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Syntheses and conformational analyses of some cyclohexane-based 1,3-dipodands and 1,3,5-tripodands

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University of New Hampshire, 1987

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SYNTHESES AND CONFORMATIONAL ANALYSES OF SOME CYCLOHEXANE-BASED 1,3-DIPODANDS AND 1,3,5-TRIPODANDS

BY

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DISSERTATION

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Nov. 25 1987

Date

DEDICATION

This thesis is dedicated to my parents, brothers and to 

It is also dedicated to the memory of

Mrs. Premavati H. Shirodkar

Ideas and theories are like the wings of birds; they allow man to soar and to climb to the heavens. But facts are like the atmosphere against which those wings must beat and without which the soaring bird will surely plummet back to Earth.

— Ivan Pavlov

ACKNOWLEDGEMENTS

All this would not have been possible, at least by me, without the support and goodwill of a lot of friends.

I would like to thank my parents, Madhu Shirodkar and Vilas Shirodkar who have done everything possible so I can be what I am today. Warm thanks to Dr. G.R. Weisman for his guidance and direction in this research project. I am indebted to Tom Pascarella who was the guiding hand when I was a bumbling novice in laboratory. Special thanks to Micheal Clark who shared this somewhat trying experience of writing a thesis with me and was always there when needed. Joe Colleluori, John Peabody and Dana Gronbeck deserve a note of thanks for good camaraderie. Thank the Lord, the new fumehoods are better!

I wish to thank Dick Sweet whose mechanical genius was of invaluable assistance. My gratitude to Dr. P.K. Aggarwal who intiated me to the then unknown field of research as a high school student.

In conclusion, I am deeply indebted to Dr. Colin D. Hubbard whose has been a pillar of support and encouragement throughout my five-year association with the department.

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ABSTRACT

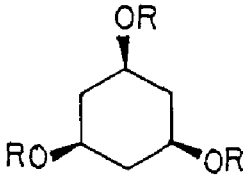
SYNTHESES AND CONFORMATIONAL ANALYSES OF SOME CYCLOHEXANE-BASED 1,3-DIPODANDS AND 1,3,5-TRIPODANDS

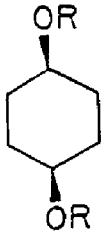
by

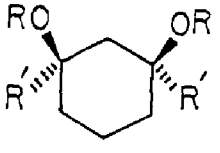
Shailaja M. Shirodkar

University of New Hampshire, December, 1987

A series of dipodands (**2**, **4** and **9**) as well as tripodands (**13**, **18**, **20**, **26** and **31**) have been synthesized and characterized. The general synthetic methodology followed involves alkylation of the cyclohexane-based alcohols with the "arm" tosylates.







2: $R'=H$; $R=(CH_2CH_2O)_2CH_3$

9: $R'=CH_3$; $R=(CH_2CH_2O)_2CH_3$

4: $R=(CH_2CH_2O)_2CH_3$

13: $R=CH_2CH_2O(CH_2)_3CH_3$

18: $R=CH_2CH_2O(CH_2)_{11}CH_3$

20: $R=CH_2CH_2OH$

26: $R=CH_2C(CH_3)_2(OCH_2CH_2)_2OCH_3$

31: $R=(CH_2CH_2O)_3CH_3$

The conformational aspects governing the complexation of these podands with alkali metal ions were studied by ^1H

NMR, ^{13}C NMR and ^{13}C dynamic NMR supported by complementary molecular mechanics studies. NMR studies have shown that dipodand **2** undergoes ring inversion to the 1,3-diaxial conformation upon complexation with $NaBPh_4$ in aprotic solvents. The relative complexing abilities of **2** and conformationally biased **9**, which served as a model for the 1,3-diaxial conformer of **2**, have been measured by ^{13}C NMR competition experiments. Experimental G^{o}_{298K} and theoretical E_S(ax-eq) are in close agreement (assuming entropy effects to be constant) indicating that podand **2** is strongly biased toward the ee conformation.

Lipophilic podand **18** and model **13** were studied for the possibility of micellar behavior of these molecules. The relative complexing abilities of podands **37**, **13**, **18** and **2** were compared by competition experiments.

"Extra long arm" podands **26** and **31** were found to be capable of complexing two Na^+ ions. The Na^+---Na^+ distance was estimated by CPK models to be approximately 3.2 A^{o}.

A concentration dependence study of 1:1 mixture of complex to free ligand was done in $CDCl_3$ by ^{13}C dynamic NMR. It reveals that the bimolecular rate constant predominates over the unimolecular rate constant and probably proceeds through a 2:1 associated intermediate thus avoiding release of naked Na^+ ion into the poor donor solvent $CDCl_3$.

I. INTRODUCTION

Scientific interest in the synthesis of macrocyclic compounds and the study of their molecular complexes has led to extensive research in the field of host-guest chemistry.

A host possesses binding sites which converge upon a guest thereby enveloping it in the cavity to form a host-guest complex. The binding forces which hold a complex together can be of a pole-pole, pole-dipole or dipole-dipole nature, more specifically hydrogen bonding, ion pairing, metal ion to ligand attractions and van der Waals attractive forces.[1] Factors such as the strength of these binding forces, number of binding sites as well as the ability of the host to organize its binding sites in a suitable geometric arrangement around the guest, all contribute to the complexing ability of the host. This organization of the binding sites can occur during complexation or may be inherent to the molecular structure of the host. The latter have received more attention since they form relatively stable complexes compared to those lacking structural pre-organization.

Two factors led to the explosive growth in the field of host-guest chemistry. In the late sixties, the unique membrane transport phenomena of ionophores such as valinomycin and nigericin were recognized. The function of these lipophilic ionophores as selective complexing agents for

ions such as Na^+, K^+ and Ca^{+2} was then established. Thus, they provided a means for transportion of cations across lipid membranes.[2-4] The other factor was Pedersen's discovery of the "crown ethers", synthetic macrocyclic polyethers which mimicked the ion-selective properties of the natural ionophores.[5]

Since then a wide variety of macrocylic polyethers compounds have been synthesized including crowns,[6] podands,[7] cryptands[8] and spherands.[9] These have been used successfully for diverse processes such as separation of ions through artificial and natural membranes, liquid-liquid and solid-liquid phase transfer reactions, dissolution of salts in apolar solvents of salts, preparation of ion-selective electrodes, and as models to aid understanding of some natural processes through mimicry of metalloenzymes.[10-11]

One aspect of host-guest chemistry which has challenged and inspired organic chemists has been to gain a precise knowledge of the conformational changes in the host molecule upon ion capture to form the complex.[1,2,12,13] Structural molecular complexation is inherent to biological phenomena such as enzyme catalysis and inhibition, biological regulatory function, drug metabolism and ion transfer through membranes. Information obtained from structural studies of macrocylic polyether compounds and their complexes provides insight into more complicated biological processes involving selective binding.

Podands or open-chain polyether ligands are of

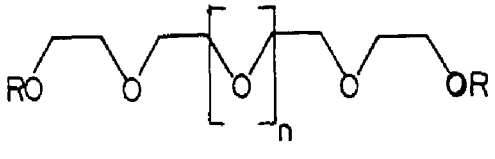
interest because their flexibility allows for an optimum topological fit between the host and guest molecules. Additionally, these ligands are easier and more economical to synthesize than their macrocylic counterparts since they require use of neither dilution principle nor template effect. However, they form weaker complexes (podates) with alkali metal ions as compared to crowns and cryptands.

This has been attributed to the "macrocylic effect"[14] which is partly entropic in origin.[15] The entropy loss upon reorganization into a suitable complexing conformation as well as the greater degree of solvation experienced by donor sites are thought to be responsible for the relative instability of podates as compared to coronand complexes.

Podands have been discussed extensively in reviews[16,17] therefore only a few examples are presented herein:-

(I) Podands without donor end groups:

The simplest podands are the linear oligoethylene glycol dimethyl ethers (glymes)[18] [Figure 1].



1: R = CH_3, n = 1

2: R = CH_3, n = 2

3: R = CH_3, n = 3

4: R = CH_3, n = 4

5: R = Ph, n = 4

6: R = Ph, n = 4

Figure 1

Ligands of this type are of great interest because, although they form relatively weak complexes with alkali metal ions, they do exhibit selectivity.[19] For example, compound **5** shows the highest selectivity for K^+ of all podands tested. Vogtle and coworkers[20] have recently reported crystalline complexes of compound **3** with $Ba(SCN)_2$, compound **4** with $Ca(SCN)_2$ and compound **6** with $Ba(SCN)_2$. An X-ray crystallographic study[21] of ligand **6** in its $Ba(SCN)_2$ complex reveals the helical manner in which it wraps around the ion.

(II) Podands with aromatic donor end groups:

Vogtle and coworkers[22,23] have shown that heteroatoms located in terminally rigid groups on the oligo(ethylene glycol) backbone as in podands **7a-g, 8a-d** and **9a-d** [Figure 2] can serve to stabilize podate formation ("terminal group concept"). They were able to obtain stable crystalline complexes of these podands with alkali and alkaline earth metal ions but unlike podands without donor groups, these types of ligands show low selectivity.

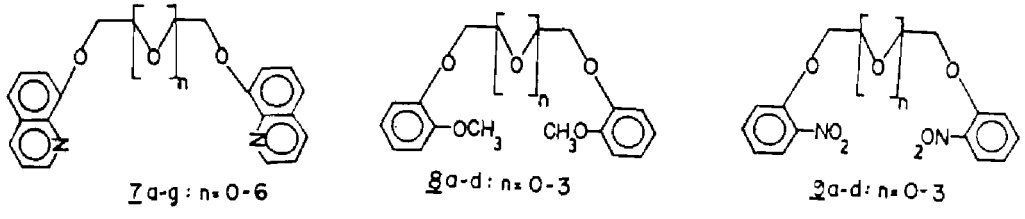


Figure 2

X-ray crystal structure studies of RbI complexes of **7a** and **7d**, carried out by Saenger et al. [24] indicate that short

ligands like **7a** (containing 5 heteroatoms) formed circular complexes; extension by one to five heteroatoms as in ligand **7d** led to helical complexes.

(III)Polypodands:

Polypodands can be defined as many-armed neutral ligands. These compounds not only hold the promise of strong complexation but also allow one an opportunity to gain an understanding of complex stereochemical conformations.

Vogtle et al.[25] were first to describe such molecules and they called their benzene-based hexapodands "Octopus molecules" [Figure 3].

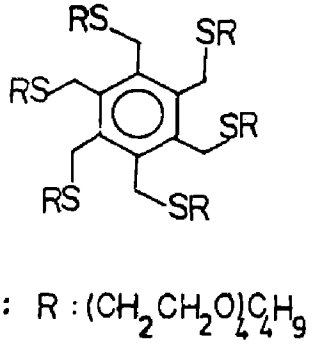


Figure 3

They have synthesized a series of these compounds and have compared their complexing abilities to find that the complexing ability diminishes when

a) the number of donor sites on the arms is decreased and

b) the number of arms successively reduced [Figure 4].

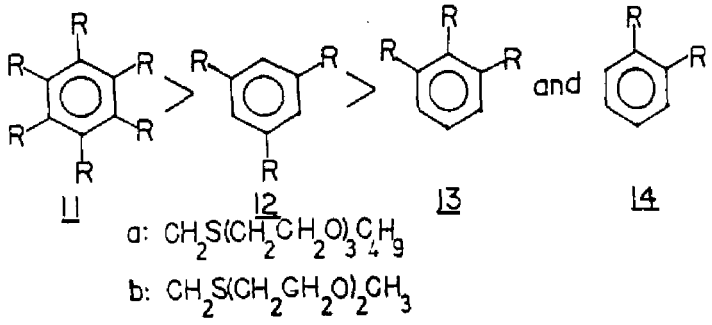


Figure 4

So, the most stable complex was formed by **11a.** Among the positional isomers, the 1,3,5 isomer, **12a** was less efficient than **11a** but more efficient than the 1,2,3 isomer, **13a** or the 1,2 isomer, **14a.**

Hyatt[26] has similarly reported hexapods derived from cyclotriveratrylene [Figure 5] and investigated their complexing ability of various salts using phase transfer methodology.

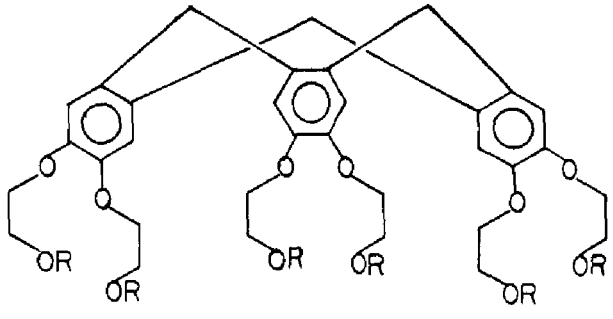
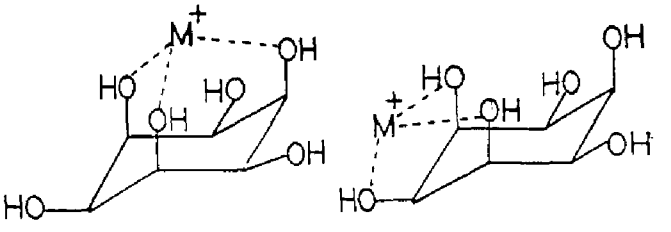


Figure 5

Complexation of cyclitols such as cis-inositol and epi-inositol has been studied extensively by Angyal and

coworkers[27-29]. Their investigations by paper electrophoresis and NMR revealed that cis-inositol **15** showed the greatest electrophoretic mobility in metal acetate solutions. This can be explained by the reasoning that cis-inositol has four potential binding sites, an a,a,a array and three a,e,a arrays. On the other hand, epi-inositol **16** which has only one a,e,a orientation of OH groups showed ca. one-third of the mobility of cis-inositol [Figure 6].



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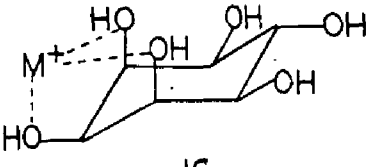


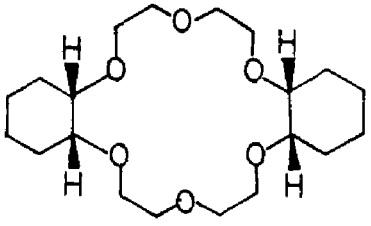
16

Figure 6

We have been particularly interested in gaining a better understanding of the conformational aspects governing complexation of cyclohexane-based podands. Some studies have been reported in literature citing conformational studies of cyclohexane-based hosts.

Buchanan and coworkers[30-34] have studied ring reversal in two configurationally isomeric dicyclohexano-18-crown-6 ethers **17** and **18** and in cis-Cyclohexyl-15-crown-5-ether **19**

by ^{13}C NMR in order to determine the free energy of activation for degenerate ring inversion in these hosts [Figure 7].



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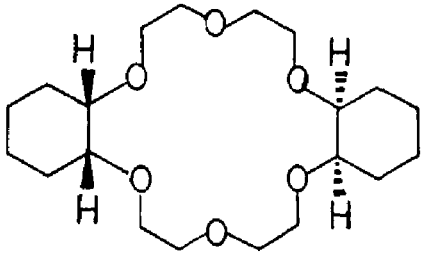

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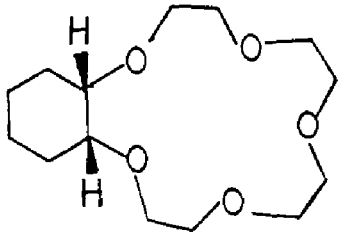


19

Figure 7

The cyclohexyl ring inversion barrier in crown ether **19** was determined to be ca 10.3 kcal mol^{-1}.[34] Sodium ion complexation increased this barrier by ca 0.5 kcal mol^{-1} whereas potassium ion complexation had no measurable effect.

Raban[35-36] et al. chose compounds **20** ("flipped out ionophores") to probe the effect of conformational biasing on the complexation ability of these compounds with alkali metal ions [Figure 8].

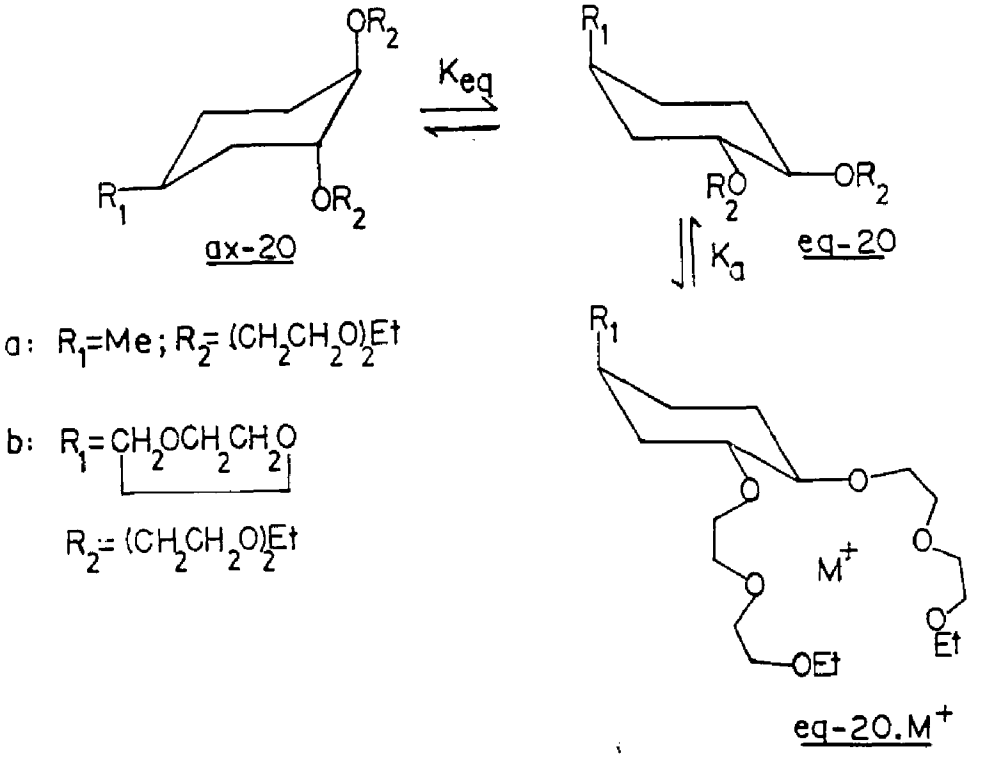


Figure 8

The equilibrium constants for potassium ion complexation by compounds **20** were calculated using low temperature NMR spectroscopy by the following equations.

For **20a:** $K_a = \dfrac{(R-K_{eq})(1+R)}{K_{eq}[M(R+1)-I(R-K_{eq})]}$

For **20b:** $K_a = \dfrac{R}{K_{eq}[M-(RI)/(1+R)]}$

where $R = [eq\text{-}(\mathbf{20})+eq\text{-}(\mathbf{20}).K^+]/ax\text{-}(\mathbf{20})$

$K_{eq} = eq\text{-}\mathbf{20}/ax\text{-}\mathbf{20}$

I= total polyether conc.; M= total metal salt conc.

For **20a:** K_{eq}= 0.1; K_a= 1600; K_aK_{eq}= 160 mol^{-1}

For **20b:** K_aK_{eq}= 23 mol^{-1}

K_aK_{eq} is a measure of how well the exothermicity of complexation can overcome the conversion of axial conformation (ax-**20**) into a conformation suitable for complexation (eq-**20**). They found this value to be larger for **20a** compared to **20b** due to the size difference in the R_1 substituents.

The intention of research presented in this thesis was twofold.

1) To carry out syntheses of various substituted cyclohexane-based podands and

2) to study by NMR, the conformational changes undergone by these hosts upon complexation by alkali metal ions and to perform complementary molecular mechanics calculations.

II. RESULTS AND DISCUSSION

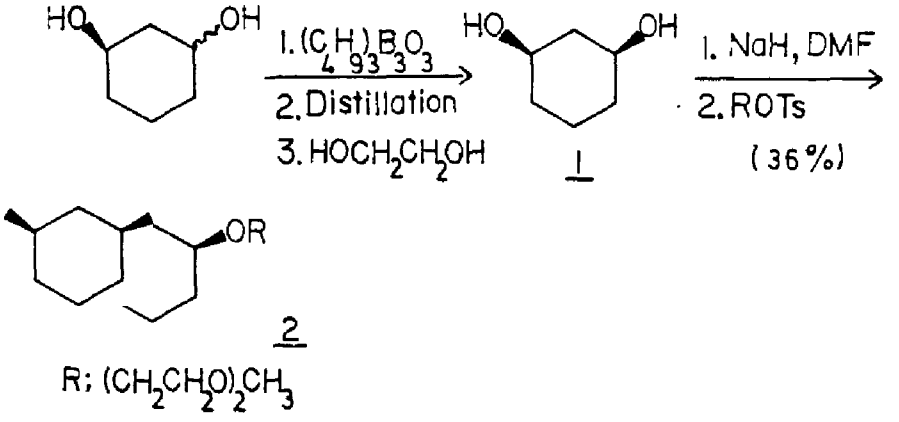
Syntheses

The general strategies and experimental concepts involved in the synthesis of macrocyclic polyethers have been extensively reviewed elsewhere.[37-39] The syntheses of a variety of cyclohexane-based podands are the focus of this chapter.

Dipodands:

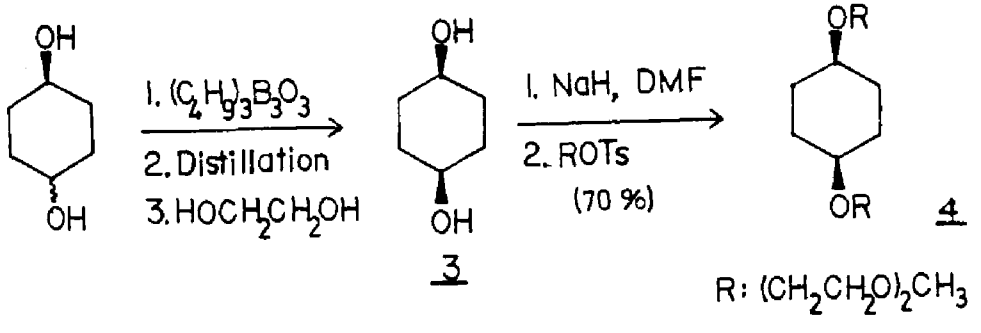
The synthesis of cis-1,3-bis(1,4,7-trioxaoctyl)cyclohexane **2** is outlined in Scheme 1. In an initial attempt a commercial cis,trans-1,3-cyclohexanediol mixture was alkylated with 2-(2-methoxyethoxy)ethyl-p-toluenesulfonate[40] However,separation by chromatography was unsuccessful in separating the two isomeric podands. Thus, the strategy used successfully involved prior separation of the cis-diol **1** from the cis-trans mixture followed by alkylation.

The precursor, cis-1,3-cyclohexanediol **1** was separated from a cis-trans mixture by esterification of the cycloalkane-1,3-diols with n-butylboroxine[41] (Scheme 1). The alkoxide of **1** was treated with 2-(2-methoxyethoxy)ethyl-p-toluenesulfonate followed by extraction, column chromatography and kugelrohr distillation to afford dipodand **2** in 36% calculated total yield.



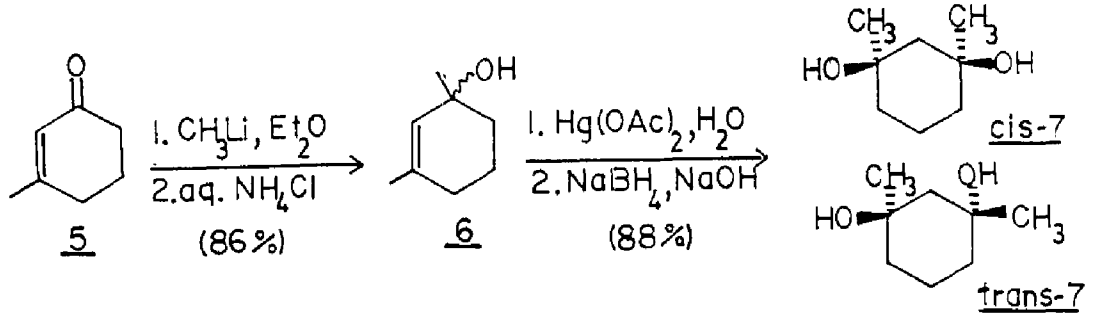
Scheme 1

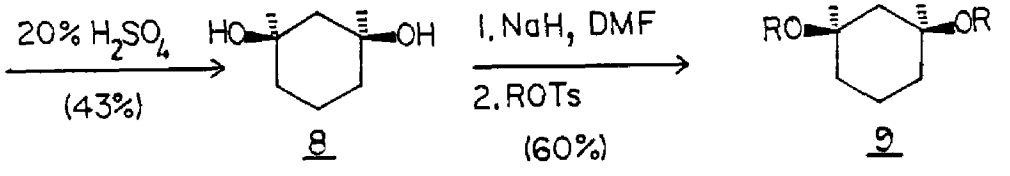
Using the same methodology as described for dipodand **2**, cis-1,4-bis(1,4,7-trioxaoctyl)cyclohexane **4** was synthesized as shown in Scheme 2. cis-1,4-Cyclohexanediol **3** was isolated from a commercial cis-trans mixture according to the procedure described by Brown and Zweifel.[41] The dipodand **4** was prepared by the reaction of diol **3** with NaH followed by treatment with 2-(2-methoxyethoxy)ethyl-p-toluenesulfonate in DMF in 70% yield.



Scheme 2

The synthetic scheme for cis-1,3-dimethyl-1,3-bis (1,4,7-trioxaoctyl)cyclohexane is delineated in Scheme 3. The reaction of MeLi in ether (conc. determined by titration[42]) with 3-methyl-2-cyclohexen-1-one **5** followed by workup and vacuum distillation produced only the 1,2-addition product,[43] 1,3-dimethyl-2-cyclohexen-1-ol **(6)**[44,45] in 86% yield. Hydroxymercuration[46] of compound **6** followed by reduction of the organomercurial intermediate by $NaBH_4$ in aq NaOH resulted in a approximately 3:1 ratio of cis-**7** to trans-**7** diols.





Scheme 3

Initial attempts to isomerize mixture **7** to the cis-1,3-dimethyl-1,3-cyclohexanediol **8** in the presence of acid were unsuccessful. Meinwald and Yankeelov[47] have reported the isomerization of trans-1,3-dimethyl-1,3-cycohexanediol to its cis isomer in 20% (v/v) H_2SO_4 in H_2O. The cis-trans mixture **7** was converted to the cis-isomer **8** only when the

precise reaction conditions reported by Meinwald and co-worker were followed. Otherwise, elimination products were the major component. It appears that concentration of the diol and the acid were critical for the isomerization to proceed successfully.

The stereochemistry of the cis-diol **8** was confirmed based on the following experimental observations. An IR study was done in CCl_4 which showed that with increasing dilution, the stretch at 3320 cm^{-1} (intermolecularly bonded OH) disappeared while the 3600 cm^{-1} stretch (free OH) and the 3520 cm^{-1} (internally bonded OH) decreased in constant ratio [Figure 9]. The experimental mp was 88-91^{o}C which compared well with the literature mp[47] of 92^{o}C. The ^{13}C NMR showed only 5 peaks compared to the cis-trans mixture which showed nine peaks.

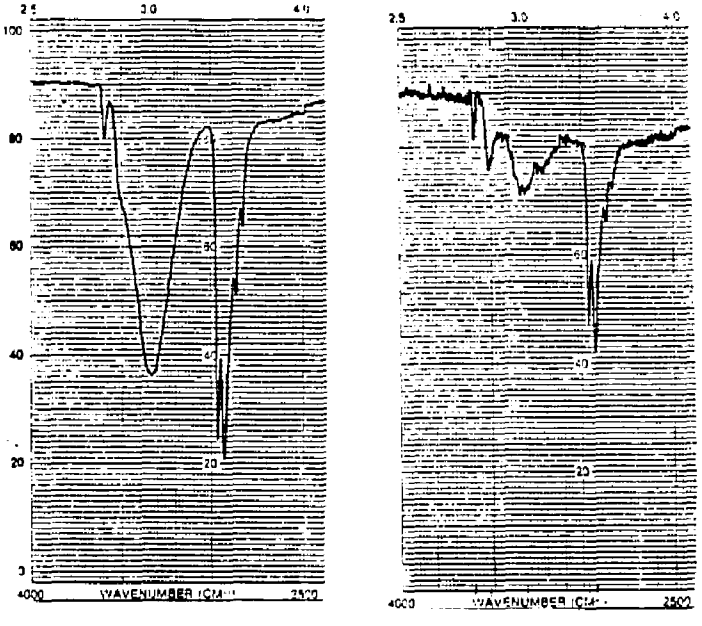


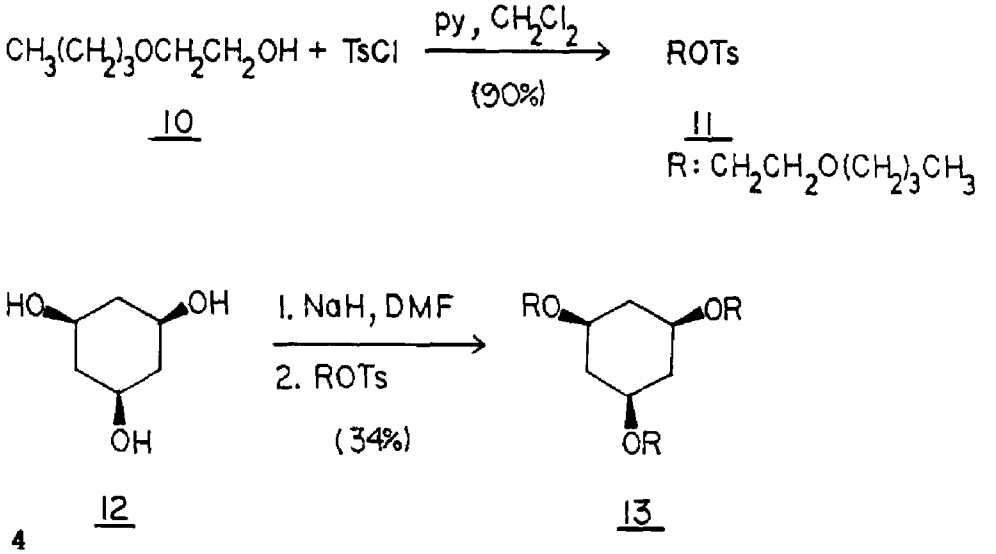
Figure 9

Deprotonation of diol **8** with NaH followed by treat-

ment with 2-(2-methoxyethoxy)ethyl-p-toluenesulfonate afforded the dipodand, cis-1,3-dimethyl-1,3-bis(1,4,7-trioxaoctyl)cyclohexane (**9**) in 60% calculated total yield. An off-resonance ^{13}C NMR spectrum revealed the correct multiplicities for the carbon resonances of podand **9**.

Tripodands:

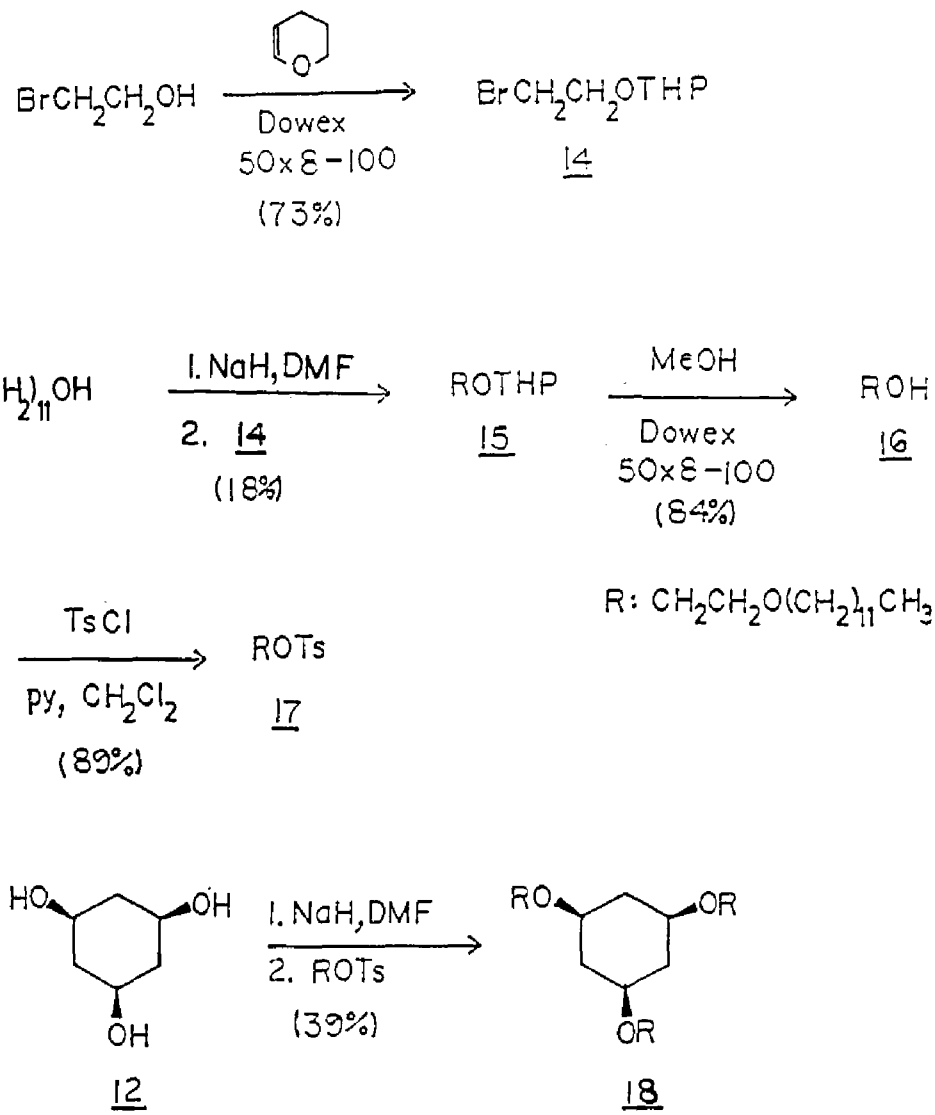
The synthesis of tripodand **13** was carried out as depicted in Scheme 4. Reaction of p-toluenesulfonyl chloride with 2-butoxyethanol **10** and pyridine under ice-cold conditions led to the formation of tosylate **11**.[48] Deprotonation of cis,cis-1,3,5-cyclohexanetriol[49] (**12**) with NaH followed by treatment with tosylate **11** in DMF gave tripodand 13 in 34% calculated total yield after column chromatography (Scheme 4).



Scheme 4

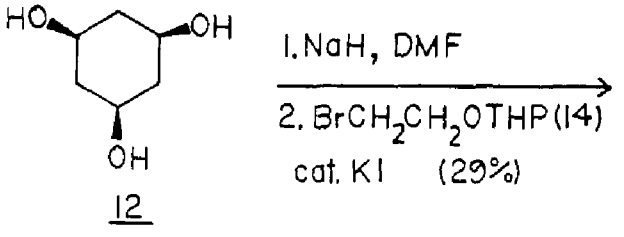
In order to synthesize tripodand **18**, (Scheme 5) 2-dodecyloxyethanol **16** needed to be prepared first. The strategy chosen was the protection[50] of 2-bromoethanol as a

tetrahydropyranyl ether **(14)**,[51] alkylation of the conjugate base of 1-dodecanol with compound **14** and finally deprotection of **15** with methanol and Dowex 50x8-100 acidic ion exchange resin to unveil alcohol **16**[52]. Tosylate **17** was formed by reaction of **16** with p-toluenesulfonyl chloride and pyridine. Deprotonation of cis,cis-1,3,5-cyclohexanetriol with NaH followed by treatment with tosylate **17** lead to tripodand **18** in 39% calculated yield.



Scheme 5

Podand **19** was prepared as shown in Scheme 6. The reaction of cis,cis-1,3,5-cyclohexanetriol with NaH followed by addition of 2-(2-Bromoethoxy)tetrahydropyran **14** in the presence of a catalytic amount of KI lead to the formation of **19** in 29% yield.



