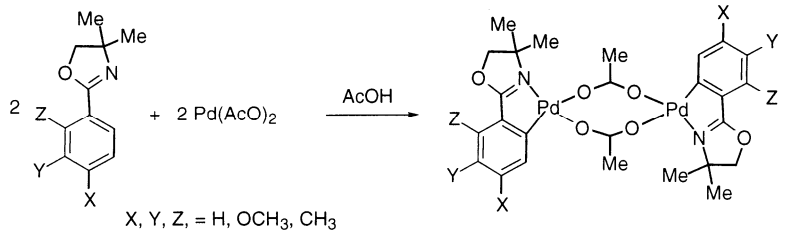
The five-membered rings of the two oxazoline ligands are nearly planar. This feature suggests that the hindrance posed by the substituent in position 2 has not effect on the geometry of the oxazoline moiety.

b. Bidentate mono(oxazoline) ligands

N,C -donor atoms

Aryloxazolines, with various substituents on the aromatic ring, as well as alkyloxazoline ligands 1, 2 and 3 (Eq. 2.36) give cyclopalladated complexes on reaction with palladium acetate in acetic acid. Oxidative addition of aromatic halides to palladium(0) complexes has been shown to provide an alternative pathway to aryloxazoline cyclopalladated compounds.

The reaction of different substituted aromatic oxazolines always leads to the formation of the dimeric species and, when the formation of regioisomers is feasible, the isomer formed by palladation at the carbon atom suffering least hindrance is preferred.

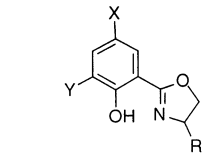


(2.37)

Steric hindrance around the amine group is not essential for this cyclometalation, since moving the gem dimethyl moiety from position 4 to 5 in the heterocyclic ring does not alter the yield. The same reaction with alkyl oxazoline (2-t -butyl-4,4-dimethyl-2-oxazoline) not only gives a 62% yield of dimeric cyclopalladated complex, but also a 16% yield of trinuclear species.

N,O -donor atoms

Several substituted phenoloxazoline compounds (NOH, 3.38) become good bidentate monooxazoline ligands (NO) after deprotonation. Reaction of metallic salts, usually containing basic anionic ligands such as acetate and acetilacetonate or even halides, with phenoloxazoline affords compounds with coordination numbers four, five or six.



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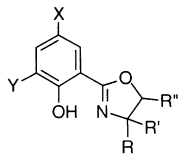

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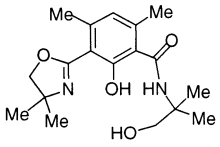

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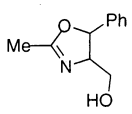


15

(2.38)

Tetracoordinate $[M(NO)_2]$ complexes were obtained with NO ligands 12 and 13, each showing different alkyl and aryl substituents in X, Y, R, R' and R" positions, and M=Cu, Zn, Ni, Co, Fe, Pd, Mn. Some of the diamagnetic complexes were characterized in solution by NMR spectroscopy revealing that whereas the palladium complex $[Pd(12)_2]$ (X=Y=H, R=Et) only showed the trans isomer, the analogous nickel complex showed two isomers (cis and trans) with a major : minor ratio 2:1. The trans is probably the major isomer. Exchange between the two isomers cannot be appreciated by NMR variable temperature experiments. X-ray structural studies conducted with $[M(12)_2]$ compounds show that the similar donor atoms N, N and O, O are trans to each other. This arrangement means molecules orient the substituent groups on the oxazoline ligands to the same side of the molecular plane, as shown in the crystal structure of various metal complexes. In all these complexes the oxazoline heterocycle is nearly planar and the angle between the phenyl ring and the six-membered metallic cycle is very small, so the two six-membered rings are nearly coplanar.

Figures 2.4-2.6 show the crystal structure of complexes $[M(12)_2]$. The coordination geometry around the central ion in palladium complexes is essentially square-planar, as shown in Figure 2.3, while the nickel complex shows distorted square-planar geometry tending to a tetrahedral configuration. Figure 2.4 shows that the Zn atom in $[Zn(12)_2]$ has a distorted tetrahedral coordination configuration. The planes between the benzene ring and the heterocycle are only slightly twisted.

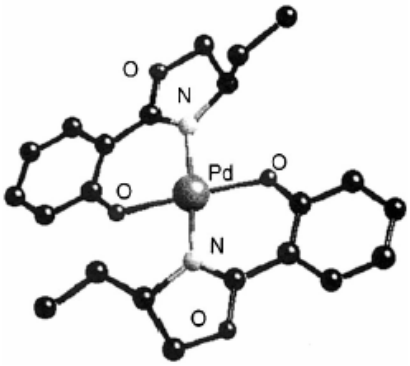


Figure 2.4. Molecular Structure of [Pd(12)$_2$] (X=Y=H, R=Et).

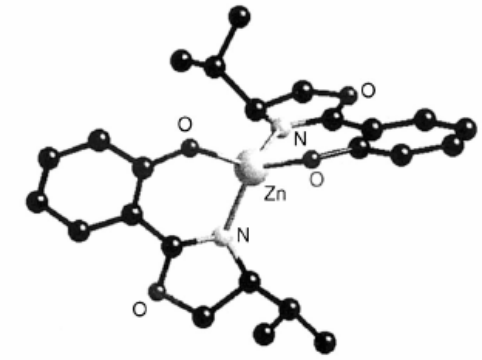


Figure 2.5. Molecular Structure of [Zn(12)2] (X=Y=H, R=i-Pr).

The copper atom of the complex shown in Figure 2.5 has a distorted square pyramidal configuration; it becomes pentacoordinated because of the interaction between the Cu atom and the phenolato ligands of the adjacent molecule (Cu(2)-O(1)), affording a pseudodimeric species. The bite angle for [M(12)$_2$]complexes varies from 90.2 to 95.2^o, with the biggest angle being that for the tetrahedral Zn comlex.

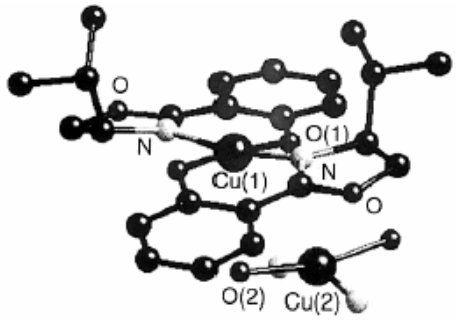
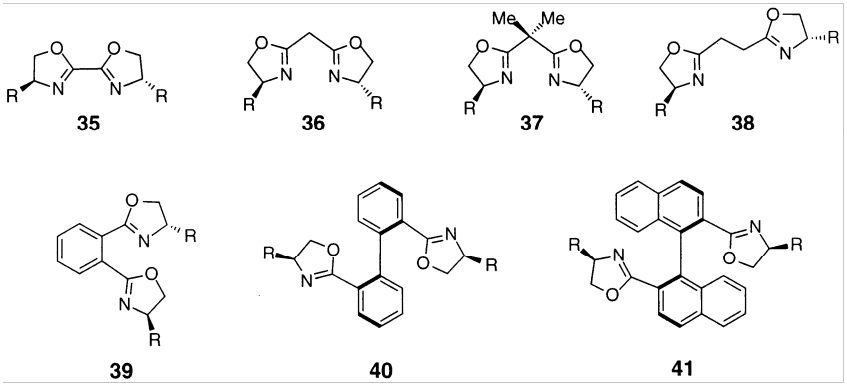


Figure 2.6. Molecular Structure of [Cu(12)$_2$] (X=Y=H, R=i-Pr) with a Fragment of a Second Molecule Showing the Pseudo-Pentacoordination of Cu(1) by the Atom O(2).

c. Bidentate bis(oxazoline) ligands

In the last decade, the C_2-symmetric chiral bis(oxazoline) ligands (NN) have received an enormous amount of attention because efficient applications have been found for them in several asymmetric organic processes. Consequently, the characterization of catalytic precursors and intermediate species was studied in order to improve and explain activity and selectivity in these organic transformations. The NN ligands that are most frequently studied in the conducting of structural research are shown in Eq. 2.39. They usually coordinate with the metal center by the nitrogen donor atoms in a bidentate fashion, giving chelate rings, from five- to nine-membered cycles. However, some of them also act as bridge ligands, where each nitrogen atom is coordinated to one metal center, stabilizing polymeric complexes.



(2.39)

Ligands 36 and 37 give six-membered anionic or neutral chelate complexes. The neutral or ionic nature of the oxazoline fragment is due to the Brønsted basicity of the methylene bridge group. Bis(oxazolines) 36 can act as anionic (by deprotonation of the CH_2 bridge unit) or neutral ligands, whereas 37 (with disubstituted methylene bridge, CR_2' is only able to coordinate as a neutral ligand. The neutral or anionic behavior of 36, reported in the literature, depends on the starting precursors used in the synthesis of the complexes (Figure 2.7).

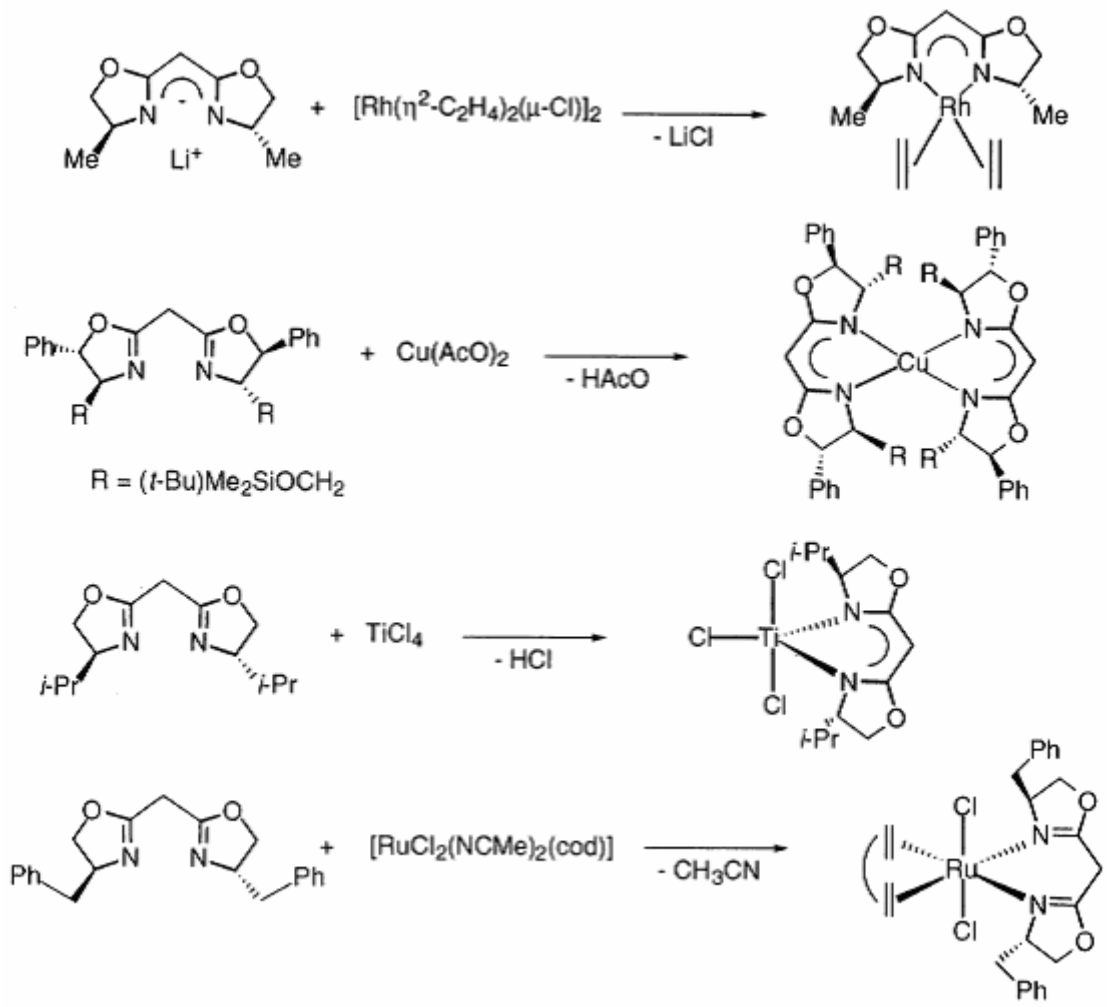
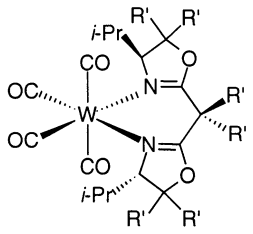


Figure 2.7. Neutral or Anionic Behavior of Some Six-Membered Chelate Complexes.

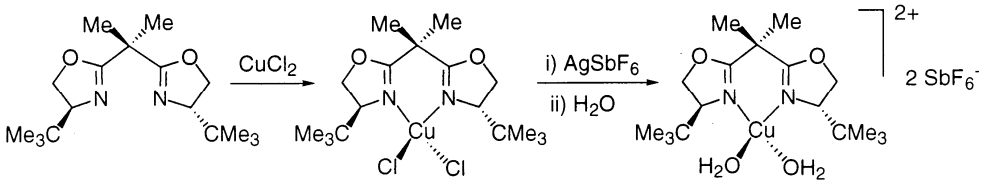
In addition, neutral 36 and 37 ligands differ in their Lewis basicity. The structural study carried out by Woodward et al. with tungsten complexes, $[W(CO)_4(36)]$ and $[W(CO)_4(37)]$ (36 and 37, R=i-Pr, Figure 2.8), proves that 37 are stronger σ donor ligands than are analogous 36. Therefore, W–N bond lengths for complex $[W(CO)_4(37)]$ (2.187, 2.192 Å) are shorter than those in $[W(CO)_4(36)]$ (2.261, 2.256 Å). Besides, the CMe_2 bridge group between the two oxazoline moieties results in deformation from an essentially planar ring for $[W(CO)_4(36)]$ to an envelope conformation for $[W(CO)_4(37)]$.



36, R' = H
37, R' = Me

Figure 2.8. Structure of the $[W(CO)_4L]$ L=36, 37 Complexes.

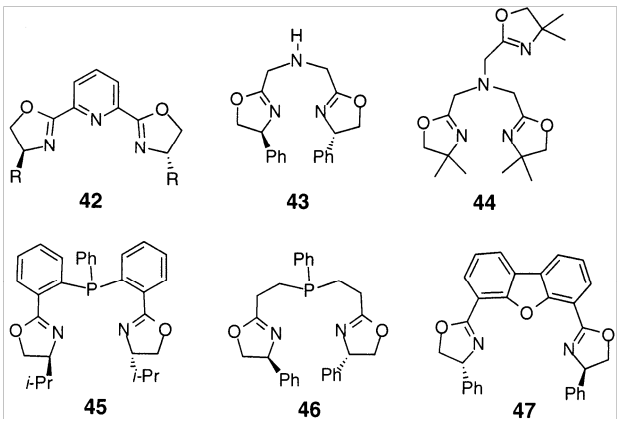
The X-ray structures of copper complexes, $[CuCl_2(\mathbf{37})]$ and $[Cu(H_2O)_2(\mathbf{37})](SbF_6)_2$ (**37**, R=*t*-Bu), exhibited a distorted square-planar arrangement around the metal atom, with the coordinated chloro or aqua ligands displaced 33-37° out of the Cu–bis(oxazoline) plane. This structural feature enabled organic dienophiles, in Diels–Alder reactions, to coordinate with the catalytic precursor in a chelating manner, giving high enantioselection in the process.



(2.40)

d. Polydentate oxazoline ligands

'Pybox' is the widely accepted name of the 2,6-(bisoxazolin-2-yl)pyridine ligands (42, 3.41), the use of which is also related to organic synthesis reactions. The complexes are mainly hexacoordinate (Ru, Rh, Mo, W, Re) or tetracoordinate (Pd, Cu).



(2.41)

Neutral and ionic ruthenium complexes trans-$[RuCl_2(42)(py)]$, and cis- and trans-$[RuCl(42)(py)_2]PF_6$ (R=i-Pr) are fully characterized in solid state and in solution.

Cyclic voltammetry studies in both $[Ru(42)(py)_2(H_2O)](PF_6)_2$ and $[Ru(42)(bipy)(H_2O)]$-$(PF_6)_2$ (R=i-Pr) suggest single, reversible, two-electron oxidation coupled with a two-proton transfer, giving $[Ru(O)(42)(py)_2](PF_6)_2$ and $[Ru(O)(42)(bipy)](PF_6)_2$ tested in oxygen transfer reactions.

The preparation of carbene compounds, proposed intermediates of the cyclopropanation reaction in which pybox ligands are efficient, were achieved by Nishiyama's group (Figure 2.9).

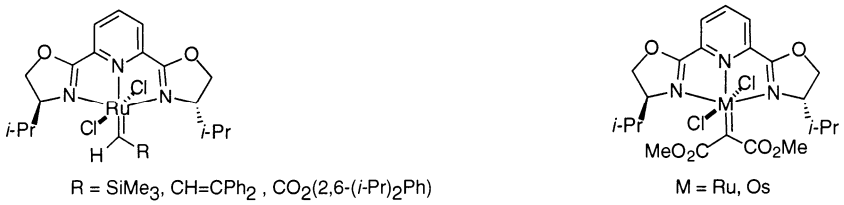


Figure 2.9. Carbene Complexes with **42** Ligands.

The pybox ligand with bulky isopropyl substituents may be necessary to stabilize the carbene complex since, when bis(oxazolinyl)pyridine was used, the analogous carbene complex could not be obtained. The molecular structure of one ruthenium–carbene complex was determined. The carbene ligand is perpendicular to the pybox equatorial plane (Figure 2.10).

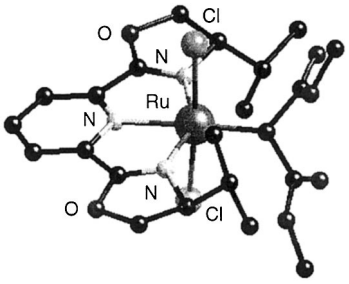


Figure 2.10. Molecular Structure of $[RuCl_2(\mathbf{42})(C(CO_2Me)_2)]$ (R=*i*-Pr).

Olefin complexes of ruthenium and osmium with pybox are useful starting materials. The molecular structure in solid state of the ruthenium ethylene complex shows that ethylene lies in the same plane as the pybox ligand (Figure 2.11).

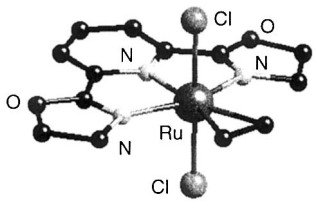


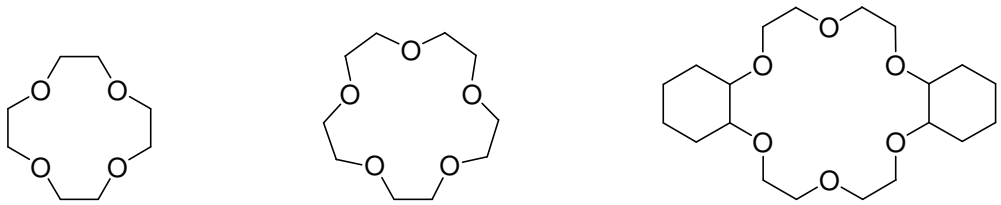
Figure 2.11. Molecular Structure of $[RuCl_2(\eta^2\text{-}C_2H_4)(42)]$ (R=H).

Given its metal coordination, the oxazoline fragment is potentially a versatile Lewis base. The oxazoline group moreover shows several coordinating modes: monodentate, bidentate, polydentate, bridge. In general it is coordinated to its metal center via the nitrogen donor atom, although a few examples have been described in which the oxazoline fragment is formed by deprotonation of an aminooxycarbene ligand and therefore, bonded by the iminic carbon atom. No complexes have been reported in which the oxygen of the oxazoline moiety acts as the donor atom. In the $[Cu(NO)_2]$ complex, where a pseudopentacoordinate copper atom is present in the crystal structure (Figure 2.6), the coordination sphere is formed from the two bidentate ligands and completed by a long-distance interaction between the copper and the oxygen atom of the phenolato fragment of an adjacent molecule.

The coordination of the oxazoline ligand may be monitored by IR spectroscopy in the 1600 cm^{-1} zone. Upon coordination the ν(C=N) generally shifts towards lower frequencies (30 cm^{-1}).

2.3. Crown Ethers

Crown ethers are large-ring polyether compounds containing several oxygen atoms, usually in a regular pattern. The essential repeating unit of any simple crown ether is ethyleneoxy, $–CH_2CH_2O–$, which repeats four times in 12-crown-4, 5 times in 15-crown-5 and six times in dicyclohexano-18-crown-6 are few examples of crown ethers. These compounds have the property of forming complexes with positive ions, generally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions [18, 19].



(2.42)

Lüttringhaus reported the first macrocyclic polyethers in 1937 as part of an investigation of medium- and large-sized rings. Since Pederson reported the formation of stable complexes between macrocyclic polyethers and salts of alkali and alkaline earth metals in 1967, many crown ethers have been synthesized and extensively studied [20]. The ability to synthesize crown ethers with complex and different architectures is becoming an increasingly important aspect of organic chemistry. Crown ethers are the group of cyclic compounds, which were first produced by Pedersen in 1967. Crown compounds possess numerous remarkable attributes, but their most important property is the ability to complex cations. Crown ethers have been extensively used in supramolecular chemistry because they have potential applications in molecular recognition, transportation, and catalysis. The most striking characteristics of crown ethers are their selective complexation ability with the cationic species [21].

These macrocyclic polyethers (crown ethers), which have “hard” donor atoms, do not readily form complexes with first-row transition metals in their low oxidation states because such metal ions provide only “soft” coordination (acceptor) sites. Only a

small number of first-row transition metal-crown ether complexes had been structurally characterized, in which the direct bond formation between the transition metal and the crown ether oxygens became possible (in complexes with the smaller ring crown ethers, e.g., 15-crown-5 and 12- crown-4 ethers). In the case of (comparatively) larger ring crown ethers, the linkage between the metal center and the crown ether is usually provided by one or more water molecules that are directly coordinated to the metal ion and hydrogen-bonded to the oxygens of the crown ether. In such cases, the crown ethers act as second-sphere ligands [18, 21]. In most cases the ions are held tightly in the center of the cavity. Each crown ether binds different ions, depending on the size of the cavity. Incorporation of heterocyclic moiety within the cavity of the crown ligands also provides rigidity and is able to participate in complexation through their soft donor atoms [22, 23]. For example, 12-crown-4 binds Li^+ but not K^+, while dicyclohexano-18-crown-6 binds K^+ but not Li^+. Similarly, dicyclohexano-18-crown-6 binds Hg^{2+} but not Cd^{2+} or Zn^{2+}, and Sr^{2+} but not Ca^{2+}. So to bind cations with different diameters, it is need to synthesis crown ethers with different holes. The method that Pedersen improved can be briefly describe as Williamson ether synthesis that is applied to difunctional compounds. Table 2.1 shows the ionic diameters of cations and Table 2.2 shows the cavity of some polyethers.

Table 2.1. Ionic Diameters of Cations.

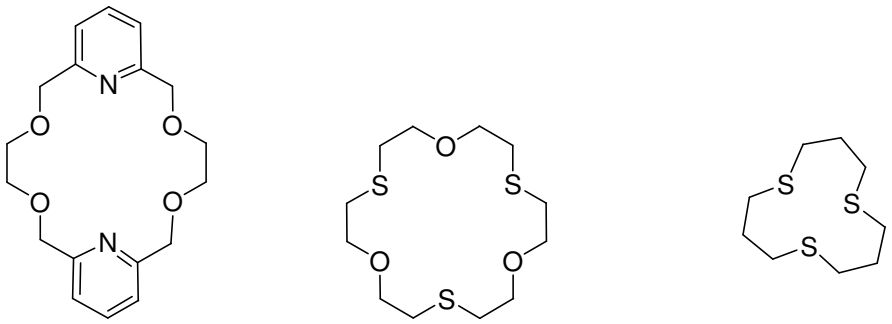
Grup I	Ionic diameter (Å)	Grup II	Ionic diameter (Å)
Li	1.20	Be	0.62
Na	1.90	Mg	1.30
K	2.66	Ca	1.98
Cu (I)	1.92	Zn	1.48
Rb	2.96	Sr	2.26
Ag	2.52	Cd	1.94
Cs	3.34	Ba	2.70
Au (I)	2.88	Hg (II)	2.20
Fr	3.52	Ra	2.80

Table 2.2. Cavity of Some Polyethers.

Polyether ring	Cavity (Å)
[12]-crown-4	1.20-1.50
[15]-crown-5	1.70-2.20
[18]-crown-6	2.60-3.20
[21]-crown-7	3.40-4.30

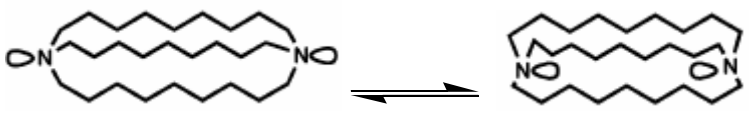
Apart from their utility in separating mixtures of cations, crown ethers have found much use in organic synthesis. Chiral crown ethers have been used for the resolution of racemic mixtures. Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed.

Heteroatoms other than oxygen have been incorporated into the macromolecular framework since macrocycles are used almost exclusively for binding cations. Macrocyclic compounds containing oxygen, sulfur and nitrogen as donor atoms have gained attention for their ability to form stable complexes with ions within their central cavity. They have similar properties, as do those containing more than one kind of heteroatom. Due to differences in polarizability, nitrogen-containing crown ethers (azacrowns) and sulfur-containing crown ethers (thiacrowns) display different ionic selectivities than oxygen-containing crown ethers [24].



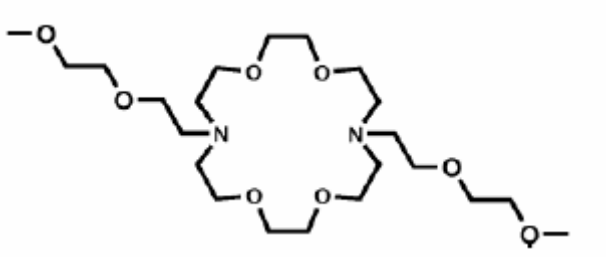
(2.43)

It is possible to design molecules in which more than one cyclic system is incorporated. Such molecules are described as *cryptands* [25].



(2.44)

Lariat ethers are a blend of crowns and cryptands. They were designed to have the three dimensionality of cryptands while retaining the faster complexation dynamics of crown ethers [26].



(2.45)

Crown ethers form essentially two-dimensional complexes. In contrast, cryptands and lariat ethers form enveloping complexes in which the cation is solvated by all donors more evenly than is typically the case in crown ether complexes. Usually, but not always, solvents and anions are excluded from the solvation sphere (Figure 2.12).

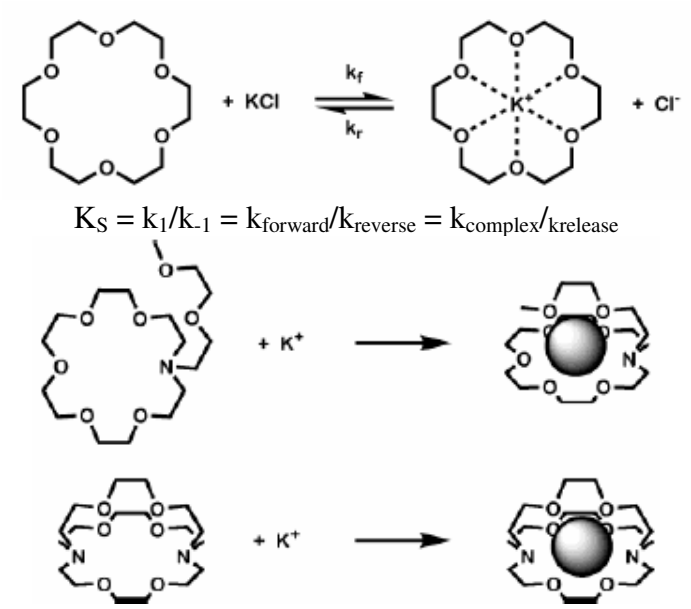


Figure 2.12. Potassium Complexes of Crown Ethers, Lariat Ethers, and Cryptands.

The ability of crown ethers to bind metallic cations is documented in hundreds of papers. Binding is understood for many macrocycles and cations in considerable detail. There are so many cations and macrocycles that a brief survey cannot possibly encompass them all. Further, solvent plays a role in binding, which multiplies the complexity of the landscape.

2.3.1. Preparations of Crown Ethers

To obtain macrocycles resembling crown ethers, the first method is Pedersen's synthesize method (Figure 2.13); the reaction of difunctionalized alcohol derivatives with difunctionalized halide derivatives. In this method forming polymerized products are natural and inevitable [27].

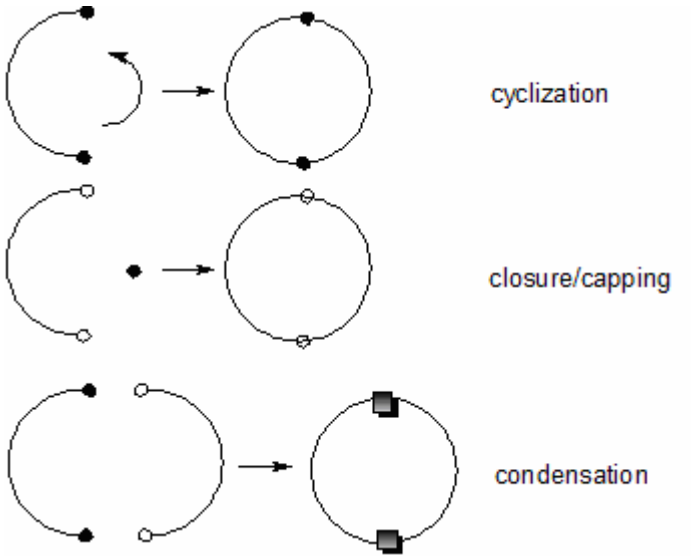
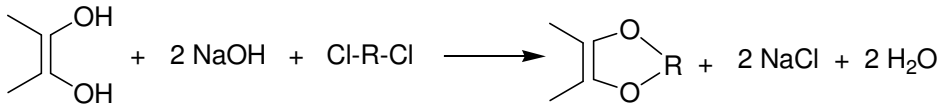


Figure 2.13. Pedersen's Synthesize Method for Crown Ethers.

