This is to certify that the

dissertation entitled

"Macrocyclic Tertiary Polyamines; Synthesis and Use in Organic Chemistry as Complexing Agents of Alkali Metals"

presented by

Robert John Hanchar

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Organic Chemistry

Donald G. Lee
Major professor

Date October 25, 1995

"MACROCYCLIC TERTIARY POLYAMINES; SYNTHESIS AND USE IN ORGANIC CHEMISTRY AS COMPLEXING AGENTS OF ALKALI METALS"

By

Robert John Hanchar

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1995

ABSTRACT

"MACROCYCLIC TERTIARY POLYAMINES; SYNTHESIS AND USE IN ORGANIC CHEMISTRY AS COMPLEXING AGENTS OF ALKALI METALS"

By

Robert John Hanchar

In the first part of the following study we investigated two possible application of alkali metal complexing agents in organic synthesis: their use with alkali metals to carry out reductions of organic compounds; their use to complex with, and thereby increase the base strength of alkyl lithium reagents.

Formaldehyde was reduced by HMHCY complexed NaK alloy. The reactions were quenched with D_2O and gave methanol-OD and dideuteromethanol in 11~81 % yield. The dideuteromethanol is believed to arise from reaction of a carbanion-like C-O synthon with the D_2O and accounts for 0.5~10 % of the reaction yield. Attempts were also made to reduce 2,2-dimethylpropanal and 2-cyclohexenone using HMHCY complexed NaK alloy. 2,2-Dimethylpropanal dimerized to give 2,2,5,5-tetramethyl-3,4-hexanediol. The reduction of 2-cyclohexenone gave over 35 separate compounds that were not identified.

In the second part we report the design and synthesis of two new complexing agents and several improvements to the methodology used to form polyazamacrocycles. It was found that by carefully controlling temperature, time, and the concentration of sulfuric acid used it was possible to limit the acid hydrolysis of the sulfonyl amide bonds of 1,4,7-tritosyl-1,4,7-triazacyclononane so that one, two or all three tosyl protecting groups were removed. This technique allows a convenient method for synthesizing polyazamacrocycles that have a unique pendant arm on one or two of the available nitrogen atoms. The methodology was used as a key step in the synthesis of the two novel tertiary polyazamacrocycles 1,2-bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane and 4,7-dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane. In addition we report some improvements for the Richman-Atkins synthesis of polyazamacrocyclic compounds. It was discovered that the use of a catalytic amount of *tert*--butyl alcohol allowed the use of only a modest excess of a hydride base in the cyclization step without decreasing the yield.

This work is dedicated to my wife Nancy,

and to my children Candice and Stephanie.

ACKNOWLEDGMENTS

I would like to thank Professor Donald G. Farnum for his friendship, understanding, and guidance, which made my time at Michigan State University both educational and enjoyable. My appreciation also goes to my parents for instilling in me the confidence necessary to attempt such an endeavor and to my wife for supporting me in ways that only she could. Although they are too numerous to name, I also offer my thanks to the many individuals that assisted me during my studies through either friendship or academic assistance. Finally, I wish to thank the Center for Materials Research for their financial support of this project.

TABLE OF CONTENTS

Table of Contents (continued)

Table of Contents (continued)

Table of Contents (continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (Continued)

LIST OF FIGURES (Continued)

LIST OF SCHEMES

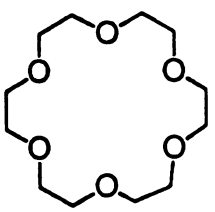
Introduction

The study of compounds that surround or associate themselves with other molecules is an exciting and expanding area of chemistry with some journals devoting themselves exclusively to this type of chemistry[1]. By taking advantage of steric and electrostatic interactions one molecule acts as a host or complexant for a second atom or molecule. A variety of compound types have been discovered that have this ability, ranging from polysaccharides and proteins to purely inorganic structures. We were interested in the use of Lewis bases, such as polyoxy, polyaza, and oxy-aza compounds to surround and associate themselves with alkali metal cations. In the first part of the following study we investigated and developed possible applications of alkali metal complexes that have already been discovered. In the second part we report the design and synthesis of new complexing agents.

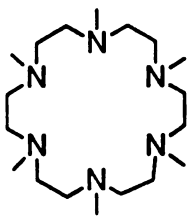
PART 1

The use of Tertiary Polyazamacrocycles as Complexants of Alkali Metal Cations in Organic Chemistry

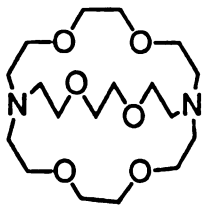
It has been known for thirty years that certain polyethers can dissolve alkali metals to form blue solutions[2]. It has since been learned that these solutions contain alkali metal cations coordinated by the polyether. Over the years many other compounds have been synthesized that also display this ability (e.g. crown ethers[3], cryptands[4], macrocyclic tertiary polyamines[5]).



18-Crown-6



1,4,7,10,13,16-Hexamethyl-
1,4,7,10,13,16-Hexaazacyclooctadecane
(HMHCY): **1**



[2,2,2]-Cryptand

Figure 1- Structure of 18-crown-6, HMHCY, and [2,2,2]-cryptand.

Although the ability of these complexants to complex alkali metal cations has been studied widely, their use in organic chemistry remains largely uninvestigated, even though they show significant promise in several areas. Dye has isolated several alkali metal complexes as reasonably stable crystals (alkalides and electrides) and can prepare more[5~8]. Since it is possible that further work may one day provide these complexes as shelf

stable reagents, and there has not been a comprehensive evaluation of the complexants in organic chemistry, we decided to investigate a number of plausible applications that would help establish these complexants and complexes as useful, well-defined reagents for organic chemical transformations.

The change in chemical behavior caused by the addition of complexants to solutions of relatively non-polar solvents (such as THF) containing alkali metals or alkali metal ions can be attributed to the complexation of the alkali metal in its plus one oxidation state. Electrostatic interactions between the cation and the lone pair electrons of the complexant stabilize the cation, much as a polar solvent solvates a cation (or anion) by creating a solvent sphere. This allows the equilibrium shown below to favor the separated ion pairs.

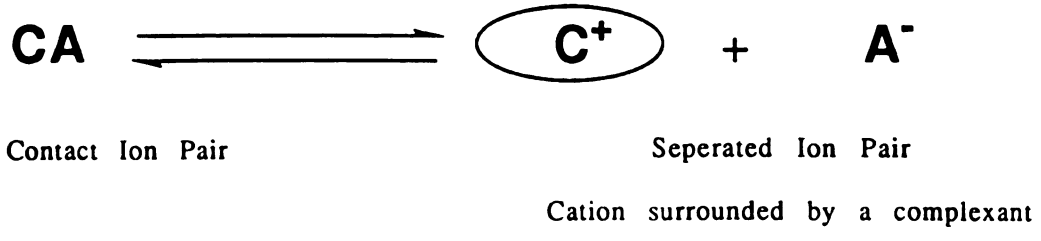


Figure 2- Complexation

In addition, since the complexing agent's lone pair electrons are facing inward toward the cation, the non-polar part of the complexant is exposed to the solvent thereby increasing the solubility of the cation in organic solvents. Lehn likens such a complex to a giant organic cation that forces the associated anion to be dissolved in a non-polar solvent where it is virtually "naked"[9]. In cases where alkali metals are used, the anion would

then be either a free electron or a metal atom in a minus one oxidation state[10]. The ability of the complexant to separate and solubilize the ions is subject to some limitations. For example even when an alkali metal cation is complexed by the cage type structure of the cryptands, if the anion is especially hard (F^-, OH^-), it is necessary to add a cosolvent ($CHCl_3$) to help solvate the anion in a non-polar solvent. Sometimes the anion and cation form ion pairs even though the cation is complexed. Although such ion pairs have increased solubility, the anion would not be as reactive under these conditions as it would be if it were not associated with the cation. The better the cation is solvated by the ligand the freer the anion, and the more active it becomes, leading to a modification in its chemistry. Dye has gone a step further and used the complexants to isolate complexes of alkali metal alkalides and electrides as stable crystalline solids[5~8]. It is reasonable to assume that the chemical behavior of these solids will be similar/identical to that of the alkalides and electrides formed *in situ* once they are in solution. A more detailed explanation of the mechanism by which these compounds can and do modify the reactivity of alkali metal containing compounds can be found in reviews by Dye and Lehn[8,9].

From our perspective there are two broad areas where crown ethers, cryptands and macrocyclic tertiary polyamines have applications in organic chemistry: 1) to activate and solubilize alkali metal salts and alkali organo compounds, 2) to solubilize alkali metals for use as organic reducing agents.

There is an abundance of literature in phase transfer catalysis (PTC), an area where organic chemists have capitalized on the ability of these

complexants to dissolve alkali metal salts into solvents which they are normally insoluble. Numerous groups have effected initiation of both anionic and free radical polymerization by PTC[11]. Typically, the complexant sequesters the salt or alkali metal into the organic phase from either a solid or an aqueous solution. The companion anion then initiates polymerization. An example of an anionic polymerization is shown below. Jedlinski reported the anionic polymerization of the β-lactones 2-oxetanone[12] and 4-methyl-2-oxetanone[13] using 18-C-6/THF/potassium metal.

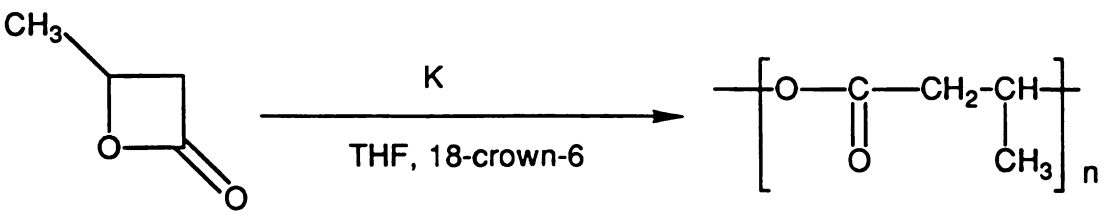


Figure 3- Polymerization of 4-methyl-2-oxetanone

In addition anionic polymerization of the monomers isoprene, styrene, butadiene, ethylene oxide, 2-vinyl pyridine, and propylene sulfide has been accomplished using cryptands to complex alkali metals or alkali metal salts[10]. Radical polymerization of acrylic and methylacrylic monomers has been reported by Rasmussen using crown ether solubilized potassium peroxydisulfate as a radical initiator[14].

PTC has been used effectively in reactions other than polymerization. In the Gomberg-Bachmann synthesis[15] 18-crown-6 solubilizes KOAc, so the acetate anion can displace the fluoroborate ion and attack the diazonium ion. A series of equilibria finally yields the desired alkyl radical.

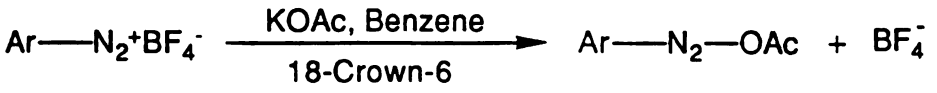


Figure 4- Gomberg-Bachmann synthesis

In the preparation of cyanformates[16] 18-crown-6 brings the inorganic salt KCN into CH_2Cl_2 solution. The ^-CN anion then displaces the chloride.

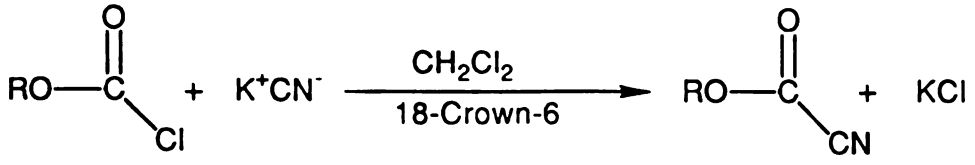


Figure 5- Preparation of cyanformates

Additional examples and reviews of this type of chemistry are given in references17-22. Since the use of complexants as PTCs for alkali metal salts has received considerable attention from other groups, we did not feel that we could significantly contribute to this area of interest. However the use of complexants to modify alkyl lithium reagents is largely uninvestigated. It is known that reactions of butyl lithium are modified by the addition of certain polyamines[23]. We felt complexants that complexed strongly with Li cation might have similar applications, as discussed in more detail later.

We also felt we could make a contribution by examining complexed alkali metals as organic reducing agents. When a crown ether or cyclen (cyclens are nitrogen analogs of crown ethers were all of the crown ethers' oxygen atoms are substituted with nitrigen atoms) is added to an alkali metal in an appropriate solvent it is possible to obtain alkalides, electrides, or solutions that contain solvated electrons. The powerfully reducing

alkalide or electride present in these solutions might perform reductions similar to those of the Birch reduction.

Since the 1950's it has been known that alkali metals can reduce aromatic compounds. In the Birch reduction the alkali metal is dissolved in liquid ammonia along with the substrate[24~26]. It is currently accepted that the reduction is carried out by solvated electrons formed from the disassociation of the alkali metal and its outer electron.

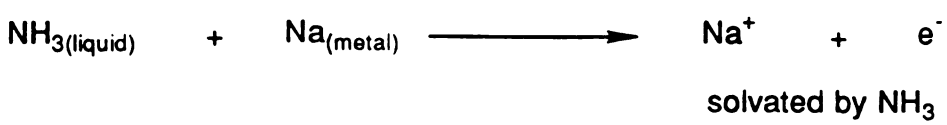


Figure 6- Birch reduction

The Birch reduction requires working at low temperatures (-33° C, the boiling point of ammonia) with hazardous liquid ammonia. In the Benkeser modification the reaction is effected in a refluxing low molecular weight amine (e.g. methylamine, ethylamine, isopropylamine, ethylenediamine), resulting in a slightly more powerful reducing medium. In both types of reductions a proton source, such as an alcohol, is sometimes needed to complete the reduction, while in other cases the ammonia or amine acts as the proton source. Both the Birch and the Benkeser reductions are limited by the solvents, which are reactive toward some functionalities such as ketones, are poor solvents for many organic molecules, and can destroy a desired reactive intermediate through proton transfer. We felt that the use of aprotic complexants to solubilize and activate alkali metals in less polar aprotic solvents might overcome some of these problems and provide a useful new procedure.

There has been scattered work on the use of crown ethers and HMHCY to solubilize alkali metals to perform organic reductions. Lehn[27], Nelson[28], and Weissman[29] have each independently reported the reduction of benzene and toluene to their radical anions with potassium and 18-crown-6. Barrett and Barton report the cleavage of alkyl carboxylic esters[30] and the deoxygenation of N,N'-Dialkylaminothiocarbonyl-oxyalkanes[31] with18-crown-6 and potassium. Ohsawa has reductively defluorinated primary, secondary, and tertiary alkyl fluorides[32], and reports a decyanation[33] reaction using K/18-C-6/toluene. Ohsawa proposes that a one electron transfer to toluene generates a toluene radical anion that then acts as the reducing agent. Guida and Mathre report the reduction of both anthracene and several non-terminal alkynes using 18-C-6/Na/THF[34]. Lastly Pez has successfully reduced benzene to cyclohexene using Na/K metal, HMHCY, and molecular hydrogen[35].

The above references suggest several advantages of using complexing agents in alkali metal reductions of organic compounds: 1) more solvent choices, 2) possible aprotic reduction of organic compounds to radical anions or dianions that could then be used as nucleophiles in further reactions, 3) a more powerful reducing medium.

The primary purpose of the following study was to help develop and understand macrocyclic tertiary polyamines as useful reagents in two areas, as complexants with alkali metals to give reducing media similar to the Birch or Benkeser reducing systems, and as complexants to increase the base strength of butyl lithium.

Complexed Alkali Metals as Reducing Agents

While it has been shown that the addition of complexing agents such as cyclens, crowns, and cryptands can affect some organic reductions[27-35], there has not been a comprehensive evaluation of this use of these types of complexants. It seemed possible that the addition of these complexants to certain reducing systems may activate them by increasing the reduction potential of the alkali metal. If so, we wanted to explore applications of these reducing agents in organic chemistry. The reduction potential of an alkali metal, as used in the Birch and Benkeser reductions, might be increased by running the reduction in a non-polar solvent, using the complexing agents to bring the alkali metal cation and it's anion into solution. In a non-polar solvent the anion is substantially less solvated and thus "activated" (as described in the introduction). It is possible that under these conditions the "naked" anion will be more reactive than the solvated electrons that are the active species in the Birch reduction. At the inception of the project there was no solid evidence supporting this hypothesis. However, if it did prove to be true, we felt that the reduction of hard to reduce organic functionalities would be a promising application of alkali metal complexes. The radical anions or dianions formed might be stable in the aprotic condition of the reductions. These anions would then be available to participate in a number of useful reactions. It was our intention to assess this possibility by attempting the two electron reduction of formaldehyde to generate the methanol dianion.

The decision to investigate the two electron reduction of formaldehyde was based on two factors. First, while the reduction of formaldehyde with hydride type or protic reducing agents is a trivial reaction, the aprotic reduction of formaldehyde to give methanol dianion is not reported. Previous attempts at the reductive formation of the methanol dianion have failed[36,37]. We felt that the radical anion formed from the addition of one electron to formaldehyde would quickly dimerize to form ethylene glycol dianion.

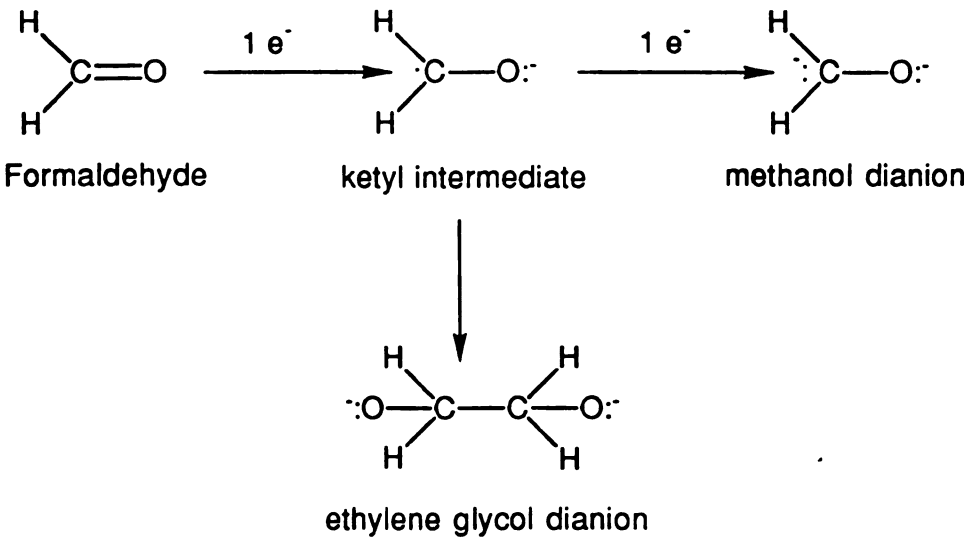


Figure 7- Reduction of formaldehyde

To accomplish the two electron reduction, a method is needed where the addition of the second electron is fast compared with the rapid dimerization of the radical anion. If the use of complexing agents does activate alkali metals, then such a system might reduce formaldehyde to the methanol dianion by two possible scenarios. The complexant might increase the reducing power of the metal to the point where addition of a second electron becomes competitive with the dimerization, or where two

electrons are transferred simultaneously from an alkalide metal complex, or by a combination of the two pathways. We felt this difficult reduction was a good test to help establish whether the addition of complexing agents to alkali metal reductions "activates" these reductions.

The second reason for selecting the reduction of formaldehyde as a test reaction was that the methanol dianion would be a useful species in organic chemistry. There are numerous examples in the literature of hydroxymethylation procedures[38]; however, the majority of these introduce the carbon oxygen fragment as an electrophile. The use of the methanol dianion as a hydroxymethylating reagent would allow the introduction of the carbon-oxygen fragment as a nucleophile, complimenting established procedures. Hydroxymethyltributyltin as a methanol dianion equivalent has been used in synthesis. The methanol dianion is presumed to be generated as the dilithium derivative by treating tributyltinmethanol with excess butyl lithium[36]. However the cost and problems associated with the synthesis has limited its use. Some drawbacks are: the reagents are costly, toxic, bulky, and the products are difficult to isolate from the tin by-products[39]. Other methods exist to accomplish nucleophilic hydroxymethylations that does not use the methanol dianion directly, but adds the C-O fragment in masked or protected form. An example is the reaction of the methylsulfinyl carbanion with particular esters to generate β-keto sulfoxides. These compounds can then be transformed into a variety of other functionalities that have a C-O fragment coupled to the carbonyl carbon atom (Figure 8)[40,41].

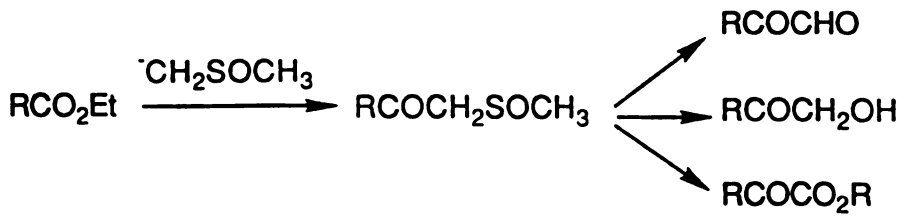


Figure 8- Reaction of methylsulfinyl carbanion with esters

Another example is the use of boron stabilized carbanions reported by Rathke. By using sterically hindered bases, Rathke was able to generate a boron stabilized carbanion that could be alkylated by an alkyl halide. The boron could then be replaced by a hydroxyl group through oxidation with peroxide. The net result was hydroxymethylation of the alkyl halide[42].

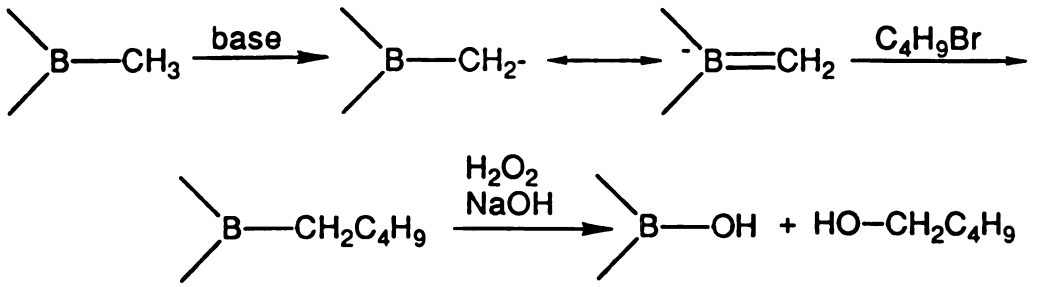


Figure 9- Reaction of boron stabilized carbanions with alkyl halides

The liabilities of these methodologies are: they are multistep procedures, they sometimes give poor yields, and they don't always work. If our efforts were successful we hoped to provide a cheap, convenient and direct source for the methanol dianion that could then be used for other organic transformations.

Reduction of a carbonyl group by 18-crown-6 and potassium has been reported by Jedlinski[43,44]. The first step in the reported reaction sequence is a one electron reduction to form a radical anion, which under

the reaction condition either abstracts a proton from another ketone to form an enolate and alcoholate, or abstracts a hydrogen atom from the THF solvent to give alcoholate (Figure 10). Although Jedlinski's work demonstrated the reduction of carbonyls by complexed alkali metals, the putative radical anions were quenched by the system components. We hoped to generate radical anions and dianions that would be stable in the reaction media by using different reaction conditions such as tertiary amine based solvents and complexants.

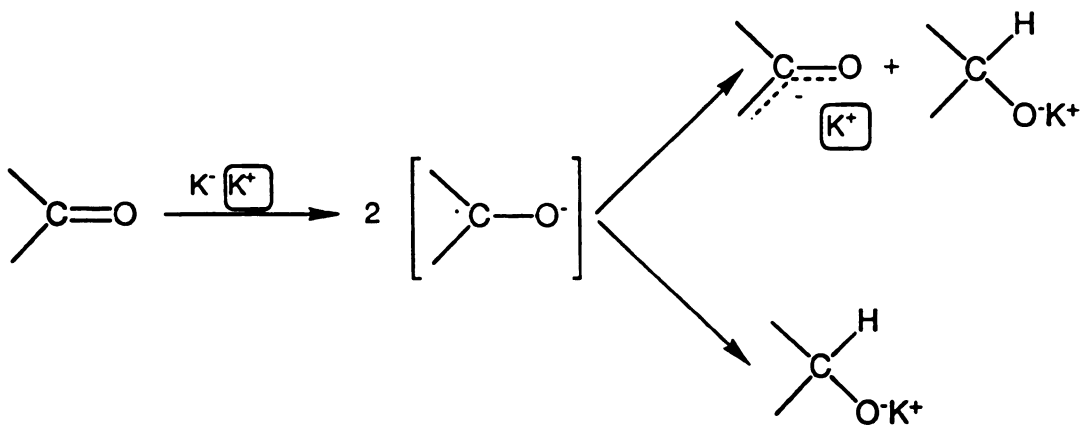


Figure 10- Reduction of a carbonyl group by 18-crown-6 and potassium

We selected macrocyclic tertiary polyamines as the complexants in our experiments because early results showed the carbon-oxygen bonds present in crown ethers and cryptands were susceptible to reductive cleavage under the reaction conditions. In addition, the α-protons of an ether are susceptible to abstraction by the very strong bases generated by complexing agents and alkali metals[43~46]. It was expected that carbon-nitrogen bonds would be much less susceptible to these types of decomposition because nitrogen is less electrophilic than oxygen. Since nitrogen cannot stabilize a negative charge as well as oxygen, the addition

of an electron (the most likely first step in reductive decomposition) or the removal of an α-proton is less favorable for nitrogen based complexants . On the other hand, a drawback to the all nitrogen complexants is that, being softer Lewis Bases, they have lower complexation constants with alkali metals than their oxygen based counterparts[48]. None the less, Dye has shown that certain cyclens can complex with alkali metals well enough to form reasonably stable alkalides[5]. We felt this demonstrated that such complexants might be acceptable for our work.

A complementary objective of this research was to develop an effective procedure for reduction, using methods and capabilities that are common to the average organic laboratory. To this end we avoided the use of ultra high vacuum, ultra pure reagents, and Schlenk line techniques. However, we did protect the reactions from air and moisture by procedures that are standard to an organic laboratory (e.g., maintaining all reactions under argon as an inert atmosphere, using dry solvents, using syringe techniques when transferring liquid compounds, etc.).

Reduction of Formaldehyde

We decided to use ^{1}H-nmr as our analytical technique to determine if we had been successful in generating the methanol dianion. Quenching methanol dianion with deuterium oxide should give dideuteromethanol with one deuterium on carbon. The ^{1}H-nmr spectrum of such a species would show a characteristic 1:1:1 triplet due to deuterium coupling. Thus, the presence of a 1:1:1 triplet in the ^{1}H-nmr of the quenched methanol product would demonstrate the presence of carbon bound deuterium. We can conceive of no other source for carbon bound deuterium under these reaction conditions than the reaction of D_2O with a carbanion like that present in methanol dianion. D_2O quenching has significant advantages over other trapping agents such as alkyl halides, since the latter would be susceptible to reduction by residual alkali metal and/or complexes. The reduction of a trapping agent would generate reactive species that would complicate and obscure the detection of the methanol dianion.

To test the viability of our analytical technique a sample of the methanol dianion synthon described by Seebach was prepared using his procedure[36], and then quenched with deuterium oxide. Excess deuterium oxide was separated from the reaction mixture, which was then examined by ^{1}H-nmr. The resulting spectrum showed a 1:1:1 triplet 0.02 ppm upfield from a smaller singlet. To confirm that the small singlet was from proteomethanol a small amount of authentic proteomethanol was added to the sample. The small singlet

dramatically increased in size while the 1:1:1 triplet remained unchanged (Figure 11). This experiment demonstrated that ^{1}H-nmr of a deuterium oxide quenched reaction is an effective analytical technique to determine the presence of methanol dianion.

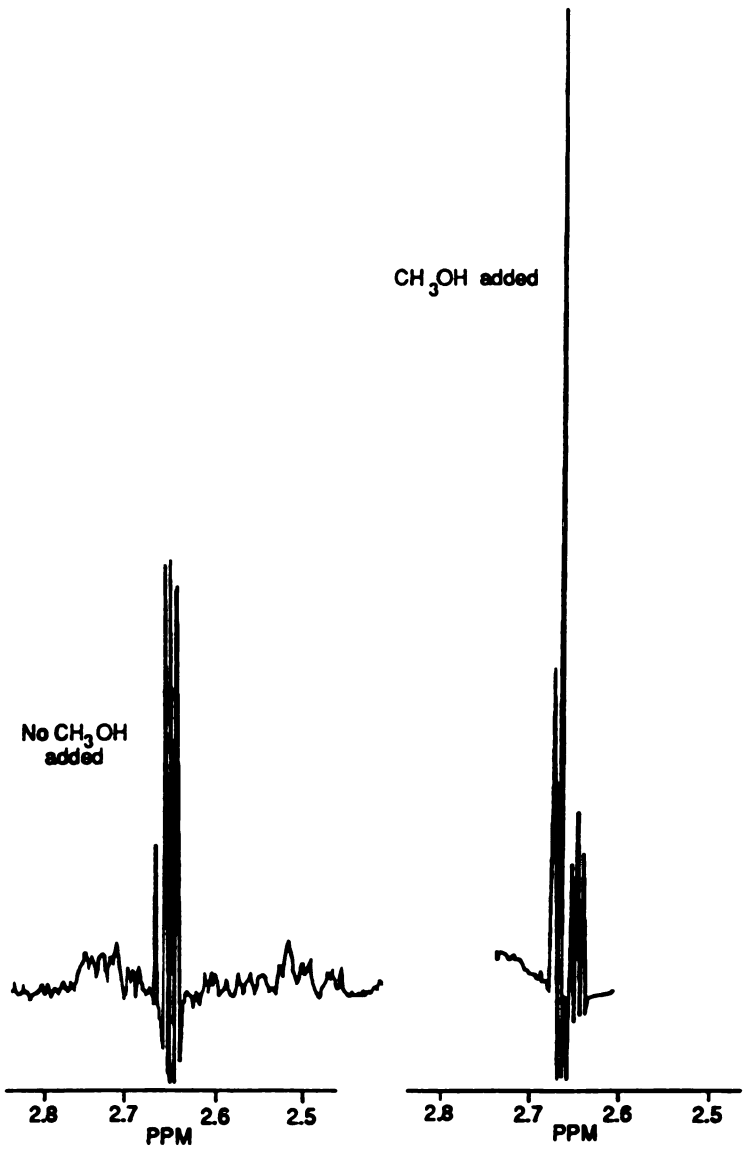


Figure 11- ^{1}H-nmr of a mixture of DCH_2OD and CH_3OH

Although we hoped eventually to generate the methanol dianion in sufficient quantities to use as a nucleophile in other reactions, a pilot study was first initiated to determine if methanol dianion could be generated at all by our proposed procedure. Thus, formaldehyde gas was passed over a neat mixture of NaK alloy and HMHCY that had been given time to complex and had developed a dark navy blue color on the surface of the metal, consistent with solvated electrons. The addition of formaldehyde gas was continued until the navy blue color disappeared and the reaction was then quenched with deuterium oxide. The deuterium oxide was separated and the reaction vessel rinsed with additional deuterium oxide that was combined with the first sample. To concentrate any methanol present the deuterium oxide solution was distilled through a micro spinning band distilling column and the first milliliter collected. ^{1}H-nmr of this sample showed a small 1:1:1 triplet that we felt confirmed the presence of methanol dianion in the reaction mixture. The spectrum also gave a correspondingly much stronger non-deuterated methanol peak. Two additional experiments were performed to confirm these results and to improve our techniques. In the first, ultra sound was used to divide the NaK alloy into a fine paste after the HMHCY had been added, we hoped this would provide a larger surface area for the reaction to take place. In the second, the NaK alloy and HMHCY were allowed to dissolve and complex using trimethylamine as a solvent, the trimethylamine was replaced with pentane before formaldehyde was added. In both these experiments ^{1}H-nmr spectra of

the quenched samples gave the characteristic 1:1:1 triplet of the deuterated methanol along with a much stronger singlet peak for the non-deuterated methanol.

We believed that ether compounds would decompose under the reaction conditions. To test this, a pilot reaction was run using 18-crown-6 as the complexant (see Variation 6 in the experimental section). If ether complexants proved to be stable in these reactions we felt they offered several advantages over nitrogen based complexants. First, many crown complexants are commercially available, and this would eliminate the time consuming synthesis necessary when working with tertiary polyamine macrocycles. Second, the oxygen atoms in crown compounds, being harder Lewis bases, should complex more efficiently with the hard alkalide Lewis acids[48]. Third, it would allow the use of an ether based solvent, like THF, in which the complexes are readily soluble. In the event the deep blue color characteristic of solvated electrons was formed more easily using THF and 18-crown-6. However, several factors led us to believe that the complexant and/or the solvent were decomposing. First, a white solid precipitate had already begun to form in the reaction flask before formaldehyde was added. Second, the reaction quench was less vigorous, whereas the quenches of the previous reactions were very energetic. Third, in previous attempts the excess NaK alloy used appeared to be present until the reaction quench, in this reaction all the NaK alloy added was consumed before the quench. Lastly the ^{1}H-nmr of the reaction work-up gave many broad and overlapping peaks

characteristic of a complex mixture of compounds. The results from this pilot reaction where not unexpected since ether linkages are more susceptible to reductive cleavage as described earlier. Furthermore, Dye has already reported some decomposition of crown complexed alkalides[47], and Jedlinski has reported decomposition of 18-crown-6 in some reactions using THF, 18-crown-6, and potassium[43,44].

At this point two control experiments were performed to verify that the deuteromethanol was formed by reduction of formaldehyde effected by a species generated by adding the complexing agent to the NaK alloy. In the first control experiment a neat mixture of NaK alloy and HMHCY was subjected to ultra sound and allowed to complex, as described in the pilot study, but no paraformaldehyde was added to the pyrrolysis chamber. All other aspects of this reaction and work up were identical to the reaction given above. ^{1}H-nmr of the quenched sample obtained from this reaction displayed no methanol peaks. The second control experiment was identical to the original experiment except that no HMHCY was used. ^{1}H-nmr of the quenched sample obtained from this experiment again showed no deuteromethanol peaks. These experiments confirmed that both HMHCY and formaldehyde were necessary for the formation of carbon-deuterated methanol.

The previous experiments confirmed that D_2O quenching provided evidence for the presence of the methanol dianion, and an opportunity to make qualitative judgments about the ratio of methanol to deuteromethanol being formed. Furthermore, crude

quantitative judgments could be made about the relative amounts of methanol in different samples by comparing the size of the methanol peaks to the size of the H_2O peak present in the D_2O solvent. However, a more accurate estimate of the amount of methanol and deutero-methanol formed could not be obtained without modifying the analytical procedure. To that end the following two changes were made. First, a known amount of a reference solution was added to the ^{1}H-nmr sample. The disodium salt of*p* -terephthalic acid provides a sharp singlet at 7.87 ppm that does not interfere with any peaks of interest. By comparing the integrated value for the disodium *p* -tere-phthalate with the integrated value for the peaks of interest, the yield and ratio of methanol and deuteromethanol could be determined (sample calculations in appendix A). To improve the reliability of our measurements using the reference solution we determine an appropriate relaxation time (see Experimental). The second change to the analytical procedure was eliminating the distillation of the crude D_2O sample. Although we had determined that the distillation of a D_2O sample containing methanol concentrates ~50 % of the methanol into the first 4 drops, we learned that by using a 500 MHz ^{1}H-nmr the distillation was unnecessary and only added another possible source for error.

Although a variety of conditions were tried, as detailed in the Experimental, the following is an example of the techniques and equipment used. For a typical reaction a pressure tube with a Teflon screw cap was used as a reaction vessel. The pressure tube was first flame dried under argon. The tube was then sealed using the Teflon screw cap and a tare weight was taken. The screw cap was replaced with a rubber septum that had an argon inlet and a vent that was attached to a bubbler (Figure 12).

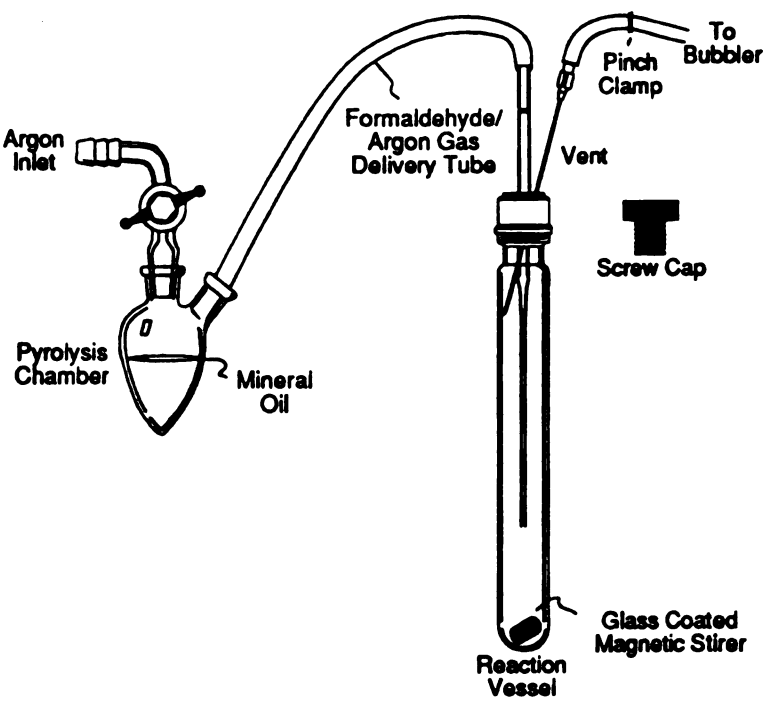


Figure 12- Apparatus for the reduction of formaldehyde

The NaK alloy was added through the septum and any pentane transferred was then evaporated using an argon flow through the reaction vessel. After the pentane had evaporated the Teflon screw cap was replaced and the reaction vessel was again weighed to determine the exact amount of alloy in the reaction vessel. The septum was reinstalled and HMHCY was added to the reaction vessel by syringe. To increase the surface area of the alloy and increase the rate of complexation the vessel was exposed to ultra sound for 30 minutes. The NaK alloy was converted to a fine paste and a blue color that darkened when the reaction was cooled appeared on the surface of the metal. The reaction vessel was cooled and trimethylamine was added by passing trimethylamine gas into the reaction vessel through the septum. The reaction vessel was sealed with the screw cap and the mixture was maintained at dry ice temperature for several hours so that the complex could form. At this point bronze metallic appearing flakes were present in the pressure tube*. The screw cap was then replaced with the septum and the trimethylamine was allowed to boil off by removing the reaction vessel from the Dry-Ice/acetone bath. Dry pentane was added to the pressure tube and formaldehyde gas was then passed over the suspension while it was exposed to ultrasound. After addition of the formaldehyde the reaction vessel was place in a Dry-Ice/acetone bath and deuterium oxide (99.996% pure) was added. The deuterium oxide froze upon addition, then slowly melted and

* No experiments were performed in our lab to positively identify the nature of the bronze flakes or blue solutions used in our experiments. However, due to the similarities in preparation and appearance of these materials to those made in the Dye lab, we felt confident that they were of a highly reductive nature containing solvated electrons and/or sodides.

quenched the reaction as the pressure tube warmed to room temperature. The liquid was removed from the reaction vessel, the deuterium oxide was separated from the pentane and tested by ^{1}H-nmr as described earlier.