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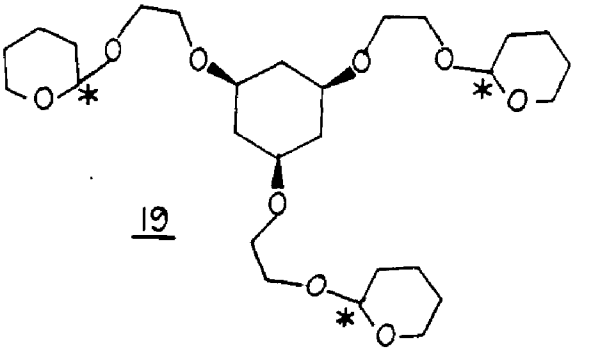
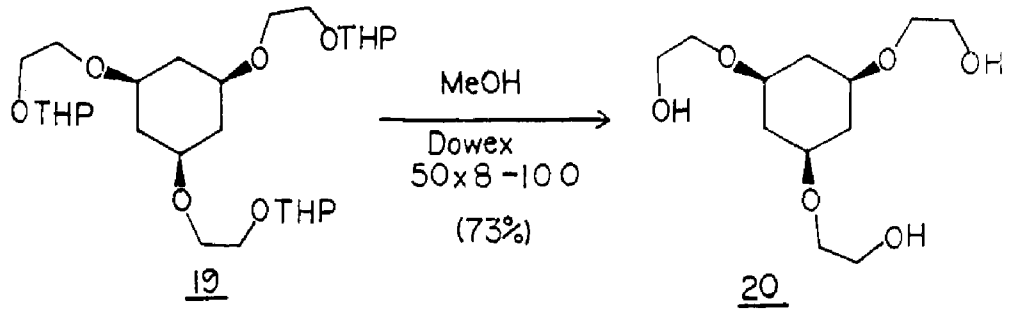


19

Scheme 6

Compound **19** was expected to be a diastereomeric mixture consisting of two enantiomeric pairs, RRR, SSS and RRS, SSR. This was proven by a ^{13}C NMR study which revealed that complexation of compound **19** with 1 eq. of $NaBPH_4$ showed distinct peaks for the two enantiomeric pairs. This study is described in detail in the next chapter.

Deprotection of THP-protected **19** to the triol **20** proved to be straightforward and provided 73% yield of the oily triol **20** after bulb-to-bulb distillation (Scheme 7).



Scheme 7

In the future, triol **20** will be a useful synthetic intermediate for the synthesis of a variety of new interesting podands [Figure 10].

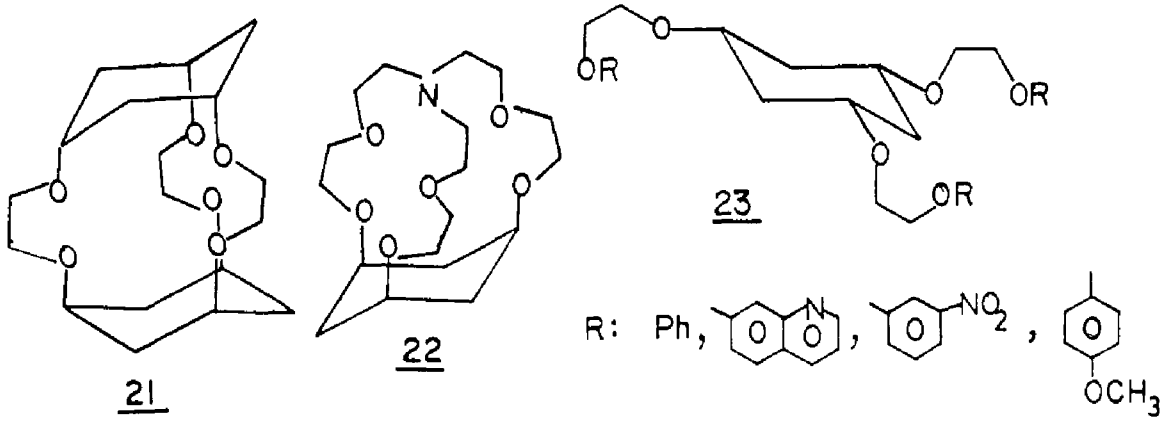


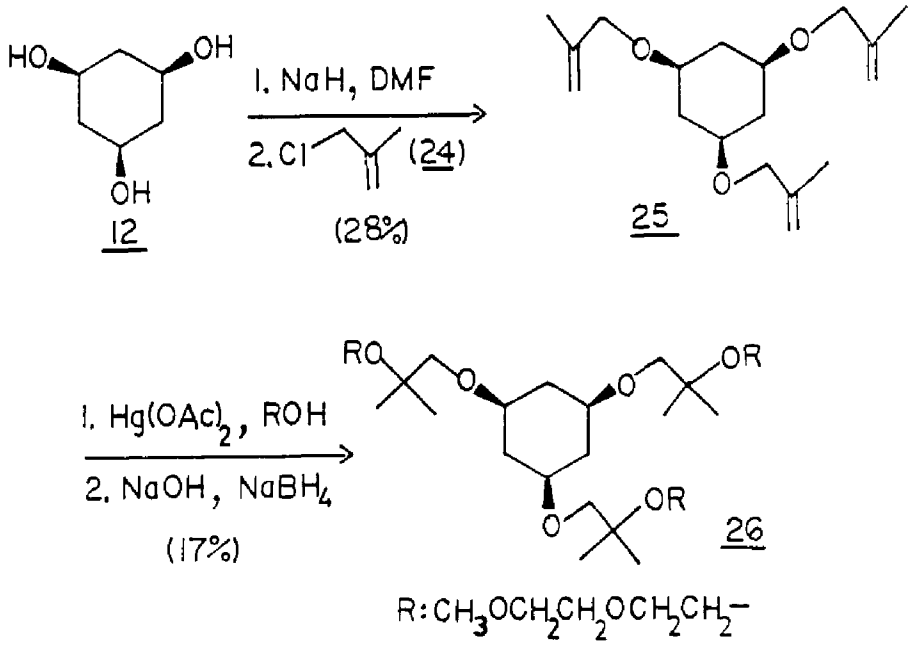
Figure 10

Compounds **21** and **22** represent examples of "capped" podands. Synthesis of the functionalized podands **23** would

allow the study of complexation of alkali metal ions as a function of their absorption spectra.

We speculated that the "extra long arm" tripodands described below would be capable of encapsulating more than one equivalent of $NaBPh_4$ per equivalent of tripodand.

A two step synthetic sequence was used for the preparation of the "extra long arm" tripodand **26** as dilineated in Scheme 8. Trimethyallyl intermediate **25**[53] was prepared by deprotonation of cis,cis-cyclohexanetriol with NaH followed by alkylation with an excess of 3-chloro-2-methylpropene **(24)** in the presence of KI. Pure **25** was obtained by column chromatography on silica gel. Alkoxymercuration[54] of **25** using a large excess of mercuric acetate in anhydrous 2-(2-methoxyethoxy)ethanol followed by demercuration of the mercurial intermediate with $NaBH_4$ and aq NaOH and distillation to remove excess alcohol afforded crude **26**. Thin layer chromatography revealed several spots. Compound **26** was obtained after column chromatography on alumina (1% EtOH-CH_2Cl_2) in slightly impure form as shown by ^{13}C NMR which showed presence of a small amount of starting material **25**.

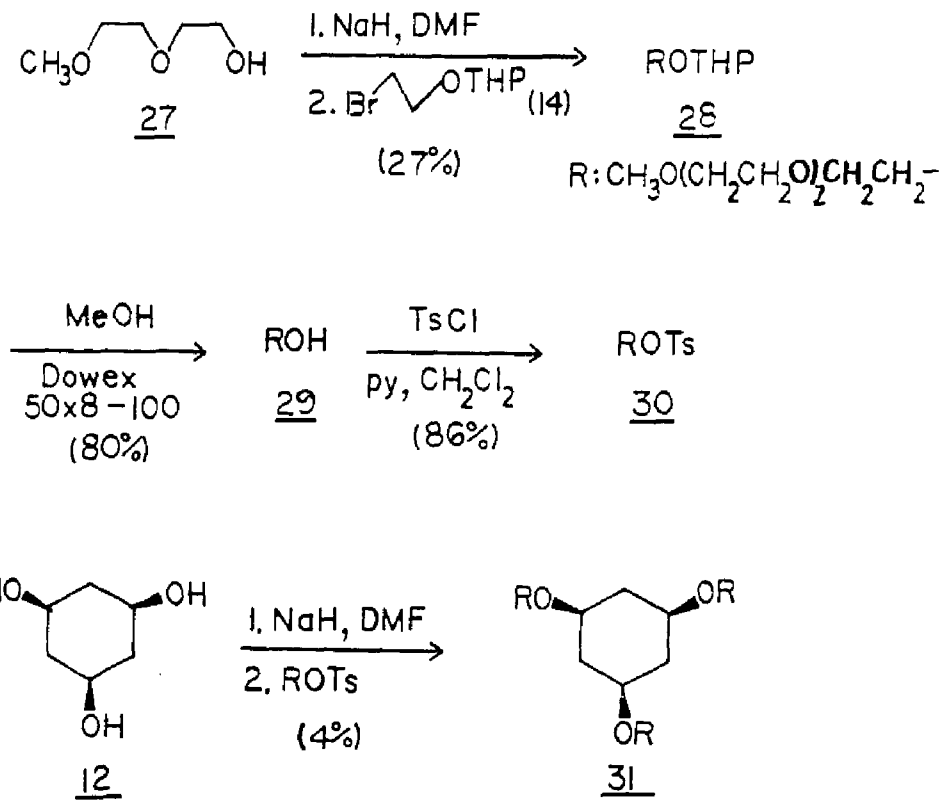


Scheme 8

Scheme 9 illustrates the strategy involved in the synthesis of tripodand **31**. The synthesis of the "arm" comprised the first stage, followed by alkylation of the cyclohexanetriol to give compound **31**.

Deprotonation of 2-(2-methoxyethoxy)ethanol **(27)** with NaH followed by alkylation with compound **14** afforded protected alcohol **28** in 27% yield. One possible reason for the low yield could be the elimination of compound **14** with excess base. Deprotection[50] of **28** with methanol and Dowex 50x8-100 was readily accomplished leading to alcohol **29**.[55] The tosylate **30**[56] was prepared by treatment of **29** with tosyl chloride and pyridine in CH_2Cl_2, in 86% yield. cis,cis-1,3,5-cyclohexane triol was subjected to alkylation conditions

using NaH as base and tosylate **30** in DMF to give tripodand **31.**



Scheme 9

Hexapodands:

We were also interested in investigating complexation of alkali metal salts by inositol-based hexapodands [Figure 11]. cis-Inositol-based hexapodand **32** contain four potential binding sites: a 1,3,5-aaa and three 1,2,3-aea and would be conformationally degenerate while scyllo-Inositol hexapodands **33** contain two cavities, each 1,3,5-aaa.

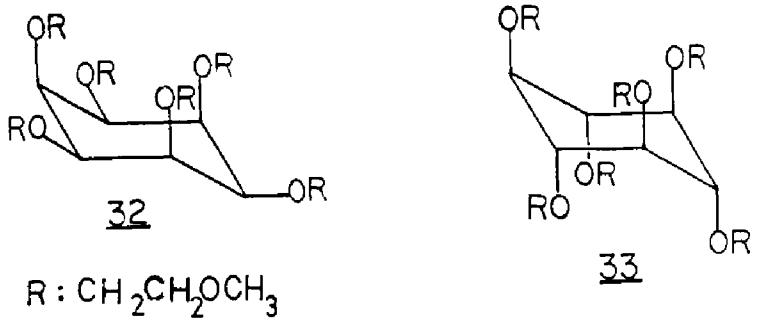
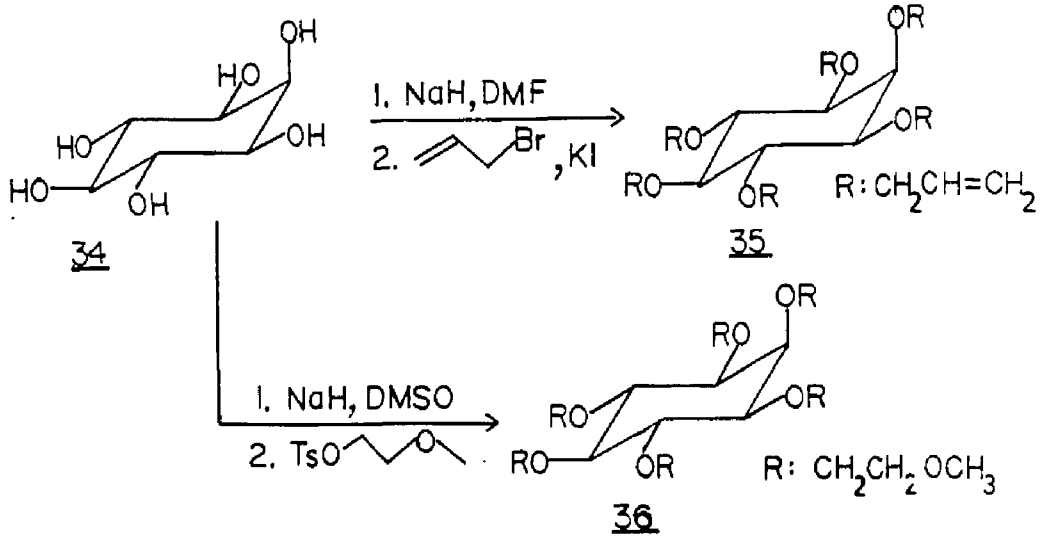


Figure 11

Therefore, we attempted to synthesize model compounds **35** and **36** from readily available myo-inositol (**34**) (Scheme 10) to see if alkylation of all six sites was feasible. All attempts, however, were unsuccessful and lead to mixtures of compounds due to incomplete alkylation of **34** as shown by TLC.



Scheme 10

One possible future solution to the problem of incomplete alkylation would be to selectively protect the three axially disposed hydroxyl groups in myo-inositol as described by Kishi and coworker[57] followed by alkylation, deprotection and further alkylation [Figure 12].

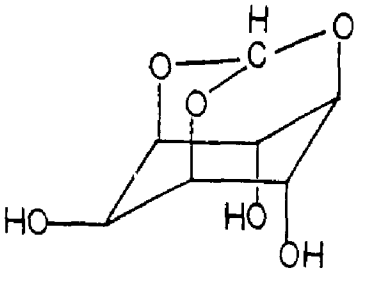


Figure 12

III. RESULTS AND DISCUSSION

Complexation Studies

Since Pedersen's discovery of the "crown ethers", complexation of macrocylic polyethers with metal ions both in polar and apolar solvents, has been studied extensively. The stability (or complexation or association) constants of the ligands have been measured as follows:

a) by potentiometry using cation selective electrodes, calorimetry, conductance, nuclear magnetic resonance (NMR) and other techniques for polar solvents[61,62] and

b) by spectroscopic methods, after a liquid-liquid extraction in apolar solvents.[61-62]

Unlike other complexing agents such as crowns and cryptands, podands form weaker complexes known as podates with alkali metal ions. To gain a better understanding of this, one must look at the ΔG^{o} of the complexation process.

The free energy of complexation of podands, ΔG^{o} for equilibrium eq. 2, can be expressed as shown in eq. 3.

$$M^{+} + L \rightleftharpoons ML^{+} \qquad (1)$$

$$K_{obs} = \frac{[ML^{+}]}{[M^{+}]\ [L]} \qquad (2)$$

$$\Delta G^{o} = -RT \ln K_{obs} \qquad (3)$$

where L = free ligand

M^+ = alkali metal cation

ML^+ = ligand-metal cation complex

and K_{obs} = stability constant

The complex stability is dependent upon the factors affecting the free energy change, ΔG^o. These factors are:

1) the binding energy due to the interaction of the ligand donor groups with the cation,

2) the relative solvation energies of ligand, cation and complex and

3) the energy associated with the conformational change of the ligand upon complexation of cation.

ΔG^o can be further broken down into enthalpic (ΔH^o) and entropic (ΔS^o) terms (eq 4).

$$\Delta G^o = \Delta H^o - T\Delta S^o \qquad (4)$$

The total conformational change of the ligand upon complexation and changes in solvation contribute to complexation enthalpy. The changes in entropy are affected by changes in the total number of species, respective solvation entropies of the ligand, free metal ion, and complex, and the differential conformational entropy of ligand vs. the complexed ligand. Thus, ΔS^o values provide information about the loss of degrees of freedom upon complexation[63,64].

The complex formation in podands is generally thought to be enthalpically favored and entropically disfavored, i.e. $\Delta H^o < 0$ and $\Delta S^o < 0$.[63,65]

We have been particularly interested in investigating the relationship between the conformational aspects of

podate formation and the thermodynamic and kinetic factors involved in the process.

The following criteria led to the choice of cyclohexane-based oligopodands as models for study of the above mentioned relationship.[66] We sought:

1) restriction of the number of ligand and complex conformers,
2) well-defined conformational changes upon complexation,
3) systems in which the ligand and complex would be suitable for study by ^{1}H NMR and ^{13}C NMR, as well as by DNMR,
4) systems which could easily be altered by addition of substituents, and
5) systems amenable to functional group modification.

Syntheses of some cyclohexane-based podands have been described in Chapter 2. Herein, the related complexation studies using ^{1}H NMR, ^{13}C NMR and DNMR, as well as molecular mechanics modeling are discussed. Methods and results are presented first followed by the discussion of results.

METHODS AND RESULTS

^{1}H NMR Complexation studies:

It has previously been shown[67] that ^{1}H NMR of podand **37** before and after addition of $NaBPh_4$ salt shows drastic differences in the splitting pattern of the ring protons. This is indicative of a cyclohexane ring inversion to the **aaa** conformation to allow the oxygen donor atoms to envelop the cation (**37.Na$^+$**) [Figure 13].

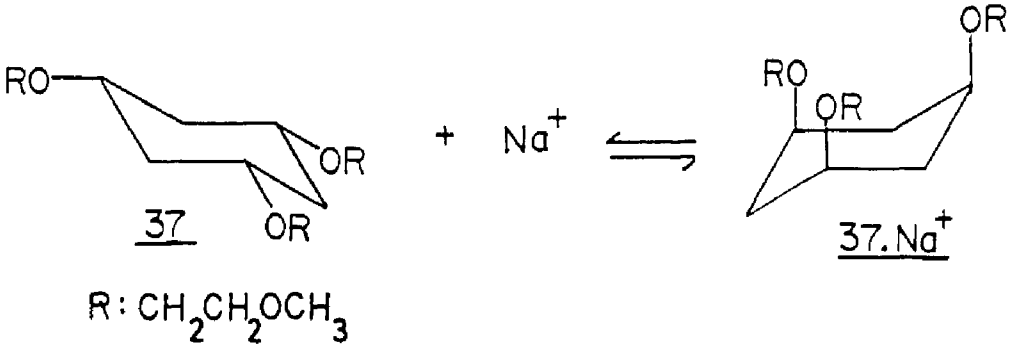


Figure 13

Reinhoudt and coworkers[68] have described a method for the direct determination of complexation constants of crown ethers in apolar solvents with alkali metal salts. The alkali salts employed were trichloro(ethylene)platinum (II) salts (Na^+, K^+, Rb^+, Cs^+) and solvent was $CDCl_3$. ^{1}H NMR was used for the determination of the equilibrium ratio of complexed to free crown ether. The relative intensities of the ethylene and crown ether protons were determined by integration. The inherent solubilities of the platinum (II) salts in the solvent were determined separately by atomic absorption spectrometry. The Reinhoudt method proved to be a simple detection technique to monitor complexation and pro-

vide complexation constants in apolar solvents by a solid-liquid two-phase method.

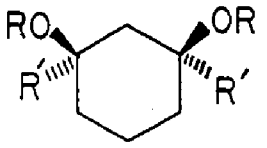
In a variation of the Reinhoudt method, we have used tetraphenylboron (BPh_4^-) as the counterion to determine the stability constant (K_{obs}) of $NaBPh_4$ complexes of various podands in $CDCl_3$.

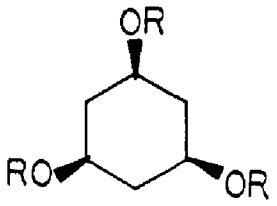
In each case, the podand and slightly more than one equivalent of $NaBPh_4$ were dissolved in $CDCl_3$ and allowed to equilibrate. The fraction of podand complexed was determined by the formula:

$$\text{Fraction of podand complexed} = \frac{\left(\frac{\text{Integrated area of the } BPh_4^- \text{ resonances}}{\text{\# of protons in guest } BPh_4^-}\right)}{\left(\frac{\text{Integrated area of podand resonances}}{\text{\# of protons in podand}}\right)}$$

Atomic absorption analysis has shown the solubility of $NaBPh_4$ in $CDCl_3$ to be (0.4×10^{-6} M < 1.24×10^{-6} M < 3.77×10^{-6}M).[67] Since this solubility is effectively negligible, one can make the assumption that dissolved salt is complexed by the podand. Substitution into eq 2 allows calculation of K_{obs} or estimation of a lower limit for K_{obs}, assuming 1:1 complexation. Results of these experiments for several podands are shown in Table 1. The spectra for ^1H NMR complexation experiments are displayed in the appendix.

Table 1: Stability constants for several podands by ^1H NMR experiment.





2: $R' = H$; $R = (CH_2CH_2O)_2CH_3$

9: $R' = CH_3$; $R = (CH_2CH_2O)_2CH_3$

13: $R = CH_2CH_2O(CH_2)_3CH_3$

18: $R = CH_2CH_2O(CH_2)_{11}CH_3$

19: $R = CH_2CH_2OTHP$

20: $R = CH_2CH_2OH$

Compound	Number of Equivalents complexed[a]	$[ML^+]/[L]$	K_{obs} (M^{-1})	$-\Delta G^\circ_{298K}$ (kcal/mole)
Dipodands				
2	0.992 ± 0.029[b]	$>\sim 20$	$> 1.61\times10^7$	> 9.8
9	1.016 ± 0.010	$>\sim 20$	$> 1.61\times10^7$	> 9.8
Tripodands				
13	0.981 ± 0.015	$>\sim 20$	$> 1.61\times10^7$	> 9.8
18	0.998 ± 0.044	$>\sim 20$	$> 1.61\times10^7$	> 9.8
19	0.946 ± 0.062	$>\sim 20$	$> 1.61\times10^7$	> 9.8
20	0.320 ± 0.007	0.47 ± 0.02	$(3.79\pm0.16)\times10^5$	7.60 ± 0.03

a: 1 equivalent plus slight excess added
b: errors represent one standard deviation

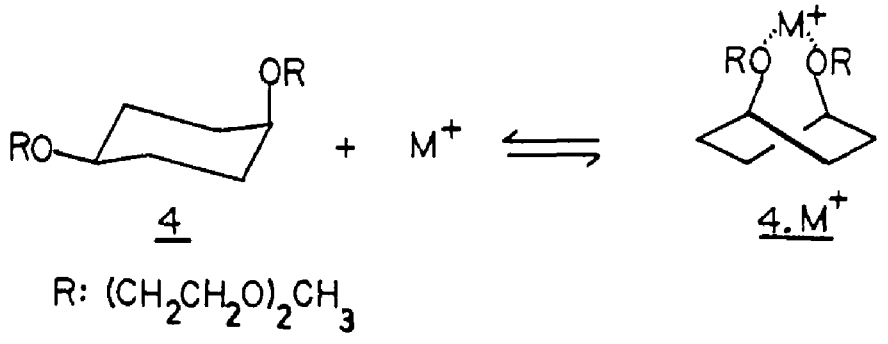
For several of the podands, one can only place a lower limit on the stability constant K_{obs} using ^1H NMR because it is impossible to measure the percentage of complexation accurately enough (> 95%).

The ^1H NMR spectra of dipodand **4** and several different alkali metal salts were examined using $CDCl_3$ and CD_3CN as solvents [Table 2].

Table 2: Complexation of dipodand **4** with alkali metal salts.

Solvent used	Alkali metal salt used			
	NaI	$NaBPh_4$	$NaBF_4$	LiBr
$CDCl_3$	Nil	Nil	Nil	Nil
CD_3CN	Nil			

It had been hoped that the complexation of **4** with metal ion would bias the stable chair conformation **4** into the energetically less stable twist-boat conformation **4.M$^+$** [Figure 14] (See Discussion section).



4 4.M$^+$

R: $(CH_2CH_2O)_2CH_3$

Figure 14

Other cyclohexane-based podands investigated by ^{1}H NMR were **26** and **31**. ^{1}H NMR experiments indicated that gem-dimethyl tripodand **26** complexes 1.770 $\pm$ 0.088 equiv of salt while tripodand **31** complexes 1.210 $\pm$ 0.014 equiv of $NaBPh_4$. It must be pointed out that in the case of podand **26**, the data is qualitative since ^{13}C NMR of the ligand indicates a small amount of impurity.

^{13}C NMR Complexation Studies:

In recent years ^{13}C spectroscopy has become one of the best methods for the elucidation of stereochemical features of molecules.[70] The application of ^{13}C NMR to the study of conformational changes in host-guest complexes has been well-established.[71,72] It has proven to be a sensitive probe for monitoring the conformational change in the host upon complexation of the guest.

The effects of substituents[73] (e.g. OH, CH_3) in the axial vs. equatorial positions upon the ^{13}C chemical shifts of the ring carbons of six-membered rings has been well-documented for e.g. pyranoses[74] and steroidal cyclohexanols[75] [Figure 15].

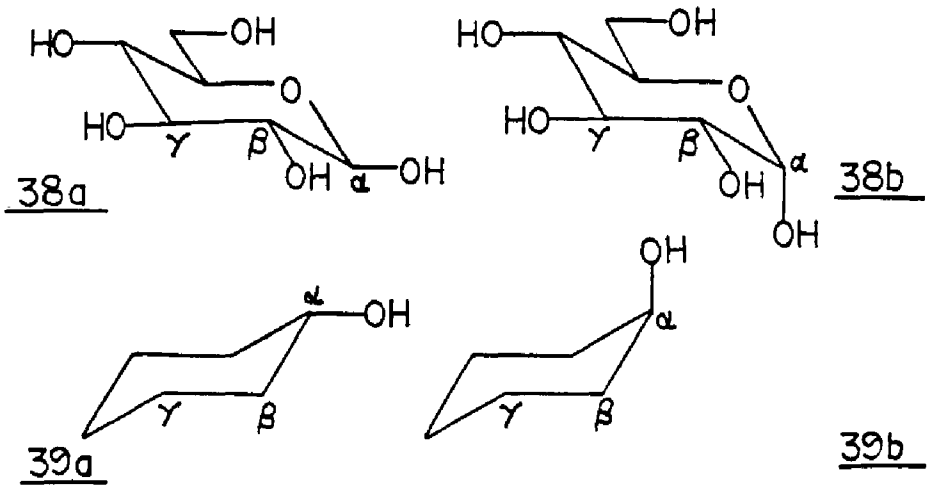


Figure 15

α-Effects:

The ^{13}C nucleus attached to an axial hydroxyl group is shielded relative to the nucleus directly attached to an equatorial hydroxyl. The chemical shift for the α carbon in α-D-glucopyranose (**38b**) is shifted ~ 3-4 ppm upfield relative to that of its β (equatorial) anomer **38a**. The α - effect is thought to be governed largely by inductive effects.[76,77]

β-Effects:

The ^{13}C nucleus adjacent to a carbon atom which carries an axial hydroxyl experiences increased shielding (β- oxygen effect) relative to a carbon adjacent to a carbon carrying an equatorial hydroxyl group. In α-D-glucopyranose (**38b**) and cyclohexanols containing axial substituents (**39b**), the β-carbons experience ~3 ppm upfield shift, compared to

their equatorial counterparts, **38a** and **39a.**

It has been proposed that this effect arises due to the steric elongation of the $C_\beta - C_\gamma$ bond by the axial substituent [Figure 16].[75]

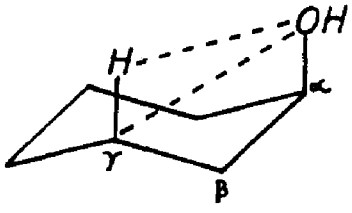


Figure 16

γ-Effects:

The ^{13}C nucleus gauche to an axial hydroxyl is shielded (γ-gauche Effect). Thus, in glucopyranose **38b** and cyclohexanol **39b,** the axial hydroxyl in the α position produces an upfield shift of about 4-5 ppm at the γ carbon atom. The earlier explanation of "steric compression" is highly controversial and presently no one concept clearly explains the transmission mechanisms involved in the γ-gauche effect.[73]

When the γ-gauche interaction is also part of a 1,3-diaxial (g^+g^-) interaction [Figure 17], a downfield shift counteracting the normal upfield γ-gauche effect is apparently operative. Thus, only relatively small chemical shift changes are observed for this situation.[76,77]

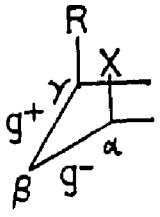


Figure 17

Lone Pair Effects:

A ^{13}C nucleus antiperiplanar to a nitrogen lone pair experiences increased shielding[73] relative to a nucleus gauche or syn to a lone pair. For example, this is shown in the upfield shift of the CH_3 carbon of orthoacetamide 40[86] [Figure 18]. The results are not as clear-cut when free electron pairs on other heteroatoms (O, S, etc.) are involved. However, one might speculate that lone-pair effects involving ether oxygen may be similar.

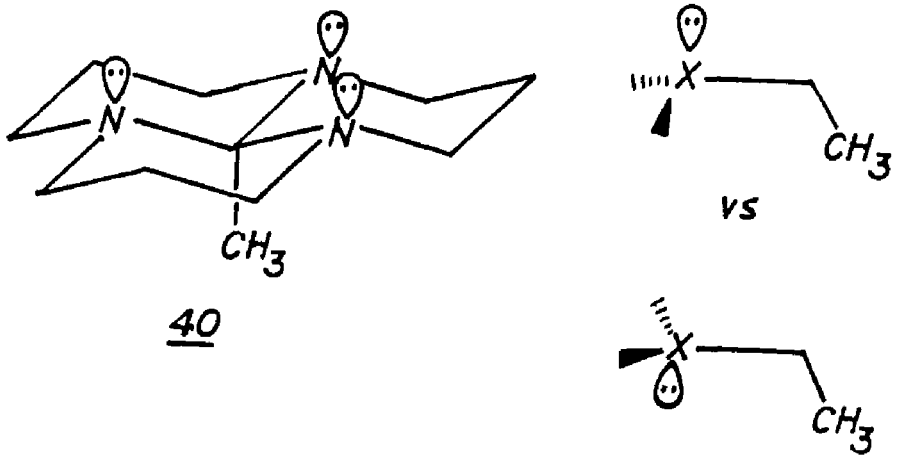


Figure 18

In summary, axial substituents like hydroxyl groups α, β

and γ-gauche to carbons in the cyclohexane ring, produce upfield shifts in those carbons relative to equatorial substituents. Some empirical rules predicting these chemical shift have been determined by analysis of monohydroxylated steroids.[93]

We planned to use ^{13}C NMR to monitor the conformational changes i.e. ring inversion of 1,3,5 and 1,3-substituted cyclohexane-based podands upon complexation (Figure 19).

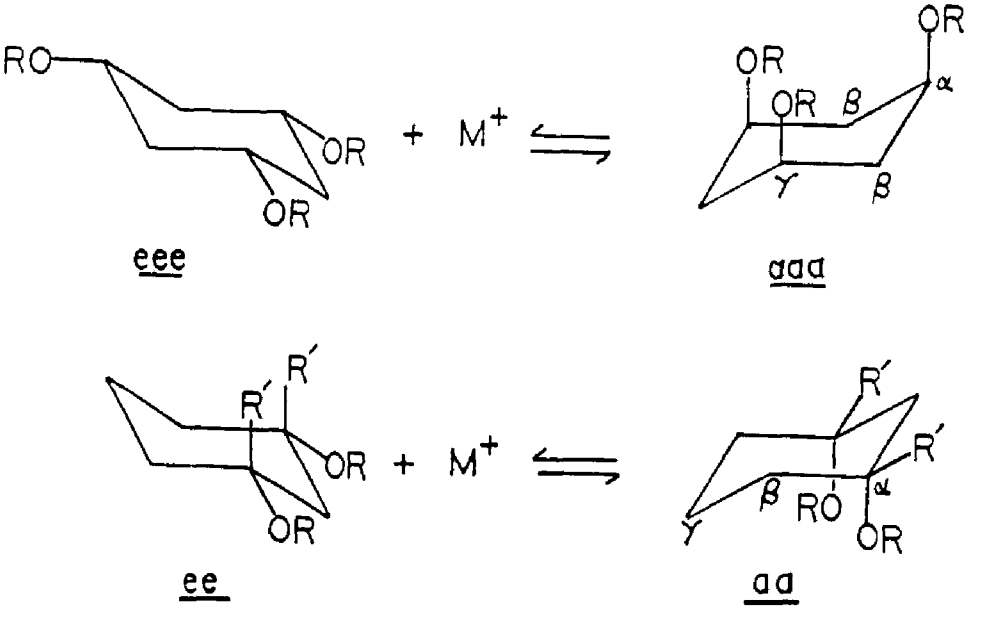
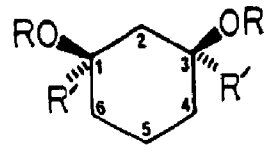
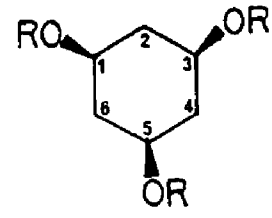


Figure 19

The chemical shifts of ring carbon atoms before and after complexation of 1 eq of salt $NaBPh_4$ in $CDCl_3$ are presented in Table 3. In each case, an excess of $NaBPh_4$ was added to the sample of podand to ensure saturation.

Table 3: Limiting chemical shifts of selected carbons.





2: $R' = H$; $R = (CH_2CH_2O)_2CH_3$

9: $R' = CH_3$; $R = (CH_2CH_2O)_2CH_3$

13: $R = CH_2CH_2O(CH_2)_3CH_3$

18: $R = CH_2CH_2O(CH_2)_{11}CH_3$

31: $R = (CH_2CH_2O)_3CH_3$

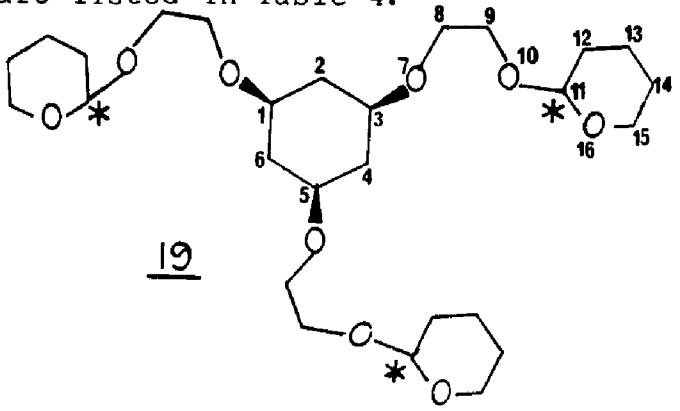
Table 3 contd.

Podand	Carbon Resonance	Uncomplexed ^{13}C shift	Complexed ^{13}C shift	$\Delta\delta_C$ [a]
2	1, 3	77.06	75.11	-1.95
	2	38.89	36.35	-2.54
	4, 6	31.80	27.64	-4.16
	5	20.81	13.72	-7.09
9	1, 3	74.75	76.02	+1.27
	2	44.94	50.72	+5.78
	4, 6	36.09	32.58	-3.51
	5	18.01	16.71	-1.3
	7 (Me)	26.21	26.47	+0.26
13	1, 3, 5	73.88	73.68	-0.20
	2, 4, 6	38.17	31.02	-6.97
18	1, 3, 5	73.88	73.88	0.00
	2, 4, 6	38.24	31.02	-7.22
31	1, 3, 5	73.75	73.29	-0.46
	2, 4, 6	38.11	31.41	-6.70

a: $(\delta_{C_{complexed}})-(\delta_{C_{uncomplexed}})$

These results will be discussed in detail in the discussion section.

We speculated that it would be possible to observe different ^{13}C NMR spectra for the two enantiomeric pairs (RRR,SSS and RSR,SRS) in THP-protected tripodand **19** after complexation with $NaBPh_4$. The ^{13}C chemical shifts with excess $NaBPh_4$ are listed in Table 4.