Methods of crown ether synthesis:



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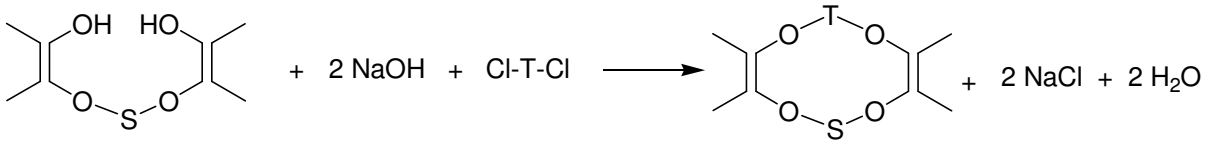

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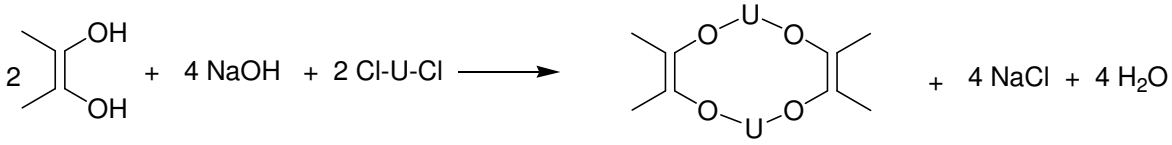

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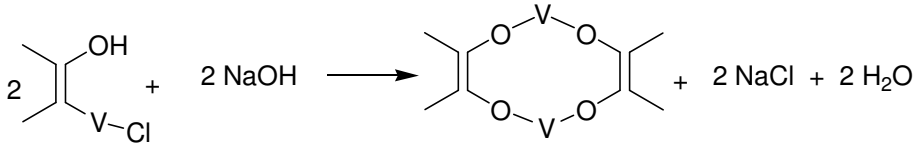

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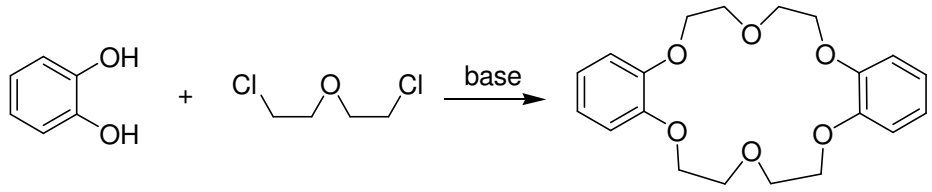
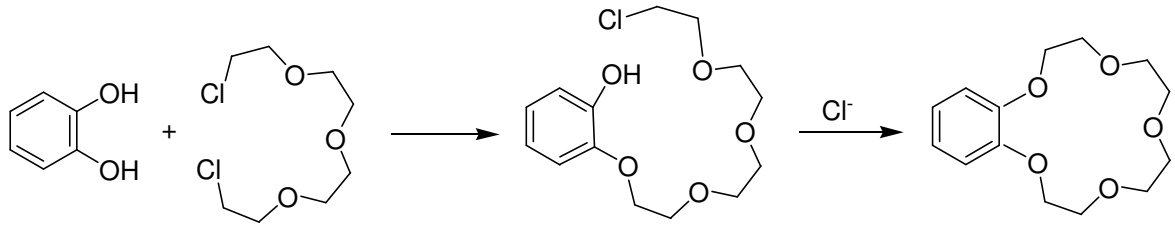


(2.50)

There are two principal ways to synthesis crown ethers without obtaining polymerized products: high dilution system and template effect. Both of these methods have various advantages and disadvantages.

a. <u>High dilution technique</u>

Without getting polymerized products, A and B reactives should drop in high dilution and at the same rate to the reaction flask. The disadvantage of this method is synthesizing of very small amount of product in a high volume of solvent. Synthesizing of Benzo-15-crown-5 product is shown below [27].



(2.51)

In order to obtain a high cyclization yield, cyclization must be favored at the expense of polycondensation. It is based on the following factors. The intramolecular ring closure reaction is first order, its rate being proportional to concentration. The intermolecular condensation reaction is second order and therefore its rate is proportional to the square of the concentration. It follows that dilution should favor the intramolecular reaction. The more rigorous procedure, which consists of determining the effective molarity of the reaction (k_{intra} and k_{inter}) and then using the results obtained to determine the ideal concentration, is rarely used.

b. <u>Template ring closure</u>

In this method two active sides of molecule are heading towards each other with the existence of metal ions (Figure 2.14).

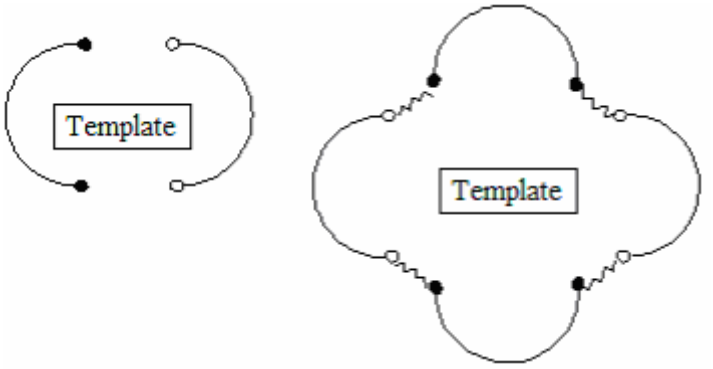
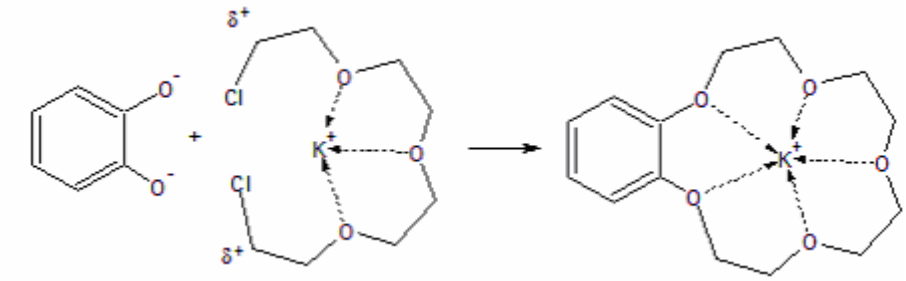


Figure 2.14. Showing the Template Effect.



(2.52)

Many cyclization methods are based on the use of a temporary or permanent template, and on specific reactions depending on the nature of the reacting groups between which the bond leading to ring closure is formed. Cyclization may take place using either an internal (endo–) or external (exo–) template [27].

Endo– template

When the formation of a macrocycle is based on a smaller ring that is then ring-enlarged to include all the pre-existing parts of the molecule, this process can be described as occurring by the use of an endo-support. An example is the insertion of a side chain into the ring. Similarly, the "zip" reaction is based on ring expansion by the process of sliding along a side chain (Figure 2.15, a,b).

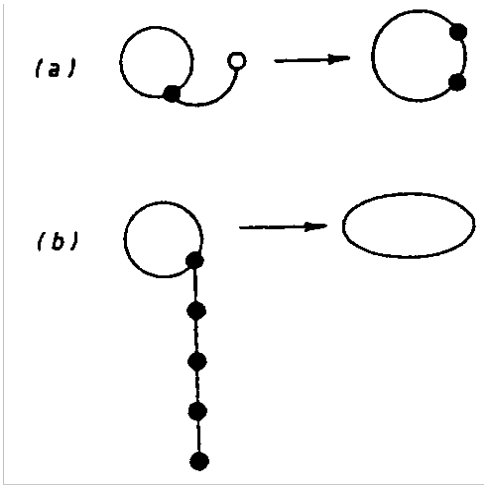


Figure 2.15. Ring Expansion Using (a) an Internal Template or (b) Successive Internal Templates.

Another approach is initial formation of a bicyclic system containing a cleavable bond, the subsequent breaking of which gives a macrocycle (Figure 2.16). Bonds which have been used to this end are C–N, N–N, C–C, and C=C [27].

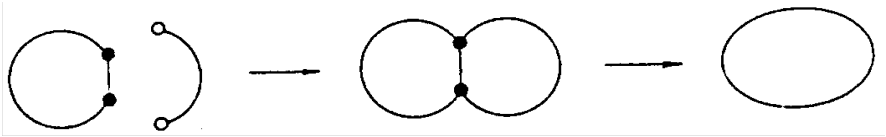


Figure 2.16. Large Ring Formation by Bond Cleavage in a Bicyclic System.

Exo– template

A temporary center or group, which may be either ionic or covalent, may be used in cyclization reactions. This serves as a template on which the macrocycle is assembled, and which is sequently eliminated.

Metal cations are by far the oldest-known and most used templates. The process may occur in a single step that assembly and connexion of the units occur simultaneously around the ion (Figure 2.17, a). Alternatively, there may be several steps in which the placing of one type of unit is followed by bridge formation by another species (Figure 2.17, b) [27].

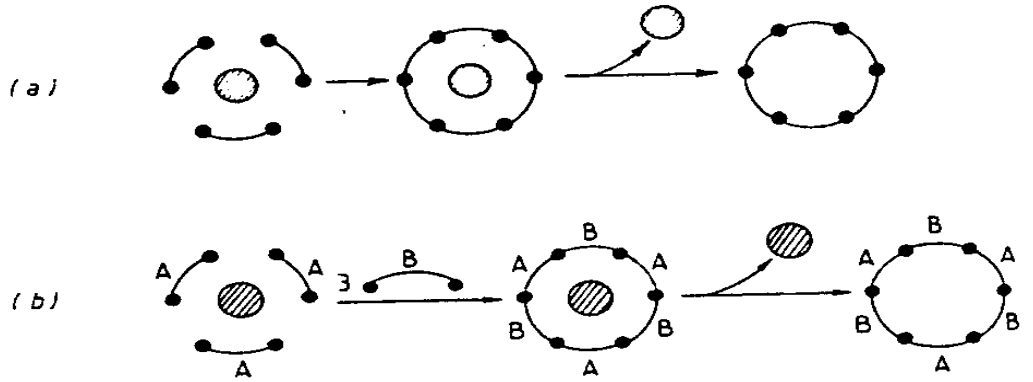


Figure 2.17. Cyclizaion Around a Metal Cation (External Template).

Metalloid derivatives (Si, Sn, B) have been used as chemical templates serving both as a template for chain assembly and as a reaction site for subsequent ring closure of the chains thus locked in position (Figure 2.18).

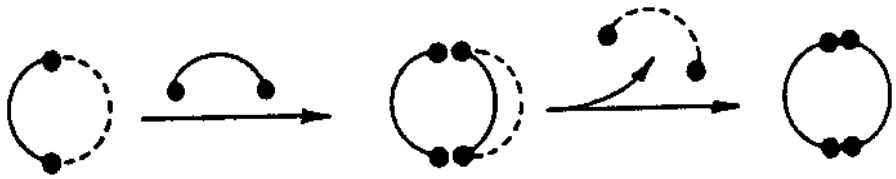


Figure 2.18. Scheme for Cyclization Using an External Template. The Template ---- is Called External Because It is Eliminated at the End of the Synthesis and Not Incorporated into the Product.

Certain atoms or molecular groups can also act as temporary templates. An example is sulfur, which after having enabled cyclization to take place is then eliminated (Figure 2.19) [27].

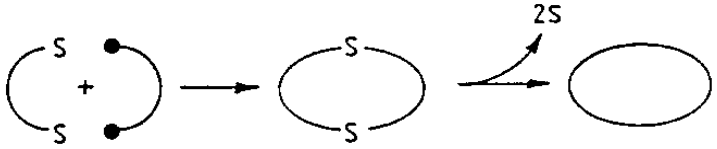


Figure 2.19. Use of Sulfur as an External Template.

2.3.2. Applications of Crown Ethers

The fields of anionic synthetic reagents, phase-transfer catalysis, biological ion transport, and other emerging disciplines benefited profoundly from the discovery of crown ethers [26].

a. Solid-liquid phase transfer catalysis

The insoluble salt incorporating the active anionic species is in suspension in the organic solvent containing the phase transfer catalyst and the substrate. In this sense, the insoluble inorganic salts could be solved in apolar solvents. So many reactions could be done in apolar solvents.

Although the majority of complexation studies conducted with crown ethers involve metal ions, many other guest species have been examined. Ammonium ion, NH_4^+, and primary alkylammonium ions, RNH_3^+ are particularly appropriate for crown complexation and amenable to study [26].

b. Azobenzenes and photochemical switching

The normal geometry of the N=N bond in azobenzene is trans (E). When irradiated at the appropriate wavelength, the double-bond geometry changes from trans to cis (E to Z). The azo linkage has been used to join the aromatic rings of two benzo-15-crown-5 molecules. When the bis(crown) is irradiated, azobenzene undergoes a light-induced E to Z isomerization. The two macrorings are remote in the former isomer and proximate in the latter. A cation may be bound in the space created by the cooperation of two rings, while two molecules of the E-isomer would be required to form a sandwich complex with a large cation. This principle was further demonstrated with a molecule containing a crown, an ammonium ion, and azobenzene to serve as the conformational switch (Figure 2.20). When the methylene chain was butylenes (n=4), aggregates were detected in solution before or after irradiation. When n=6 or 10, only monomers were detected, suggesting intramolecular crownammonium ion complexation [26].

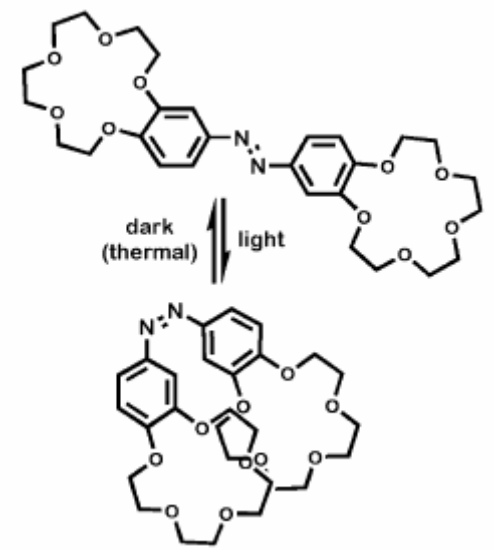


Figure 2.20. Photochemical Switching of Crown Ether Systems.

c. Crown ethers as sensors

Their selective receptor properties in conjunction with the relative ease of synthesis and structural modification make crown ethers attractive targets as ionophores shown in Figure 2.21.

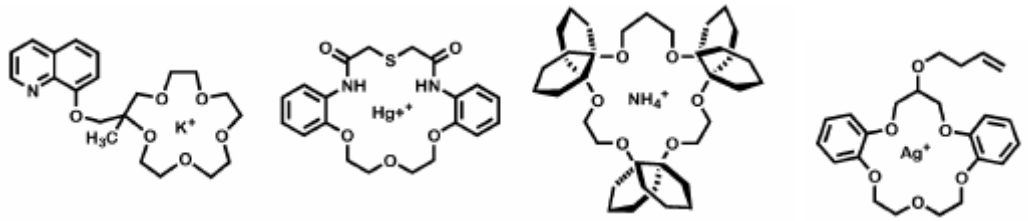


Figure 2.21. Crown-based Ionophores (Ion Sensors).

Although many crown-based sensors are developed for use in ion-selective electrodes (ISEs) there are many other applications [28].

d. Crown ethers as dyes

The first compounds reported were 4'-picrylamino-substituted derivatives of benzo-15-crown-5. These dyes, most of which are nearly insoluble in aqueous solvents, can efficiently extract cations at the organic/aqueous interface.

The 15-crown-5 derivative shown in the left panel of Figure 3.20 turns from orange to red when bound to K^+ or Rb^+. The host is unable to bind either Li+ or Na+. Such dyes have been designed to incorporate azacrowns and lariat ethers to alter cation selectivity, water solubility, and pH dependence but still extract ions efficiently. In the right panel of Figure 2.22 there is a crown ether dye that incorporates a phenolic

hydroxyl group as part of the crown ether backbone. Addition of LiCl and excess pyridine to the ligand results in a color change from purple to red. This effect was not observed upon addition of other metal cations [26].

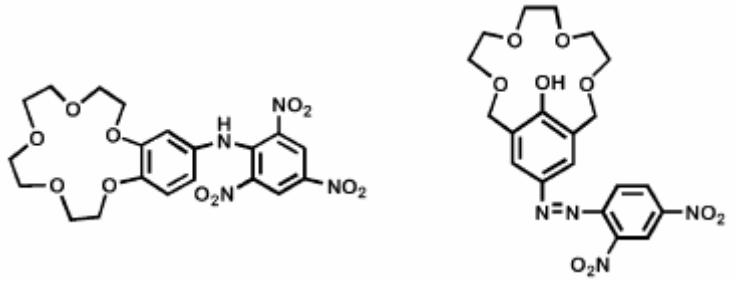


Figure 2.22. Crown-based Dyes for Spectrophotometric Detection.

e. Crown ethers as photochromic sensors

Several of the chromogenic crowns involve the spirobenzopyran subunit have been widely used in developing photochromic sensors.

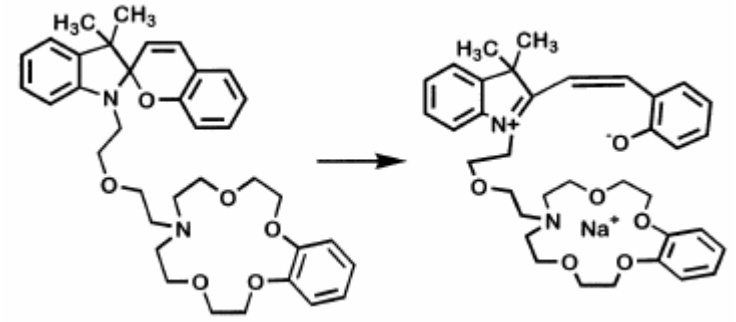


Figure 2.23. Changes in the Spirobenzopyran-Based Crown Ether for Ion Sensing.

Figure 2.23 shows how the structural and photophysical changes correlate to permit ion sensing. This methodology has also been used in tandem with mass spectrometric analysis [26].

f. Crown ethers as fluorescence sensors

De Silva and co-workers pioneered the use of crown-based ionophores for fluorescence sensing. Such sensors integrate a receptor, in this case a crown ether, and a fluorophore for detection. Photoinduced electron transfer (PET) is the most common fluorescence technique used in these systems, whereby fluorescence is quenched by a partial charge, typically the free lone pair of electrons on a nitrogen atom.The first molecule of this type that was studied is shown in Figure 2.24.

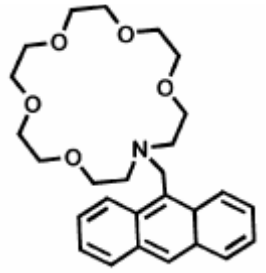


Figure 2.24. De Silva's Anthracenylmethyl Lariat Ether for Fluorescence Signaling.

One noteworthy example is the development of a fluorophore that can bind γ-aminobutyric acid (GABA) zwitterions via a guanidinium moiety incorporated into the fluorophore, giving a valuable approach to tracking the neurotransmitter.

This fluorescent sensor and a related coumarinbased macrocycle have been used as chemosensors for the marine toxin saxitoxin (Figure 2.25).

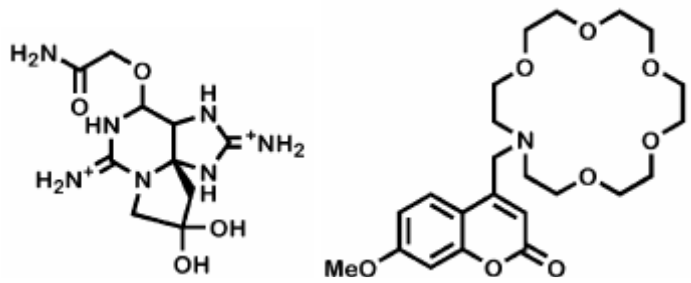


Figure 2.25. Saxitoxin (Left) and a Saxitoxin Sensor (Right).

The fluorescent unit (the ruthenium tris(bipyridyl) complex) was then formed by treatment with two additional 2,2'-bipyridine units. Alternately, a corresponding bipyridyl ruthenium tetracarbonyl unit could be prepared. The former is shown in the adjacent figure (Figure 2.26) [26].

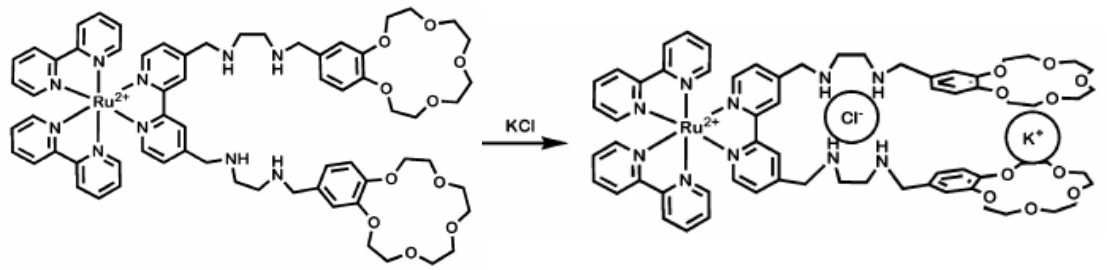


Figure 2.26. Luminescent Sensor for Ion Pairs.

g. Molecular mousetraps

The ability of crown ethers to bind the positively charged side chains of lysine or arginine has long been known. Julian and Beauchamp exploited this recognition property by developing a family of receptors that they call "molecular mousetraps:"

crown-based compounds that utilize the strong interaction between 18-crown-6 and protonated primary amines. Compounds (MT1 and MT2, Figure 2.27) complex the cations in solution. The mixture is then subjected to electrospray ionization mass spectrometry (ESI-MS).

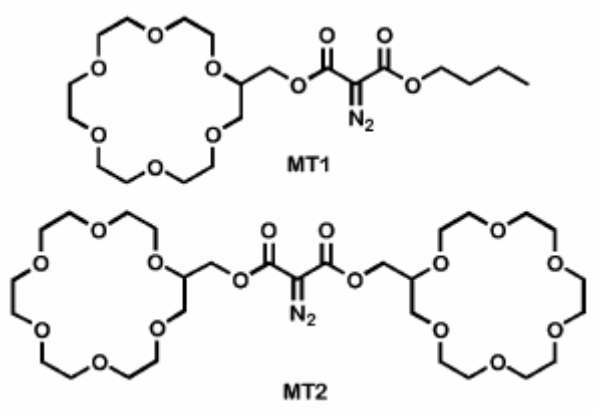


Figure 2.27. Molecular Mousetrap Sensors for ESI-MS.

The derivatization of 18-crown-6 was done to introduce specific functional groups that can couple the host to target molecules. This "molecular mousetrap" approach offers a useful adjunct to traditional mass spectral analyses of biological substrates [26].

h. Biological model systems

The cells and organelles that are the fundamental macroscopic elements of living systems are dauntingly complex. The common chemical structures such as proteins, RNA, and DNA strands are simpler but incredibly complicated at the chemical level. One approach is to prepare structures that are designed to mimic or probe specific chemical interactions thought to be involved in biological function. A different approach involves the preparation of simplified models that function in the same way as a biologically important structure.

Crown ether compounds have played a role in both approaches. Some simple crown ethers exhibit biological activity. Some biologists feel that no model system is sufficiently sophisticated to provide useful information about the complex activity observed in nature [26].

i. Crown ethers as amphiphiles for membrane formation

It is not surprising that crowns exhibit surface-active properties. Kuwamura, Okahara, and their respective coworkers recognized the potential amphiphilicity of alkyl-substituted crown ethers. Both groups demonstrated the formation of aggregates from a variety of crown compounds.

Cholesterol is an important component of most mammalian plasma membranes and is thought to help organize or "rigidify" the bilayer. When cholesterol was linked to an aza-15-crown-5 residue, it fostered crystallization, making possible the solid-state structure shown in Figure 2.28.

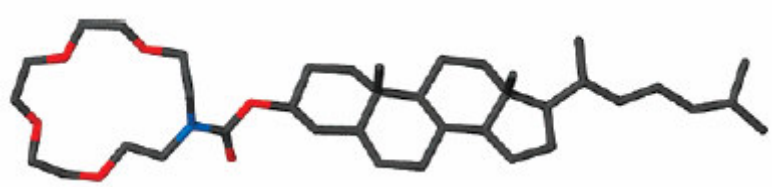


Figure 2.28. X-Ray Structure of Cholesteryl Lariat Ether.

Substituted cryptands also form stable aggregates when sonicated in aqueous suspension. A broad range of crown ethers was eventually shown to form aggregates generally or liposomes in particular. These included two- and three-armed diazacrowns in addition to the previously known single-armed macrocycles. When a hydrocarbon chain connects two crowns, the so-called bola-amphiphiles (Figure 2.29) may also form stable vesicles or other aggregates. Fyles and co-workers recently showed that certain crown bola-amphiphiles function as "membrane disruptors" [26].

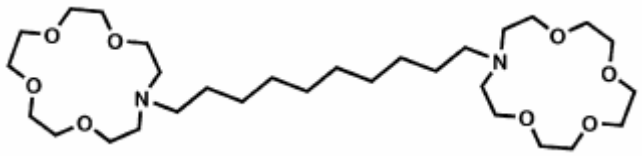


Figure 2.29. An Example for Bola-Amphiphiles.

j. Ion channel model systems

During the past two decades, the preparation of synthetic ion channels has been undertaken in an attempt to model protein channels and to develop therapeutic agents [29].

Notable among the crown ether-based channels are the "chundles" reported by Lehn, the bola-amphiphiles of Fyles, Voyer's crown-substituted peptides, the redox-

switchable systems of Hall, and the steroid-substituted crowns of Pechulis. Figure 2.30 shows the channel systems developed by Voyer (top), Fyles (middle), and Hall (bottom). These are noted particularly as conductance data have been acquired for them, either in planar bilayers or as patches that show the classic open-shut behavior of protein channels.

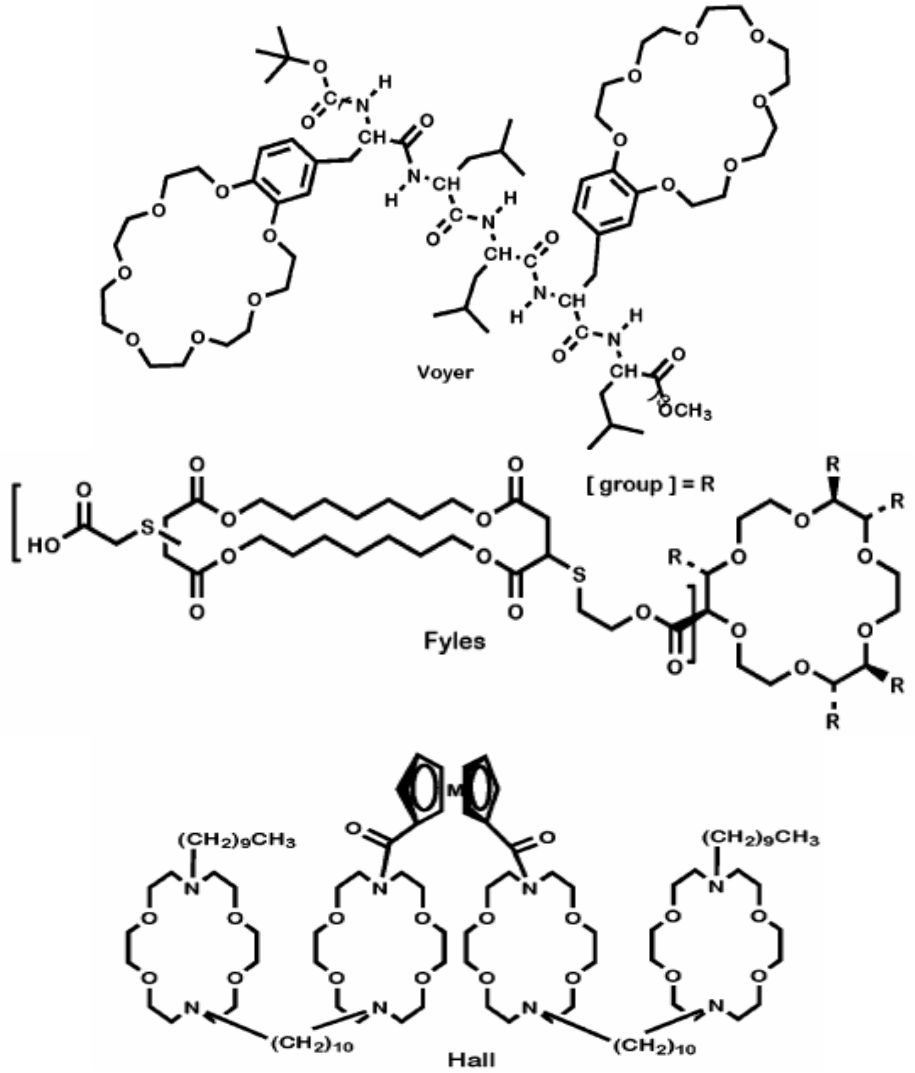


Figure 2.30. Synthetic Model Ion Channel Systems.