After completion of the pilot study and control experiments we attempted the reaction using a variety of conditions in an effort to increase the yield of methanol dianion being formed in the reaction. By comparing the size of the methanol peak to the size of the solvent peak a qualitative judgment was made that the third experiment (where trimethylamine was used as a solvent for complexation) in the pilot study appeared to give the best results. This experiment was then repeated and the modified analytical procedure was used so a quantitative result could be obtained (see Table 1, basic procedure).

Table 1- Results from reduction of formaldehyde

Experiment[a]	Ratio DCH_2OD:CH_3OD	Overall yield	% yield DCH_2OD
Basic procedure	1:3	18 %	4.5 %
Variation 1	1:4	26 %	5.2 %
Variation 2	1:40	19 %	0.5 %
Variation 3	1:19	30 %	1.5 %
Variation 4	b	0 %	-
Variation 5	1:5	11 %	1.8 %
Variation 6	b	-%	-
Variation 7	1:10	81 %	10 %

a) Conditions for each variation are described in the experimental. b) No dideuteromethanol was identified in this sample.

It was noticed that during the addition of formaldehyde gas to all the previous reactions a fine white solid formed in the reaction vessel. We felt this solid was paraformaldehyde. Although monomeric formaldehyde polymerizes easily, we initially felt that the

polymerization of formaldehyde would not compete successfully with the desired reduction. The presence of the solid in the reaction vessel suggested that our initial expectations were wrong and that the polymerization was competing with the reduction. To retard this undesired side reaction the experiment was run at a reduced temperature by cooling the suspension of complex and pentane in an ice bath during the addition of formaldehyde. This change, variation 1, gave results similar to the first reaction with a slightly higher yield 26 % but slightly lower ratio 1:4. However, the presence of what appeared to be paraformaldehyde was again observed.

The apparent presence of paraformaldehyde in the reaction mixture suggested a simplified procedure. If the paraformaldehyde were in equilibrium with formaldehyde under the reaction conditions, then it might provide an*in situ* source of formaldehyde and eliminate the need for the generation of formaldehye by pyrolysis. The use of paraformaldehyde would also permit the use of trimethylamine as a solvent. In previous reactions it was necessary to sweep the formaldehyde into the reaction chamber using a stream of argon. When attempts were made to use trimethylamine as a solvent for the reduction the stream of argon quickly evaporated the trimethylamine, often causing bumping even when the reaction vessel was cooled.

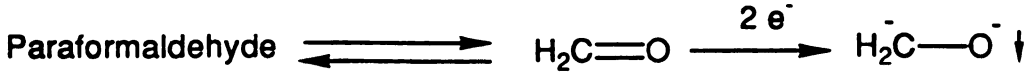


Figure 13- Reduction of paraformaldehyde

Two experiments were run in which paraformaldehyde was substituted for formaldehyde gas. In the first experiment the basic procedure was used, variation 2. ^{1}H-nmr showed the amount of methanol formed in this reaction was about equal to previous attempts. However, the ratio of dideuteromethanol to methanol dropped dramatically to 1:40.

In the second experiment trimethylamine was used as the solvent. All reductions up to this point were run either neat or in pentane. In either case we felt it likely that the reaction was occurring at the surface of the metal and was therefore dependent on the surface area of the metal. The metallic surface could also be catalyzing undesirable side reactions. Running the reaction with the alkali metal "in solution" we hoped would diminish these problems. In variation 3 we did not boil off the trimethylamine, no pentane was added, and paraformaldehyde was used instead of formaldehyde gas. After the pressure tube was sealed, the mixture was subjected to ultra sound. Although the mixture had been allowed to pre complex, the dark blue color disappeared quickly after the paraformaldehyde was added. This variation did give a slightly higher yield than any previous attempt but the ratio of dideuteromethanol to methanol was still low 1:19.

In the previous reactions the HMHCY and NaK alloy were given time to complex and the bronze metallic flakes that developed were suspended in pentane before formaldehyde was added. Once the addition of formaldehyde had begun the bronze metallic flakes disappeared or changed color within a few minutes, and fine silvery flakes appeared. It

seemed reasonable to assume that the silvery flakes might be NaK alloy no longer complexed with HMHCY. The rapid disappearance of the bronze metallic flakes and deep blue color characteristic of complexes suggested that reduction might continue even in the absence of observable complex. A reaction was attempted under conditions where the NaK alloy and HMHCY were not given an opportunity to complex before the formaldehyde was added (Variation 5). Although the results for this reaction were somewhat worse than results obtained in other trials, suggesting that for this reduction the pre-complexation step is beneficial, the experiment did demonstrate that the addition of complexing agents alone to alkali metals in non-polar solvents like pentane can promote alkali metal reductions and that pre complexation is not necessarily required for reduction to take place.

Since the use of paraformaldehyde consistently led to a decrease in the dideuteromethanol : methanol ratio and the use of a solution of the NaK/HMHCY gave slightly higher absolute yields of methanol, we decided to find a different solvent for the reductions that would allow the use of formaldehyde gas while maintaining the complex in solution. As stated earlier, there are significant advantages and reasons to use a solvent that maintains the reducing agent in solution; however, solvents commonly used to solubilize these agents (TMA, THF) were either incompatible with the use of formaldehyde gas or decomposed under the reaction conditions. A solvent that allowed the slow addition of formaldehyde gas into a "solution of reducing agent" should give better results than those obtained in previous attempts. We felt the ideal solvent would: (i) form a blue solution of the

complex at or near room temperature, (ii) have a high enough boiling point to be compatible with the use of formaldehyde gas, and (iii) be robust to the conditions of the reduction. Besides the above criteria we felt the solvent should also be inexpensive and easy to separate from desired products.

It was discovered that dimethylethylamine (DMEA) appeared to be an acceptable solvent for the HMHCY, NaK system, forming a dark blue solution when added to the mixture. Although qualitatively DMEA did not appear as efficient a solvent as TMA (it was more limited in the range of concentration and temperature over which a dark blue solution could be maintained), DMEA did appear to be as robust as TMA concerning decomposition, and its boiling point was high enough that it was compatible with the introduction of formaldehyde gas. The high boiling point of DMEA also simplified the procedure by eliminating the need to use a pressure tube as a reaction vessel. With these improvements in mind, reaction was run using DMEA as the solvent. The mixture of DMEA, HMHCY and NaK was given time to complex before addition of formaldehyde. The formaldehyde was added at a rate such that the blue color was maintained in the solution throughout the addition. Although DMEA has a higher boiling point than TMA, some DMEA did evaporate during the addition of the formaldehyde and additional DMEA was occasionally added to maintain the reaction volume. This experiment, variation 7, gave a yield of methanol of 81 % with a ratio of dideuteromethanol to methanol of 1:10.

A possible explanation for the low ratio in this experiment might have been that the DMEA used in the reaction was substanially wetter than the solvents used in other attempts. To test this, variation 7 was repeated, adding only a partial equivalent of formaldehyde to the reaction. If the DMEA was wetter than other solvents studied, the ratio of dideuteromethanol to methanol in this trial should decrease dramatically compared to trial 7. This reaction, however, gave a slightly better ratio than the first attempt (1:6) implying the problem was not water in the solvent.

Until the last two experimental results were obtained, we beleived that the proteomethanol was formed from H_2O and other protonic impurities in the system. However, the results of these experiments eliminated that explanation and forced us to look elsewhere for the source of the proteomethanol

One possible source of proteomethanol would be from the Cannizzaro reaction. In high concentrations of base formaldehyde can act as a hydride reducing agent. One formaldehyde donates a hydride to a second formaldehyde molecule generating an equivalent of methanol and formic acid. We therefore searched for formate in the ^{1}H-nmr of several reaction mixtures. Although a peak characteristic of formate (~ 8.1 ppm) did appear in some, it was of variable intensity and was never sufficient to account for all the proteomethanol formed.

If this technique were to be developed into a useful synthetic technique a way of either minimizing the formation of

proteomethanol or dramatically increasing the relative amount of dideuteromethanol formed had to be developed. We felt that the complexing agent or decomposition by-products of the complexing agent might be sources of protons that we had not eliminated. If the extraneous protons were coming from the complexing agent we felt it was unlikely that the methanol dianion could be synthesized in synthetically useful amounts since it would be impossible to eliminate this source of protons. To determine if HMHCY was losing a proton during the reaction, the HMHCY used in variation 7 was recovered and analyzed by ^{1}H-nmr and mass spectroscopy. If a HMHCY molecule lost a proton during the reaction it would then add a deuterium in the reaction quench. As with methanol, the presence of the deuterium on HMHCY should result in a 1:1:1 triplet in the ^{1}H-nmr and/or an increase in the weight of the molecular ion peak. HMHCY recovered from variation 7 showed no sign of deuterium incorporation, giving a ^{1}H-nmr and mass spectrum identical to a HMHCY sample that had not been used in a reduction. If a substantial amount of proteomethanol arose from the extraction of a proton from HMHCY without decomposition, then there would have been an observable increase in the M+1 peak of the mass spectrum.

Although the decomposition of a small amount of HMHCY could lead to the release of a large number of protons, the lack of any evidence for the decomposition in recovered HMHCY, the robust nature of this type of complexing agent as determined by Dye, the difficult nature of trying to isolate and identify small amounts of decomposition by-products, the fact that another group was unable to

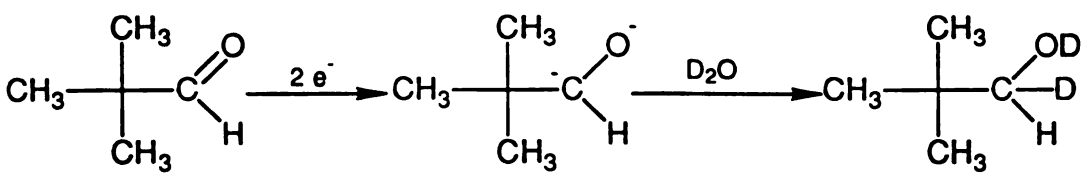
determine the source of extraneous protons in a similar system[47], and the feeling that even if we did identify decomposed HMHCY as the proton source it was unlikely that we would be able to overcome the problem, led us to terminate this line of investigation.

The main obstacle that could not be overcome in this series of experiments was the poor ratio of methanol dianion to methanol formed during the reaction. Since the reduction of formaldehyde seemed a necessary first step in any mechanism for the formation of methanol under these conditions, we felt the root of the problem was an unexplained source of protons or hydrogen that quenched the methanol dianion or radical anion after it was formed. Our attempts to isolate and eliminate these extraneous sources of protons failed. We concluded that although it was possible to generate the methanol dianion through the reduction of formaldehyde using HMHCY and NaK alloy it was unlikely that we were going to be able to generate the methanol dianion in sufficient quantities by this method to make it a practical technique. However, the experiments did support the idea that difficult reductions could be accomplished using HMHCY and NaK alloy in aprotic non-polar solvents.

Reduction of pivalaldehyde

Since it was possible that the difficulties associated with generating and using formaldehyde gas were adversely affecting our attempts to reduce formaldehyde, we decided to explore the reduction of a different aldehyde using HMHCY and NaK alloy. It has been

of a different aldehyde using HMHCY and NaK alloy. It has been reported that the reaction between ketones with *alpha* protons and potassium potasside gave an enolate[43]. Since we were still interested in generating a stable dianion we elected to attempt the reduction of the non-enolizable aldehyde 2,2-dimethylpropanal (pivalaldehyde). Although we had no practical application for this limited reduction we felt that it might provide insight into the reductive capabilities of complexed alkali metals. The reduction of pivalaldehyde would form a dianion similar to the methanol dianion, with the anionic charges residing on adjoining carbon and oxygen atoms.



Pival Aldehyde

neo-Pentyl alcohol

Figure 14- Reduction of pival aldehyde

As with the reduction of formaldehyde, these reactions were quenched with deuterium oxide and tested by ^{1}H-nmr for the presence of carbon bound deuterium. We tried several times to reduce pivalaldehyde to its dianion. The methodology used was the same as that followed for the reduction of formaldehyde. A dilute solution of pivalaldehyde in DMEA was added slowly to a suspension of NaK alloy in TMA containing HMHCY. After each reaction a white crystalline solid slowly precipitated out of the reaction mixture. The solid was collected and characterized by ^{1}H-nmr, melting point and mass spec. It was identified

as 2,2,5,5-tetramethyl-3,4-hexanediol and was recovered in 70 % isolated yield based on the amount of pivalaldehyde used. It appeared that the radical anion formed from the addition of one electron to pivalaldehyde dimerized before a second electron could be added.

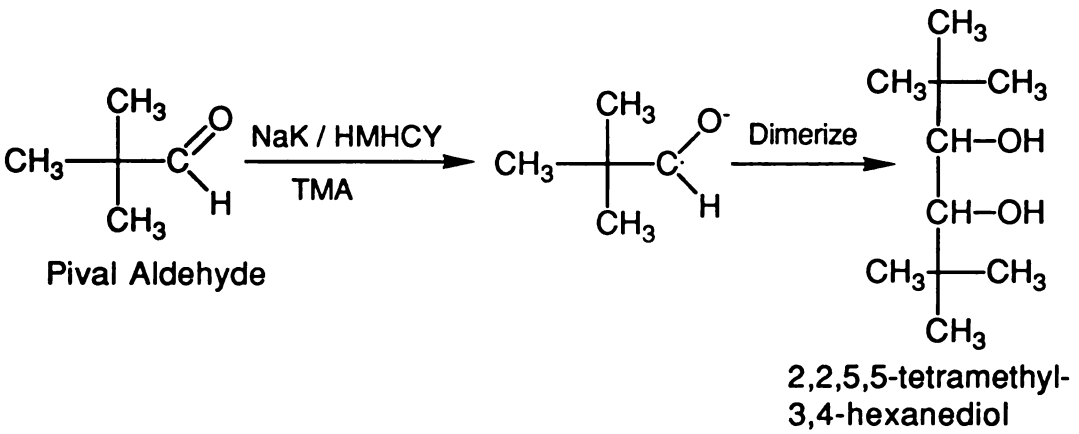


Figure 15- Formation of 2,2,5,5-tetramethyl-3,4-hexanediol

It is possible the small electron donating character of alkyl groups was making the addition of a second electron unfavorable, giving the radical anion time to dimerize. Another possible mechanism is that some pivalaldehyde is reduced to the dianion that then reacts with unreduced pivalaldehyde giving the diol. We were unable to propose a technique that would distinguish between these two mechanisms and did not pursue this limited reaction further.

Reduction of cyclohexenone.

The reduction of α–β unsaturated ketones was another possible application and/or test for the use of cyclen complexed alkali metals as reducing agents. When α–β unsaturated ketones are reduced using

alkali metals (the Birch and Benkeser reductions) it is believed that a radical anion or dianion is generated. Under normal circumstances this intermediate abstracts a proton from the amine or ammonia solvent forming an enolate[49,50]. There are reported exceptions: The first is when the anionic charge can be stabilized by a nearby group. Hauser reported that the alkali metal-ammonia reduction of benzyl acetophenone gives a dianion that undergoes alkylation b to the carbonyl carbon[51].

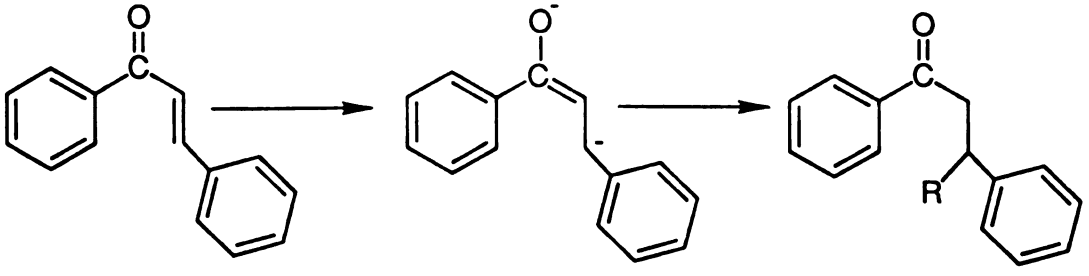


Figure 16- Alkali metal-ammonia reduction of benzyl acetophenone

Another exception is intramolecular electrophilic attack by a suitable electrophile appropriately positioned. Stork reported that the alkali metal reduction of the tosylate of 10-hydroxymethyl-D-2-octalone gives a cyclopropyl derivative[52]. Reusch reported the formation of a cyclopropane in the alkali metal reduction of a diketone[53].

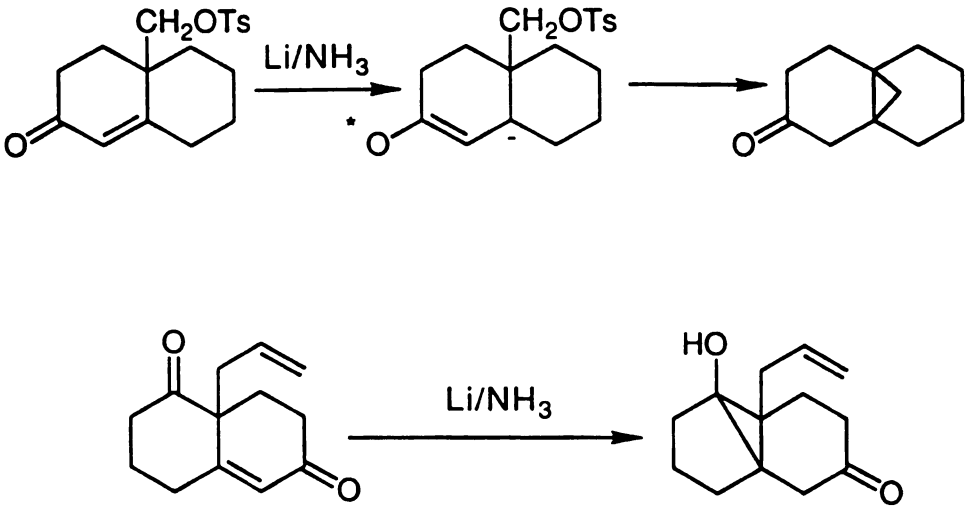


Figure 17- Alkali metal reductions of α,β-unsaturated ketones

We felt that, by taking advantage of the aprotic conditions, it might be possible to use cyclen complexed alkali metals to reduce ordinary α,β-unsaturated ketones to dianions that would be stable in the reaction mixture.

We attempted to reduce 2-cyclohexenone using NaK alloy and HMHCY in DMEA. As with the previous reductions the alloy and HMHCY were given time to complex before the substrate was added and the addition of cyclohexenone was done at a rate so the dark blue color that developed was maintained. The addition was stopped when the blue color completely disappeared. The reaction was then quenched by addition of methyl iodide followed by an aqueous work-up. 3-Methylcyclohexanone was the desired product, however several other products could also be justified.

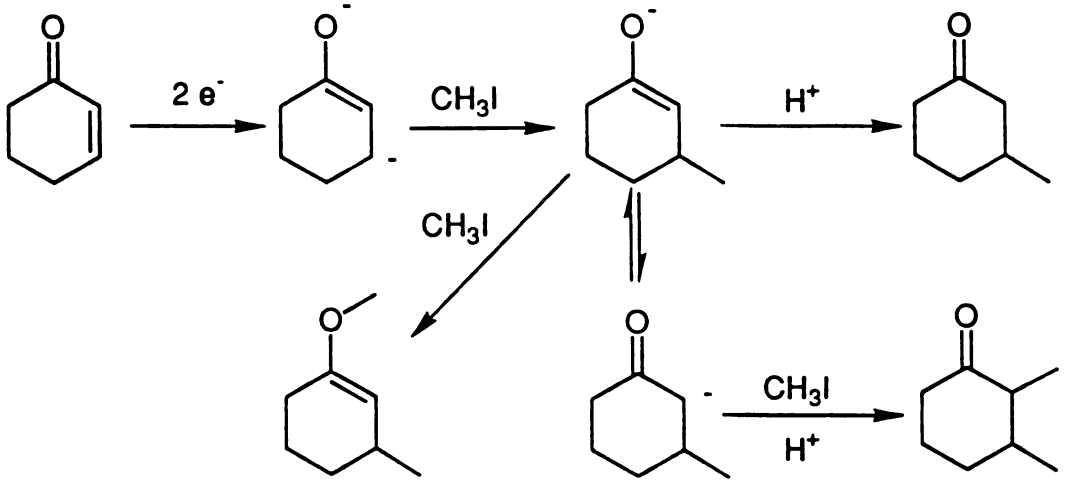


Figure 18- NaK/HMHCY reduction of 2-cyclohexenone

The reaction work-up gave a complex mixture of compounds, as evidenced by a ^{1}H-nmr that had many broad and overlapping peaks, and a gas chromatograph that gave over 35 separate peaks. We could not separate this mixture using the several different techniques of extraction, distillation, and column chromatography. Some of the by-products might have come from *beta* -elimination of the complexant (HMHCY) that had been methylated with methyl iodide. However since these byproducts would also be amines it seems likely that they would have been eliminated from the mixture by an acid extraction that was part of the work-up.

Although it seemed unlikely that methylation-elimination was responsible for all the by-products, the reaction was nonetheless repeated using 18-crown-6 as the complexant. It was felt that the poly ether would be less susceptible to the methylation step and therefor might be more suitable for this reaction. However, the result for this

experiment was similar to that when HMHCY was used. The reaction work-up gave a complex mixture that we were unable to separate and characterize.

Although we were unable to isolate any products from the above reactions it was obvious that the cyclohexenone was undergoing a reaction(s). It was also clear that it would be a major research project to separate the complex product mixture and identify enough of the products to determine the significance of the reaction and modify it for synthetic use. We chose to leave that investigation for a future time and direct our efforts to other goals.

1,4,7-Trimethyl-1,4,7-triazacyclononane (TriMTCY, 2) and 1,4,7,10,13-Pentamethyl-1,4,7,10,13-Penta-azacyclopentadecane (PMPCY, 3) as Complexants for Alkyl Lithium Reagents

Another area we were interested in was the use of tertiary polyamine macrocycles as complexants for alkyl lithium reagents. It has been known that the addition of certain tertiary amines, such as tetramethylethylene-diamine TMEDA, to reactions involving alkyl lithium reagents can perturb their course. Some of the reported effects are; increased reaction rates, increased product yields, and changed product composition[23]. Viewing alkyl lithium reagents as monomers is a vast oversimplification of their structure. Alkyl lithiums exist as aggregates, and both the degree of aggregation and solvent interaction are believed to effect their reactivity greatly[54]. The popular mechanism thought to be responsible for the change in reactivity caused by the addition of TMEDA to alkyl lithium reactions is the breakdown of aggregates of alkyl lithium by the strong complexation of TMEDA with the lithium cation[55]. It is also possible that complexation of the lithium cation by TMEDA might increase the reactivity of the alkyl anion just as HMHCY may be increasing the reduction capabilities of NaK alloy. It is known that the addition of TMEDA to solutions of butyl lithium in the absence of other proton sources results in the deprotonation of TMEDA[23]. The deprotonation occurs preferentially at one of the terminal methyl groups (Figure 19).

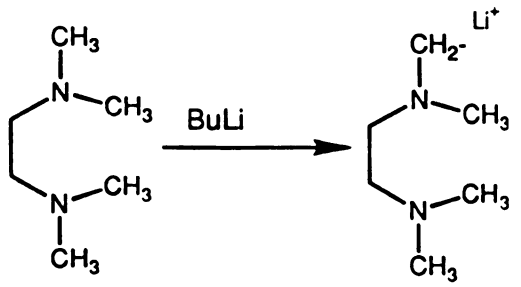
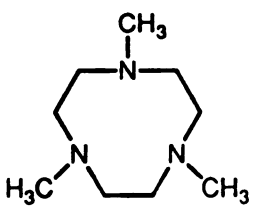
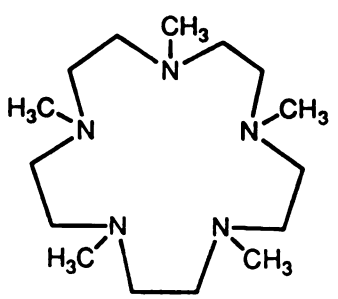


Figure 19- Deprotonation of TMEDA

It was our opinion that this result was caused by TMEDA complexing with the lithium cation, thereby increasing the base strength of the butyl anion which then deprotonated the TMEDA. If a liquid reagent was used that could complex with lithium more strongly than TMEDA, it might offer another path to the methanol dianion.



TriMTCY, 2
1,4,7-trimethyl-
1,4,7-triazacyclononane



PMPCY, 3
1,4,7,10,13-pentamethyl-
1,4,7,10,13-pentaazacyclonpentadecane

Figure 20- Chemical structure of TriMTCY and PMPCY

We felt compounds like PMPCY and TriMTCY (Figure 20) might activate butyl lithium to the point where the butyl anion could pull two protons off methanol, the hydroxyl proton and a methyl proton, providing a convenient route to methanol dianion.

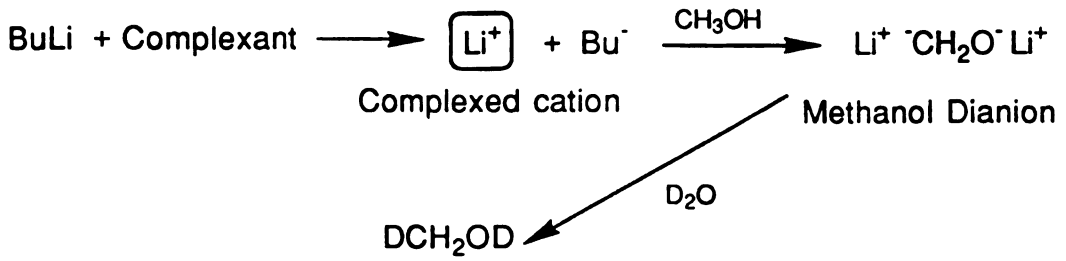


Figure 21- Formation of the methanol dianion using alkyl lithiums

Use of TriMTCY as a Complexant of Alkyl Lithium Reagents

Preliminary data from Dye suggested that TriMTCY was a good complexant for lithium cation. It was first believed that two TriMTCY molecules complexed with lithium cation to form a sandwich type complex. This was later shown by Dye to be incorrect[56]. However before this was realized we conducted several experiments with TriMTCY as a complexant for alkyl lithium reagents.

In the first experiment, dry methanol and TriMTCY were slowly added to a cooled solution of *tert*-butyl lithium in pentane. This experiment was run twice; in the first attempt methanol was added after TriMTCY, in the second attempt methanol was added before TriMTCY. In both cases the addition of TriMTCY to the reaction mixture appeared to release energy, as evidenced by the boiling of the pentane solvent at the point of entry. As TriMTCY was added an insoluble precipitate also formed. After the addition of TriMTCY the mixture was allowed to react while it warmed to room temperature. The reaction mixture was then recooled and quenched by the addition of D_2O. The D_2O was separated and distilled through a micro spinning

band column to concentrate the methanol. The first fraction was collected and examined by ^{1}H-nmr. The spectrum showed no sign of a 1:1:1 triplet indicating no deuterium incorporation in the methanol. Therefore there was no evidence that the methanol dianion had been generated by these conditions.

The second experiment we attempted, tested whether TriMTCY would behave like TMEDA and be deprotonated by butyl lithium in the absence of other proton sources.

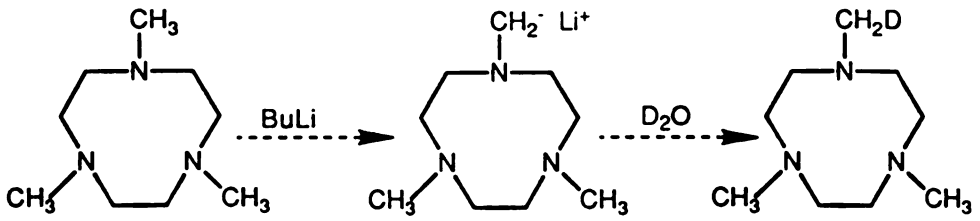


Figure 22- Attempted deprotonation of TriMTCY

This experiment not only would determine whether TriMTCY could activate alkyl lithium, but we felt it could be developed into a possible synthesis of bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane (BDMTNE). A solution of *tert*-butyl lithium in pentane was slowly added to a cooled solution of the TriMTCY in pentane. As with the previous experiment, the mixing of butyl lithium and TriMTCY appeared to release considerable heat, as evidenced by boiling of the pentane solvent. After the addition, the mixture was refluxed to drive the reaction to completion. It was then cooled and quenched with D_2O. The TriMTCY was recovered by extraction and tested by ^{1}H-nmr for the presence of deuterium. As with methanol, carbon bound deuterium in TriMTCY would be detectable by the presence of a 1:1:1

triplet in the H-nmr spectra. However, examination of the ^{1}H-nmr spectrum of the TriMTCY used in the experiment showed no changes, indicating that the TriMTCY was not being deprotonated by the *tert*-butyl lithium reagent.

Since it has been shown that the choice of alkyl lithium reagent can effect experimental results[23], the previous two experiments were repeated using *sec*-butyl lithium as the alkyl lithium reagent. Although *sec*-butyl lithium is a weaker base than *tert*-butyl lithium, it is less sterically hindered. We felt that this difference might change the reaction results. As with the previous reactions, the addition of TriMTCY to *sec*-butyl lithium showed exothermicity, indicating that a reaction was taking place. However, as before, there was no sign of deuterium incorporation in TriMTCY or methanol in the work-up of either experiment.

Deprotonation of TMEDA

We decided to test our procedures and analytical technique to see if we could generate and detect carbon bound deuterium on a complexing agent. To do this we attempted to deprotonate TMEDA, as reported in the literature[23], using our techniques and equipment. After TMEDA was added to a solution of *sec*-butyl lithium in hexane the mixture was allowed to react for one hour and then quenched by addition of D_2O. The TMEDA was recovered by extraction and tested by ^{1}H-nmr and ^{13}C-nmr. The addition of TMEDA to *sec*-butyl lithium

does not appear as exothermic as the addition of TriMTCY to *sec*-butyl lithium; the hexane solvent does not boil. However, a 1:1:1 triplet can easily be identified in both nmr spectra, appearing slightly up field from the singlet corresponding to the methyl groups of TMEDA. This confirmed the literature report, and demonstrated that the procedures we used were sufficient to deprotonate an amine and could easily detect carbon bound deuterium on a polyamine complexant.

The last experiments we tried using TriMTCY with butyl lithium were to see if TriMTCY would act as a proton source for TMEDA activated butyl lithium. TriMTCY and TMEDA were added to a cooled solution of *sec*-butyl lithium in hexane. The reaction was then run in the same manner as the previous reactions. However, neither the TriMTCY or TMEDA recovered from the experiment showed any signs of deuterium incorporation. The reaction was then run again using *tert*-butyl lithium as the alkyl lithium, with identical results. TriMTCY not only fails to be deprotonated, but appears to somehow interfere with the deprotonation of the TMEDA.

The considerable release of heat and the formation of a solid when TriMTCY was added to butyl lithium gives the appearance that a reaction was occurring. However, the fact that TriMTCY was recovered unchanged from these experiments led us to the conclude that no chemical reaction was taking place. We theorize that the apparent release of energy upon addition of TriMTCY to butyl lithium is caused by TriMTCY complexing with butyl lithium thereby breaking down the aggregates. Unfortunately this is accomplished without the "activating"

effect hoped for. While it is often beleived that such monomers will be more reactive than the aggregates, Collum has recently challenged this thinking. He points out that in order for a complexant to break down aggregates effectively, it must form monomers that are at a lower energy level than the aggregates. This will in effect increase the activation energy of a subsequent reaction if the transition state energy remains unchanged, resulting in an apparent decrease in the reactivity of the butyl lithium. This may be an explanation for the results we obtained when using TriMTCY as a complexant for butyl lithium.

Use of PMPCY as a Complexant of Alkyl Lithium Reagents

Since the results we anticipated were not observed using TriMTCY as a complexant, we examined PMPCY as the complexant in this type of reaction. Freshly distilled PMPCY was added to a cooled solution of *n*-butyl lithium and methanol in hexane. The mixture was stirred and allowed to react. After cooling, the reaction was quenched by the addition of D_2O, and methanol and PMPCY were recovered from the reaction mixture. The recovered methanol showed no sign of deuterium incorporation. The recovered PMPCY was also tested by H-nmr for deuterium incorporation. However, the spectrum contained many broad overlapping unidentifiable peaks indicating that the PMPCY had decomposed in the presence of the butyl lithium. This experiment was repeated, keeping the reaction cold, and the results were confirmed. PMPCY is decomposed by *n*-butyl lithium under these conditions.

The reaction was then repeated under conditions that were known to not decompose TriMTCY. PMPCY was added to a cooled solution of *sec*-butyl lithium in hexanes. No methanol was used in this reaction. The recovered material gave a ^{1}H-nmr with many broad, overlapping, and unidentifiable peaks, again indicating that the PMPCY had decomposed when mixed with butyl lithium.

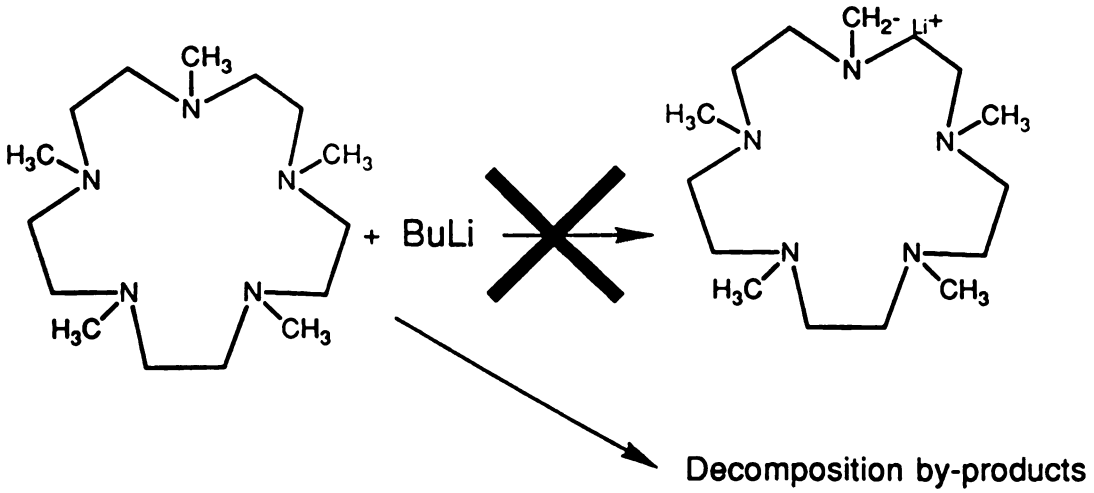


Figure 23- Attempted deprotonation of PMPCY

Although TriMTCY is inert to butyl lithium and appears to actually decrease the reactivity of butyl lithium, we believed it possible that the decomposition of the PMPCY was caused by PMPCY "activated" sec-butyl lithium attacking the PMPCY. However, we felt the fact that PMPCY was susceptible to decomposition excluded any possibility of using PMPCY and butyl lithium under these conditions to form the methanol dianion. Previous work has shown that the methanol dianion is an extremely efficient proton scavenger. We believe that the decomposition of even a small amount of a

complexant like PMPCY would release a large number of protons thereby quenching any methanol dianion formed.

Use of TMEDA as a Complexant of Alkyl Lithium Reagents

Of the three complexants that we had used in this series of experiments only TMEDA had given positive results. We confirmed previous reports that TMEDA "activated" the butyl lithium and was deprotonated by it. In addition, this seemed to occur without the decomposition observed with PMPCY. On the basis of these results we attempted to use TMEDA as a complexant in an attempt to form methanol dianion from methanol. TMEDA and dry methanol were added to a cooled solution of sec-butyl lithium. The mixture was then heated and allowed to react, before quenching with D_2O and the usual worked-up. ^{1}H-nmr of the isolated methanol showed no sign of carbon bound deuterium. In addition a ^{1}H-nmr of recovered TMEDA also showed no sign of deuterium incorporation. It appears that the presence of methanol is either inhibiting the proton abstraction from TMEDA or is preventing TMEDA from complexing with the butyl lithium.

Whatever the reasons for the failure of these attempts to generate the lithium derivative of methanol dianion by double deprotonation of methanol, it is clear that any possible success awaits the discovery of some effective combination of complexant and reaction conditions that will not result in competitive decomposition of the complexant.

Conclusion:

Although we did not fully develop a new useful synthetic technique using complexants, we did make several significant discoveries and contributions that help define their properties. In our attempts to use these complexants as reductants, we demonstrated that using HMHCY to activate NaK alloy could create a powerful reducing system. We presented the first known example of the direct reduction of formaldehyde to the methanol dianion by using HMHCY activated NaK alloy. We demonstrated that it is possible to form these reducing complexes or solutions using standard organic laboratory techniques. We discovered a new solvent, DMEA, for solubilizing the HMHCY/NaK complex that allowed the manipulation of the reactions at room temperature and atmospheric pressure. We demonstrated that HMHCY could activate NaK alloy as a reducing agent even in non-polar solvents, such as pentane.

Our experiments on the use of TriTCY and PMPCY as complexants for alkyl lithium reagents also gave no definitive results. However, it might be suggested that the decomposition of PMPCY in the presence of butyl lithium is caused by attack of PMPCY activated butyl lithium on PMPCY. This was not investigated further since we felt the decomposition of PMPCY would interfere with other changes taking place. Nevertheless, the experiments we performed using TriTCY and PMPCY may help define the role that complexation and de-aggregation have in alkyl lithium chemistry, possibly supporting

the emerging theory that complexation and de-aggregation of alkyl lithium does not automatically lead to increased reactivity.

The discoveries and results of our work suggest several possible areas where this research might be continued. First, the reduction of a,b-unsaturated ketones could be examined more closely; identifying the reaction products, determining the dynamics of the reaction, modifying the procedures used, and examining a wider variety of conditions and reagents. Completion of such a study might lead to the development of a useful synthetic technique.

Second, the use of lithium sodides or lithium electrides to reduce formaldehyde to the methanol dianion could be examined. Lithium is more electronegative than sodium or potassium and forms bonds having less ionic character. Methanol dianion formed with lithium as one or both of the counter ions might prove to be easier to form, more stable to reaction components, and less prone to protonation from extraneous proton sources. We initially proposed doing this work. However, the discovery that the structure of the TriMTCY complex incorporated a deprotonated primary amine, the fact that it is necessary to use a primary amine as a solvent to form lithium complexes with currently available complexants, and our conviction that we would be unable to completely remove any primary amine used in the complexation, led us to limit our work in this area. We feel that success in this area requires either the availability of gram quantities of pure lithium sodides or lithium electrides, or the

development of a nitrogen based complex that can be formed without the use of primary or secondary amines.

Third, the use of other lithium complexing agents with alkyl lithiums could be examined. Since TriTCY was inert to butyl lithium, appearing to deactivate it, while PMPCY was decomposed, possibly by activating the butyl lithium, it seems possible that a complexant that falls in between the capabilities of these two reagents might be successful in activating butyl lithium as described in the discussion section. Such a complexant might accomplish this activation without suffering the decomposition that hampers the use of PMPCY.

Experimental:

General (see the experimental in Part 2)

Reduction of formaldehyde

Determination of relaxation delay

300 MHz ^{1}H-nmr (Varian VXR-300)

A solution of disodium *p*-terephthalate (0.5 mL, 0.006 M) in D_2O was added to a solution of methanol (0.5 mL, 0.029 M)in D_2O. The solution was then analyzed by ^{1}H-nmr with the relaxation delay varied from 10 to 60 seconds.