19

Table 4: ^{13}C NMR chemical shift changes for podand **19** in $CDCl_3$

Carbon Resonance	Uncomplexed ^{13}C shift	Complexed ^{13}C shift
1, 3, 5	73.81	73.81
2, 4, 6	38.30	31.21, 31.48
8, 9, 15	62.23 66.92 67.76	65.55 67.57, 67.76 68.98, 69.13
11	98.98	101.71
12, 13, 14	19.51 25.49 30.63	21.33 24.91 30.76

Indeed, separate chemical shifts were observed for the enantiomeric pairs upon complexation with $NaBPh_4$ and will be discussed in the latter section.

Competition Studies:

The relative complexing abilities of pairs of podands were compared by competition experiments. This method was used to compare podands for which the $[ML^+]/[L]$ ratio was shown to be >20 by ^1H NMR, indicating high complexing ability.

Equimolar amounts of the two podands were dissolved in $CDCl_3$ followed by addition of one equivalent of salt, $NaBPh_4$. Thus, two strong complexers (L_1 and L_2) compete for the salt (M^+X^-). The equilibrium for the reaction is represented by eq 5.

$$(ML_1^+)X^- + L_2 \rightleftharpoons (ML_2^+)X^- + L_1 \qquad (5)$$

This equation is derived from individual equilibrium eqs. 6 and 7.

$$M^+X^- + L_1 \rightleftharpoons (ML_1^+)X^- \qquad (6)$$

$$K_1 = \frac{[(ML_1^+)X^-]}{[M^+X^-]\ [L_1]}$$

$$M^+X^- + L_2 \rightleftharpoons (ML_2^+)X^- \qquad (7)$$

$$K_2 = \frac{[(ML_2^+)X^-]}{[M^+X^-]\ [L_2]}$$

Thus, the ratio K_1/K_2 is given by eq 8.

$$\frac{K_1}{K_2} = \frac{[(ML_1^+)X^-]\ [L_2]}{[(ML_2^+)X^-]\ [L_1]} \qquad (8)$$

The free energy of competition ΔG^{o}_{298K} can be represented as

$$\Delta G^{o}_{298K} = -RT \ln \frac{K_1}{K_2} \qquad (9)$$

Such experiments were monitored by ^{13}C NMR in order to determine the values of $\Delta\delta_{obs}/\Delta\delta_{max}$ where $\Delta\delta_{obs}$ is the chemical shift change for a ligand carbon in the competition experiment and $\Delta\delta_{max}$ is the total change in chemical shift of a ligand carbon upon complexation of 1 eq of salt. Equations 10 and 11 show the relationships between $\Delta\delta_{obs}/\Delta\delta_{max}$ and host and guest concentrations at equilibrium.

$$[(ML^{+})X^{-}]/[L_T] = \Delta\delta_{obs}/\Delta\delta_{max} \text{ where} \qquad (10)$$

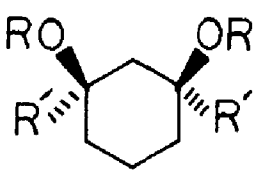
$[L_T]$ = Total ligand concentration

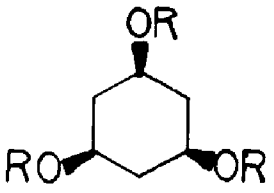
$$\text{Therefore, } [(ML^{+})X^{-}]/[L] = \frac{\Delta\delta_{obs}/\Delta\delta_{max}}{1-(\Delta\delta_{obs}/\Delta\delta_{max})} \qquad (11)$$

Insertion of ratios $\Delta\delta_{obs}/\Delta\delta_{max}$ into eq 11 allows determination of $[(ML^{+})X^{-}]/[L]$ values, which can be substituted into eq 8 to give K_1/K_2. Since the ratio of ligands to guest is set equal to 1:1:1 and all guest is assumed to be complexed, then determination of one $\Delta\delta_{obs}/\Delta\delta_{max}$ provides all of the data necessary for determination of K_1/K_2. Independent chemical shift measurements provide independent measures of K_1/K_2. The results of competition experiments for podands are shown in Table 5. The raw data for each independent measurement, ^{13}C NMR δ_C competition are given

in the Appendix.

Table 5: Results from competition experiments between podands for $NaBPh_4$ in $CDCl_3$.





2: R'=H; R=$(CH_2CH_2O)_2CH_3$

9: R'=CH_3; R=$(CH_2CH_2O)_2CH_3$

13: R= $CH_2CH_2O(CH_2)_3CH_3$

18: R= $CH_2CH_2O(CH_2)_{11}CH_3$

37: R= $CH_2CH_2OCH_3$

Podand 1	Podand 2	K_1/K_2	$\Delta\Delta G^o_{298K}$[a] (kcal/mol)
37	**2**	6.95±0.05	1.14±0.01
9	**2**	6.82±0.07	1.14±0.01
13	2	2.74±0.05	0.60±0.01
18	**2**	0.96±0.13	0.0

a: Errors correspond to one standard deviation

Stability Constant Determination by Titration using ^{13}C NMR Chemical Shift Data:

Spectroscopic methods such as ^{13}C NMR are useful techniques for the titrimetric determination of stability constants, K_{obs}. Chemical shifts, coupling constants or relaxation times are some of the parameters which can be

used to monitor titrations for the evaluation of K_{obs}. A requirement for the use of titration is that all species must be completely soluble in the chosen solvent over the concentration range of the titration. The subject has been reviewed fully elsewhere[78,79,67] and only aspects applicable to the determination of K_{obs} by chemical shifts are discussed herein.

When the exchange rate, i.e. complexation-decomplexation, is fast on the NMR timescale, then one time-averaged peak is observed for each unique NMR active nucleus. This peak is the weighted average of the chemical shifts for this nucleus in the complexed and uncomplexed ligand. For a 1:1 complex, the titration function T[80] is given by eq 12

$$T = [ML^+]/[L_T] = 0.5\{(1+A+X)-[(1+A+X)^2-4X]^{1/2}\} \quad (12)$$

where $A = 1/K[L]_T$

$[L]_T$ = Total ligand concentration

$X = [M^+]_T/[L]_T$

$[M^+]_T$= Total metal ion concentration

Substitution of eq 12 into eq 13 (which has been derived elsewhere[81]) yields eqs 14 and 15

$$(\delta_{obs} - \delta_L) = ([ML^+]/[L]_T)(\delta_{ML} - \delta_L) \quad (13)$$

$$\Delta\delta_{obs} = T(\delta_{ML} - \delta_L) \quad (14)$$

or

$$\Delta\delta_{obs} = 0.5\ B\{(1+A+X)-[(1+A+X)^2-4X]^{1/2}\} \quad (15)$$

where $B = (\delta_{ML} - \delta_L)$

A titration curve is obtained by plotting a measured chemi-

cal shift change $\Delta\delta_{obs}$ versus $[M^+]_T/[L]_T$. A non-linear least squares analysis can then be performed to obtain K_{obs} and B values. (See experimental section)

Some of the limitations of application of NMR to the determination of stability constants are the chemical shift dependence on the concentration of solution as well as the assumption of 1:1 complexation. A priori NMR chemical shifts do not distinguish between 1:1 and 2:1, ligand:guest complexes under fast-exchange conditions.

The method just described was used to obtain K_{obs} and corresponding ΔG^{o}_{298K} values for dipodand **2** in acetone with $NaBPh_4$ salt. The titration was carried out at constant podand concentration and several aliquots of $NaBPh_4$ were added. Starting with approximate values of A and B, the best fit data was obtained by varying these parameters (See experimental section). A table of ^{13}C chemical shift data for the titration and the non-linear regression fits are displayed in the appendix section. The stability constants for dipodand **2** are shown in Table 6.

Table 6: Stability constants for dipodand **2** for $NaBPh_4$ in acetone-d_6

Podand	Carbon Resonance	$\Delta\delta_{ML^+-L}$ (ppm)	log K_{obs}	$-\Delta G^{o}_{298K}$ (kcal/mol)
2	C-5	-7.03	0.84±0.35	1.15±0.48
	C-2	-4.36	0.65±0.19	0.89±027

The relative values of the two independent measures of log K_{obs} give an indication of the accuracy of the method.

The error limits were calculated using the difference of A values for C-2 and C-5 carbons as the standard deviation and the standard method of quotients and products.

Potentiometric Studies:

The potentiometric method is a widely applicable technique for the determination of stability constants in polar solvents because of its high accuracy and precision.[82,83] It has been used extensively to measure the stability constants of polyethers in solvents such as H_2O, MeOH, MeCN and others.[61]

We made an attempt to measure the stability constant of tripodand **37** in MeOH by a modification[84,92] of Frensdorff's method.[85] Initially, the log K_{obs} value for 18-Crown-6 was measured and it was found to be 3.80 (lit.[84]: 4.36, 4.35). Using the same experimental conditions, we attempted to determine the log K_{obs} for tripodand **37**. We were only able to place a upper limit for K_{obs} of 1.92.

Molecular Mechanics Studies:

The "molecular mechanics" method (MM), also known as "empirical force field" (EFF) calculations or the "Westheimer method" is a useful non-quantum mechanical computational method. It provides information on molecular conformations, vibrational spectra and thermodynamic properties of compounds.[87,88] In a case where one needs to evaluate possible molecular geometries of a molecule, this method allows an alternative to the conventional path of

synthesis followed by evaluation of molecular geometry by X-ray, electron diffraction, NMR or other techniques. For many functional group types, one can instead calculate the most favorable geometry of the molecule to a good approximation.

In the MM method, molecules are treated as a collection of atoms held together by harmonic or elastic forces, much like balls on springs. These forces are described by a set of potential functions called the force field which, taken together, give the steric energy (E_s), of the molecule. E_s is made up of several components including bond compression and stretching ($E_{stretch}$), bond angle compression (E_{bend}), torsional energy ($E_{torsion}$) and non-bonding interaction (E_{VDW})[89] (eq 16). An electrostatic term must also be included for compounds other than hydrocarbons.

$$E_s = E_{stretch} + E_{bend} + E_{torsion} + E_{VDW} \qquad (16)$$

For a particular conformation of a molecule, starting geometries were constructed using the interactive program MMHELP.[90] The calculations were then run on a VAX 11-780 computer using the MM2 program developed by Allinger and coworker[91].

Molecular mechanics calculations were carried out for dipodand **4** and on model compounds **41** and **42** in an attempt to predict the gain in complexation energy by addition of the methyl groups in the 1,4-positions of the ring [Figure 20].

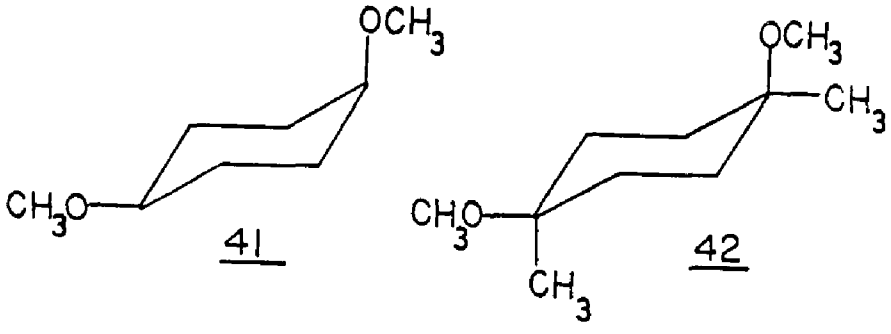
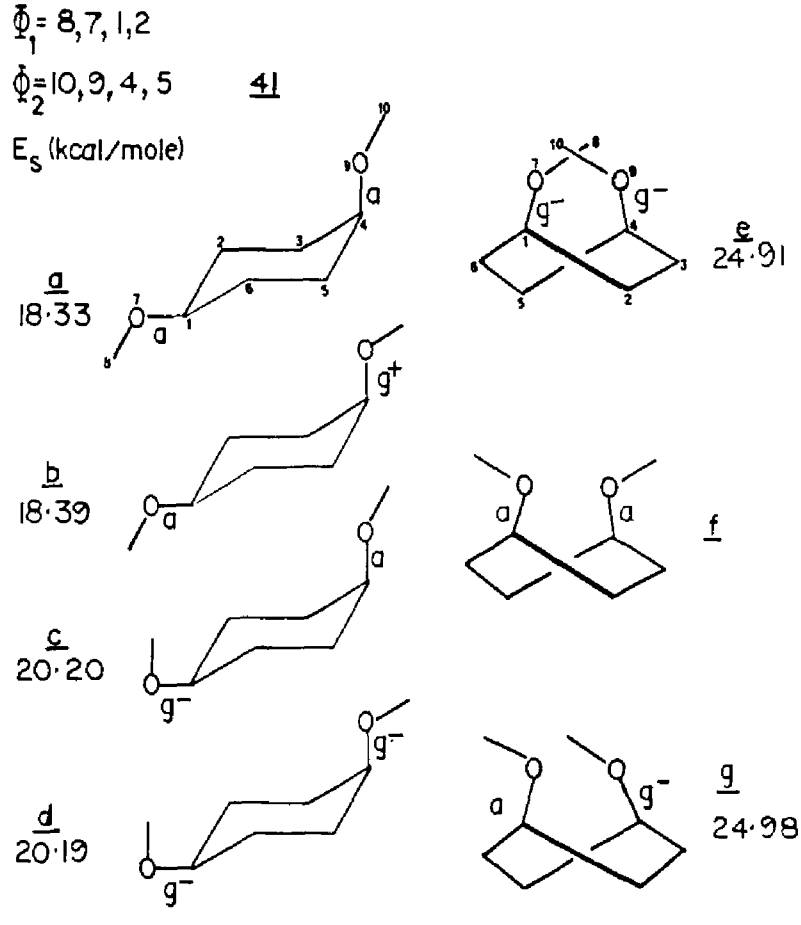


Figure 20

We speculated that model **42** would show greater relative stabilization of the twist boat conformation. The results from these calculations are presented in Table 7. An attempt was made to calculate the steric energy for **41f**, however, this conformation was driven into another boat conformation after MM calculation. We hoped to be able to estimate the gain in complexation energy by addition of the methyl groups in the 1,4-positions of the ring.

Table 7: Results from MM calculations on models **41** and **42**



ΔE_s (twist boat - chair) = **41e - 41a**

ΔE_s = 24.91 - 18.33 = 6.58 kcal/mole

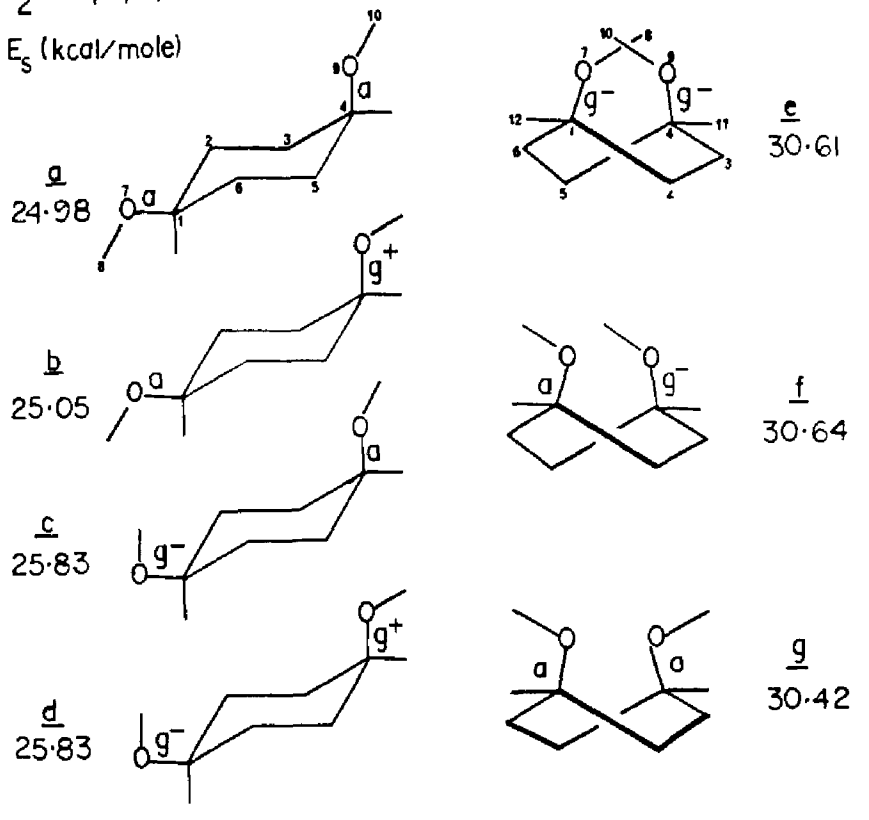
Table 7 contd.

$\Phi_1 = 8,7,1,2$

$\Phi_2 = 10,9,4,5$

E_S (kcal/mole)

42



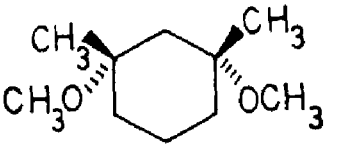
ΔE_S (twist boat - chair) = **42g - 42a**

ΔE_S = 30.42 - 24.98 = 5.44 kcal/mole

$\Delta\Delta E_S = \Delta E_S$ (**41**) - ΔE_S (**42**)

= 6.58 - 5.44 = 1.14 kcal/mole

MM calculations were also done to predict the most favorable conformation of podand **9**. Model **43** was used and several conformations of **43** were optimized [Figure 21]. These results indicate that the steric energy difference between the minimum energy diaxial dimethyl conformation **43d** and the minimum energy diaxial methoxy conformation **43b** is 3.4 kcal/mole. Thus, model **43** is strongly biased toward the diaxial dimethoxy conformers. Results of these calculations are shown in Table 8.



43

Figure 21

Table 8: Results of MM calculations on model **43**

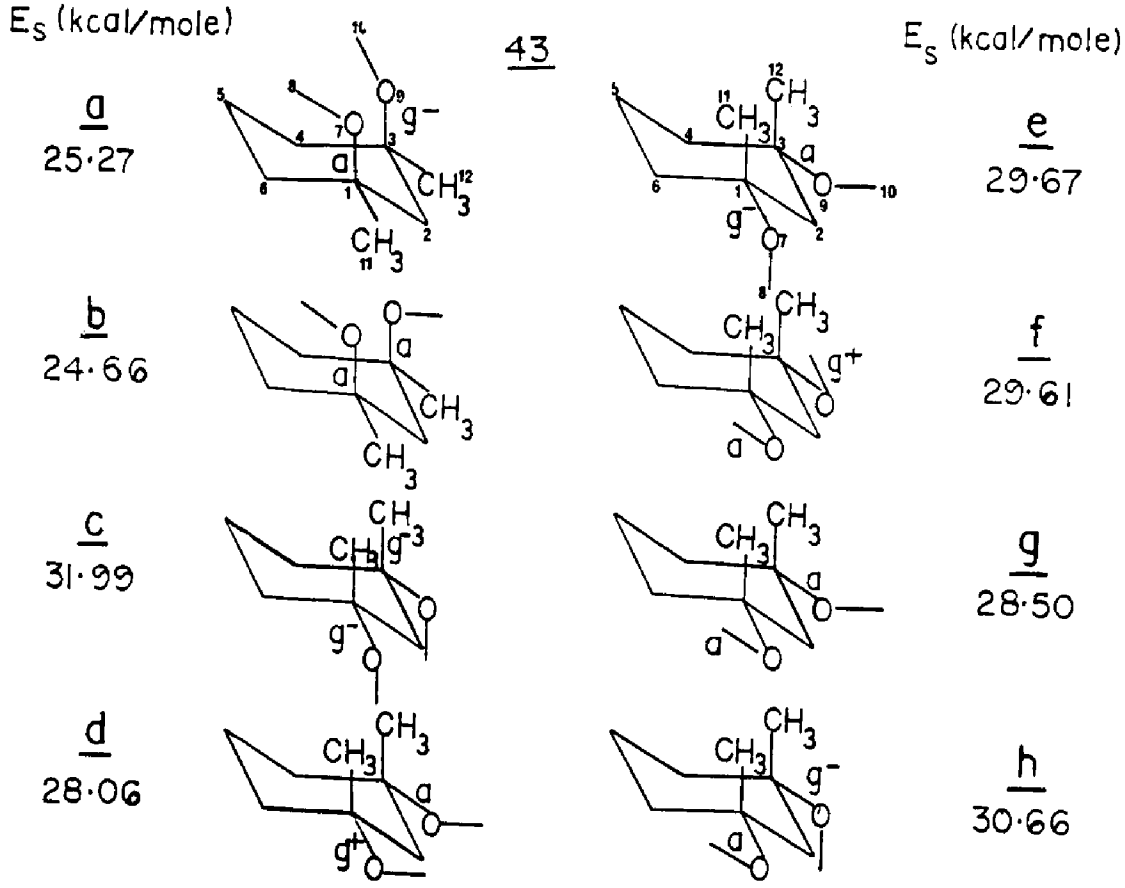
Φ_1 = 2,1,7,8

Φ_2 = 10,9,3,4

E_S (kcal/mole)

43

E_S (kcal/mole)



ΔE_S = **43d - 43b**

ΔE_S = 28.06 - 24.66 = 3.4 kcal

^{13}C Dynamic NMR study of tripodand 37:

^{13}C dynamic NMR has been used extensively to study the conformational changes in ring compounds. It allows investigation of a dynamic process such as ring inversion and has been the subject of several reviews.[111,112]

In the presence of 0.5 mole of $NaBPh_4$ salt, the podand **37** exhibited slow exchange of Na^+ in $CDCl_3$ at ambient probe temperature. The ring $\underline{CH_2}$ carbons were monitored and showed up as two sharp resonances, attributed to complexed and uncomplexed podand.

The mechanism by which cation exchange occurs between uncomplexed ligand **37** and complexed ligand **37.Na$^+$** can be a unimolecular or bimolecular process. The unimolecular process involves dissociation of complex **37.Na$^+$**, followed by uptake of the cation by an available uncomplexed ligand. On the other hand, a bimolecular process would entail passage of the cation Na^+ from a complexed ligand to a uncomplexed ligand through a 2:1 associated intermediate (**37.Na$^+$.37**). A concentration study was necessary in order to ascertain the operative mechanism. It was done in an analogous fashion to a previously reported study.[115]

$$k_{obs}(\mathbf{37.Na^+}) = k_1 + k_2[\mathbf{37}]$$

^{13}C NMR was used to monitor the peak shape of $\underline{CH_2}$ ring carbons at various concentrations, keeping the temperature constant. A two-site line shape analysis was then done to

provide the rate constants, using the user friendly DNMR.c simulation program[113] on a Digital VAX 11-780 and Tektronix 4662 interactive plotter. The results are listed in Table 9.

Table 9 : ^{13}C Dynamic NMR data for tripodand **37**

Conc [M][a]	taua (sec)	k_{obs} (sec^{-1})
0.167	0.045	22.22
0.204	0.040	25.00
0.305	0.030	33.33
0.373	0.015	66.66
0.560	0.008	125.00
0.684	0.006	166.67

a: represents the concentration of free ligand.

The graph (Figure 22) was plotted on the VAX-780 using the linear least squares fit in RS-1 software package (Version 12.00, BBN Research Systems, 1983). The dotted lines in the figure are representative of the confidence limits for the linear regression.

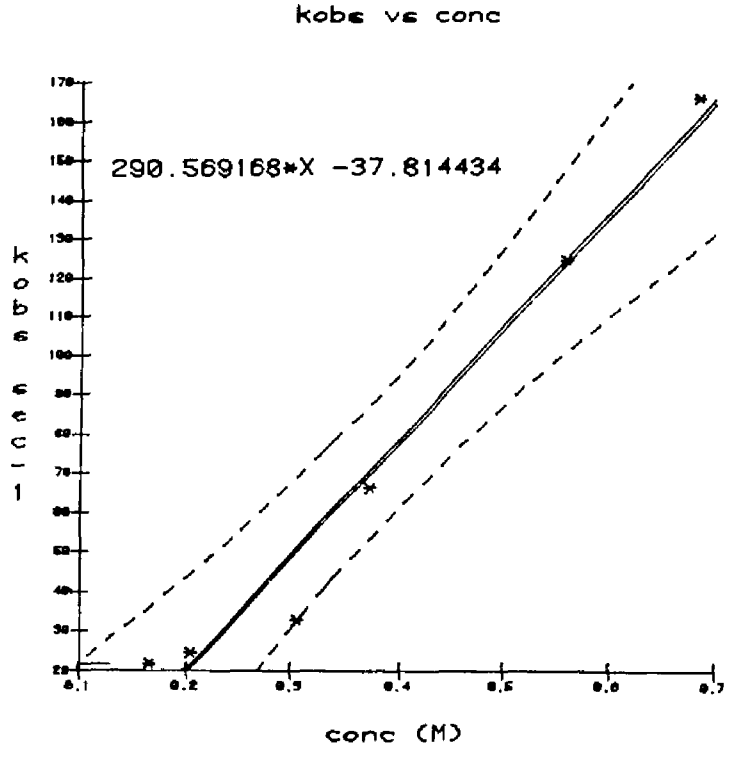


Figure 22

The values of k_1 and k_2 and the error limits obtained from the fit are presented in Table 10. The parameters, variance and residuals for the fit are listed in Table 15 in the Appendix section.

Table 10: Derived values of k_1 and k_2[a]

Complex	k_1 (sec^{-1})	k_2 ($M^{-1}sec^{-1}$)
37.Na^+	-37.81 + 21.00	290.57 + 49.44

a: Errors represent two standard deviations

The range of Υ was also estimated for each concentration by direct simulation and is presented in Table 16 in the Appendix. This was done in an attempt to account for systematic as well as random error. After plotting the concentration versus the range of k_{obs} values (graph #3 displayed in the Appendix section) the slope (k_2) can be estimated to be in the range of 400-200 $M^{-1}sec^{-1}$ and the intercept (k_1) is estimated to be in range of 4 - (-52) sec^{-1}. A more accurate study of concentration versus rate constants is needed on an higher-field instrument because of the poor S/N on the experimental spectra.

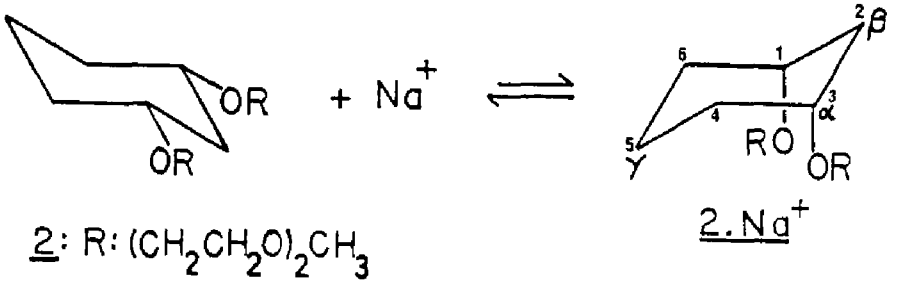
DISCUSSION

The results tabulated earlier in this chapter are discussed in this part.

DIPODANDS

1,3-Dipodands **2** and **9**:

The K_{obs} values of $>1.61 \times 10^7$ M^{-1} (Table 1) illustrate the superior complexing ability of dipodands **2** and **9**. The ^{13}C NMR complexation experiments (Table 3) show that in 1,3-dipodand **2**, the ring inversion upon complexation results in an upfield shift of C-2 ($\Delta\delta$ = -2.54 ppm). This may be attributed to a double β-oxygen effect. The C-4,6 resonances shift -4.16 ppm, also due to a β-oxygen effect. The chemical shift change of -7.09 ppm in C-5 is consistent with a double γ-gauche effect. C-1 and C-3, which are both γ-gauche to an axial "arm" as well as part of a g^+g^- sequence in the complexed conformer show a smaller upfield shift of -1.95 ppm [Figure 23].

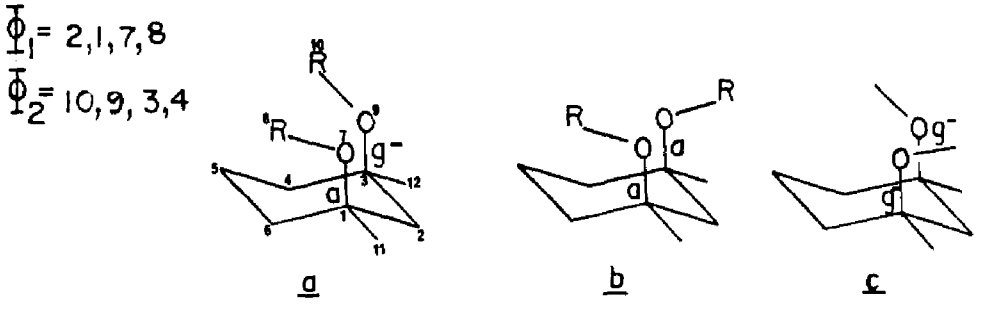


2: R: $(CH_2CH_2O)_2CH_3$

2.Na^+

Figure 23

Uncomplexed podand **9** is a mixture of conformers [Figure 24] where the mixture of conformers b and **c** (which are enantiomeric to each other) are entropically favored over the conformer **a.**



43 : R : Me

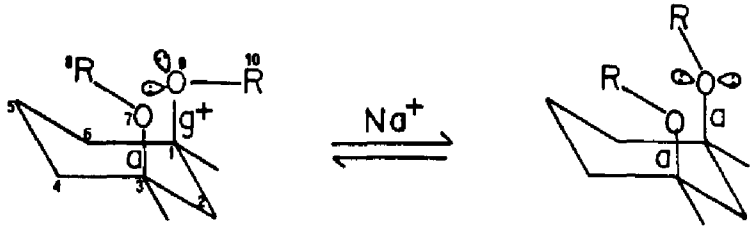
9 : R : $(CH_2CH_2O)_2CH_3$

Figure 24

MM2 calculations show (Table 8) (<u>vide supra</u>, pp 50) that model **43b** is lower in steric energy compared to **43a.**

The conformer best suited for complexation of Na^+ ion is **a.** Upon complexation, the C-1 and C-3 carbons which are each γ-gauche to an axial "arm" oxygen as well as part of a g^+g^- sequence, show a chemical shift change of +1.27 ppm. This small change in chemical shift could also be possible due to proximity of the charged species, Na^+, in the complex.[103,104] We attribute the downfield shift of +5.78 ppm in C-2 to a loss of at least one gauche and one lone pair interaction [Figure 25] from a change in the "arm" conformation. Lone pair interactions have been well documented in cases where a ^{13}C nucleus antiperiplanar to a nitrogen lone

pair experiences an upfield shift[73]. However, the results are less clear when lone pairs on other heteroatoms are involved.



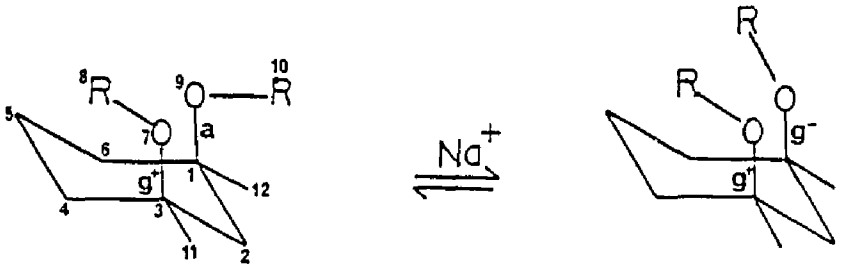
2: R: $(CH_2CH_2O)_2CH_3$

Φ_1 = 8,7,3,2

Φ_2 = 10,9,1,2

Figure 25

The C-4,6 resonance shifts upfield (-3.51 ppm) due to increased gauche interaction, from "arm" conformational change upon complexation [Figure 26]. The C-5 resonance and the resonances, C-11 (Me) however, shift only by -1.3 and +0.26 ppm respectively, indicating absence of ring inversion upon complexation. The chemical shift changes in C-5 and C-11 may be due partly to small torsional changes in the ring upon complexation. Evidence for the absence of ring inversion in podand 9 also comes from absence of chemical shift change[116] in methyl protons (before and after complexation = 1.1 ppm) in the ^1H NMR complexation experiment.



2: R: $(CH_2CH_2O)_2CH_3$

Φ_1 = 8,7,3,4

Φ_2 = 10,9,1,6

Figure 26

A competition experiment (Table 5) (<u>vide supra</u>, pp 41) between **9** and **2** indicates that the $K_1/K_2 = 7$ and $\Delta\Delta G^{\circ}_{298K}$ = 1.1 kcal/mole. One possible conclusion is that dipodand **9** is the better complexing ligand for Na^+ ion in $CDCl_3$ since it does not have to undergo ring inversion for complexation to occur. In other words, the methyl groups of **9** bias it toward the complex conformation.

Conformational considerations of chemical equilibria in substituted cyclohexanes[94] include preference of substituents in the axial vs equatorial positions and position of equilibrium between two conformers.

The measured stability constant K_{obs} can be denoted as in eq 18

$$M^+ + L \underset{}{\overset{K_{obs}}{\rightleftharpoons}} ML^+ \qquad (17)$$

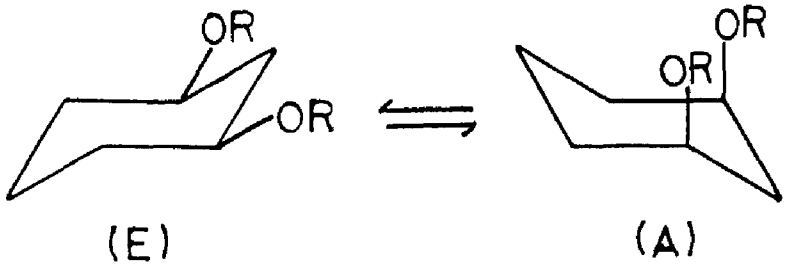
where L = Dipodand **2**

M^+ = Cation

K_{obs} = Measured stability constant

$$K_{obs} = \frac{[ML^+]}{[M^+]\ [L]} \qquad (18)$$

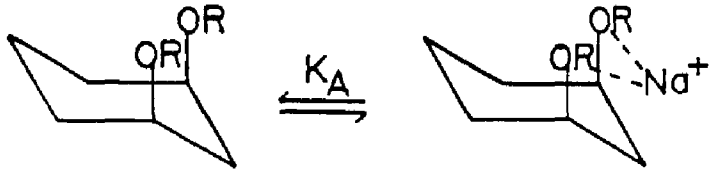
For equilibrium 19,[95] the conformational equilibrium constant K can be simply written as eq 20



(19)

$$K = \frac{[A]}{[E]} \qquad (20)$$

The stability constant K_A for conformer A is given by eq 21



$$A + M^+ \rightleftharpoons MA^+$$

$$K_A = \frac{[MA^+]}{[A]\ [M^+]} \qquad (21)$$

$[MA^+]$ = concentration of complex

$$[MA^+] \equiv [ML^+] \qquad (22)$$

The total ligand concentration [L] is given by eq 23

$$[L] = [A] + [E] \qquad (23)$$

Substitution of eqs 22 and 23 into eq 18 gives eqs 24 and 25

$$\frac{1}{K_{obs}} = \frac{[M^+]\ ([A] + [E])}{[MA^+]}$$

$$= \frac{[M^+]\ [A]}{[MA^+]} + \frac{[M^+]\ [E]}{[MA^+]} \qquad (24)$$

$$\frac{1}{K_{obs}} = \frac{1}{K_A} + \frac{[M^+]\ [E]}{[MA^+]} \qquad (25)$$

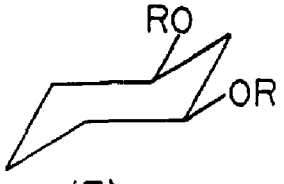
Further simplification of eq 25 by substitution of eq 20 gives eqs 26 to 28.

$$\frac{1}{K_{obs}} = \frac{1}{K_A} + \frac{1}{KK_A} \qquad (26)$$

$$\frac{1}{KK_A} = \frac{1}{K_{obs}} - \frac{1}{K_A} = \frac{K_A}{K_{obs}} - 1 \qquad (27)$$

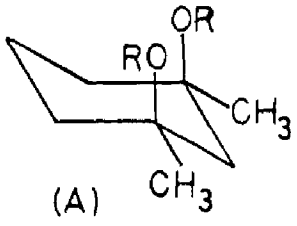
or $K = \dfrac{1}{\left(\dfrac{K_A}{K_{obs}}\right) - 1}$ (28)

Dipodand **9** then can be used as a model for conformer A of **2**



(E)

2



(A)

9

Table 8 (<u>vide supra</u>, pp 50) shows MM2 calculations that were carried out to predict the most favorable conformation for podand 9 using model **43.** The steric energies for the 1,3- diaxial dimethoxy conformers **43a-b** were substantially lower than 1,3-diaxial dimethyl conformers **43c-h.** The steric energy difference between minimum energy diaxial dimethyl conformation **43d** (E_s= 28.06 kcal/mole) and that having diaxial methoxy groups, **43b** (E_s= 24.66 kcal/mole) is 3.4 kcal/mole. Thus, **43** and **9** are strongly biased toward diaxial dimethoxy conformers. Therefore, one can conclude that dipodand **9** is indeed a suitable model for the conformer A of **2.**

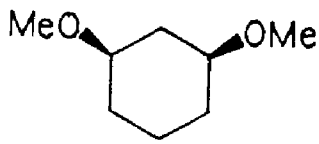
The ^{13}C NMR competition experiment between 9 and **2** showed that

$$K_A/K_{obs} = 7$$

Substitution of this experimentally determined value into eq 28 gives

$K = 1/6$ and $\Delta\Delta G^{\circ}_{298K} = 1.1$ kcal/mole

Independent support for this experimental value of of conformational equilibrium constant comes from MM2 calculations on model **44**.