Voyer's approach to channels used the De Grado peptide backbone, to which is attached a benzo-21-crown-7 at every fourth residue. This peptide is thought to form an R-helix in the membrane, which then aligns the crown ethers to form a tube through the bilayer. These channels have shown Cs^+ transport activity comparable to that of gramicidin in vesicles and have demonstrated single-channel behavior in bilayer patch studies [29].

The overall length of the compound shown in Figure 2.31 is about 42 Å, which is the approximate distance needed to span the membrane hydrocarbon insulator regime. The arrangement of the compound in the bilayer in the figure is based on extensive structural and fluorescence studies.

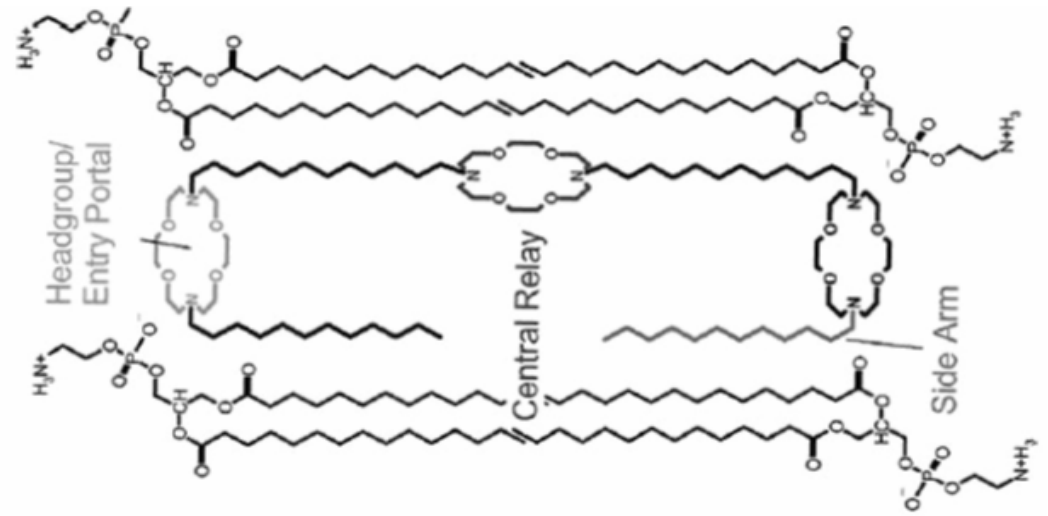


Figure 2.31. Synthetic Hydraphile Channels of Gokel and Co-workers as They Align in the Membrane.

k. Biological activity of crown ethers

Their applications in biology include the ability to regulate enzyme activity, interact with and cleave DNA, and act as antimicrobial agents. Functionalized crowns have been synthetically designed to achieve these functions; however, the basic heterocycles themselves yield beneficial biological interactions as well. Simple crown compounds such as 18-crown-6 and 15-crown-5 have the ability to interact with enzymes. This interaction boosts the activity of enzymes when used in organic solvents. Numerous enzymes exist that benefit from the presence of crown ethers, including lipases, the enzyme subtilisin Carlsberg, and R-chymotrypsin.

Crown ether compounds have been designed and synthesized to interact with DNA, the double-stranded oligonucleotide helix that encodes life. Both Kerwin and Brandt developed compounds that can not only cleave DNA, but also halt the growth of cancer cells.

These lytic crown ethers are shown Figure 2.32. Compound DNA-2 is proposed to act through a mechanism by which the 1-aziridinyl groups form carbocations that

interact with and cleave DNA. The DNA damage halts cell proliferation, making DNA-2 a cytostatic drug.

Macrocycle DNA-3 (Figure 2.32) is involved in an electrophilic alkylation reaction with the DNA phosphate backbone that leads to strand cleavage. Both DNA-2 and DNA-3 have been tested against cancer cell lines to assay their ability to inhibit growth in tissue culture.

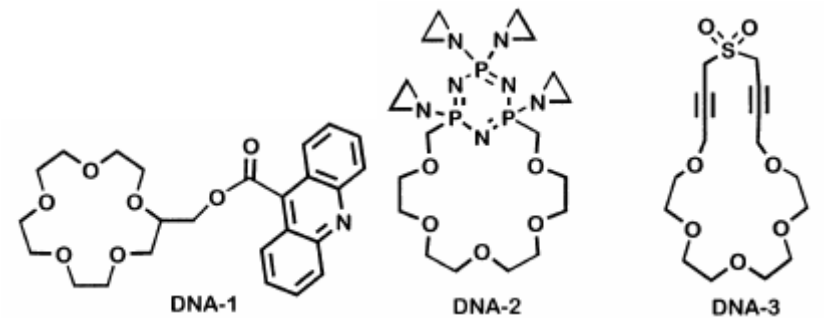
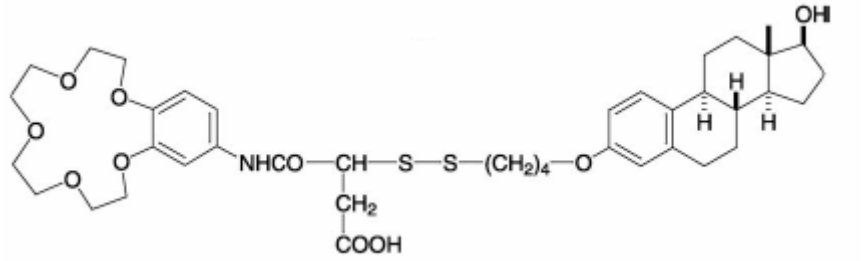


Figure 2.32. Crown Ether DNA Mimics.

l. Crown ethers in clinical usage

Current interest in the clinical use of chelating agents as vehicles for delivery of metals to sites in biological systems has led to the synthesis and study of a large number of new cyclic polyoxa and polyaza ligands [20]. A novel measuring method (electroimmunoassay) of 17β-estradiol (E2) in urine or blood was proposed on the basis of a competition between E2 and a labeled E2 against an immobilizing antibody. To evaluate the principle, 3-{4-[17β-hydroxy-1,3,5(10)-estratrien-3-yloxy] butyldisulfanyl}-N-(6,7,9,10,12,13,15,16-octahydro-5, 8, 11, 14, 17 pentaoxabenzo cyclopenta decen-2-yl) succinamic acid was designed and synthesized as a novel aminobenzo-15-crown-5-containing E2 tethered with disulfide linkage [30].



(2.53)

m. Crown ethers in chromatography

Chromatography is utilized to purify drugs, proteins, ions, racemic mixtures, and numerous other organic molecules. Several clever techniques have been developed to accomplish each of these separations, including the use of crown ether compounds. Cram and co-workers reported the first example of chiral crown ethers attached to silica and a polymer resin in the late 1970s. This work led to numerous examples of crown ethers incorporated as a stationary phase in chromatography. Hyun demonstrated crown-based separation of enantiomeric compounds that possess a primary amino group.

In one case, a diphenyl-substituted 1,1'-binaphthyl crown ether bonded to silica gel (Figure 2.33, top panel) separated fluoroquinolone enantiomers (gemifloxacin shown at bottom left) by HPLC [31].

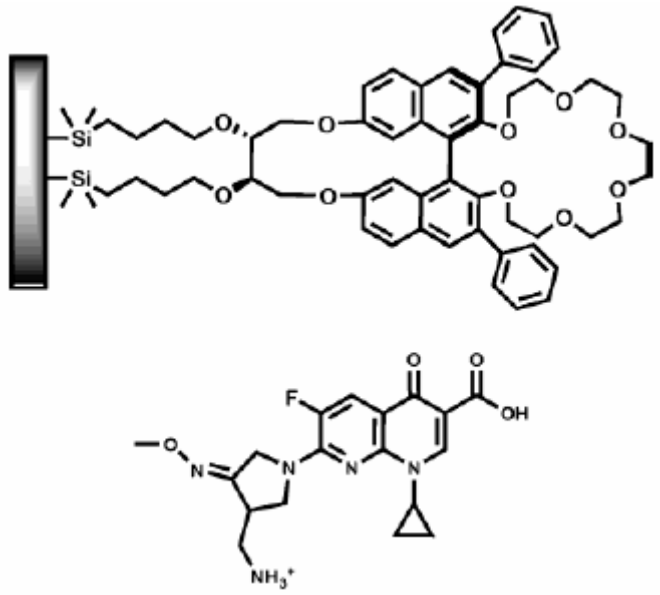


Figure 2.33. Solid Support for Chiral Separation (Top) and Gemifloxacin (Bottom).

Crowns have been applied in stationary and mobile phases for ion chromatography and proven very effective [31].

n. Crown ethers as cleaning agents

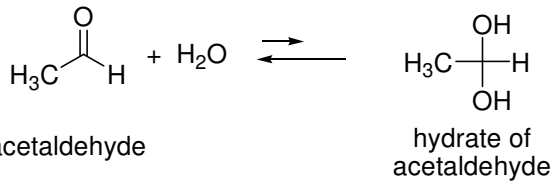
The selective complexing properties exhibited by crown ethers towards metal ions have led to their incorporation into polymeric matrices. Polymer-supported reagents offer many advantages, including ease of handling and recoverability when used in the removal of toxic metal ions from the environment. Due to increased concern with

the remediation of wastewater, polymer-supported reagents, including immobilized crown ethers, have been studied for the selective removal of targeted metal ions [24].

Of particular importance is the size and shape of the cavity relative to the cation size. If the ion is larger than that of the crown cavity, there is a tendency for the crown ether moieties to “sandwich” the metal ions between adjacent crown units [24].

2.4. Acetals

When carbonyl compounds are dissolved in water, they exist in equilibrium with low concentrations of their hydrates, which are compounds in which water has been added to the carbonyl group [32].



(2.54)

Alcohols react aldehydes in an equilibrium process, just as water does, to yield compounds known as hemiacetals. In a hemiacetal, a hydroxyl group and an alkoxy group are bonded to the same carbon atom. Hemiacetals, after losing a molecule of water, react with yet another molecule of alcohol to give acetals. In an acetal, two alkoxy groups are bonded to the same carbon atom. Ketons give hemiketals and ketals with alcohols.

Hemiacetals and hemiketals are generally unstable compounds unless the alcohol and carbonyl groups are part of the same molecule, in which case equilibrium favors the formation of stable cyclic hemiacetals and hemiketals containing five- or six-membered rings (Figure 2.34).

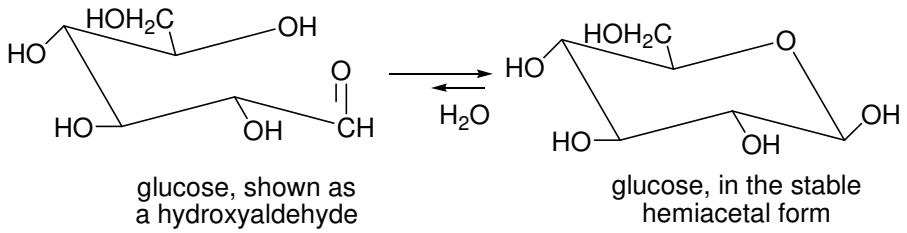
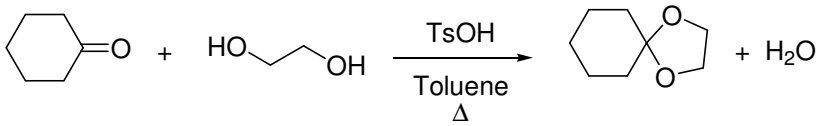


Figure 2.34. Formation of Stable Cyclic Hemiacetals and Hemiketals Containing Five- or Six-Membered Rings.

If an aldehyde or ketone is placed in an excess of an alcohol in the presence of an acid, an acetal or ketal is formed. The acetal is the most common protecting group for either carbonyl groups or alcohols [33]. The protection of carbonyl compounds plays an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry. Among carbonyl protecting groups, 1,3-diothiolanes, 1,3-oxathiolanes, and 1,3-dithianes are important, as they are quite stable under both mildly acidic and basic conditions [34, 35]. The protection of the hydroxyl group serves three functions: it allows a Grignard reagent to be made from an alkyl halide containing a hydroxyl group, it differentiates that hydroxyl group from a new hydroxyl group created in the Grignard reaction, it allows the original hydroxyl group to be restored at a later stage of the synthsis.

Ethylene glycol is used to make cyclic acetals or ketals in which both alcohol groups that react with the carbonyl group are on the same molecule. The formation of cyclic acetals or ketals is much more easily then their acyclic counterparts for reasons of entropy.



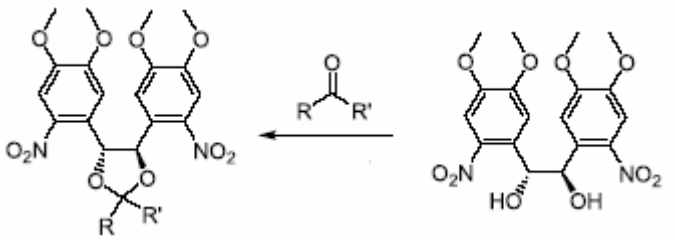
(2.55)

Selective protection and deprotection of hydroxyl groups are very important procedures in multi-step syntheses of complicated molecules. Acetal type protecting groups such as methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), and tetrahydropyranyl (THP) are commonly used for alcohols and phenols. An acetal or ketal structurally resembles a diether and as such is stable to bases, reducing agents, and nucleophilic reagents.

Although many methods to deprotect them (mild acidic conditions) have already been reported, most were accomplished under acidic conditions, which often causes

adverse reactions. Recently, Lee et al. are reported on the deprotection of MOM and MEM protecting groups by reactions with CBr_4 and i-PrOH. Seemingly, this reaction proceeded under neutral conditions. However, HBr, generated from CBr4 and i-PrOH in situ, causes deprotection [36].

There are also some acetals and ketals that are stable against acidic and basic reaction conditions and are cleaved smoothly on irradiation at 350 and 400 nm with regeneration of carbonyl compounds in high yields and efficiency [37].



(2.56)

Carbonyl compounds have been successfully converted into their corresponding oxathiolane, dithiolane and dithiane derivatives (thioacetals) in excellent yields with 2-mercaptoethanol, 1,2-ethanedithiol and 1,3-propanedithiol using a catalytic amount of molybdenyl acetylacetonate (Figure 2.35) [38, 39].

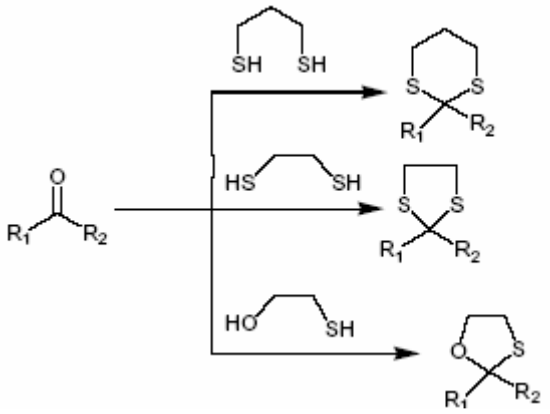


Figure 2.35. Convertion of Carbonyl Compounds into Their Corresponding Thioacetals with Thiol Compounds.

3. EXPERIMENTAL

3.1. Instruments and Materials

Reactions were stirred magnetically. Unless otherwise noted, commercially available materials were used without further purification. ^{1}H and ^{13}C NMR spectra were obtained using Bruker (250 MHz) magnetic resonance spectrometer. Melting points were measured with a Gallenkamp capillary melting point apparatus. Infrared spectra were measured on a Perkin Elmer Spectrum One with an ATR attachment by FT-IR reflectance spectrometry (with a diamond and ZnSe crystal). Thin-layer chromatography was performed on 3.25 mm thickness, 245 nm floresans indicator silica gel plates. Silica gel used for colon chromatography (Kieselgel 60H, 0,040-0,063 mm) was obtained from Merck. GC-MS spectra were obtained using GC-MS Finnigen 70 ev (sensitivity: 1074 m/e) spectrophotometer. List of chemicals used in experiments are shown in Table 3.3.

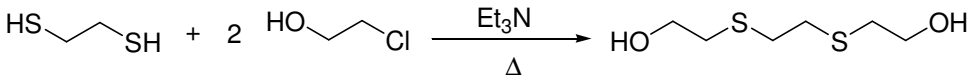
Table 3.3. List of Chemicals Used in Experiments.

1,2-Ethane dithiol	(Lab-Scan)	Glyoxal bis(sodium hydrogen sulfite) Adduct	(Fluka)
1,4-Dioxane	(Acros)	Hexane	(J.T. Baker)
2-Mercaptoethanol	(Acros)	Lanthanum chloride	(Acros)
Formic acid 98%	(J.T. Baker)	Malononitrile	(ABCR)
Acetic acid 99%	(Baker)	Methanol	(Lab-Scan)
Benzene	(J.T. Baker)	*β*-Naphthol	(Riedel-de Haen)
Benzyl chloride	(Merck)	Nitric acid	(Merck)
Brom	(Merck)	*p*-Formaldehyde	(Merck)
n-Butil Lithium	(Acros)	*p*-toluenesulfonic acid monohydrate	(Fluka)
Chlorobenzene	(Acros)	Sodium cyanide	(Merck)
Chloroform	(J.T. Baker)	Sodium hydroxide	(J.T. Baker)
Copper (II) Chloride anhydrous 99%	(Acros)	Sodium metabisulphite	(Acros)
Dichloromethane	(J.T. Baker)	Sodium sulfate	(Riedel-de Haen)
Dimethyl malonate	(Acros)	Sodium sulfide ($Na_2S.9H_2O$)	(Merck)
Ethanol	(J.T. Baker)	Sulfuric acid	(Carlo Erba)
Ethanol amine	(Acros)	Tetrachloromethane	(J.T. Baker)
Ethyl acetate	(J.T. Baker)	Toluene	(J.T. Baker)
Ethylene chlorohydrin	(Acros)	Triethyl amine	(Merck)
Ethylene glycol	(Merck)	Zinc chloride	(Baker)
Glyoxal 40%	(Acros)		

3.2. Methods and Descriptions Used for Preparation of Compounds

3.2.1. Preparation of 3,6-Dithiaoctane-1,8-diol [40]

In a 50 mL round-bottomed flask fitted with a reflux condenser 6.00 mL Et_3N and 1.70 mL (0.02 mol) 1,2-ethane dithiol were placed, and 2.60 mL (0.04 mol) ethylene chlorohydrin was added dropwise to the mixture. Reaction mixture was refluxed for 3 h. Extracted with EtOAc, crystallized from CH_2Cl_2.



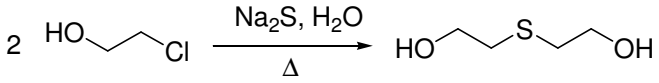
3.2.2. Preparation of β-Thiodiglycol [41]

In a 2-nacked flask 9.00 g (0.11 moles) of 20% ethylene chlorohydrin solution and 23.00 mL of water were placed. The flask was set in an empty pan of suitable size to serve as a bath in case cooling becomes necessary. With the stirrer in operation, 15.00 g (0.06 moles) of crystalline sodium sulfide containing nine molecules of water of crystallization was added to the chlorohydrin solution at a rate which would maintain the temperature at 30–35°C. After all the sodium sulfide has been added the solution was stirred for 30 min. The flask was fitted with a reflux condenser and a thermometer that dipped into the liquid. The flask was then heated on a steam bath until the temperature of the liquid was 90°C, and for a period of 45 min. the temperature was held at 90–95°C. The solution was then cooled to r.t. and neutralized to turmeric paper by adding concentrated hydrochloric acid drop by drop[1]. After filtering, the solution was returned to the flask for concentration at reduced pressure.

The residue in the flask, which consisted of sodium chloride and thiodiglycol, was extracted twice with 20.00 mL portions of hot absolute alcohol in order to dissolve the sulfide. After the second extraction, the salt was transferred to a Büchner funnel and was washed with a little hot alcohol.

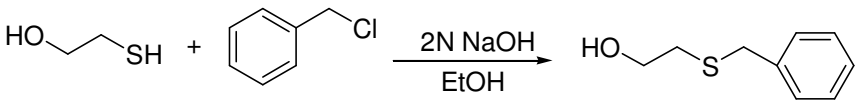
[1] At the end of the reaction the liquid is alkaline and must be neutralized; otherwise considerable decomposition occurs during distillation. Care must be taken not to pass the neutral point, as a small amount of mustard gas may be formed. Furthermore, if much acid is present, the heat necessary for vacuum distillation causes resinification and the yield of distilled material falls to about 50 %. The use of litmus paper for the neutralization is not satisfactory.

The extract and washings were returned to the distilling flask, and the alcohol was removed under reduced pressure.



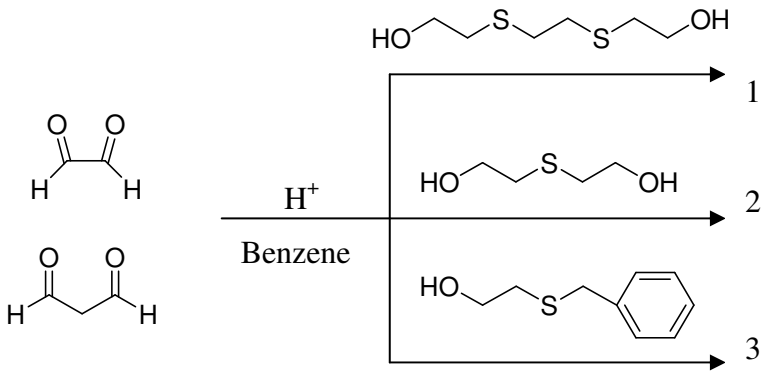
3.2.3. Protection of 2-Mercaptoethanol With Benzyl Chloride [42]

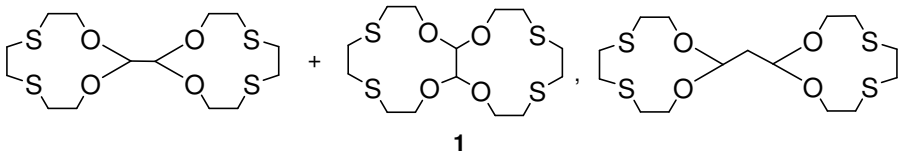
1.38 mL (0.02 mole) of 2-mercaptoethanol was dissolved in 2 N NaOH solution (15.00 mL) and ethanol (25.00 mL). Benzyl chloride was added with stirring. Stirring was continued for 1 h, the pH adjusted to 6-7. Add some water to the mixture and filter the precipitated white solid.



3.2.4. General Procedure For The Preparation of Acetals

In a 100 mL flask equipped with Dean Stark apparatus and condenser, to obtain cyclic acetals: one mole of either glyoxal bisulfite or malon aldehyde, 2 moles of 3,6-Dithiaoctane-1,8-diol or β-Thiodiglycol, and to obtain tetraacetals: one mole of either glyoxal bisulfite or malon aldehyde, 4 moles of 2-(Benzylthio)-ethanol, catalytic amount of *p*-toluenesulfonic acid monohydrate, 30 mL benzene were placed. Heating is continuing till stopping any drop of water. Benzene removed under vacuum, extracted the mixture with EtOAc.





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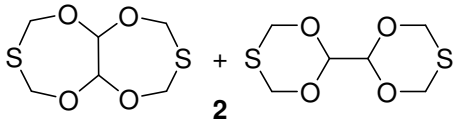

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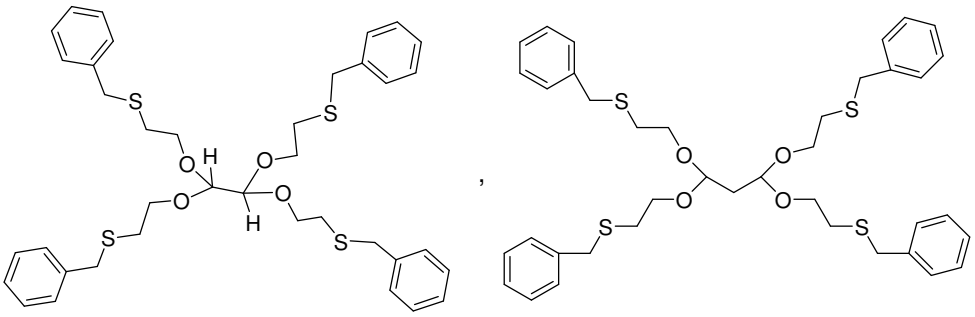
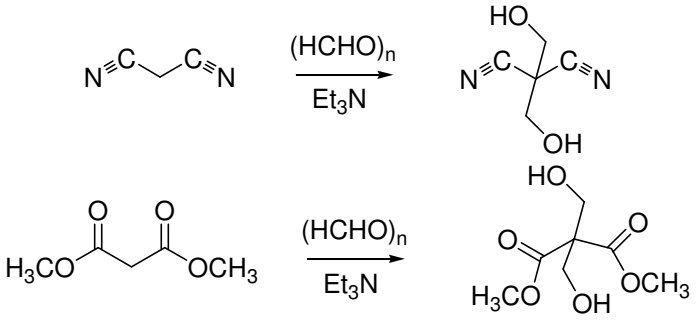


3

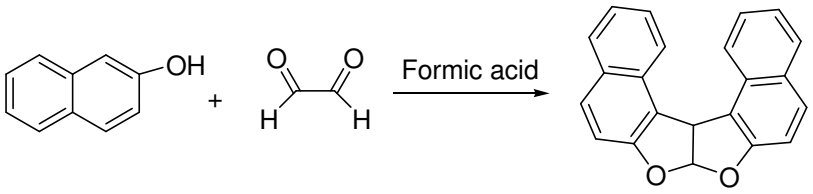
3.2.5. General Procedure For The Preparation of Bis-hydroxymethyl Compounds [43]

Et_3N was added to a stirred solution of malonitrile (0.01 mole) in 20% aq *p*-formaldehyde (3.30 g, 22.00 mmole) and dioxane (10.00 mL) at 4-6°C (ice-water bath), and the mixture was stirred for 20 min. Then the mixture was kept at r.t. for 6-8 hrs. The mixture was diluted with H_2O (150.00 mL) and the product was extracted (3x50 mL) with EtOAc. Organic extracts were dried over Na_2SO_4 and solvent was evaporated.



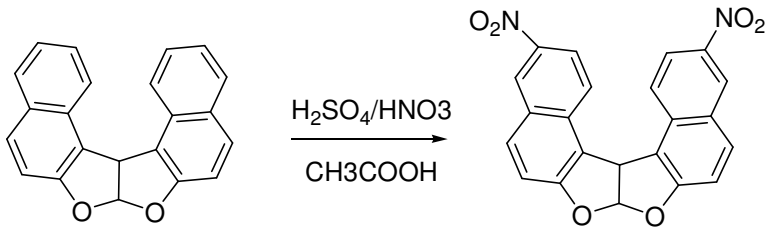
3.2.6. Synthesis of Naphthofuranonaphthofuran [44]

Two moles of β-naphthol was dissolved in 98% formic acid and mixture was heated to 50-60°C, then one mole glyoxalbisulphite was added to the solution and stirred at that temperature for 4 h. Reaction mixture was poured into water and the precipitate was filtered and washed with water till neutralizing occurred. The crude product was boiled with water to remove the unreacted β-naphthol. The product was crystallized from toluene. Yield: 70%, M.p.=238°C



3.2.7. Synthesis of 3,12-Dinitro-7a,14c-dihydro-naphtho[2,1-b] naphtho [1'2';4,5] furo[3,2d] furan [44]

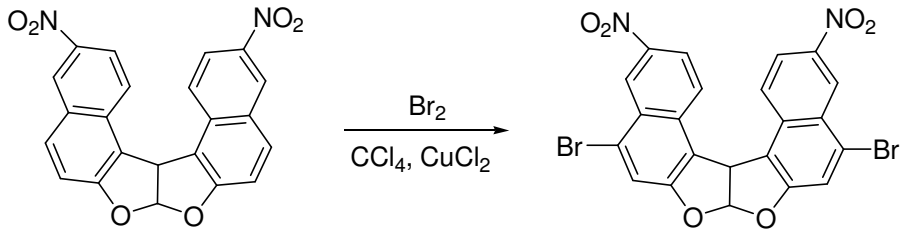
3.00 g of Naphthofuranonaphthofuran was dissolved in 10.00 mL acetic acid and heated to 50-60°C on the water bath. Mixture of HNO_3/H_2SO_4 1.50 mL/2.50 mL was added dropwise to the mixture at this temperature. After the end of the addition, reaction mixture was stirred additional 1 h and then poured into 100.00 mL cold water. The yellow precipitate was filtered, washed with water several times. Then, the solid material was put into 10% sodium hydroxide solution and stirred for 15 min., filtered and washed with water. Dried solid product was boiled with 150.00 mL ethanol. Undissolved part was separated by filtration and crystallized from dioxane. Yield: 40%, M.p.=290°C



3.2.8. Bromination of 3,12-Dinitro-7a,14c-dihydro-naphtho[2,1-b] naphtho [1'2';4,5] furo[3,2d] furan [45a]

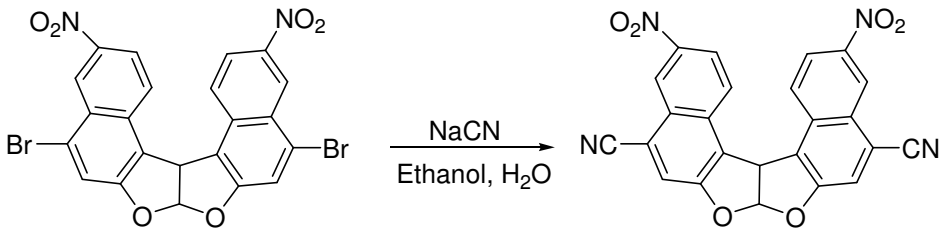
0.10 g (0.25 mmol) nitro compound, 0.05 g of $CuCl_2$, and 10.00 mL CCl_4 were put in a double-necked flask equipped with a condenser and heated to 50-60^oC on the water bath. Then 0.03 g (0.5 mmol, 0.01 mL) Br_2 was added dropwise to the mixture at this temperature. To prevent bromine and HBr vapors, the condenser connected to a gas trap. After 2-3 h, some more $CuCl_2$ and Br_2 were added and while stirring heated at that temperature for 72 h.