Table 2

Delay (sec)	Area of terephthalate	Area of Methanol	Ratio
10	34.1	111.2	3.261
20	34.5	117.0	3.391
30	34.6	119.1	3.443
40	34.8	119.9	3.445
60	34.9	121.1	3.470

500 MHz ^{1}H-nmr (Varian VXR-500)

A portion (0.5 ml) of the aqueous solution from the reduction of formaldehyde (variation 9) was mixed with a solution of disodium *p*-terephthalate (0.5 mL, 0.006 M) in D_2O. The solution was then analyzed by ^{1}H-nmr with the relaxation delay being varied from 0 to 40 seconds.

Table 3

Delay (sec)	Area of terephthalate	Area of Methanol	Ratio
0	8.13	16.33	2.009
20	8.71	18.32	2.103
30	8.66	18.40	2.124
40	8.61	18.27	2.122

The reactions in this section were analyzed by quantitative ^{1}H-nmr using a known amount of sodium terephthalate as a reference. A relaxation delay of 30 seconds was used between pulses when acquiring data for the spectra. Based on a comparison of the integrated values for the respective peaks of terephtalate, methanol, and monodeuteromethanol the amount of methanol and monodeuteromethanol were determined (see sample calculations appendix A).

Preparation of sodium/potassium alloy The outer layer (oxide coating) of sodium and potassium bars were shaved off under mineral oil until only the shiny inner metal was exposed. Equal molar amounts of sodium (23.0 g, 1 mol) and potassium (39.1 g, 1 mol) were placed in a round bottom flask and covered with fresh mineral oil. The flask was then heated (~100°) until the potassium metal melted. The sodium metal was then pushed into the molten potassium and heating was continued until the sodium metal dissolved. The alloy was heated for an additional hour and then allowed to cool to room temperature and stand for 12 h. The NaK alloy remained a liquid at room temperature and was stored under mineral oil. Immediately before use, a portion of the alloy was removed by withdrawing it from below the surface of the liquid alloy using an oven dried pipette. It was transferred to a flame dried pear shaped flask where it was washed five times with dry pentane under an argon atmosphere to

remove the mineral oil. The clean alloy remained covered with pentane until it was transferred to the reaction vessel. Any remaining pentane superfluously transferred to the reaction vessel was then removed by evaporation under a stream of argon.

Generation of formaldehyde gas Formaldehyde gas was generated as described in *"Formaldehyde 3rd ed."* [57]. Paraformaldehyde (0.036 g, 1.2 mmol) suspended in fresh mineral oil (1~2 mL) was heated (100°~120°) until constant bubbling occurred. The liberated formaldehyde gas was swept into the reaction vessel with a stream of argon. This procedure is reported to give formaldehyde gas with a purity of ~98 %. Alternatively, a pearshaped flask containing paraformaldehyde (0.036 g, 1.2 mmol) covered with P_2O_5 was heated (120 °~140°) gently and the liberated gas was swept into the reaction vessel with a stream of argon. This procedure is reported to give drier formaldehyde gas but no quantitative values are given[57]. Both methods of generating formaldehyde gas gave similar results in our experiments.

1,4,7,10,13,16-hexamethyl-1,4,7,10,13,16-hexaazacyclooctadecane HMHCY, **1** was prepared by Eshweiler-Clark methylation[58~60] of the trisulfate salt of hexacyclen obtained from Aldrich. To determine the optimum reaction conditions the reaction was monitored for the liberation of carbon dioxide gas (a by product of the Eshweiler-Clark methylation) and the end point of the reaction was determined. Subsequent reactions were run for at least twice this time to ensure that only fully methylated material was obtained.

A solution of hexacyclen trisulfate (0.5 g, 0.91 mmol) in 90 % formic acid (0.46 mL, 10 mmol) and 37% formaldehyde (2 mL, 24.4 mmol) was heated to 100° for 20 h. Hydrochloric acid (2 mL, 2 N) was then added to the solution, which was then allowed to stir for an additional 8 h. The solution was cooled to room temperature, and washed with ether (3 x 10 mL). The aqueous solution was made basic (pH > 14) with cold aqueous KOH solution (30 %) and extracted with chloroform (3 x 25 mL). The chloroform extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give 0.24g of a clear oil. The oil was vacuum distilled (100°~110°, 0.05 mmHg) from NaK alloy. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 2.26 (S, 18 H), d 2.51 (S, 24 H). ^{13}C-nmr ($CDCl_3$, 75 MHz), d 44.03, 55.41

Basic procedure

a) (Pre-complexation) A dried reaction vessel was charged with NaK alloy (0.15 g, 2.4 mmol) under pentane, and the pentane was evaporated under a stream of Argon. HMHCY, **1** (0.42 g, 1.2 mmol) was then added and the mixture was subjected to ultra sound for 30 minutes. The reaction vessel was cooled to -78° and trimethylamine (4 mL) was then condensed into the vessel. The reaction vessel was then sealed and the mixture was exposed to ultra sound at room temp for 3 h. The mixture was cooled to -78° and maintained at that temperature for 12 h. The trimethylamine was boiled off under a stream of argon as the mixture warmed to room temperature. After the trimethylamine had evaporated, pentane (4 mL) was added to the mixture to give a suspension.

b) (Reduction of formaldehyde) Formaldehyde gas (0.036 g, 1.2 mmol) in an argon carrier stream was passed over the suspension while it was subjected to ultra sound (addition took ~30 minutes). After addition of the formaldehyde was complete, the reaction was removed from the sonification bath and cooled to -78°. Deuterium oxide (1ml) was then added to the reaction mixture, which was then allowed to warm to room temperature. As the deuterium oxide melted the reaction quenched.

c) (work-up) The reaction mixture was diluted with additional deuterium oxide (4 mL) and the aqueous portion was separated. A sample (0.5 mL) of the separated aqueous solution was mixed with a reference solution of disodium *p*-terephthalate (0.5 mL, 0.0062 M). The sample was analyzed by ^{1}H-nmr (500 MHz) as described above. Yield (CH_3-OH + CH_2D-OD) 26.0 %; and ratio (CH_3-OH : CH_2D-OD) 4 : 1

Variation 1

In part "b" the suspension of NaK/HMHCY, **1** was cooled to 0° in an ice bath and the subsequent addition of formaldehyde gas was done at 0°. ^{1}H-nmr (500 MHz) Yield (CH_3-OH + CH_2D-OD) 18.0 %; and ratio (CH_3-OH : CH_2D-OD) 3 : 1

Variation 2

In part "b" paraformaldehyde was added directly to the reaction mixture instead of passing formaldehyde gas into the suspension. After the paraformaldehyde was added, the mixture was subjected to ultrasound for 3 h before being quenched. ^{1}H-nmr (500 MHz) Yield (CH_3-OH + CH_2D-OD) 19.1 %; ratio (CH_3-OH : CH_2D-OD) 40 : 1

Variation 3

In part "a" the trimethylamine was not boiled off and no pentane was added, the trimethylamine was then used as the solvent for part "b". In part "b" paraformaldehyde was added directly to the reaction mixture instead of passing formaldehyde gas into the suspension. ^{1}H-nmr (500 MHz) Yield (CH_3-OH + CH_2D-OD) 29.8 %; ratio (CH_3-OH : CH_2D-OD) 19 : 1

Variation 4

In part "b" the suspension was cooled to -78°, paraformaldehyde was then added directly to the reaction mixture. Ultra sound was not used. After the addition of the paraformaldehyde the reaction was stirred at -78° with a glass coated magnetic stir bar for 3 h.

In part "c" the crude D_2O sample was distilled through a micro-spinning band column and the first 4 drops were collected as an nmr sample. ^{1}H-nmr (300 MHz) No CH_2D-OD was detected.

Variation 5

Part "a" was skipped totally. The reaction vessel was charged with NaK, HMHCY, **1**, and pentane. This mixture was used directly in part "b" without being given a chance to complex before the reaction with formaldehyde was attempted. ^{1}H-nmr (500 MHz) Yield (CH_3-OH + CH_2D-OD) 11.1 %; ratio (CH_3-OH : CH_2D-OD) 5 : 1

Variation 6

In part "a" 18-crown-6 was used as the complexing agent instead of HMHCY, 1 and THF was used as the solvent during both the complexation step and the addition of formaldehyde.

In part "c" the crude D_2O sample was distilled through a micro-spinning band column and the first 4 drops were collected as an nmr sample. The ^{1}H-nmr (300 MHz) had many unidentified peaks which obscured the spectral area where the signals from methanol and dideuteromethanol would appear this prevented the identification of a methanol or dideuteromethanol peak(s).

Variation 7

Instead of using part "a" and "b" from the general procedure the following procedure was used.

To a reaction vessel that was charged with NaK alloy (0.15 g, 2.4 mmol) and HMHCY, 1 (0.31 g, 0.9 mmol) was added dimethylethylamine (4 mL). The mixture was then subjected to ultra sound for 30 minutes at 0° and formaldehyde gas was passed over the cooled solution while sonification was continued. To maintain the reaction volume dimethylethylamine was occasionally added. The mixture was then cooled to -78° and pentane (4 mL) was added to the mixture, followed by D_2O (1 mL). The work-up for this reaction was the same as for the general procedure. ^{1}H-nmr (500 MHz) Yield (CH_3-OH + CH_2D-OD) 80.7 %; ratio (CH_3-OH : CH_2D-OD) 10 : 1.

Control reaction 1

No formaldehyde was added to the reaction in this control experiment. In part "c" the crude D_2O sample was distilled through a micro-spinning band column and the first 4 drops were collected as an nmr sample. No peaks from CH_3-OH or CH_2D-OD were identified in the ^1H-nmr (500 MHz).

Control reaction 2

No complexing agent was used in this control reaction.
In part "c" the crude D_2O sample was distilled through a micro-spinning band column and the first 4 drops were collected as an nmr sample. No peaks from CH_2D-OD were identified in the ^1H-nmr (300 MHz).

Reduction of Pivalaldehyde

a) A pressure tube was charged with NaK alloy (1:1 alloy, 0.14 g, 2.2 mmol equivalent), HMHCY, **1** (0.35 g, 1.0 mmol), and TMA (3 ml). The tube was sealed, subjected to ultrasound for 2 h, and then cooled in a Dry Ice/acetone bath (-78°) for 3 h. The TMA was then boiled off and the remaining material slurried with dry pentane. The mixture was cooled (-78°) and pivalaldehyde (0.086 g, 1.0 mmol) in pentane (1 ml) was added dropwise (~10 minutes). The reaction vessel was then placed in an ultrasound for 1/2 h. To quench the reaction, the mixture was cooled (-78°) and D_2O (1 ml) was added. The reaction was then allowed to warm to room temperature during which time the D_2O melted and quenched the

reaction. The mixture was allowed to stand at room temperature overnight and a solid precipitated from the reaction mixture. The solid was collected to give 0.11 grams of wet, white crystals. The solid was recrystallized once from ethanol and water to give 0.060 grams (69 %) of a dry, white crystalline solid. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 1.0 (S, 9H), d 3.2 (S, 1H)

b)A pressure tube was charged with NaK alloy (1:1 alloy, 0.08 g, 1 mmol equivalent), HMHCY, 1 (0.3 g, 0.9 mmol), and TMA (3 ml). The tube was sealed, subjected to ultrasound for 1 h, and then cooled in a Dry Ice/acetone bath (-78°) for 16 h. To this cold mixture was then added dropwise (~10 minutes) pivalaldehyde (0.03 g, 0.4 mmol) dissolved in DMEA (1 ml). After the addition the reaction was maintained at -78° for 1/2 h before quenching. To quench the reaction D_2O (1 ml) was added to the cold mixture. The reaction was then allowed to warm to room temperature during which time the D_2O melted and quenched the reaction. The mixture was allowed to stand at room temperature over night. The product was then collected to give 0.03 grams of a wet, white crystalline solid. The solid was recrystallized once from ethanol and water to give 0.02 grams (~70 %) of a dry, white crystalline solid with a melting point and nmr spectrum identical to those of the solid isolated in procedure "a". This procedure was repeated with a slower addition of pivalaldehyde (~20 min.) to give the same results.

Reduction of 2-cyclohexen-1-one

a) A pressure tube was charged with NaK alloy (1:1 alloy, 0.07 g, 1 mM equivalent), and HMHCY, **1** (0.3 g, 0.9 mM). It was then cooled in a Dry Ice/acetone bath (-78°) and TMA (3 ml) was condensed into the pressure tube.The tube was sealed and placed in an ultra sound bath for 1 h. The reaction was cooled to -78° and maintained at this temperature for 24 h. The reaction was then allowed to warm to -40° and 2-cyclohexen-1-one (0.08 g, 0.9 mM) in DMEA (1 ml) was added dropwise to the reaction. After standing at -40° for 1 h the mixture was cooled to -78° and methyl iodide (0.07 g, 0.5 mM) was added to the reaction. The reaction was allowed to proceed for 2 h. The TMA was removed by evaporation and H_2O was added to the cold residue to quench the reaction. After the aqueous mixture warmed to room temperature 10 % HCl (pH ~ 1). The acidic solution was extracted with deuterochloroform and the extracts were combined and dried with Na_2SO_4. ^{1}H-nmr of the sample gave a spectrum that contained many broad and overlapping peaks (0.5~3.0 ppm)that we where unable to identify. Gas chromatography gave over 30 separate signals none with intensity greater than 17 %.

b) Procedure "a" was repeated except that the reaction was maintained at -78° during the addition of the 2-cyclohexen-1-one. The work-up of this reaction gave a ^{1}H-nmr spectrum that also contained many very broad and overlapping peaks that we where unable to identify. Gas chromatography gave over 30 separate signals.

c) The reaction flask was charged with Nak alloy (1:1 alloy, 0.13 g, 2.1 mmol equivalent), THF (12 ml), and 18-crown-6 (0.53 g, 2.0 mmol). The mixture was then exposed to ultrasound and 2-cyclohexen-1-one (0.242 g, 2.5 mmol) was added dropwise. The reaction was then cooled (-78°) and methyl iodide was added to the reaction. The mixture was allowed to react for 18 h at -10°. The reaction was then quenched by addition of H_2O. The material recovered from this reaction also gave a ^{1}H-nmr spectrum that contained broad overlapping peaks that we were unable to identify.

Use of polyaza complexants with BuLi

TriMTCY, **2** and PMPCY, **3** were obtained from the Michigan State University Synthesis Laboratory (MSUSL) and were prepared by the Richman-Atkins synthesis[61], using the modifications described in the Experimental section for the second part of this work.

tert-Butyllithium and TriMTCY

a)To a cooled solution of *tert*-butyllithium (23.1 mL ,0.65 M) in pentane was added TriMTCY, **2** (2.5 g, 11.6 mmol) followed by dropwise addition of dry methanol (0.253g, 7.9 mmol). The mixture was warmed to room temperature and stirred for 2 h. The solution was then cooled to 0°, and D_2O (1 mL, 55 mmol)) was added slowly. After warming to room temperature, the D_2O was separated from the pentane and distilled on a micro spinning band column. The first four drops were collected and diluted with D_2O (1 mL). The ^{1}H-nmr (D_2O) had no 1:1:1 triplet, indicating there was no deuterium incorporation in the methanol.

b) Identical to version "a" except the methanol was added dropwise to a cooled solution of *tert*-butyllithium before the TriMTCY, **2** was added. The ^{1}H-nmr (D_2O) again showed no 1:1:1 triplet, indicating there was no deuterium incorporation in the methanol.

c) To a solution of trimethyltriazacyclononane (0.25 g, 1.5 mmol) in pentane (5 mL), cooled to 0°, was slowly added a solution of tert-butyllithium (2.3 mL, 0.65 M, 1.5 mmol) in pentane. The mixture was heated to reflux for 45 minutes, cooled to 0°, and D_2O (5 mL) was slowly added. The mixture was warmed to room temperature, hydrochloric acid (1 N, 1 mL) was added, and the mixture was then washed with ether. KOH was then slowly added to the aqueous solution until a pH > 14 was reached. The aqueous solution was then extracted with deuterated chloroform (5 mL). The chloroform was dried with Na_2SO_4, and examined by ^{1}H-nmr. The ^{1}H-nmr was identical to TriMTCY, **2** and showed no sign of C-duetuered methanol.

sec-Butyllithium and TriMTCY

a) A solution of *sec*-butyllithium (0.75 mL, 2.0 M, 1.5 mmol) in hexanes was cooled to 0° and TriMTCY, **2** (0.20 g, 1.2 mmol) was slowly added . The solution was heated to 55° for two h, after which it was cooled to 0° and D_2O (1 mL) was carefully added. The mixture was then allowed to warm to room temperature and diluted with water (4 mL), The aqueous layer was separated and HCl (1 N, 1 mL) was added. The aqueous solution was washed with ether and KOH was slowly added until a pH > 14 was reached. The aqueous solution was extracted with chloroform (3 x 5 mL).

The chloroform extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. The residue was test by ^{1}H-nmr. The ^{1}H-nmr ($CDCl_3$) was identical to that of trimethyltriazacyclononane and showed no sign of deuterium incorporation.

b) To a solution of *sec*-butyllithium (4.8 mL, 2.0 M, 9.6 mmol) in hexanes was added dry methanol (0.13 mL, 3.0 mmol). The mixture was stirred for 15 minutes and TriMTCY, **2** (1.03 g, 3.0 mmol) was added dropwise. The mixture was heated to 50° for 2 h, then cooled to 0° and D_2O (4 mL) was added. The mixture was then allowed to warm to room temperature slowly and the D_2O layer was separated. The D_2O was fractionally distilled through a micro spinning band column. The first four drops were collected and diluted with D_2O (1 mL). The^{1}H-nmr (D_2O) had no 1:1:1 triplet indicating there was no deuterium incorporation in the methanol.

PMPCY and *n*-Butyllithium

a) *n*-Butyllithium (3.0 mL, 0.005 M, 15 mM) in hexanes was added to a cooled solution (0°) of methanol (0.05 g, 1.6 mM) in hexane (6 mL). After stirring the solution for 15 min. PMPCY, **3** (0.44 g, 1.6 mmol) was added dropwise. The solution was then stirred for 3 h at room temperature, cooled to 0°, and D_2O (1mL) was carefully added. The mixture was allowed to warm to room temperature and it was diluted with D_2O (4 mL). The aqueous layer was then separated from the hexane layer. A portion of the D_2O was tested directly by ^{1}H-nmr. The spectrum had an identifiable methanol singlet (70 % recovery of proteomethanol) and no sign of deuterium incorporation.

Aqueous HCl (1N, 1mL) was added to a portion of the separated aqueous layer. This solution was washed with ether, and KOH pellets were then added until a pH > 14 was reached. The alkaline solution was extracted with chloroform (3 * 5ml) the extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. The ^{1}H-nmr ($CDCl_3$) had many broad overlapping unidentifiable peaks suggesting decomposition of the PMPCY, 3.

b) Identical to version "a" except for the following changes. The amount of *n*-butyllithium used was reduced (2 mL, 0.005 Molar, 10 mmol). The reaction was cooled to -40° before PMPCY, 3 was added. The reaction was cooled to -40° for the reaction quench with D_2O. The results of this reaction were identical to those of version "a".

PMPCY and *sec*-Butyllithium

A solution of *sec*-butyllithium (0.75 mL, 2.0 M) in hexanes was cooled to 0° and PMPCY, 3 (0.35 g, 1.2 mmol) was slowly added . The solution was then heated to 55° for 2 h, then was cooled to 0° and D_2O (1mL) was carefully added. The mixture was allowed to warm to room temperature and diluted with water (4 mL). The aqueous layer was separated and HCl (1 N, 1mL)was added.. The aqueous solution was washed with ether, and KOH was slowly added until a pH > 14 was reached. The basic solution was extracted with chloroform (3 x 5mL). The extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. The residue was tested by ^{1}H-nmr. The ^{1}H-nmr ($CDCl_3$) had many unidentified peaks that suggested decomposition of the PMPCY, 3.

Sec-Butyllithium and TMEDA

a)TMEDA (1.4 g, 12.5 mmol) was added to a stirred, cooled solution of *sec*-butyllithium (6.25 mL, 2.0 M) in hexanes. The mixture was allowed to stir for 30 minutes and then dry methanol was added dropwise. The reaction mixture was heated to 55° for two h. The mixture was cooled (0°) and D_2O (6 mL) was added dropwise. The mixture was then allowed to warm to room temperature and the D_2O layer was separated. The D_2O was then fractionally distilled through a micro spinning band column. The first fraction was tested by ^1H-nmr and ^{13}C-nmr. There was no sign of deuterium incorporation in the methanol or the TMEDA.

b)The reaction was tried again using a four fold excess of *sec*-butyllithium. The same results were obtained.

Part 2

Synthesis of Tertiary Polyazamacrocycles

Recently, there has been considerable interest in the synthesis of polyazamacrocyclic compounds (cyclens, cyclams, aza crowns). Compounds of this type have been designed and shown to complex with the cations of a wide variety of alkali, alkaline earth, and transition metals[62,63]. There has also been biological interest in these compounds as complexants for metal cations used in radio labeling experiments[64], as possible anti viral agents[65], and as possible enzyme models or mimics[66,67]. In addition, chiral polyazamacrocycles are being investigated for use in enantiomeric recognition[68]. Our interest in cyclens has focused on the ability of tertiary polyamine macrocyclic complexants to form alkalides and electrides[3~5] that might have application as reducing agents for use in organic chemistry, or as complexants of alkyl lithium reagents. While attempting the synthesis of two new macrocyclic tertiary polyamines, we worked on improving the methodology used in the synthesis of these compounds.

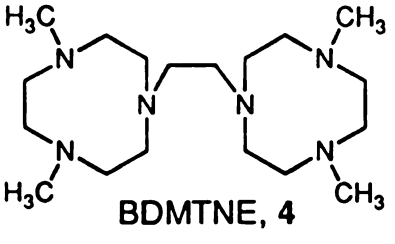
We considered several factors when selecting our target compounds. Early results suggested that although it was possible to produce the methanol dianion by reduction of formaldehyde, a much greater amount of methanol was produced, possibly from the methanol dianion reacting with an unknown proton source, as described earlier. In selecting new complexants we attempted to minimize possible sources of protons in the hopes of minimizing the

formation of methanol in the reaction. We felt the ideal complexants would not have any ether bonds. Hydrogen atoms alpha to oxygen are more acidic than hydrogen's alpha to amine nitrogen. Also oxygen's higher affinity for electrons makes the addition of an electron, a likely first step in reductive cleavage, more favorable for ether linkages than for similar compounds having all-amine linkages. This factor alone eliminated any crown, cryptand, or aza-crown complexants. We also believed this criterion was justified, since the decomposition of even a small percentage of the complexant could lead to the release of a large number of protons that would be immediately scavenged by any dianion that was formed.

The complexes we hoped to prepare should be formed in the absence of protic solvents. Since solvents like water and alcohol react more strongly with alkali metals than do most complexing agents these obviously cannot be used. Several techniques for the formation of alkalides and electrides use a primary amine as a solvent to dissolve the alkali metal first before forming the complex[5]. Since part of the goal of our research was to develop procedures that could be used in the standard organic chemistry lab, we felt it would be difficult to completely remove all of any primary or secondary amine used while forming a complex. Any remaining primary or secondary amine would then act as a proton source for the methanol dianion and destroy it.

The macrocycle HMHCY met the above criteria and complexed well with sodium. However the most likely complexants for lithium, PMPCY and TriTCY, gave disappointing results both in meeting the

qualifications put forth above, and in their ability to alter the reactivity of complexed alkyl lithium reagents, another area of interest to us. A methanol dianion synthon has been formed previously from butyl lithium and tributyltinmethanol, generating tri-*t*-butyl tin and the synthon in the dilithium form[36]. We felt a reducing system that also generated the dianion in a lithiated form, such as lithium electride or lithium sodide, offered the best chance for success. In addition there seems to be a growing interest in the use of complexants to alter the chemistry of alkyl lithium reagents[55]. On the basis of the above reasoning we decided to attempt the synthesis of two new compounds that we hoped would be good complexants for the lithium cation. Examination of space filling models showed that the novel bimacrocyclic complexant 1,2-bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane **4** (BDMTNE) could adopt a configuration where all six of the nitrogen lone pairs could be directed at a central cavity that was the right size for a Li^+ cation.



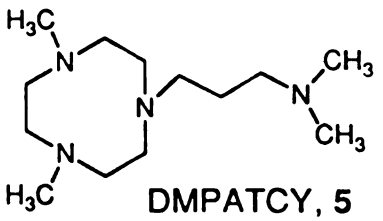
BDMTNE, **4**

1,2-Bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane

Figure 24- Structure of BDMTNE

A lithium cation inside this cavity would be coordinated by all six of the nitrogen lone pairs and we felt that this made BDMTNE a good potential lithium cation complexant. We originally believed that two

TriMTCY molecules came together in a similar configuration when complexing a lithium cation. Later it was shown that this was incorrect and that a deprotonated primary or secondary amine was necessary in order for the TriMTCY molecules to complex with a lithium cation[56], but we still felt that BDMTNE was a promising target compound. Our second target compound was the novel lariat complexant 4,7-dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane 5 (DMPATCY).



DMPATCY, 5

4,7-Dimethyl-1-(3-dimethylaminopropyl)-
1,4,7-triazacyclonoane

Figure 25- Structure of DMPATCY

Examination of space filling models of this compound showed that the four nitrogens could adopt a pseudo tetrahedral configuration around a lithium cation with all lone pairs facing the cation. Besides the possible use of DMPATCY as a lithium complexant, similar compounds have been investigated as possible enzyme mimics[66,67]. We felt these factors made DMPATCY a good target compound for synthesis.

Previously reported compounds similar to our targets are 1,4,7-tris(3-aminopropyl)-1,4,7-triazacyclononane and 1,2-bis(1,4,7-triazacyclononyl)ethane (BTNE). 1,4,7-tris(3-aminopropyl)-1,4,7-

triazacyclononane has been formed by reaction of unprotected 1,4,7-triazacyclononane with an excess of acrylonitrile followed by reduction to give the product[69].

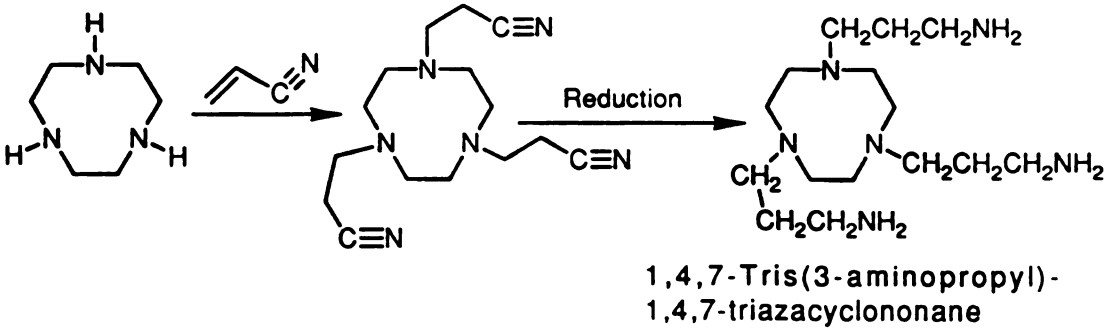
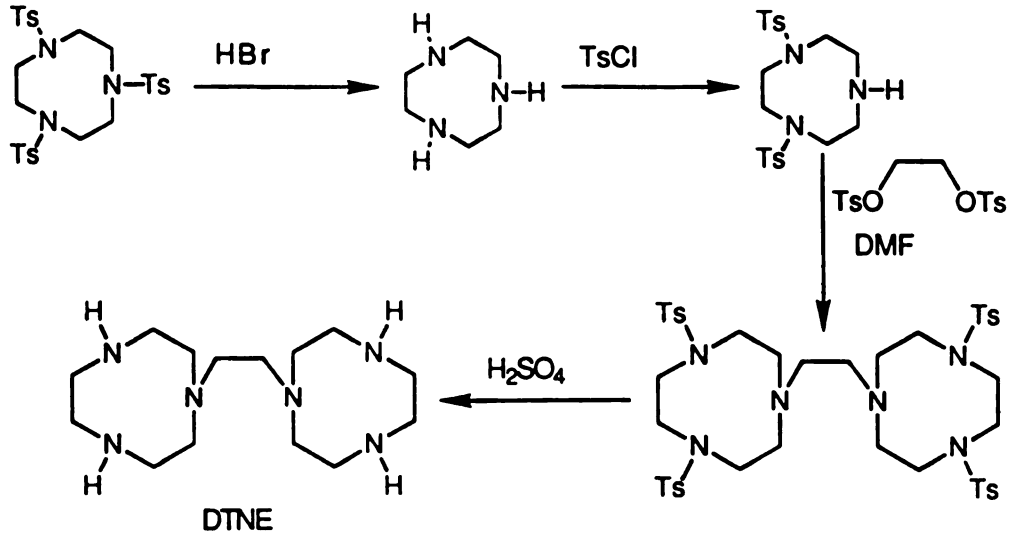


Figure 26- Synthesis of 1,4,7-tris(3-aminopropyl)-1,4,7-triazacyclononane

1,2-bis(1,4,7-triazacyclononyl)ethane BTNE, the obvious precursor to MDTNE, has also been successfully prepared. The original synthesis gave extremely low yields (~1%)[70], and was improved by Wieghardt[71]. Wieghardt reacted 1,4-ditosyl-1,4,7-triazacyclononane (DTTACN) with ethylene glycol ditosylate to give the tetratosyl protected bimacrocycle. The protecting groups were then removed by standard sulfuric acid hydrolyses to give DTNE as the sulfate salt, which was then transformed into the free amine.



1,2-Bis(1,4,7-triazacyclononyl)ethane

Figure 27- Synthesis of 1,2-Bis(1,4,7-triazacyclononyl)ethane

The considerable work given to the synthesis of cyclens and other crown type compounds has been reviewed recently by Bradshaw[72] and others[62, 73]. While the synthesis of symmetrical cyclens has been well developed[74], the routes to cyclens with a pendant arm or other unique features present on one or two of the nitrogen atoms, as is the case for MDTNE and DMPATCY, pose a more difficult synthetic challenge[75-86]. Several approaches have been used to form such compounds; attachment of the side-chain before cyclization, selective alkylation, and alkylation of a selectively protected macrocycle.

Mono-alkylated polyamine macrocycles have been synthesized by attaching the desired side arm before cyclization[75].

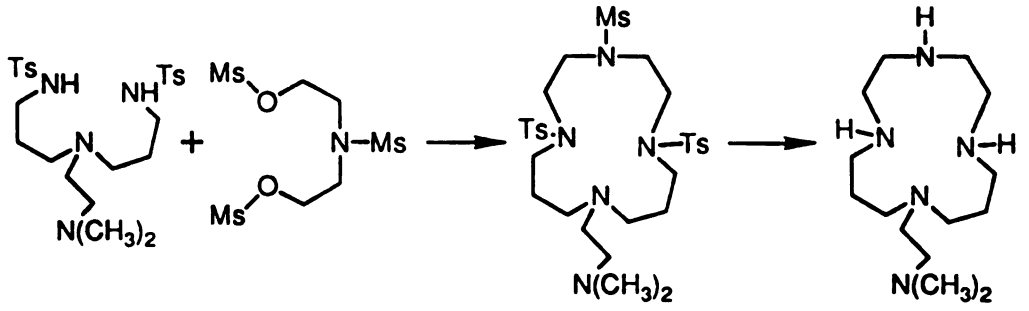


Figure 28- Synthesis of mono-alkylated polyamine macrocycles

This represents a divergent approach, requiring an individual synthesis and difficult cyclization step for each new complexant formed. In addition, it is not very adaptable, since a completely new synthesis is required if a different pendant arm is later desired. Although a number of mono-alkylated polyamines have been formed using this method, it is time consuming and labor intensive, especially when a large number of different compounds is desired. Approaches where the pendant arm is attached after cyclization are less labor intensive and allow for the easy substitution of a variety of pendant arms to a cyclized parent structure.

Selective alkylation using an alkyl halide with a large excess of the cyclized parent polyamine is an obvious approach to a mono alkylated polyamine. Several polyazamacrocycles have been selectively alkylated by this method, using 5-10 equivalents of the free amine during the reaction[76]. The obvious drawback of this method is that it requires a large excess of a cyclized compound that may be expensive and difficult to make. However, Rudolf has shown that the use of a large excess of free amine is not always necessary[77]. Using a 1:1 ratio of free amine to alkyl halide in a non-protic solvent ($CHCl_3$, CH_2Cl_2), he

was able to get 40:1 selectivity towards the mono-alkylated product. However, the reaction conditions used do not represent a general procedure, with yield and selectivity greatly varying depending on the size of the polyazamacrocycle, the alkyl halide, and the solvent.

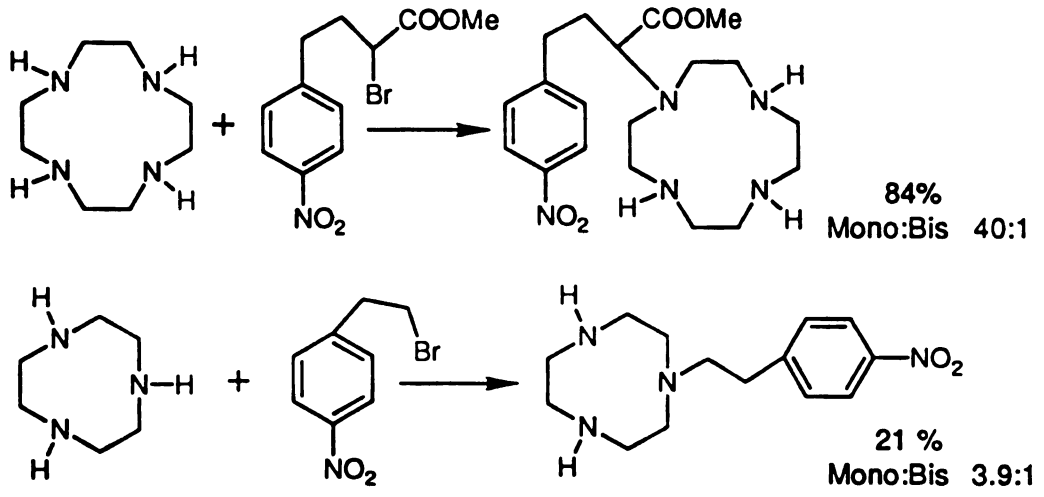


Figure 29- Synthesis of mono-alkylated polyamine macrocycles

More recently, Bradshaw and others have developed new methods of forming polyazamacrocycles, in which the cyclized product is formed with one secondary nitrogen available for further reaction[78].

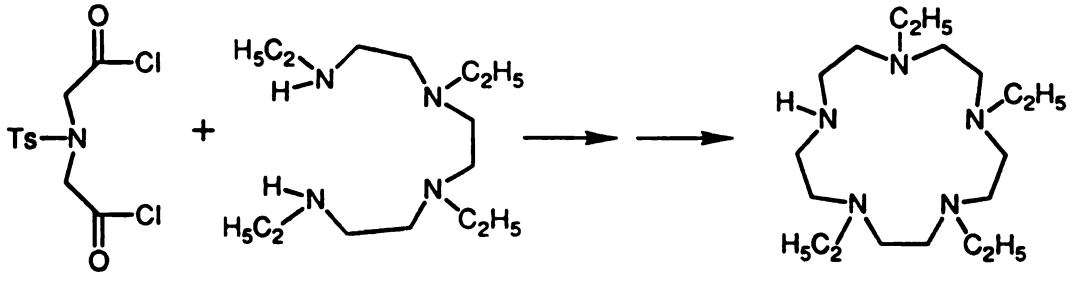


Figure 30- Bradshaw's synthesis of polyamine macrocycles

These methods not only represent new routes to non-symmetrical cyclens but also to the symmetrical cyclens. However, the yields for

some of these syntheses can be low (18%) and reduction is sometimes required. Another liability of this approach is that other tertiary amine groups present on the polyamine have nucleophilic lone pairs. These lone pair electrons can interfere with attempts to attach a group to the secondary nitrogen.

The use of protecting groups to partially mask some of the nitrogens, while leaving others available for reaction, is another route to non-symmetrical cyclens. Several different approaches have been used to obtain partially protected polyazamacrocycles.

In a modified Richman-Atkins synthesis, Lehn reports using mesyl groups along with tosyl groups to generate asymmetrical cyclens[4]. The tosyl groups can then be removed without affecting the mesyl protecting groups. Methylation of the unprotected nitrogens followed by removal of the mesyl protecting group generates a cyclen with one secondary amine.

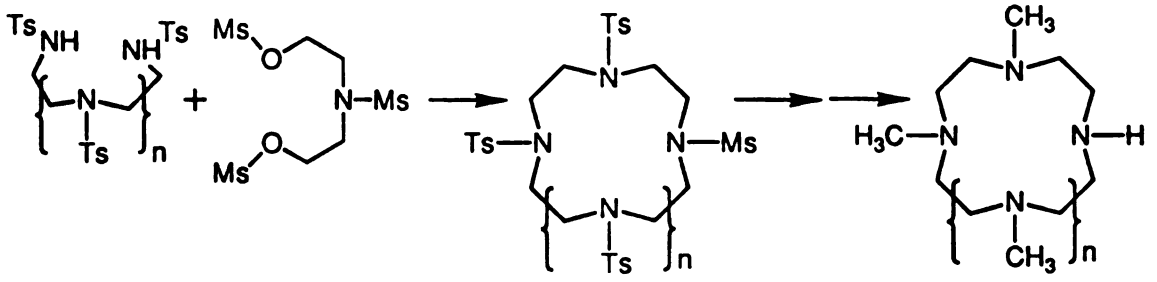


Figure 31- Synthesis of mesyl protected polyamine macrocycles

As in the previous method, this approach gives a species with reactive tertiary nitrogens that can interfere with additional reactions. An

untried modification would be the use of mesyl protecting groups on all but one of the amines. The remaining amine would be protected with a tosyl group that could be selectively removed to give one active amine. However, the difficulties involved in removing the mesyl group (discussed later) make this an undesirable approach.

Kaden reports using both benzyl and trityl protecting groups in the formation of polyazamacrocycles[79]. Both the benzyl and trityl protecting groups can be removed selectively, without affecting tosyl protecting groups, to generate a single reactive nitrogen. The benzyl group is selectively cleaved by catalytic hydrogenation, while the trityl group can be removed by a mild acid hydrolysis using HCl and CH_3OH. However the yield of the cyclization step where the trityl group is used is less than 50 %.

The selective reprotection of an unsubstituted cyclen is another method that has been used to form non-symmetrical cyclens. Weighardt reports using a limited amount of p-toluenesulfonyl chloride to protect all but one of the available nitrogens[71]. The unique group is then attached and the remaining tosyl groups removed (this work is discussed in detail later in the paper).

Another approach transaminates tris(dimethylamino)-borane with a tetraaza cyclen[80].The borane reacts with three of the amine functions leaving one nitrogen unprotected and available for further reaction. Once the desired group is attached the boron moiety is removed by hydrolysis. The disadvantage of these synthetic sequences

is that they are unnecessarily long . In addition, the use of boranes to protect three nitrogens appears limited to tetraazacyclens.