ΔE_s (ax-eq) = 1.34 kcal/mole

44

If entropy effects are assumed to be the same for complexation of podands **2** and **9**, then the experimental value of $\Delta\Delta G^{\circ}_{298K}$ of 1.1 kcal/mole is in reasonable agreement with the empirical force field derived value of 1.34 kcal.

The stability constant for complexation of dipodand **2** with $NaBPh_4$ in acetone-d_6 was determined by a ^{13}C NMR titration experiment. The C-2 and C-5 chemical shift changes were monitored. As seen in Table 6 (<u>vide supra</u>, pp 43) the K_{obs} value for dipodand **2** in acetone-d_6 is six orders of magnitude lower than the lower limit for K_{obs} in $CDCl_3$ (Table 1) (<u>vide supra</u>, pp 29). This effect can be attributed to the relative solvation of podand, $NaBPh_4$ and complex by acetone-d_6 and $CDCl_3$.

Gutmann's solvent donor-acceptor concept[96] allows differentiation between the electrophilic (acceptor) and nucleophilic (donor) properties of the solvent. The donicity

or donor number (DN) is defined as the negative $\triangle H$ value for the 1:1 adduct formation between $SbCl_5$ and solvent molecules in dilute solution of 1,2-dichloroethane.[105]

$$DN = - \triangle H \text{ Lewis base.} SbCl_5$$

The acceptor number[106] which is a measure of the electrophilic property of a solvent was deduced by ^{31}P NMR studies of triethylphosphine oxide in different solvents. It is defined as a dimensionless number related to the relative chemical shift of ^{31}P in Et_3PO in a solvent $\{\delta_{corr}\}$, with hexane as reference (0) and Et_3PO-$SbCl_5$ in 1,2-dichloethane $\{\delta_{corr}(SbCl_5.Et_3PO)\}$ taken as the maximum shift change. The correction is made for the difference in volume susceptibilities between hexane and other solvents.

$$AN = \frac{\delta_{corr}}{\delta_{corr}\ (SbCl_5.Et_3PO)} \times 100$$

$$= \delta_{corr} \times 2.348$$

Gutmann's solvent donor-acceptor concept[96] assigns acetone a solvent acceptor (AN) number of 12.5 while its donor number (DN) is 17.0. This indicates that acetone is capable of solvating both the podand and the ion. Chloroform on the other hand has a AN of 23.1 but the DN is not assigned[106] so it is capable of solvating the podand but the cation is poorly solvated. Therefore the solvation energy increases in acetone, leading to a decrease in the complexation constant. We tried to trace a similar trend for crowns

in the hope of supporting our analysis that the primary difference lies in the different cation solvation ability for these two solvents but were unable to do because of lack of data.

Table 11: Maximum ^{13}C chemical shifts for dipodand **2**

Carbon Resonance	$\Delta\delta_{ML^+ - L}$ [a]	$\Delta\delta_{ML^+ - L}$ [b]
5	-7.03	-7.09
2	-4.36	-4.16

a: Predicted from plot for titration in acetone-d_6/ $NaBPh_4$
b: Observed in $CDCl_3/NaBPh_4$ ^{13}C NMR expt.

As seen in Table 11, the C-5 carbon is predicted by nonlinear regression analysis to shift a maximum of -7.03 ppm in acetone-d_6 which is in good agreement with the experimental value of -7.09 ppm as limiting chemical shift in $CDCl_3$. The regression value for C-2 of -4.36 ppm is also in close agreement with the $CDCl_3$ experimental value of -4.16 ppm. This indicates that podand **2** is mainly in the 1,3-diaxial conformation upon complexation in acetone-d_6, just as it is in $CDCl_3$ solution.

However, attempts to fit the data to the titration function T gave shallow curves, providing no information about the stoichiometry of complexation [Figure 27]. One explanation for this behavior could be presence of 2:1

podand:ion complexes in conjunction with 1:1 complexes. One would expect 2:1 podand:ion complexes at low concentration of ion. Indeed, extrapolation of the initial slope and final slope reveals the stoichiometry to be greater than 2:1.

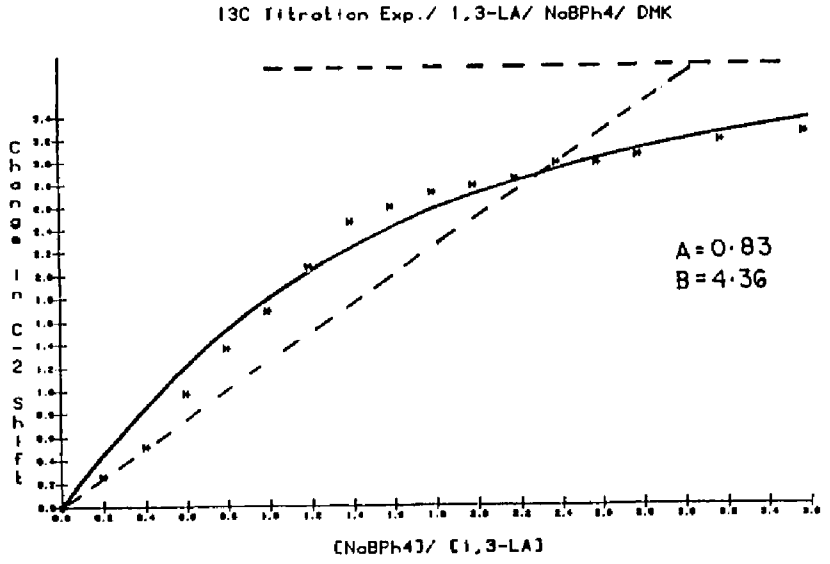


Figure 27

1,4-Dipodand **4**:

It had been hoped that complexation of dipodand **4** with metal ion would bias the stable chair conformation into the energetically less stable twist-boat conformation **4.M**$^+$ [Figure 28].

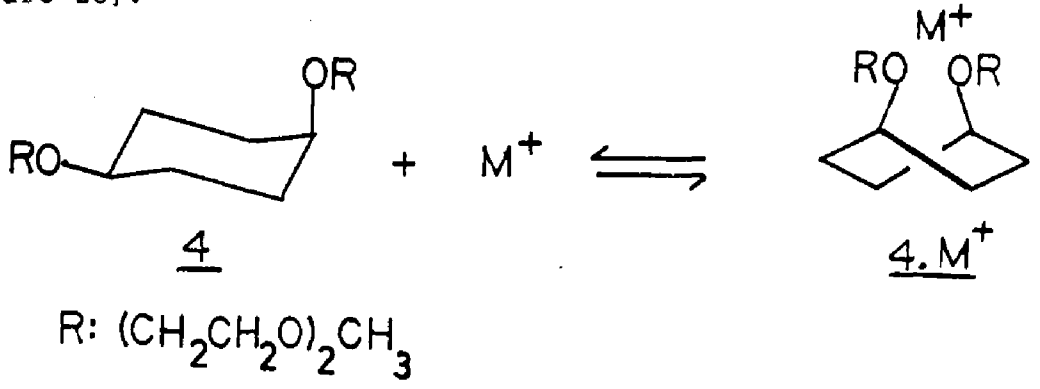


Figure 28

However, when the ^1H NMR experiments were conducted with a series of salts (Table 2), no such observation of a conformational change of **4** to **4.M$^+$** could be made. It can be hypothesized that the gain in complexation energy was unable to overcome the destabilization due to torsional strain from the eclipsing interactions in the complexing conformation **4.M$^+$**. We reasoned that perhaps this destabilization could be overcome by arm-biasing the dipodand as shown in Figure 29.

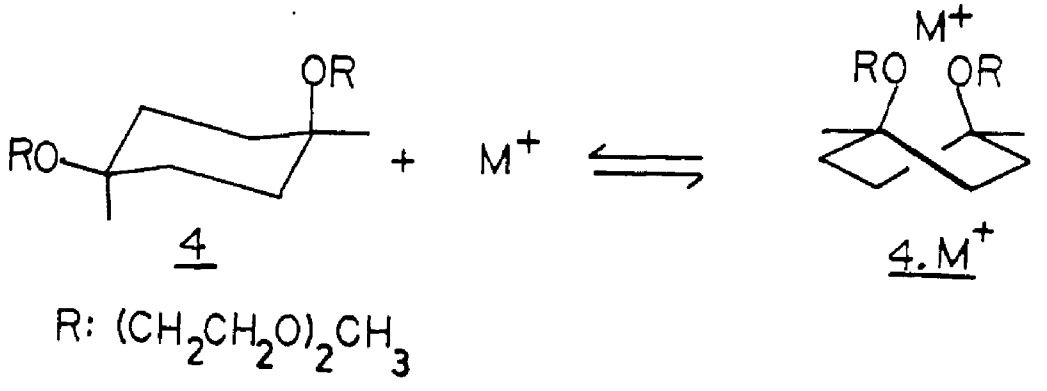
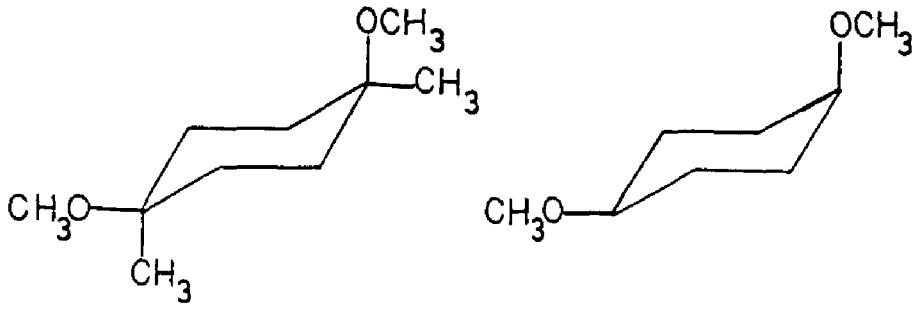


Figure 29

Thus, molecular mechanics calculations were carried out on model compounds **41** and **42** [Figure 30] in an attempt to assess the gain in complexation energy due to the addition of the methyl groups in the 1,4-positions of the ring.



42 41

Figure 30

Steric energies were calculated for several conformations in the uncomplexed chair and complexed twist-boat geometries for both **41** and **42** (Table 7).

ΔE_S = E_S (**41e - 41a**)

= 24.91 - 18.33 kcal/mole = 6.58 kcal/mole

ΔE_S = E_S (**42g - 42a**)

= 30.42 - 24.98 kcal/mole = 5.44 kcal/mole

$\Delta\Delta E_S$ = 1.14 kcal/mole

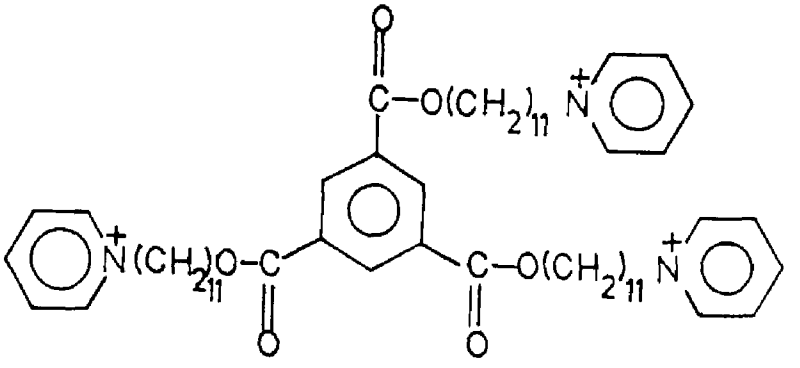
The results from MM2 calculations predict a gain of 1.14 kcal/mole. This suggests that conformational biasing by the methyl groups in the 1,4-positions would lead to a small gain in energy. Thus, one can conclude that perhaps arm-biasing the dipodand **4** would lead to stabilization of the complexing conformation **4.M$^+$**.

TRIPODANDS

Tripodand **13** and **18**:

Our original motivation for studying lipophilic tripodands **13** and **18** stemmed from the possibility of micellar behavior. Micelles are spherical aggregates consisting of 30-150 surfactant chains each bearing a polar head and a hydrocarbon tail. Micelles are capable of solubilizing organic compounds in water. When the surfactant concentration exceeds the critical micelle concentration (CMC) then micelles are formed. Otherwise, the surfactant exists in a monomeric state. If one thinks of tying several chains together by covalent bonds then such a "multi-armed" ligand could perhaps behave like a micelle. If it were polar enough at one "end" then, upon complexation it could even form micelles.

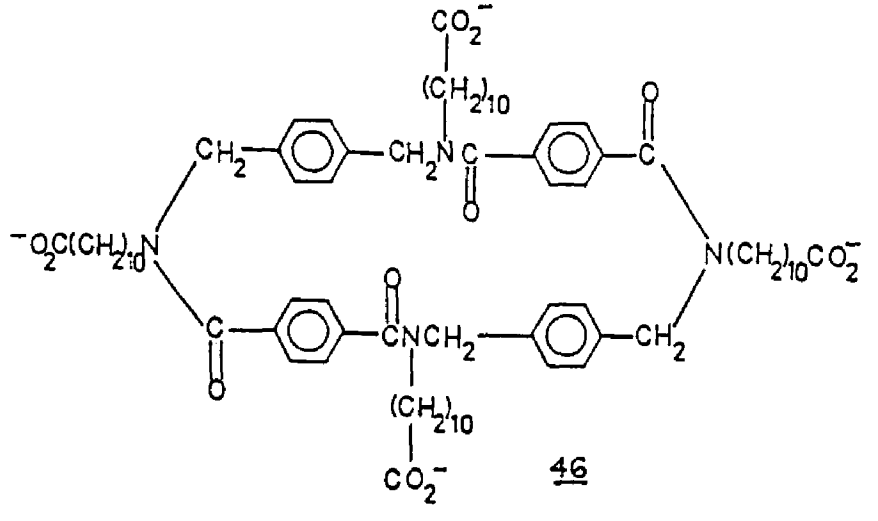
There are a few reports in the literature relating to this idea.[97] Amphiphiles like "tentacle" molecules **45** were investigated by Suckling and coworkers.[98] It was found that **45** was able complex small aromatic molecules in methanol or acetonitrile [Figure 31].



45

Figure 31

Murakami et al[99] reported the micelle-like behaviour of cyclophane **46** which showed a critical micelle concentration and bound ionic and neutral dyes [Figure 32].



46

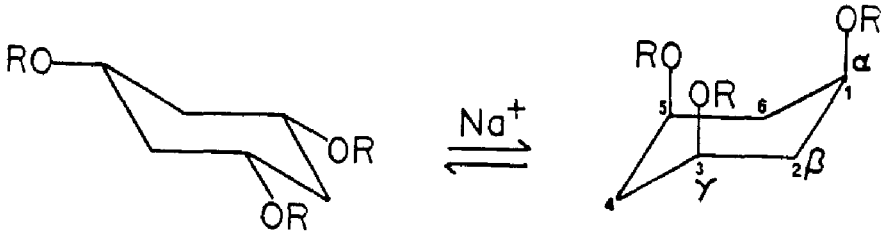
Figure 32

These earlier ventures of "multi-armed" ligands into

micelle-like chemistry stimulated a collaborative investigation[100] on our part to examine the behaviour of lipophilic tripodand **18**. Tripodand **13** was employed as a model system.

Aggregation of tripodand **18** was studied in the presence of water and Na^+ ion by polarizing microscopy. A small amount of aggregation was observed in water and the presence of Na^+ ion helped stabilize the aggregation. When an acetate or phosphate buffer was used, thus increasing the polarity of the medium, aggregation increased but a critical micelle concentration was not reached.[108]

The stability constants for complexation of $NaBPh_4$ by tripodands **13** and **18** in $CDCl_3$ exceed 1.61×10^7 M^{-1}, indicating strong complexing ability (Table 1). The ^{13}C NMR complexation studies (Table 3) reveal significant changes in the C-2,4,6 ring carbons. This behavior is consistent with the NMR results for tripodand **37** and is in accord with the conclusion that a ring inversion occurs upon complexation of $NaBPh_4$ [Figure 33].



13: R : $CH_2CH_2O(CH_2)_3CH_3$
18: R : $CH_2CH_2O(CH_2)_{11}CH_3$

Figure 33

C-2,4,6 experience double β-oxygen effect leading to an upfield shift of -7 ppm. C-1,3,5 which are γ-gauche to an

axial "arm" as well as part of a g^+g^- sequence, shift 0.20 ppm in **13** and 0.00 ppm in **18** with the two effects apparently counteracting one other.

The relative complexing abilities of 1,3,5-substituted **13** and **18** and 1,3-substituted **2** were compared. The results presented in Table 5 (<u>vide supra</u>, pp 41) indicate the K_1/K_2= 2.7 and $\Delta\Delta G^\circ_{298K}$= 0.6 kcal/mole for the competition between **13** and **2** for $NaBPh_4$. It can be concluded that **13** is a somewhat better complexer than **2** but not to a considerable extent.

For the competition between **18** and **2** for $NaBPh_4$ in $CDCl_3$, the K_1/K_2 = 1$(\Delta\Delta G^\circ_{298K} = 0)$.

Since the relative equilibrium ratios for **37** and **2** (K_1/K_2 = 7) and **13** and **2** (K_1/K_2 = 2.7) are known, ratio for podands **37** and **13** can be calculated as K_1/K_2 = 2.6 (Table 12)

Since the relative equilibrium ratios for **13** and **2** (K_1/K_2 = 2.7) and **18** and **2** (K_1/K_2 = 1) are known, ratio for podands **13** and **18** can be calculated as K_1/K_2 = 2.7 where K_1 is the equilibrium constant for **13** and K_2 is the equilibrium constant for **18.**

Table 12: Relative equilibrium constants for podands

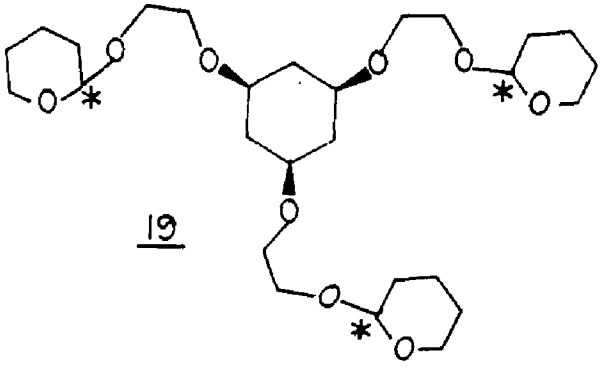
Podand 1	Podand 2	K_1/K_2
37	**2**	7
13	**2**	2.7
18	**2**	1.0
37	**13**	2.6
13	**18**	2.7

Two effects can be used to explain these results. As the lipophilic chain length in the "arms" increases, there is a greater loss in degrees of freedom and thus entropy, resulting from the conformational change from the "free" uncomplexed **eee** conformation to the "organized" complexed **aaa** conformation. The lipophilicity of the ligand [110] and its complexes also plays an important role in solvents with low polarity. As the ligand thickness increases, the cation becomes shielded from the medium leading to an increase in the cation-anion distance thus destabilizing the complex. One can hypothesize that both these factors lead to a decrease in the relative complexing ability as the lipophilic chain length increases.

Tripodand **19**:

Table 4 (<u>vide supra</u>, pp 38) showed the C-13 chemical shifts for tripodand **19** after complexation with 1 eq of $NaBPh_4$. Tripodand **19** contains three stereogenic centers

[Figure 34] and is a mixture of two dl pairs, RRR,SSS and RSR,SRS. It was envisioned that these two dl pairs (diastereomeric to each other) could be observed separately by ^{13}C NMR upon complexation with the $NaBPh_4$ because of the proximity of the stereocenters, leading to NMR distinct arm conformations upon complexation for each pair. Indeed, data in Table 4 indicates separate peaks for the two pairs at (δ 31.21,31.48), (δ 67.57,67.76) and (δ 68.98,69.13). This suggests that the orientation of the "arms" in the complexing **aaa** conformation is different for the two enantiomeric pairs leading to small changes in the chemical shifts upon complexation.



19

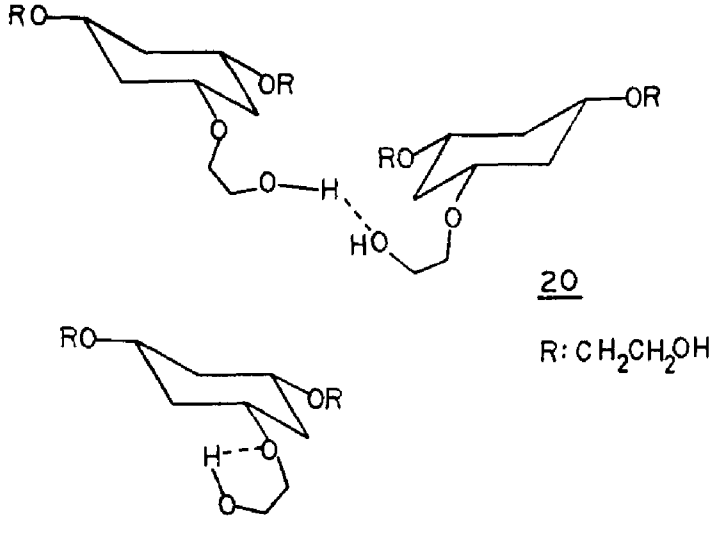
Figure 34

Tripodand **20:**

The most logical explanation for the relatively weak complexing ability of tripodand **20** in $CDCl_3$ with $NaBPh_4$ (Table 1) is based upon the solvation of hydroxyl groups in the "arms" by the solvent molecules as well as internal

hydrogen bond formation in the "arm".

Gutmann's solvent concept[96] assign $CHCl_3$ a solvent acceptor number (AN) of 23.1 while its donor property is negligible. This indicates that chloroform is a good solvating medium for the podand and the hydroxy groups in it but is a poor solvent for the positively charged ion, Na^+. Therefore in order to complex the cation, the "arms" have to move into the **aaa** conformation carrying along the heavily solvated hydroxy groups. Before the hydroxyl groups can participate in complexation of the cation, they must shed the shell of solvent molecules in order to participate in the ion-dipole interaction with the ion. Another factor that needs to be considered is intramolecular[107] and intermolecular hydrogen bonding in the podand **20** when dissolved in an aprotic solvent such as $CHCl_3$ [Figure 35]. The energy costs involved in breaking the hydrogen bonds in order to participate in ion-dipole interaction with the ion would be considerable.



20

R: CH_2CH_2OH

Figure 35

Therefore, these factors increase the differential solvation energy thereby making the complexation process a relatively unfavorable one.

Tripodands **26** and **31:**

Guinand and coworkers[101] have recently reported the crystal structure of a crown ether containing two Na^+ cations per molecule of ligand. The molecule is centrosymmetric and the two Na^+ cations are surrounded by seven O atoms each, five of them lying in a plane [Figure 36].

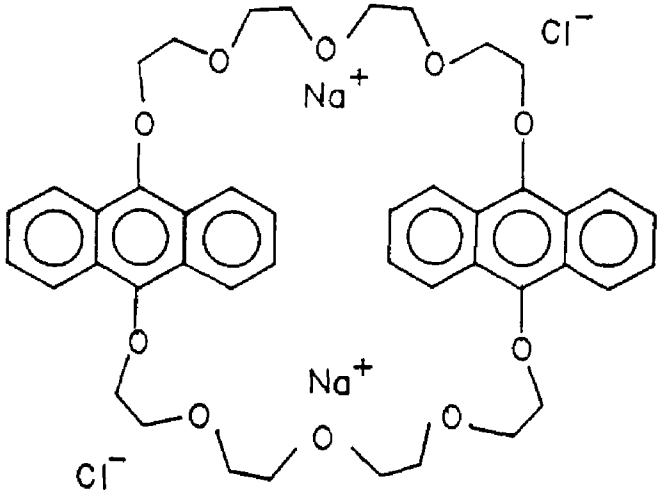
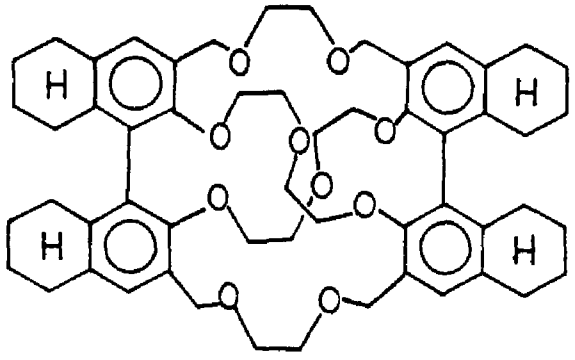


Figure 36

Similarly, Cram et al[102] synthesized host **47** [Figure 37] after CPK (Corey-Pauling-Koltun) models predicted its potential to complex two Na^+ ions simultaneously. Unfortunately, **47** was unable to encapsulate two ions. They reasoned that the energy expended was too high for the host to organize its electron pairs in the oxygens inward to complex the cations.



47

Figure 37

Hughes[109] has reported the crystal structure of dibenzo-24-crown-8 (Figure 38). The ligand is folded around the pair of sodium ions. Each ion interacts with three oxygens of the ligand. The $Na^+...Na^+$ distance is 3.383 Å which is similar to that found in other bridging systems like $Na_3Fe_5O_9$ (3.23, 3.51 Å) $Na_2CO_3.10H_2O$ (3.55 Å).[69]

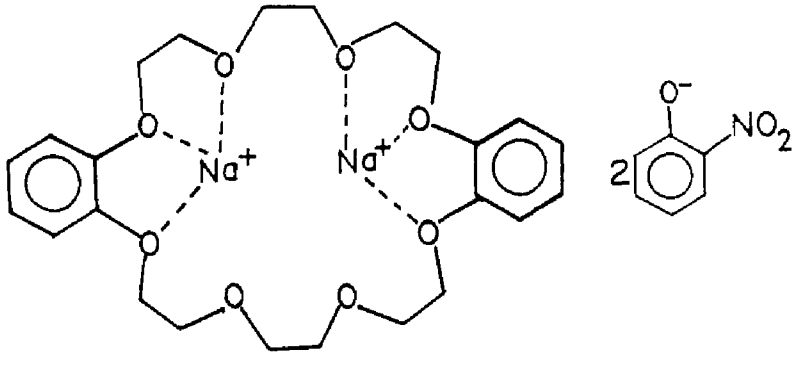


Figure **38**

We envisioned that the "extra long" arm tripodands **26** and **31** would be capable of complexing more than one equivalent of $NaBPh_4$ [Figure 39]. Indeed, ^1H NMR experiments

indicate that gem-dimethyl podand **26** complexes 1.770 ± 0.088 equivalent of salt while tripodand **31** complexes 1.210 ± 0.014 equivalent of $NaBPh_4$. Inspection of the ^{13}C NMR of tripodand **31** upon addition of salt reveals that ring inversion, monitored by the upfield chemical shift of C-2,4,6 is complete after addition of 1 eq of salt. Further additions of salt vary the C-2,4,6 carbon resonance only to a small extent, allowing one to qualitatively hypothesize that the first stability constant $K_1 >> K_2$, the second stability constant. We believe this to be an example of complexation induced complexation where the complexation of the first equivalent of salt conformationally facilitates the complexation of the second equivalent. Inspection of CPK models allows estimation of the $Na^+ - Na^+$ ion distance to be approximately 3.2 A°.

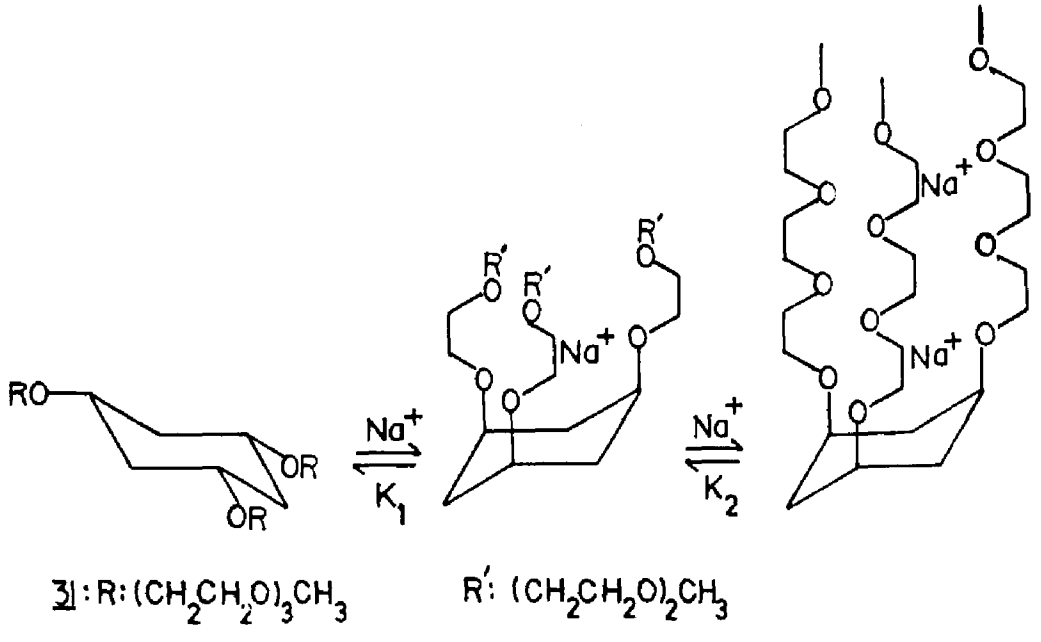


Figure 39

Tripodand **37:**

Potentiometry was used in an attempt to measure the log K_{obs} for tripodand **37.** No measurable emf difference was seen before and after addition of podand to the Na^+ salt solution, thus preventing calculation of log K_{obs} value in methanol and allowing only a upper limit of 1.92 to be put on the log K_{obs} .

This result can be explained on the basis of Gutmann's solvent donor-acceptor concept[96]. Methanol is assigned a solvent acceptor (AN) number of 41.3. Thus, it is a good solvating medium for the podand. Therefore, the solvation energy of the system increases considerably in methanol causing absence of complexation of Na^+ by the heavily solvated podand **37.**

The ^{13}C NMR dynamic NMR concentration study of the 1:1 mixture of complex to ligand in $CDCl_3$ reveals (Table 10) that the bimolecular rate constant (k_2 = 290.57 ± 24.72 $M^{-1}sec^{-1}$) predominates over the unimolecular term which is negligible (k_1 = -37.81 ± 10.50 sec^{-1}). Therefore, a bimolecular mechanism is predominant and probably proceeds through a 2:1 associated intermediate (**37.Na$^+$.37**)BPh_4^-, thus avoiding release of naked Na^+ cation into the poor donor solvent $CDCl_3$. This concept is consistent with the Gutmann donicity concept outlined earlier in this chapter.

IV. EXPERIMENTAL

General Experimental

Proton Nuclear Magnetic Resonance Spectra (^{1}H NMR) were obtained using a Varian EM-360A NMR spectrometer, operating at 60 MHz. Chemical shifts are reported relative to Me_4Si unless otherwise noted.

Carbon-13 Nuclear Magnetic Resonance Spectra (^{13}C NMR) were obtained using a Jeol FX 90Q fourier transform NMR spectrometer operating at 22.5 MHz. Chemical shifts are reported relative to Me_4Si unless otherwise specified.

Infrared spectra (IR) were obtained using a Perkin-Elmer 283B grating infrared spectrophotometer. Absorptions are reported in wavenumbers (cm^{-1}), with polystyrene (1601 cm^{-1}) as the calibration peak.

Low Resolution Mass Spectra were obtained using a Hitachi-Perkin-Elmer RMU-6E mass spectrometer, operated by University Instrumentation Center Personnel.

High Resolution Mass Spectra were obtained from the Massachusetts Institute of Technology Mass Spectrometry Facility in Cambridge, Massachusetts.

Elemental Analyses (CHN) were obtained on a Perkin-Elmer 240B elemental analyzer, operated by University Instrumentation Center personnel.

Melting Points (mp) were obtained using a Thomas-Hoover melting point apparatus.

Solvents:

Toluene (reagent grade) was freshly distilled prior to use.
Dimethylformamide (DMF)was vacuum distilled from CaH_2 after predrying over molecular sieves.
Methylene Chloride (CH_2Cl_2) and Hexane were distilled from CaH_2 and stored over molecular sieves.
Ethanol: Absolute ethanol was used without further purification.
Ethyl Acetate: Reagent grade material was used without further purification.
Tetrahydrofuran was freshly distilled from purple sodium benzophenone ketyl under a nitrogen atmosphere and used immediately.
Ether: Anhydrous ether was stored over sodium wire and used directly.
Carbon tetrachloride: Spectral grade CCl_4 was used without further purification.
Pyridine was distilled from CaH_2 and stored over 3A molecular sieves.
Methanol: Reagent and spectral grades of methanol were used without further purification.

Column Chromatography Solid Supports:

Silica gel: 60-200 mesh Baker Analyzed silica gel was used as obtained from J.T.Baker.

Alumina: Aluminum oxide powder " suitable for chromatography" was used as obtained from J.T.Baker.

Miscellaneous Chemicals

Tributylboroxine was used as obtained from Alfa Chemical Co.

Ethylene glycol was obtained from Aldrich Chemical Co. It was stored over soduim hydroxide pellets overnight and distilled prior to use.

1,3-Cyclohexanediol (cis-trans mixture) was used as obtained from Aldrich Chemical Co.

2-(2-Methoxyethoxy)ethyl-p-toluenesulfonate was prepared by D.A.Gronbeck according to the method of Kyba et al.[40]

Sodium Hydride (NaH) was obtained from Alfa Chemical Co. as a 57% dispersion in mineral oil.

1,4-Cyclohexanediol (cis-trans mixture) was used as obtained from Aldrich Chemical Co.

3-Methyl-2-cyclohexen-1-one was purchased from Aldrich Chemical Co. and used without further purification.

Methyllithium in ether was used as obtained from Aldrich Chemical Co.

Mercuric acetate was purchased from Aldrich Chemical Co. and used without further purification.

2-Butoxy-ethanol was used as obtained from Alfa Chemical Co.

cis,cis-1,3,5-Trihydroxycyclohexane was prepared by John D. Peabody III according to a method described by Caywood[58] as well as Steinacker and Stetter[49].

2-Bromoethanol was used as obtained from Aldrich Chemical Co.

3,4-Dihydro-2H-pyran was purchased from Aldrich Chemical Co. and was freshly distilled before further use.

Dowex 50x8-100 ion exchange resin was used as obtained from Aldrich Chemical Co.

1-Dodecanol was obtained from Aldrich Chemical Co. and used without further purification.

Analytical Procedures

Experimental for Complexation Experiment:

(Using the numerical data for the complexation of podand **18**):

The podand **18** (0.026g, 3.3×10^{-2} mmol) was weighed into a 1-dram vial, dissolved in ca. 0.5 mL $CDCl_3$ and transferred to a 5mm NMR tube. After the ^1H NMR of the host was recorded, slightly more than 1 equiv (typical 1.x equiv) $NaBPh_4$ (0.016g, 4.62×10^{-2} mmol) was added to the tube which was then shaken and allowed to reach equilibrium at room temperature. A ^1H NMR spectrum was then taken with several integrations.