The resulting dark reddish-brown liquid was poured into 50.00 mL of water to which 5.00 mL of saturated sodium metabisulphite solution to remove the excess of bromine. The mixture was filtered and dried. Yield: 80%, M.p.=250^oC.



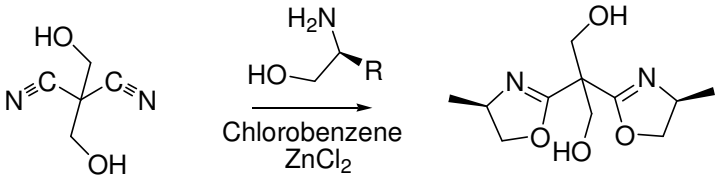
3.2.9. Nitrillation of 3,12-Dinitro-5,10-Dibromo-7a,14c-dihydro-naphtho[2,1-b] naphtho [1'2';4,5] furo[3,2d] furan [45b]

A mixture of 1.00 g (0.02 mol) brominated compound, 1.80 g (0.04 mol) sodium cyanide, 100.00 mL ethanol, and 50.00 mL water were put in a flask, and refluxed for 1 h. Alcohol was distilled and the residue was washed with water. The solid material was filtered and dried. Yield: 90%, M.p.=303^oC.

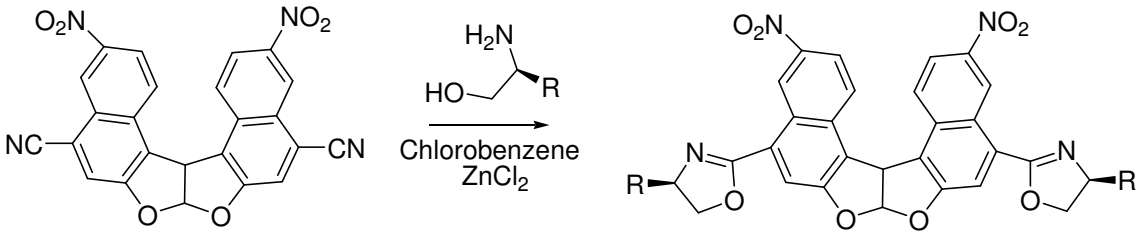


3.2.10. General Preparation of Bisoxazolines from Nitriles [46, 47]

Zinc chloride (68 mg, 0.5 mmol) was fused under high vacuum in a 50 mL Schlenk flask and cooled under nitrogen. After cooling to r.t., chlorobenzene (30 mL) was added followed by dicyano compound (10 mmol), and the amino alcohol (13 mmol). The reaction mixture was heated at reflux temperature for 48 h. The solvent was removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (100 mL). The solution was stirred for 2 h and water (50 mL) was added. The CH_2Cl_2 layer was separated and washed by Na_2CO_3 (satd, 30 mL x 2), brine (30 mL), and dried with sodium sulfate. The solvent was removed and the product was purified by chromatography on silica gel (methanol/CH_2Cl_2: from 2% to 10%).



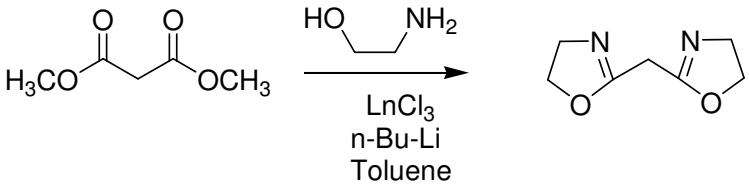
R=H, Ph



R=H, Ph

3.2.11. General Preparation of Bisoxazolines from Esters [48]

To a flask charged with anhydrous lanthanum chloride (0.20 mmol) was added 20 mL dry toluene and ethanolamine (5 mmol), then n-BuLi (1.99 M in hexane, 4.4 mmol) was added to this suspension at 0°C. After the reaction was stirred at 0°C for 15 min. the flask was warmed to reflux (100°C). Carboxylic ester (2 mmol) was added and the reaction mixture was refluxed for additional 12 h. The suspension was cooled to room temperature, after filtration washed with chloroform (3 x 15 mL).



4. RESULTS AND DISCUSSION

The aim of this project is to synthesize novel cyclic compounds containing heteroatoms that act as polydentate ligands and have the ability of both binding metals and the catalytic activity. Two main groups of compounds have been chosen as polydentate ligand compounds: bis-crown ethers and bis-oxazolines.

The first part of the project is about new type of crown ethers –bis crown ethers– and their synthesis by using a new method. Crown ethers are used mainly as phase-transfer catalysis and biological ion transport. Crown ethers are basically synthesized beginning from diol and dihalides (Figure 4.36).

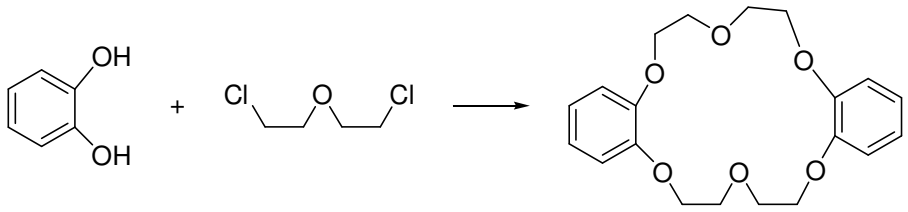
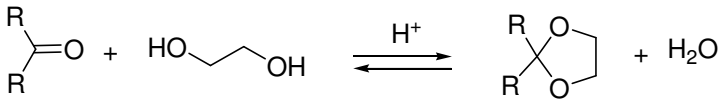


Figure 4.36. The Reaction of the Diols and Dihalide Derivatives in the Presence of a Base.

However, in order to increase the formation of crown ethers, two approaches are used: high dilution method and template effect. Both methods have some advantages and disadvantages. In high dilution method, despite the yield of reaction is high, since reactant concentrations are about 10^{-9} – 10^{-10} M (very low concentrations) the obtained product is few. The other one, template effect method eliminates the low yield disadvantages. In this method a metal is used to bring the alcohol or halide derivatives closer (templation). However, the disadvantage of this method is to find a proper metal for templation and sometimes it is difficult to get rid of the metal from formed crown ether.

In this project we aimed to synthesize the crown ethers using a new method - acetalization reaction- in order to eliminate the disadvantages mentioned before. As known, acetalization is a classical method for the protection of carbonyl groups by using alcohols.



As seen in the former reaction carbonyl compounds react with diols and give cyclic acetals. So, we wanted to apply this procure to synthesis novel crown ethers. As novel crown ethers we targeted bis- crown ethers bearing O and S together in the ring. The aims of synthesizing bis-crown ethers are binding two moles of metal atoms with one mole of crown ether and to achieve the sandwich effect. There are two reasons for preparing crown ethers bearing O and S together; (1) since sulfur atom (104 pm) is larger than that of oxygen atom (73 pm), the size of cavity would be slightly larger than the cavity of O bearing crown ethers (Figure 4.37). Consequently, it causes binding variety of suitable metal cations with ion-dipole attraction. (2) Sulfur has the higher ability of metal binding than oxygen.

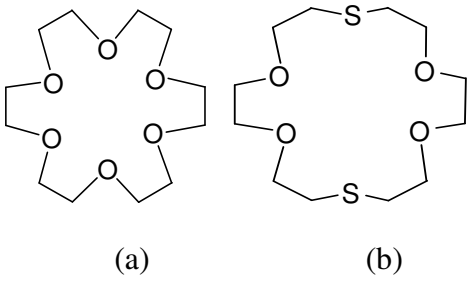
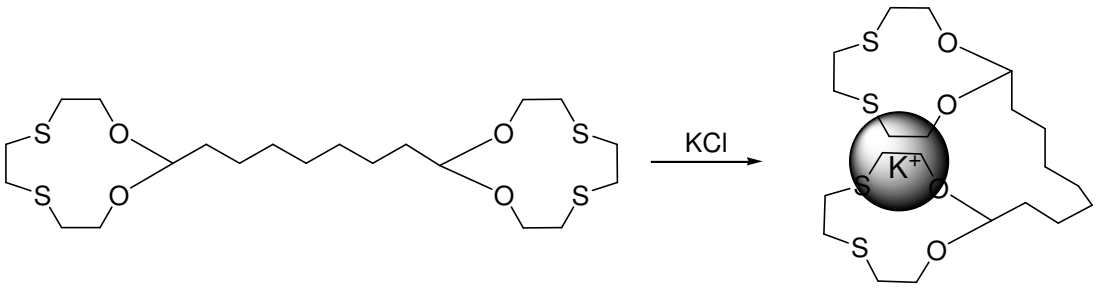
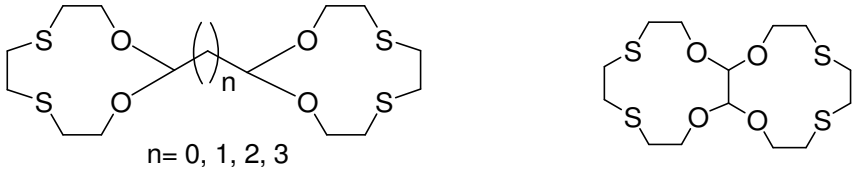


Figure 4.37. Comparison of Two Crown Ethers (a) All Heteroartoms Are Oxygen, (b) Oxygen and Sulfur Are Heteroatoms.

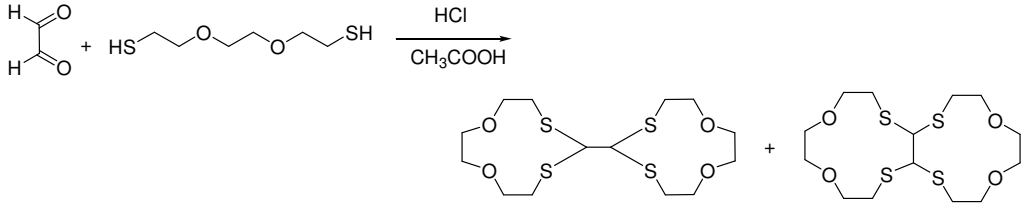
Since the cavity of the synthesized compounds is not fit actually with 12-crown-4 (1.20-1.50 Å) because of the presence of both O and S atoms, we want to see that these compounds will bind which metals in their cavity. If the ionic diameter of the metals does not fit with the cavity of the compound, does the sandwich effects occur? In sandwich effect depending on the "n" number of the $-CH_2$ bridges between two crown groups in the molecule, 1 mole of compound will bind 1 mole of metal or two moles of compounds will bind two moles of metals between their cavities.



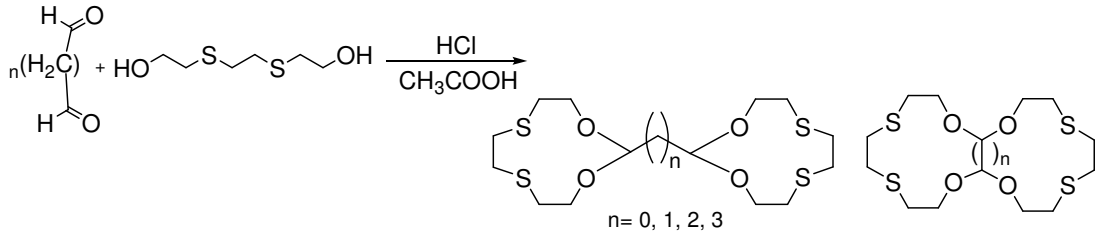
The formula of the target compounds are given below:



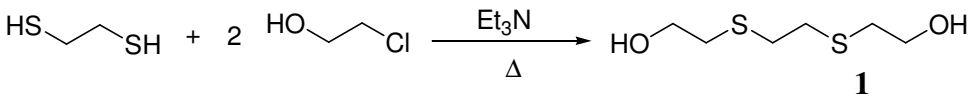
However, different from the above-mentioned method, thioacetalic bis-crown ethers were prepared by the thioacetalization reaction in the previous study [49]. In that study, glyoxal bisulfite reacted with dithiol in the presence of acid catalyst and two types of crown ethers were produced.



In this study, we want to use diols containing thioether groups to synthesize acetalic bis-crown ethers. Another point is to increase the number of $–CH_2$ groups between two rings for being formed the sandwich effect.



In order to synthesize of bis- crown ethers with n= 0, the glyoxal bisulfite and diols containing thioether groups were reacted in the presence of *p*-toluene sulfonic acid. Desired diol **(1)** was synthesized from dithiol and chlorohidrin as formulated below.

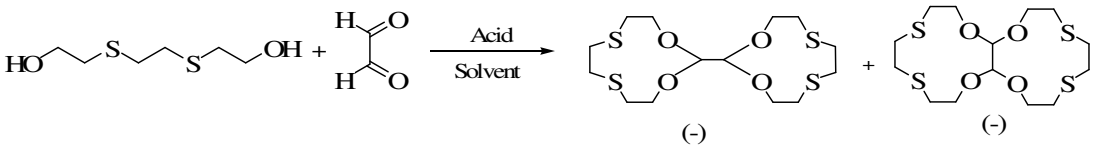


1

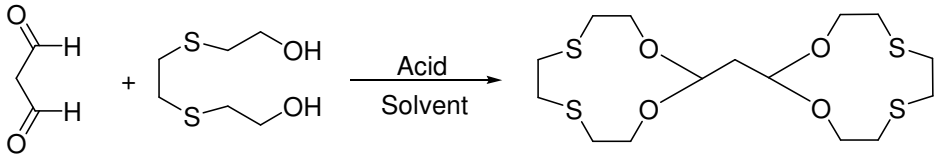
Spectroscopic data is confirmed the structure of 3,6-Dithia-1,8-octanediol **(1).** ^{1}H-NMR (d_1-chloroform) is shown in Figure A-1. 2.23 (brd. s, 2H, –OH), 2.76 (m, 8H, –SC<u>H</u>$_2$), 3.75 ppm (t, 4H, –C<u>H</u>$_2$OH, J=5.8). IR spectrum (ATR) of 3,6-Dithia-1,8-octanediol is shown in Figure A-2. 3408 (–OH), 2917 ($–CH_2$), 1424 and 1267 (C–S–C), 1050 cm^{-1} (C–O). GC-Ms spectra for 3,6-Dithia-1,8-octanediol have shown in

Figures A-3 and A-4 respectively. Fragments of this molecule are (M-18) 164, (M-77) 105, (M-120) 62, and (M-137) 45.

When compound (1) was reacted with glyoxal, the expected crown ethers could not be obtained.

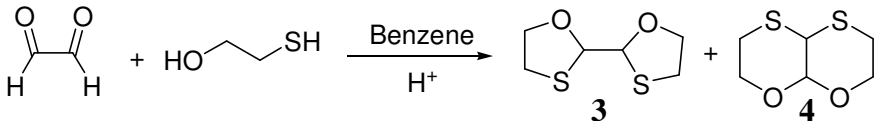


Similar method was tried with malonaldehyde (n= 1) since it is a rather flexible molecule than glyoxal.



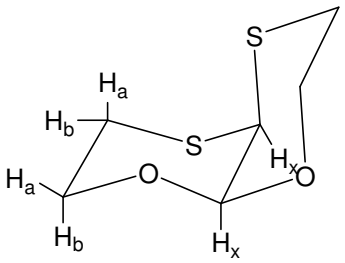
At the end of the reaction, TLC chromatography was applied to the reaction mixture, and it was observed that there were several products. Although we tried to separate the products with using different methods such as column chromatography and extraction techniques, we could not succeed to separate desired product from the mixture.

The reason of the reactions which occurred with dithiol compounds did not succeed with diols is attributed that the C–S bonds can easily break when compared to C–O bonds. From IR spectroscopy it was understood that the acetalization reaction was occurred because there was not any band around 1700 cm^{-1} belonging to carbonyl groups. In order to confirm this result, similar acetalization reaction was tried with 2-mercaptoethanol and glyoxal, and expected products were obtained.



^{1}HNMR (d_1-chloroform) spectrum of **3** and **4** are shown in Figure A-9. For species 3: 4.99 (d, 2H, –C<u>H</u>, J=1.6), for species 4: 5.28 (d, 1H, O–C<u>H</u>–O, J=2.7), 3.91 (d, 1H, S–C<u>H</u>–S, J=2.7), 3.88 and 4.26 (m, 4H, –C<u>H</u>$_2$O), 2.76 and 2.53 ppm (m, 4H, –C<u>H</u>$_2$S).

Despite molecules are symmetric, the reason of the multiplet methylene is the different shielding of axial and equatorial protons.



To achieve desired products another synthesizing method was tried. According to the new method, tetraacetalic compounds will be prepared from dicarbonyl compounds and S-protected thioalcohols. After deprotection reaction free –SH groups will be obtained, then ring closure will be realized with 1,2-dichloroethane as formulated in Figure 4.38.

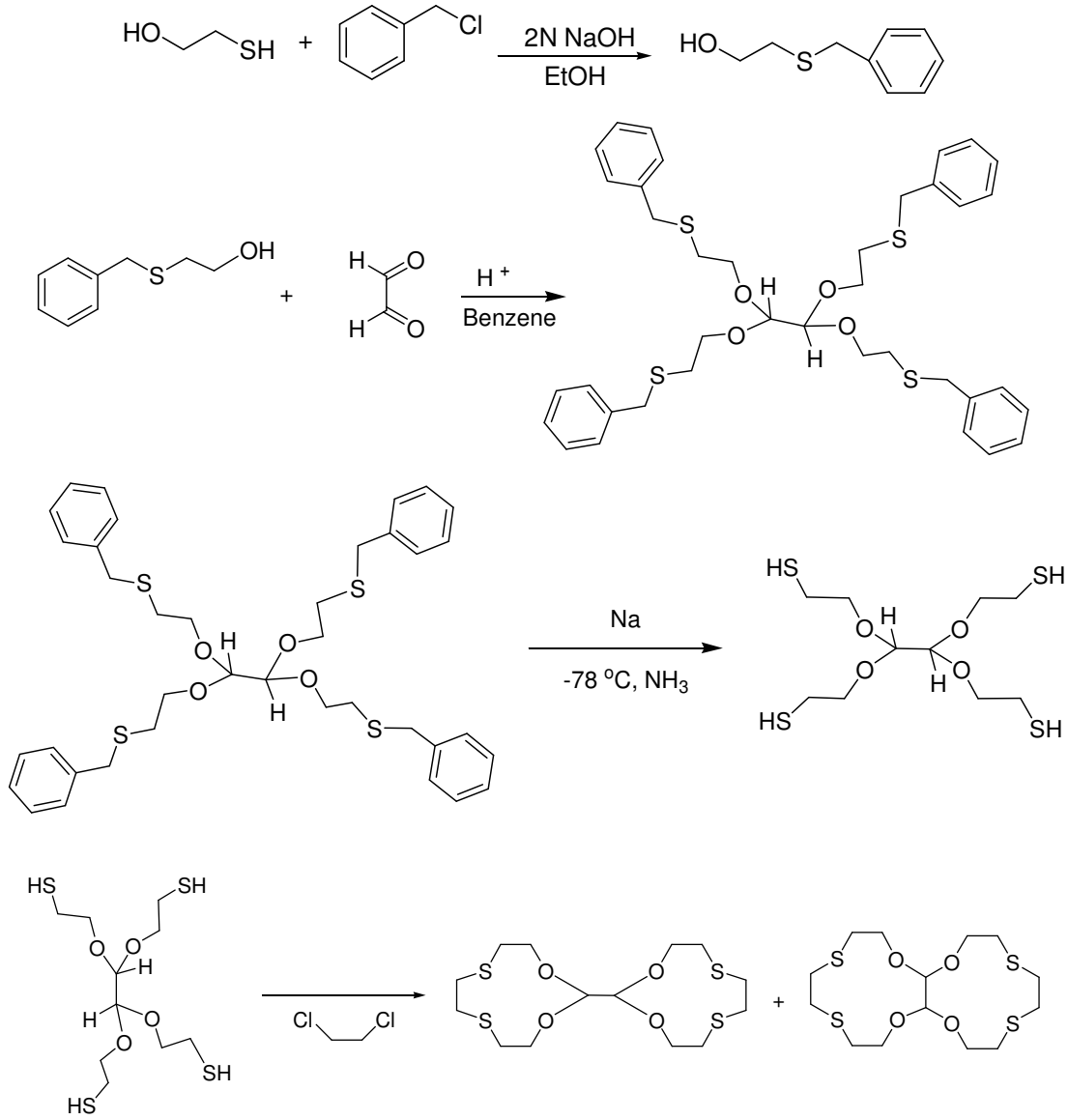
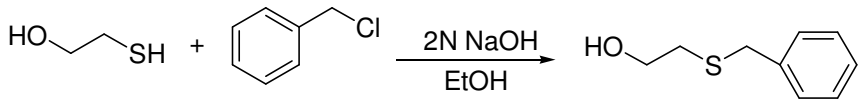


Figure 4.38. Preparation of the Bis-Crown Ethers from Tetraacetalic Product (1,1,2,2-Tetrakis(2-(Benzylthio)Ethoxy)Ethane).

For this aim, 2-(Benzylthio)-ethanol was obtained by the protection of thiol group of 2-mercaptoethanol with benzyl chloride in ethanol and 2N NaOH. Together with desired product a little amount of O-protected compound formed, which is separated by column chromatography.



5

IR spectrum (ATR) of 2-(Benzylthio)-ethanol **5** is shown in Figure A-10. 3376 (–OH), 3000 (aromatic –CH), 1044 (–CH_2OH, primer alcohol C–O), 1421and 1266 (C–S–C), 710 and 865 cm^{-1} (C–S). GC-Ms spectrum of 2-(Benzylthio)-ethanol is shown in Figures A-11 and A-12 respectively. Fragments of this molecule are (M-45) 123 and (M-77) 91.

Protected product was reacted with glyoxal bisulfide to prepare the tetraacetalic product (1,1,2,2-tetrakis(2-(benzylthio)ethoxy)ethane) as given above in Scheme 4.6.

Unfortunately, instead of desired product another product was predominantly obtained: *dibenzylsulfane*, which is shown below. GC-Ms spectrums are shown in Figures 4.39 and 4.40.

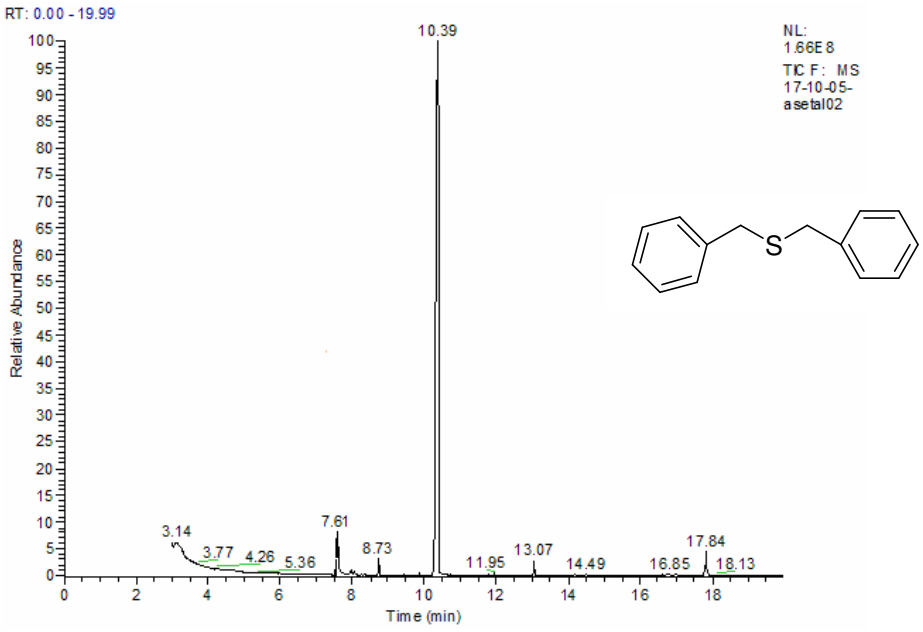


Figure 4.39. GC Spectrum of Dibenzylsulfane.

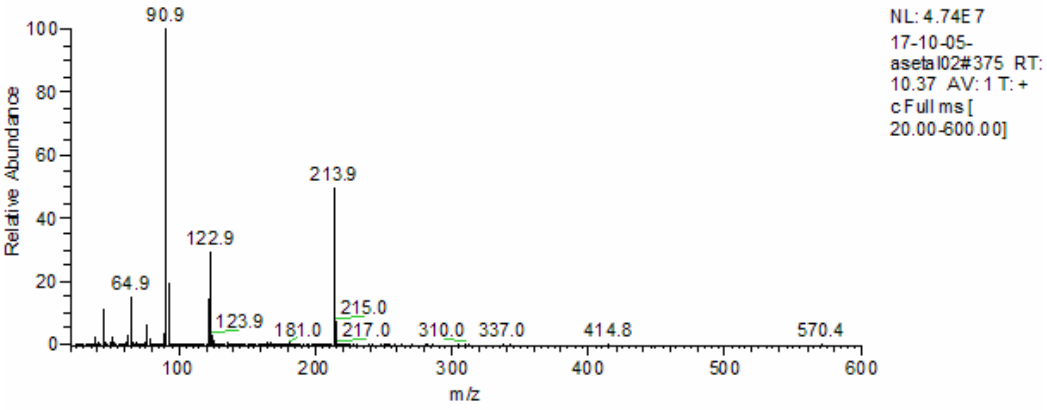
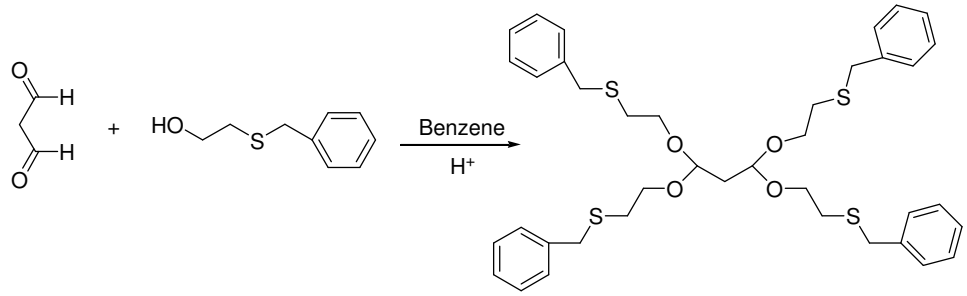


Figure 4.40. Ms Spectrum of Dibenzylsulfane.

Fragments of this molecule are M/z 214, (M-91) 123, (M-149) 65.

The same acetalization reaction was tried with malonaldehyde. It was reacted with 2-(Benzylthio)-ethanol, but the result was undesired.



(-)

Again instead of desired product predominantly obtained another product: *[(benzyldithio)methyl]benzene*, which is shown below. ^{1}HNMR spectrum is shown in Figure 4.41.

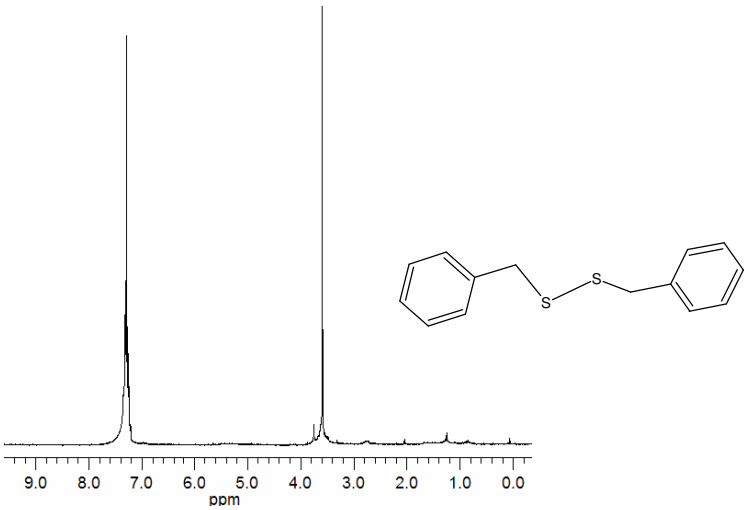
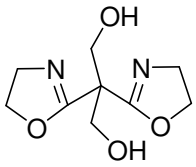


Figure 4.41. ^{1}HNMR Spectrum of [(Benzyldithio)methyl]benzene.

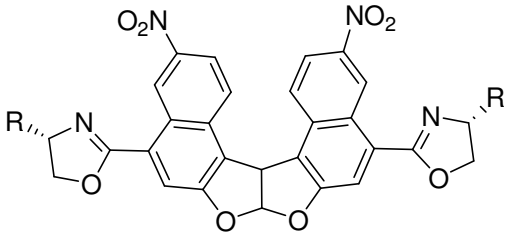
Phenyl protons resonated at ~7.2 ppm (m, 10H) and 4 benzylic S–C$\underline{H_2}$ protons resonated as a singlet at 3.7 ppm.

Unfortunately, the results of these reactions were not in accordance with the expectations and we did not want to continue on this subject and began the second part of the project; synthesis of bis-oxazolines.