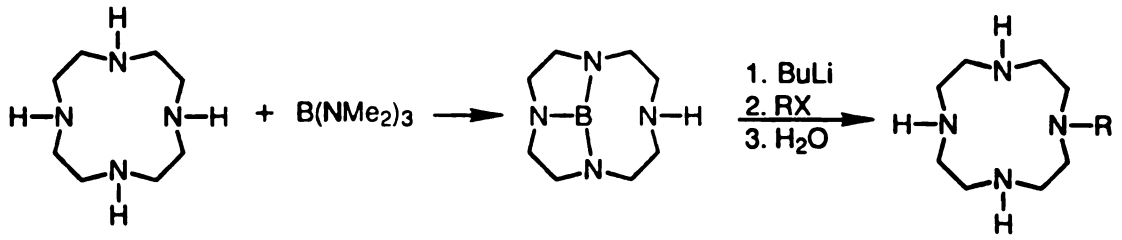
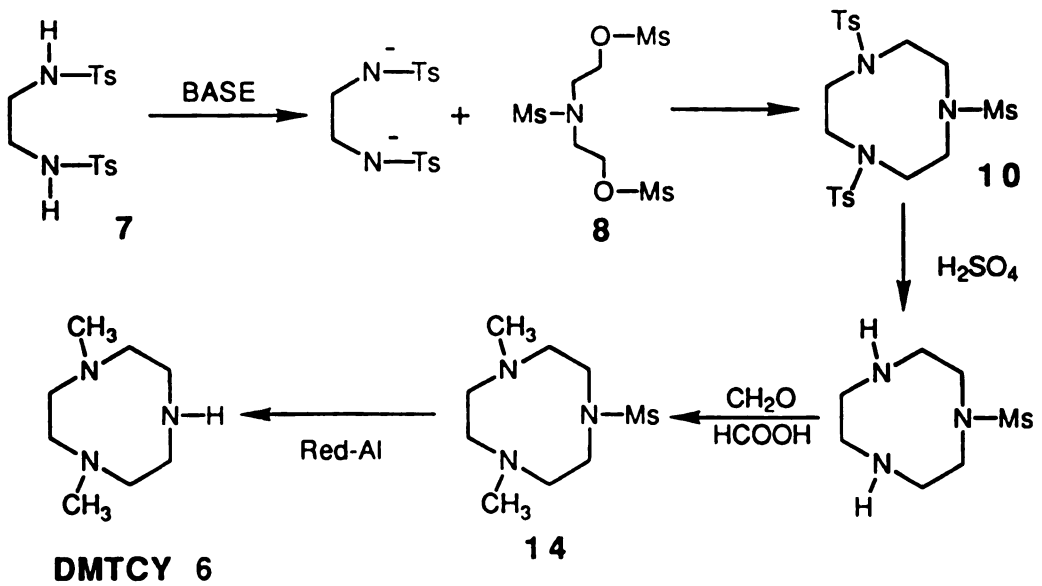


Figure 32- Use of boranes to protect tetraazacyclens

While all of these pathways have been used successfully to synthesize a large number of ligands they often are hampered by a variety of problems. It was our intent of to develop improved methods for the formation of asymmetrical cyclens, while synthesizing the two target compounds discussed earlier.

Synthesis of 1,4-dimethyl-1,4,7-triazacyclononane 6 (DMTCY) Using a Modified Richman-Atkins Synthesis.

Of the procedures available, the Richman-Atkins synthesis[61] still represents a competitive route to cyclens. Our initial strategy was to generate 1,4-dimethyl-1,4,7-triazacyclononane DMTCY, a cyclen that has a unique secondary nitrogen, using the modified Richman-Atkins synthesis reported by Lehn[4].



Scheme 1- Synthesis of DMTCY using the Lehn modification of the Richman-Atkins synthesis

We felt it would then be possible to couple two of the DMTCY molecules with an ethylene bridging group to give BDMTNE. We also felt that our second target compound could be synthesized by reacting DMTCY with acrylonitrile, reducing, and then methylating to give DMPATCY.

The first step in the Richman-Atkins synthesis is the double deprotonation of an appropriate ditosyl protected diamine. A variety of bases have been used to form this dianion; alkoxides, hydrides, carbonates, and alkyl lithium reagents. However, a liability is associated with the use of each of these bases. Alkyl lithium reagents offer the advantage of speed but are expensive to use on a large scale. Alkoxides can also be used to form the disodium salt quickly, but generate an equivalent of alcohol that competes with the cyclization, decreasing yield. More recently several groups have achieved cyclization using carbonate as the base, however carbonate is not very soluble in the reaction solvents resulting in a reaction that takes days to complete. Poor solubility, and the resulting slow reaction rate, also occur when using hydrides as the base. The reaction can be accelerated by a large excess (ten equivalents) of hydride reagent. However the large excess of hydride creates a different problem, a dangerous filtration step to remove the excess reactive hydride before the reaction can be completed[87].

Modification of the Cyclization Step.

We felt a better procedure would be to the addition of a small amount of *tert*-butyl alcohol to a reaction mixture containing only a modest excess sodium hydride. The *tert*-butyl alcohol would act as a phase transfer catalyst reacting with the insoluble sodium hydride to form sodium *tert*-butoxide. The sodium *tert*-butoxide, soluble in the THF solvent, could then deprotonate the N, N'-ditosylethylenediamine generating the desired sodium salt while regenerating the *tert*-butyl alcohol. Since this is a catalytic cycle the reaction would require only a

fractional equivalent of *tert*-butyl alcohol that we hoped would not significantly affect the yield of the cyclization step.

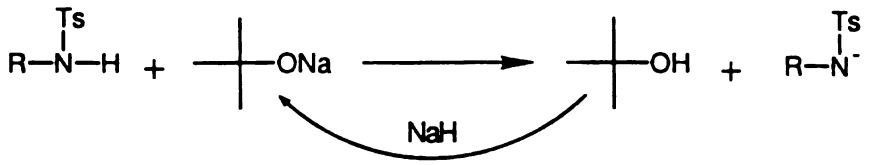
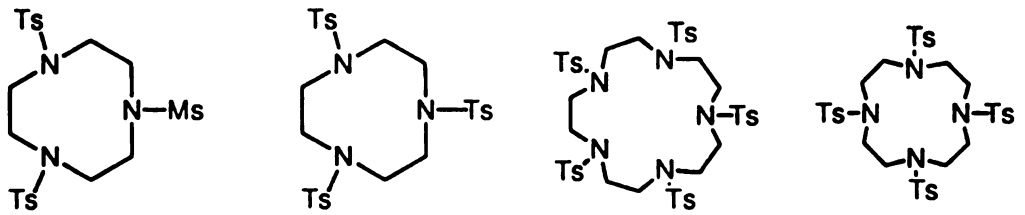


Figure 33- Catalytic cycle of *tert*-butyl alcohol

We found that the addition of 0.1 equivalents of *tert*-butyl alcohol allowed the use of only a slight excess, 1.1 equivalents, of NaH while still forming the dianion in 2 hours. The use of 0.2 equivalents *tert*-butyl alcohol was also tried, giving similiar results. This modification was used in the synthesis of four cyclens shown below.



10 **11** **24**[97] **25**[97]

Figure 34- Macrocycles prepared by modified cyclization step

Deprotection

4,7-Ditosyl-1-mesyl-1,4,7-triazacyclononane formed by this modified procedure was detosylated by sulfuric acid hydrolyses. The sulfate salt product was collected and used without purification in the Eschweiler-Clark methylation procedure. This gave a 71 % yield of 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane, based on the amount of 4,7-ditosyl-1-mesyl-1,4,7-triazacyclononane used.

A standard procedure for the removal of the sulfonyl group is acid catalyzed hydrolyses. However, since the mesyl group on 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane was mostly unaffected by the strenuous acid cleavage of the tosyl groups, another approach was required. Lehn reports the cleavage of the mesyl group from similar compounds using Red-Al[4]. Although the reaction of 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane with 3 equivalents of Red-Al gave a 68 % yield, we found that this reaction had serious deficiencies, requiring an excess of reagent that is costly and inconvenient to use on a large scale, and generating by-products that emitted a foul stench. The large mass of by-products generated by Red-Al reeked so badly that they could not be disposed of until after some effort was made to reduce their odor. The odor presumably comes from the reduction of the sulfonyl group to a mercaptan, sulfinic acid, or disulfide[95]. Treatment of the by-products with $KMnO_4$ moderated the odor, presumably by oxidizing the sulfur to a higher oxidation state, so they could then be disposed of properly.

At this time we discovered that the extraction solvent used during work-up of this reaction could affect the yield. If methylene chloride was substituted for chloroform as the extraction solvent, and the product remained in solution for several hours, no useful DMTCY could be obtained. It was assumed that the free secondary amine on DMTCY, acting as a nucleophile, reacts with the methylene chloride thereby destroying the DMTCY.

Final Synthesis of DMTCY

Several other methods have been reported for cleavage of a mesyl group from a secondary amine[88]. However most of these methods were also reductive cleavage reactions that we felt would not eliminate the problem of the offensive odor. In addition, the reducing agents in these procedures were more expensive than Red-Al. Another possible method for the cleavage of mesyl groups is base catalyzed hydrolyses. Bryon Merril[89] reported the cleavage of a mesyl group from a furan derivative using alcoholic base. However, after refluxing 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane in a solution of *tert*-butyl alcohol and KOH for twenty hours the 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane was recovered unchanged. Although useful quantities of DMTCY could be obtained using the Red-Al cleavage procedure the negative aspects of this reaction ultimately led us to examine different routes to the DMTCY that did not use the methane sulfonyl protecting group.

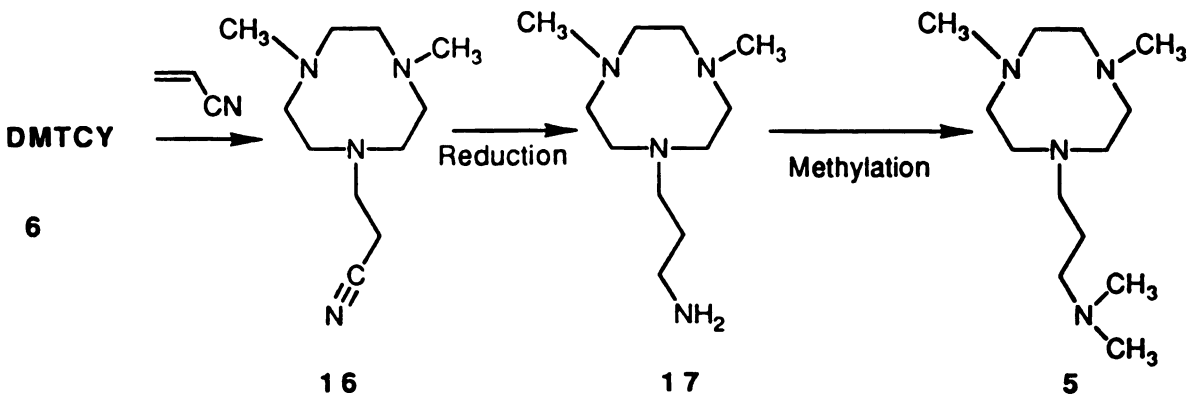
While trying to develop an efficient method for the formation of 1,4-ditosyl-1,4,7-triazacyclononane we discovered a better route to DMTCY that did not use the methane sulfonyl protecting group. Tosyl-1,4,7-triazacyclononane was prepared in one step in 60 % yield from 1,4,7-tritosyl-1,4,7-triazacyclononane by a selective detosylation procedure described later*. It was then methylated with the Eschweiler-Clark procedure, and the remaining tosyl group removed by acid hydrolysis to give DMTCY in 91 % yield over the last two steps.

---

* After we began this work Sessler reported the formation of Monotosyl-1,4,7-triazacyclonanone by selective detosylation of 1,4,7-tritosyl-1,4,7-triazacyclononane. His work is discussed in detail later.

Synthesis of 4,7-dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane 5 (DMPATCY)

Our approach to the novel lariat complexant 4,7-dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane **5** (DMPATCY) from DMTCY is outlined in Figure 34.



Scheme 2- Synthesis of DMPATCY

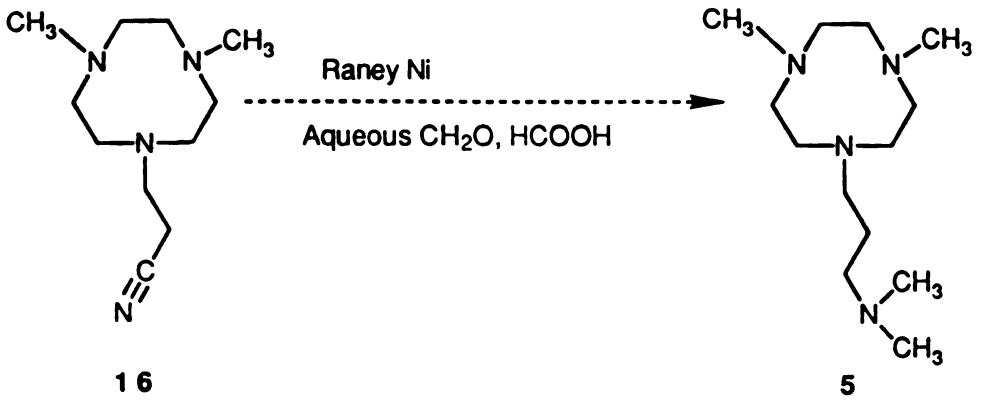
The Michael reaction of DMTCY with freshly distilled acrylonitrile in dry iso-propanol gives an 80 % yield of **16**. A number of procedures are available for the reduction of the nitrile group[90]. We first used, fresh, very active Raney Ni catalyst and hydrazine hydrate to effectively reduce the nitrile group. However this method gave inconsistent results. Only the most active batches of Raney Ni catalyst gave a clean reaction. Any degeneration of the catalyst or the alloy used to generate the Raney Ni catalyst quickly led to a decrease in yield and the formation of many by-products that were difficult to separate. Raney

Nickel obtained from commercial sources also gave poor results, giving less than a 50 % yield of the desired product.

We found that $LiAlH_4$ was an acceptable alternative for reducing the nitrile, even though it catalyzed a retro Michael reaction regenerating DMTCY. The retro Micheal reaction was most prevalent when solid $LiAlH_4$ was added to a solution of the nitrile in ether at room temperature. Under these conditions equal amounts of the reduced nitrile and DMTCY were obtained. The retro Michael reaction however could be minimized by using a cooled solution of $LiAlH_4$. Running the reduction at 0^o C in ether solubilized $LiAlH_4$ gave a 19 : 1 ratio of reduced nitrile to DMTCY. In addition, the product generated by the $LiAlH_4$ reduction proved to be easier to purify than the product formed from the Raney Nickel reduction.

Although the catalytic hydrogenation using Raney Nickel and hydrazine did not give satisfactory results we felt a new procedure might be developed that would combine the reduction of the nitrile and the methylation procedure. The reduction using Raney Nickel and hydrazine relies on the Raney Nickel's ability to decompose hydrazine to liberate hydrogen and nitrogen gas. Some of the liberated hydrogen is then absorbed on the catalyst and effects the reduction. Raney Nickel, however, will also decompose formic acid to liberate hydrogen and carbon dioxide gas. It was our hope that formic acid would serve in a manner similar to hydrazine and effect the reduction of the nitrile while in the presence of Raney Nickel. If this were the case we felt it would be possible to add excess formic acid and formaldehyde to a

solution of the nitrile containing Raney Nickel and thereby effect the reduction of the nitrile and the methylation of the resulting amine in one step.



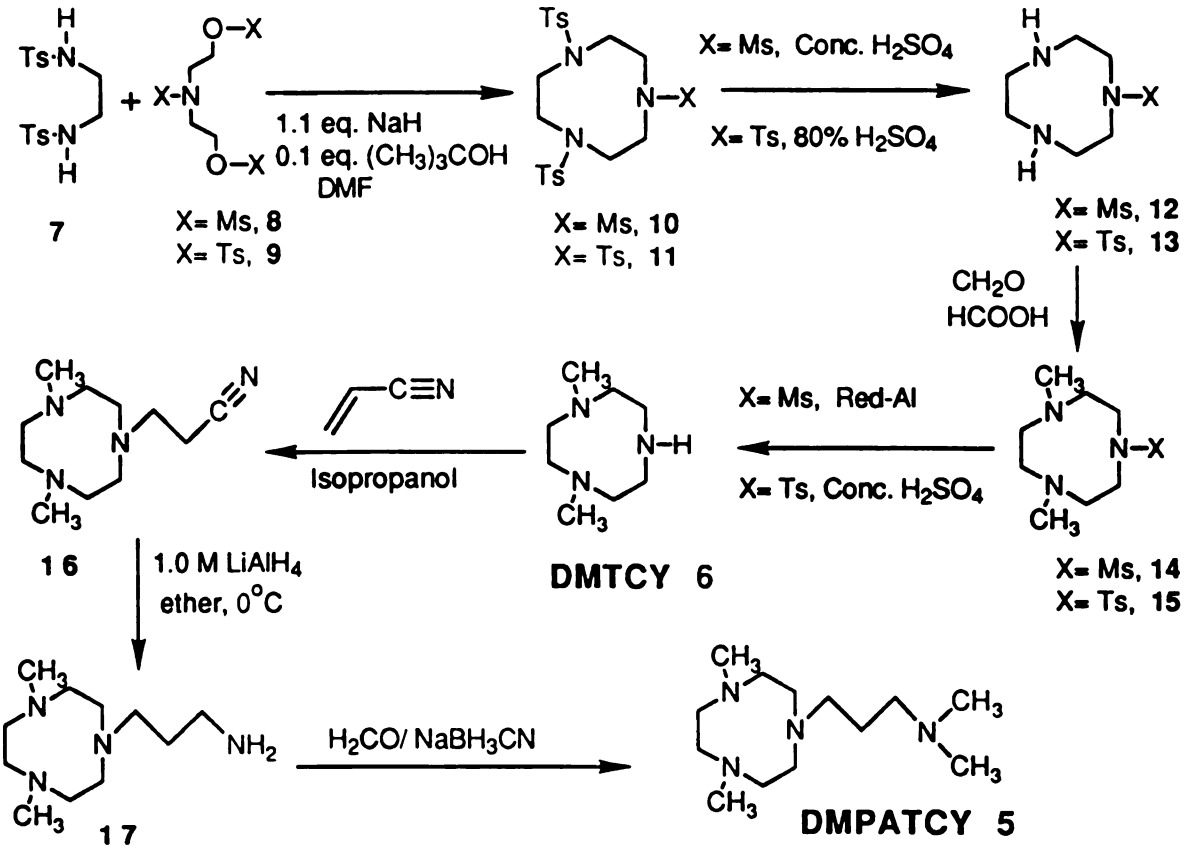
16 5

Figure 35- Attempted reduction of lariat nitrile

Raney Nickel did initially decompose formic acid, however, as the reaction progressed deactivation of the Raney Nickel occured. Eventually the Raney Nickle was unable to decompose the formic acid. In addition the combination of the Raney Nickel and formic acid did not appear to reduce the nitrile in any detectable amounts. We concluded therefor that formic acid could not substitute for hydrazine in this type of reduction.

The last step in the synthesis of 1,4-dimethyl-7-(N,N-dimethyl-3-aminopropyl)-1,4,7-triazacyclononane is the methylation of the primary amine on the propyl sidearm. The standard Eschweiler-Clark methylation procedure was tried and gave a 94 % crude yield of a product that G.C. analysis showed to contain only ~65% of the desired product. In addition the product from this reaction proved to be difficult to separate from the by-products. Borch[91] reported a modification of the Eschweiler

Clark methylation that uses $NaBH_3CN$ as a source of hydride instead of formic acid. This modification gave us a 88 % crude yield of a product that G.C. analysis showed to contain ~90 % of the desired product. In addition the crude product from this reaction was easily purified by vacuum distillation to give pure DMPATCY.

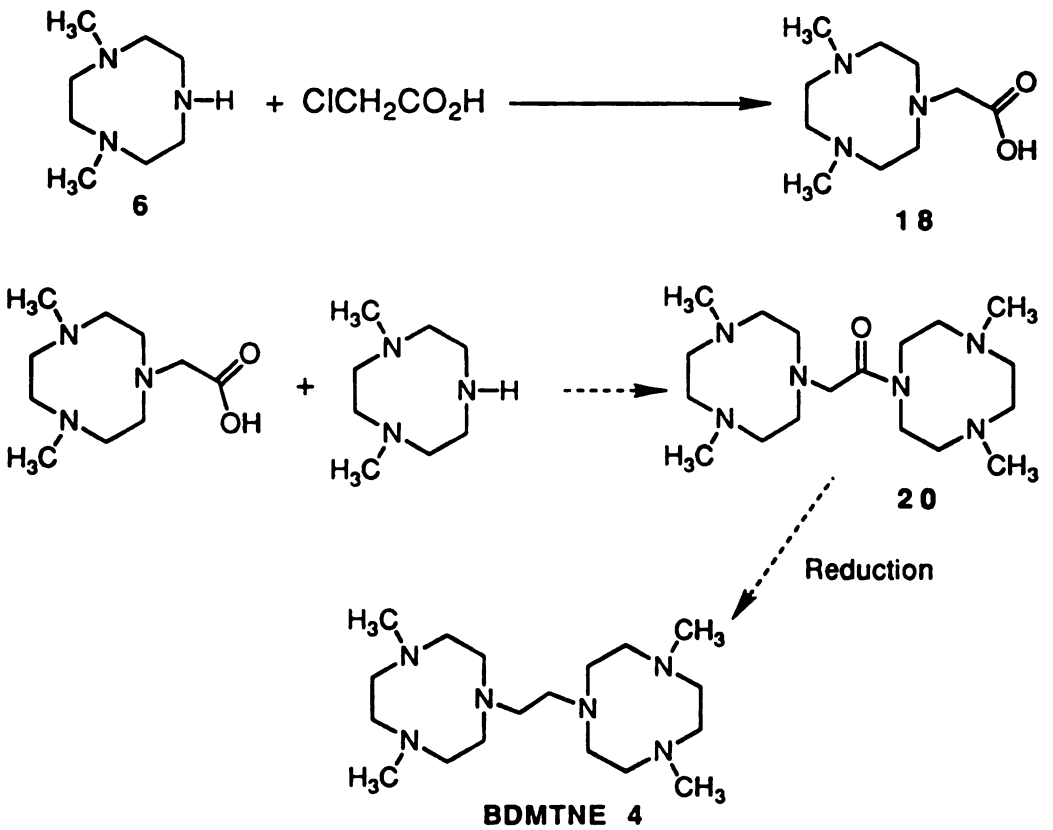


Scheme 3- Final Synthesis of DMPATCY 5

The pure DMPATCY was given to the Dye group for use as a lithium complexant. While it did appear to complex with lithium to some degree, the qualitative opinion was that it was a poorer complexant than several cyclens already available.

Synthesis of 1,2-bis(4,7-dimethyl-1,4,7-triazacyclononyl)-ethane 4 (BDMTNE)

We felt the second target compound, BDMTNE, could be synthesized by reacting DMTCY with chloroacetic acid to generate an amino acid. We then hoped to capitalize on the numerous methods available[92] for coupling aminoacids to add a second DMTCY molecule to the N,N'-dimethyl-1,4,7-triazacyclononyl-N"-acetic acid giving the desired skeletal structure. The synthesis of BDMTNE would then be completed by the reduction of the resulting amide.



Scheme 4- Proposed synthesis of BDMTNE

We hoped this method might result in better overall yield than an approach that used Weigharts' synthesis of 1,2-di(1,4,7-triazacyclononyl)ethane. In addition, our proposed route eliminates the large protecting groups, a liability of the Richman-Atkins synthesis, at an earlier stage.

Reaction of DMTCY with chloroacetic acid gave the desired amino acid in 56 % yield. While this was substantially lower than we expected, it did provide enough material to continue with the reaction sequence. Our intention was to determine whether the entire scheme worked before optimizing individual reactions in the sequence.

Attempted Coupling of the Amino Acid

The next step in the sequence is the coupling of the newly formed aminoacid with a second DMTCY. Activation with N-hydroxysuccinimide and/or dicyclohexylcarbodiimide (DCC) is a commonly used method to couple aminoacids[93]. The resulting activated complex is then mixed with the appropriate amine to couple the two compounds. Dicyclohexylurea, a by-product of this reaction, is normally insoluble in the solvent and can be filtered from the mixture. The remaining solution is then evaporated to give the desired product. This method offered the advantages of mild conditions, reliability and good yield. We tried this method using our substrates several times, varying the length of reaction time, the order in which the reactants were added, and the solvent used for the reaction. The DMTCY appeared to solubilize the urea formed during the reaction, and this complicated our attempts, with only a fraction of the expected urea

precipitating out of solution. The ability of DMTCY to solubilize the urea was verified by adding DMTCY to a suspension of urea in DMF. Unfortunately in all our attempts to couple the amino acid we were unable to obtain any verifiable evidence that the aminoacid had reacted with N-hydroxysuccinimide or dicyclohexylcarbodiimide, or that the coupling reaction had proceeded. Thus, we never isolated the desired product. Work-up of reaction mixtures yielded an emulsion residue that when analyzed by H-nmr displayed many broad and overlapping peaks. This type of spectrum was indicative of a sample that contained a large number of different compounds. Attempts were made to develop a method to separate the resulting reaction mixture using column chromatography, but a suitable solvent system was never found. We also made additional unsuccessful attempts to isolate the activated complex of the amino acid, and tried to verify that the activated complex had been formed. Although the use of DCC and N-Hydroxysuccinimide to couple aminoacids to amines is well characterized, in our situation the increased solubility of the urea by-product greatly complicated the reaction mixture and we were unable to determine the results of the reaction.

Attempted Coupling of Two DMTCY using Chloroacetyl Chloride

In attempts using DCC we were unable to confirm whether the DCC was activating the carboxylic acid or to isolate any pure material from the reactions. In order to avoid the uncertainty of this activation, we tried an acid chloride, a very reactive derivative of a carboxylic acid, to form the amide. This approach avoids the urea by-product that complicated the work-up of the previous reactions. We chose

chloroacetyl chloride since it has two very reactive sites that would easily react with two DMTCY molecules. In the event, we tried coupling two DMTCY molecules by adding chloroacetyl chloride to a solution of DMTCY in methylene chloride. Unfortunately, as with the DCC coupling reactions, we were unable to determine what reaction had occurred. The only compound we were able to isolate from this reaction was TriMTCY in ~25% yield. We later discovered that the DMTCY we were using was contaminated with TriMTCY, the most likely origin of the TriMTCY isolated in the reaction. However, since we were unable to obtain any desired product from the reaction, since it is not likely that a useful competitive methylation procedure could be developed out of such a reaction and since such an investigation was outside our interests we elected not to investigate the source of the TriMTCY more fully.

Attempted Coupling of an Ester with DMTCY

We also tried to form the amide bond by heating methyl 4,7-dimethyl-1,4,7-cyclononyl-1-acetate with the DMTCY [94]. Although the reaction requires more strenuous reaction conditions than used in previous attempts, the reagent is milder. Esters are less reactive than acid chlorides, and there are no major organic by-products from the reaction. 4,7-dimethyl-1,4,7-cyclononyl-1-acetic acid was converted to its' methyl ester by acid catalyzed esterification in dry methanol (75 % yield). The ester, isolated as the trihydrobromide salt, was placed in a pressure tube along with an equivalent of DMTCY with methanol as a solvent. Upon heating, the solution slowly discolored. After heating for seven days, the reaction was worked up, however no sign of the

coupled product could be observed. The H'-nmr of this material was identical to the mixture of the starting materials, leading us to believe that no significant reactions were taking place.

Other Attempts at the Direct Coupling of Two DMTCY

Besides our attempts to form the bivalve by coupling 4,7-dimethyl-1,4,7-cyclononyl-1-acetic acid with DMTCY, we tried several reactions to couple DMTCY directly. The first was a novel approach based on the Eschweiler-Clark methylation procedure. If glyoxal is substituted for the formaldehyde in the Eschweiler-Clark procedure it was hoped that it would react with the secondary amines on the DMTCY to form an imine that could then be reduced by formic acid to give the bivalve.

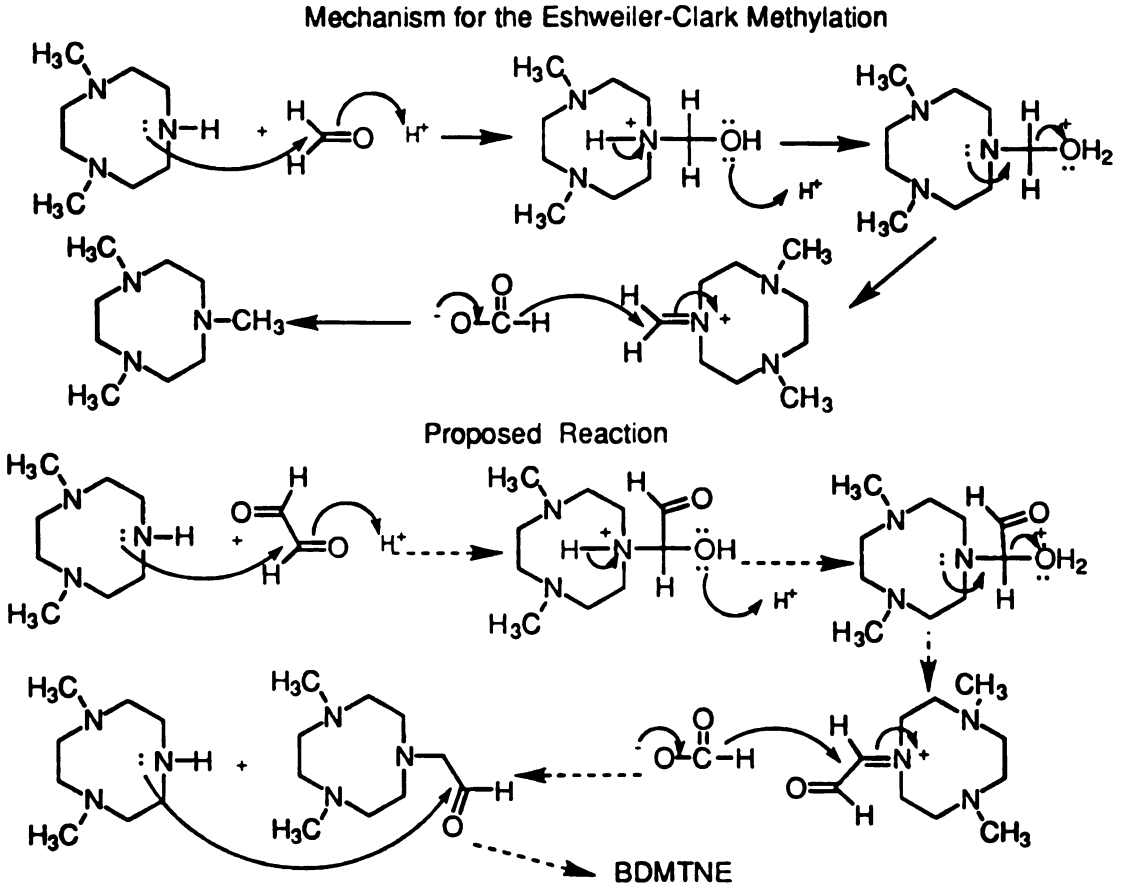


Figure 36- Mechanism of proposed coupling reaction

A solution of glyoxal and formic acid was added directly to neat DMTCY that was then heated for 23 hours. Although it appeared that a reaction took place we were unable to identify or isolate any product or starting materials from the reaction mixture.

Another approach considered was the oxidative coupling of two TriMTCY molecules. If TriMTCY behaved like TMEDA, we felt it might be possible to deprotonate TriMTCY with butyllithium, as discussed earlier. The resulting anion might then be coupled by oxidative coupling using Iodine[95]. Unfortunately we were unable to

deprotonate TriMTCY using butyllithium and attempts at this reaction resulted in only the recovery of the TriMTCY unchanged by the reaction.

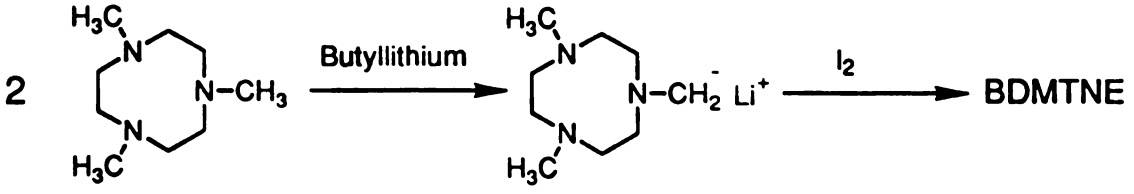


Figure 37- Attempted coupling of two TriMTCY

Based on the initially low yield for forming the amino acid and the degree of difficulty we were having coupling two TriMTCY rings we felt that an entirely different pathway should be considered. It no longer seemed reasonable to expect our proposed route to give results better than Wieghart's approach for making 1,2-bis(1,4,7-triazacyclononyl)ethane (BTNE), an obvious precursor of BDMTNE. Once the BTNE was obtained it would only be necessary for us to methylate the secondary amines to generate our target compound.

Synthesis of BTNE

Wieghart[71] started with 1,4,7-tritosyl-1,4,7-triazacyclononane synthesized by the standard Richman-Atkins synthesis. He then detosylated using hydrobromic acid to give the trihydrobromide salt of 1,4,7-triazacyclononane (TACN). The key step in the synthesis, the formation of 1,4-ditosyl-1,4,7-triazacyclononane (DTTACN), was accomplished by the reaction of the trihydrobromide salt of 1,4,7-triazacyclononane with a limited amount of base and *p*-tolylsulfonyl chloride. Using this procedure, Wieghart reported a ~ 70% yield of a

product that was contaminated with some 1,4,7-tritosyl-1,4,7-triazacyclononane. This is the key step in the reaction sequence, because it is at this point that a unique nitrogen is generated on the macrocycle. The ditosyl protected cyclen was coupled using ethylene glycol ditosylate to generate 1,2-bis(4,7-ditosyl-1,4,7-triazacyclononyl)ethane. Detosylation then gave 1,2-bis(1,4,7-triazacyclononyl)ethane (see Figure 27).

We tried several times to duplicate the key step reported by Wieghart to form ditosyl protected DTTACN. For these attempts we used 1,4,7-triazacyclononane prepared in our labs, and 1,4,7-triazacyclononane obtained from Aldrich as its sulfate salt. Although we were able to make a limited amount of the ditosyl protected cyclen using this procedure, we were unable to duplicate the Wieghart results or to obtain DTTACN in sufficient yield and purity to satisfy our needs. Our attempts mostly gave approximately equal yields of mono, di, and tritosyl-protected cyclen with no noticeable selectivity. Unrecovered starting material was assumed to account for missing triazacyclononane in the mass balance. Not only did the reaction give a poor yield, it also required two steps. The 1,4,7-tritosyl-1,4,7-triazacyclononane formed from the Richman-Atkins synthesis was first completely detosylated to form TACN that was then retosylated in a second step. We felt removal of only one of the tosyl group from 1,4,7-tritosyl-1,4,7-triazacyclononane would be a more efficient route to DTTACN.

Selective Detosylation of 1,4,7-Tritosyl-1,4,7-Triazacyclononane

Several plausible mechanisms for the acid catalyzed hydrolyses of the sulfonamide bond involve the attack of an electrophile, such as H^+, HSO_3^+, or possibly SO_3, on the nitrogen atom, generating a positive charge on the parent molecule. Nucleophilic attack of water on the sulfur atom would then result in either the cleavage of the sulfonamide bond to give the secondary amine or desulfonation to give toluene and an aminosulfonic acid. Fast hydrolysis of the resulting aminosulfonic acid would also give a free secondary amine, which would be immediately protonated in the acidic solution. Cleavage of a second tosyl group would then require electrophilic attack on a molecule that already had a positive charge and would result in a molecule that had two positive charges. The increase in charge density necessary for the cleavage of the second tosyl group would most likely be reflected by an increase in the activation energy required to effect the second cleavage. Under the right reaction conditions we felt it might be possible to exploit this energy difference to selectively remove only one tosyl group from 1,4,7-tritosyl-1,4,7-triazacyclononane, thereby forming DTTACN in one step from the Richman-Atkins product. This would eliminate one reaction from the synthesis used by Wieghart and possibly give better results. In addition we felt this methodology might also allow the selective remove of two tosyl groups from 1,4,7-tritosyl-1,4,7-triazacyclononane to generate 1-tosyl-1,4,7-triazacyclononane. This would give an alternative method

for synthesizing DMTCY that would avoid the methanesulfonyl protecting group and the resulting reductive cleavage.

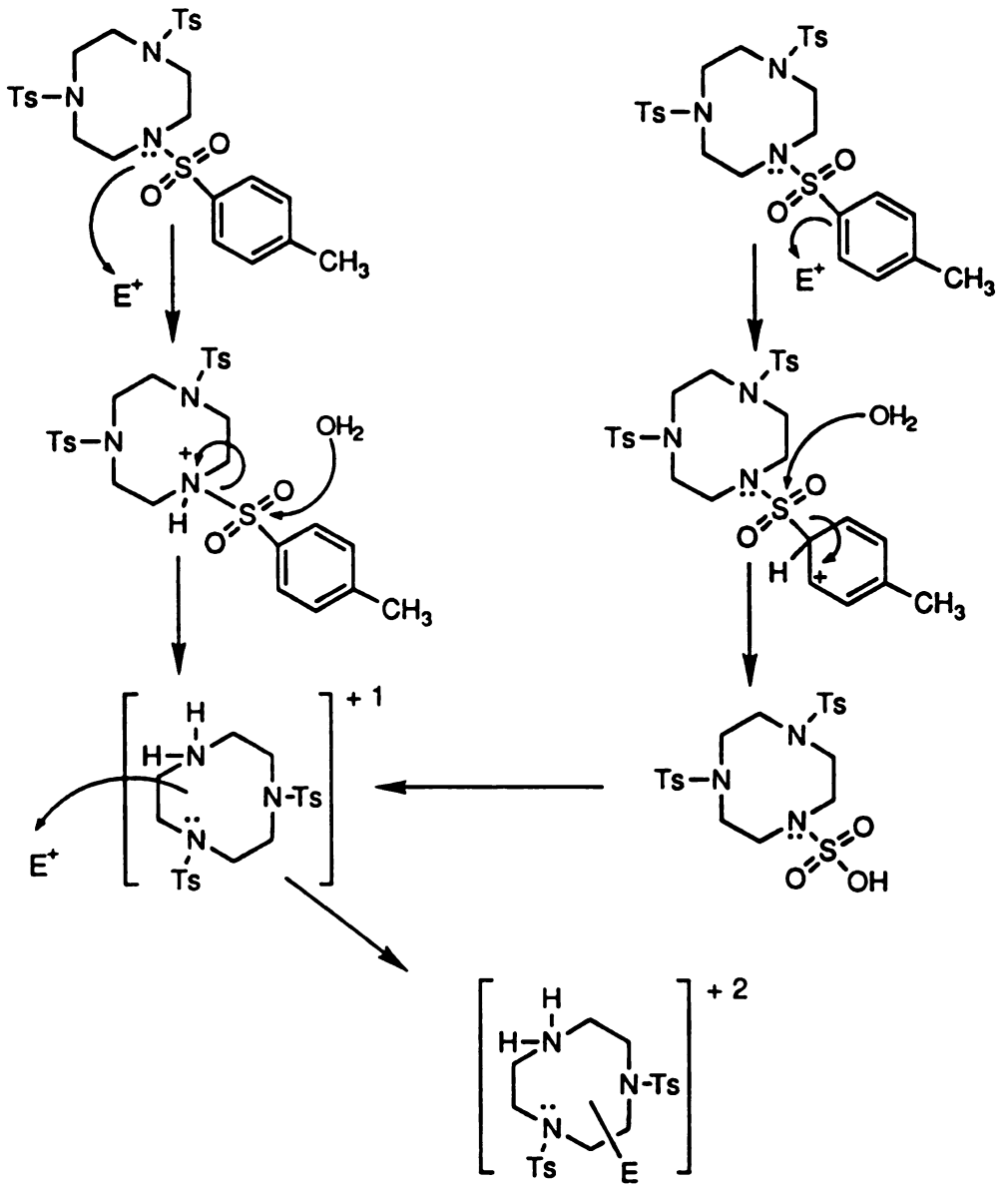


Figure 38- Mechanism of selective detosylation

We undertook a series of reactions varying the concentration of the sulfuric acid, the temperature, and the reaction time. The results are summarized in Table 4.