The fraction of the total host complexed was calculated by comparing the relative integrations of the BPh_4^- peaks to the podand peaks by the formula:

$$\text{Fraction of host complexed} = \frac{\left(\frac{\text{Integrated area of the } BPh_4^- \text{ resonances}}{\text{\# of protons in guest } BPh_4^-}\right)}{\left(\frac{\text{Integrated area of podand resonances}}{\text{\# of protons in podand}}\right)}$$

Statistical analysis of the data was carried out to determine the standard deviation (equation 1) and the 95% confidence interval for the mean value (equation 2).

$$S_y = \sqrt{\frac{\sum_i (y_i - \bar{y})^2}{n-1}} \qquad (1)$$

$$\mu = \bar{y} \pm \frac{t.S_y}{\sqrt{n}} \qquad (2)$$

μ is the 95% confidence interval for the mean value, S_y is the standard deviation, y_i is the i^{th} value, $\bar{y}$ is the sum of all values divided by the number of values and n is the number of values. The t-value is obtained from the one-tailed t-distribution table [59].

The chemical shifts of the fully complexed podand were determined by taking the ^{13}C NMR spectrum of the ^{1}H NMR sample.

^{13}C NMR Competition Experiment

Using the numerical data for the competition expt. of podand **2** and podand **9**):

The two podands **2** (0.019g, 5.83×10^{-2} mmol) and **9** (0.02g, 5.83×10^{-2} mmol) were weighed into 1 dram vials, dissloved in ca. 0.5 mL (total volume) $CDCl_3$ and transferred to a 5mm NMR tube. One equivalent of salt $NaBPh_4$ (0.02g, 5.83×10^{-2} mmol), was added directly to the NMR tube via a glassine funnel. The tube was shaken until all the salt had dissolved and the ^{13}C NMR of the sample was recorded.

^{13}C NMR Titration Experiment

(Using the numerical data for the titration of podand **2**):

The podand **2** (0.174g, 0.542 mmol) was weighed into a 1-dram vial, dissolved in ca. 2 mL $CDCl_3$ and transfered to 10 mm NMR tube. The ^{13}C NMR spectrum of the podand solution was recorded. Subsequently, measured increments of the salt $NaBPh_4$, (0.037g, 0.108 mmol), were added to the NMR tube via

a glassine paper funnel. The podand/salt solution was allowed to reach equilibrium (by shaking the tube at room temperature) and the ^{13}C NMR spectrum was recorded.

Aliquots of the salt were added, until no further change was observed in the ^{13}C chemical shifts. The change in a certain ^{13}C chemical shift vs the ratio $[M^+]_T/[L]_T$ was plotted. The stability constant (K_{obs}) was obtained by fitting the curve to equation 3:

$$|\delta_{obs} - \delta_L| = 0.5B\{(1+A+X)-[(1+A+X)^2-4X]^{1/2}\} \qquad (3)$$

$A = 1/K.L_T$

$B = |\delta_{ML} - \delta_L|$

$X = [M^+]_T/[L]_T$

The curve fitting was done on a Digital Equipment VAX-780 computer using the Marquadt-Levenberg least squares procedure in the RS/1 software package (version 12.00, BBN Research Systems, 1983).

Potentiometric titration of **37** with NaCl

The emf was measured by an Orion Research digital ionalyzer/501. A sodium ion-selective electrode (Fisher cat. no. 13-639-20) was used for measurement of activity of Na^+ ions in solution with a silver electrode (Fisher 13-639-53) as the reference. All measurements were conducted at room temperature (25^oC) under N_2 atmosphere. The sodium selective electrode was calibrated in a range of 10^{-5}-10^{-2}M of NaCl solution. It was also conditioned to methanol by a stepwise conditioning in aqueous solutions of increasing methanol content upto pure methanol[92].

The binding constants were determined by a modification[84] of Frensdorff's method[85]. A three-necked 100 mL flask was fitted with a magnetic stirrer, septa with apertures for the electrodes and a nitrogen inlet tube. A solution of NaCl ($2x10^{-3}M$, ACS certified) was prepared in anhy MeOH along with a solution of the ligand (18-Cr-6: $6x10^{-3}M$; tripodand **37**: $1.2x10^{-2}M$) in anhy MeOH. 10mL of salt solution was mixed with 10 mL of MeOH for 5 min followed by 1 min quiescent time. The activity of Na^+ was then measured in the absence of ligand every 1/2 min until three consecutive readings differed by $\pm$ 1mV. The emf of the salt-ligand mixture was similarly obtained by mixing 10 mL of salt solution with 10 mL of ligand solution. Three runs were done for each ligand in order to calculate the K_{obs} for complexation.

<u>^{13}C Dynamic NMR experiment: podand **37** with 1/2 equiv of $NaBPh_4$ in $CDCl_3$</u>

The podand **37** (0.22 g, 0.7033 mmol) was weighed into a clean vial using a 0.5 mL Hamilton syringe equipped with a teflon needle. The salt, $NaBPh_4$ (0.12 g, 0.3517 mmol) was added to the vial by a glassine funnel. $CDCl_3$ (0.5 mL) was added to make up 1.40 M ligand concentration and 0.68 M salt concentration and the solution was transferred to a clean NMR tube. Further concentrations were made up by dilution of this solution. The temperature of the probe was measured before and after each run by a ^{13}C NMR thermometer[114].

cis-1,3-Cyclohexanediol (1).

The diol was isolated from a commercial cis-trans mixture according to a procedure described by Brown and Zwiefel[41]; the only modification was the use of toluene instead of benzene as a solvent: mp 84-86°C (lit. mp 85-86°C[41]); ^{1}H NMR (Me_2SO-d_6, 60 MHz) δ 0.7-2.25 (m, 8H), 3.05-3.55 (m, 2H), 3.55-3.77 (br s, 2H); ^{13}C NMR (Me_2SO-d_6, 22.5) δ_C20.77, 34.82, 45.29, 67.66.

cis-1,3-Bis(1,4,7-trioxaoctyl)cyclohexane (2).

A three-necked 100 mL flask was fitted with a condenser, a magnetic stir bar and a nitrogen adaptor. In a separate flask, a 57% dispersion of NaH in mineral oil was washed with hexane and residual hexane was removed under a nitrogen stream. The dry NaH (0.61 g, 0.0254 mol) was added to the three-necked flask along with 50 mL of dry DMF. The cis-1,3-Cyclohexanediol 1 (0.37 g, 3.15 mmol) was added to this solution; the reaction mixture was warmed to 60°C for 1h and then cooled to RT. 2-(2-methoxyethoxy)ethyl-p-toluene-sulfonate (1.81 g, 6.60 mmol) was then added and the solution was stirred at ambient temperature for 12h. A subsequent addition of NaH (0.36 g, 0.015 mmol) and the tosylate (2.31 g, 8.4 mmol) was carried out in the same fashion, and the resulting mixture was stirred for six days. A few drops of H_2O were then added to quench excess NaH and the solvent was removed under reduced pressure. The brown residue was resuspended in CH_2Cl_2 and filtered through a celite pad. Removal of CH_2Cl_2 in vacuo yielded 1.52 g of a

golden yellow oil. Chromatography (265 g of alumina; 1% (v/v) EtOH-CH_2Cl_2) of 1 g of the crude product provided 0.27 g of the desired product (R_f= 0.30). The compound was kugelrohr distilled (150°C at 0.1 torr) to yield 0.24 g (0.74 mmol) of a clear colourless liquid **2** (36% estimated total yield) : IR (neat) 2880, 1460, 1360, 1110, 850 Cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.0-2.8 (m, 8H), 3.45 (s, 6H), 3.55-3.90 (m, 18H); ^{13}C NMR ($CDCl_3$, 22.5MHz) δ_C 20.74, 31.74, 38.76, 58.98, 67.50, 70.56, 70.88, 71.99, 77.00; Mass Spectrum, m/z (Rel. Intensity) 103(18), 59(100), 58(28),; Anal. Calcd. for $C_{16}H_{32}O_6$: C, 59.98; H, 10.07. Found: C, 60.15; H, 10.26.

cis-1,4-Cyclohexanediol (**3**).

The diol was isolated from a commercial cis-trans mixture according to the procedure described by Brown and Zwiefel.[41] Contrary to the reported value of 200°C at 0.05 torr, the cyclic boronate of the above alcohol distilled at 50°C at 0.05 torr. The only modification in the procedure was the use of toluene instead of benzene as the solvent. Recrystallization from EtOAc provided white needles of **3**: mp 111-112° (lit. 105-107°C[41]; 108-110°C[60]); ^1H NMR (Me_2SO-d_6, 60 MHz) δ 1.2- 1.7 (m, 8H), 3.3-3.7 (br s, 4H); ^{13}C NMR (Me_2SO-d_6, 22.5 MHz) δ_C 30.11, 65.68.

cis-1,4-Bis(1,4,7-trioxaoctyl)cyclohexane (**4**).

A three-necked 100 mL flask was equipped with a condenser and a nitrogen adaptor. To the flask, dry DMF (25 mL)

was added together with NaH (0.5074 g, 0.021 mol) which had previously been washed with dry hexane and dried under a nitrogen stream. A solution of cis-1,4-cyclohexanediol **3** (0.76 g, 6.51mmol) in DMF (5 mL) was then added and the reaction mixture was heated to 65°C for 0.5 h followed by cooling to room temperature. 2-(2-methoxyethoxy)ethyl-p-toluenesulfonate (3.99 g, 0.0145 mol) was added and the reaction mixture was stirred for 12 h. Addition of a further aliquot of NaH (0.38 g, 0.0158 mol) and the tosylate (3.61 g, 0.0131 mol) was then carried out in the same manner. The mixture was stirred at 70°C for 45 min, allowed to cool, and a few drops of H_2O were added to quench excess NaH. DMF and H_2O were removed in vacuo leaving a brown residue which was resuspended in CH_2Cl_2. Particulate matter was removed by suction filtration through a celite pad and CH_2Cl_2 was subsequently removed under pressure to afford an oil. Bulb-to-bulb distillation of the oil (100°C, 0.5 torr) removed traces of the impurity, 2-(2-ethoxymethoxy)ethanol to yield 2.76g of an oil. Further purification by column chromatography (alumina, 1% (v/v) EtOH-CH_2Cl_2) of 1.25 g of the crude product gave 0.64 g (70% estimated total yield) of a clear colorless oil **4** : IR (neat) 2960, 2880, 1460, 1350, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.45-2.05 (m, 8H), 3.4 (s, 6H), 3.50-3.85 (m, 18H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 27.44, 58.98, 67.18, 70.62, 70.95, 71.99, 75,37; Mass spectrum, m/z (Rel. Intensity) 320(0.5, M^+), 202(31), 201(70), 102(28), 89(66), 81(100), 80(82), 67(36), 59(100), 58(94), 54(35); Anal. Calcd. for $C_{16}H_{32}O_6$: C, 59.98; H, 10.07. Found: C,

59.63, H,10.40.

1,3-Dimethyl-2-cyclohexen-1-ol (6).

A 250 mL three-necked flask equipped with an addition funnel, reflux condenser and nitrogen adaptor was flame dried under a positive stream of nitrogen and allowed to cool. The MeLi in ether (186 mL, 0.21 mol, 1.1M) was cannulated into the flask which was partially immersed in an ice bath, followed by the addition of dry THF (50 mL). A solution of 3-methyl-2-cyclohexen-1-one (5) (8.89 g, 0.0807 mol) in THF (25 mL) was added dropwise over a 1 h period and the reaction mixture was allowed to stir for 2 h at room temperature. Cold saturated NH_4Cl (75 mL) was then added, THF was evaporated, and the resulting aq. solution was extracted with ether (5 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and solvent was evaporated to give a light brown liquid. The liquid was purified by vacuum distillation to give 1,3-dimethyl- 2-cyclohexen-1-ol 6 (8.80g, 0.070mol, 86%): bp 25-33°C , 0.25 torr (lit. bp [44] 25-26°C, 1 torr); IR (neat) 3400, 2960, 1450, 1390, 1120, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25 (s, 3H), 1.4-2.1 (m, 7H), 1.68 (br s, 3H), 5.32 (br s, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 19.83 (t), 23.61 (q), 29.72 (q), 30.11 (t), 37.59 (t), 68.28 (s), 128.96 (d), 136.04 (s).

cis & trans-1,3-Dimethyl-1,3-cyclohexanediol (7).

This procedure was adapted from a procedure described

by Brown and coworkers[46].

Mercuric acetate (7.97 g, 0.025 mol) and H_2O (20 mL) were added to a three-necked 100 mL round bottom flask equipped with a condenser and a nitrogen inlet tube. The reaction mixture was stirred vigorously at room temperature. THF (25 mL) was then added causing the solution to turn canary yellow in color. A solution of 1,3-dimethyl-2-cyclohexene-1-ol **6** (3.15 g, 0.025 mol) in THF (15 mL) was added in one portion. The yellow solution turned clear within 1 min. The mixture was allowed to stir for 15 min. Aq. 3 M NaOH (25 mL) was then added, which produced a yellow suspension, followed immediately by the addition of 0.5 M $NaBH_4$ in 3 M aq NaOH (25 mL) which turned the solution a grey colour. The suspended Hg was allowed to precipitate and the supernate was decanted into a separatory funnel leaving behind the coagulated Hg. The reaction mixture was saturated with solid NaCl which caused the phase separation of an upper THF layer. The THF layer was removed and the water layer was further washed with ether (2 x 50 mL). The combined ether and THF phases were dried over anhydrous Na_2SO_4 and solvents were evaporated to yield 3.46 g (0.024 mmol) of white crystalline solid ,consisting of a mixture of the cis-**7a** and trans-**7b** diols (88%). (Based upon the relative intensities of the ^1H methyl resonances and the ^{13}C resonances, it is estimated that the mixture is ca. 3:1/cis:trans). It was used as is in future steps, without further purification: mp 58-68°C; IR (CCl_4) 3600, 3350, 2920, 1450, 1370, 1180, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.1 (s, 3H, cis),

1.2 (s, 3H, trans), 1.3-1.9 (m, 8H), 3.9 (br s, 2H); ^{13}C NMR ($CDCL_3$, 22.5 MHz) cis isomer δ_C 17.49, 31.02, 38.17, 48.12, 71.14, trans isomer δ_C 20.03, 30.37, 39.34, 51.76, 71.14; Mass spectrum, m/z (Rel. Intensity) 144(3, M^+), 111(98), 108(57), 101(68), 98(37), 93(47), 91(37), 83(69), 71(93), 69(51), 68(47), 59(31), 58(100).

cis-1,3-Dimethyl-1,3-cyclohexanediol (**8**).

This procedure was adapted from that described by Meinwald and Yankeelov[47].

A mixture of cis and trans-1,3-dimethyl-1,3-cyclohexanediols (ca. 3:1) **7** (0.52 g, 3.6 mmol) was placed in a 25 mL round bottom flask fitted with a magnetic stirrer and a nitrogen inlet tube. The flask was partially immersed in a ice-water bath and a 3.7M H_2SO_4 in H_2O solution (18 mL) was added and the reaction mixture was stirred while allowing the ice-bath to slowly warm up to room temperature for 24 h. The reaction mixture turned from clear to turbid over that period.

Subsequently, the rapidly stirred reaction mixture was cooled with an ice-water bath. A 5M NaOH in H_2O solution was added dropwise until pH paper indicated neutralization. Extraction of the reaction mixture with ether (4 x 100 mL), drying of the extracts over anhydrous Na_2SO_4, and evaporation of ether led to 0.24 g of light yellow crystalline cis-diol (43%) which was used without further purification. ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2 (s, 6H), 1.3-2.15 (m, 8H), 3.5-3.8

(br s, 2H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C17.56, 31.21, 38.20, 48.19, 71.14. A spectroscopic sample was prepared by recrystallizing a small amount from cyclohexane to give white solid **8** : mp 88-91°C (lit. mp[47] 92°C); IR (CCl_4, dilute) 3600, 3520, 3320, 2970, 2920, 1450, 1365, 1180, 890 cm^{-1};

cis-1,3-Dimethyl-1,3-bis(1,4,7-trioxaoctyl)cyclohexane (**9**).

A 57% dispersion of NaH in mineral oil was washed with hexane and dried under a nitrogen stream. A three necked 100 mL flask was equipped with a condenser and a nitrogen inlet tube. A suspension of the dry NaH (0.14 g, 5.83 mmol), diol **8** (0.11 g, 0.743 mmol) and DMF (20 mL) was heated at 70°C for 1.5 h. The solution was allowed to cool to room temperature and 2-(2-methoxyethoxy)ethyl-p-toluene sulfonate (0.47 g, 1.71 mmol) was added in one portion. The addition of dry NaH (0.20 g, 8.33 mmol) and the tosylate (0.46 g, 1.70 mmol) was done twice, in the same way over a period of 2 days. Following addition of a few drops of water to quench excess NaH, the reaction mixture was concentrated to a brown-white residue. The residue was resuspended in CH_2Cl_2, filtered through a celite pad and the solvent was removed under reduced pressure, yielding 0.246 g of crude product (yellow oil). A portion of this (0.20 g) was purified by column chromatography (260 g of alumina; 1% (v/v) EtOH-CH_2Cl_2) to afford 0.13 g (60%, estimated total yield) of a clear oil **9**. An analytical sample was obtained by bulb-to-bulb distillation (115-125°C; 0.05 torr): IR (NaCl, neat) 2920, 1445, 1350, 1180, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.1 (s, 6H),

1.2-2.25 (m, 8H), 3.35 (s, 6H), 3.4-3.8 (m, 16H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C18.01 (t), 26.21 (q), 36.09 (t), 44.94 (t), 58.98 (q), 60.48 (t), 70.56 (t), 71.27 (t), 72.05 (t), 73.75 (s); Mass spectrum, m/z (Rel. Intensity) 121(100), 110(79), 109(100), 103(100), 95(44), 59(100), 58(67); Anal. Calcd. for $C_{18}H_{36}O_6$: C, 62.04, H, 10.41. Found: C, 62.27; H, 10.64.

3-Oxaheptyl-p-toluene sulfonate (11).

To an ice-cold solution of p-toluenesulfonyl chloride (95.33 g, 0.5000 mol) in dry CH_2Cl_2 (500 mL) was added an ice-cold solution of 2-butoxyethanol (59.09 g, 0.5000 mol) and pyridine (79.10 g, 1.000 M) in dry CH_2Cl_2 (500 mL). The flask was stoppered and stored at 4°C until pyridinium chloride crystals were observed in the flask (5 days). The reaction mixture was filtered and washed successively with ice-cold water (2 x 250 mL), ice-cold 10% HCl (5 x 200 mL) and again with ice-cold water (2 x 500 mL). The resulting organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to yield 123 g (90%) of a pale yellow oil **11** which was used without further purification in future steps . An small sample was purified by kugelrohr distillation at 120-135°C (0.05 torr); lit. bp.[48] 130-8°C (0.1-0.2 torr): IR (NaCl, neat) 2900, 1600, 1450, 1350, 1180, 920, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.65-1.7 (m, 7H), 2.4 (s, 3H), 3.40 (m, 2H), 3.6-4.2 ($AA'BB'$, 4H), 7.25-7.95 ($AA'BB'$, 4H); Mass spectrum, m/z (Rel. Intensity) 272(M^+, 0.8), 173(44), 172(38), 155(48), 100(39), 92(33), 85(33), 65(35), 57(100), 56(57).

cis,cis-1,3,5-Tris-(1,4-dioxaoctyl)cyclohexane (**13**).

To a three-necked 250 mL flask equipped with a condenser and a nitrogen inlet tube, DMF (50 mL) was added. Powdered NaH (0.35 g, 0.014 mol) which had previously been

washed free of mineral oil with hexane and dried under a nitrogen stream, was then added to the flask. A solution of the cis,cis-1,3,5-Cyclohexanetriol **12** (1.79 g, 0.135 mol) in DMF (10 mL) was added, the resultant mixture was heated to 60°C for 1h, and then allowed to cool to room temperature. 3-oxaheptyl-p-toluene sulfonate **11** (3.7 g, 0.014 mol) was added in one portion and the reaction was stirred for 12 h. Four subsequent additions of NaH (0.35 g, 0.014 mol, 1 equiv) followed by tosylate **11** (3.7 g, 0.014 mol, 1 euqiv) were carried out in the same fashion over a period of 5 days. Water (6 mL) was added to quench excess NaH and the solvent was removed under reduced pressure. The brown residue was resuspended in CH_2Cl_2, filtered through a celite pad and CH_2Cl_2 was removed from the filtrate under reduced pressure to yield 7.07g of a yellow oil. Purification by column chromatography (260 g of alumina ; 1% (v/v)EtOH-CH_2Cl_2) of 0.756 g of the crude compound afforded 0.209 g (34% estimated total yield) of the desired product **13**. An analytical sample was prepared by kugelrohr distillation, 165-175°C (0.01 torr): R_f=0.36; IR (NaCl, neat) 2920, 2850, 1450, 1345, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.7-1.85 (m, 24H), 2.2-2.7 (m, 3H), 3.0-3.8 (m, 21H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C13.92, 19.31, 31.74, 38.17, 67.83, 70.36, 71.21, 73.81; Mass spectrum, m/z (Rel. Intensity) 432(M^+, 1), 197(48), 196(30), 171(36), 119(22), 101(79), 100(34), 63(24), 57(100), 56(28), 55(27); Anal.Calcd. for $C_{24}H_{48}O_6$: C, 66.63; H, 11.18. Found: C, 66.28; H, 11.46.

2-(2-Bromoethoxy)tetrahydropyran (**14**).

2-Bromoethanol (52.89 g, 0.423 mol) and anhydr ether (40 mL) were placed in a 250 mL round bottom flask covered with aluminum foil to exclude light and fitted with a nitrogen inlet tube. Freshly distilled 3,4-dihydro-2H-pyran (36.88 g, 0.438 mol) and Dowex 50x8-100 acidic ion exchange resin (3.58 g) were added and the reaction mixture was stirred for 24h. It was then filtered and the filtrate was concentrated under reduced pressure. The dark colored crude product was distilled, bp 65-73°C (15 torr); lit. bp[51] 94°C (14 torr) to afford 64.7 g (73%) of a colorless liquid **14** which darkened upon standing in light. A small amount of impurity, 2-Bromoethanol remained in the distilled product : R_f=0.8 (1% (v/v) EtOH-CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.3-2.0 (br m, 6H), 3.22-4.2 (m, 6H), 4.55-4.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz)δ_C 19.12, 25.24, 30.31, 30.63, 62.11, 67.44, 98.79; Mass spectrum m/z (Rel. Intensity) 209(M^+, 5), 109(25), 107(28), 85(100), 56(77), 55(37).

2-(2-Dodecyloxyethoxy)tetrahydro-2H-pyran (**15**).

Into a 1 L three-necked bottom flask equipped with a mechanical stirrer,condenser and a nitrogen inlet tube, DMF (200 mL) was introduced. Dry NaH (6.07 g, 0.253 mol) which had previously been washed free of mineral oil with hexane and dried under a nitrogen stream was then added to the flask followed by a solution of 1-dodecanol (40.11 g, 0.215 mol) in DMF (5 mL). The reaction mixture was stirred at 40°C for 1 h and then allowed to cool to room temperature. A

solution of 2-(2-bromoethoxy)tetrahydropyran **14**(45.03 g, 0.215 mol) in DMF (40 mL) was introduced together with a catalytic amount of solid KI (25 mg). The reaction mixture was stirred for five days. Two subsequent additions of NaH (2.5 g, 0.105 mol) were made during this period. Excess NaH was quenched by the addition of water (5 mL) and the solvent was removed in vacuo. The grey residue was resuspended in CH_2Cl_2 and filtered through a celite pad. The filtrate was extracted with water (3 x 200 mL), dried over anhydrous Na_2SO_4 and concentrated. Distillation (135-144°C; 0.05 torr) afforded 10.37 g (18%) of a clear liquid **15** : R_f= 0.80 (2% (v/v) EtOH-CH_2Cl_2); IR (NaCl, neat) 2920, 2850, 1470, 1340, 1120, 1070 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9(t, 3H), 1.3-1.5 (m, 20H), 1.5-1.8(m, 6H), 3.3-4.0(m, 8H), 4.55-4.85(m, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 14.11, 19.51, 22.76, 25.62, 26.21, 29.46, 29.59, 29.72 (degenerate resonances), 30.69, 32.00, 62.10, 66.72, 70.10, 71.53, 98.91; Mass spectrum, m/z (Rel. Intensity) 314(M^+, 27), 101(58), 86(41), 84(100), 83(27), 57(94), 56(38), 55(66); Anal. Calcd. for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.71; H, 12.35.

2-Dodecyloxyethanol (**16**).

To a solution of 2-(2-dodecyloxyethoxy)tetrahydro-2H-pyran**15** (11.38 g, 0.036 mol) in methanol (70 mL), Dowex 50x8-100 acidic ion exchange resin (4.0 g) was added. The heterogeneous reaction mixture was stirred for 11 h, fil-

tered and the solvent was removed from the filtrate under reduced pressure. Distillation (bp 134-137°C, 0.05 torr; lit. bp [52] 137°C, 2.2 torr) provided 6.98 g (84%) of a clear oil **16**: IR (NaCl, neat) 3410, 2920, 2840, 1460, 1350, 1110, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (m, 3H), 1.1-1.8(m, 20H), 2.2(br s, 1H), 3.3-3.9(m, 6H); ^{13}C NMR[55] δ_C 14.11, 22.70, 26.14, 29.39, 29.52, 29.65 (degenerate resonances), 32.00, 61.85, 71.47, 71.86.

3-Oxapentyldecyl-p-toluenesulfonate (17).

To an ice-cold solution of p-toluenesulfonyl chloride (5.60 g, 0.0292 mol) in CH_2Cl_2 (30 mL) was added an ice-cold solution of 2-dodecyloxyethanol **16** (6.73 g, 0.0292 mol) and pyridine (4.75 mL, 0.0585 mol) in CH_2Cl_2 (30 mL). The flask was stored at 4°C until a mass of pyridinuim chloride crystals were observed in the flask (ca. 8 days). The reaction mixture was filtered and then washed successively with ice-cold water (2 x 250 mL), ice-cold 10% HCl (2 x 75 mL) and ice-cold water (2 x 250 mL). The CH_2Cl_2 layer as dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to yield 10.01 g of a pale yellow oil (89%) which was used without further purification. An analytical sample was obtained by column chromatography of 0.17 g of the compound (70 g silica; CH_2Cl_2): IR (NaCl, neat) 2920, 2840, 1450, 1360, 1170, 1120, 1010, 920, 800, 765, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9(m, 3H), 1.1-1.7(m, 20H), 2.45(s, 3H), 3.40(m, 2H), 3.5-4.30(AA'BB', 4H), 7.25-7.90(AA'BB', 4H);

^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C14.11, 21.59, 22.70, 26.01, 29.33, 29.46, 29.59 (degenerate resonances), 31.93, 68.09, 69.32, 71.60, 127.98, 129.74, 133.31, 144.69; Mass spectrum, m/z (Rel. Intensity) 385(M^+, 2), 217(40), 173(70), 172(32), 155(30), 91(73), 85(34), 83(29), 82(25), 71(47), 69(35), 57(100), 56(29), 55(69); Anal. Calcd. for $C_{21}H_{36}O_4S$: C, 65.59; H,9.44. Found: C, 65.63; H, 9.38.

cis, cis-1,3,5-Tris(1,4-dioxahexadecyl)cyclohexane (**18**).

A three-necked 100 mL flask was equipped with a condenser and a nitrogen inlet tube and was charged with DMF (25 mL). In a separate flask a 57% dispersion of NaH in mineral oil was washed with dry hexane and residual hexane was evaporated under a nitrogen stream. The dry NaH (0.42 g, 0.0175 mol) was introduced into the three-necked flask followed by the addition of cis,cis-1,3,5-cyclohexanetriol **12** (0.34 g, 2.60 mmol). After the reaction mixture was warmed to 65°C for 0.5 h. and cooled to room temperature, tosylate **17** (3.07 g, 7.99 mmol) was added and the reaction mixture was stirred for two days. A subsequent addition of dry NaH (0.37 g, 0.0154 mol) and tosylate **17** (0.76 g, 1.98 mmol) was made in a same fashion and the reaction mixture was stirred for 5 days.

A few drops of water were added to quench excess NaH and the solvent was removed under reduced pressure yielding a brown residue. The residue was dissolved in CH_2Cl_2, filtered, and the solvent was removed under reduced pressure to

yield 2.25 g of the crude product. Column chromatography (100 g silica, 1% (v/v) EtOH-CH_2Cl_2) of 1.03 g of the crude product afforded 0.40g (39% estimated overall yield) of white low melting solid **18**: mp 32-33°C; R_f= 0.14 (1% (v/v) EtOH-CH_2Cl_2); IR (NaCl, neat) 2920, 2855, 1470, 1350, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.85 (m, 9H), 1.07-1.85 (m, 63H), 2.15- 2.6 (m, 3H), 3.3-3.7 (m, 21H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 14.05, 22.70, 26.14, 29.33, 29.65 (degenerate resonances), 31.93, 38.24, 67.83, 70.36, 71.60, 73.88; Mass spectrum, m/z (Rel. Intensity) 85(34), 71(52), 69(30), 63(47), 57(100), 55(47); Anal. Calcd. for $C_{48}H_{96}O_6$: C, 74.94; H, 12.58. Found: C, 74.71; H, 12.84.

cis,cis-1,3,5-Tris[1-oxa-(4-tetrahydropyranyl)ethyl] cyclohexane (**19**).

To a 250 mL three-necked flask equipped with a condenser, stirrer and a nitrogen inlet tube, DMF (75 mL) was added. A 57% mineral oil dispersion of NaH was washed with hexane and residual hexane was removed under a nitrogen stream. The dry NaH (1.65 g, 0.069 mol) was added to the reaction flask, followed by the addition of cis,cis-1,3,5-trihydroxy-cyclohexane **12** (3.00 g, 0.0227 mol). Hydrogen evolution was observed while warming the solution to 60°C for 1 h. A solution of 2-(2-Bromoethoxy)tetrahydropyran **14** (14.49 g, 0.0693 mol) in DMF (25 mL) was added to the flask along with a catalytic amount of solid KI (0.50 g) and the reaction was stirred for 6 days. Two additional equivalents of dry NaH (0.99 g, 0.041mol) and compound **14** (4.74 g, 0.0227 mol) were introduced in the same way and stirred for 5 days .

The excess NaH was quenched by the addition of H_2O (5 mL) and DMF and H_2O were removed *in vacuo* yielding a brown residue. The residue was taken up in CH_2Cl_2, the mixture was filtered through a celite pad, and the filtrate was concentrated. This process yielded a golden yellow oil which was purified by column chromatography on alumina. Elution of 3.90 g of the oil with 1% (v/v) EtOH-CH_2Cl_2 furnished 1.33 g (29%) of clear viscous product **19** which was diastereomeric mixture : R_f= 0.25 (1% EtOH-CH_2Cl_2); IR (NaCl, neat) 2920,

2830, 1445, 1340, 1115, 1060, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.0-2.0 (m, 21H), 2.14-2.51 (d of t, 3H), 3.0-4.1 (m, 21H), 4.5-4.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 19.50, 25.49, 30.63, 38.24, 62.23, 66.92, 67.70, 73.81, 98.98; Mass spectrum, m/z (Rel. Intensity) 88(29), 86(45), 85(100), 84(67), 58(42), 57(20); Anal. Calcd. for $C_{27}H_{48}O_9$: C, 62.77; H, 9.36. Found: C, 62.37; H, 9.63.

cis,cis-1,3,5-Tris(2-hydroxyethoxy)cyclohexane (**20**).

Tris-THP-ether diastereomeric mixture **19** (0.47 g, 0.92 mmol) dissolved in MeOH (10 mL) was introduced into a 50 mL round bottom flask. Dowex 50x8-100 acidic ion exchange resin (1.25 g) was added and the contents were stirred under nitrogen at room temperature for 28 h. The resin was then removed by filtration and the solvent was removed from the filtrate to afford 0.23 g of a viscous oil. Bulb-to-bulb distillation (210°C, 0.1 torr) provided 0.18 g (73%) of oily triol **20** : IR (NaCl, neat) 3390, 2940, 2860, 1690, 1350, 1070 cm^{-1}; ^1H NMR (Me_2CO-d_6, 60 MHz) δ 1.1(q, 3H, J = 10 Hz), 2.5(m, 3H), 3.39(t of t, 3H, J = 12 Hz), 3.6(br s, 12H); ^{13}C NMR (Me_2CO-d_6, 22.5 MHz) δ_C39.34, 62.30, 70.70, 74.27; Mass spectrum, m/z (Rel. Intensity) 109(52), 65(100), 64(36), 63(42), 59(23); Anal. Calcd. for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.58; H, 9.29.

cis,cis-1,3,5-Tris(3,3-dimethyl-1,4,7,10-tetraoxaundecyl) cyclohexane (**26**).

Mercuric acetate (0.86g, 2.73 mmol) was placed in a 50 mL flask, followed by the addition of freshly distilled 2-(2-methoxy ethoxy)ethanol (10 mL). The solution was allowed to stir for 10 min. A solution of cis,cis-1,3,5-tris(3-methyl-1-oxa-3-butenyl)cyclohexane **25** (0.10g, 0.34 mmol) in 2-(2-methoxyethoxy)ethanol (4 mL) was then added to the flask. The reaction mixture was stirred for 12 h, followed by quenching of the reaction by addition of 3M aq NaOH (10 mL) and 0.5 M $NaBH_4$ in 3M aq NaOH (10 mL). The suspended Hg was allowed to precipitate overnight and the supernate was decanted into a separatory funnel. Extraction with CH_2Cl_2 (3x50 mL), drying the combined extracts over anhyd Na_2SO_4, followed by evaporation of the solvent left a clear liquid. The contaminant 2-(2-methoxyethoxy)ethanol was removed by distillation (73-74^oC, 5mm) from the liquid to yield 0.1222 g of a clear oil. Column chromatography (260 g of alumina; 1.5% (v/v) EtOH-CH_2Cl_2) of the crude product with fraction cutting provided 0.0393 g of product **26** (17% yield). A small amount of the ligand **25** remained in the chromatographed product (< 10%) : Rf= 0.41; IR (neat) 2880, 1465, 1360, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (s, 18H), 2.1-2.6 (m, 3H), 3.3-3.75 (m, 45H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 23.02, 38.17, 58.98, 61.52, 70.56, 71.14, 72.05, 74.00, 74.92; Mass Spectral peak match calcd. for $C_{33}H_{67}O_{12}$: 655.8948. Found: 655.4609. Only the M+H peak was observed in

the high resolution EI spectrum.

2-(1,4,7,10-tetraoxaundecyl)tetrahydro-2H-pyran (**28**):

Into a 500 mL three-necked flask equipped with a teflon stirrer, condenser and a nitrogen inlet tube, DMF (200 mL) was introduced. Dry NaH (4.97g, 0.207 mol) which had previously been washed free of mineral oil with hexane and dried under a nitrogen stream was then added to the flask followed by a solution of 2-(2-methoxyethoxy)ethanol (**27**) (13.45g, 0.1119 mol) in DMF (15 mL). The reaction mixture was stirred at room temperature until evolution of H_2 gas subsided. A solution of 2-(2-bromoethoxy)tetrahydropyran (**14**) (23.39g, 0.1119 mol) in DMF (10 mL) was introduced together with a catalytic amount of solid KI (1g). The reaction mixture was stirred for 5 h. A second addition of NaH (1.11g, 0.0462 mol) was done and the reaction mixture was stirred for 12 h. A third addition of NaH (0.42g, 0.0175 mol) was done and the reaction mixture was stirred for 5 h after which th excess NaH was quenched by the addition of H_2O (10 mL) and the solvent was removed in vacuo. The brown residue was suspended in H_2O, extracted with CH_2Cl_2 (4x100 mL), dried over anhyd Na_2SO_4 and concentrated. Distillation (84-105°C; 0.2 torr) afforded 7.49g (27%) of a clear liquid **28**: IR (NaCl, neat) 2900, 1450, 1350, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.3-1.8(m, 6H), 3.4(s, 3H), 3.5-3.8(m, 14H), 4.55-4.75(m, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 19.51, 25.49, 30.63, 58.98, 62.17, 66.66, 70.69, 71.99, 98.91; Mass

spectrum, m/z (Rel.Intensity) 85(100), 84(90), 73(72), 67(44), 57(639); Anal. Calcd. for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74. Found: C, 58.27; H, 9.47.