The aim of the synthesizing bis-oxazolines is same as the synthesizing crown ethers: to synthesize novel cyclic compounds containing heteroatoms that act as polydentate ligands and have the ability of both binding metals and the catalytic activity. The targeted bis- oxazoline compounds are given below:

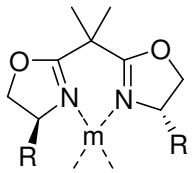


7

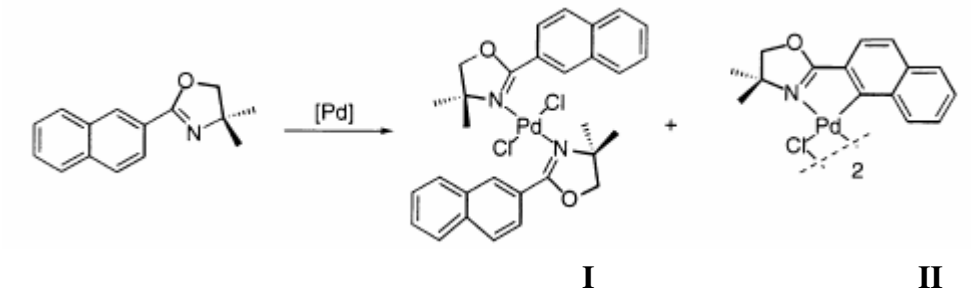


R = H, -C_6H_5 **12**

The compound **7** was targeted because of the possibility to obtain polydentate ligand. Also through the help of the reactive groups on the compound, it seems possible to get access to new compounds.



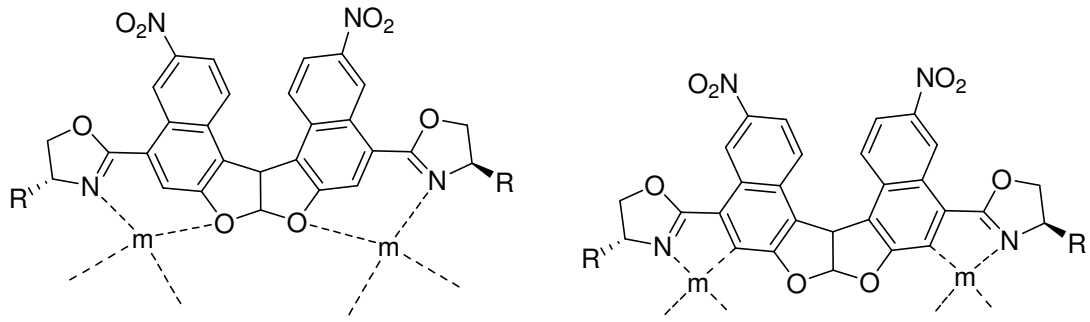
The oxazoline groups attached to the aromatic ring can hold the metals by two ways. It can hold the metals like compound (I), however it can also hold metals by using the neighbor aromatic carbon atom different from the compound **7** as seen in Figure 4.42.



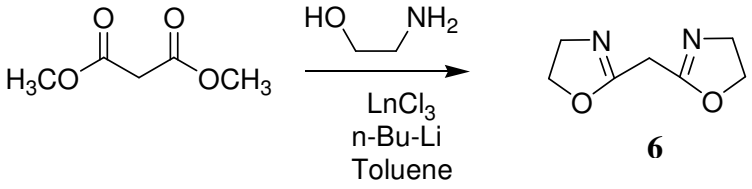
I **II**

Figure 4.42. Holding of Metals Together in the Oxazoline Groups Attached to the Aromatic Ring Using the Neighbor Aromatic Carbon Atom.

In a similar manner, the compound **12** can hold metals, but this time two metals can be held on the same molecule. The oxazoline rings of compound **12** can bind metal atoms in two ways: one is between the N atom of oxazoline ring and O atom of the aromatic ring and the other is between the N atom of oxazoline ring and the H of the aromatic ring. In this fact, various metals with different diameters can be bound to the novel oxazoline substituted naphthofuranonaphthofuran molecule. Since compound **12** is a novel compound, after synthesizing the ligand, it will be used in some reactions (Diels-Alder and cyclopropanation reactions) to see whether it has catalytic activity.



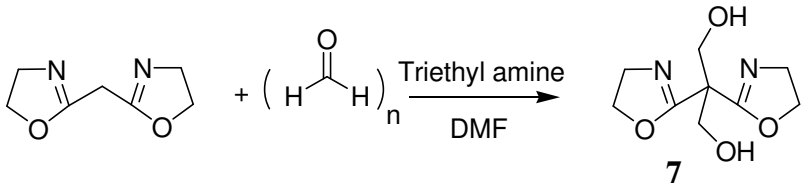
Oxazolines as a member of aliphatic chain were synthesized from reaction of malon ester, ethanolamine, n-Bu-Li as base, and $LnCl_3$ as catalyst.



6

^{1}HNMR (d_4-methanol) spectrum of 2,2'-methylene-bis(2-oxazoline) **6** is shown in Figure A-13. 3.5 (m, 4H, $–CH_2$-O), 3.32 (s, 2H, $-CH_2-$), 3.2 ppm (m, 4H, $-CH_2$-N). IR spectrum (ATR) of 2,2'-methylene-bis(2-oxazoline) is shown in Figure A-14. 1655 the (C=N) specific band of oxazoline ring, 1080 cm^{-1} (C–O–C). The band at 3400 cm^{-1} is due to the humidity of the weather (–OH). Oxazoline compounds are very hygroscopic.

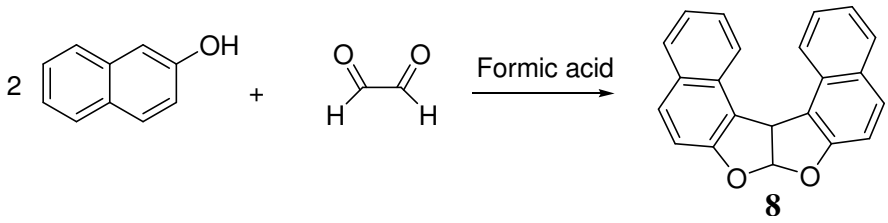
2,2'-dihydroxymethylmethylene-bis(2-oxazoline) was prepared from 2,2'-methylene-bis(2-oxazoline) in the ratio of 1:2 with paraformaldehyde. The spectroscopic data is confirmed the structure.



7

^{1}HNMR (d_4-methanol) spectrum of 2,2'-dihydroxymethylmethylene-bis(2-oxazoline) **7** is shown in Figure A-15. 3.75 (m, 4H, –C<u>H$_2$</u>-OH), 3.68-3.64 (m, 4H, –CH$_2$-O), 3.4-3.3 (m, 4H, –C<u>H$_2$</u>-N), 2.75-2.4 ppm (m, 2H, –OH). IR spectrum (ATR) of 2,2'-dihydroxymethylmethylene-bis(2-oxazoline) is shown in Figure A-16. 1655 the (C=N) specific band of oxazoline ring, 1080 cm^{-1} (C–O–C), 3400 cm^{-1} (–OH).

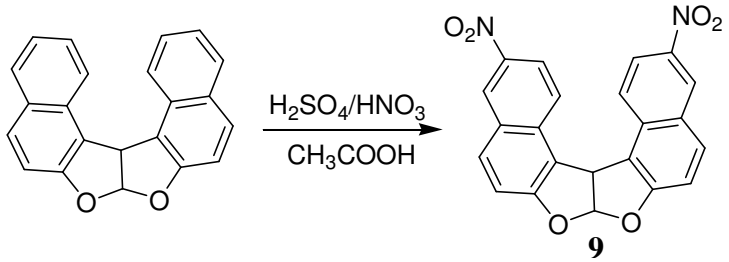
To obtain oxazoline rings as a part of aromatic ring, we worked with naphthofuranonaphthofuran obtained from β-naphthol and glyoxal in the presence of formic acid [44].



8

^{1}HNMR (d_1-chloroform) spectrum of naphthofuranonaphthofuran **8** is shown in Figure A-17. 8.25 (d, H_1, H_{14}, J=8.4), 7.72 (d, H_4, H_5, H_{10}, H_{11}, J=8.7), 7.51 (t, H_2, H_{13}, J=8.1), 7.48 (t, H_3, H_{12}, J=7.8), 7.33 (d, H_6, H_9, J=7.8), 7.11 (d, H_{7a}, J=6.1), 5.56 ppm (d, H_{14c}, J=6.0). IR spectrum (ATR) of naphthofuranonaphthofuran is shown in Figure A-18. 3000, 810, and 750 (aromatic –CH), 1520 (aromatic C=C), 2960-28050 (aliphatic –CH), and 1100 cm^{-1} (C-O-C).

In order to attach oxazoline rings to the aromatic ring adjacent to furan rings of naphthofuranonaphthofuran **8**, we have to deactivate the latter aromatic rings, because, it was shown in the previous study that the electrophile goes to latter ring during electrophilic substitution reaction. So, nitro groups were introduced to these rings. Nitro groups would deactivate these rings, so functional groups would go to the targeted rings easily [44].

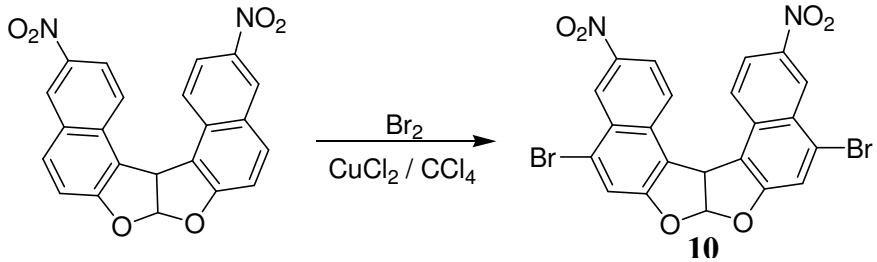


9

^{1}HNMR (d_1-chloroform) spectrum of 3,12-dinitro naphthofuranonaphthofuran **9** is shown in Figure A-19. 8.80 (d, H_4, H_{11}, J=2.1), 8.36 (dd, H_2, H_{13}, J=9.3, J=2.2), 8.28 (d, H_1, H_{14}, J=9.2), 8.00 (d, H_5, H_{10}, J=8.8), 7.40 (d, H_6, H_9, J=8.8), 7.23 (d, H_{7a}), 5.67 ppm (d, H_{14c}, J=6.1). IR spectrum (ATR) of 3,12-dinitro naphthofuranonaphthofuran is shown in Figure A-20. 3000, 810, and 750 (aromatic –CH), 1520 (aromatic C=C), 2960-28050 (aliphatic –CH), and 1143 (C-O-C), 1570-1500 and 1390 cm^{-1} (C-NO_2).

After synthesizing nitro compound **9**, functional –Br groups were directed to the targeted rings. From the ^{1}H-NMR data it is detected that –Br groups are on 5 and 10 position of the molecule.

Because, the peaks belonging to the proton 5 and proton 10 of compound **9** were disappeared and proton 6 and proton 9 gave singlet instead of doublets.

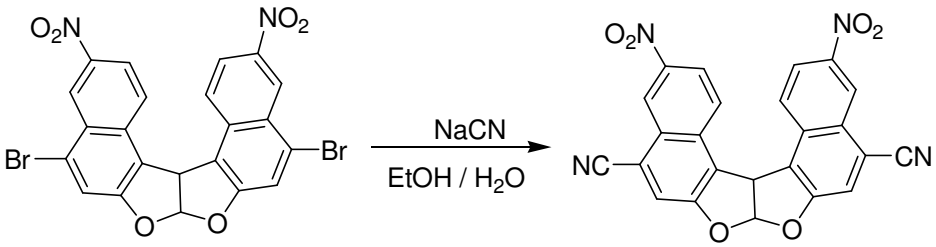


10

^{1}HNMR (d_6-dimethyl sulfoxide) spectrum of 3,12-dinitro-5,10-dibromo-naphtho furanonaphthofuran **10** is shown in Figure A-21. 9.01 (s, H_4, H_{11}), 8.55 (d, H_2, H_{13}), 8.28 (d, H_1, H_{14}), 7.56 (s, H_6, H_9), 7.53 (d, H_{7a}), 6.19 ppm (d, H_{14c}).

IR spectrum (ATR) of ,12-dinitro-5,10-dibromonaphtho furanonaphthofuran is shown in Figure A-22. 3000, 810, and 750 (aromatic –CH), 1520 (aromatic C=C), 2960-28050 (aliphatic –CH), and 1143 (C-O-C), 1570-1500, and 1390 (C-NO_2), 1750 cm^{-1} (C-Br). The overlap IR spectrum of **9** and **10** is shown in Figure A-23.

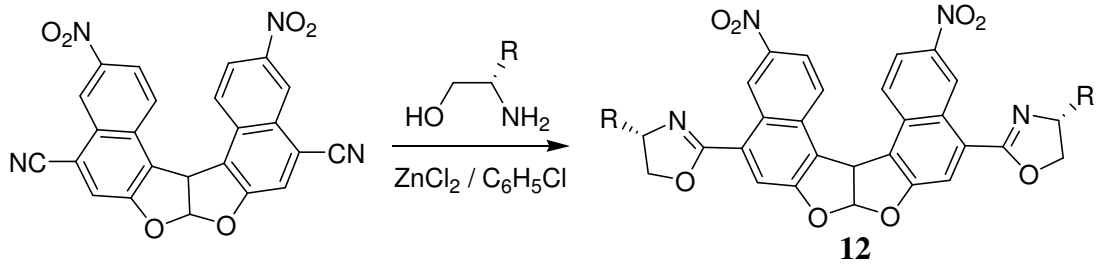
Br groups of **10** were substituted with nitrile groups. Nitrile groups were tried to attach to the naphthofuranonaphthofuran because –CN is one of the good functional groups that can form oxazoline ring in the presence of $ZnCl_2$ catalyst.



11

^{13}CNMR (d_6-dimethyl sulfoxide) spectrum of 3,12-dinitro-5,10-dinitril-naphthofurano naphthofuran **11** is shown in Figure A-24. 160 (C_9, C_{10}), 143 (C_5, C_{16}), 114.4 (C_8, C_{13}), 120.6 (C_{21}, C_{22}), 134.1 (C_2, C_{19}), 132.8 (C_9, C_{12}), 128.4 (C_2, C_{14}), 126 (C_3, C_{18}), 125.3 (C_6, C_{15}), 119.8 (C_4, C_{17}), 115.5 (C_1, C_{20}), 112.2 (C_{10a}), 48.5 ppm (C_{20a}). IR spectrum (ATR) of 3,12-dinitro-5,10-dinitril-naphthofuranonaphthofuran is shown in Figure A-25. 3000, 810, and 750 (aromatic –CH), 1520 (aromatic C=C), 2960-28050 (aliphatic –CH), 1143 (C-O-C), 1570-1500 and 1390 cm^{-1} (C-NO_2), 2170 cm^{-1} (–CN). The overlap IR spectrum of **10** and **11** is shown in Figure A-26.

Nitrile groups of 3,12-dinitro-5,10-dinitril-naphthofuranonaphthofuran **11** were converted to oxazoline groups in presence of $ZnCl_2$, ethanol amine, and chlorobenzene under reflux temperature.



12

R = H, -C_6H_5

IR spectrum (ATR) of **12** is shown in Figure A-27. 7. 3000, 810, and 750 (aromatic –CH), 1534 (aromatic C=C), 2960 (aliphatic –CH), 1150 (C-O-C), 1534 and 1390 cm^{-1} (C-NO_2). The (C=N) specific band of oxazoline ring occurs at 1580 cm^{-1}. 3D Scheme of oxazoline substituted naphthofuranonaphthofuran **12** is shown in Figure 4.43.

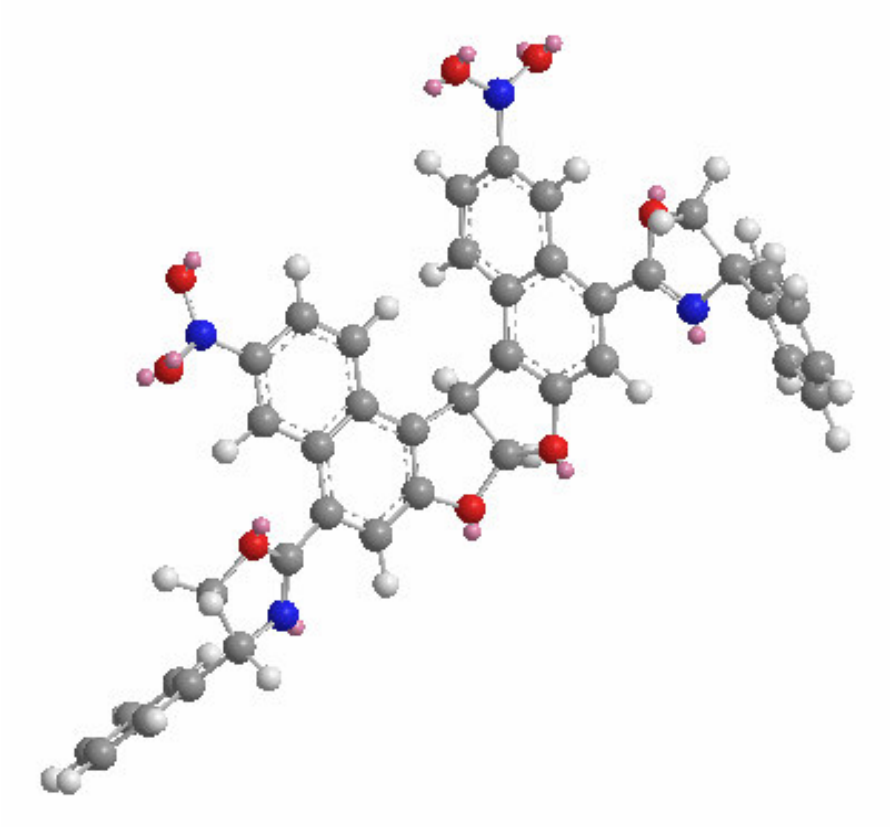


Figure 4.43. 3D Scheme of Oxazoline Substituted Naphthofuranonaphthofuran.

5. CONCLUSION

Synthesizing of novel cyclic compounds containing heteroatoms that act as polydentate ligands is the aim of this project. They can have the ability of both binding metals and the catalytic activity. Two main groups of compounds have been chosen as polydentate ligand compounds: bis-crown ethers and bis-oxazolines. The first part of the project is about new type of crown ethers –bis crown ethers– and their synthesis by using a new method. Synthesizing of novel bis-oxazolines either as a part of aliphatic chain or aromatic ring is the second part of the study. While the first part of the study was unsuccessful and desired products were not obtained, in the second part of the study the desired products 2,2'-dihydroxymethylmethylene-bis(2-oxazoline) and oxazoline substituted naphthofuranonaphthofuran were successfully synthesized.

Our future research interest will be in the field of binding transition metal complexes to oxazoline substituted compounds that have been synthesized. The versatility of metals located near the donor atoms oxygen and nitrogen will cause to obtain different ligands that may be used in the field of homogeneous catalysis.

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APPENDIX

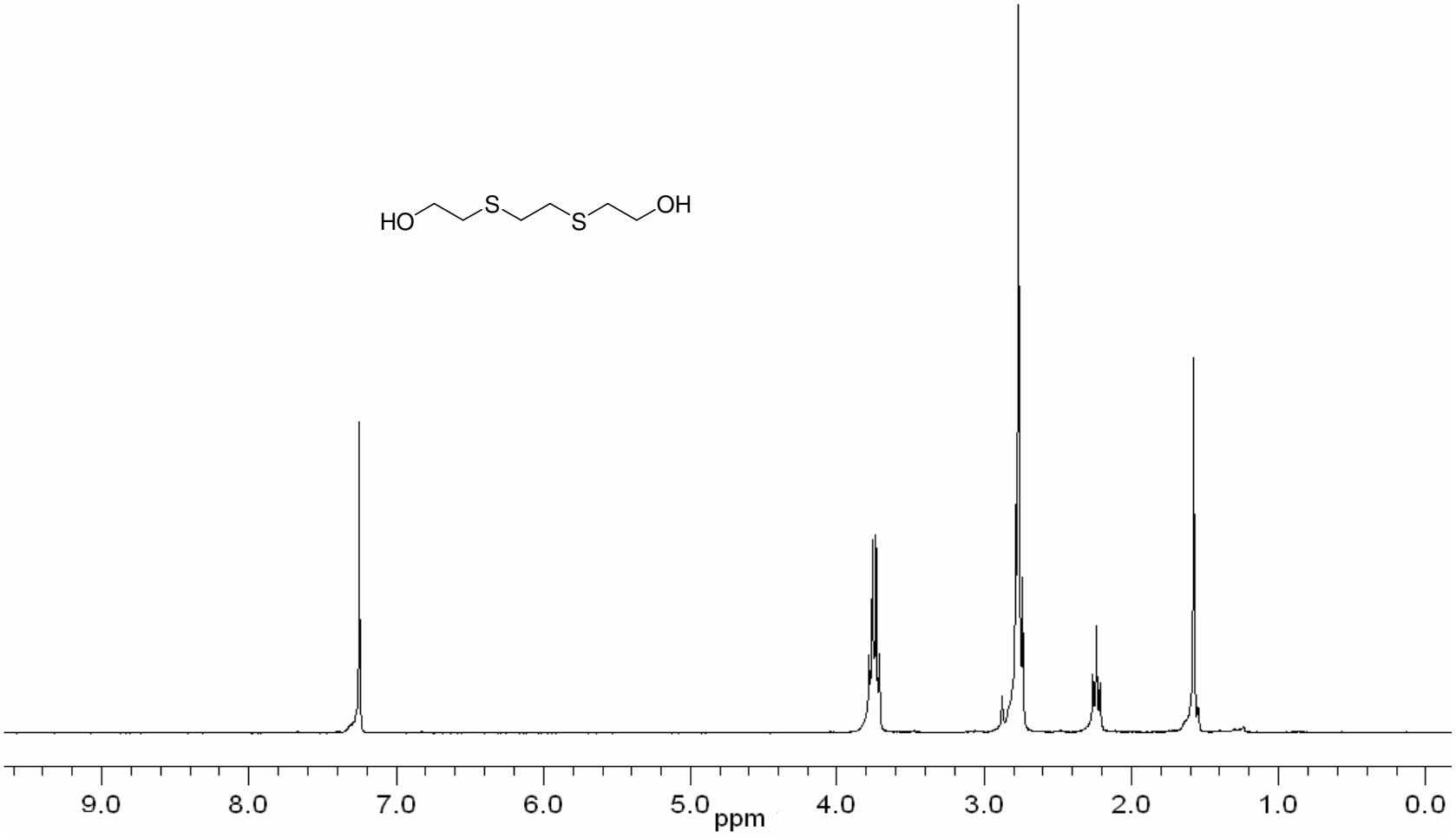

Figure A-1. ^{1}HNMR Spectrum of 3,6-Dithiaoctane-1,8-diol.

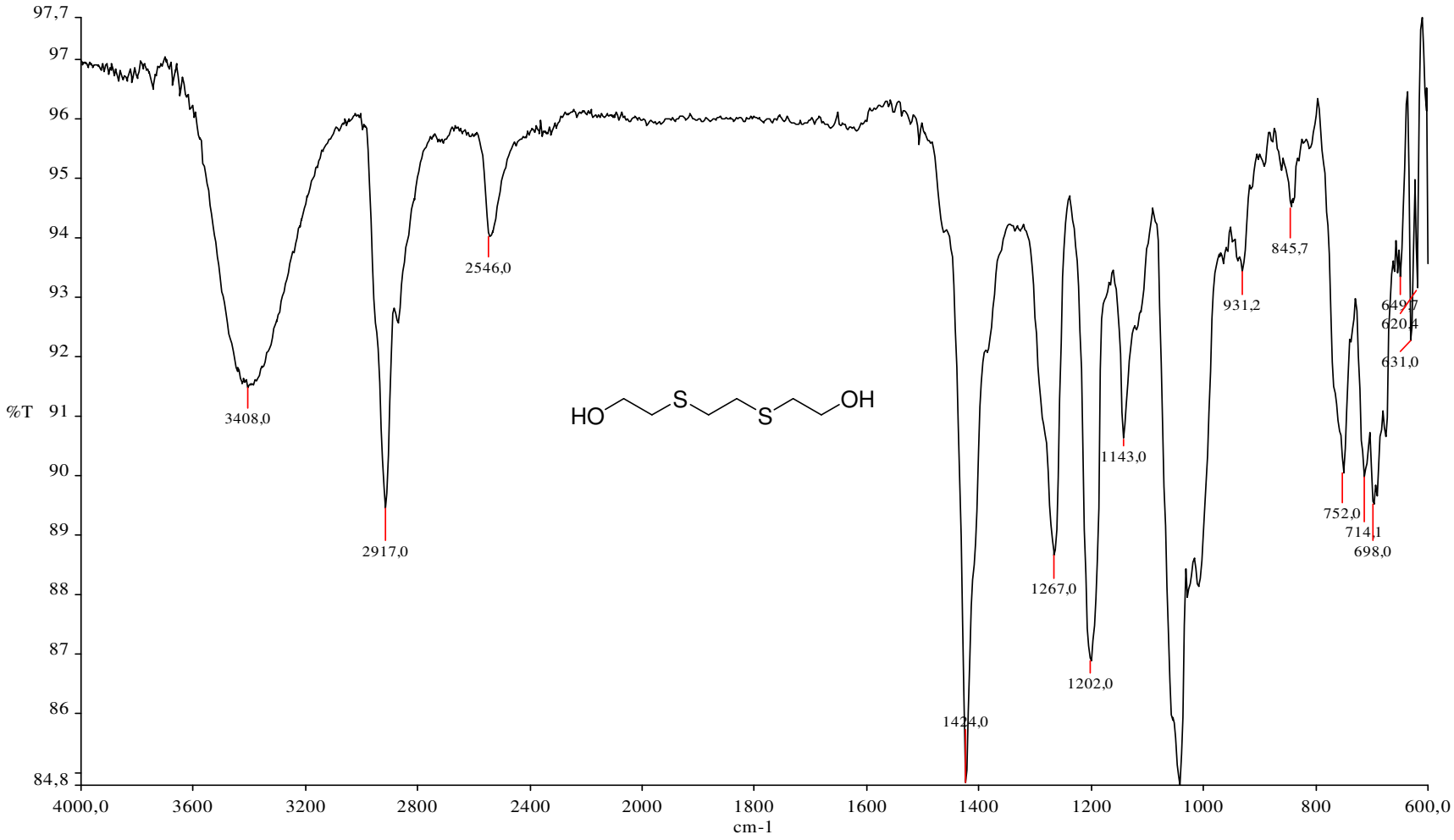

Figure A-2. IR Spectrum of 3,6-Dithiaoctane-1,8-diol.

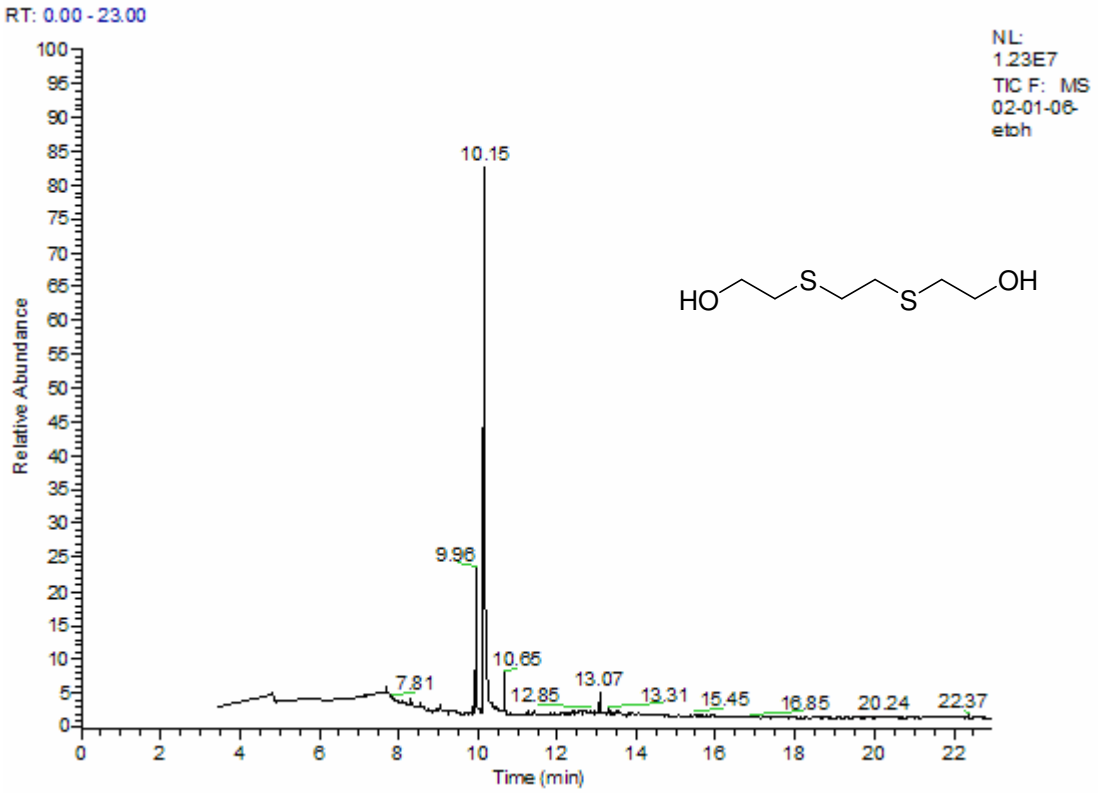

Figure A-3. GC Spectrum of 3,6-Dithiaoctane-1,8-diol.