Table 4- Results from selective detosylation experiments

Conc. of H_2SO_4[d]	Temp. C	Time Hours	Tritosyl	Ditosyl	Mono-tosyl	TACN
100 %	110	24	-	-	-	~100 %
100 %	70	72	-	-	25 %	~75 %
90 %	70	72	-	-	42 %	~58 %
100 %	65	72	-	39 %	40 %	a
90 %	65	72	-	44 %	33 %	a
80 %	60	24	50 %	50 %	-	-
80 %	60	48	33 %	67 %	-	-
80 %	60	72	8 %	92 %	-	-
80 %	72	30	-	65 %	35 %	-
80 %	72	96	-	45 %	50 %	a
80 %	76	24	-	65 %	17 %	a
80 %	76	48	-	38 %	33 %	a
80 %	76	72	-	26 %	38 %	~36 %
75 %	72	4	~100 %[b]	-	-	-
70 %[c]	65	72	-	88 %	trace	-
100 %	65	72	33 %	33 %	33 %	-
80 %	72	144	-	33 %	67 %	-

a) The amount of this compound was not determined however it was assumed to account for the missing mass. b) The sample was not appreciably soluble in this concentration so the reaction was stopped and the starting material recovered after 4 hours. c) 1,4-Ditosyl-1,4,7-triazacyclononane was used as the starting material for this reaction. d) Percentage of concentrated acid used.

1,4,7-Tritosyl-1,4,7-triazacyclononane was formed from tritosyl-diethanolamine by the modified Richman-Atkins procedure discussed earlier. The most favorable results for removing one tosyl group were obtained by stirring 1,4,7-tritosyl-1,4,7-triazacyclononane in 80% H_2SO_4 at 60° for 72 hours. 80 % H_2SO_4 represented the lowest concentration that would completely solubilize 1,4,7-tritosyl-1,4,7-triazacyclononane. Because of the variable water content of conc. sulfuric acid it was occasionally necessary to add a few extra drops of the acid to insure complete solubility of the tritosyl compound in the acidic medium. The best results using these conditions gave a product that was 92%

ditosyl-1,4,7-triazacyclononane (88% yield) and 8% unreacted starting material. This reaction was run an additional seven times under these reaction conditions, giving ditosyl-1,4,7-triazacyclononane in 74-88% yield. The best results for the removal of two tosyl groups were obtained at 72° for six days. Under these conditions it was possible to obtain a 60 % yield of the mono-tosyl compound directly after work up that was of sufficient purity for our work. Although there was some variation in product yield and purity in each of these reactions, they were sufficiently reproducible for our synthetic purposes.

Wieghart[71] reported using ^{13}C-nmr to judge the degree of contamination of his products. We found that the relative amounts of the different tosylamides in a sample could be measured more accurately using ^{1}H-nmr, by comparing the respective integrated values for the methylene protons of each component (see appendix B). To determine the composition of these mixtures accurately it is necessary to use a concentrated sample for the ^{1}H-nmr measurement. Contrary to what is normally observed, a concentrated sample of these compounds gave a substantially better resolved ^{1}H-nmr than a dilute sample (see appendix C).

After we had begun work on the selective detosylation of 1,4,7-tritosyl-1,4,7-triazacyclononane, Sessler[96] reported a selective detosylation using 30% HBr/AcOH in the presence of phenol.

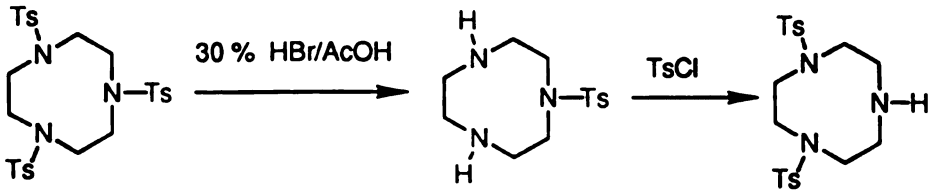


Figure 39- Sessler's reported selective detosylation

His procedure seems to rely on the insolubility of the dihydrobromide salt to prevent further reaction, and efficiently removes two tosyl groups from the tritosyl-1,4,7-triazacyclononane to give 1-tosyl-1,4,7-triazacyclononane. Reprotection of one nitrogen gives 1,4-ditosyl-1,4,7-triazacyclononane. Sessler's method requires two steps to form the ditosyl derivative, whereas our procedure accomplished this in one step and provided slightly better overall yield. Sessler's method appears to offer an excellent approach to the monotosyl compound; however our method is superior for forming 1,4-ditosyl-1,4,7-triazacyclononane.

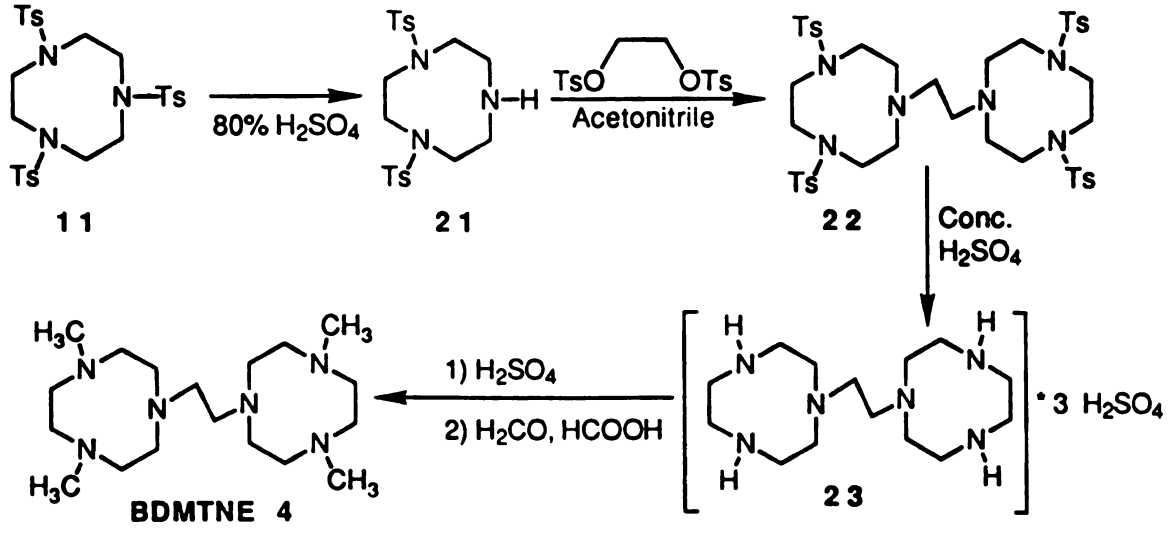
Final Synthesis of BDMTNE

Although we found the procedure used by Weighart to couple two ditosyltriazacyclononane molecules acceptable we were able to obtain better results with slightly different conditions. The product from selective detosylation of tritosyltriazacyclononane, still contaminated with tritosyltriazacyclononane, was used directly in the next step. Weighart used DMF as the solvent to react 1,4-ditosyl-1,4,7-triazacyclonanone with ethylene gylcol ditosylate and obtained a product still contaminated with 1,4,7-tritosyl-1,4,7-triazacyclononane. We found that if dry acetonitrile was used as the solvent in the precence of excess Na_2CO_3 the product precipitated out of solution as the reaction progressed to give a 77 % yield of 1,2-bis(4,7-ditosyl-1,4,7-

triazacyclononyl)ethane that was free from 1,4,7-tritosyl-1,4,7-triazacyclononane. We found this improvement gave a product that could be used without further purification, whereas Weighart's conditions gave a product that required recrystallization before further use.

The 1,2-bis(4,7-ditosyl-1,4,7-triazacyclononyl)ethane formed above was detosylated using standard sulfuric acid hydrolyses and the resulting sulfate salt was use directly in the Eschweiler-Clark Methylation procedure. The final product was purified by vacuum distillation and gave an 86 % yield over the last two steps.

In addition to ethylene glycol ditosylate we also attempted to use chloroacetylchloride to couple two 1,4-ditosyl-1,4,7-triazacyclononane molecules. Reaction of 4,7-ditosyl-1,4,7-triazacyclononane with chloroacetyl chloride gave an 86 % yield of what appeared to be 1,2-bis(4,7-ditosyl-1,4,7-triazacyclononyl)ethanone. Reduction to the ethane group was accomplished by either $LiAlH_4$ or borane. This method however gave substanially lower yield and poorer purity than obtained when the 1,4-ditosyl-1,4,7-triazacyclononane was coupled using ethylene gylcol ditosylate.



1,2-Bis(4,7-dimethyl-
1,4,7-triazacyclononyl)ethane

Scheme 5-Final Synthesis of BDMTNE

As with our first target compound, a pure sample of the 1,2-di(4,7-dimethyl-1,4,7-triazacyclononyl)ethane was given to the Dye group to use as a lithium complexant. While it did appear to complex with lithium to some degree, the qualitative opinion was that it was a poorer complexant than several cyclens already available.

Conclusion:

Our work on the synthesis of the chosen target compounds led to several significant contributions to the methodology used to synthesize polyazamacrocyclic compounds. We successfully synthesized 4,7-dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane (DMPATCY) and 1,2-bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane (BDMTNE) as well as several novel intermediates. We improved the Richman-Atkins synthesis by using a partial equivalent of *tert*-butanol as a phase transfer reagent permitting us to use only a slight excess of a cheap base, NaH, in the cyclization step, while still completing that step in less than a day. We developed a new method for generating partially protected TACN. By controlling the time, temperature, and concentration of the sulfuric acid we were able to selective remove one, two, or all three tosyl groups from 1,4,7-tritosyl-1,4,7-triazacyclononane. This provided a route to non-symmetrical triazacyclononanes that was shorter and gave better yields than previous methods. While our work was limited to triazacyclononane derivatives it is possible that the selective detosylation methodology developed in our work might also have applications with other cyclens. An investigation of this possiblity would be an obvious continuation of this work.

EXPERIMENTAL

General

All solvents used were obtained from commercial suppliers and were used with no further purification except as noted otherwise. Ethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from sodium benzophenone ketyl. Dimethylformamide (DMF) was dried by vacuum distillation from Brockman activity 1 neutral alumina onto 4 Å molecular sieves, or it was obtained in dry form from the Aldrich Chemical Corporation. Pentane was dried by passage through a column of Brockman activity 1 neutral alumina. Methanol was dried by distillation under an argon atmosphere from CaH_2 onto 4 Å molecular sieves. Dimethylethylamine (DMEA), and triethylamine (TEA) were purified by distillation under an argon atmosphere from $LiAlH_4$ onto 4 Å molecular sieves. Sieves were activated by heating the sieves under a vacuum (150°, 0.1 mmHg). Infra red information was obtained on a Nicolet FT-IR spectrometer with an IR/42 optical bench. Gas chromatography information was obtained on a Hewlett-Packard 5880A series gas chromatograph with a flame ionization detector and an Anspec restek 30 meter capillary column RT-1, with an inside diameter of 0.32 mm and a 0.25 mm film thickness. Gas chromatography-mass spectra were obtained on a V. G. Trio-1 benchtop GC-MS using a Hewlett-Packard 5890 series II gas chromatography with an Anspec restek 30 meter capillary column RT-1, with an inside diameter of 0.32 mm and a 0.25 mm film thickness. Low resolution mass spectra were obtained on either a V. G. Trio-1 bench top GC-MS or on a Jeol JMS-HX110 mass spectrometer using FAB. High resolution mass spectra were obtained

on a Jeol JMS-HX110 mass spectrometer using FAB. ^{1}H-nmr were performed on a Varian Gemini (300 MHz), Varian VXR-300 (300 MHz), Varian VXR-500 (500 MHz), or a Bruker 250 (250 MHz) instrument. ^{13}C-nmr were performed on a Varian Gemini (75 MHz) or a Varian VXR-300 (75 MHz). All ^{1}H-nmr in $CDCl_3$ were referenced to tetramethylsilane (0.0 ppm) or residual $CHCl_3$ (7.24 ppm) as an internal standard. ^{1}H-nmr in all other solvents were referenced to the solvent peak. The following abbreviations are used for describing ^{1}H-nmr data; S - singlet, D - doublet, T- triplet, M - multiplet, OM - overlapping multiplet, O-overlapping, OB-overlapping broad, BS-broad singlet. Melting point ranges were obtained on a Hoover-Thomas melting point apparatus in glass capillary pipettes and are uncorrected. All reactions sensitive to water or oxygen were run in glassware that had been oven (110°) dried for 24 hours or was flame dried under argon directly before use. The reactions were then run under argon.

N,N'-ditosylethylenediamine (7) O,O',N-tritosyldiethanolamine (9) and O, O', N-trimesyldiethanolamine (8) were obtained by procedures described by Lehn[4].

4,7-Ditosyl-1-mesyl-1,4,7-triazacyclononane (10) To a solution of N,N'-ditosylethylenediamine7 (36.8 g, 100 mmol) in dry DMF (1200 mL) was added sodium hydride (9.60 g, 240 mmol, 60% dispersion in oil) and a catalytic amount of *tert*-butyl alcohol (3.80 mL, 50 mmol). The mixture was then heated to 110° for 2 h and O,O', N-trimesyldiethanolamine 8 (33.9 g, 100 mmol) dissolved in dry DMF (400 mL) was added dropwise to the mixture. After reacting for 1 h at 110°

the solution was allowed to cool to room temperature and it was poured into ice water (4 L). The solid was collected and recrystallized from chloroform to give fine white square crystals (26.5 g, 51 %) ^{1}H-NMR ($CDCl_3$, 300 MHz) d 2.41 (S, 6 H), d 2.95 (S, 3 H), d 3.37 (BS, 8 H), d 3.58 (OM, 4 H), d 7.31 (D, 2 H, J= 8.3 Hz), d 7.65 (D, 2 H, J= 8.3 Hz), impurity peak d 1.59. ^{13}C-NMR ($CDCl_3$) d 21.52, 37.76, 50.74, 52.07, 52.50, 127.38, 129.93, 134.31, 144.05

1,4,7-Tritosyl-1,4,7-triazacyclononane (11) To a solution of N,N'-ditosylethylenediamine 7 (51.0 g, 138 mmol) and *tert*-butyl alcohol (1.2 mL, 16 mmol) in dry DMF (1200 mL) was added NaH (12.1 g, 60% dispersion in oil, 303 mmol). The mixture was heated to 110° and maintained at this temperature throughout the reaction. After reaching 110° the solution was stirred for 20 minutes and then a solution of O,O',N-tritosyldiethanolamine 9 (78.6 g, 138 mmol) in dry DMF (200mL) was added dropwise over 1 h with stirring. The solution was heated and stirred for an additional 2 h after the addition was completed. Water was slowly added to the hot DMF solution until a white solid began to form. The mixture was then allowed to cool to room temperature and additional water (total amount of water 4 L) was added. The solid was collected, washed with water, and recrystallized from ethanol/chloroform to give 41.6 grams (51 %) of a white solid; m. p. 216.2-217.8° ^{1}H-NMR ($CDCl_3$), d 2.41 (S, 9 H), d 3.40 (S, 12 H), d 7.30 (D, 6 H, J=8.5 Hz), d 7.68 (D, 6 H, J=8.3 Hz), ^{13}C-NMR ($CDCl_3$), d 21.50, 51.82, 127.46, 129.84, 134.54, 143.86.

4,7-Dimethyl-1-mesyl-1,4,7-triazacyclononane (14) A solution of 4,7-ditosyl-1-mesyl-1,4,7-triazacyclononane **10** (58.6 g, 114 mmol) in concentrated sulfuric acid (290 mL) was heated to 110° for 28 h. The solution was cooled to room temperature and ether was slowly added with stirring. The resulting off white solid (the hydrosulfate salt of **12**) was collected and immediately dissolved in formic acid (151 mL, 88 %, 2.89 mol) and formaldehyde (209 mL, 37 %, 2.58 mol). This solution was heated to 95° for 1 h. The solution was cooled to room temperature, aqueous HCl (60 mL, 6 N) was added and it was then stirred for 1 h. Aqueous KOH (30 %) was added until a pH > 14 was reached. The alkaline solution was extracted with chloroform (3 x 250 mL), the extracts were combined, dried with sodium sulfate , and the solvent was removed under reduced pressure to give 19.1 grams (71 %) of a slightly brown oil which crystallized readily upon addition of a seed crystal. ^{1}H-NMR ($CDCl_3$), d 2.36 (S, 6 H), d 2.61 (S, 4 H), d 2.74 (S, 3 H), d 2.82 (OM, 4 H), d 3.29 (OM, 4 H)

1-Tosyl-1,4,7-triazacyclononane (13) A solution of 1,4,7-Tritosyl-1,4,7-triazacyclononane **11** (0.125g, 0.211 mmol) in 80% H_2SO_4 (1mL) was heated to 72° with stirring. Concentrated H_2SO_4 was added dropwise until a solution was obtained. Heating and stirring was then continued for 6 days. The solution was diluted with water (15 mL), and aqueous KOH (30 %) was added slowly until a pH > 14 was reached. The solution was allowed to cool, filtered, and extracted with chloroform (3 x 15mL). The chloroform extracts were combined, dried with Na_2SO_4, and the solvent was removed under reduced pressure to give 0.60 g (60 %) of a white solid. The solid was used with no further purification.

^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.10 (BS, 2 H), d 2.39 (S, 3 H), d 2.87 (S, 4 H), d 3.06 (OM, 2H), d 3.15 (OM, 2H), d 7.28 (D, 2 H, J=9.1 Hz), d 7.65 (D, 2 H, J=9.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), d 21.47, 48.98, 49.31, 53.85, 127.19, 129.68, 135.28, 143.38

4,7-Dimethyl-1-tosyl-1,4,7-triazacyclononane (15) A solution of the 1-Tosyl-1,4,7-triazacyclononane **13** (1.0 g, 3.5 mmol), formic acid (88 %, 15.0 mL, 286 mmol), and formaldehyde (37 %, 15.0 mL, 185 mmol) was heated to 109° for 18 h. To the solution was added HCl (20 mL, 1.0 N) and it was stirred for an additional 2 h. Aqueous KOH (30 %) was then added until a pH > 14 was reached. The basic solution was then extracted with chloroform (3 x 50 mL), the extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give 1.1 grams (-100 %) of a light brown clear oil. This oil was used in the next reaction with no further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.36 (S, 6 H), d 2.39 (S, 3 H), d 2.66 (S, 4 H), d 2.87 (M, 4 H), d 3.22 (M, 4 H), d 7.26 (D, 2 H, J= 8.4 Hz), d 7.64 (D, 2 H, J= 8.4 Hz), impurity peaks d 1.18, 3.38, 3.65, 4.75 (M), d 5.13 (S)

1,4-Dimethyl-1,4,7-triazacyclononane (6) a)To a stirred solution of 4,7-Dimethyl-1-mesyl-1,4,7-triazacyclononane **14** (14.7 g, 63 mmol) in fresh toluene (125 mL)was added dropwise Red-Al (100 mL, 2 M) in toluene, followed by additional toluene (20 mL). The mixture was heated to 113.0° for 18 h. After cooling the reaction was quenched by the slow addition of H_2O (65 mL) followed by addition of KOH (9.0 g, 0.16 mol). The solution was poured into benzene (400 mL) and the benzene solution was filtered through Celite (50 g). The Celite was then

washed with additional hot benzene (500 mL). The benzene solutions were combined and the solvent was removed under reduced pressure to give a brown clear oil. The oil was dissolved in 10% HCl (100 mL), washed with ether (3 x 25 mL) and aqueous KOH was then added until a pH >14.0 was reached. The alkaline solution was extracted with chloroform (3 x 50 mL), the extracts were combined, dried with Na_2SO_4, and the solvent was removed under reduced pressure to give -10 grams of a brownish oil. The oil was vacuum distilled at 83-86° / 1 mmHg to give 6.73 grams (68% yield) of a clear oil, ^{1}H-NMR ($CDCL_3$), d 2.37 (S, 6 H), d 2.49 (OM, 8 H), d 2.63 (OM, 4 H), d 2.72 (B, 1 H). ^{13}C-NMR ($CDCL_3$), d 45.51, 46.33, 53.56, 54.49

b)A solution of 4,7-Dimethyl-1-tosyl-1,4,7-triazacyclononane **15** (1.12 g, 3.6 mmol) in concentrated H_2SO_4 (25 mL) was heated to 109° for 18 h. The solution was cooled to 0° and ether (200mL) was slowly added to precipitate a black solid. The solid was collected, dissolved in water and KOH was added until a pH > 14 was reached. The basic solution was extracted with chloroform (3 x 50mL), the extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. The residue was vacuum distilled to give 0.45 grams (80 % over last two steps) of a clear oil. The ^{1}H-NMR spectra of this oil was identical to the spectra of 1,4-Dimethyl-1,4,7-triazacyclononane made by procedure (a).

c)Procedure (a) was repeated except the extraction solvent was changed to methylene chloride. The extracts were combined, dried over Na_2SO_4 for 24 h and then removed under reduced pressure. The resulting light

brown oil decomposed to a dark brown wet solid on attempts to vacuum distill it. There was no distillate.

d)To a solution of KOH in *tert*-butanol was added 4,7-dimethyl-1-mesyl-1,4,7-triazacyclononane **14**, the mixture was then refluxed for 20 h. The mixture was then diluted with water and extracted with ether. The extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give a white solid. ^{1}H-nmr spectra of the white solid was identical to the starting material.

4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane (16)

To a solution of 1,4-Dimethyl-1,4,7-triazacyclononane (DMTCY) **6** (4.23 g, 27 mmol) in dry iso-propyl alcohol was added acrylonitrile (1.80 mL, 27 mmol). The solution was allowed to stir for 4 h in the dark at rt. The solvent was removed under reduced pressure and the residue was vacuum distilled (0.04 mmHq, 50°) to give a clear oil (4.54 g, 22 mmol, 80%). ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.38 (S, 6 H), d 2.45 (T, 2 H, J=7.5 Hz), d 2.73 (OM, 12 H), d 2.92 (T, 2 H, J=7.5 Hz), ^{13}C-NMR ($CDCl_3$), d 16.24, 46.52, 54.17, 55.55, 56.67, 56.78, 56.95 impurity peak d 119.14 Mass Spec. m/e (relative. intensity), 211 m+1 (3.2), 140 m-70 (82.2), 58 m-152 (100)

4,7-Dimethyl-1-(3-aminopropyl)-1,4,7-triazacyclononane (17)

Method A

1) To a solution of 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane **16** (0.345 g, 1.6 mmol) in dry *iso*-propanol (5 mL) was added wet Raney Ni (0.37 g) that had been activated the previous

day. The solution was heated to 70° and hydrazine hydrate (2 mL) was added dropwise at a rate that maintained a reflux. The mixture was filtered and the solvent removed under reduced pressure to give 0.35 g (-100%, crude yield) of a slightly pruple clear oil. ^{1}H-nmr ($CDCL_3$, 300 MHz), d 1.61 (M, 2 H), d 2.37 (S, 6 H), d 2.55 (OM, 2 H), d 2.68 (BS, 8 H), d 2.74 (OM, 6 H) unidentified peaks d 0.91 (M), d 1.32 (B), d 2.24, 2.41 (S).

2) The following changes were made to procedure 1. The raney Ni used had been prepared 1 month before it's use, instead of being activated the day before use. It had been stored under absolute ethanol at 3°. This attempt yielded 0.35 grams of a clear purple oil. The ^{1}H-nmr of the oil was similar to the starting nitrile. ^{1}H-nmr (CDCL3, 300 MHz), d 2.38 (S, 6 H), d 2.45 (T, 2 H), d 2.73 (OM, 12 H), d 2.90 (T, 2 H), unidentified peaks d 2.39 (S), d 2.50 (OM).

3) The following changes were made to procedure 1. A fresh batch of Raney Ni was prepared. This attempt gave 0.35 g of a clear purple oil with ^{1}H-nmr similar to the starting material. ^{1}H-nmr (CDCL3, 300MHz), d 2.37 (S, 6 H), d 2.45 (T, 2H), d 2.73 (OM, 12 H), d 2.90 (T, 2 H) unidentified peaks d 1.19 (O), d 2.40, 3.39 (S), d 2.51 (O).

4) The following changes were made to procedure 1. The Raney Ni used was obtained from Aldrich Chemical Company in active form. This attempt gave 0.30 g of a light brown clear oil. ^{1}H-nmr (CDCL3, 300 MHz), d 1.57 (M, 2 H), d 1.90 (B, 2 H), d 2.33 (s, 6 H), d 2.55 (OM, 2 H), d 2.63 (BS, 8 H), d 2.70 (OM, 6 H) unidentified peaks d 1.40, 2.20, 2.38,

2.48 (S). G. C. data, retention time (area %), 8.35 (30), 8.62 (13), 14.17 (47), 17.34 (10). G.C. mass spec. peak 14.17 m/e (relative int.), 215 M+1 (1), 158 m-56 (10), 144 m-70 (35), 113 m-101 (56), 101 m-113 (88), 58 m-156 (100).

Method B

1) To a cooled (-0°) solution of $LiAlH_4$ (40 mL, 1.0 M) in ether was added a solution of 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane **16** (1.07 g, 5 mmol) in ether (6 mL). The mixture was allowed to react for 30 min. The reaction was then quenched by addition of aqueous KOH (2 mL, 30%). The ether was decanted and the residue was washed with additional ether (3 x 30 mL). The ether fractions were combined, dried with Na_2SO_4, and the solvent was removed under reduced pressure to give a clear colorless oil. This oil was used with no further purification in the next step. G. C. data, retention time (area %), 8.56 (5), 14.47 (94), 13.11, 15.13, 15.47 (-1)

2) The following changes were made to procedure 1. To a solution of 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane (0.53 g, 2.5 mmol) in dry ether (50 mL) was added solid $LiAlH_4$ (0.5 g, 13.0 mmol) at room temperature. This procedure gave 0.5 g of a cloudy oil. G. C. data. retention time (area %), 8.51 (47), 14.16 (49), 14.89 (3).

3) The following changes were made to procedure 1. To a solution of 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane **16** (0.53 g, 2.5 mmol) in dry ether (50 mL) was added solid $LiAlH_4$ (0.5 g, 13.0 mmol)

at 0°C. This procedure gave 0.5 g of a cloudy oil. G. C. data. retention time (area %), 8.35 (9), 8.78 (18), 13.95 (69).

4) The following changes were made to procedure 1. Solid $LiAlH_4$ (0.5 g, 13.0 mmol) was refluxed in dry ether (50mL) for 24 hours to dissolve the $LiAlH_4$. This mixture was cooled to 0°and a solution of 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane **16** (0.53 g, 2.5 mmol) in dry ether (5 mL) was added dropwise with cooling. This procedure gave 0.5 g of a cloudy oil. G. C. data. retention time (area %), 8.34 (27), 14.33 (73).

A sample of the 4,7-Dimethyl-1-(3-aminopropyl)-1,4,7-triazacyclononane **17** was further purified by vacuum distillation, 100°, 1 mmHg. ^{1}H-NMR ($CDCl_3$, 300 MHz), d 1.58 (M, 2 H), d 1.90 (Br, 2 H), d 2.33 (S, 6 H), d 2.51 (OM, 2 H), d 2.63 (S, 8 H), d 2.72 (OM, 6 H), unidentified peaks d 1.20, 2.20, and, 2.38. Mass spec. m/e (relative intensity), 215 m+1 (1), 184 m-30 (1), 170 m-44 (8), 101 m-113 (88), 58 m-156 (100).

4,7-Dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triaza-cyclononane (5) a)A solution of 4,7-Dimethyl-1-(3-aminopropyl)-1,4,7-triazacyclononane **17** (0.40 g, 1.9 mmol) in formaldehyde (4 mL, 37 %, 49.3 mmol) , and formic acid (6 mL, 88 %, 114.8 mmol) was heated to 110° for 18 hours. The solution was cooled to room temperature, HCl (10 %, 5 mL) was then added and the resulting solution was stirred for 4 hours. The acidic solution was washed with ether (25 mL) and then aqueous KOH (30 %) was added until a pH > 14 was reached. The basic solution

was extracted with chloroform (3 x 75 mL), the extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give 0.43 grams (93.5 % yield) of a light brown clear oil. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 1.60 (M, 6.6), d 2.18 (S, 18.2), d 2.20 (S, 22.4), d 2.22 (S, 12.6), d 2.35 (OM, 24.5), d 2.45 (OM, 15.1), d 2.70 (OM, 19.1). G. C. data, retention time (area %), 8.38 (16), 8.61 (8), 14.07 (65), 14.34 (7), 3.47, 13.73, 14.46 (-4). G. C. mass spec. of peak 14.07 m/e (relative intensity), 242 m (1), 225 m-17 (1), 211 m-31 (1), 198 m-44 (2), 127 m-115 (8), 115 m-127 (6), 101 m-141 (35), 84 m-158 (22), 58 m-184 (100)

b) To a solution of the crude 4,7-Dimethyl-1-(3-aminopropyl)-1,4,7-triazacyclononane **17** (1.07 g, 5.1 mmol) in acetonitrile (40 mL) was added formaldehyde (37 %, 5.0 mL, 62 mmol) and $NaBH_3CN$ (1.0 g, 16 mmol). The mixture was then stirred for 18 h. Glacial Acetic acid was slowly added to the solution until a pH - 7.0 was reached. The solution was then stirred for 1 h with additional acetic acid periodically added to maintain a pH - 7.0. The solvent was removed under reduced pressure and the residue was dissolved in aqueous KOH (2 N, 40 mL). The basic solution was extracted with ether (4 x 25 mL), the extracts were combined, dried with Na_2SO_4, and the solvent was then removed under reduced pressure to give 1.09 g of a clear light brown oil. The oil was purified by vacuum distillation at 65°, 0.04 mmHg to give 0.78 g (63 % over the last two steps) of a clear oil. ^{1}H-NMR ($CDCl_3$, 300 MHz), d 1.57 (M, 2 H), d 2.17 (S, 6 H), d 2.23 (M, 2 H), d 2.32 (S, 6 H), d 2.46 (M, 2 H), d 2.63 (OM, 8 H), d 2.69 (S, 4 H). ^{13}C-NMR ($CDCl_3$, 75 MHz), 26.35, 45.58, 46.76, 56.30, 56.96, 57.27, 57.54, 58.02. HRMS M+1, calculated for $C_{13}H_{31}N_4$ 243.2542, found 243.2550.

(4,7-Dimethyl-1,4,7-triazacyclononyl)acetic acid (18) To a solution of 1,4-dimethyl-1,4,7-triazacyclononane DMTCY **6** (1.05g, 6.69mmol) in water (3ml) was added aqueous NaOH (2.1 mL, 3.5 M). The solution was then cooled to 0° and chloroacetic acid (0.70 g, 7.4mmol) dissolved in water (1.5 mL) was added dropwise with stirring. The mixture was allowed to warm to room temperature while stirring for 3 hours. The solvent was taken off under reduced pressure and the residue dissolved in methylene chloride. The methylene chloride was dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure to give 0.80 grams (55.6 % yield) of a very viscous brown oil. The oil was used as is with no other purification. ^{1}H-nmr (D2O), d 2.40 (S, 6 H), d 2.56 (M, 8 H), d 2.73 (S, 4 H), d 3.05 (S, 2 H).

Methyl (4,7-Dimethyl-1,4,7-triazacyclononyl)acetate (19) Dry HBr gas was passed over a solution of 4,7-Dimethyl-1,4,7-triaza-cyclononane-1-acetic acid **18** (0.28 g, 1.3 mmol) in dry methanol (8 mL) for 5 minutes. The solution was then allowed to stir at room temperature for 4 hours. Dry ether was added to the solution to precipitate an off white solid. The solid was collected and washed with ether (3 x 4 mL), the product was dried in a vacuum dessicator. The free base was obtained by shaking the sample with aqueous carbonate and extracting with ether.

1,2-bis(1,4-dimethyl-1,4,7-triazacyclononane)ethanone (20)

Method 1 (dicyclohexylcarbodiimide and N-hydroxysuccinimide coupling)

a) A solution of N-hydroxysuccinimide (0.07 g, 0.6 mmol) and 1,3-dicyclohexylcarbodiimide (0.13 g, 0.6 mmol) in dry DMF (2 mL) was added to 1,4-dimethyl-1,4,7-triazacyclononane-N"-acetic acid **18** (0.11 g, 0.5 mmol). The solution was stirred at room temperature for 24 hours and the liquid was decanted away from the solid. The liquid portion was added to 1,4-dimethyl-1,4,7-triazacyclononane DMTCY **6** (0.23 g, 1.3 mmol), and the mixture was allowed to stir for 24 hours. The solid was collected and the remaining DMF/H2O solution was then diluted with water (50 mL). To the aqueous solution was added HCl (1 M, 20 mL). The solution was extracted with ether (3 x 50 mL). The ether extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. H-nmr ($CDCl_3$), d 0.7-2.0 (many broad and overlapping peaks), d 2.68, 2.86, 2.92, 4.05 (S), d 3.1-3.7 (broad overlapping peaks), d 4.29 (T), d 7.2-7.8 (OM). To the acidic solution was then added KOH until a pH > 14 was reached. The basic solution was extracted with chloroform (3 x 50 mL), the chloroform extracts were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure. ^{1}H-nmr ($CDCl_3$, 250 MHz), d 2.57 (S), d 2.73 (S), d 1.0-2.5 (small overlapping peaks).

b) To a solution of 1,3-dicyclohexylcarbodiimide (0.5 g, 2.4 mmol) and 1,4'-dimethyl-1,4,7-triazacyclononane DMTCY **6** (0.36 g, 2.3 mmol) in methylene chloride (-5 mL) was added a solution of the 1,4-dimethyl-1,4,7-triazacyclononane acetic acid in methylene chloride (5 mL). The solution was allowed to stir for 18 hours at room temperature. Three drops of glacial acetic acid was added to the solution and it was stirred for

one hour. The methylene chloride solution was then extracted with HCl (1 N, 3 x 10 mL). Aqueous KOH (30 %) was then added to the combined acidic extracts until a pH > 12.5 was reached. The solution was then extracted with $CDCl_3$ (5 mL). The chloroform was dried with Na_2SO_4, filtered and tested by ^{1}H-nmr. The ^{1}H-nmr ($CDCl_3$, 250 MHz) contained many unidentifiable peaks.

c) A solution of chloroacetic acid (0.34 g, 3.6 mmol) and DCC (0.74 g, 3.6 mmol) in methylene chloride (5 mL) was added dropwise to a solution of 1,4-dimethyl-1,4,7-triazacyclononane **6** (0.282 g, 1.8 mmol) in methylene chloride (10 mL) at room temperature. The mixture was allowed to stir for 12 hours. The solution was filtered and the solvent was removed under reduced pressure. The residue was dissolved in chloroform, it was washed with equal portions of saturated aqueous Na_2CO_3, and water. The chloroform solution was dried with Na_2SO_4, and the solvent was removed under reduced pressure. ^{1}H-nmr ($CDCl_3$, 250 MHz), contained many unidentifiable peaks.

d) To a solution of N-hydroxysuccinimide (0.165 g, 1.4 mmol) and DCC (0.295 g, 1.43 mmol) in dry DMF (4 mL) was added a solution of 1,4-dimethyl-1,4,7-triazacyclononane acetic acid **18** (0.28 g, 1.3 mmol) in dry DMF (4 mL). The mixture was allowed to stir for 24 hours. The liquid was decanted from the solid and the liquid was added to a solution of the 1,4-dimethyl-1,4,7-triazacyclononane **6** (0.68 g, 1.3 mmol) in water (12 mL). The mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water (20 mL) and was extracted with chloroform (3 x 5 mL). The chloroform extracts were combined, dried

with Na_2SO_4, and the solvent removed under reduced pressure. ^{1}H-nmr ($CDCl_3$, 250 MHz) contained many unidentifiable peaks. Aqueous KOH (30 %) was then added to the aqueous solution until a pH > 14 was reached. The basic solution was extracted with chloroform (3 x 10 mL), the extracts were combined, dried with Na_2SO_4, and the solvent was removed under reduced pressure. ^{1}H-nmr ($CDCl_3$), The ^{1}H-nmr contained many unidentifiable

Method 2 (Coupling using an acid chloride) To a solution of the 1,4-dimethyl-1,4,7-triazacyclononane **6** (0.25 g, 1.6 mmol) in methylene chloride (3 mL) was added chloroacetyl chloride (0.09 g, 0.8 mmol) dropwise with stirring. The mixture was allowed to stir at room temperature for 6 hours and then filtered. The methylene chloride solution was washed with saturated aqueous Na_2CO_3, dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. The ^{1}H-nmr contained many unidentifiable peaks.

Method 3 (coupling of methyl ester) The hydrobromic acid salt of methyl 4,7-dimethyltriazacyclononylacetate **19** (0.35 g, 1.1 mmol), 1,4-dimethyl-1,4,7-triazacyclononane **6** (0.22 g, 1.4 mmol) and methanol (1mL) was placed in a pressure tube. The pressure tube was then sealed and heated to 100^o for 18 hours there was coloration of the solution but ^{1}H-nmr showed only starting materials. The tube was then heated for an additional 7 days. ^{1}H-nmr of the recovered material was identical to the starting mixture.

1,4-Ditosyl-1,4,7-triazacyclononane (20) A suspension of 1,4,7-tritosyl-1,4,7-triazacyclononane **11** (1.25 g, 2.11 mmol) in 80% H_2SO_4 (10 mL) was heated to 60° with stirring. When necessary, concentrated H_2SO_4 was added dropwise until all the solid dissolved, heating was then continued with stirring for an additional 3 days. The solution was poured into 150 mL of cold H_2O and stirred for 1 h. Aqueous KOH (30 %) was slowly added until a pH > 14 was reached, the solution was cooled to rt. The precipitate was collected, washed with cold H_2O (20 mL), and then washed with chloroform (2 x 20 mL). The chloroform washes were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give 0.88 grams of a white solid. ^{1}H-NMR of the solid showed it to be 91.7% ditosyl (88 % yield) and 8.3% tritosyl, this purity was sufficient for our purposes.

A higher purity sample of the ditosyl compound was obtained by filtering the diluted acid solution before adding the base. Recrystallization (CH_2Cl_2/ethanol 1:9) of the solid obtained on workup provided a small sample of pure 1,4-Ditosyl-1,4,7-triazacyclononane **20.** Work up of the filtrate gave a mixture of tritosyl **11** and ditosyl triazacyclononane **20**. Combination of the pure sample and the mixture gave an overall yield comparable to the above procedure. m. p. 223.0-224.2° (lit[70]. mp195-197°, lit[71]. mp 217-218°); ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.41 (S, 6 H), d 3.17 (BS, 8 H), d 3.42 (S, 4 H), d 7.30 (D, 2 H, J= 8.1 Hz), d 7.65 (D, 2 H, J= 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), d 21.50, 48.74, 53.06, 53.25, 127.21, 129.84, 134.84, 143.75. HRMS M+1, calculated for $C_{20}H_{28}O_4N_3S_2$ 438.1515, found 438.1544.