2-[2-(2-Methoxyethoxy)ethoxy]ethanol (**29**):

To a solution of THP-protected alcohol **28** (7.49g, 0.0302 mol) in methanol (50 mL) Dowex 50x8-100 acidic ion exchange resin (3.0g) was added. The heterogenous mixture was stirred for 10h, filtered and the solvent was removed from the filtrate under pressure. Distillation (bp 68-74°C, 0.2 torr; lit. bp 249°C) provided 3.96g (80%) of a clear oil **29**: IR (NaCl, neat) 3420, 2860, 1430, 1340, 1190, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.90(s, 1H), 3.38(s, 3H), 3.45-3.85(m, 12H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C58.92, 61.58, 70.36, 70.62, 71.92, 72.64; Mass spectrum, m/z (Rel. intensity) 89(77), 88(23), 59(100), 58(94); Anal. Calcd. for $C_7H_{16}O_4$: C, 51.12%; H, 9.82%. Found: C, 51.45%; H, 10.08%.

3,6,9-tetraoxadecyl-p-toluenesulfonate (**30**):

To an ice-cold solution of p-toluenesulfonyl chloride (4.39g, 0.0203 mol) in dry CH_2Cl_2 (20 mL) was added an ice-cold solution of alcohol **29** (3.78g, 0.0203 mol) and pyridine (3.64g, 0.0460 mol) in CH_2Cl_2. The flask was stoppered and stored at 4°C until pyridinium chloride crystals were observed in the flask (ca. 2 days). The reaction mixture was filtered and washed successively with ice-cold water (2x100 mL), ice-cold 10% HCl (2x50 mL) and again with ice-cold

water (2x100 mL). The resulting organic phase was dried over anhyd Na_2SO_4 and the solvent was removed in vacuo to yield 5.54g (86%) of a clear liquid **30** which was used without further purification in future steps. An analytical sample was obtained by column chromatography of 0.21g of the compound (90g silica; 2% EtOH-CH_2Cl_2); IR (NaCl, neat) 2880, 1440, 1350, 1170, 1090, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz)δ 2.45 (s, 3H), 3.40 (s, 3H), 3.55-4.40 (m, 12H), 7.3-8.0 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 21.46, 58.79, 68.55, 69.13, 70.43, 70.63, 71.80, 127.70, 129.68, 133.07, 144.63; Mass spectrum, m/z (Rel. Intensity) 318(M^+, 10), 199(68), 155(46), 91(75), 89(20), 59(100), 58(54); Anal. Calcd. for $C_{14}H_{22}O_6S$: C,52.81; H,6.97. Found: C,53.03; H,7.24.

cis,cis-1,3,5-Tris(1,4,7,10-tetraoxaundecyl)cyclohexane (**31**):

A three necked 250mL flask was equipped with a condenser and a nitrogen inlet tube was charged with DMF (25 mL). In a separate flask a 57% dispersion of NaH in mineral oil was washed with dry hexane and residual hexane was evaporated under a nitrogen stream. The dry NaH (0.30 g, 0.0125 mol) was introduced into the three-necked flask followed by the addition of cis,cis-1,3,5-cyclohexane triol **12** (0.40 g, 0.0030 mol). After the reaction mixture was warmed at 65°C for 0.5 h and cooled to room temperature, tosylate **30** (2.90 g, 0.0091 mol) was added and the reaction mixture was stirred for 12 h. Another addition of NaH (0.38 g, 0.0158 mol) and tosylate (0.48 g, 0.0015 mol) were done in a simi-

lar fashion and the reaction mixture stirred for another 12 h. H_2O (10 mL) was added to quench excess NaH and the solvent was removed under reduced pressure to give a brown residue. The residue was dissolved in CH_2Cl_2, filtered and the solvent removed in vacuo to afford 2.04 g of a brown oil. Column chromatography (250 g alumina, 1.5% (v/v) EtOH-CH_2Cl_2) of 0.87 g of crude product yielded 0.07 g (4%) of an oil: R_f=0.4; IR (NaCl, neat) 2860, 1450, 1340, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.8-1.5 (q, 3H), 2.1-2.7 (m, 3H), 2.8-3.35 (m, 3H), 3.35 (s, 9H), 3.5-3.8 (m, 36H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ_C 38.17, 58.98, 67.76, 70.49, 70.62, 70.82, 71.99, 73.75; Mass spectrum, m/z (Rel. intensity) 103(17), 87(14), 86(19), 85(14), 59(100), 58(46), 57(13); Mass Spectral peak match calcd. for $C_{27}H_{55}O_{12}$: 571.7322. Found: 571.3718. Only the M+H peak was observed at 250°C for high resolution EI spectrum. CI mass spectrum showed the correct M+H peak at m/e 571.

REFERENCES:

1. Cram, D.J.; Trueblood, K.N. In "Host Guest Complex Chemistry Macrocycles"; Vogtle, F., Weber, E., Ed., Springer-Verlag: Berlin, 1985, pp 125-188.
2. Hilgenfeld, R.; Saenger, W. In "Host Guest Complex Chemistry Macrocyles"; Vogtle, F., Weber, E., Ed.; Springer-Verlag: Berlin, 1985, pp 43-124.
3. Lindenbaum, S.; Rytting, J.H.; Sternson, L.A. In "Progress in Macrocyclic Chemistry"; Izatt, R.M., Christensen, J.J., Ed.; Wiley: New York, 1979; Vol. 1, pp 219-254.
4. Painter, G.R.; Pressman, B.C. In "Host Guest Complex Chemistry II"; Vogtle, F., Ed.; Springer-Verlag: New York, 1982, pp 83-110.
5. Pedersen, C.J. J. Am. Chem. Soc. **1967**, 89, 7017-36.
6. Gokel, G.W.; Korzeniowski, S.H. "Macrocylic Polyether Syntheses"; Springer-Verlag: Berlin, 1982; Chapter 3.
7. Menger, F.m. In "Biomimetic and Biorganic Chemistry III"; Vogtle, F., Weber, E., Ed.; Springer-Verlag: New York, 1986, pp 1-15.
8. Lehn, J.M. Acc. Chem. Res. **1978**, 11, 49-57.
9. Cram, D.J. Science, **1983**, 219, 1177-79.
10. Weber, W.P., Gokel, G.W. "Phase Transfer Catalysis In Organic Synthesis"; Springer-Verlag: New York, 1977.
11. Liotta, C.L. In "Synthetic Multidentate Macrocylic Compounds"; Izatt, R.M., Christensen, J.J., Ed.; Academic: New York, 1978; pp 111-205.

12. Endo, T. In "Biomimetic and Biorganic Chemistry"; Boschke, F.L., Ed.; Springer-Verlag: New York, 1985; pp 91-111.

13. Dalley, K.N. In "Synthetic Multidentate Macrocylic Compounds"; Izatt, R.M., Christensen, J.J., Ed.; Academic: New York, 1978; pp 207-243.

14. Cabbiness, D.K.; Margerum, D.W. J. Am. Chem. Soc. **1969**, 91, 6540.

15. Fabbrizzi, L.; Paoletti, P.; Lever, A.B.P., Inorg. Chem. **1976**, 15, 1502.

16. Gokel, G.W.; Korzeniowski, S.H. "Macrocyclic Polyether Syntheses"; Springer-Verlag: Berlin, 1982, Chapter 7.

17. Vogtle, F.; Weber, E., Agnew. Chem. Int. Ed. Engl. **1979**, 18, 753.

18. Chaput, G.; Jeminet, G.; Juilliard, J., Can. J. Chem. **1975**, 53, 2240.

19. Tummler, B.; Maass, G.; Vogtle, F.; Sieger, H.; Heimann, U.; Weber, E., J. Am. Chem. Soc. **1979**, 101, 2588.

20. Sieger, H.; Vogtle, F., Agnew. Chem. Int. Ed. Engl. **1978**, 17, 198.

21. Ref 2, pp 112-113.

22. Vogtle, F.; Sieger, H. Agnew. Chem. Int. Ed. Engl. **1977**, 16, 396.

23. Weber, E.; Vogtle, F. Tetrahedron. Lett. **1975**, 29, 2415.

24. Saenger, W.; Suh, I.H.; Weber, G. Isr. J. Chem. **1979**,

18, 253.

25. Vogtle, F.; Weber, E. Agnew. Chem. Int. Ed. Engl. **1974**, 13, 814.

26. Hyatt, J.A. J. Org. Chem. **1978**, 43, 1808.

27. Angyal, S.J.; Davies, K.P. Chem. Commun. **1971**, 500.

28. Angyal, S.J. Tetrahedron, **1974**, 30, 1695.

29. Angyal, S.J. Pure Appl. Chem. **1973**, 35, 131-146.

30. Buchanan, G.W.; Bourque, K.; Bovenkamp, J.W.; Rodrigue, A.; Bannad, R.A.B. Tetrahedron. Lett. **1984**, 3963.

31. Buchanan, G.W.; Bourque, K.; Bovenkamp, J.W.; Rodrigue, A. Can. J. Chem. **1985**, 63, 2747.

32. Buchanan, G.W.; Ripmeester, J.A.; Bovenkamp, J.W.; Rodrigue, A. Tetrahedron. Lett., **1986**, 27, 2239.

33. Buchanan, G.W.; Bourque, K.; Diedrich, G.K.; Khan, M.Z. Magn. Reson. Chem. **1987**, 25, 65.

34. Buchanan, G.W.; Kirby, R.A. Tetrahedron. Lett. **1987**, 28, 1507.

35. Raban, M.; Hortelano, E.; Quin, J.III; King, N.; Koch, J. J. Chem. Soc. Chem. Commun. **1985**, 1557.

36. Raban, M.; Burch, D.; Hortelano, E. Tetrahedron. Lett., personal communication, **1987**.

37. Laidler, D.A.; Stoddart, J.F. In "The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Sulphur Analogues"; Supplement E of The Chemistry of Functional Groups, Patai, S., Ed.; John Wiley and Sons: New York, 1980; Chapter 1.

38. Gokel, G.W.; Korzeniowski, S.H. "Macrocyclic Polyether Syntheses"; Springer-Verlag: New York, 1982.

39. "Synthesis of Macrocyles: The Design of Selective Complexing Agents"; Izatt, R.M., Ed.; Progress in Macrocyclic Chemistry, Vol.3; John Wiley and Sons: New York, 1987.

40. Kyba, E.P.; Helgeson, R.C.; Madan, K.; Gokel, G.W.; Tarnowski, T.L.; Moore, S.S.; Cram, D.J. J. Am. Chem. Soc. **1977**, 99, 2564.

41. Brown, H.C.; Zwiefel, G. J. Org. Chem. **1962**, 27, 470°.

42. Juaristi, E.; Martinez-Richa, A.; Garcia-Rivera, A.; Cruz-Sanchez, J.S. J. Org. Chem. **1983**, 48, 2603.

43. Roshkov, I.N.; Makin, S.M. Zh. Obshch. Khim. **1964**, 34, 59.

44. Braude, E.A.; Gofton, B.F.; Lowe, G.; Waight, E.S. J. Chem. Soc., **1956**, 4, 4054.

45. Servis, K.L.; Shue, F.F. J. Am. Chem. Soc. **1980**, 102, 7233.

46. Brown, H.C.; Goeghegan, P.J. J. Am. Chem. Soc. **1967**, 89, 1522.

47. Meinwald, J.; Yankeelov, J.A.Jr. J. Am. Chem. Soc., **1958**, 80, 5266.

48. Sterling Drug Inc. Brit. Patent 869,083, 1961; Chem. Abstr. **1962**, 56, 4684.

49. Steinacker, K.H.; Stetter, H. Chem. Ber. **1952**, 85, 451.

50. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. Synthesis, **1979**, 618.

51. Parham, W.E.; Anderson, E.L., J. Am. Chem. Soc. **1948**, 70, 4187.

52. Wrigley, A.N.; Stirton, A.J.; Howard, E., J. Org. Chem. **1960**, 25, 439.

53. Gronbeck, D.A., B.S Thesis, The University of New Hampshire, Durham, N.H. **1985**, 19.

54. Brown, H.C.; Rei, M.-H. J. Am. Chem. Soc. **1969**, 91, 5646.

55. Stadler

56. Adams, F.H. U.S. Patent 2,266,141, 1941; Chem. Abstr. **1942**, 36, 2270.

57. Lee, H.W.; Kishi, Y. J. Org. Chem. **1985**, 50, 4402.

58. Caywood, G. BS Thesis, University of New Hampshire, Durham, NH 1981.

59. Miller, J.C.; Miller, J.N. "Statistics for Analytical Chemistry"; Wiley: New York, 1984, Chapter 2.

60. Owen, L.N.; Robins, P.A. J. Chem. Soc., **1949**, 320.

61. Izatt, R.M.; Bradshaw, J.S.; Nielson, S.A.; Lamb, J.D.; Christensen, J.J. Chem. Rev. **1985**, 85, 271.

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

63. Tummler, B.; Maass, G.; Vogtle, F.; Sieger, H.; Heimann, U.; Weber, E. J. Am. Chem. Soc. **1979**, 101, 2588.

64. Vogtle, F.; Weber, E. In "The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulfur Analogues"; Patai, S., Ed.; Wiley: Chichester, 1980; Part 1, Chapter 2.

65. Grandjean, L.; Lazlo, P.; Offermann, W.; Rinaldi, P.L. J. Am. Chem. Soc. **1981**, 103, 1380.

66. Weisman, G.R. Personal Communication.

67. Pascarella, T.P. Master's Thesis, The University of New Hampshire, Durham, NH. 1986.

68. Reinhoudt, D.N.; Gray, R.T.; DeJong, F.; Smit, C.J. Tetrahedron, **1977**, 33, 563.

69. Taga, T. Acta Cryst. **1969**, B25, 2656.

70. Wilson, N.K.; Stothers, J.B. In "Topics in Stereochemistry"; Eliel, E.L.; Allinger, N.L., Eds.; Wiley: New York, 1974, 8, 1.

71. Sutherland, I.O. In "Applications of NMR Spectroscopy to Problems in Stereochemistry and Conformational Analysis", Takeuchi, Y.; Marchand, A.P., Eds.; VCH: Deerfield, 1986, Chapter 1.

72. Live, D.; Chan, S.I. J. Am. Chem. Soc. **1976**, 98, 3769.

73. Duddeck, H. In "Topics in Stereochemistry"; Eliel, E.J.; Wilen, S.H.; Allinger, N.L., Eds.; Wiley: New York, 1986, 16, 219.

74. Stoddart, J.F. "Stereochemistry of Carbohydrates"; Wiley-Interscience: New York, 1971, pp 129-145.

75. Roberts, J.D.; Weigert, F.J.; Kroschwitz, J.I.; Reich, H.J. J. Am. Chem. Soc. **1970**, 92, 1338.

76. Grover, S.H.; Guthrie, J.P.; Stothers, J.B.; Tan. C.T. J. Mag. Reson. **1973**, 10, 227.

77. Ayer, W.A.; Browne, L.M.; Fung, S.; Stothers, J.B. Org. Mag. Reson. **1978**, 11, 73.

78. Hartley, F.R.; Burgess, C.; Alcock, R.M. "Solution Equilibria"; Wiley: Chichester, 1980, Chapter 9.

79. Rossotti, F.J.C.; Rossotti, H. "The Determination of

Stability Constants in Solution"; MaGraw-Hill: New York, 1961, pp 291.

80. Tummler, B.; Maass, G.; Vogtle, F.; Sieger, H.; Heimann, U.; Weber, E. J. Am. Chem. Soc. **1979**, 101, 2588.

81. Pascarella, T.M. Ref. 67, pp 36.

82. Ref 78, Chapter 7.

83. Ref. 79, Chapter 7.

84. Gokel, G.W.; Goli, D.M.; Minganti, C.; Echegoyen, L. J. Am. Chem. Soc. **1983**, 105, 6786.

85. Frensdorff, H.K.; J. Am. Chem. Soc. **1971**, 93, 600.

86. Nelsen, S.F.; Weisman, G.R.; Clennan, E.L.; Peacock, V.E. J. Am. Chem. Soc. **1976**, 98, 6893.

87. Osawa, E.; Musso, H. In "Topics in Stereochemistry", Allinger, N.L.; Eliel, E.L.; Wilen, S.H. Eds.; Wiley: New York, 1982, 13, pp 117.

88. Boyd, D.B.; Lipkowitz, K.B. J. Chem. Ed. **1982**, 59, 269.

89. Burkert, U.; Allinger, N.L. "Molecular Mechanics", ACS Monograph 177, American Chemical Society, Washington, D.C., 1982.

90. Coolidge, M.A.; Petillo, P.A.; Weisman, G.R. Quantum Chemistry Program Exchange, **1984**, 4(2), 476.

91. Allinger, N.L.; Yuh, Y.H. Quantum Chemistry Program Exchange, **1980**, 12, 395.

92. Arnold, K.A.; Gokel, G.W. J. Org. Chem. **1986**, 51, 5015.

93. Ref. 73, pp 298.

94. Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. "Conformational Analysis", Interscience: New York, 1965, pp 58.

95. Personal communication, Dr. G. R. Weisman.

96. Gutmann, V. CHEMTECH, **1977**, 7, 255.

97. Menger, F. M. In "Topics in Current Chemistry"; Vogtle, F.; Weber, E. Eds.; Springer-Verlag: New York, 1986, pp 2.

98. Suckling, C.J. J. Chem. Soc., Chem. Commun. **1982**, 661.

99. Murakami, Y.; Nakano, A.; Miyata, R.; Matsuda, Y. J. Chem. Soc., Perkin I Trans, **1979**, 1669.

100. Trend, J., 3M Corporation.

101. Guinand, P.; Marsau, P.; Laurent, H.; Castellan, H.; Desvergne, J.P.; Lamotte, M. Acta. Crystallogr., Sect. C: Cryst. Struct. Commun. **1987**, C43(5), 857.

102. Cram, D.J.; Trueblood, K.N. In "Host-Guest Chemistry", Vogtle, F.; Weber, E., Eds.; Springer-Verlag: New York, 1985, pp 153.

103. Dale, J. Isr. J. Chem. **1980**, 20, 3.

104. Dale, J. Tetrahedron, **1974**, 30, 1683.

105. Gutmann, V. Agnew. Chem. Int. Ed. **1970**, 9, 843.

106. Mayer, U.; Gutmann. V.; Gerger, W. Monatsh. Chem. **1975**, 106, 1235.

107. Aaron, H.S. In "Topics in Stereochemistry"; Allinger, N.L., Eliel, E.L., Eds.; Interscience: New York, 1979, 11, pp 1.

108. Work carried out at 3M by Dr. J.E. Trend.

109. Hughes, D.L. J. Chem. Soc., Dalton Trans, **1975**, 2374.

110. Lehn, J.M. In " Structure and Bonding", Dunitz, J.D. Ed.; Springer-Verlag: NY, 16, pp 1.

111. Oki, M. "Applications of Dynamic NMR Spectroscopy to Organic Chemistry"; Marchand, A.P. Ed.; VCH: Deerfield, 1985.

112. Bovey, F.A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969, Chapter 7.

113. Petillo, P.A. University of New Hampshire, Durham, NH 1984.

114. Led, J.J.; Petersen, S.B. J. Mag. Res. **1978**, 32, 1.

115. McLain, S.J. J. Am. Chem. Soc. **1983**, 105, 6355.

116. Friebloin, H.; Schmid, H.G.; Kabub, S.; Faibt, W. Org. Mag. Reson. **1969**, 1, 147.

APPENDIX

Index

A. Tables of Data

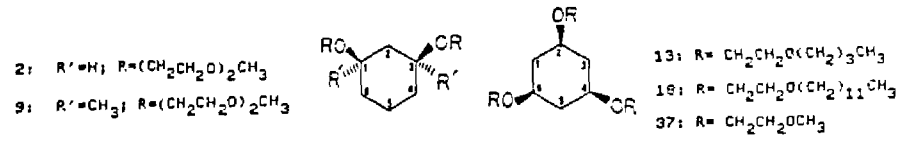
Table 13: ^{13}C NMR Titration of **2** with $NaBPh_4$ in Acetone-d_6

$[2]_{initial}$ = 0.269M

	^{13}C Chemical Shifts in ppm	
$[NaBPh_4]/[2]$	C-5	C-2
0.000	21.33	39.99
0.199	20.87	39.74
0.396	20.29	39.47
0.596	19.51	39.02
0.795	18.73	38.63
0.994	18.01	38.30
1.193	17.43	37.91
1.391	16.78	37.52
1.589	16.52	37.39
1.788	16.26	37.26
1.987	16.13	37.20
2.186	16.06	37.13
2.384	15.93	37.00
2.583	15.93	37.00
2.782	15.87	36.94
3.179	15.74	36.81
3.576	15.74	36.74

(See page 43)

Table 14: Tables of data for ^{13}C NMR competition experiments



Podand	Carbon resonance	Uncomplexed (A)	Competition (B)	Fully Complexed (C)	obs (B-A)	max (C-A)
Podand 37 versus podand 2						
2	2	38.89	38.17	36.35	-0.72	-2.54
	1,3	77.06	76.54	75.11	-0.52	-1.95
	5	20.81	18.86	13.72	-1.95	-7.09
Podand 9 versus podand 2						
2	2	38.89	38.12	36.35	-0.78	-2.54
	4,6	31.80	30.56	27.64	-1.24	-4.16
	5	20.80	18.60(br)	13.72	-2.20	-7.08
9	2	44.94	49.23	50.72	4.29	5.78
	4,6	36.10	33.43	32.58	-2.67	-3.52
	5	18.01	17.04	16.71	-0.97	-1.30
Podand 13 versus podand 2						
2	5	20.81	18.14	13.72	-2.67	-7.09
Podand 18 versus podand 2						
2	2	38.89	37.59	36.35	-1.30	-2.54
	3	77.06	76.09	75.11	-0.97	-1.95

Table 15: Parameters, variance and residuals for DNMR experiment of **37** (See page 53)

Parameter Table

0	1 PARAMETER	2 VALUE	3 STANDARD DEVIATION	4 T-VALUE	5 SIG. LEV.
1	INTERCEPT	-37.814434	10.496337	-3.602632	0.022705
2	SLOPE	290.569168	24.718684	11.755042	0.001000

Analysis of Variance Table

0	1 SOURCE	2 SUM OF SQUARES	3 D.F.	4 MEAN SQUARE	5 F VALUE
1	REGRESSION	17468.774743	1	17468.774743	138.181017
2	RESIDUAL	505.677990	4	126.419498	

0	6 SIG. LEV.	7 MULT R-SQ	8 STD DEV OF REGR
1	0.001	0.971867	11.243643
2			

Residuals Table

0	1 X VALUE	2 Y OBS.	3 Y PRED.	4 RESIDUAL
1	0.16645	22.22	10.550804	11.669196
2	0.20345	25.00	21.301863	3.698137
3	0.30515	33.33	50.852747	-17.522747
4	0.37295	66.66	70.553337	-3.893337
5	0.55945	125.00	124.744487	0.255513
6	0.68380	166.67	160.876763	5.793237

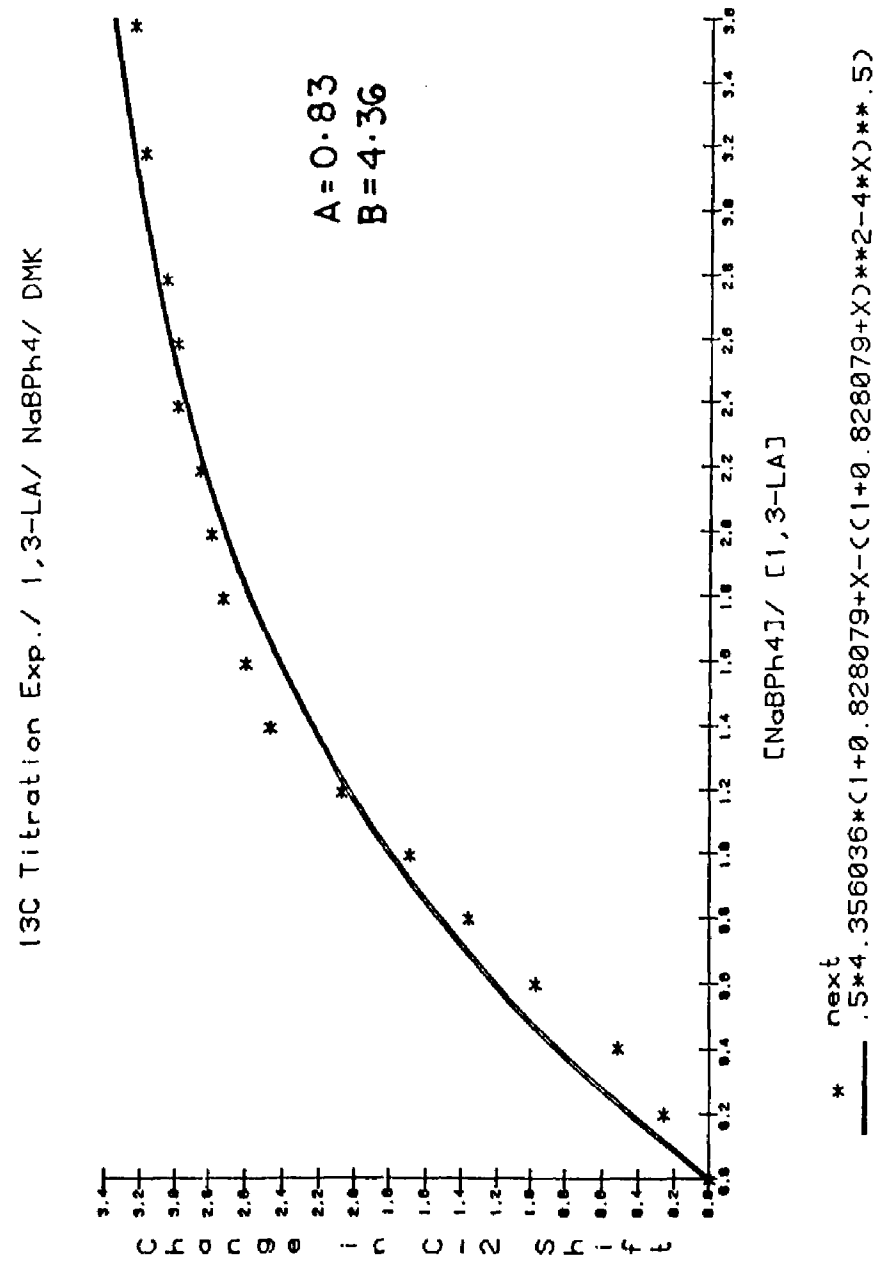
Table 16: Range of τ and k_{obs} for DNMR experiment[a]

Conc. (M) free ligand	$taua^+$ (sec)	$taua^-$ (sec)	k_{obs}^+ (sec^{-1})	k_{obs}^- (sec^-)
0.167	0.055	0.025	18.18	40.00
0.204	0.055	0.025	18.18	40.00
0.305	0.040	0.025	25.00	40.00
0.373	0.020	0.010	50.00	100.00
0.560	0.0085	0.0065	117.64	153.85
0.684	0.0070	0.0045	142.86	222.22

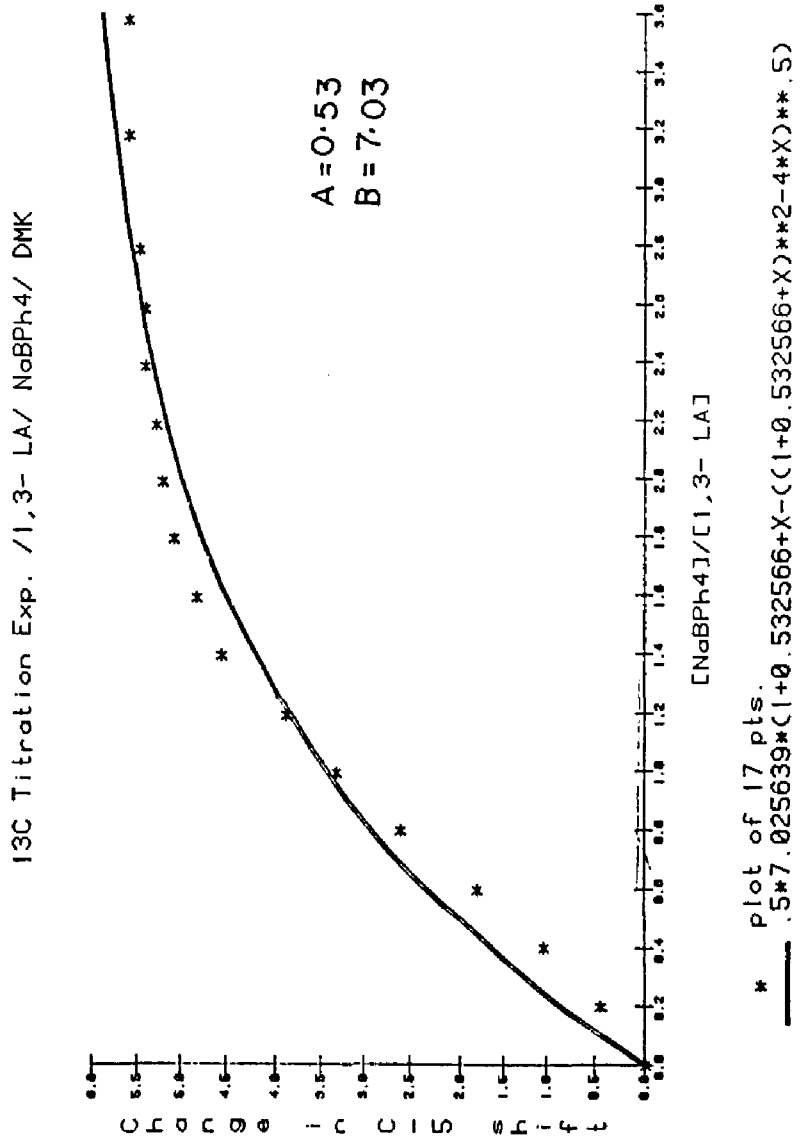
a. See page 51

B. Graphs

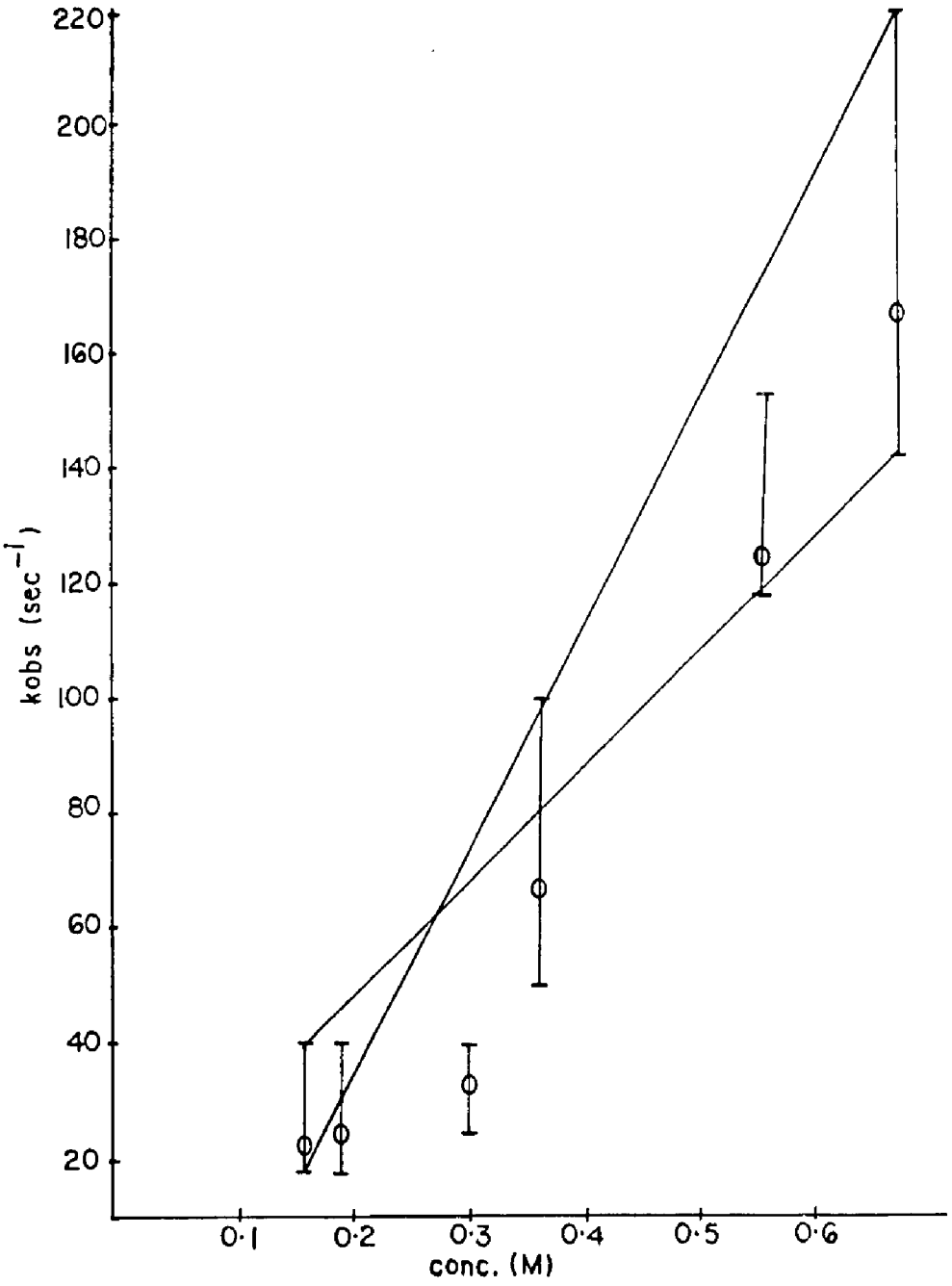
^{13}C NMR Titration Experiments: Graph of Results for Dipodand **2** following C-2.



^{13}C NMR Titration Experiments: Graph of Results for Dipodand **2** following C-5.

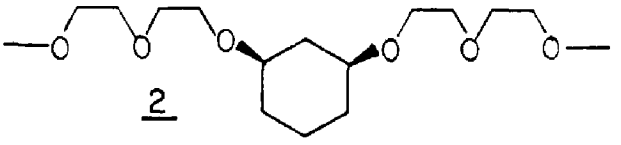


Graph of range of k_{obs} versus concentration for DNMR experiment (See page 54).



The error bars represent acceptable fit for the experimental spectra by simulating the spectra.