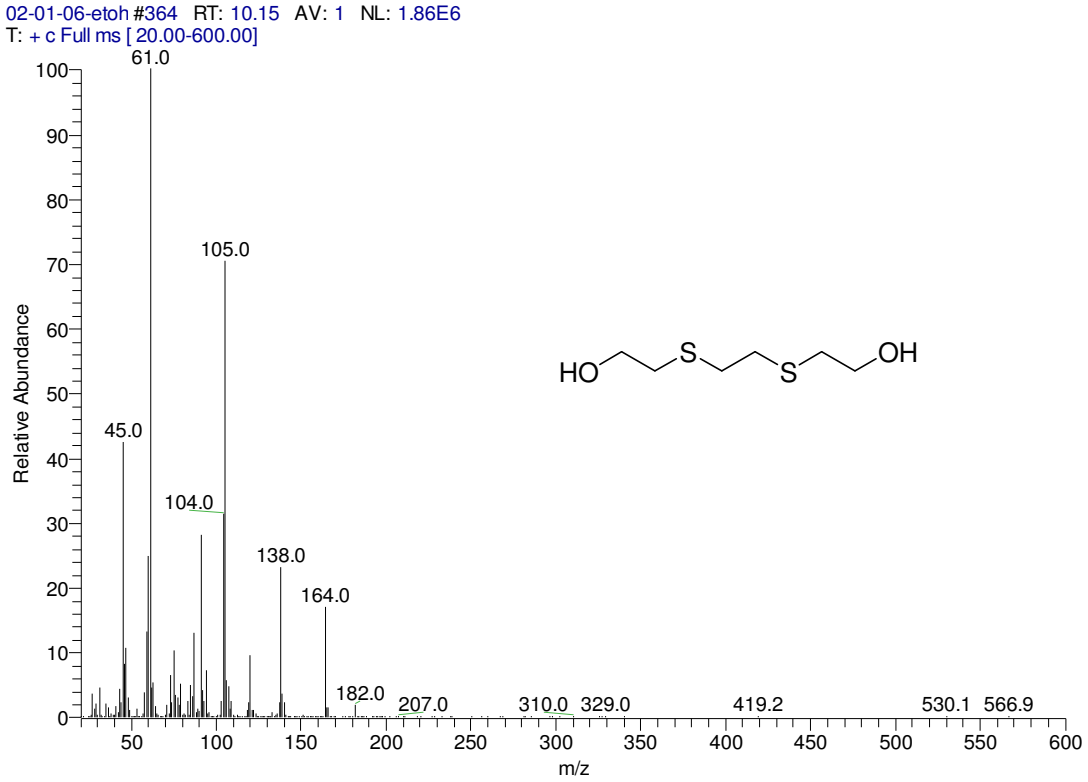

Figure A-4. Mass Spectrum of 3,6-Dithiaoctane-1,8-diol.

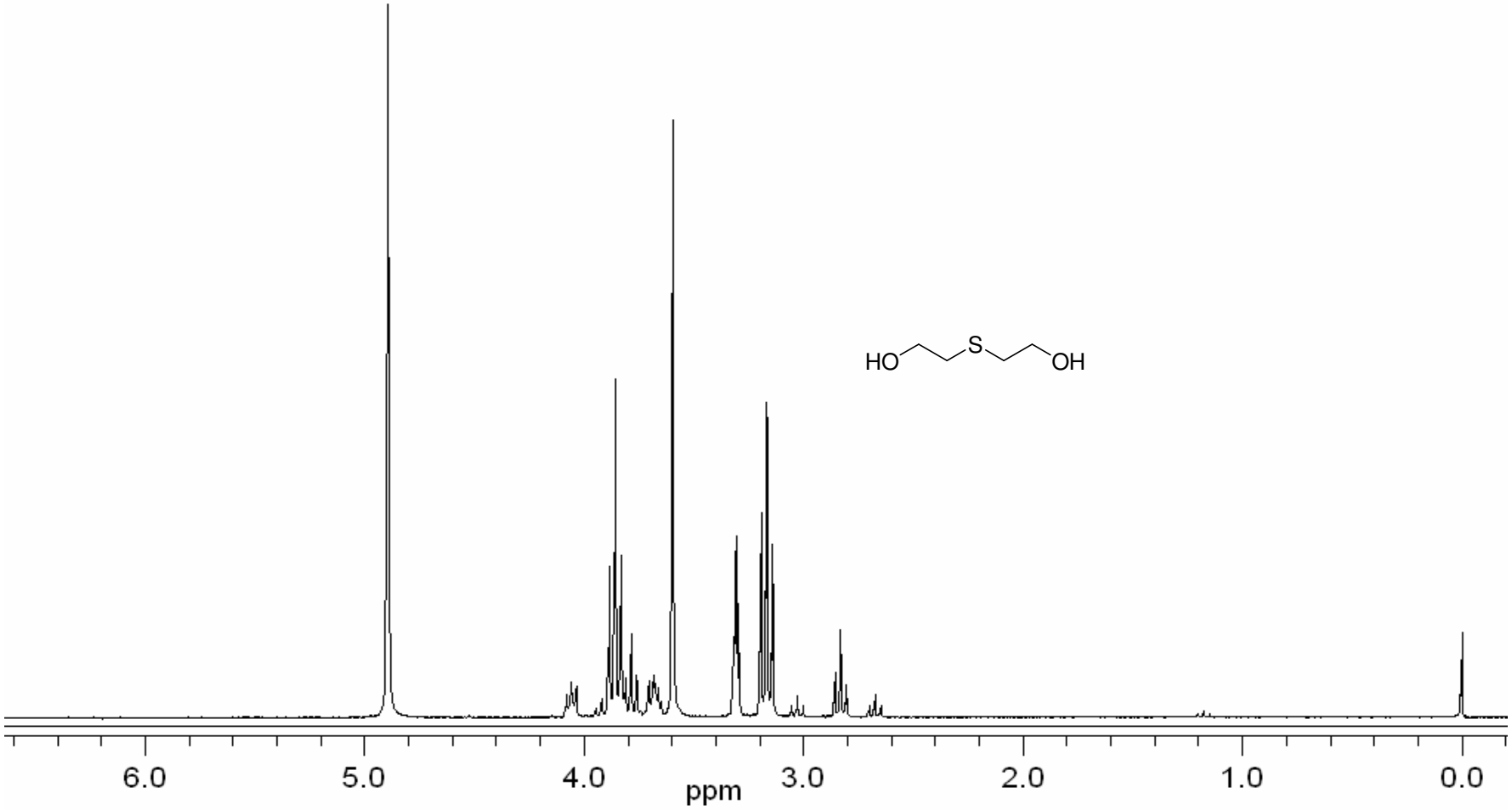

Figure A-5. [1]HNMR Spectrum of β-Thiodiglycol.

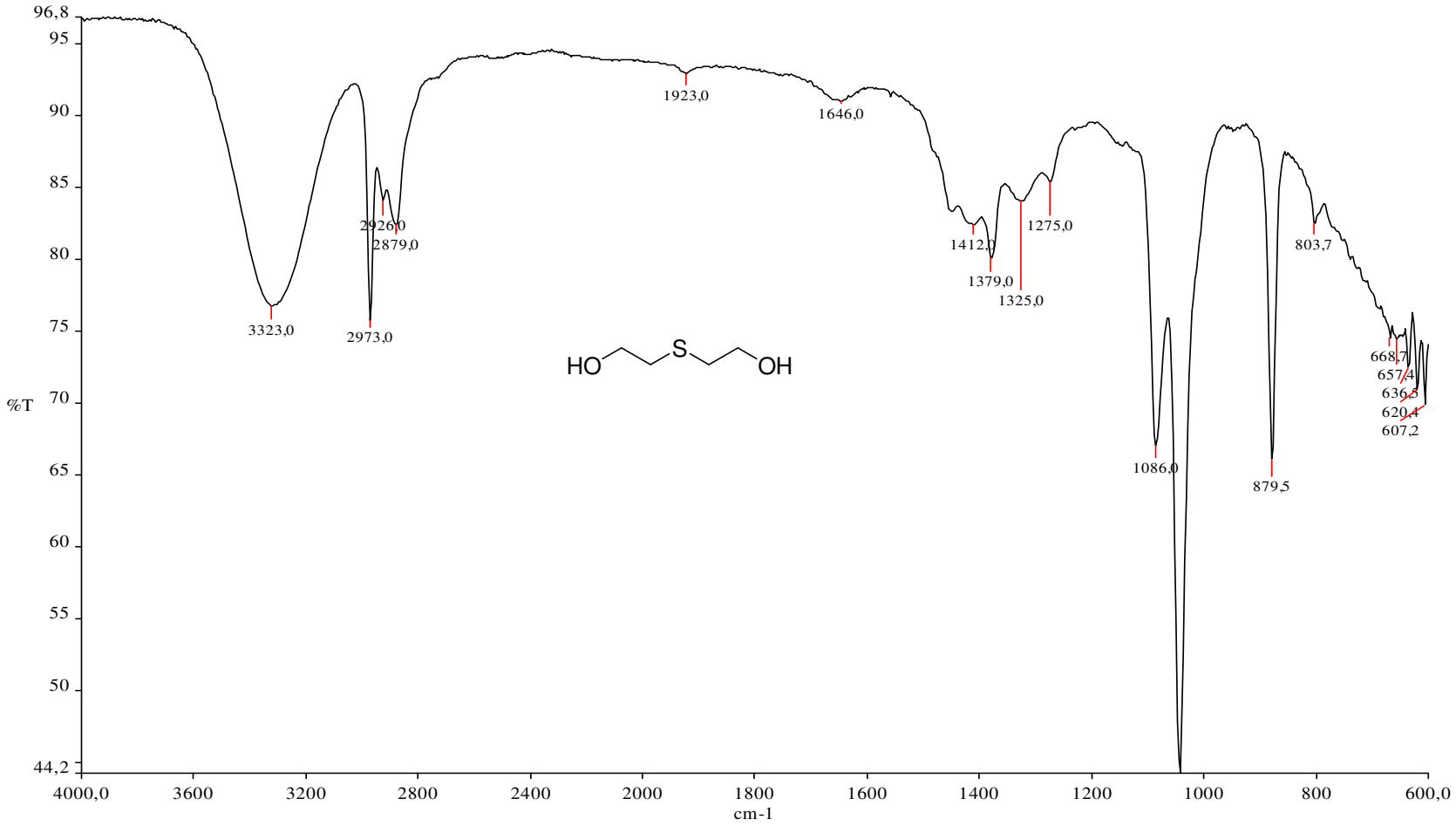

Figure A-6. IR Spectrum of β-Thiodiglycol.

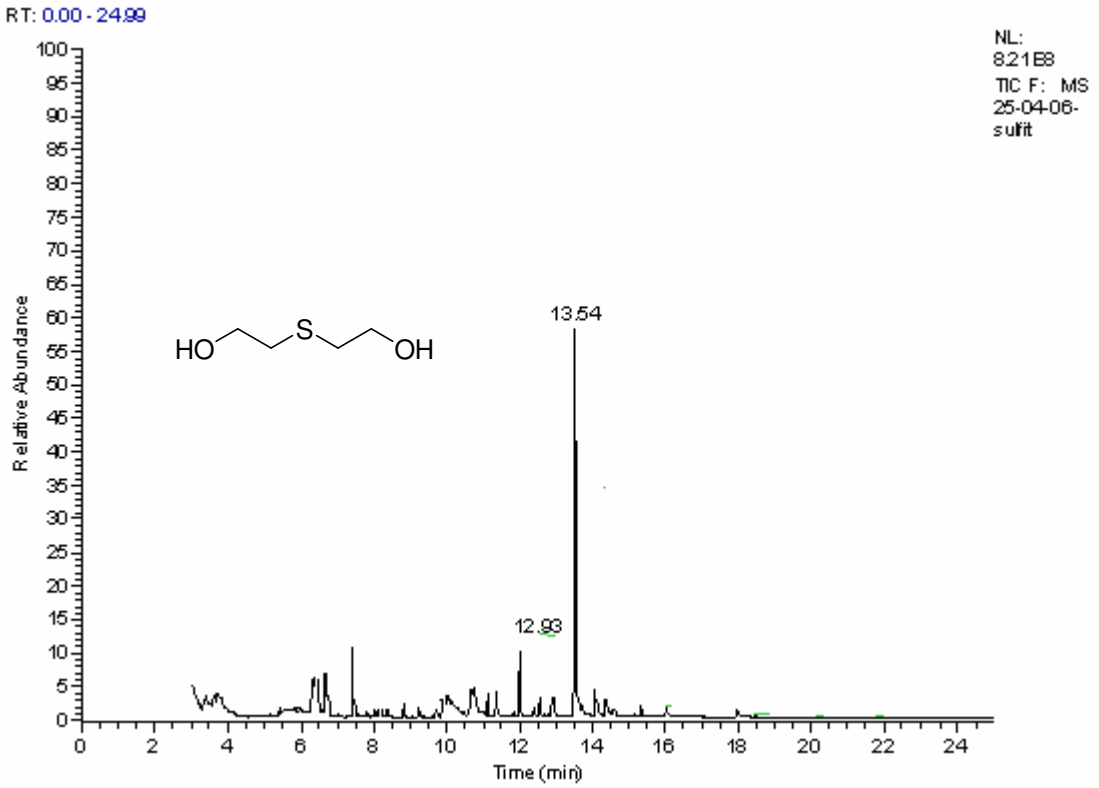

Figure A-7. GC Spectrum of β-Thiodiglycol.

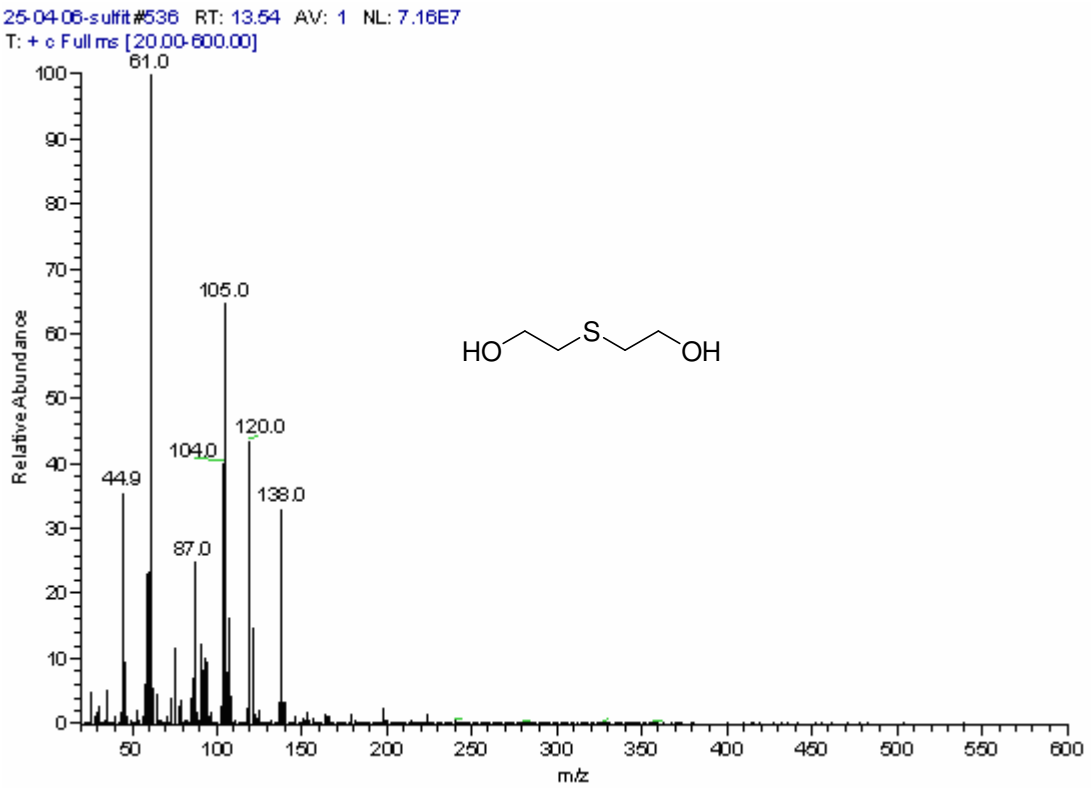

Figure A-8. Mass Spectrum of β-Thiodiglycol.

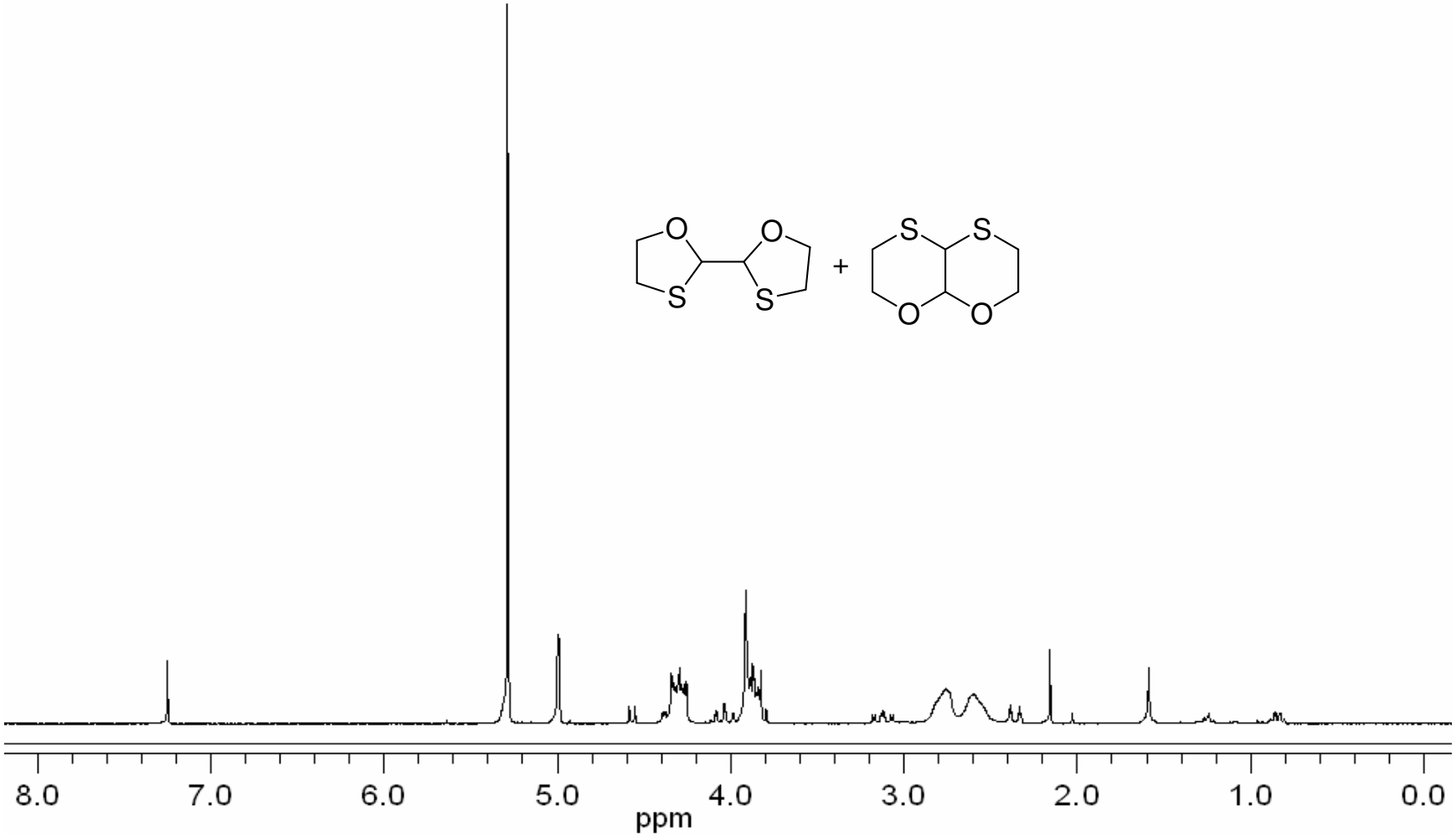

Figure A-9. ^{1}HNMR Spectrum of hexahydro[1,4]oxathiino[2,3-*b*][1,4]oxathiine.

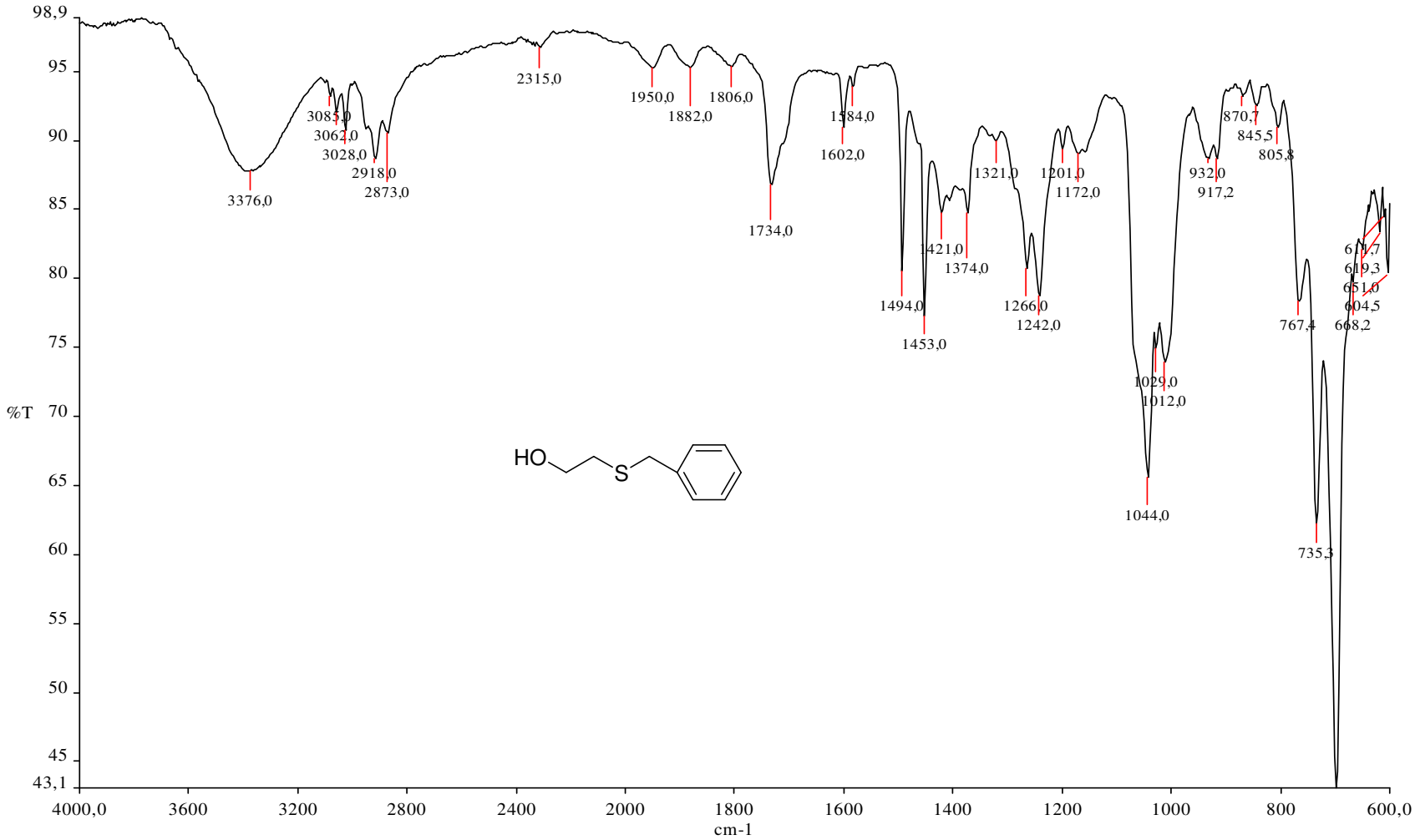

Figure A-10. IR Spectrum of 2-(Benzylthio)-ethanol.

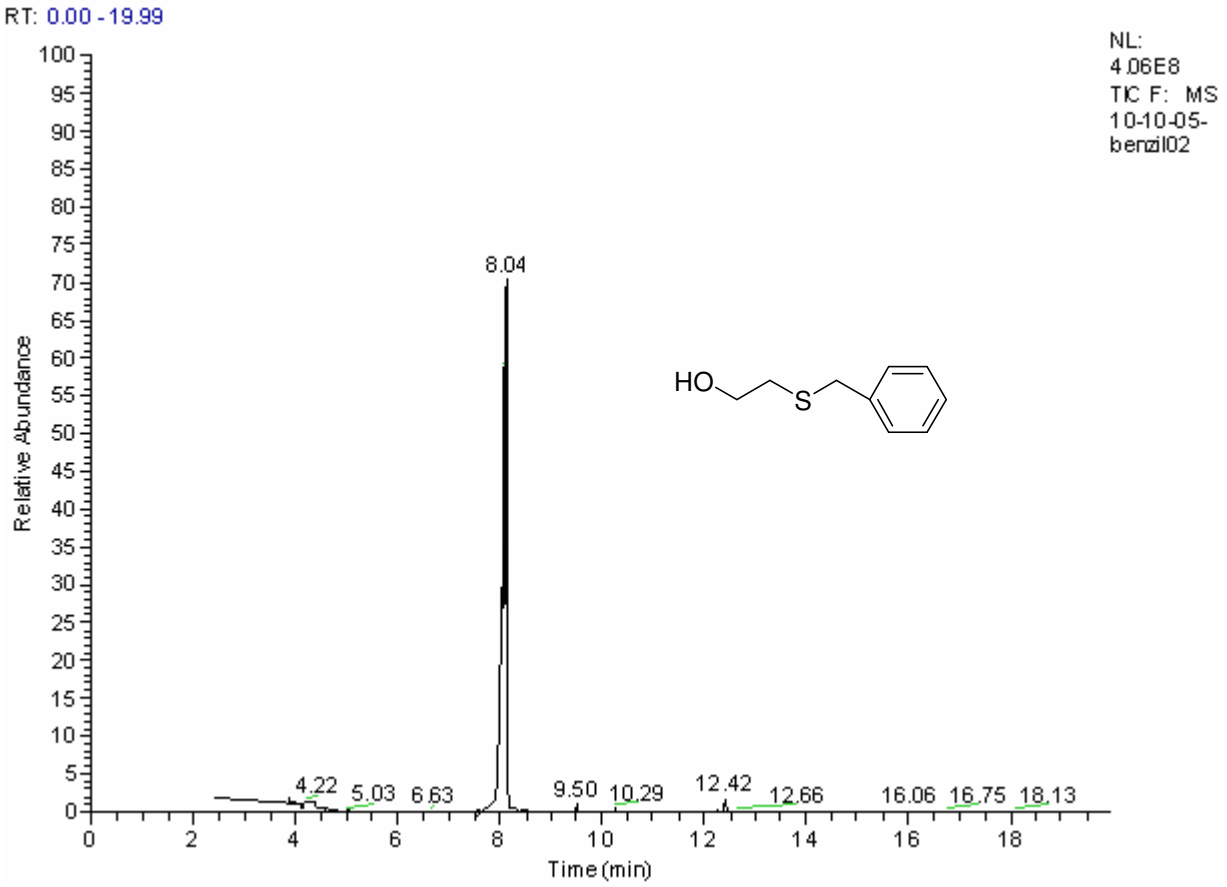

Figure A-11. GC Spectrum of 2-(Benzylthio)-ethanol.

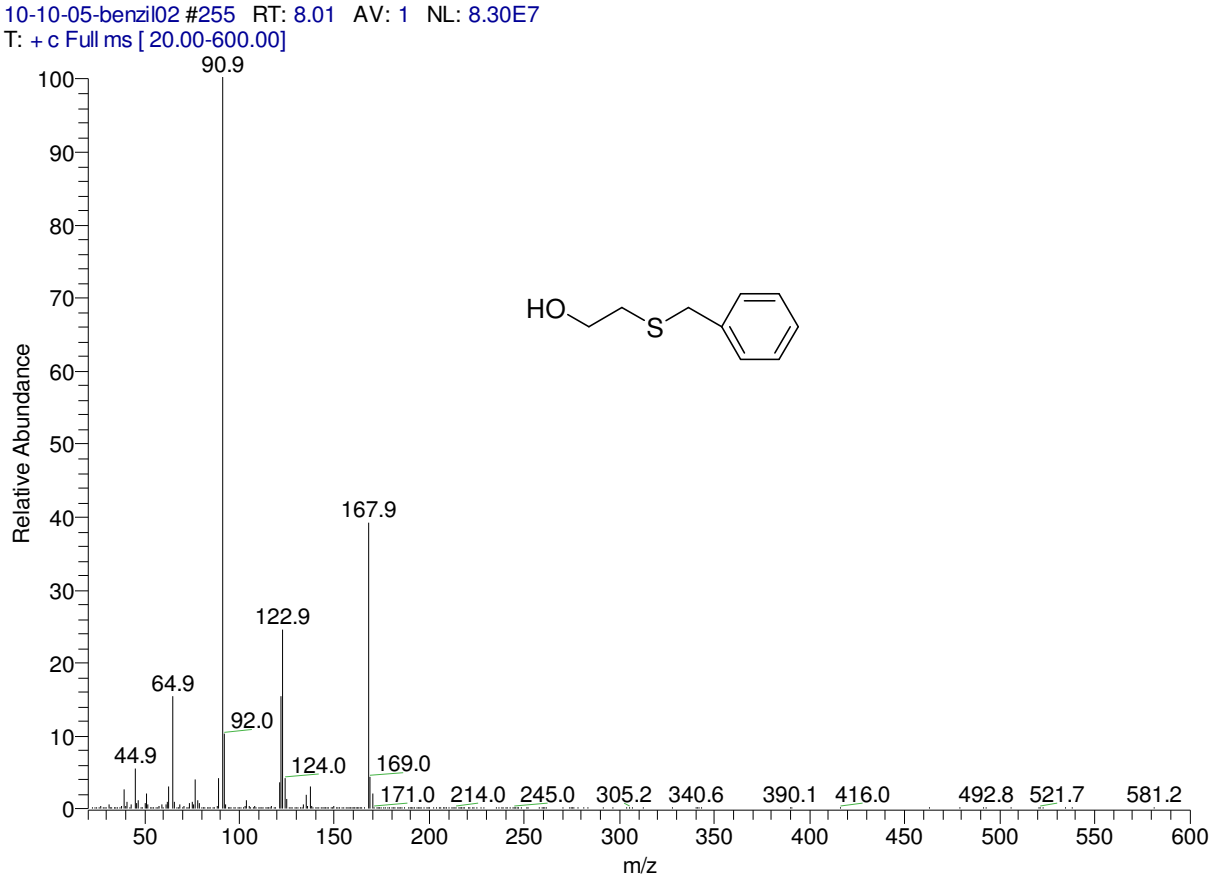

Figure A-12. Mass Spectrum of 2-(Benzylthio)-ethanol.