1,2-Bis(4,7-ditosyl-1,4,7-triazacyclononyl)ethane (22) a) A solution of crude 1,4-Ditosyl-1,4,7-triazacyclononane **21** (2.0 g, 4.3 mmol) and ethylene glycol ditosylate (0.80 g, 2.2 mmol) in dry acetonitrile (25 mL) was heated to reflux for 30 min. Na_2CO_3 (2 g, 18.9 mmol) was then added to the solution and the mixture refluxed for 48 h with brisk stirring. The solution was cooled 3° and the solid was collected. The solid was washed with chloroform (2 x 50 mL). The washes were combined, dried with Na_2SO_4, and the solvent removed under reduced pressure to give 1.5 grams (77 %) of a foamy white solid. mp 228-229°(lit.[71] mp 220-222°); ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.40 (S, 12 H), d 2.71 (BS), d 2.91 (BS), d 3.17 (BS), d 3.49 (BS), d 7.28 (D, 2 H, J= 8.2 Hz), d 7.64 (D, 2 H, J= 8.2 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz), d 21.48, 51.17 (B), 52.53, 55.55, 55.60, 127.15, 129.77, 135.13, 143.46. HRMS M+1, calculated for $C_{42}H_{57}O_8N_6S_4$ 901.3108, found 901.3151.

b) A solution of 1,4-ditosyl-1,4,7-triazacyclononane **21** (1.21 g, 2.8 mmol) and ditosylethylene glycol (0.48 g, 1.3 mmol) in dry DMF (5 mL) was heated to 110° for one hour. Na_2CO_3 (0.33 g, 3.1 mmol) was added to the solution and the mixture was then heated to 120° for 18 hours. The solvent was then removed under reduced pressure and the residue was suspended in hot ethanol (25 mL). The hot ethanol suspension was then poured into ice water (100 mL) and the solid was collected. The solid was refluxed with ethanol (175 mL) and the hot ethanol solvent was decanted from the remaining solid. The solid was dried to give 0.40 grams (32 %) of a light brown solid. m. p. 239-240°. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 2.42, 2.44 (OS, 28.1), d 2.75-2.95 (B, 6.2), d 2.95-3.33 (B, 15.5), d 3.33-3.35 (B, 15.6), d 3.42 (S, 5.7), d 3.46 (S, 15.6), d 7.31 (O, 19.0), d 7.66

(O, 19.0). ^{13}C-nmr ($CDCl_3$, 75 MHz), d 21.49, 52.51, 127.17, 127.48, 129.81, 129.97, 135.06, 143.55. The ethanol solution was concentrated under reduced pressure (50 mL) and the solution was allowed to cool (0°) and 0.10 grams (8 %) of a brown solid was collected. m. p. 229-231° The remaining ethanol was removed under reduced pressure to give 0.48 grams (39 %) of a foamy light brown solid. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 2.41, 2.43 (OS, 16.5), d 2.9 (OM, 6.0), d 3.1-3.5 (OM, 26.3), d 7.30 (OM, 10.9), d 7.65 (10.8)

c)To a solution of the crude bis (1,4-ditosyl-1,4,7-triazacyclononane) acetate **20** (0.90 g, 1.0 mmol) in dry THF was added $LiAlH_4$ (1.0 g, 26.3 mmol) at room temperature. The reaction mixture was allowed to stir for 30 minutes after the bubbling ceased. Cold aqueous KOH (30 %) was added dropwise to quench the reaction. The THF was separated from the aqueous layer, the aqueous layer was then washed with THF (2 x 15 mL). The THF fractions were combined and removed under reduced pressure to give 0.30 grams of a white solid. m. p. 90-100° ^{1}H-nmr ($CDCl_3$, 300 MHz), d 1.58 (B), d 2.39, 2.41 (OS), d 2.70 (S), d 2.91 (B), d 3.15 (B), d 3.40 (S), d 3.46, 3.48 (OS)

d) A solution of the crude bis (1,4-ditosyl-1,4,7-triazacyclononane) acetate **20** (0.50 g, 0.55 mmol) in dry THF (30 mL) was added dropwise (30 minutes) to a solution of borane in THF (3.63 mL, 0.17 M, 0.62 mmol) that had been cooled to 0°. The mixture was then allowed to warm to room temperature and was stirred for 2 hours. The reaction was quenched by the dropwise addition of aqueous HCl (10 %, 1 mL), followed by the addition of aqueous KOH (2 mL). The THF was separated

from the aqueous solution, the aqueous solution was then washed with THF (2 x 20 mL). The THF fractions were combined and the solvent removed under reduced pressure to give 0.41 grams (82 %) of a foamy white solid. ^{1}H-nmr ($CDCl_3$, 300 MHz), d 2.41 (O, 37.1), d 2.95-3.90 (OB, 70.7), d 7.28 (M, 24.2), d 7.65 (M, 24.0).

1,2-Bis(1,4,7-triazacyclononyl)ethane trihydrosulfate (23) A solution of the 1,2-Bis(4,7-ditosyl-1,4,7-triazacyclononyl)ethane **22** (1.0 g, 1.1 mmol) in concentrated H_2SO_4 (10 mL) was heated to 100° for 24 h. The acidic solution was cooled to rt and ether (100 mL) was slowly added to it with stirring to give a sticky white solid. This solid was used with no further purification in the next reaction. A sample (0.5 mL) of the concentrated acidic solution was removed before work-up and was diluted with H_2O (4 mL). Aqueous KOH (30 %) was added to this sample until a pH > 14 was reached and then it was extracted with $CDCl_3$ (4 mL). The $CDCl_3$ was dried with Na_2SO_4 and filtered and then analyzed by NMR. ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.57 (M, 8 H), d 2.66 (S, 4 H), d 2.73 (OM, 16 H), d 1.84-1.98 (B). ^{13}C-NMR ($CDCl_3$, 75 MHz), d 45.66, 46.03, 52.53, 55.87

1,2-Bis(4,7-dimethyl-1,4,7-triazacyclononyl)ethane (4) a) A solution of the **23** (0.64 g, 1.1 mmol) in formic acid (88 %, 15.0 mL, 287 mmol) and formaldehyde (37 %, 15.0 mL, 185 mmol) was heated to 100° for 24 h. The solution was cooled to rt, HCl (1N, 20 mL) was added and it was stirred for 1 h. Aqueous KOH (30 %) was added to the solution until a pH > 14 was reached and the alkaline solution was then extracted with chloroform (3 x 30 mL). The extracts were combined,

dried with $MgSO_4$, and the solvent was removed under reduced pressure to give 0.45 g of clear brownish oil. The oil was vacuum distilled at 130°-134°/0.04 mmHg to give 0.32 g (86 % over the last two steps) of a clear oil ^{1}H-NMR ($CDCl_3$, 300 MHz), d 2.34 (S, 12 H), d 2.64 (OM, 12 H), d 2.70 (OM, 16 H). ^{13}C-NMR ($CDCl_3$, 75 MHz), d 46.73, 56.50, 56.87, 57.45, 57.56. HRMS M+1, calculated for $C_{18}H_{41}N_6$ 341.3384, found 341.3404.

b) 1,4,7-trimethyl-1,4,7-triazacyclononane (TriMTCY) **2** obtained from the Michigan State University Synthesis Laboratory was distilled from NaK alloy at 0.05 mmHg 50°-55° to give a clear oil. ^{1}H-nmr ($CDCl_3$), d 2.32 (S, 9 H), d 2.60 (S, 12 H). ^{13}C-nmr ($CDCl_3$) d 46.74, 56.98. A solution of *tert*-butyl lithium in pentane (0.65 M, 2.3 mL) was added to neat 1,4,7-trimethyl-1,4,7-triazacyclononane (TriMTCY) **2** (0.25 g, 1.5 mmol) that had been cooled to 0° with stirring. The solution was then allowed to warm to room temperature and finally heated to reflux for 5 minutes. The mixture was then a cooled to 0° and a saturated solution of iodide (50 mL) in pentane was then added. This was followed by the addition of iodided (0.2 g, 0.8 mmol). The mixture was then refluxed for 15 minutes. The pentane solution was then extracted with 1N HCl. The acidic extracts were combined, washed with ether (30 mL), and then aqueous KOH was added until a pH > 14 was reached. The aqueous solution was then extracted with chloroform (3 x 30 mL), the extracts were combined, dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure to give slightly brown oil that had a ^{1}H-nmr identical to the 1,4,7-trimethyl-1,4,7-triazacyclononane (TriMTCY) **2**.

c) To neat 1,4-dimethyl-1,4,7-triazacyclononane DMTCY **6** (0.15 g, 0.1 mmol) was added an aqueous solution of gyloxal (40 %, 0.2 mL, 1.4 mmol), formic acid (88 %, 0.1 mL, 1.9 mmol) and water (2 mL). The solution was heated to 102° for 23 hours. The aqueous solution was brought to a pH > 14 with the addition of aqueous KOH (30 %) and it was then extracted with $CDCl_3$ (5 mL). The chloroform was dried with Na_2SO_4. The ^1H-nmr contained many unidentifiable peaks.

APPENDIX A

Appendix A

Sample calculation for the precent yield of methanol and methanol dianion based on H-nmr data

Correction for different number of contributing protons

$$\frac{\text{Integrated area of the disodium p-terephthalate peak.}}{\text{Number of protons contributing to the peak.}} = \text{Corrected area for Reference peak}$$

$$0.51/4 = 0.1275$$

$$\frac{\text{Integrated area of the Proteomethanol peak}}{\text{Number of protons contributing to the peak.}} = \text{Corrected area for Proteomethanol peak}$$

$$0.37/3 = 0.1233$$

$$\frac{\text{Integrated area of the deuteromethanol}}{\text{Number of protons contributing to the peak.}} = \text{Corrected area for deuteromethanol peak}$$

$$0.05/2 = 0.025$$

Normalizing to the reference peak

Corrected peak areas / Corrected area for Reference peak

Reference	0.1275 / 0.1275 = 1.000
Proteomethanol	0.1233 / 0.1275 = 0.9670
Deuteromethanol	0.025 / 0.1275 = 0.196

Number of moles of deuteromethanol and proteomethanol in the sample

The reference solution contained 6.24×10^{-5} moles / ml. 0.5 ml of the reference is mixed with an equal amount of the reaction sample.

Proteomethanol	$3.12 \times 10^{-5} \times 0.9670 = 3.02 \times 10^{-5}$ moles
Deuteromethanol	$3.12 \times 10^{-5} \times 0.196 = 6.12 \times 10^{-6}$ moles

Appendix A
Continued

Total number of moles in the entire reaction sample.

The work-up from this reaction gave a total of 4.8 ml of D_2O solution.

Proteomethanol $3.02 \times 10^{-5} \times 9.6 = 2.90 \times 10^{-4}$

Deuteromethanol $6.12 \times 10^{-6} \times 9.6 = 5.86 \times 10^{-5}$ moles

Ratio of Proteomethanol : Deuteromethanol

$2.90 \times 10^{-4} / 5.86 \times 10^{-5} = 4.9 \sim 5 : 1$

Total % yield of methanol based on the amount of paraformaldehyde pyrolized

$$\frac{\text{Moles of proteomathanol + Moles of Deuteromethanol}}{\text{Moles of paraformaldehyde added to the pyrolysis chamber}} \times 100 = \% \text{ yield}$$

$$\frac{2.90 \times 10^{-4} + 5.86 \times 10^{-5}}{1.33 \times 10^{-3}} \times 100 = 26.2 \% \text{ yield}$$

APPENDIX B

Appendix B

Sample calculation to determine the composition of detosylated 1,4,7-tritosyl-1,4-7-triazacyclononane

By comparing the integrated areas of the ethylene protons the composition a mixture of 1,4,7-triazacyclononane could be determined.

Correction for the different number of contrbuting protons.

$$\frac{\text{Integrated area of the tritosyl species}}{\text{Number hydrogens contributing to the peak}} = \text{Correct integrated area for the tritosyl species}$$

$$1.8 / 12 = 0.15$$

$$\frac{\text{Integrated area of the ditosyl species}}{\text{Number hydrogens contributing to the peak}} = \text{Correct integrated area for the ditosyl species}$$

$$10.4 / 4 = 2.6$$

Mole ratio of each component

$$\frac{\text{Correct integrated area for the tritosyl species}}{\text{Correct integrated area for the ditosyl species} + \text{Correct integrated area for the tritosyl species}} = \frac{0.15}{2.6 + 0.15} = 0.055 \text{ mole fraction tritosyl}$$

$$\frac{\text{Correct integrated area for the ditosyl species}}{\text{Correct integrated area for the ditosyl species} + \text{Correct integrated area for the tritosyl species}} = \frac{2.6}{2.6 + 0.15} = 0.945 \text{ mole fraction ditosyl}$$

Percent compisition by weight

mole fraction x molecular weight

$0.05 \times 591 = 29.55$ tritosyl

$$\frac{29.55}{29.55 + 415.15} \times 100 = 6.6 \text{ \% tritosyl compound}$$

$0.95 \times 437 = 415.15$ ditosyl

$$\frac{415.15}{29.55 + 415.15} \times 100 = 93.4 \text{ \% ditosyl compound}$$

APPENDIX C

Appendix C

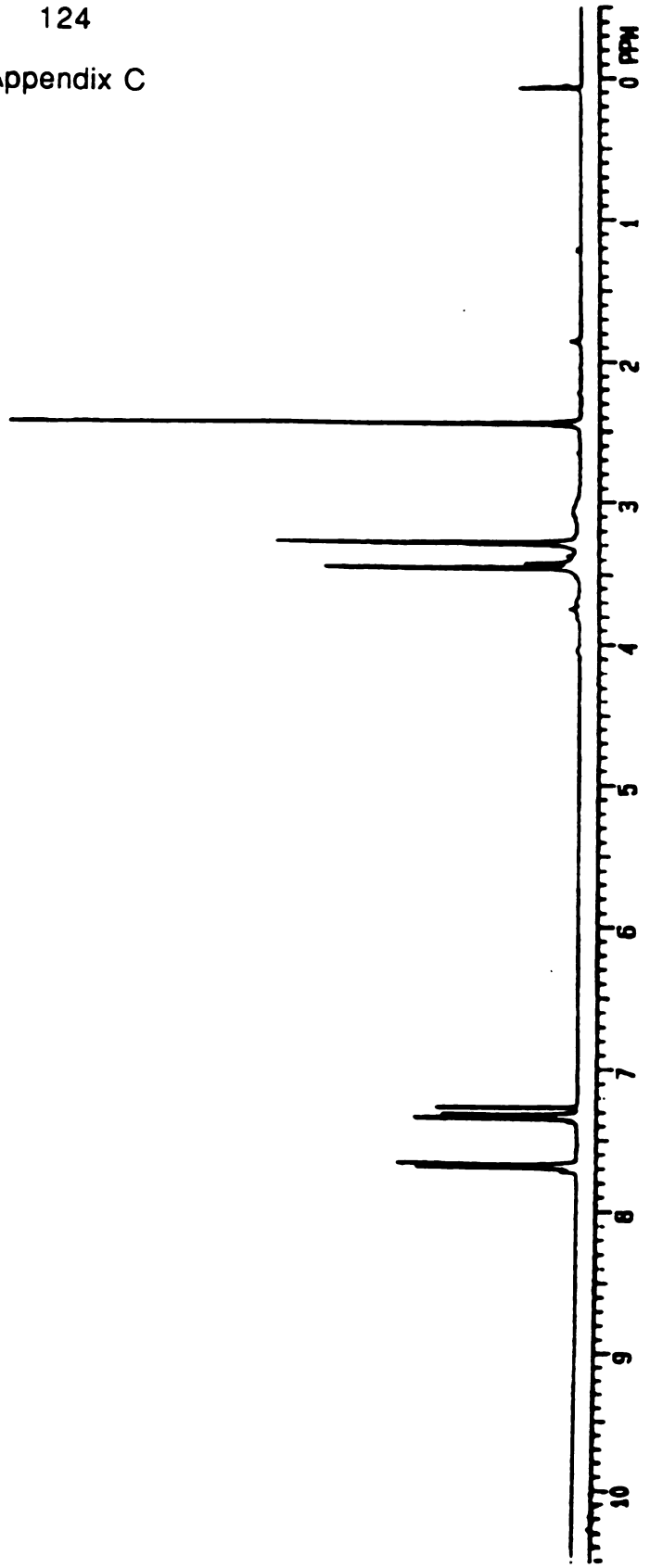


Figure 40- 1H-nmr of a mixture of triazacyclononanes, 19 mg/ml

Appendix C

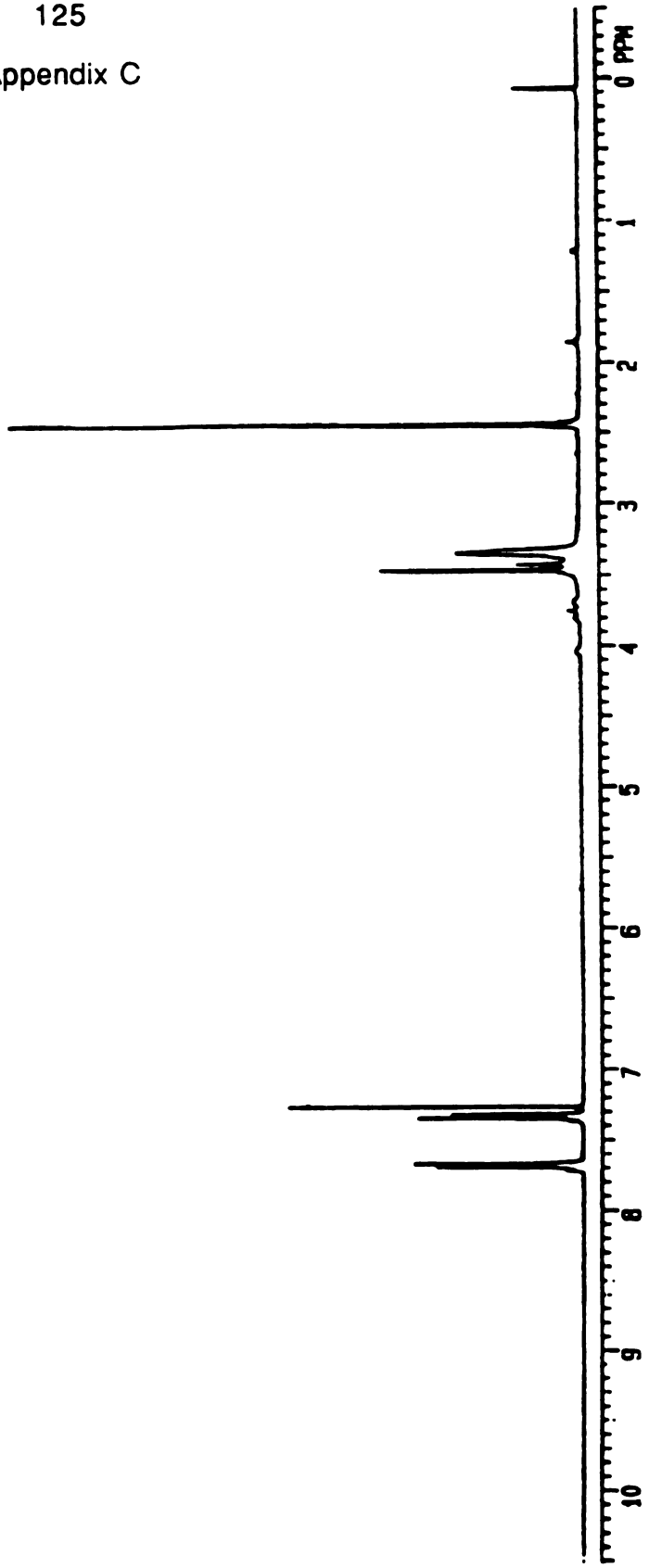


Figure 41- 1H-nmr of a mixture of triazacyclononanes, 9 mg/ml

Appendix C

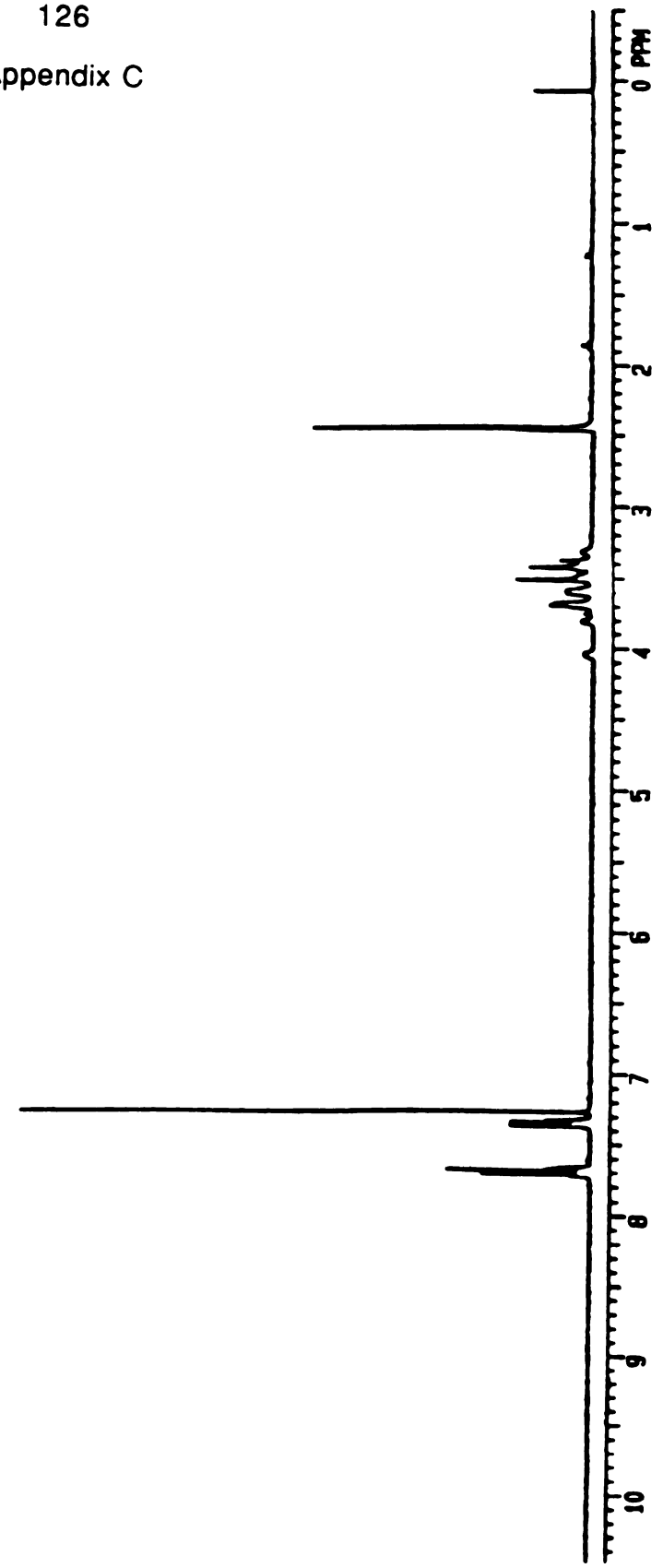


Figure 42- 1H-nmr of a mixture of triazacyclononanes, 3 mg/ml

APPENDIX D

Appendix D

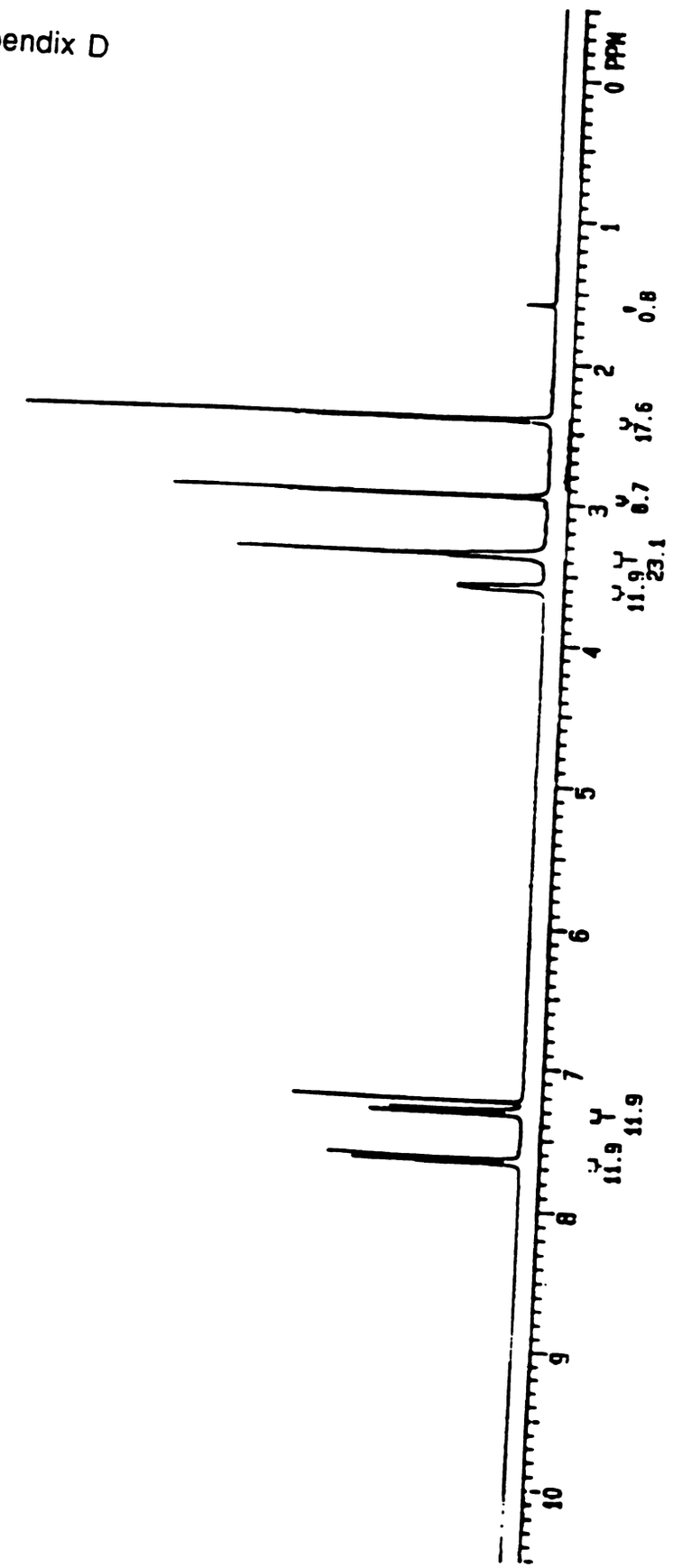


Figure 43- ^{1}H-nmr 4,7-Ditosyl-1-mesyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

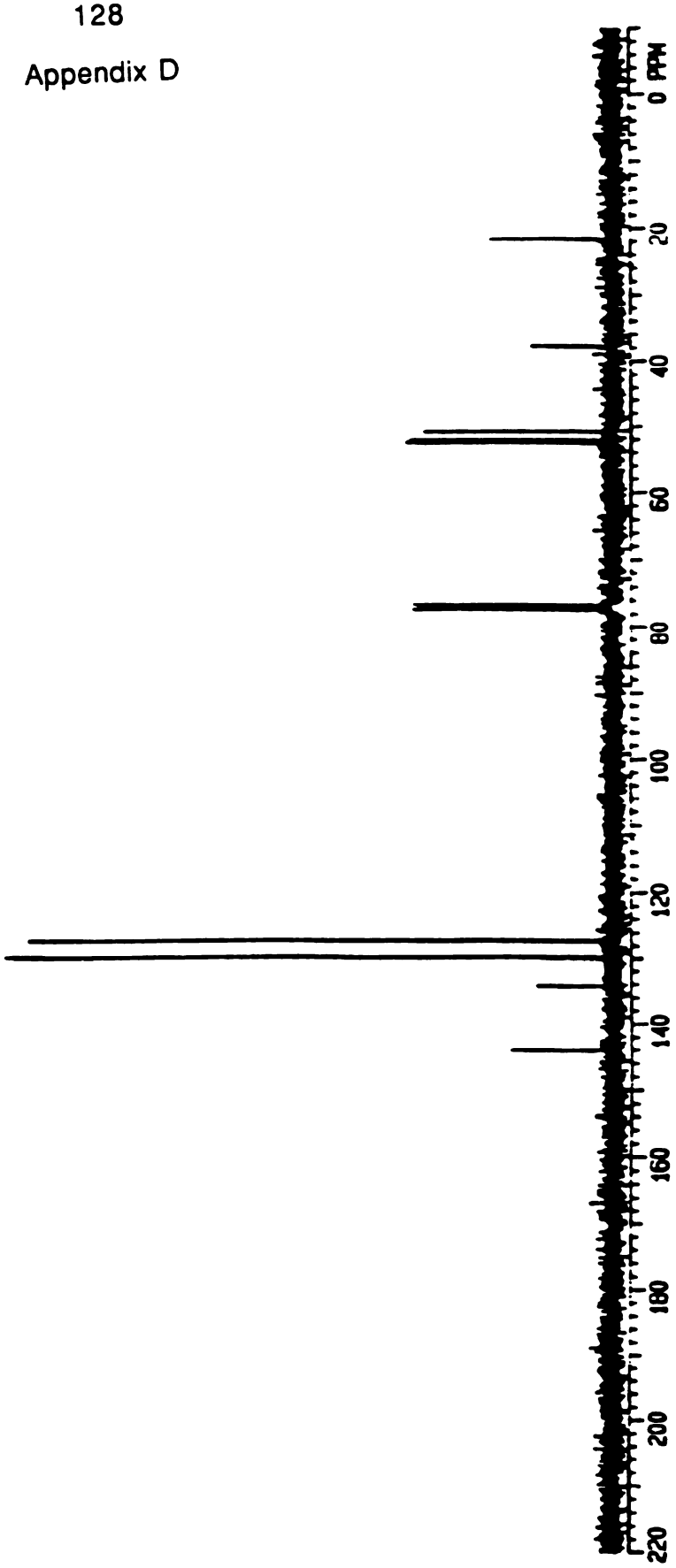


Figure 44- ^{1}H-nmr 4,7-Ditosyl-1-mesyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

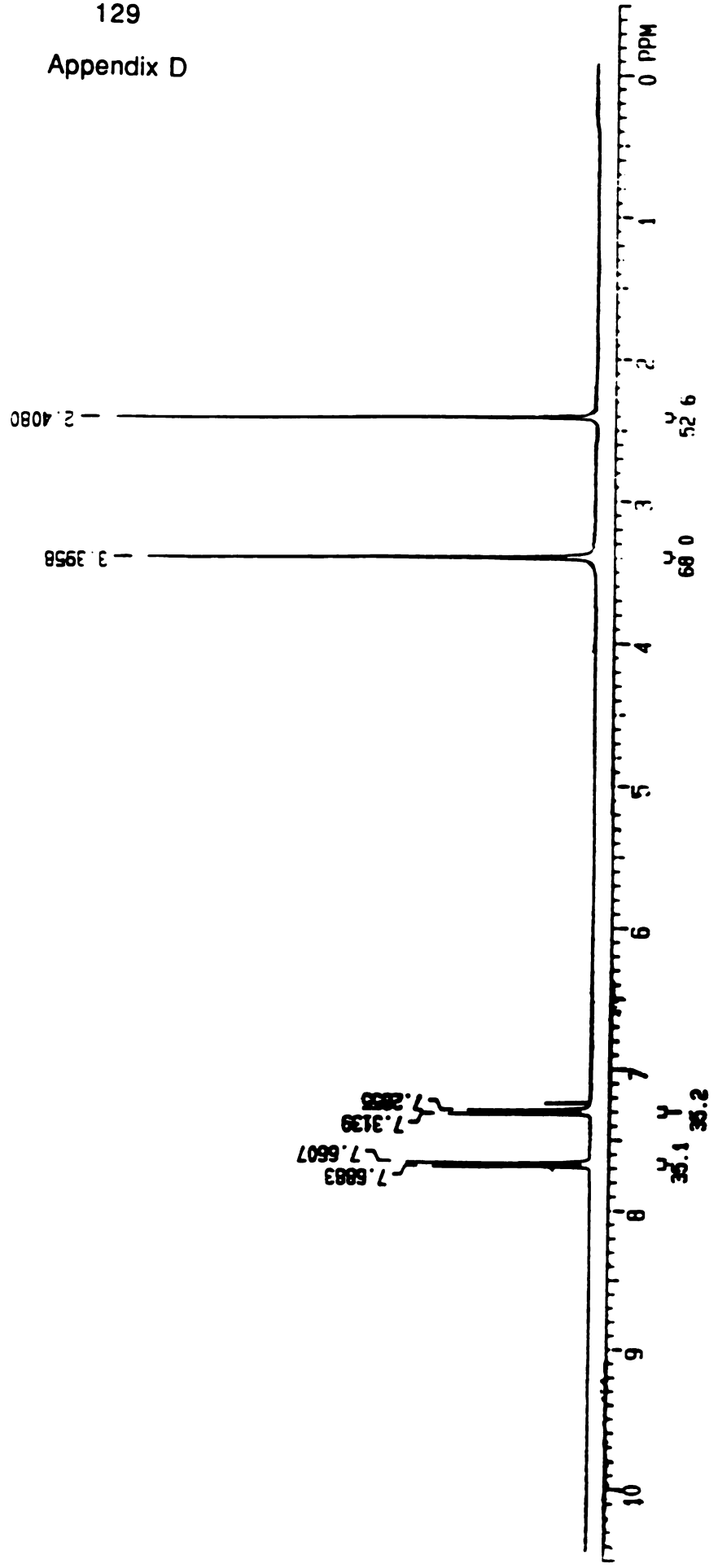


Figure 45- ^{1}H-nmr 1,4,7-Tritosyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

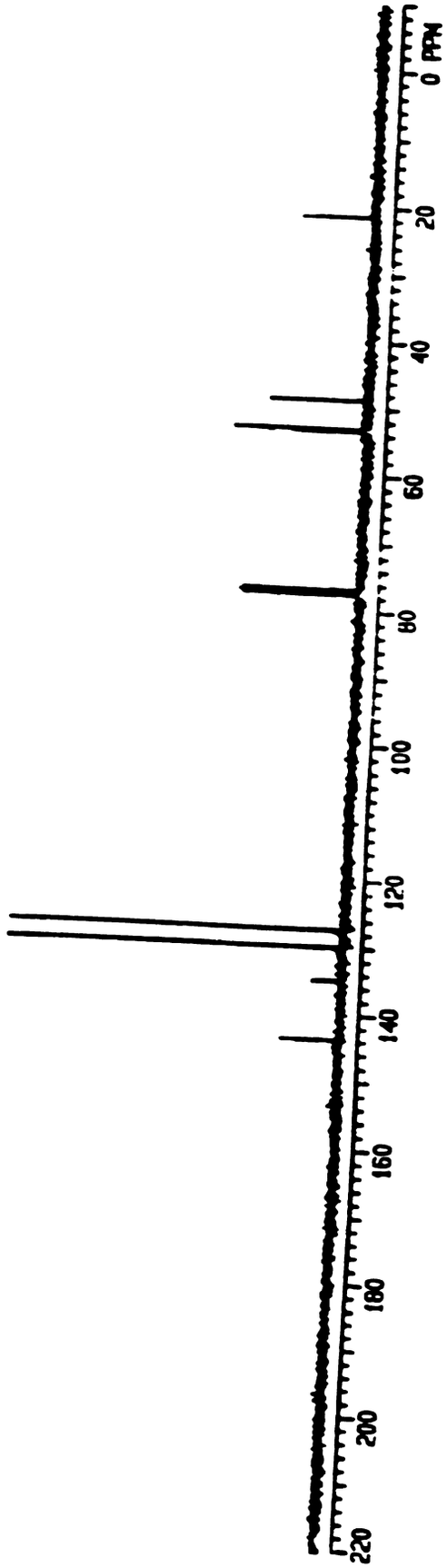


Figure 46- ^{13}C-nmr 1,4,7-Tritosyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

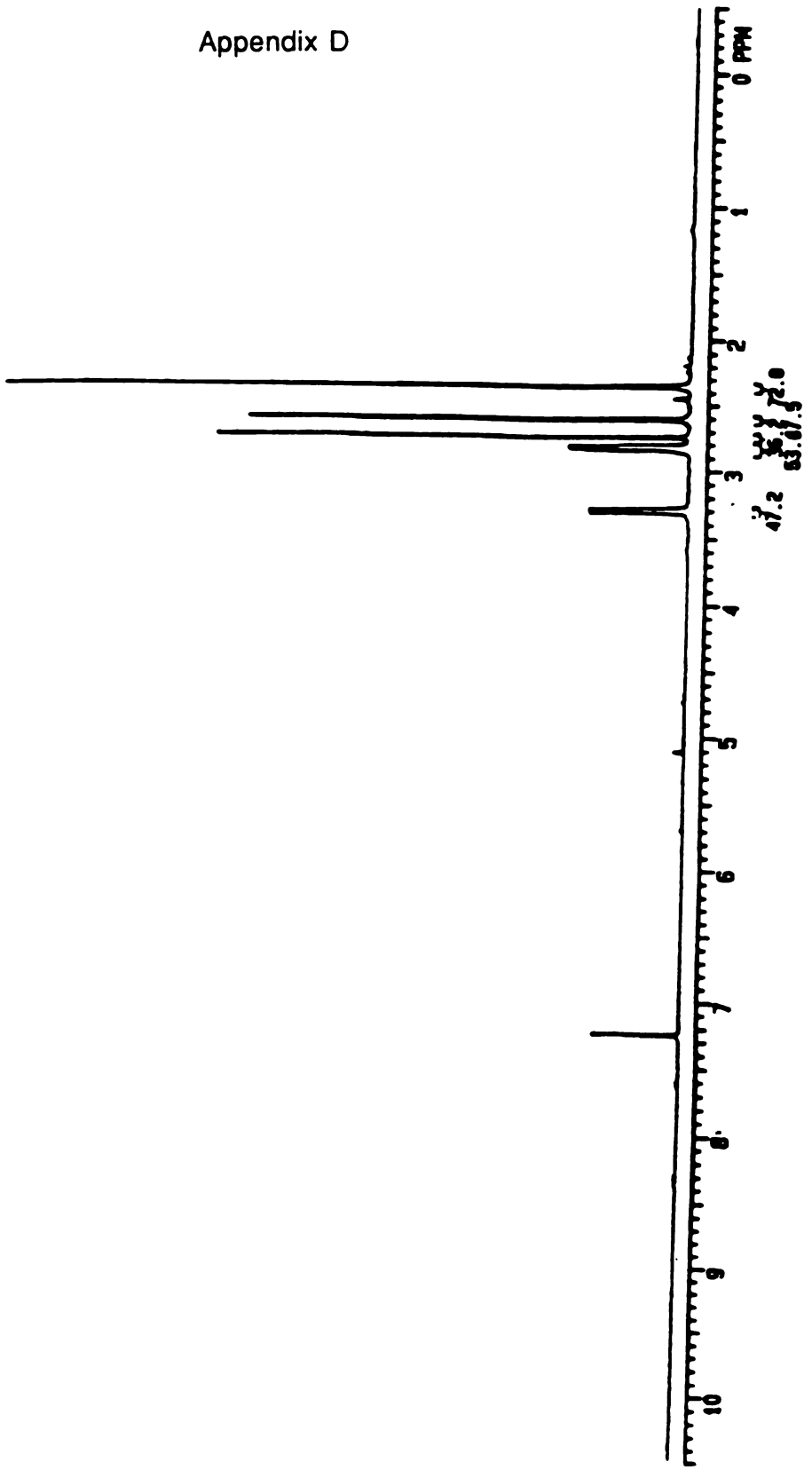


Figure 47- ^{1}H-nmr 4,7-Dimethyl-1-mesyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