C. ^1H NMR Complexation Experiments Spectra



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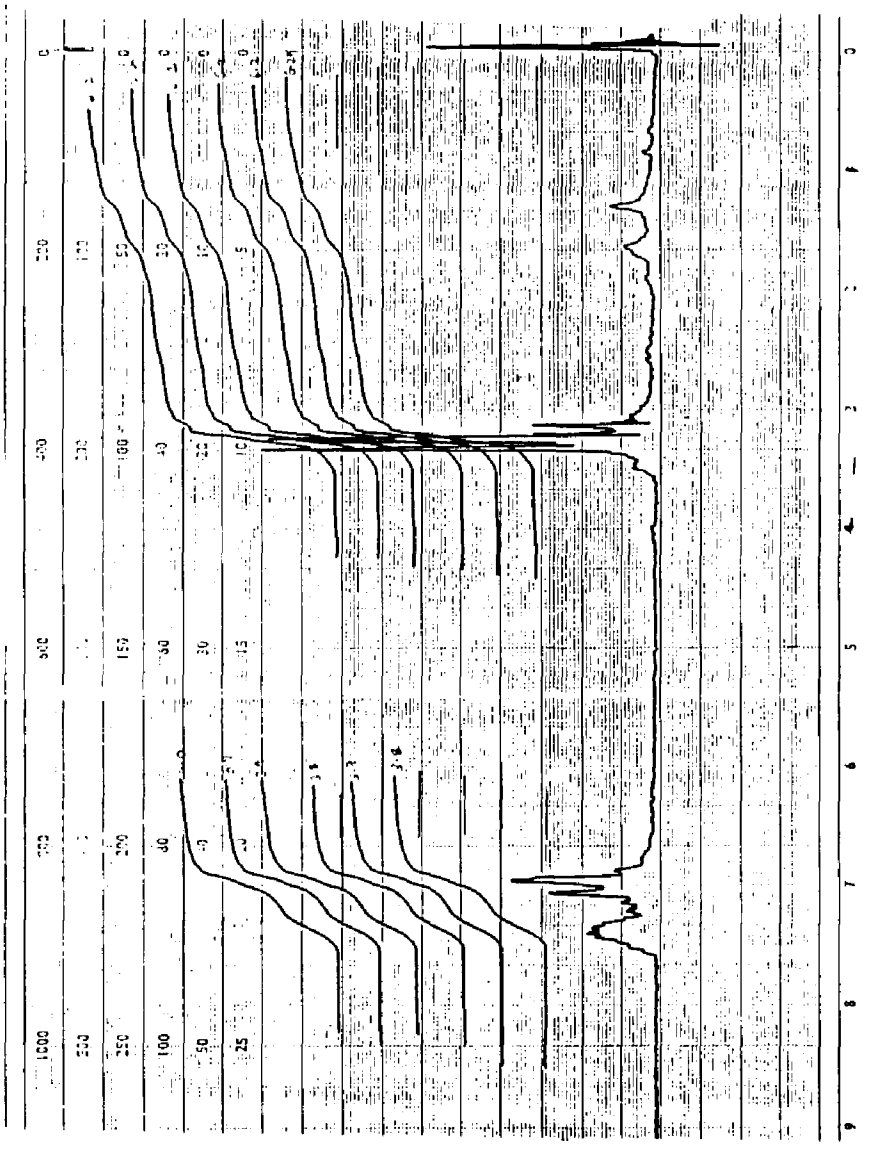
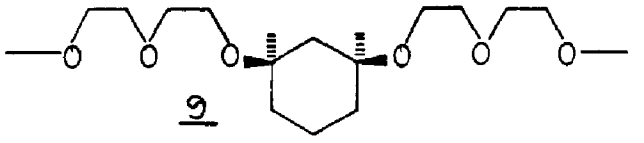
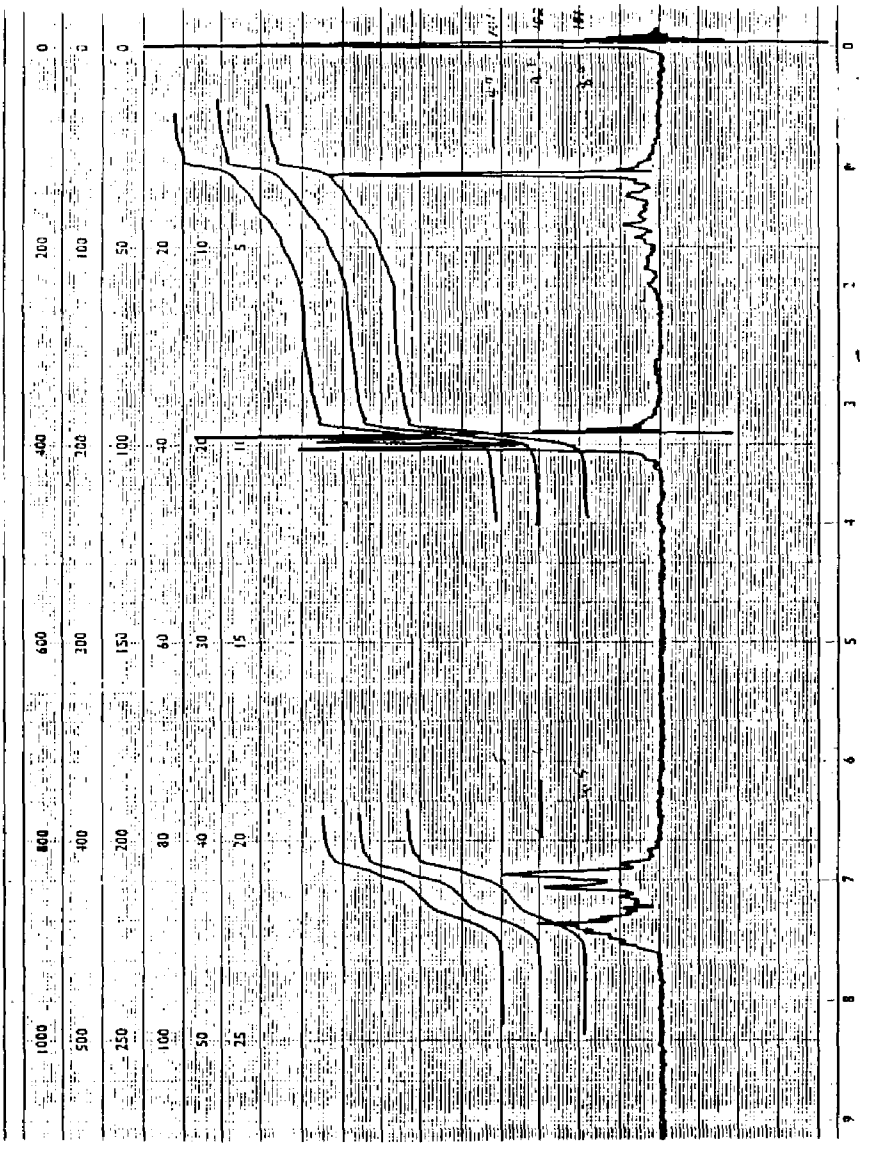
0.0649 mmol of ligand/ $NaBPh_4$/ $CDCl_3$

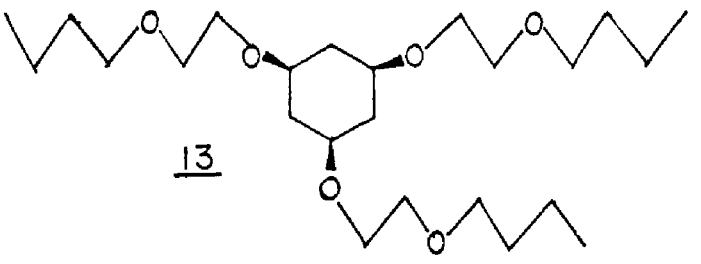




9

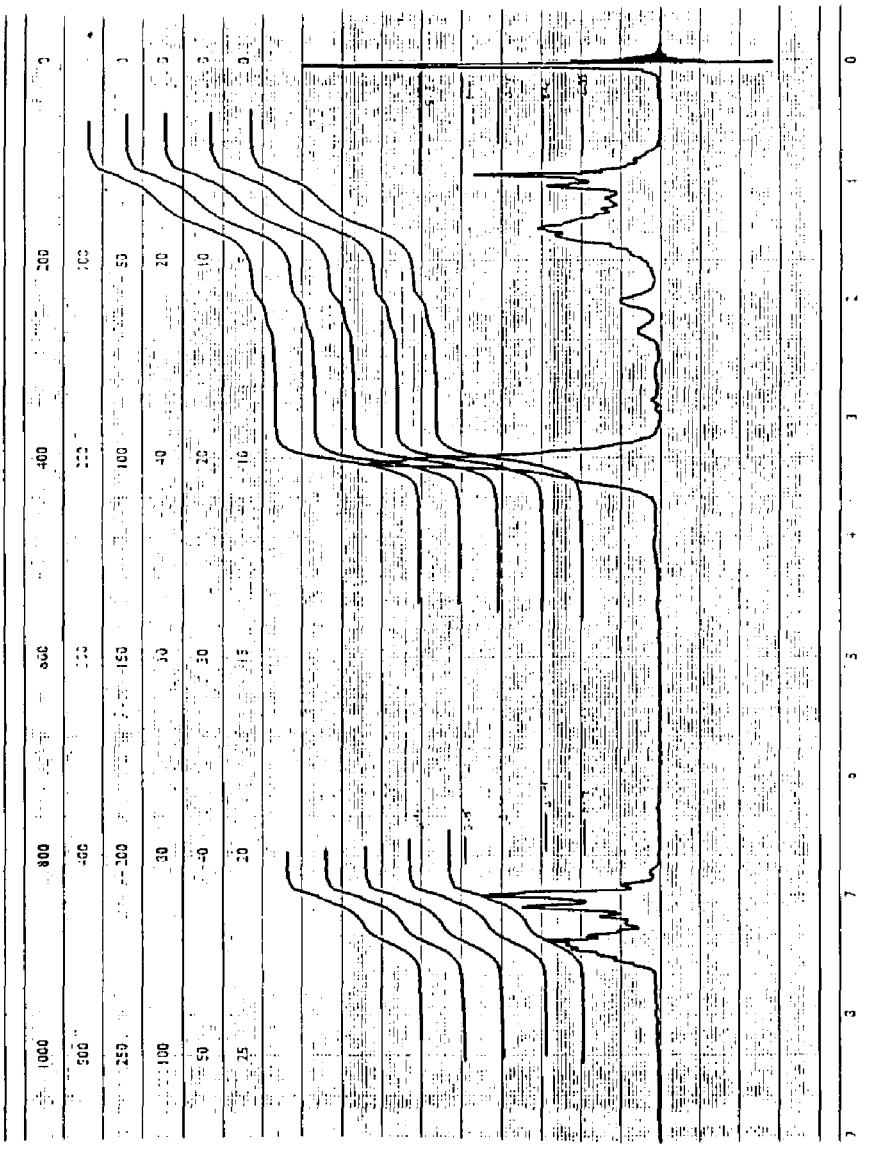
0.0488 mmol of ligand/ $NaBPh_4$/ $CDCl_3$

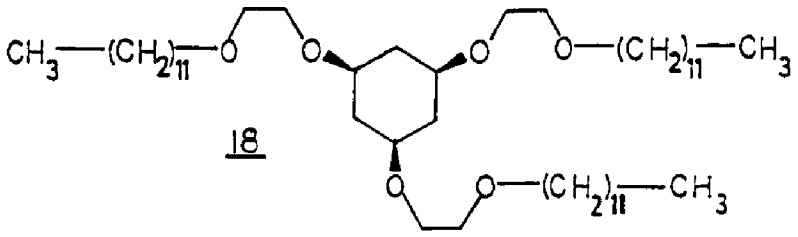




13

0.1826 mmol of ligand/ $NaBPh_4$/ $CDCl_3$





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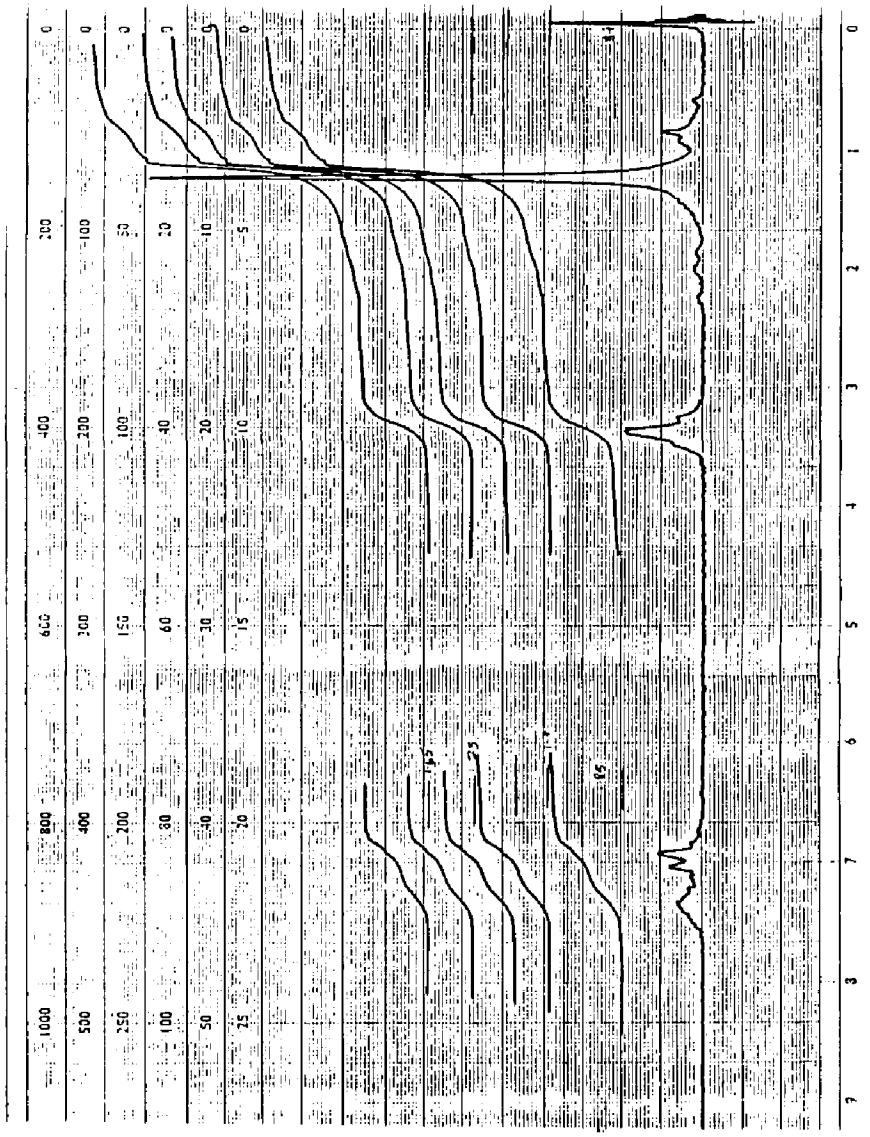
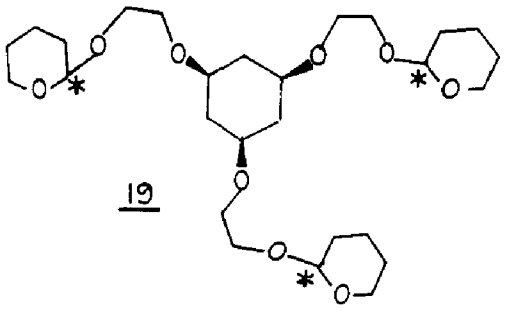
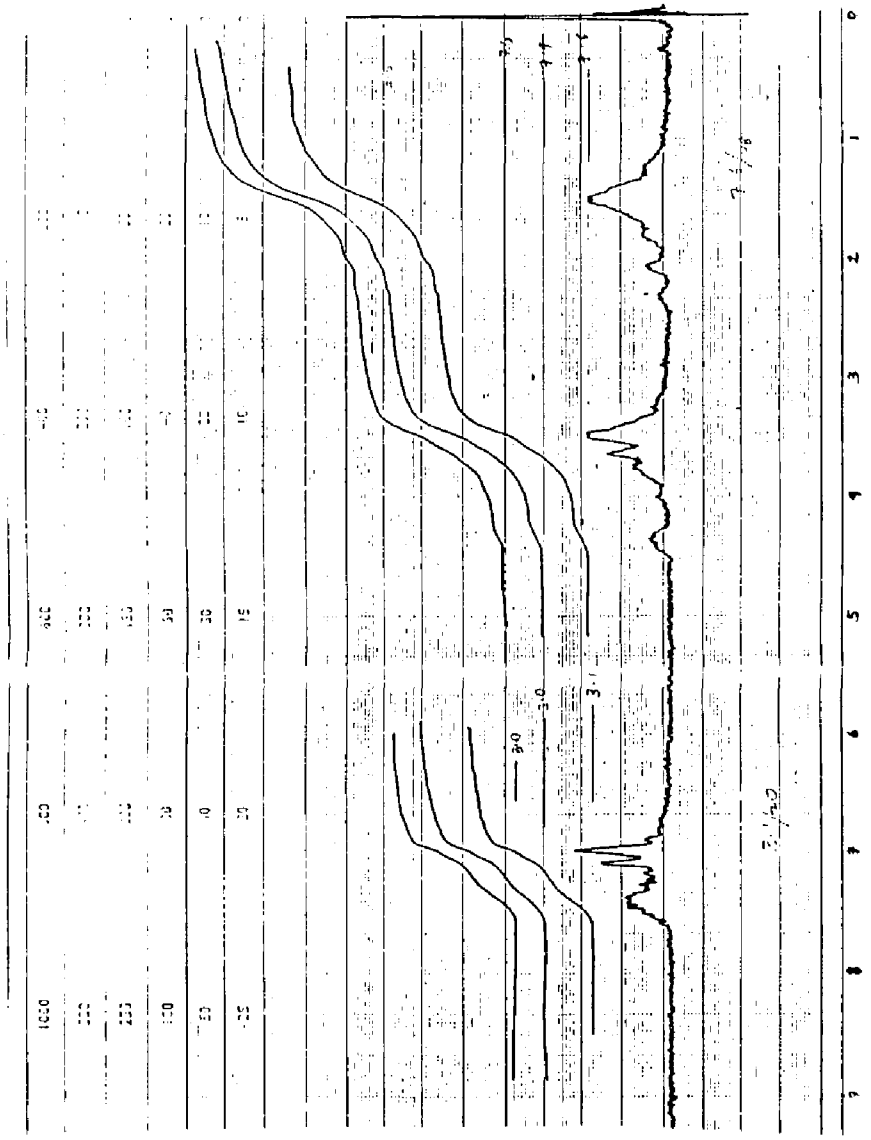
0.0331 mmol of ligand/ $NaBPh_4$/ $CDCl_3$



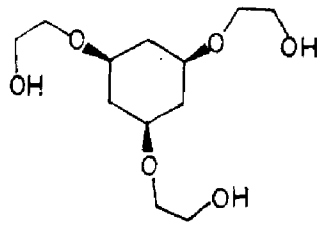


19

0.0536 mmol of ligand/ $NaBPh_4$/ $CDCl_3$



0.0987 mmol of ligand/ $NaBPh_4$/ $CDCl_3$



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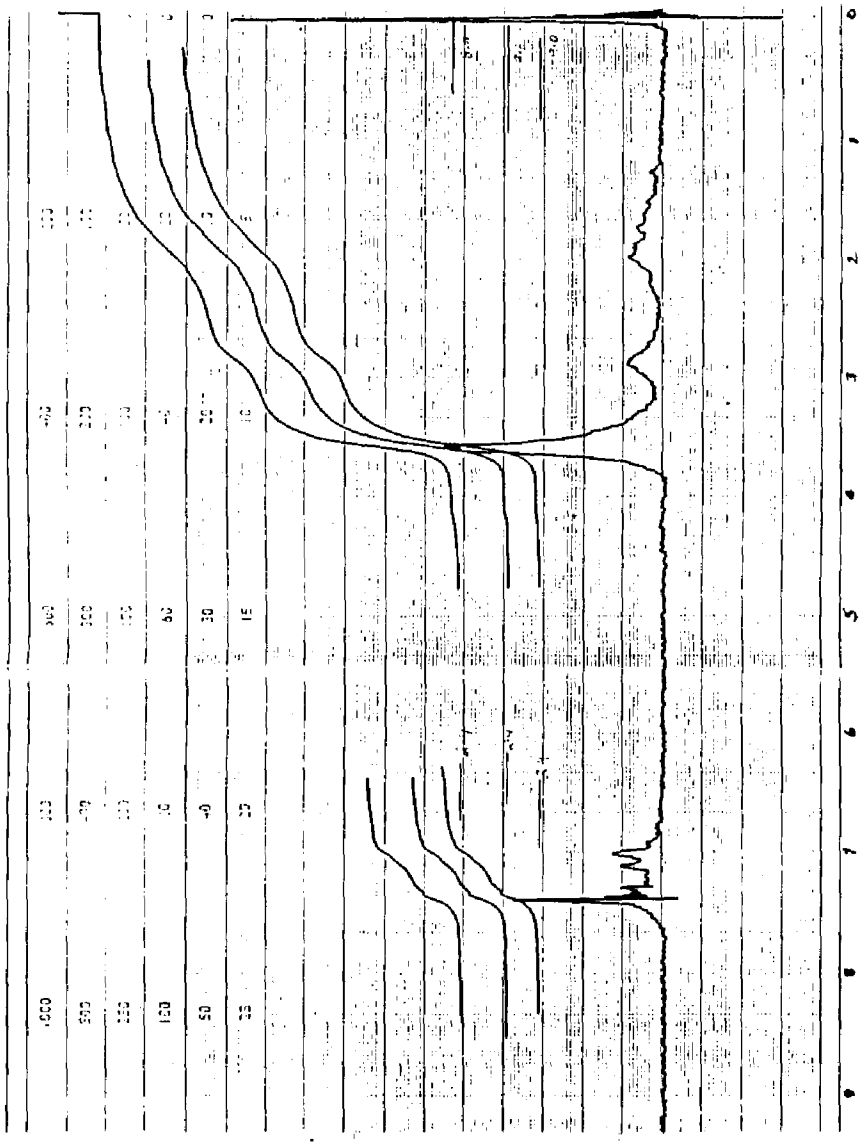
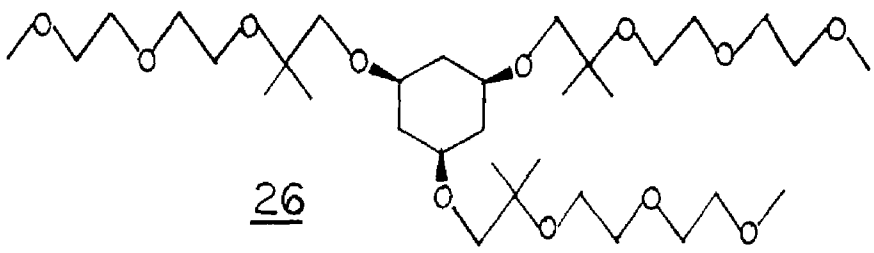
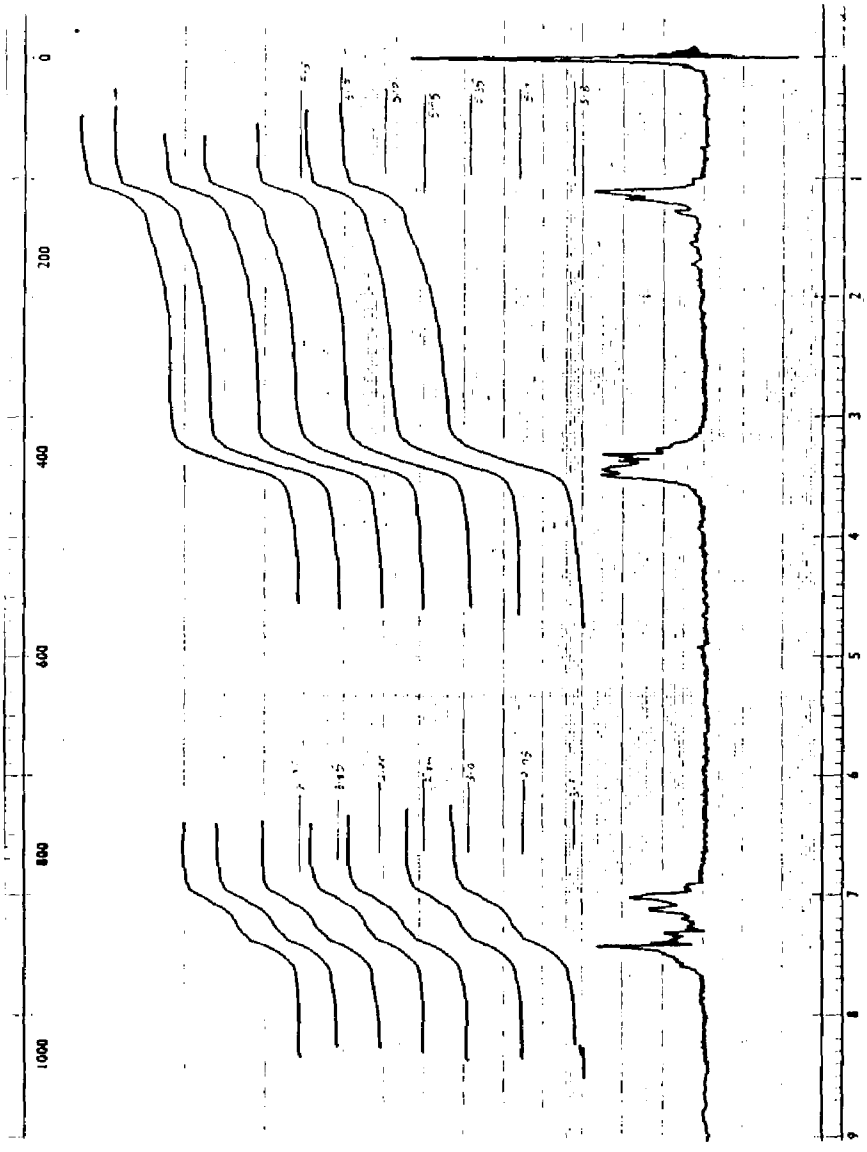
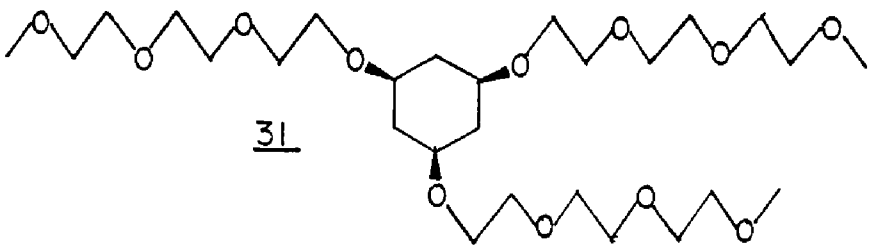




26

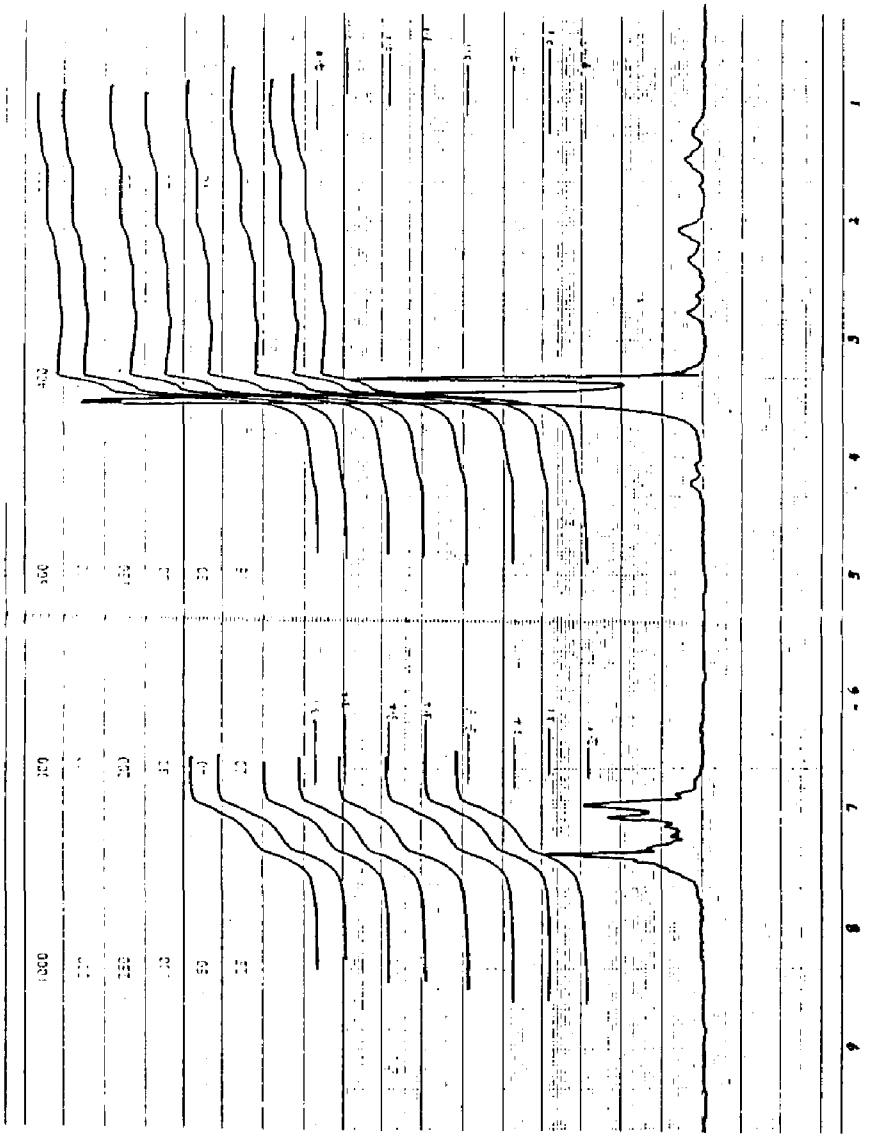
0.0370 mmol of ligand/ $NaBPh_4$/ $CDCl_3$



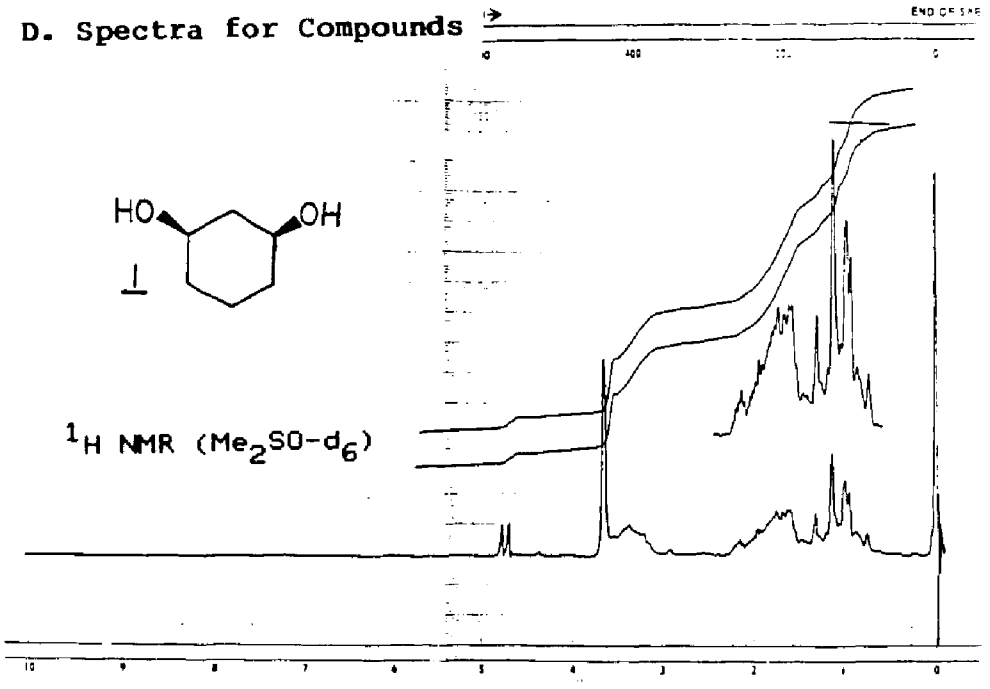


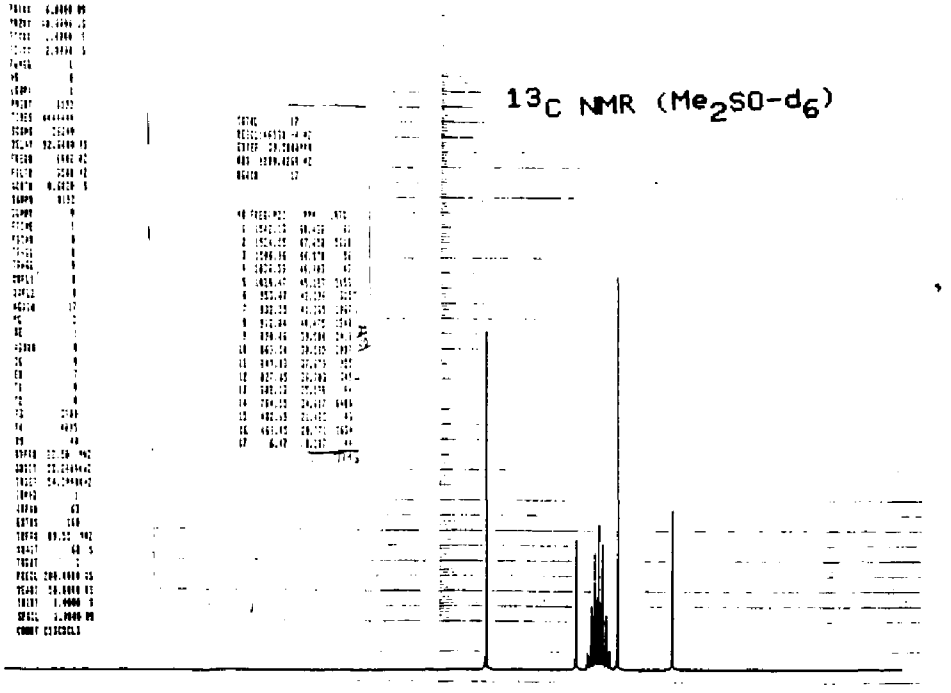
31

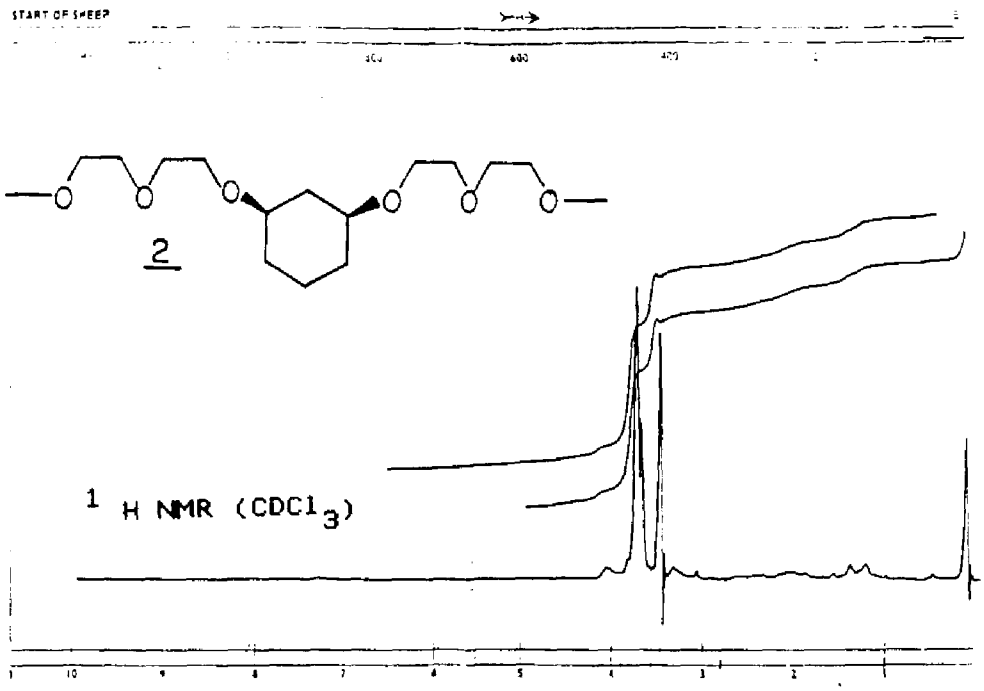
0.0648 mmol of ligand/ $NaBPh_4$/ $CDCl_3$