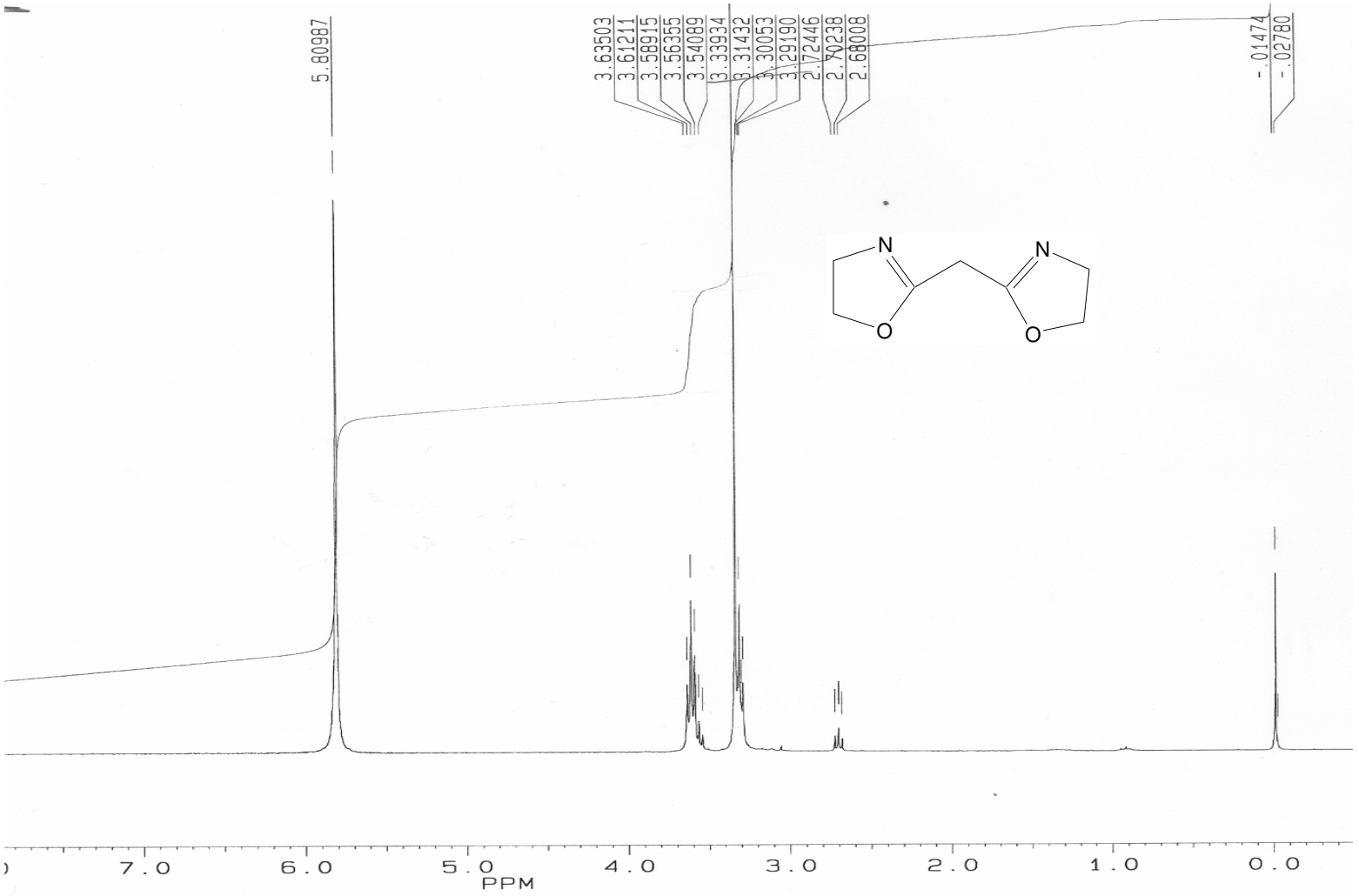

Figure A-13. [1]HNMR Spectrum of 2,2'-methylene-bis(2-oxazoline).

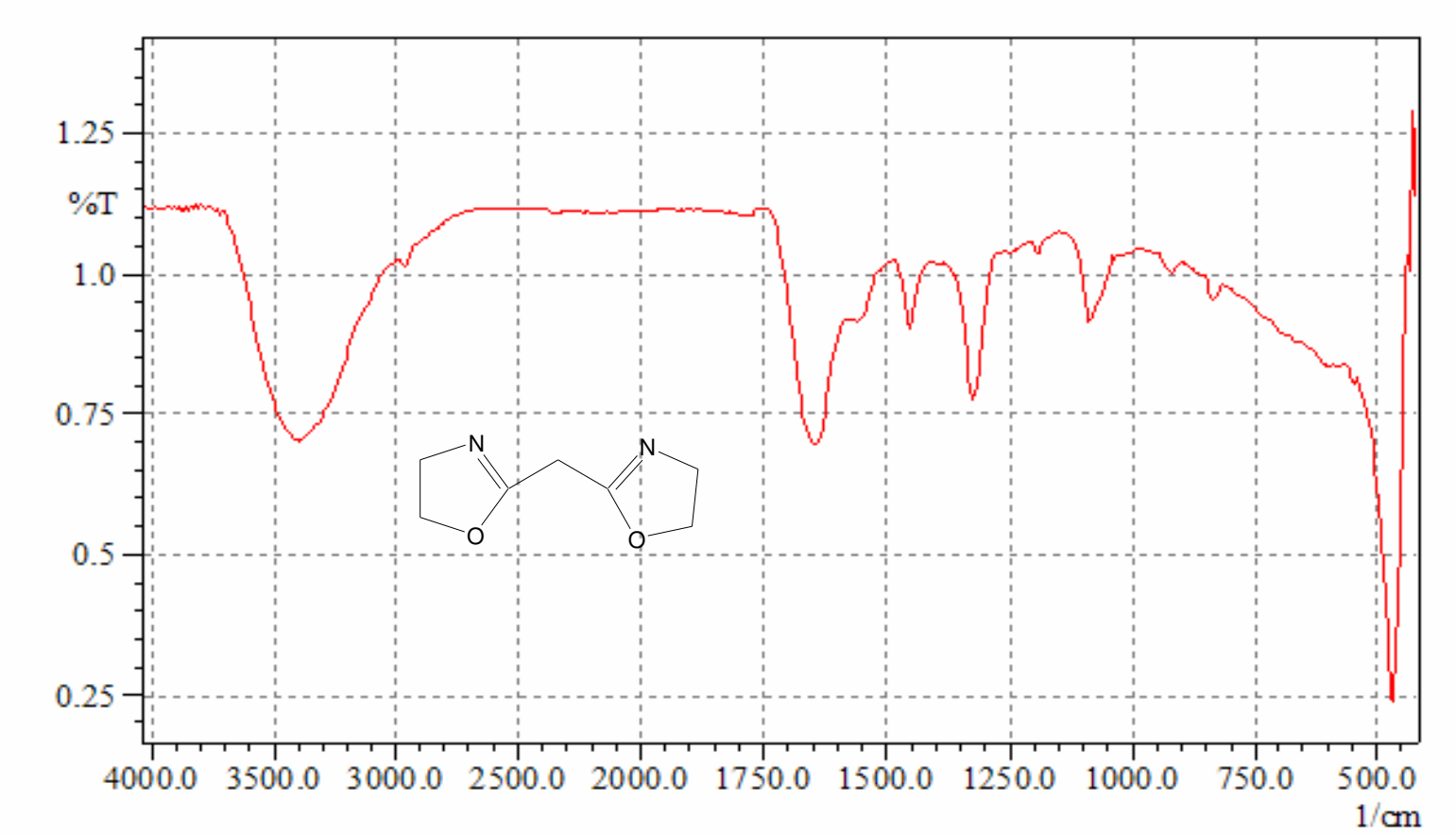

Figure A-14. IR Spectrum of 2,2'-methylene-bis(2-oxazoline).

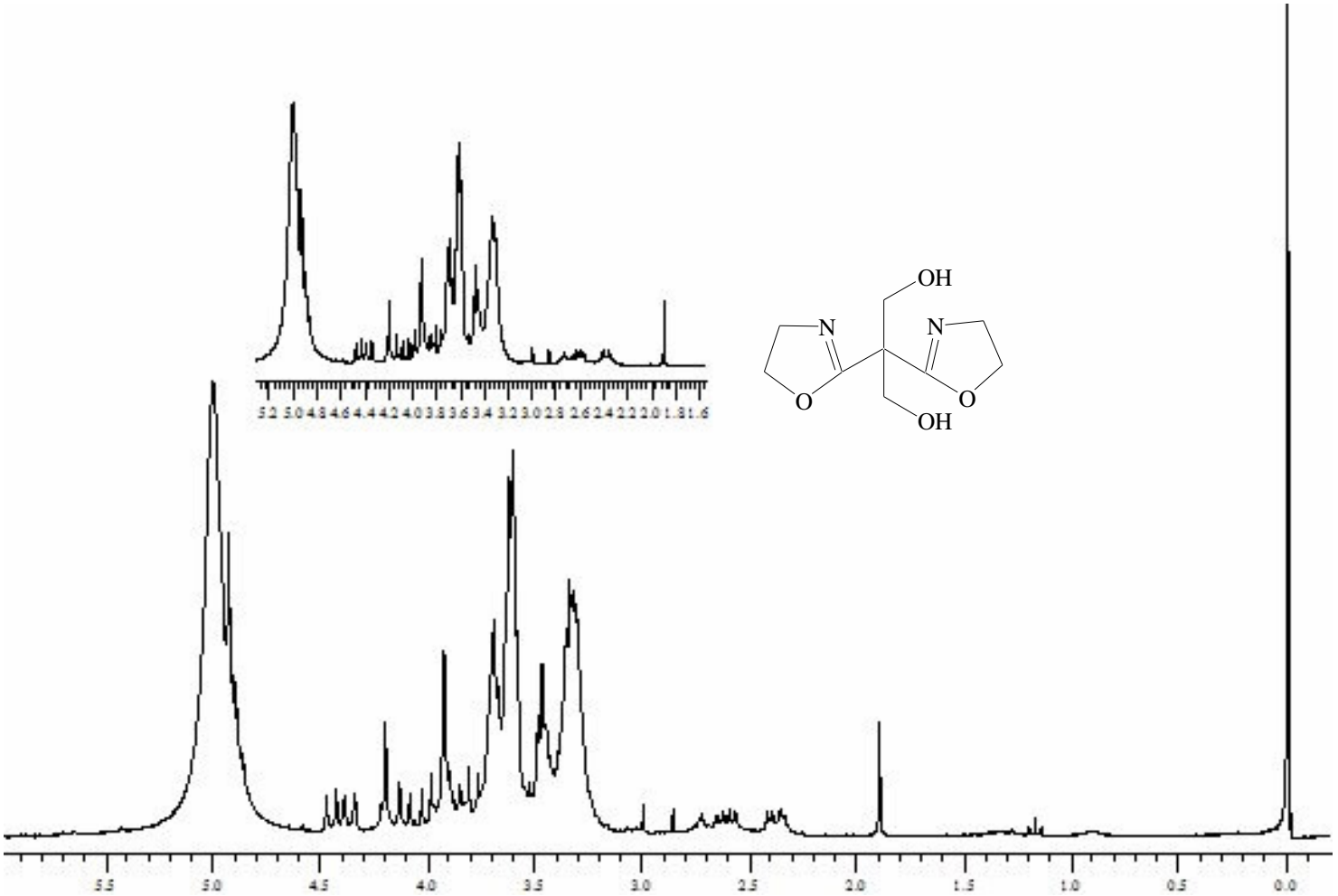

Figure A-15. ^{1}H NMR Spectrum of 2,2'-dihydroxymethylmetylene-bis(2-oxazoline).

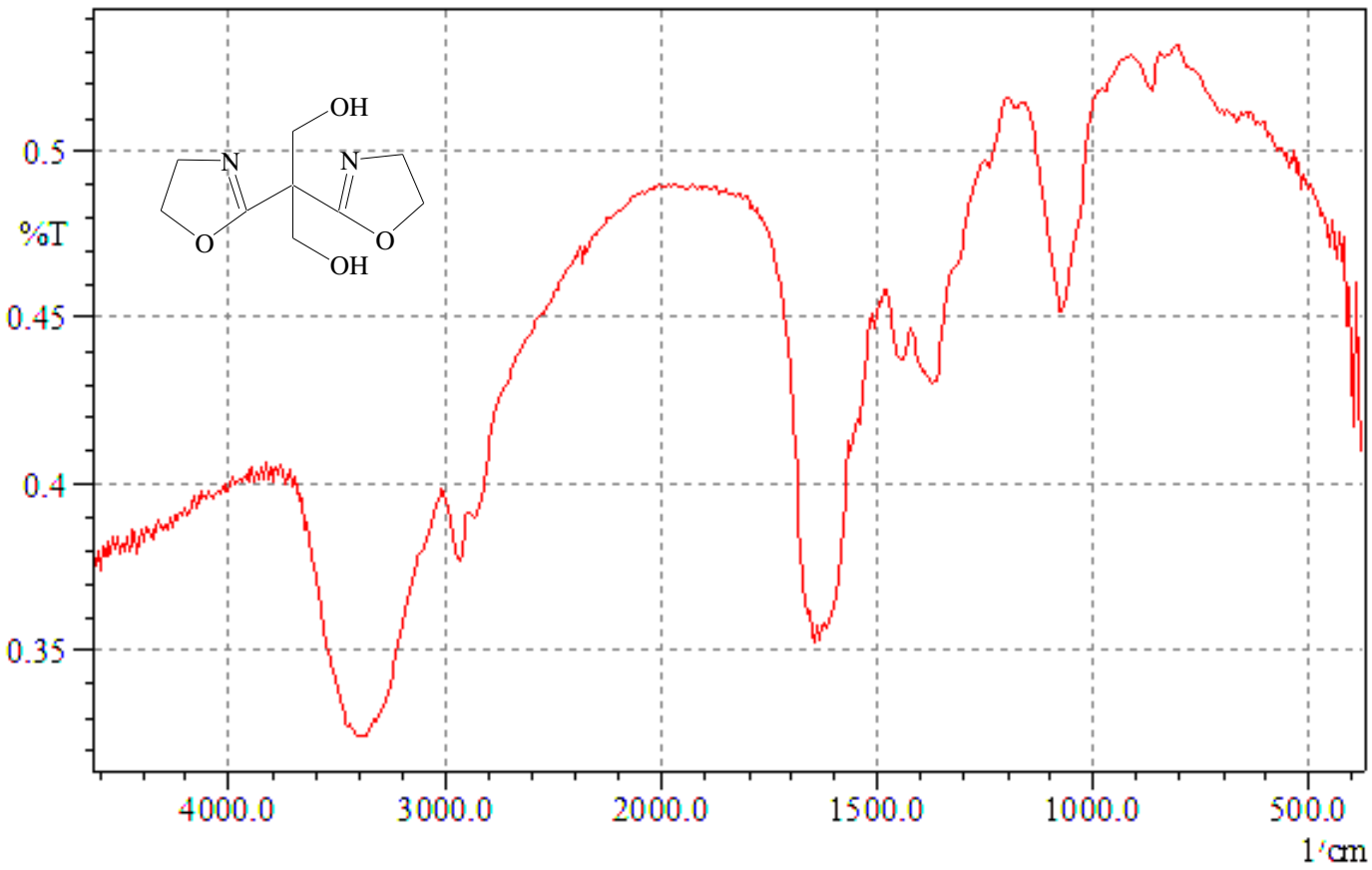

Figure A-16. IR Spectrum of 2,2'-dihydroxymethylmetylene-bis(2-oxazoline).

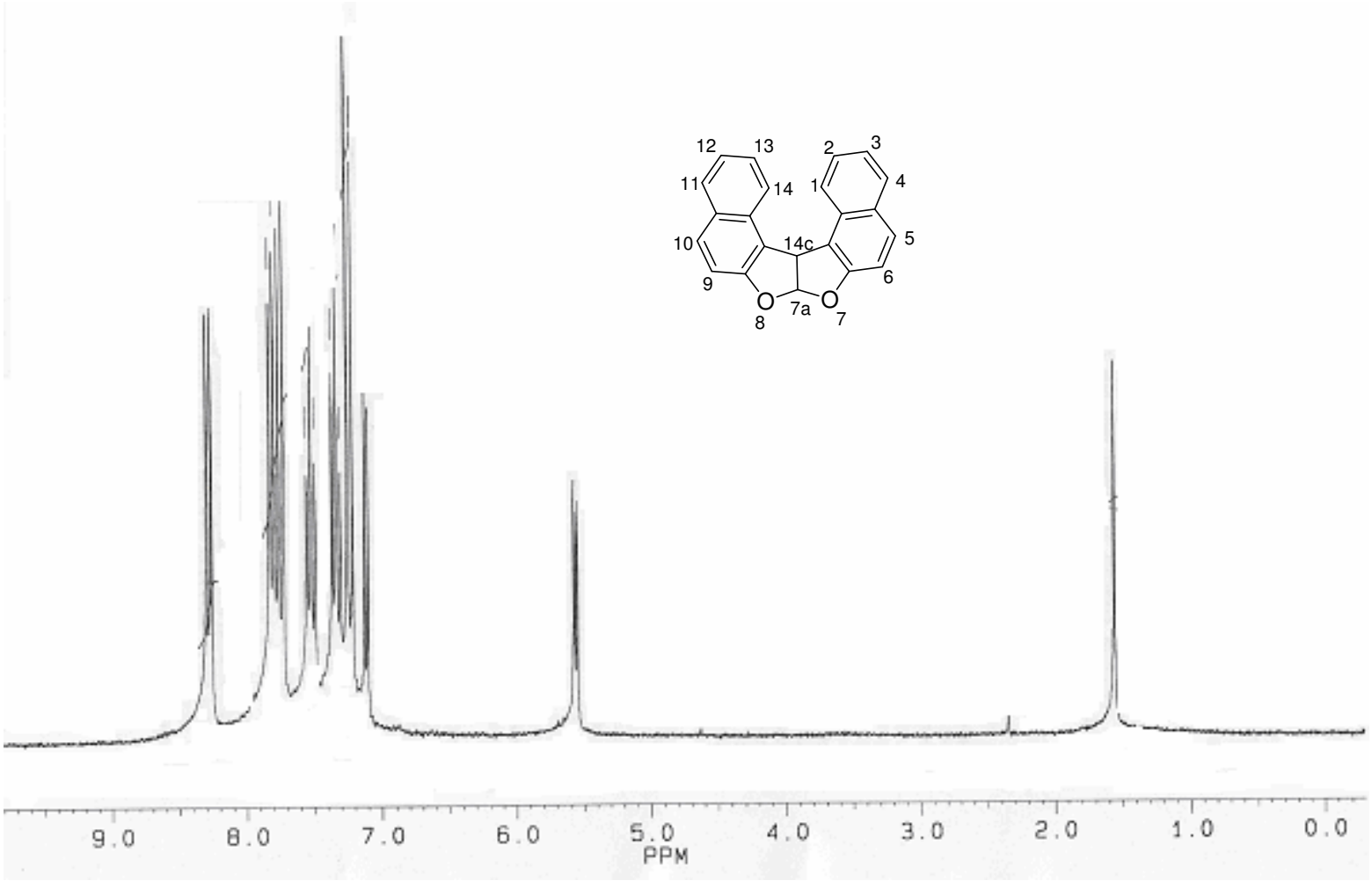

Figure A-17. ^{1}HNMR Spectrum of Naphthofurano naphthofuran.

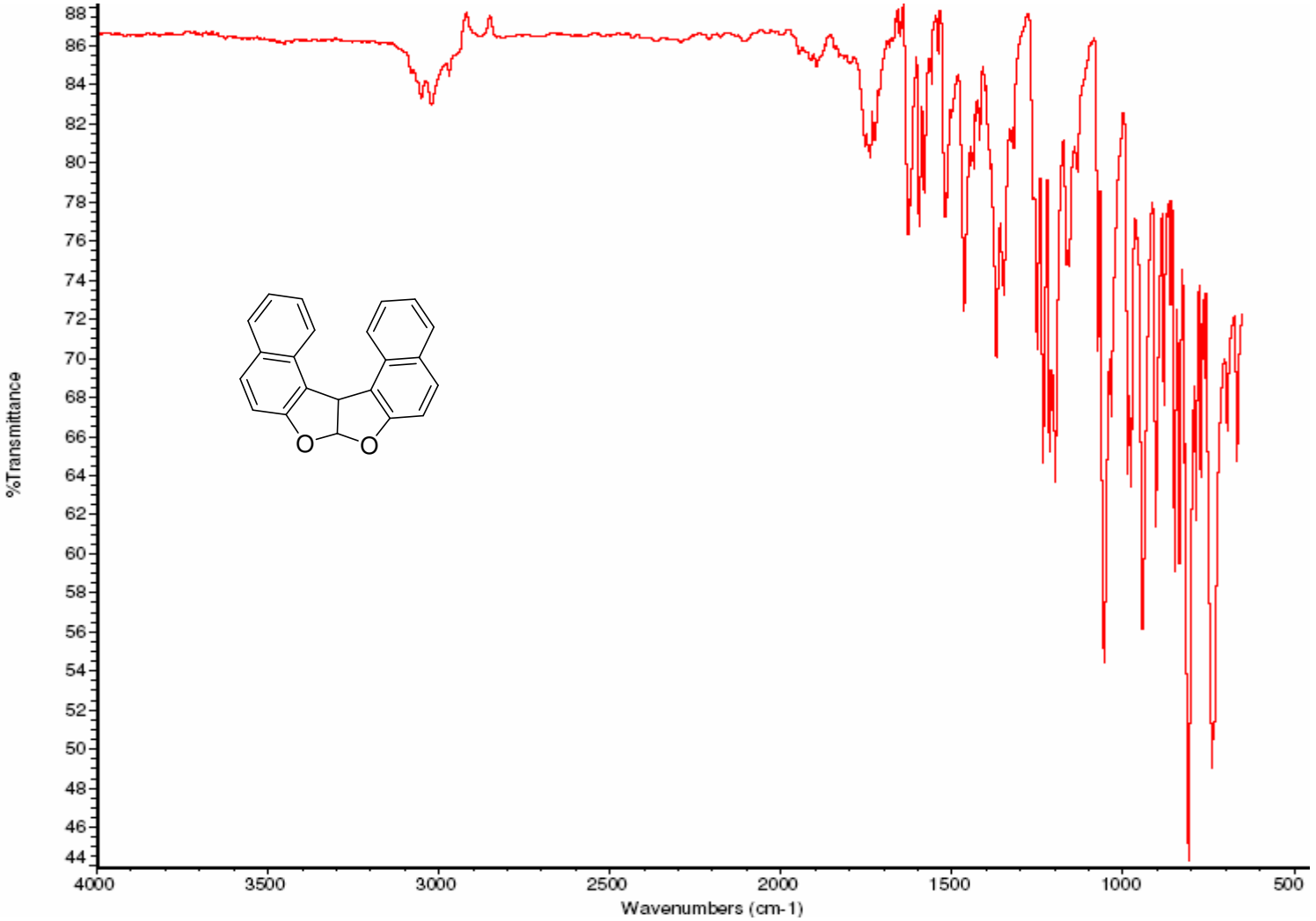

Figure A-18. IR Spectrum of Naphthofurano naphthofuran.

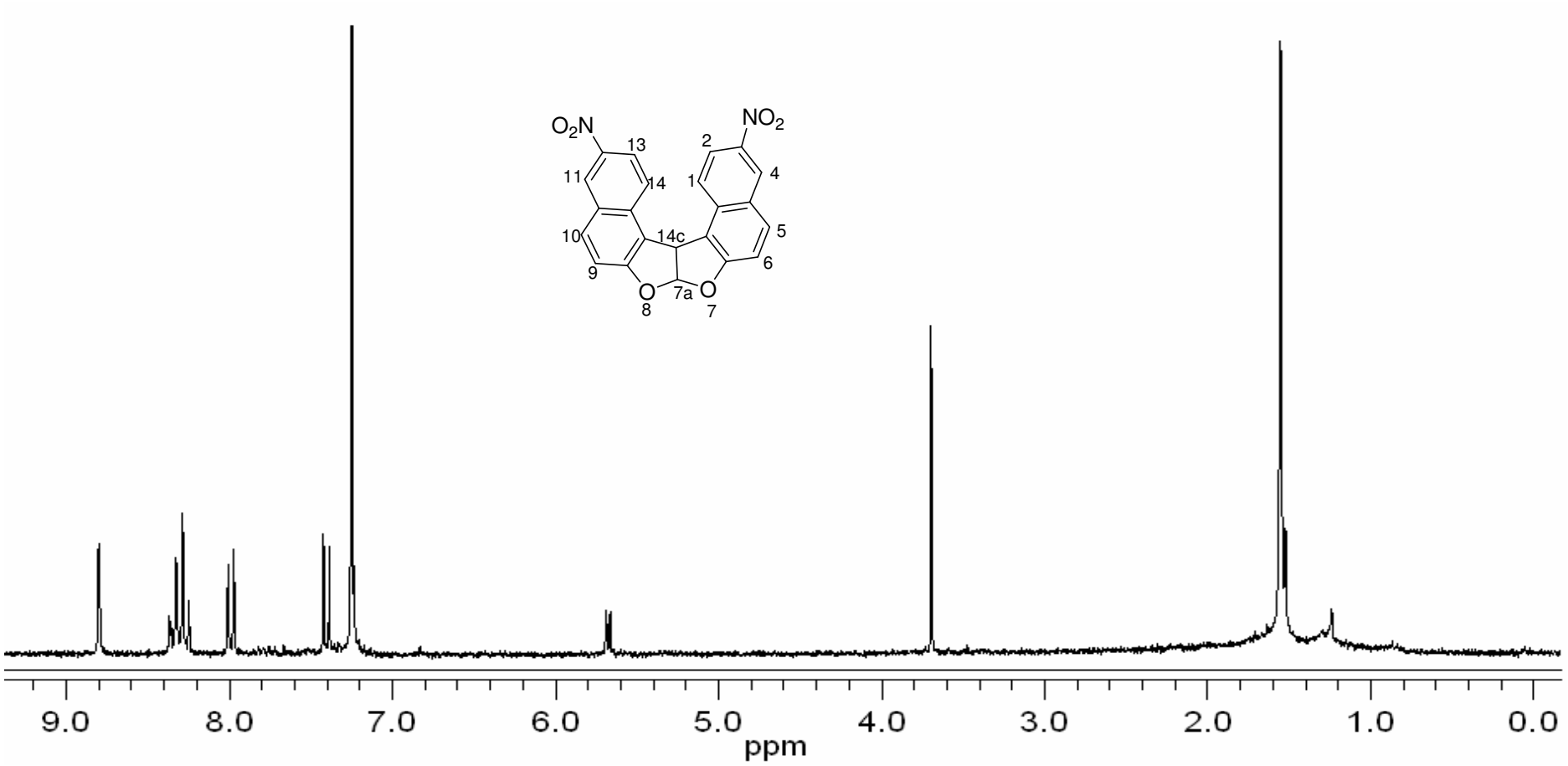

Figure A-19. [1]HNMR Spectrum of 3,12-Dinitro Naphthofurano naphthofuran.

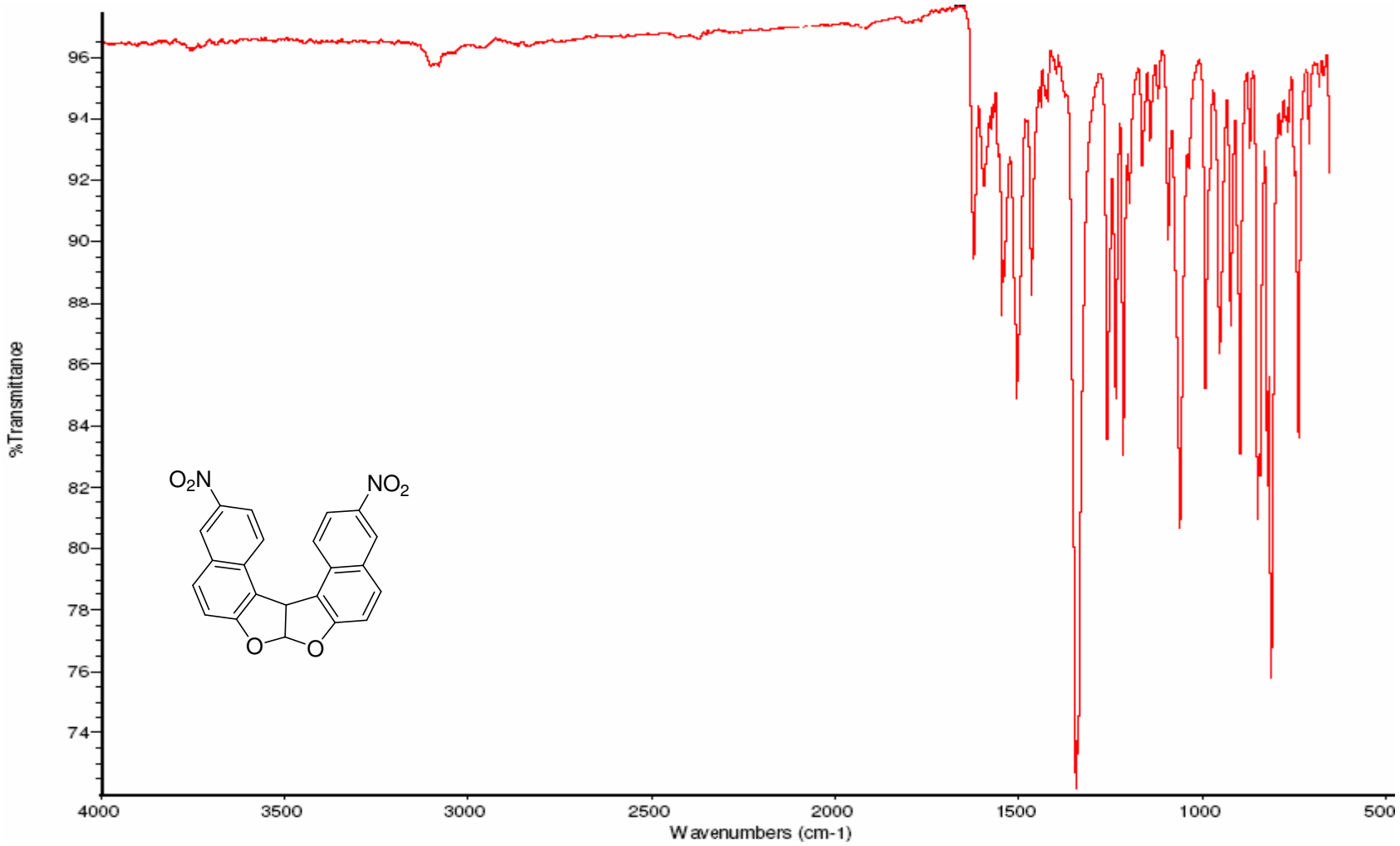

Figure A-20. IR Spectrum of 3,12-Dinitro Naphthofurano naphthofuran.