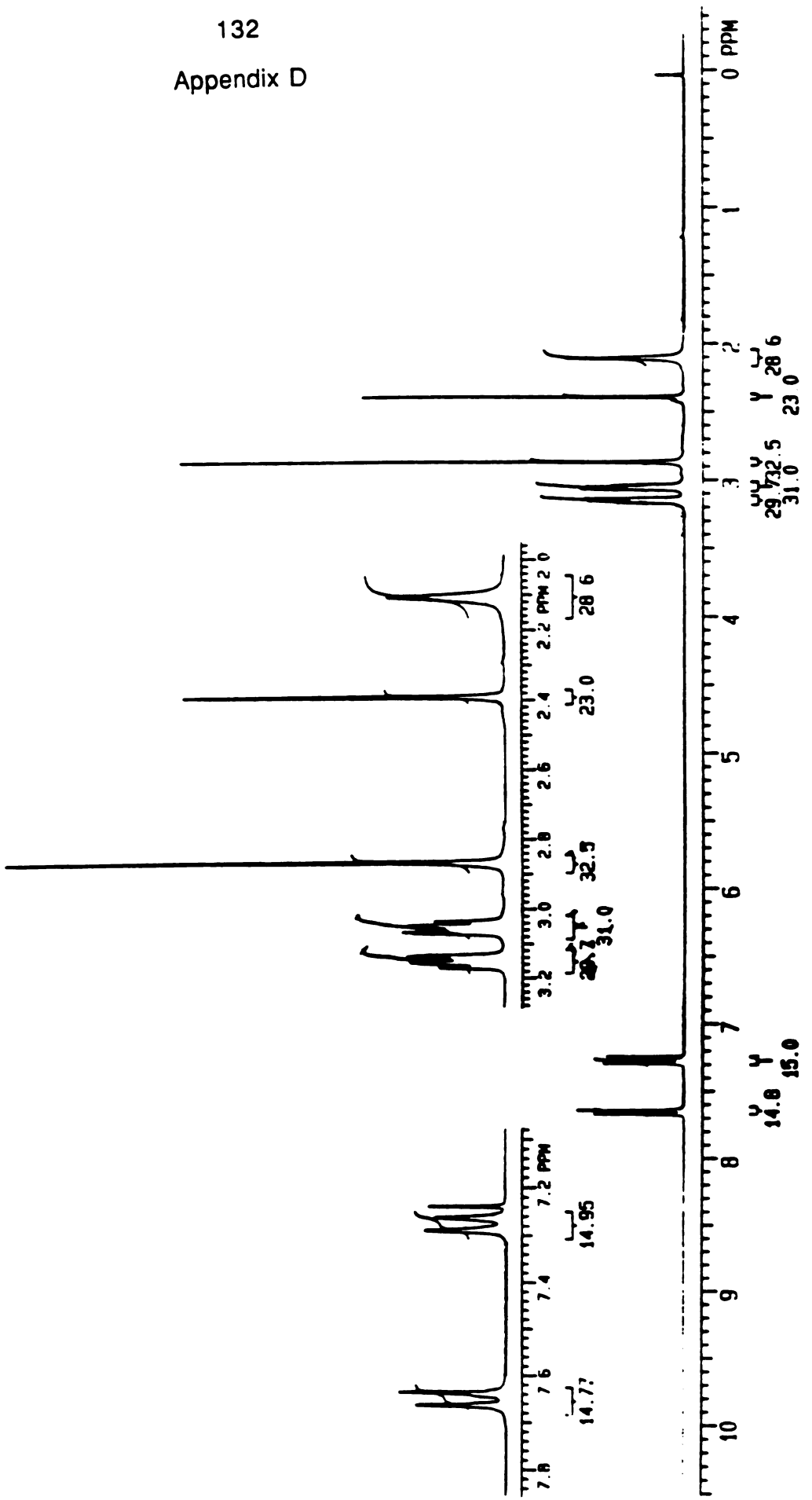


Figure 48- ^{1}H-nmr 1-Tosyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

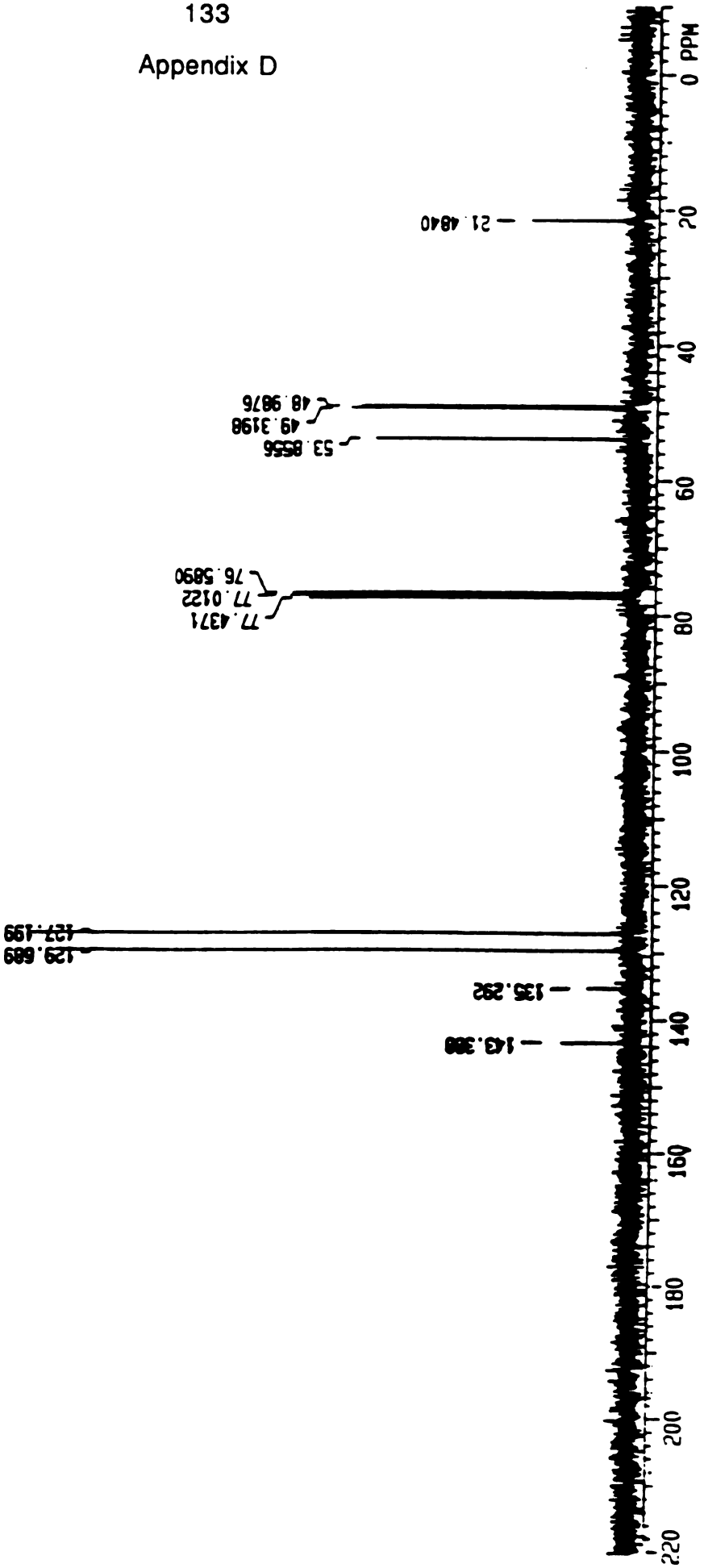


Figure 49- ^{13}C-nmr 1-Tosyl-1,4,7-Triazacyclononane in $CDCl_3$

Appendix D

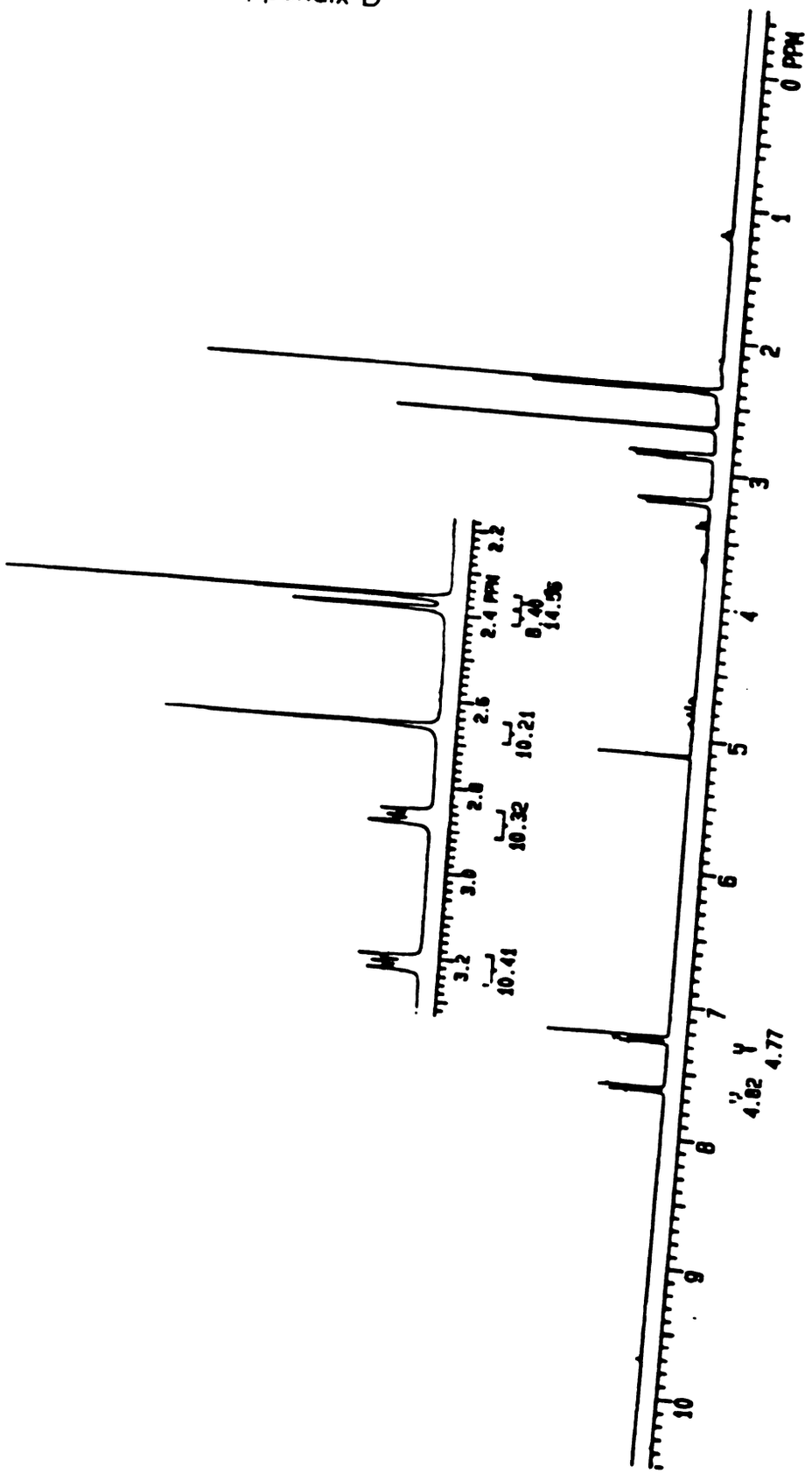


Figure 50- ^{1}H-nmr 4,7-Dimethyl-1-tosyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

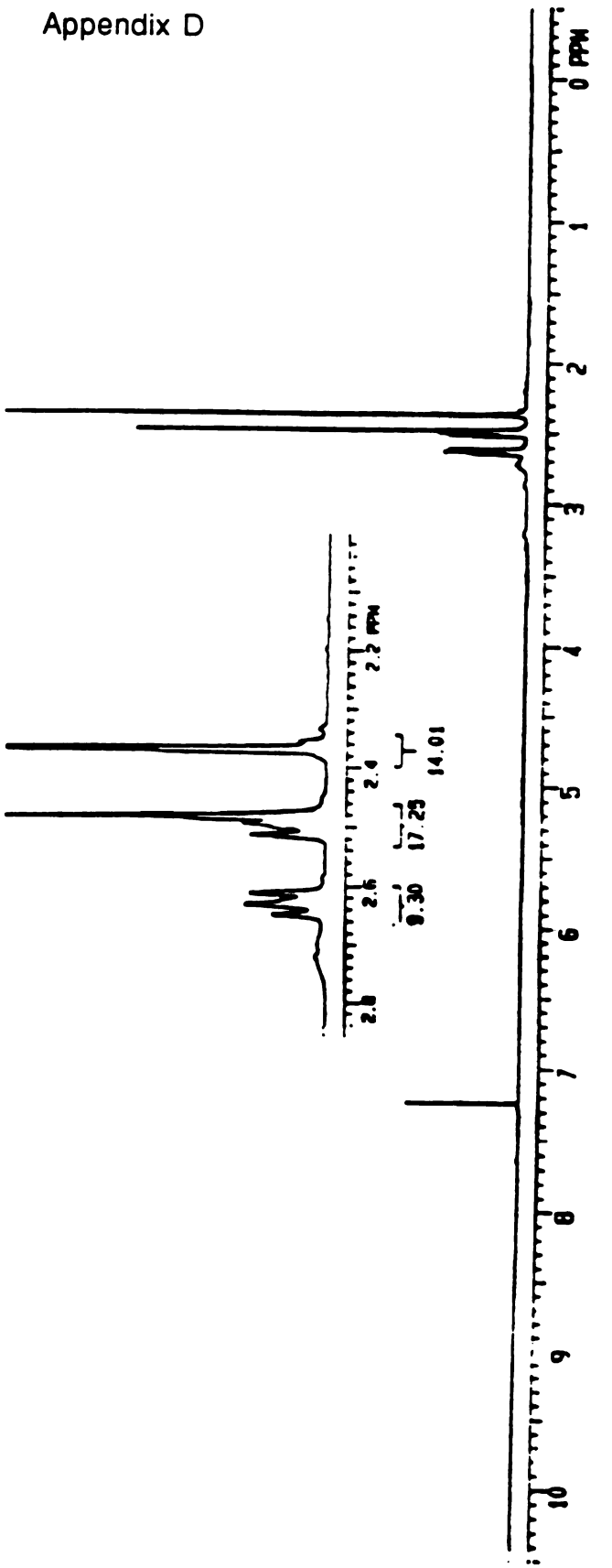


Figure 51- ^{1}H-nmr 1,4-Dimethyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

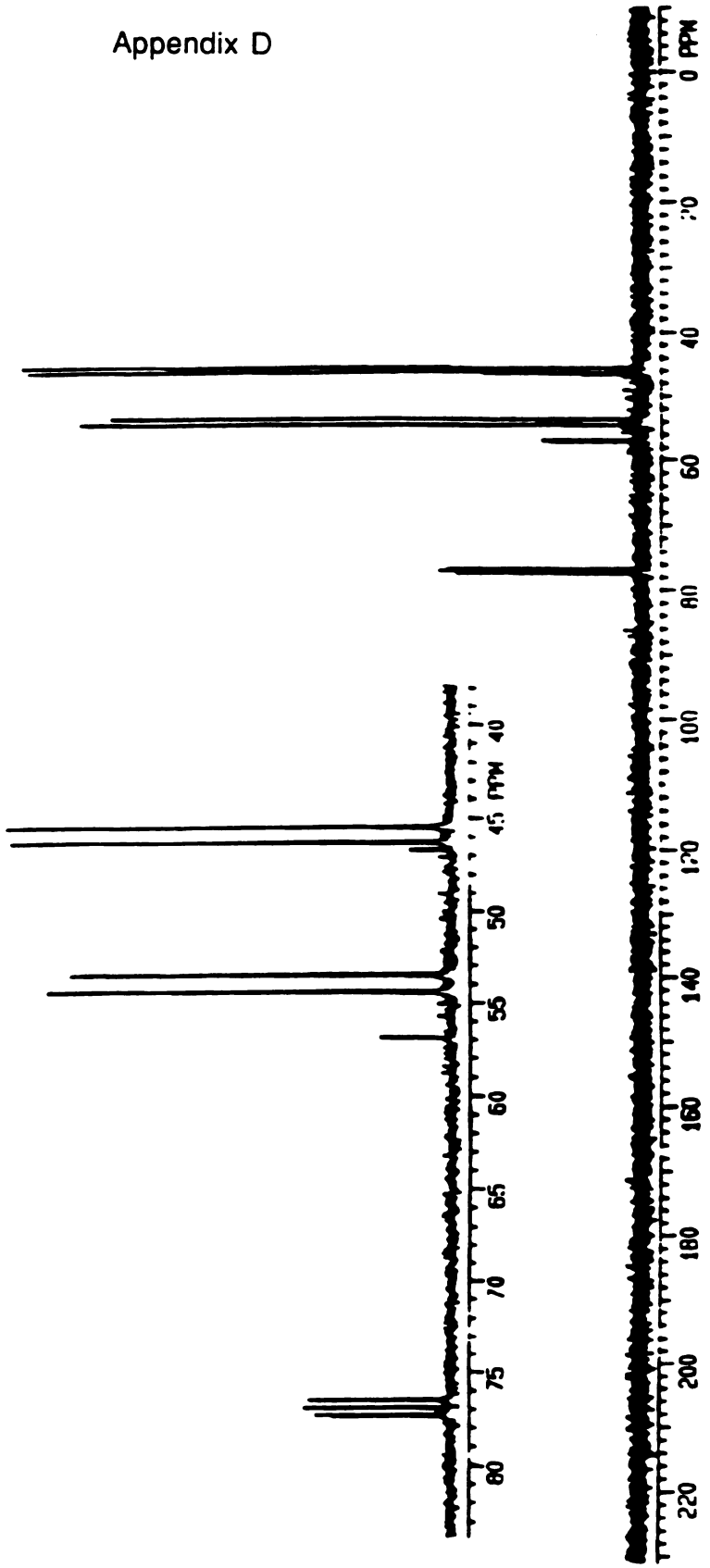


Figure 52- ^{13}C-nmr 1,4-Dimethyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

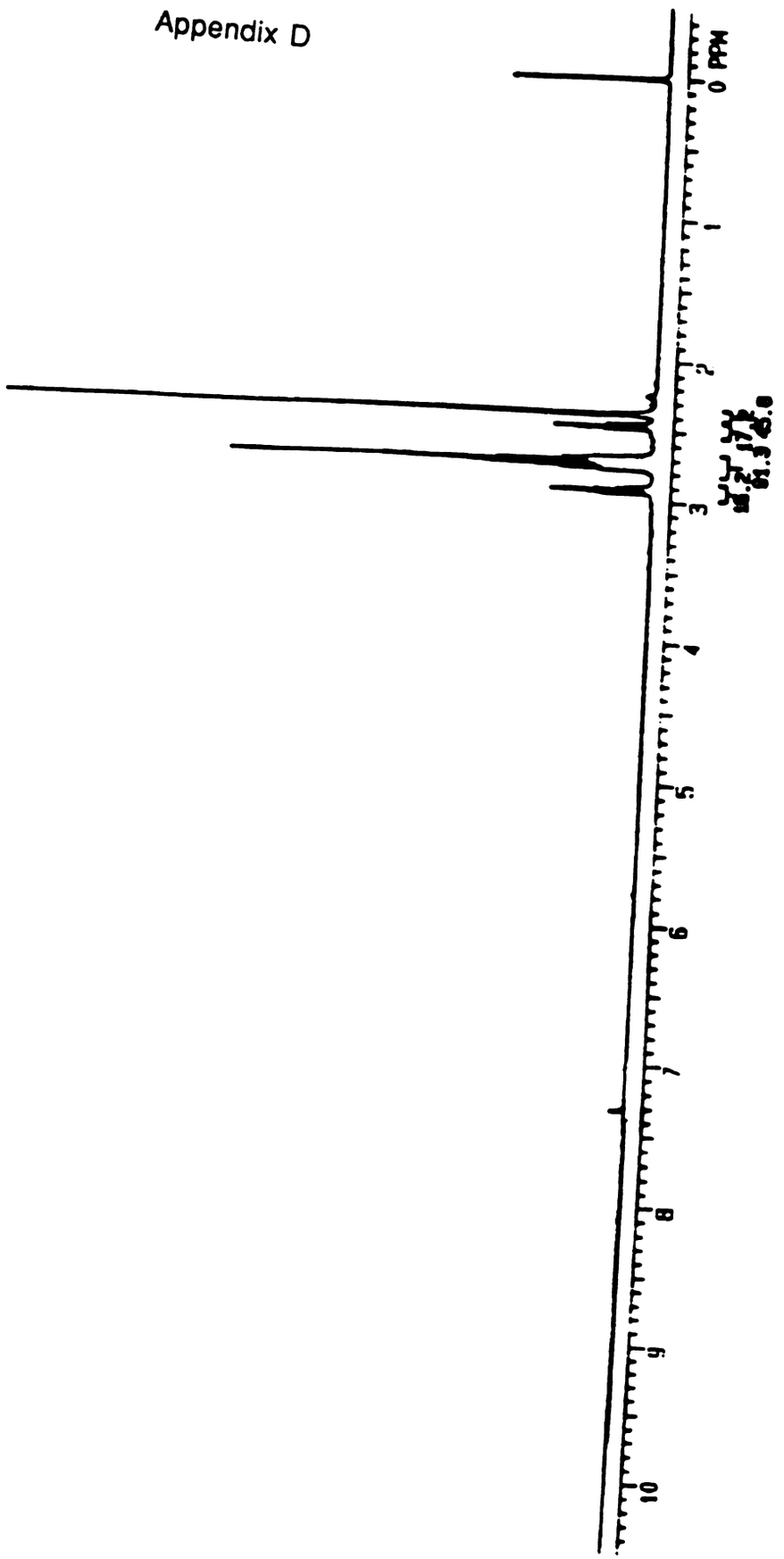


Figure 53- ^{1}H-nmr 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

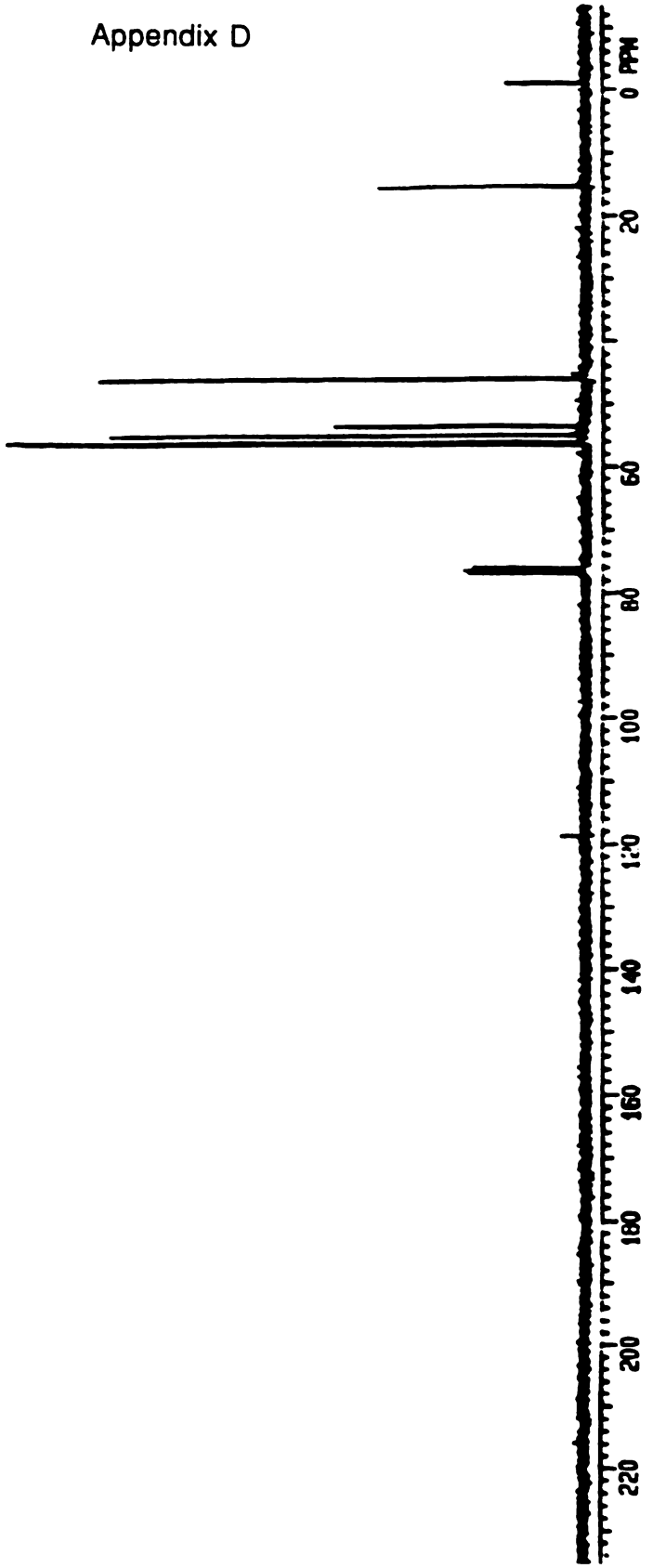


Figure 54- ^{13}C-nmr 4,7-Dimethyl-1-(3-propionitrile)-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

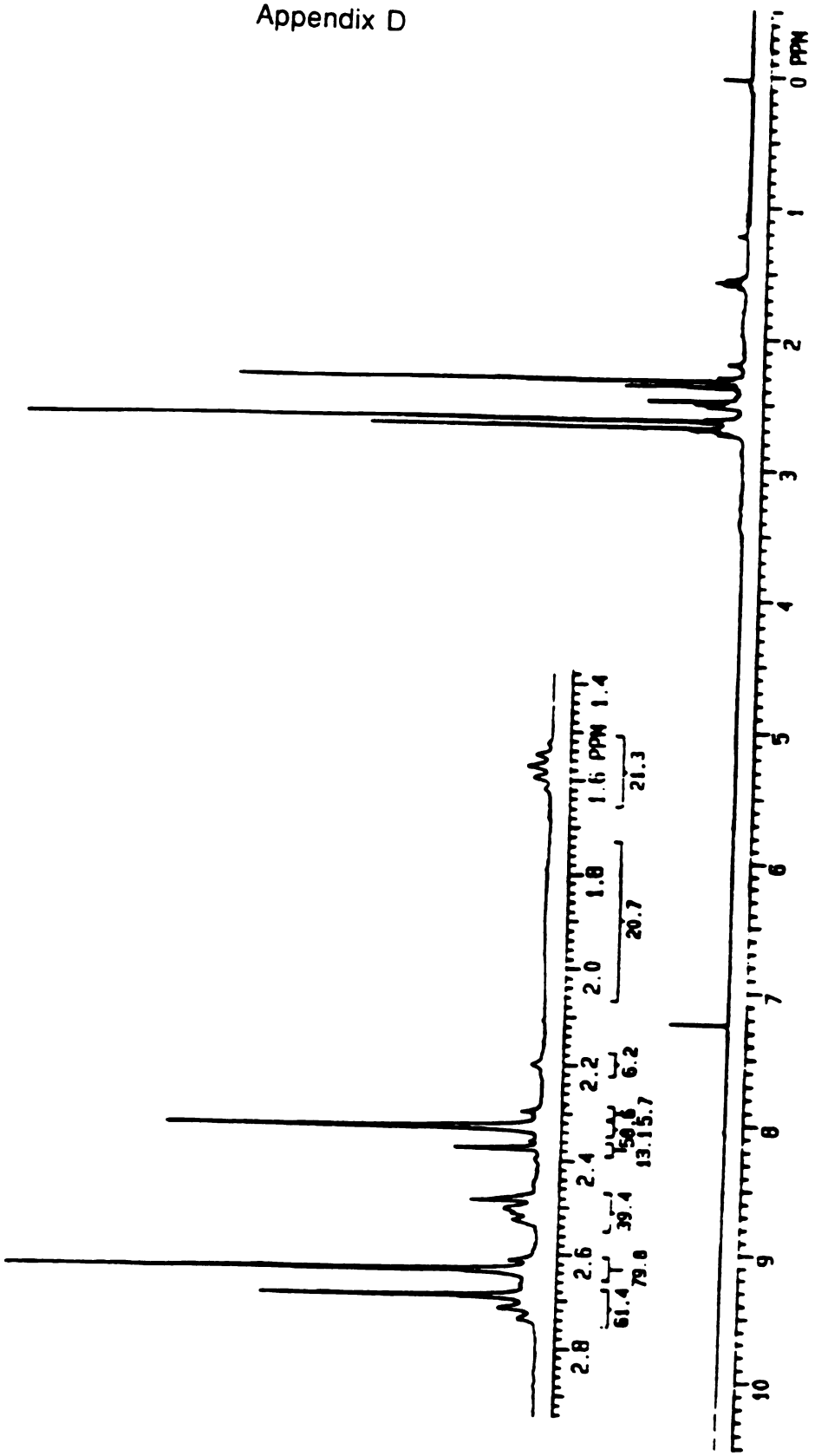


Figure 55- ^{1}H-nmr 4,7-Dimethyl-1-(3-aminopropyl)-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

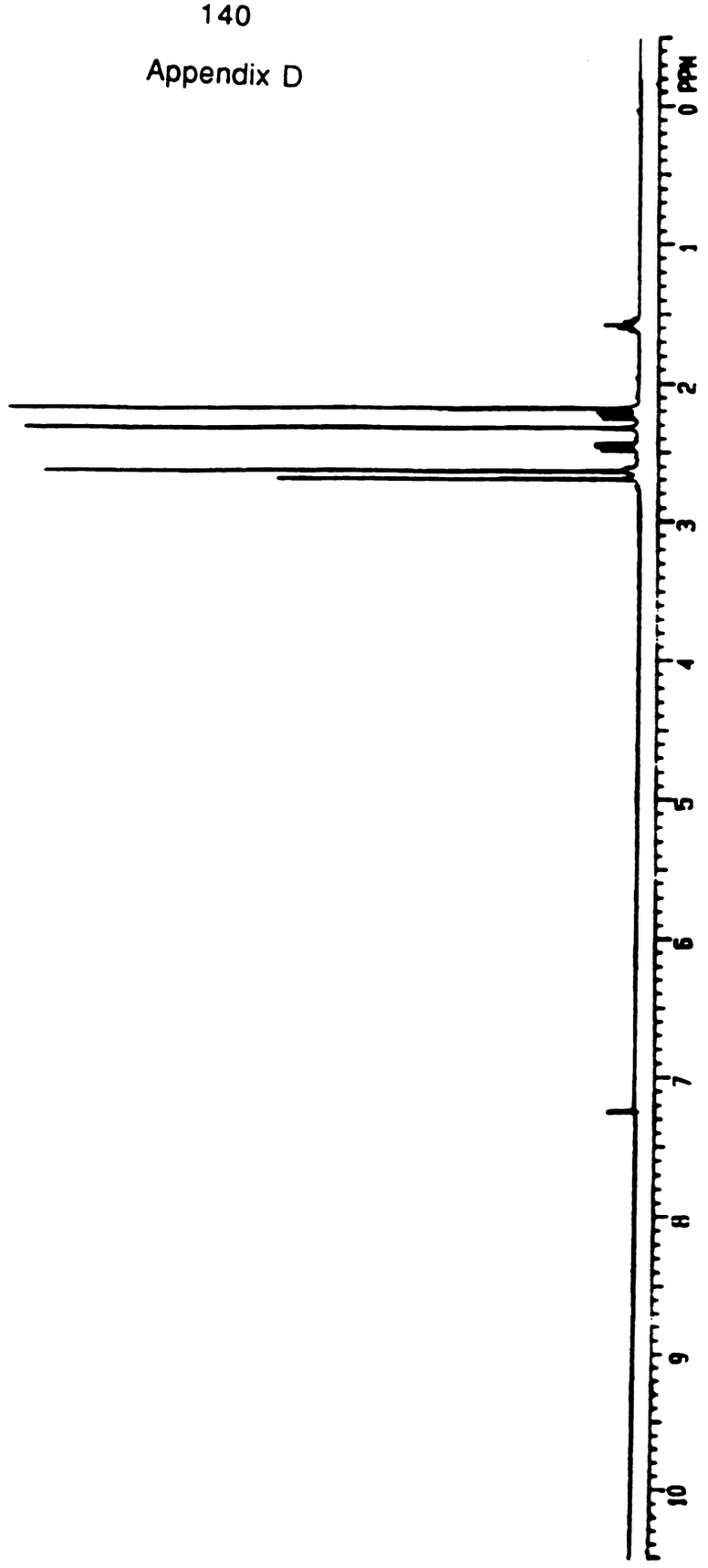


Figure 56- ^{1}H-nmr 4,7-Dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

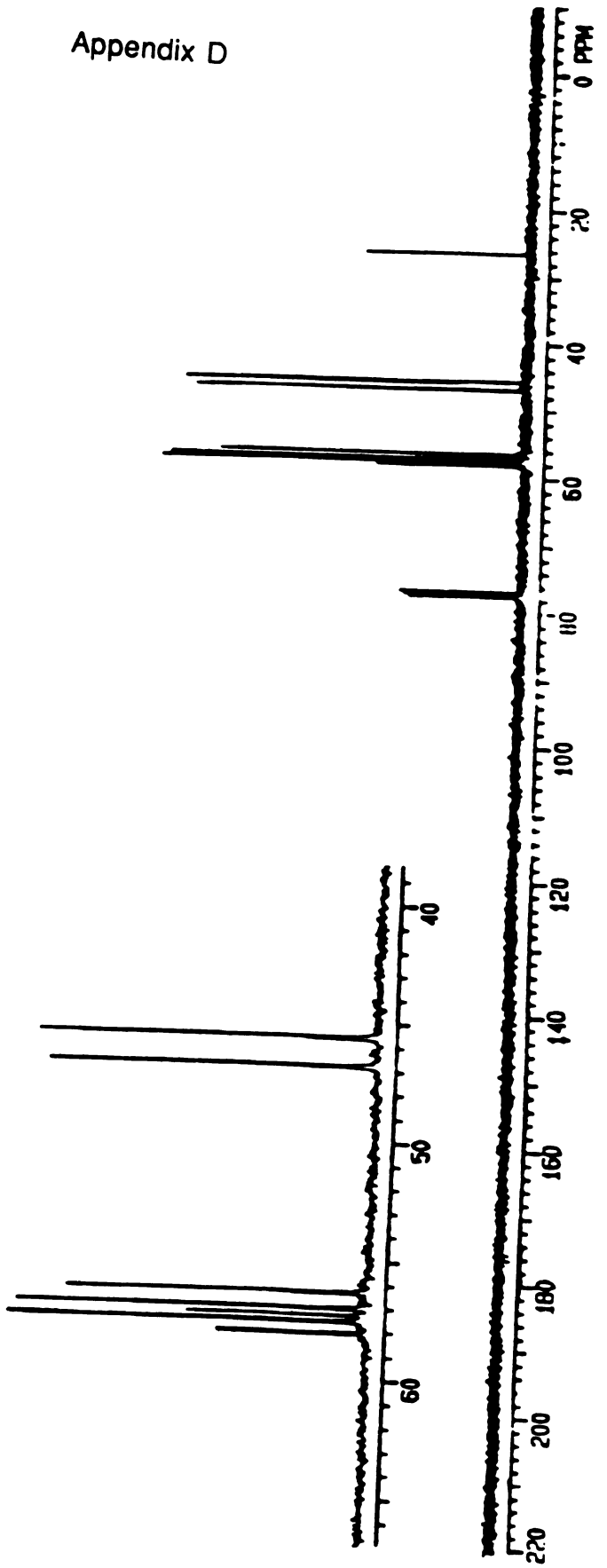


Figure 57- ^{13}C-nmr 4,7-Dimethyl-1-(3-dimethylaminopropyl)-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

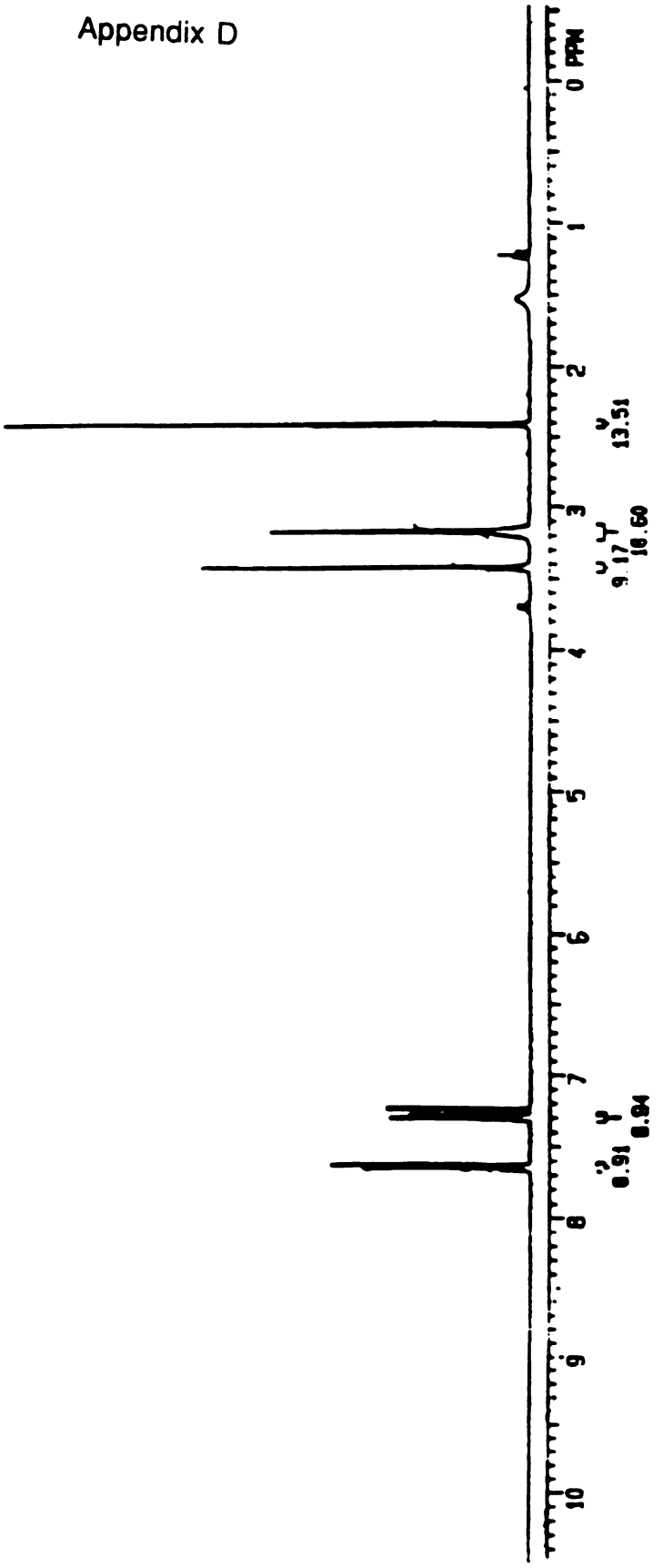


Figure 58- ^{1}H-nmr 1,4-Ditosyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