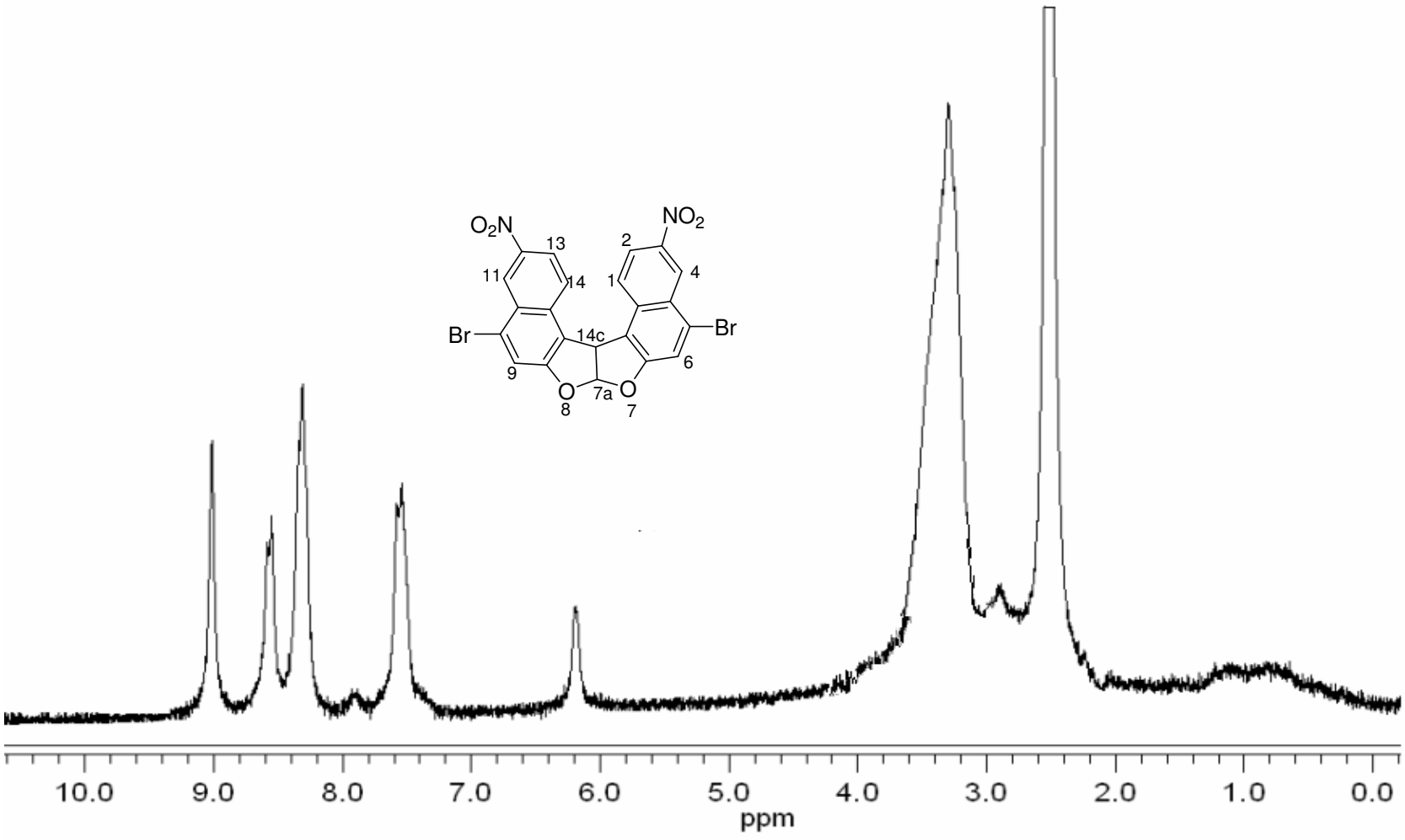

Figure A-21. [1]HNMR Spectrum of 3,12-Dinitro 5,10-Dibromo Naphthofurano naphthofuran.

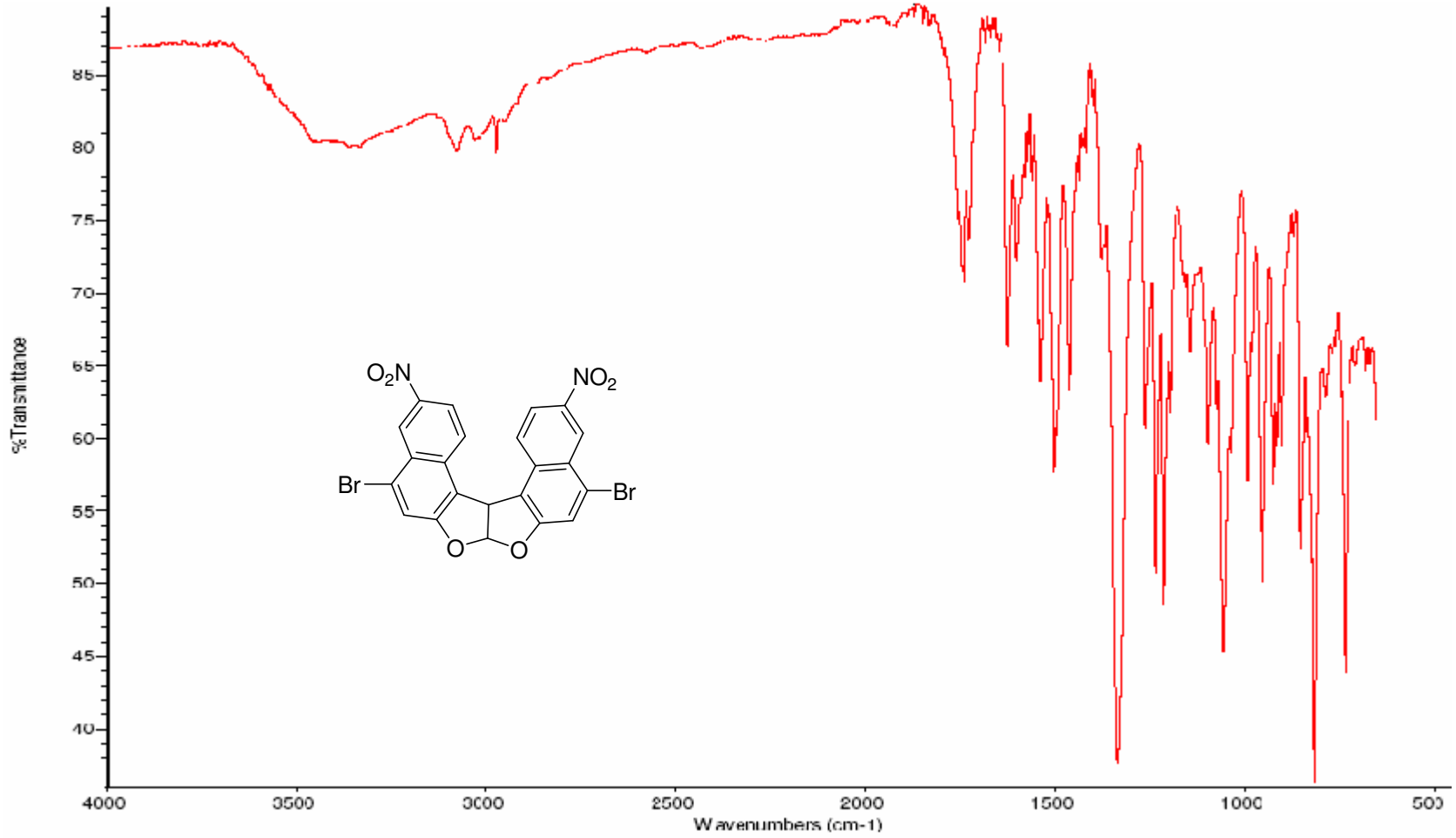

Figure A-22. IR Spectrum of 3,12-Dinitro 5,10-Dibromo Naphthofurano naphthofuran.

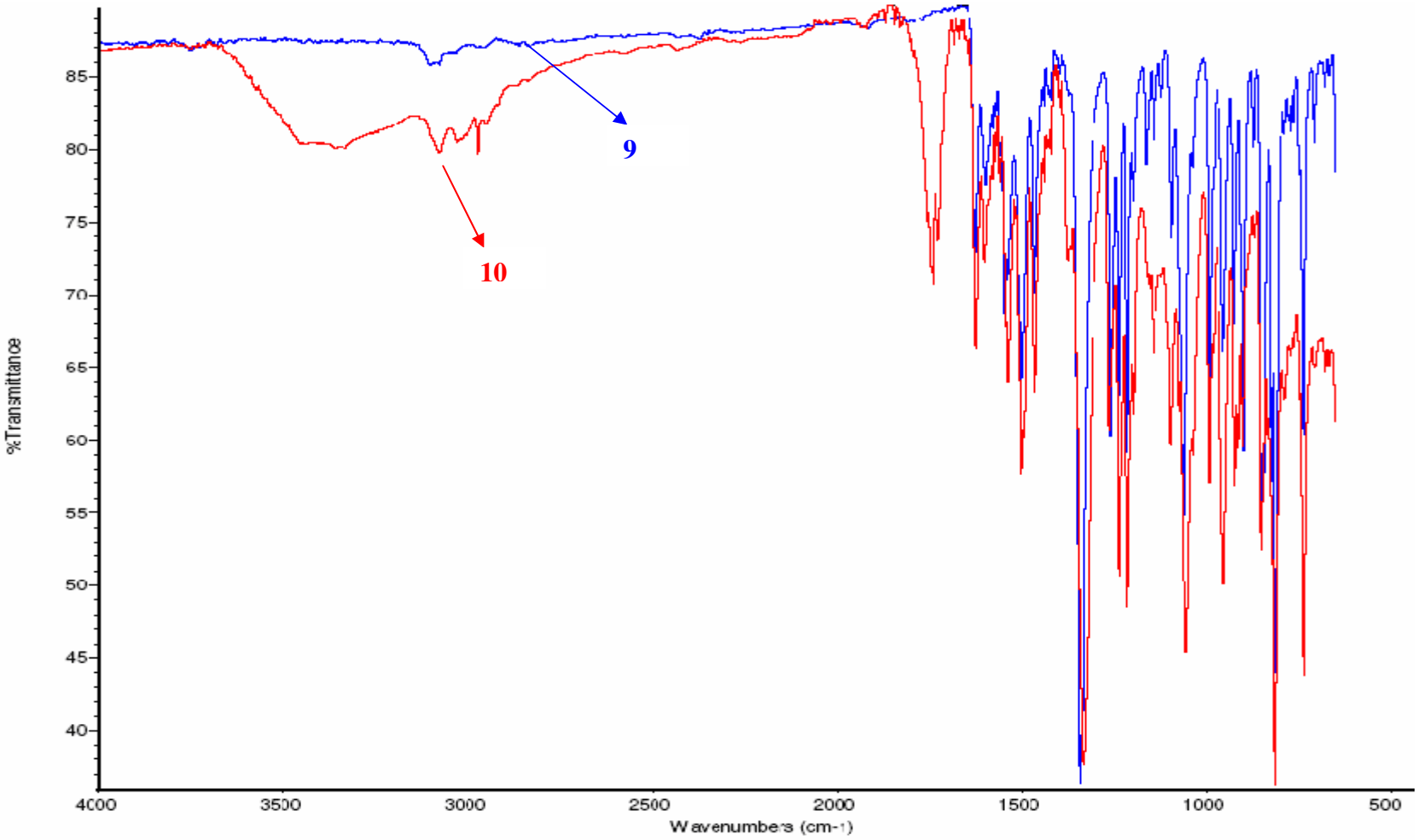

Figure A-23. Overlap IR Spectrum of 3,12-Dinitro 5,10-Dibromo Naphthofurano naphthofuran **10** and 3,12-Dinitro Naphthofurano naphthofuran **9**.

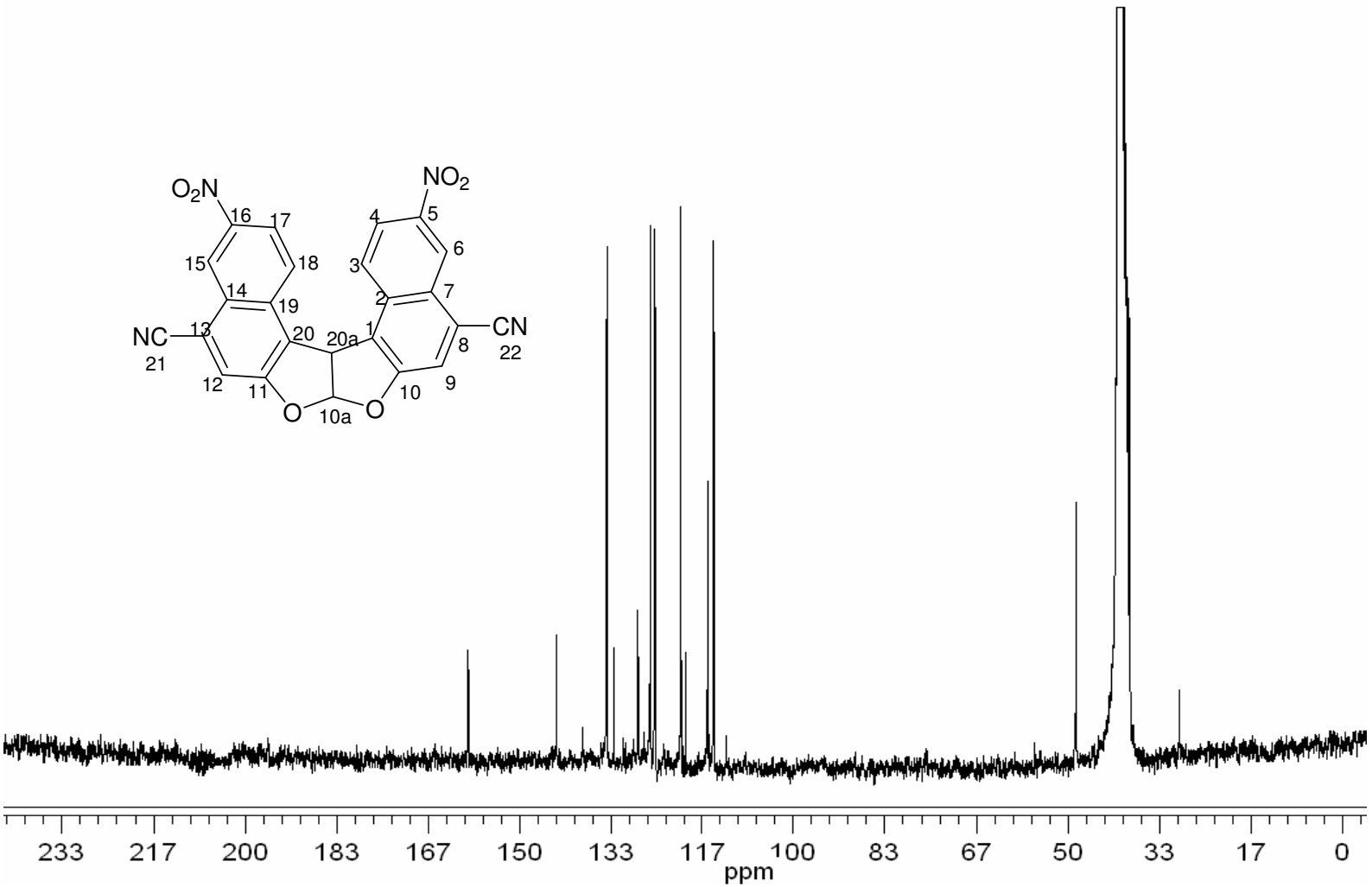

Figure A-24. ^{13}CNMR Spectrum of 3,12-Dinitro 5,10-Dinitrile Naphthofurano naphthofuran.

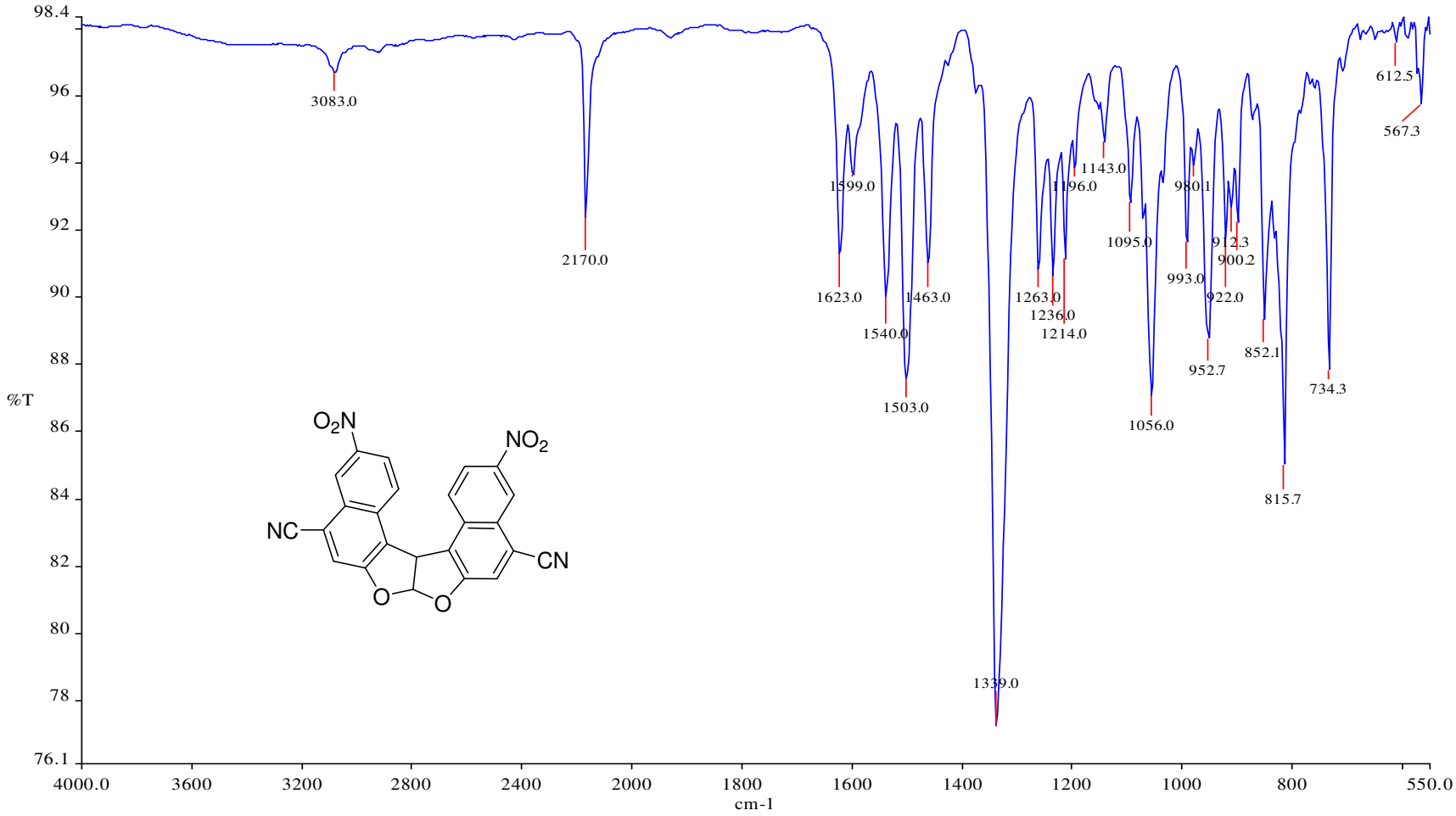

Figure A-25. IR Spectrum of 3,12-Dinitro 5,10-Dinitrile Naphthofurano naphthofuran.

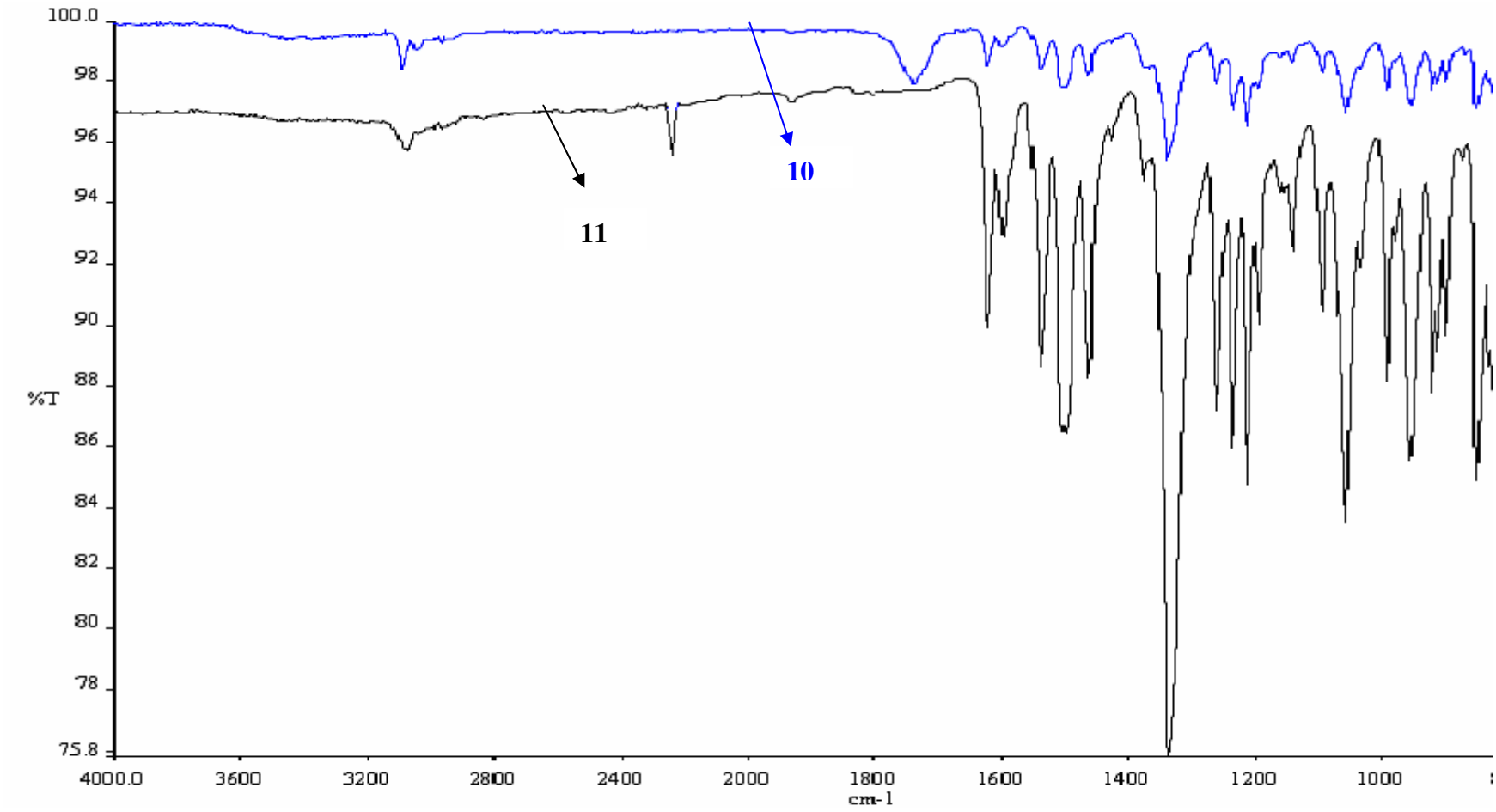

Figure A-26. Overlap IR Spectrum of 3,12-Dinitro 5,10-Dibromo Naphthofuranonaphthofuran **10** and 3,12-Dinitro 5,10-Dinitrile Naphthofurano naphthofuran **11**.

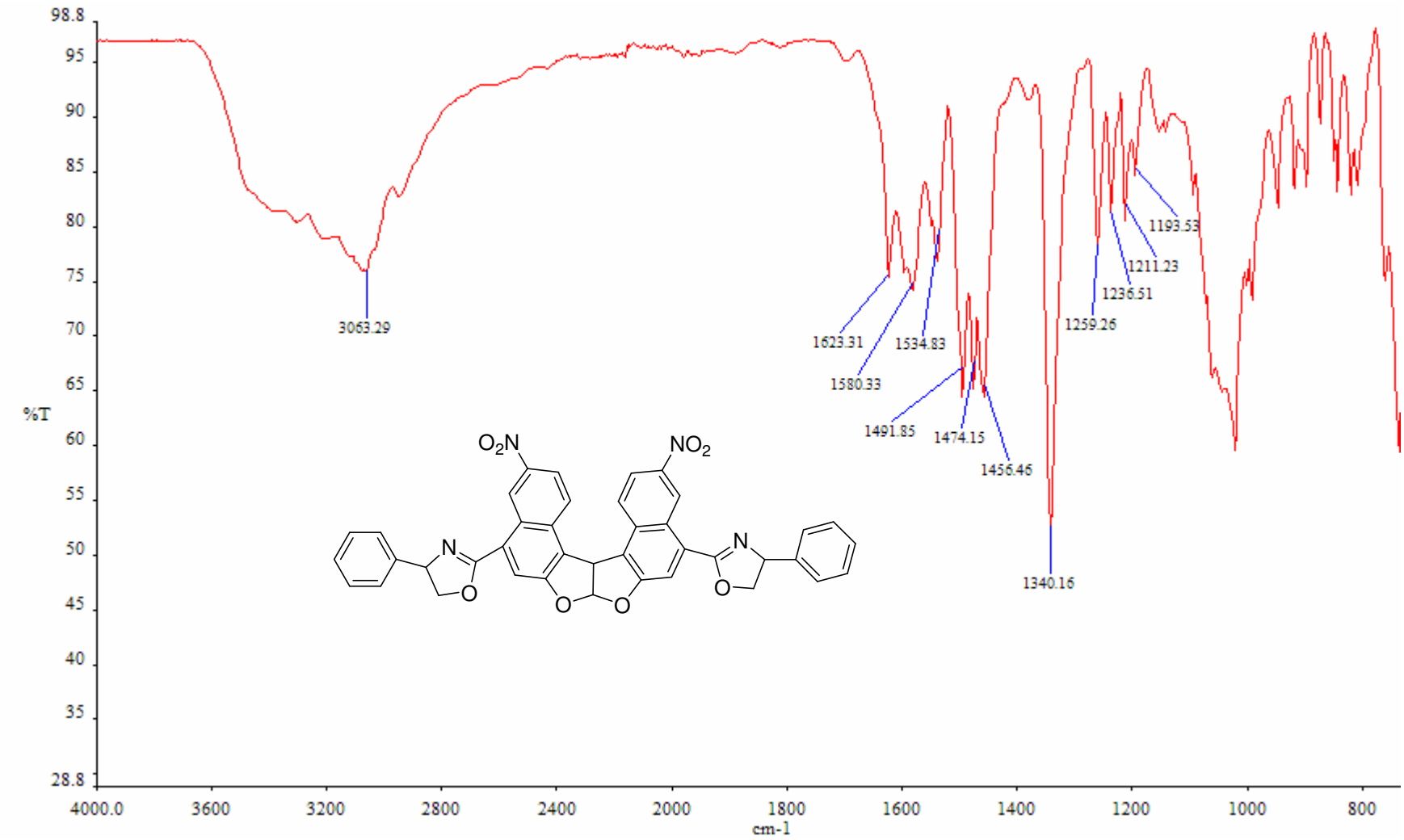

Figure A-27. IR Spectrum of 3,12-Dinitro 5,10-Di-4-Phenyl-4,5-dihidrooxazoline Naphthofuranonaphthofuran.

AUTOBIOGRAPHY

She was born in 1979 in Tehran. In 1995, she graduated from Anakent College and attempted to Chemistry Department of Istanbul Technical University in 1997. In 1999, she did double majoring with Chemical Engineering.

After graduating from Istanbul Technical University in 2002, she was accepted as a master student to Istanbul Technical University, Chemistry Department of the Institute of Science and Technology in which she is about to graduate at the moment. In 2006, she became a Research Assistant.