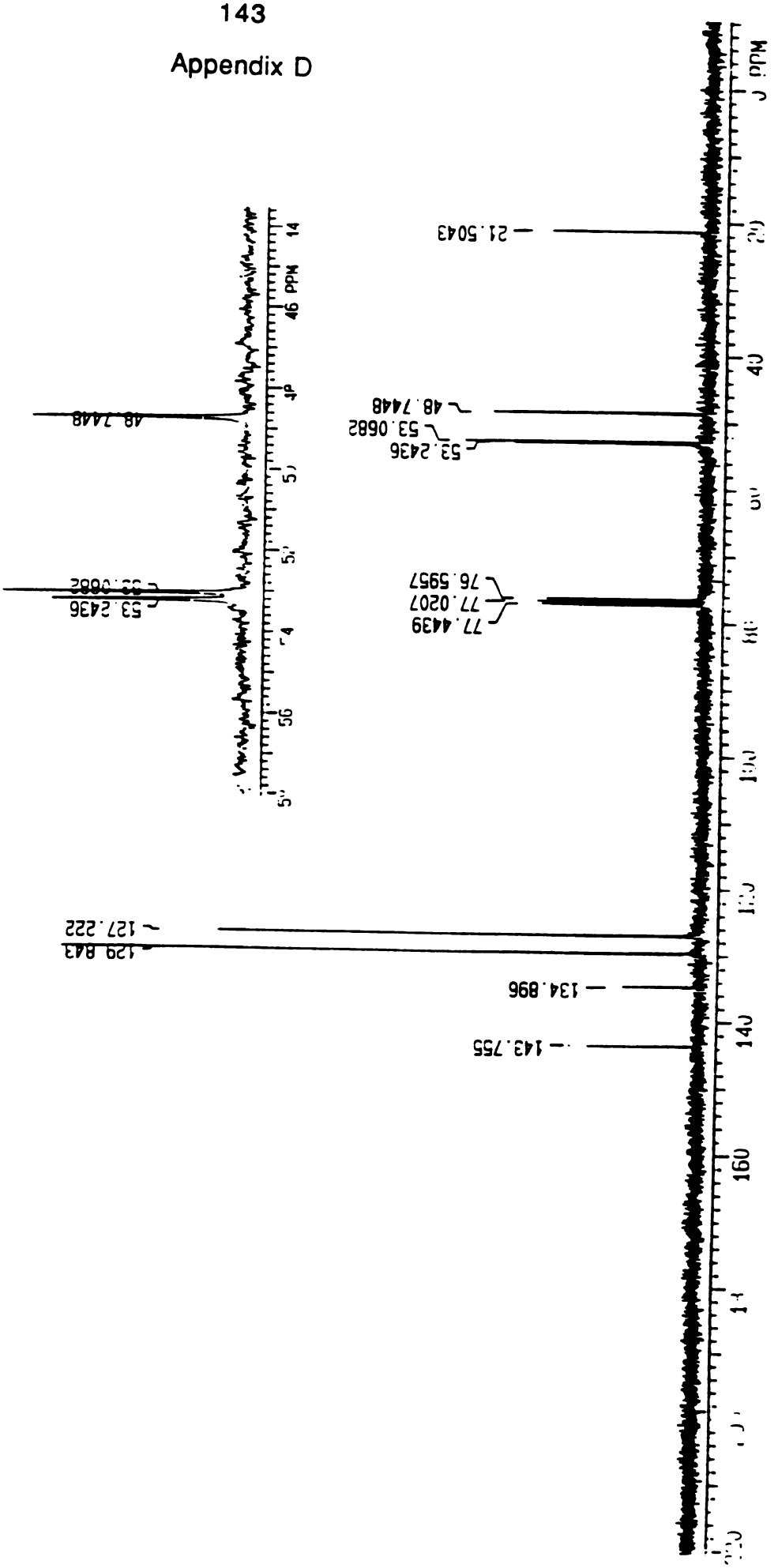


Figure 59- ^{13}C-nmr 1,4-Ditosyl-1,4,7-triazacyclononane in $CDCl_3$

Appendix D

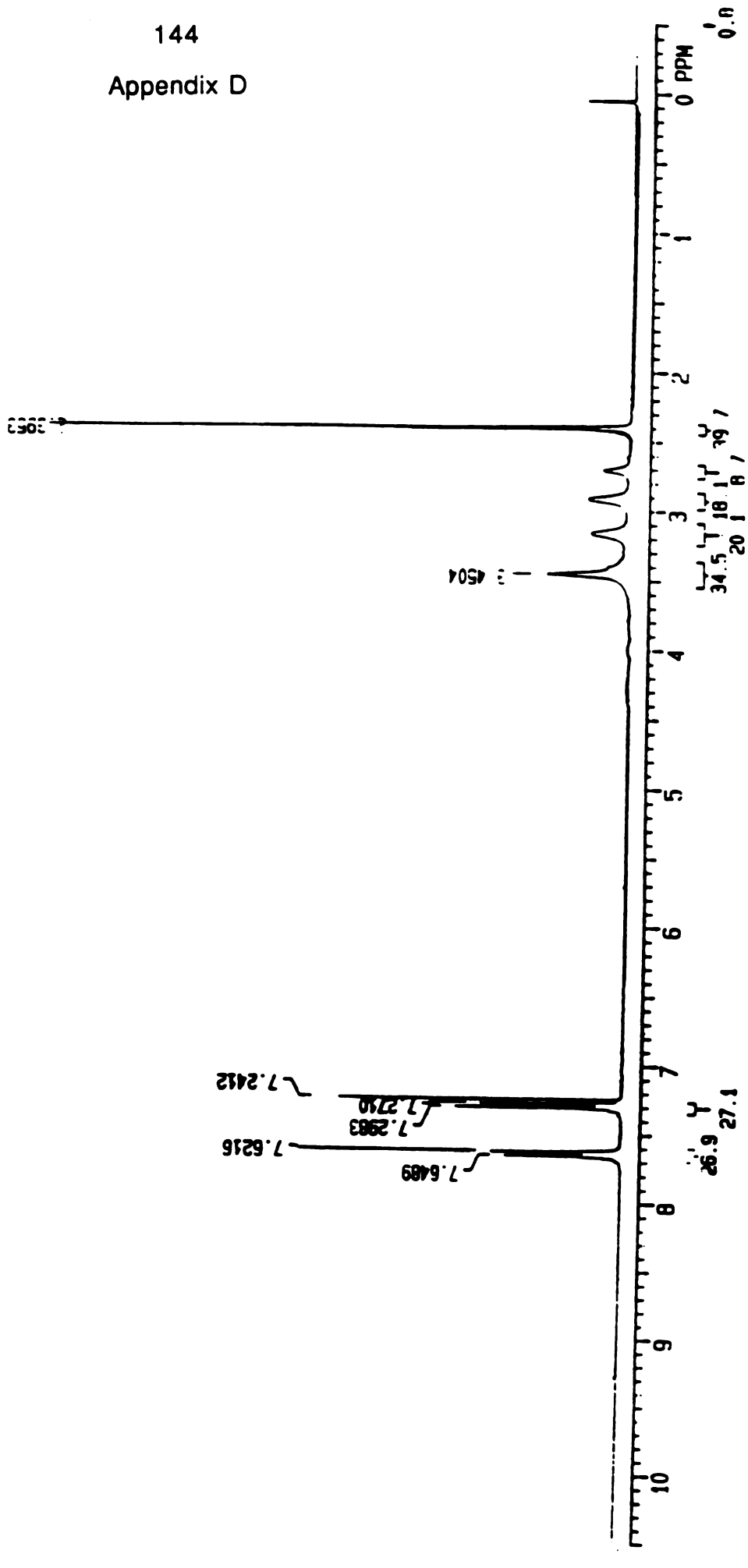


Figure 60- ^{1}H-nmr 1,2-Bis(4,7-Ditosyl-1,4,7-triazacyclononyl) ethane in $CDCl_3$

Appendix D

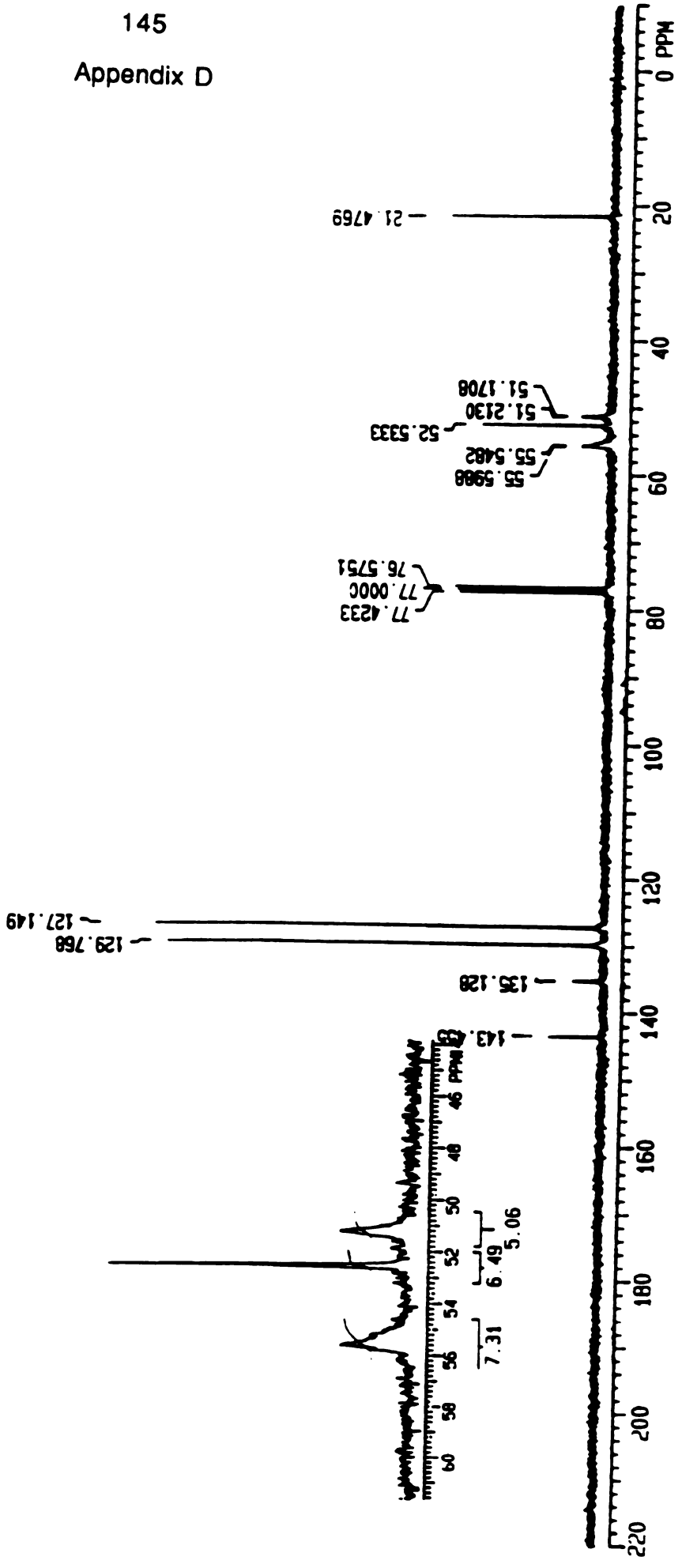


Figure 61- ^{13}C-nmr 1,2-Bis(4,7-Ditosyl-1,4,7-triazacyclononyl) ethane in $CDCl_3$

Appendix D

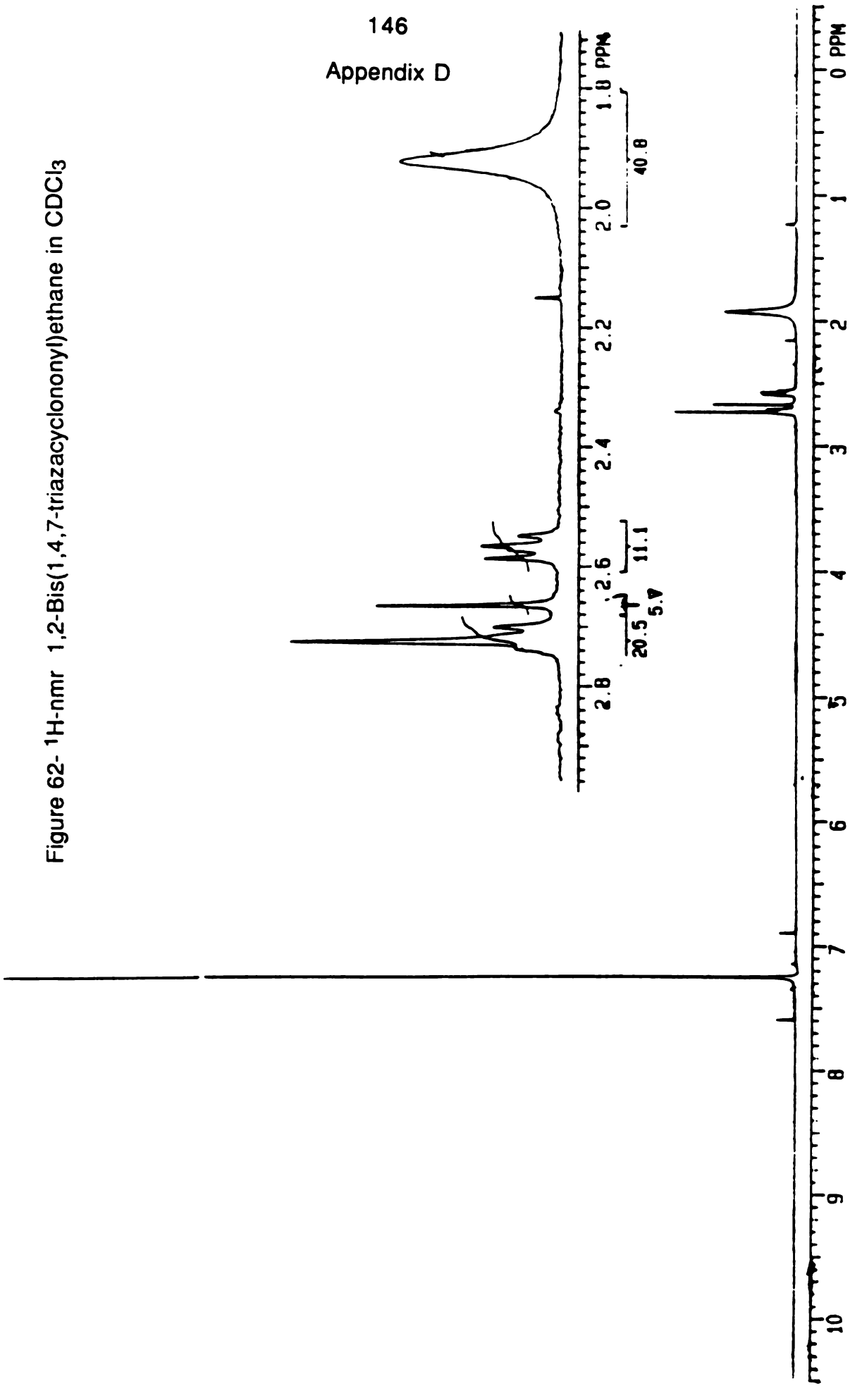


Figure 62- ^{1}H-nmr 1,2-Bis(1,4,7-triazacyclononyl)ethane in $CDCl_3$

Appendix D

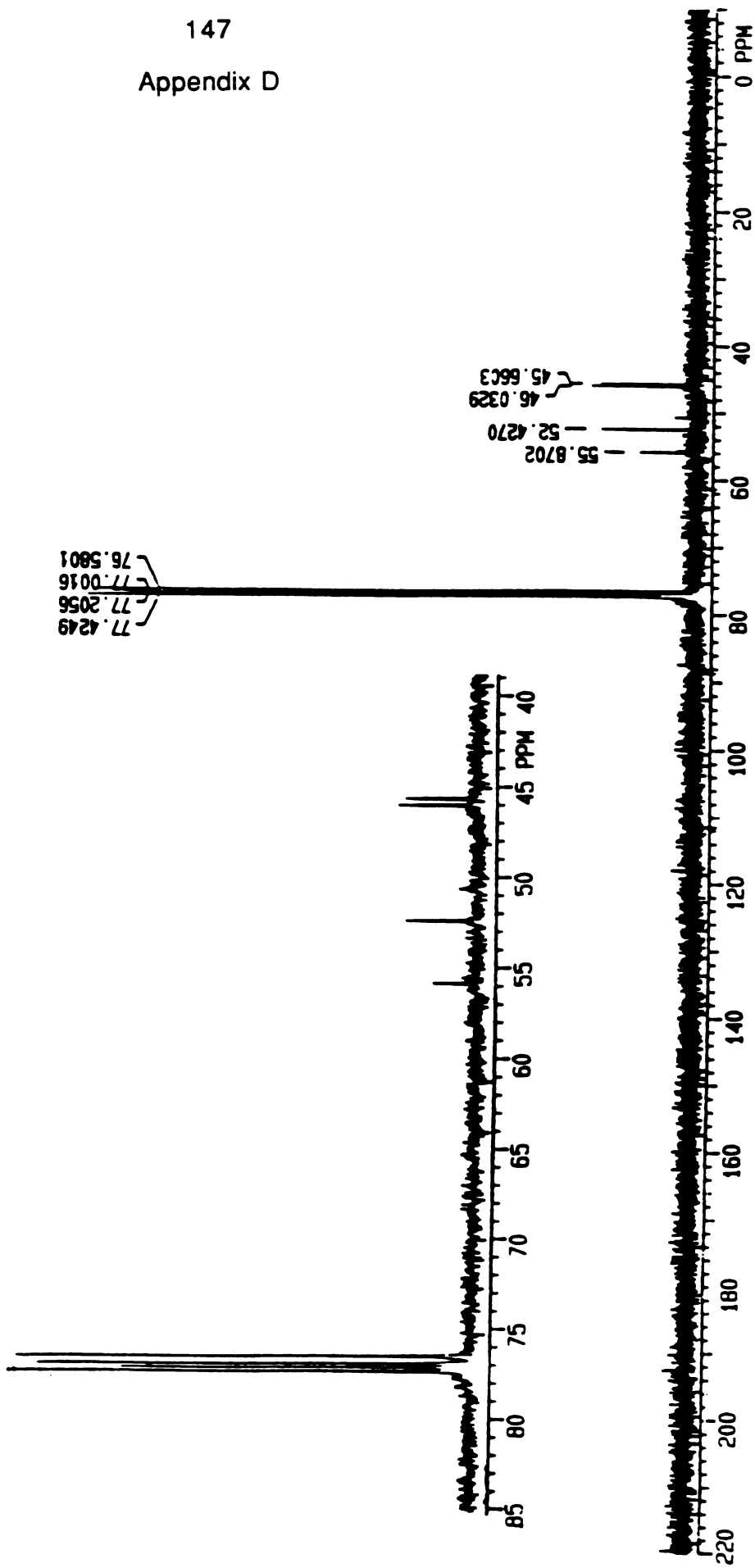


Figure 63- ^{13}C-nmr 1,2-Bis(1,4,7-triazacyclononyl)ethane in $CDCl_3$

Appendix D

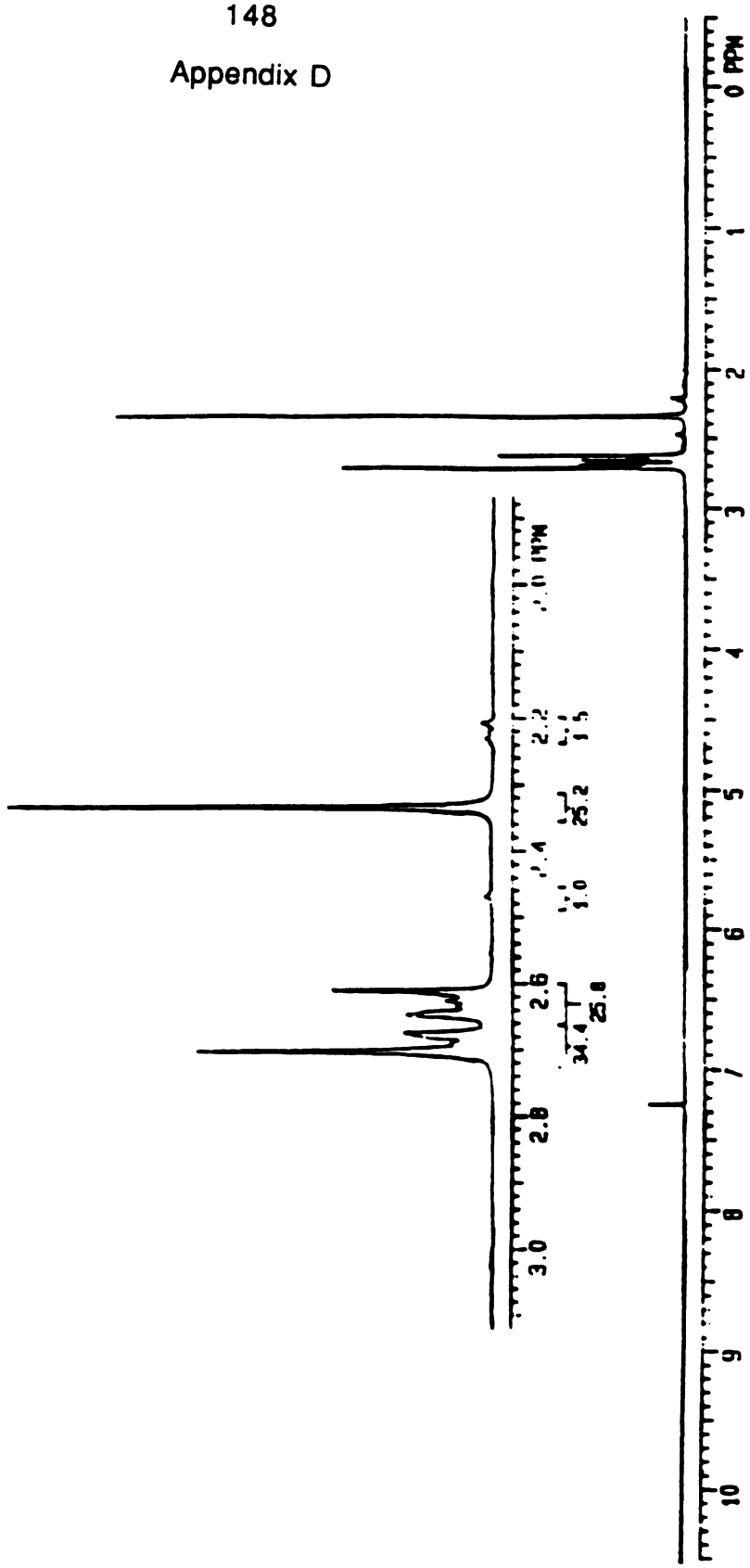


Figure 64- ^{1}H-nmr 1,2-Bis(4,7-Dimethyl-1,4,7-triazacyclononyl) ethane in $CDCl_3$

Appendix D

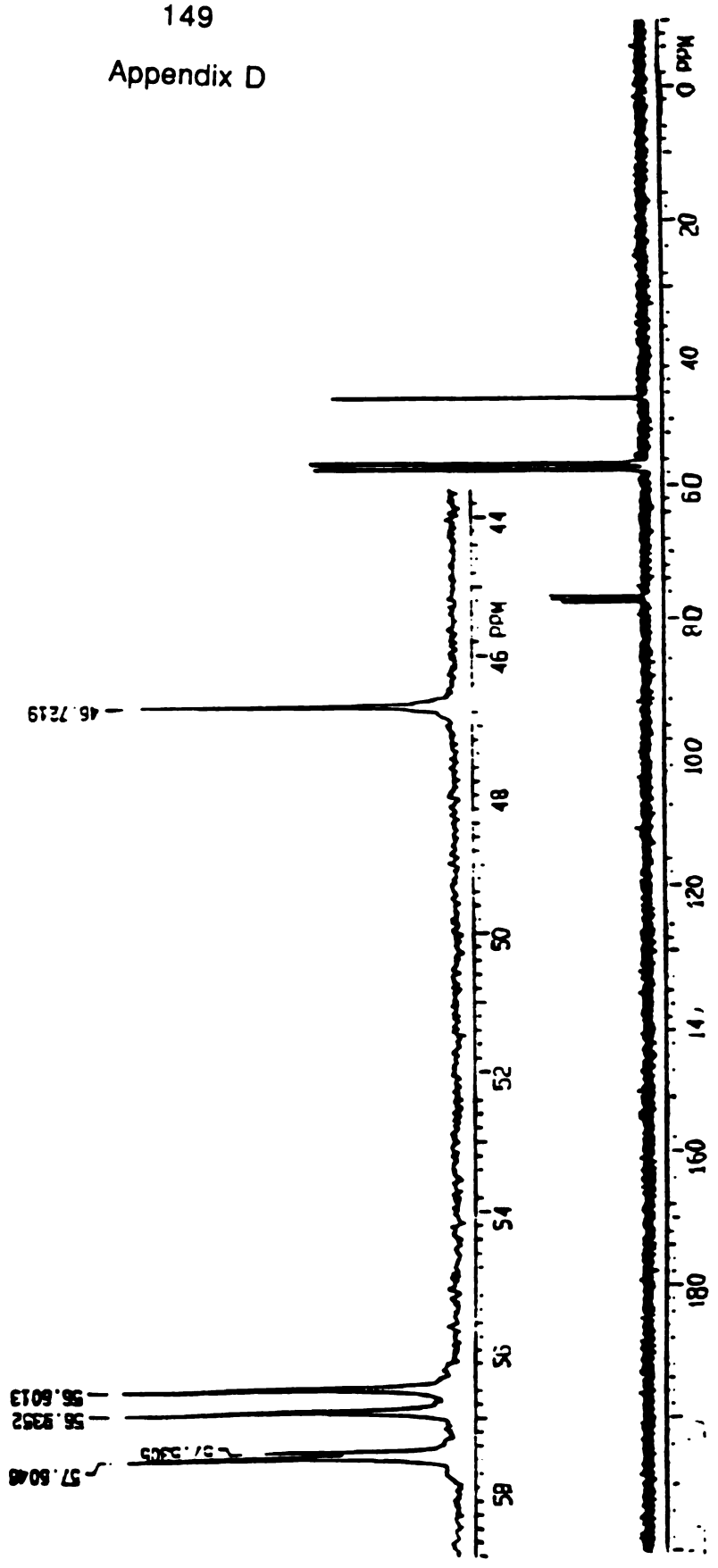


Figure 65- ^{13}C-nmr 1,2-Bis(4,7-Dimethyl-1,4,7-triazacyclononyl) ethane in $CDCl_3$

LIST OF REFERENCES

LIST OF REFERENCES

1) *Journal of Inclusion Phenomena, Coordination Chemistry Reveiws, Journal of Coordination Chemistry.*

2) Down, J. L.; Lewis, J.; Moore, B.; Wilkinson, G. *J. Chem. Soc.* **1959**, 3767.

3) Dye, J. L.; DeBacker, M. G.; Nicely, V. A. *J. Am. Chem. Soc.* **1970**, *92(17)*, 5226.

4) Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron* **1973**, *29*, 1647.

5) Kuchenmeister, M.; Dye, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 935.

6) a) Tehan, F. J.; Barnett, B. L.; Dye, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7203. b) Ellaboudy, A; Dye, J. L.; Smith, P. B. *J. Am. Chem. Soc.* **1983**, *105*, 6490. c) Dawas, S. B.; Ward, D. L.; Huang, R. H.; Dye, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 3534. d) Dye, J. L.; Ceraso, J. M.; Lok, M. T.; Barnett, B. L.; Tehan, F. J. *J. Am. Chem. Soc.* **1974**, *96*, 608. e) Eck, B. V.; Le, L. D.; Issa, D.; Dye, J. L. *Inorg. Chem.* **1982**, *21*, 1966. f) Wagner, M. J.; Huang, R. H.; Eglin, J. L.; Dye, J. L. *Nature* **1994**, *368*, 726.

7) a) Dye, J. L.; Lok, M. T.; Tehan, F. J.; Coolen, R. B.; Papadakis, N.; Ceraso, J. M.; Debacker, M. G. *Ber. Bunsenges. Phys. Chem.* **1971**, *75*, 659. b) Lok, M. T.; Tehan, F. J.; Dye, J. L. *J. Phys. Chem.* **1972**, *76*, 2975. c) Faber, M. K.; Fussa-Rydel, O.; Skowyra, J. B.; McMills, L. E. H.; Dye, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 5957.

8) Dye, J. L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 587.

9) Lehn, J. M. *Pure Appl. Chem.* **1980**, *52*, 2303.

10) This is believed to be a multi step process with solvated e- formed first and then the alkalide. Jedlinski, Z.; Kowalczuk, M.; Kurcok, P. *Makromol. Chem. Macromol. Symp.* **1986**, *3*, 277.

11) Mathias, L. J. *J. Macromol. Sci-Chem.*, **1981** *A15(5)*, 853, and the references contained within.

12) Jedlinski, Z.; Kolwalczuk, M.; Gtobelny, Z.; Tolarzewicz, A. S. *Makromol. Chem. Rapid Commun.* **1983**, *4*, 355.

13) Jedlinski, Z.; Kolwalczuk, M.; Kurcok, P.; Brazoskowska, L.; Franek, J. *Makromol. Chem.* **1987**, *188*, 1575.

14) Rasmussen, J. K.; Smith, H. K., II. *J. Am. Chem. Soc.* **1981**, *103*, 730.

15) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594.

16) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41(21)*, 3486.

17) Stott, P. E.; Bradshaw, J. S.; Parish, W. W. *J. Am. Chem. Soc.* **1980**, *102*, 4810.

18) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172.

19) Dehmlow, E. V.; Thieser, R. *Tet. Lett.* **1985** *26(3)*, 297.

20) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis 2nd rev. ed.* **1983** Weinheim, Florida,

21) Gokel,G. W.; Durst, H. D. *Synthesis* **1976**, 168.

22) Freedman, H. H. *Pure Appl. Chem.* **1986**, *58*, 857.

23) Langer, A. W.,Jr. *Polyamine-Chelated Alkali Metal Compounds*, American Chemical Society, WAshington, D. C., **1974**.

24) Birch, A. J. *Advances in Organic Chemistry, Methods and Results* Wiley, New York **1972**.

25) Smith, M. *Reduction* edit by Augustine pg 95, Marcel Dekker, New York **1968**.

26) Kaiser, E. M. *Synthesis*, **1972** 391.

27) Kaempt, B.; Raynal, S.; Collet, A.; Schue, F.; Boileau, S.; Lehn, J-M. *Angew. Chem. Int. Ed.* **1974**, *13*, 611.

28) Nelson, G. V.; Zelewsky, A. V. *J. Am. Chem. Soc.* **1975**, *97(21)*, 6279.

29) Komarynsky, M. A.; Weissman, S. I. *J. Am. Chem. Soc.* **1975**, *97(6)*, 1589.

30) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc. Perkin 1*, **1981**, 1501.

31) Barrett, A. G. M.; Prokopiou, P. A.; Barton, D. H. R. *J. Chem. Soc. Perkin 1*, **1981**, 1510.

32) Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tet. Lett.* **1981**, *22*, 2583. Ohsawa, T.; Oishi,T. *J. Inclussion Phenomena* **1984**, *2*, 185.

33) Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saicoh, T.; Oishi, T. *Tet. Lett.* **1985**, *26*, 6103.

34) Mathre, D. J.; Guida, W. C. *Tet. Lett.* **1980**, *21*, 4773.

35) Pez, G. P.; Mador, I. L.; Galle, J. E.; Crissey, R. K.; Forbes, C. E. *J. Am. Chem. Soc.* **1985**, *107*, 4098.

36) a) Seebach, D.; Meyer, N. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 438.
b) SeeBach, D.; Meyer, N. *Chem. Ber.* **1980**, *113*, 1290.

37) DePree, D. O.; Johnston, J. D. *U. S. Patent 3239568, Chem. Abstr*, **1966**, *64*, 15921e.

38) In *Chemical Abstracts* 12^{th} *Collective Index* **1987~1991**, there are over 100 entries for Hydroxymethylation.

39) Unreported results of the Farnum group.

40) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965** *87*, 1345.

41) Russel, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966** *88*, 5498.

42) Rathke, M. W.; Kow, R. *J. Am. Chem. Soc.* **1972**, *94*, 6854.

Kow, R.; Rathke, M. W. *J. Am. Chem. Soc.* **1973**, *95*, 2715.

43) Jedlinski, Z.; Misiolek, A.; Glowkowski, W.; Janeczek, H.; Wolinska, A. *Tetrahedron* **1990**, *46*, 3547.

44) Jedlinski, Z.; Misiolek, A.; Glowkowski, W. *Synlett* **1990**, 213.

45) Pierre, J. L.; LeGoaller, R.; Handel, H. *J. Am. Chem. Soc.* **1978**, 100, 8021.

46) Maercker, A. *Angew. Cehm. Int. Ed. Engl.* **1987**, *26*, 972.

47) Cauliez, P. M.; Jackson, J. E.; Dye, J. L. *Tet. Lett.* **1991**, *32*, 5039.

48) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600.

49) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1964**, *86*, 1761.

50) Williams, D. H.; Wilson, J. M.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 6280.

51) Hamrick, P. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 493.

52) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

53) Venkataramani, P. S.; Reusch, W. *Tet. Lett.* **1968**, *51*, 5283. Reusch, W.; Grimm, K.; Karoglan, J. E.; Martin, J.; Subrahamanian, K. P.; Toong, Y-C.; Venkataramani, P. S.; Yordy, J. D.; Zoutendam, P. *J. Am. Chem. Soc.* **1977**, *99*, 1953. Reusch, W.; Grimm, K.; Karoglan, J. E.; Martin, J.; Subrahamanian, K. P.; Venkataramani, P. S.; Yordy, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 1958.

54) Schleyer, P.v.R. *Pure & Appl. Chem.* **1984**, *56*, 151.

55) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448 and reference contained within.

56) Dye, J. L.; Huang, R. H. *Pure & Appl. Chem.* **1993**, *65*, 435.

57) Walker, J. F. *Formaldehyde 3rd* Reinhold Publishing Co., New York, **1964**.

58) Eschweiler, W. *Chem. Ber.* **1905**, *38*, 880.

59) Clarke, H. T.; Gillespie, H. B.; Weishuas, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571.

60) Moore, M. L. *Org. React.* **1949**, *5*, 301.

61) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268.

62) Bianchi, A.; Micheloni, M.; Paoletti, P. *Coord. Chem. Rev.* **1991**, *110*, 17

63) Christensen, J. J.; Eatough, D. J.; Izatt, R. M. *Chem Rev.* **1974**, *74*, 351.

64) Parker, D. *Chem. Soc. Rev.*, **1990**,*19*, 271

65) Bridges, G. J.; Skerlj, R. T.; Thornton, D.; Padmanabhan, S.; Martellucci, S. A.; Henson. G. W.; Abrams, M. J.; Yamamoto, N.; DeVreese, K.; Pauwels, R.; DeClercq, E. *J. Med. Chem.* **1995**, *38*, 366.

66) Koike, T.; Kimura, E. *J. Am. Chem. Soc.* **1991**, *113*, 8935.

67) Nam, W.; Ho, R.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7052

68) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.*, **1992**, *57*, 5383

69) Bushnell, G. W.; Fortier, D. G.; McAuley, A. *Inorg. Chem.*, **1988**, *27*, 2626

70) Tanaka, N.; Kobayashi, Y.; Takamoto, S. *Chem. Lett.*,**1977**, 107

71) Wieghardt, K.; Tolksdorf, I.; Herrmann, W. *Inorg. Chem.*, **1985**, *24*, 1230

72) Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. J. *Chem. Rev.*, **1989**, *89*, 929.

73) Bernhardt, P. V.; Lawrance G. A. *Coord. Chem. Rev.*, **1990**, *104*, 297.

74) Chavez, F.; Sherry, A. D. *J. Org. Chem.*, **1989**, *54*, 2990 and references contained in it. Tomohiro, T.; Uoto, K.; Okuno, H. *J. Heterocyclic Chem.*, **1990**, *27*, 1233.

75) Alcock, N. W.; Kingston, R. G.; Moore, P.; Pierpoint, C. *J. Chem. Soc. Dalton Trans.* **1984**, 1937. Alcock, N. W.; Moore, P.; Pierpoint, C. *J. Chem. Soc. Dalton Trans.* **1984**, 2371.

76) Studer, M.; Kaden, T. A. *Helvetica Chimica Acta,* **1986**, *69*, 2081. Akkaya, E. U.; Huston, M. E.; Czarnik, A. W. *J. Am. Chem. Soc.* **1990**, *112*, 3590. Helps, I. M.; Parker, D.; Morphy, J. R.; Chapman, J. *Ter. Lett.* **1989**, *45*, 219. Kimura, E.; Fujioka, H.; Kodama, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1158.

77) Kruper, W. J.; Rudolf, P. R.; Langhoff, C. A. *J. Org. Chem.*, **1993**, *58*, 3869.

78) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M.; Zamecka-Krakowiak, D. J. *Tet. Lett.*, **1990**, *31*, 1077. Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *J. Heterocyclic Chem.*, **1989**, *26*, 1431.

79) Hediger, M.; Kaden, T. A. *Helvetica Chimica Acta*, **1983**, *66*, 861.

80) Bernard,H.; Yaouanc, J. J.; Clement, J. C.; Abbayes, H.; Handel, H. *Tet. Lett.*, **1991**, *32*, 639.

81) Alder, R. W.; Mowlam, R. W.; Vachon, D. J.; Weisman, G. R. *J. Chem. Soc., Chem. Commun.*, **1992**, 507

82) Ciampolini, M.; Micheloni, M.; Nardi, N.; Paoletti, P. *J. Chem. Soc. Dalton Trans.* **1984**, 1357.

83) Ciampolini, M.; Fabbrizzi, L.; Perotti, A.; Poggi, A.; Seghi, B.; Zanobini, F. *Inorg. Chem.* **1987**, *26*, 3527.

84) Qian, L.; Sun, Z.; Mertes, M. P.; Mertes, K. B. *J. Org. Chem.* **1991**, *56*, 4904.

85) Lazar, I.; Sherry, A. D. *J. Chem. Soc., Chem. Commun.*, **1991**, 1252.

86) Studer, M.; Riesen, A.; Kaden, T. A. *Helvetica Chimica Acta*, **1989**, *72*, 307

87) An unreported procedure of the Farnum group.

88) Ohsawa, T.; Takagaki, T.; Ikehara, F.; Takahashi, Y.; Oishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 3178 and references contained within.

89) Merril, B. A. Phd. Dissertation, Michigan State University, **1990**.

90) Larock, R. C. *Comprehensive Organic Transformations* VCH Publishers, Inc., New York, New York, **1989** page 437.

91) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

92) Page 972~976 of reference 90.

93) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589, and references contained within.

94) Roe, E. T.; Scanlan, J. T.; Swern, D. *J. Am. Chem. Soc.* **1949**, *71*, 2215.

95) March, J. *Advanced Organic Cheimstry: Reactions, Mechanisms, and Structure* 4^{th} *Ed.*, John Wiley & Sons, New York, New York, **1992**, page 1203. Kaiser, J. *J. Am. Chem. Soc.* **1967**, *89*, 3659.

96) Sessler, J. L.; Sibert, J. W. *Tetrahedron*, **1993**, *49*, 8727. Sessler, J. L.; Sibert, J. W.; Lynch, V. *Inorg. Chem.*, **1990**, *29*, 4143

97) Compounds **24** and **25** were made in the Michigan State University Synthesis Laboratory using the modified procedure.