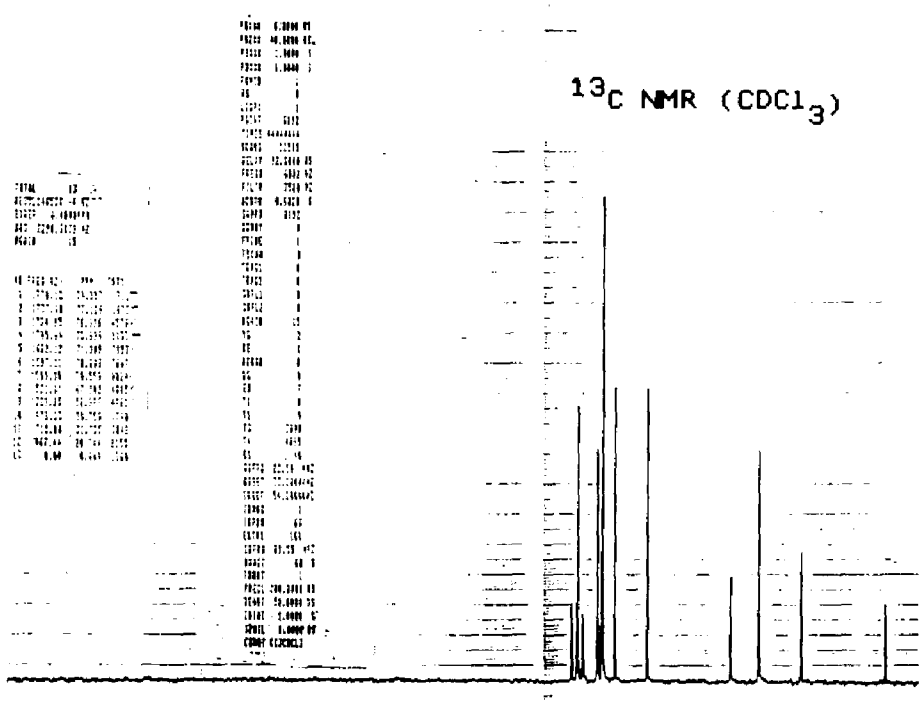


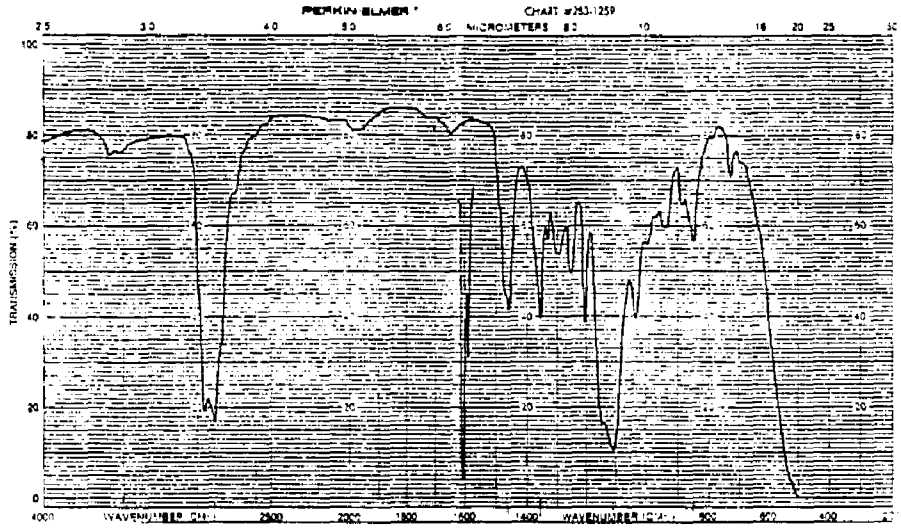
D. Spectra for Compounds



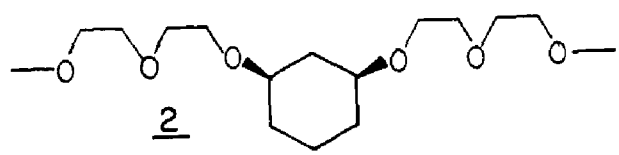



START OF SWEEP
2
1 H NMR (CDCl3)


13C NMR (CDCl3)



IR (Neat)



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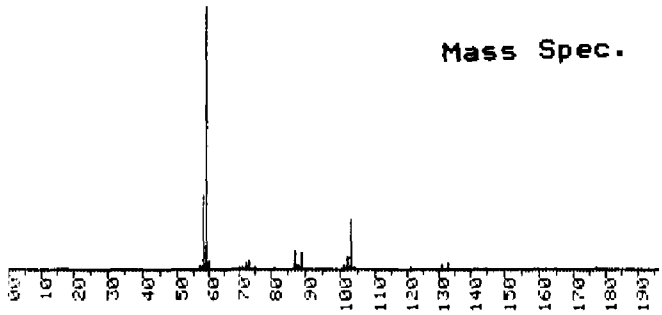
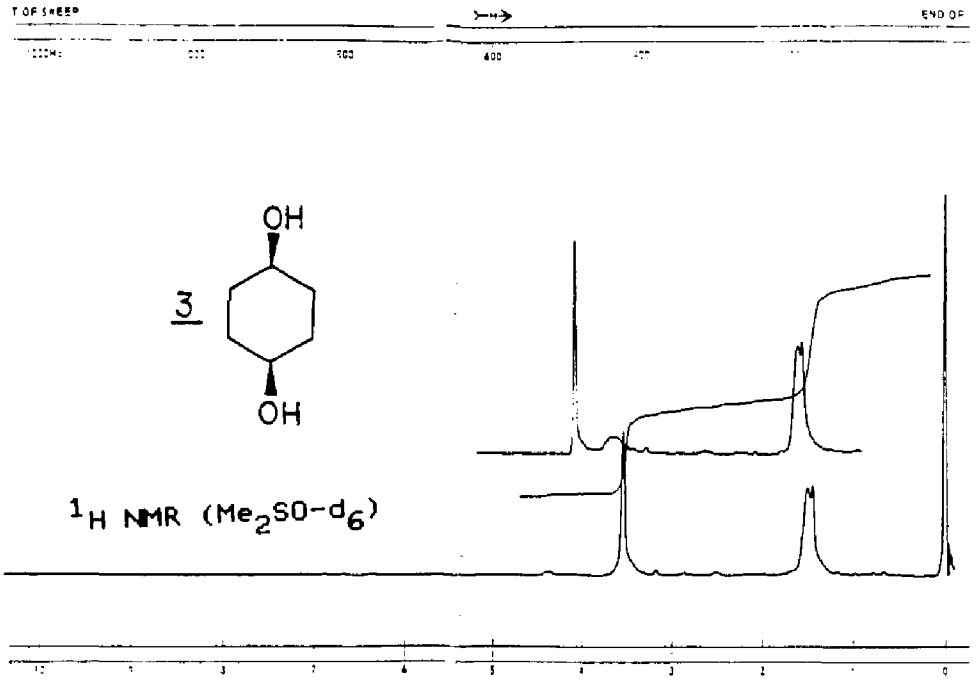
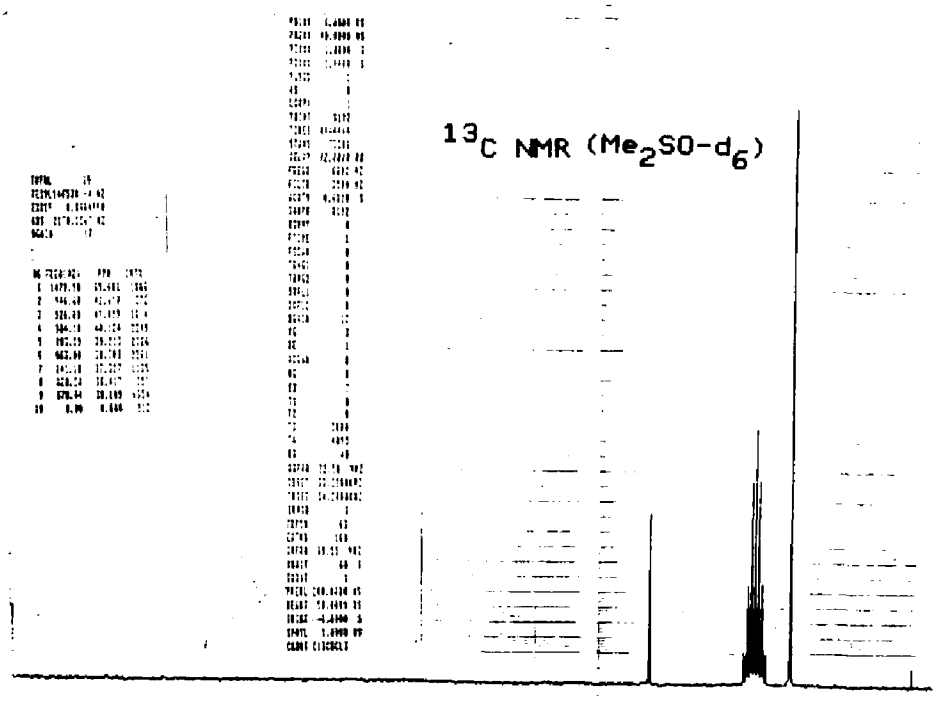
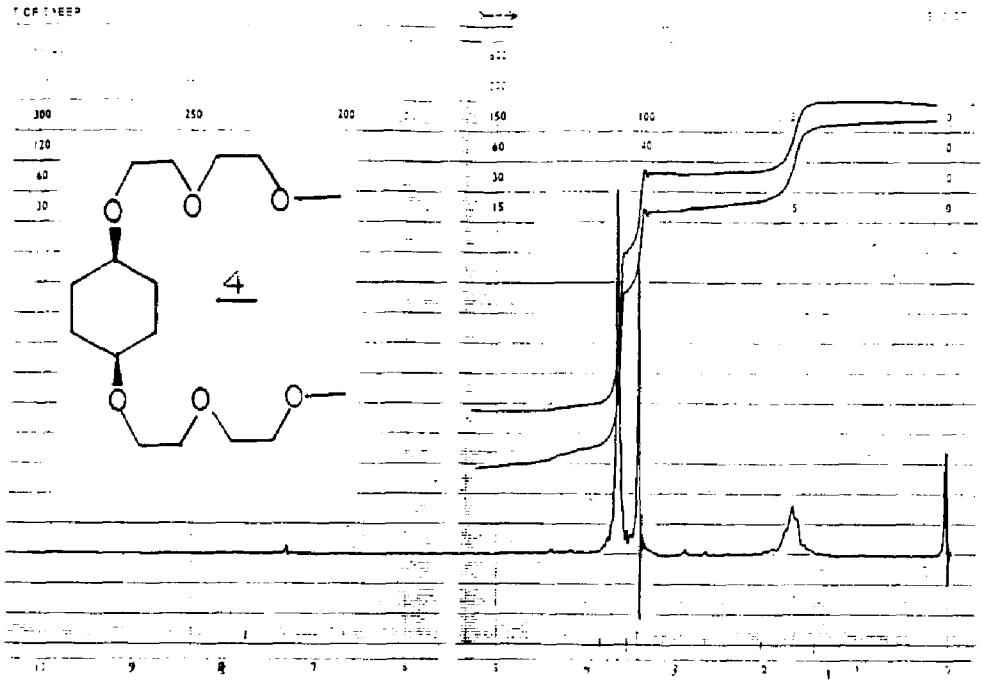


Mass Spec.

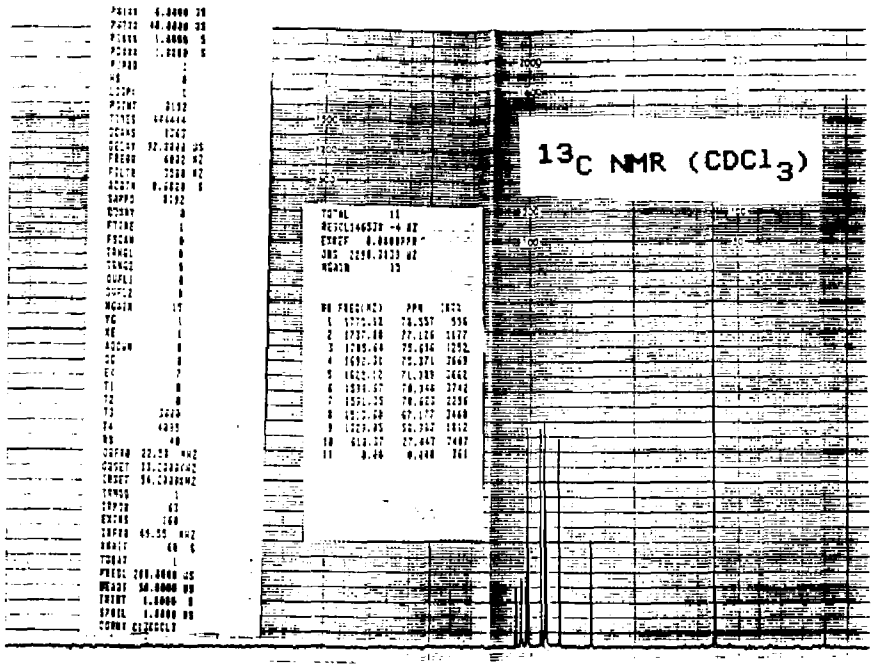
M/Z	REL INT
57	15
58	275
59	1000
60	33
70	10
71	8
72	23
73	30
75	7
81	6
87	69
88	16
89	60
101	14
102	41
103	188
104	11
121	7
131	12
133	21
177	4

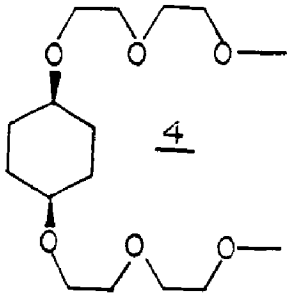

OH
3
OH
^{1}H NMR (Me_2SO-d_6)


^{13}C NMR (Me_2SO-d_6)



^{1}H NMR ($CDCl_3$)





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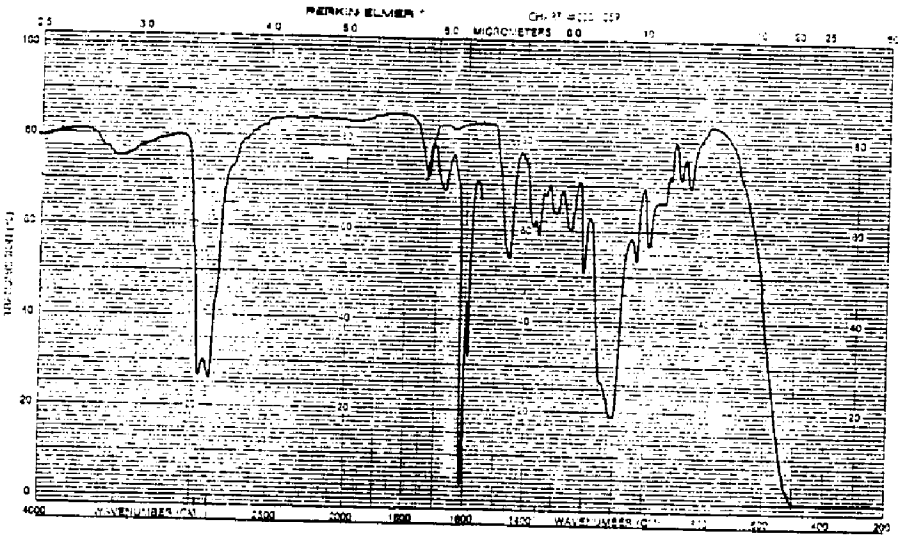
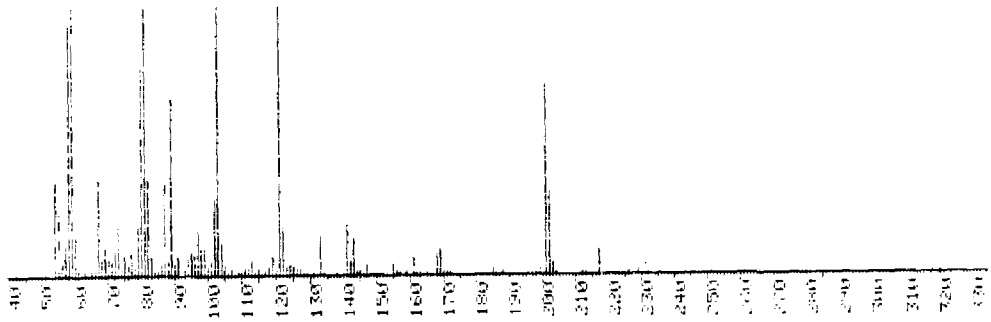
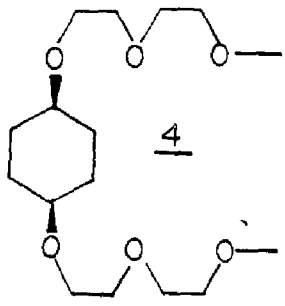


IR (Neat)



Mass Spec.



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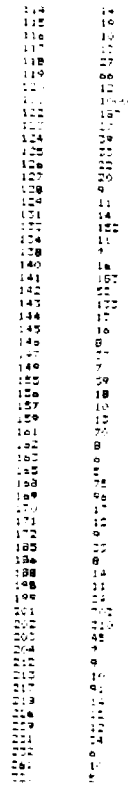
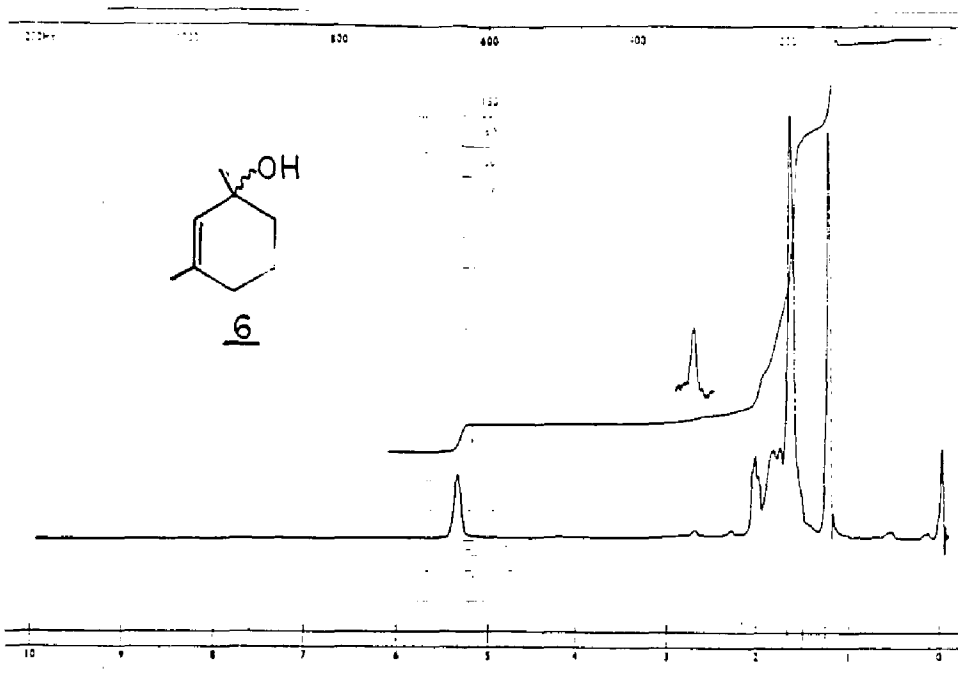
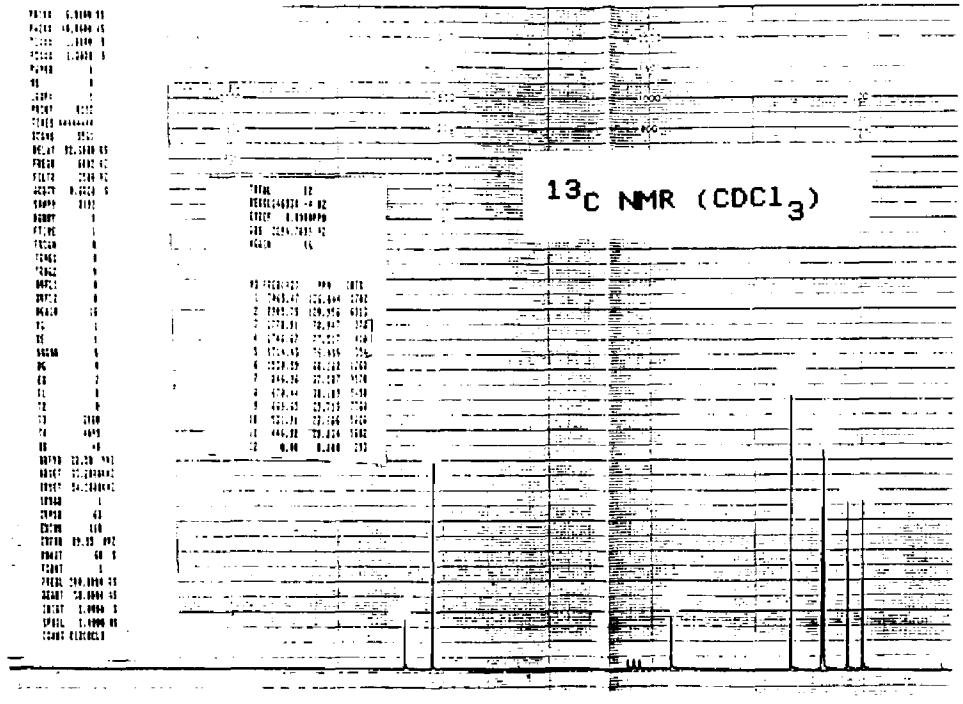


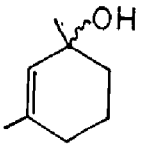


6

^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)



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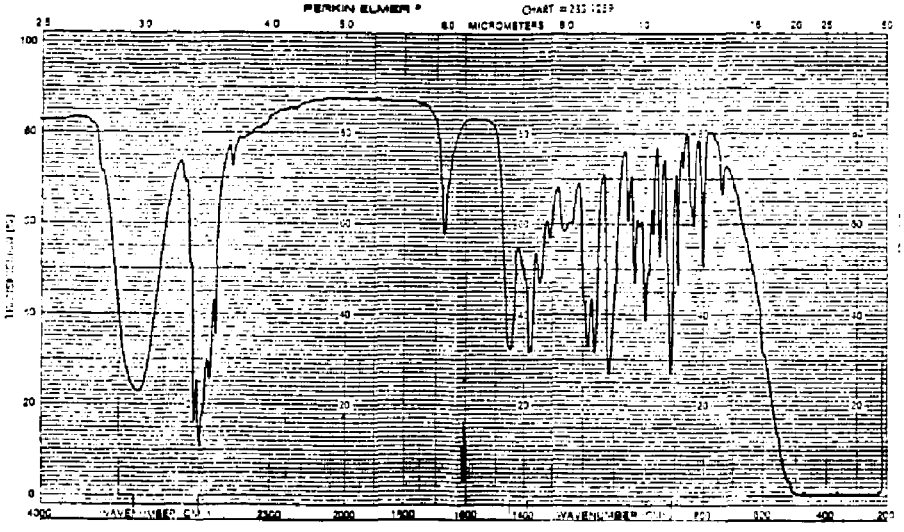

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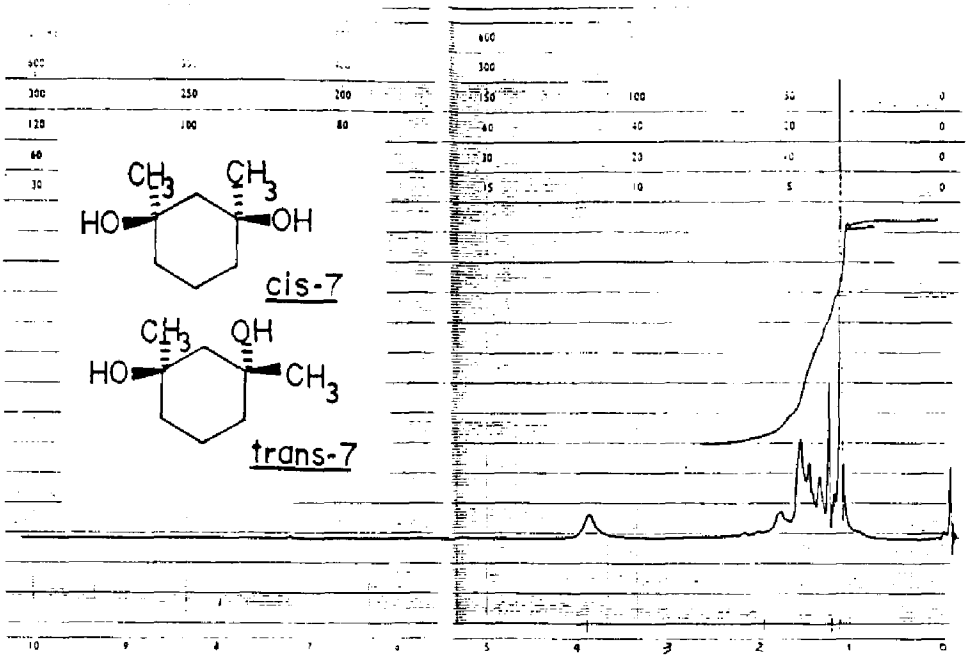
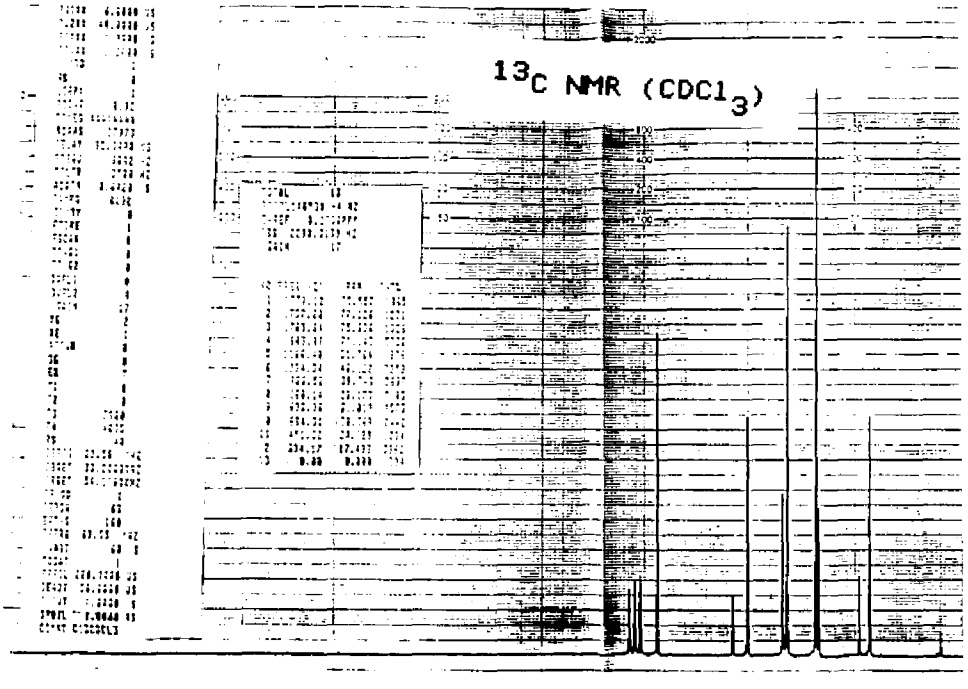
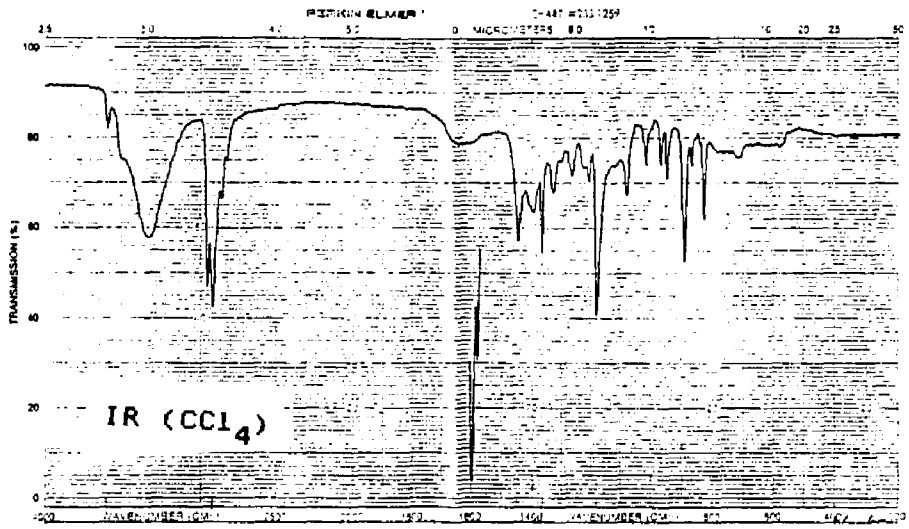
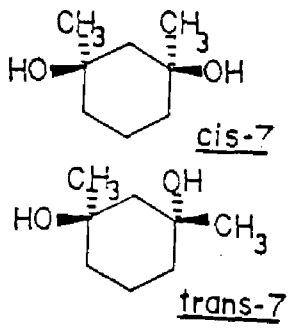


^{1}H NMR ($CDCl_3$)

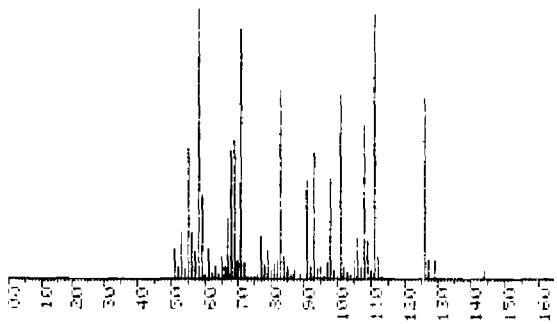




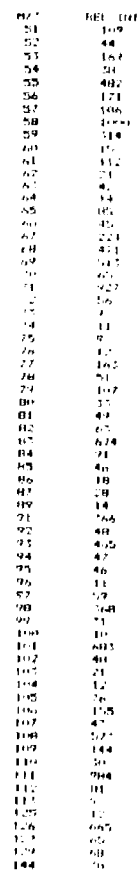


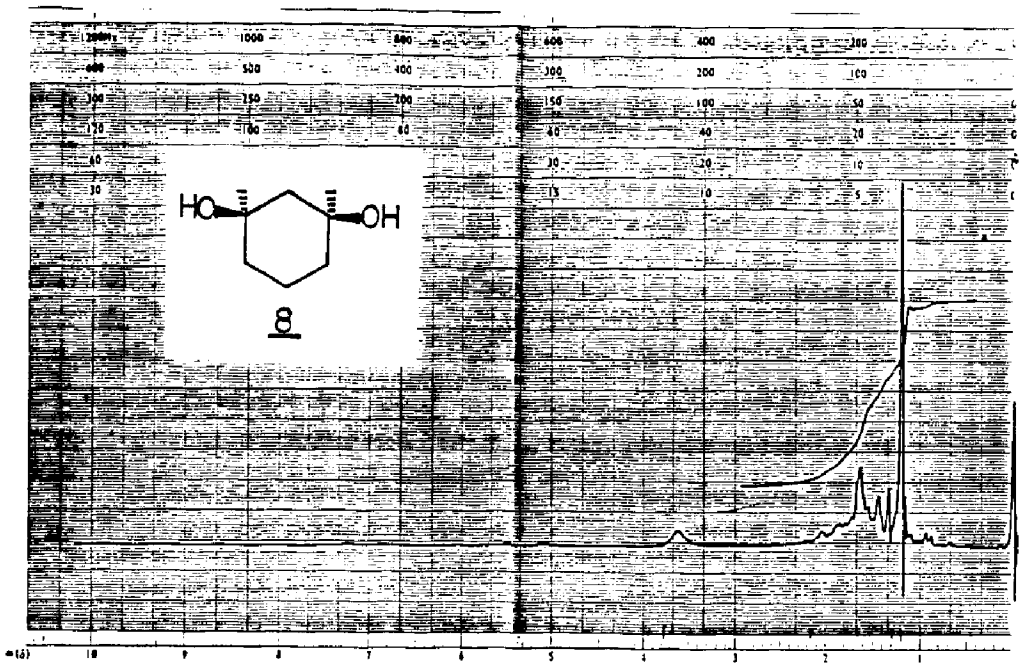
cis-7

trans-7



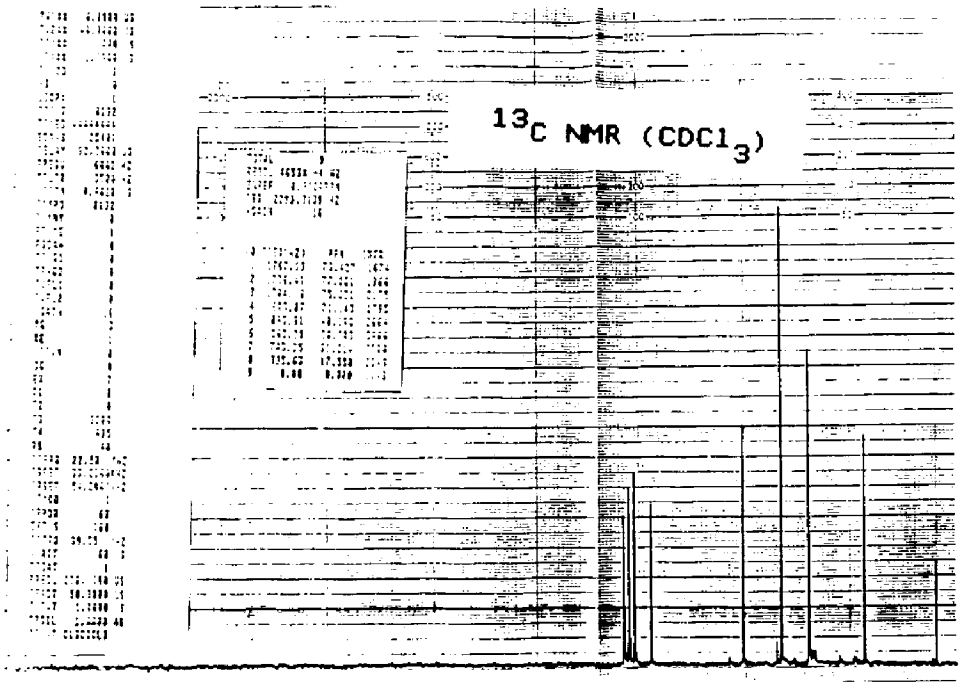
Mass Spec.



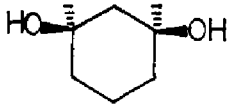


8

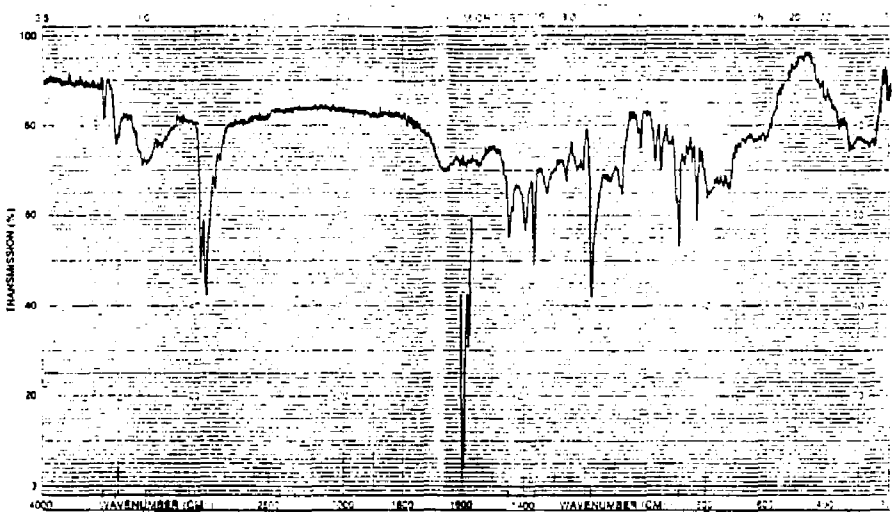
^{1}H NMR ($CDCl_3$)



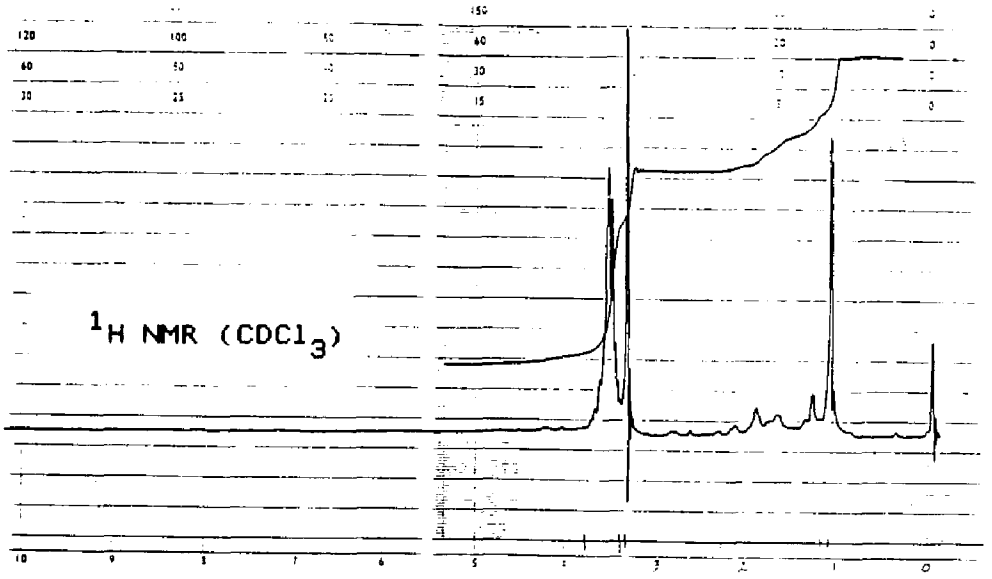
^{13}C NMR ($CDCl_3$)

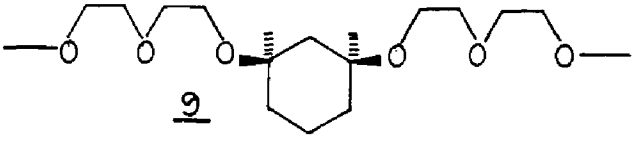


8

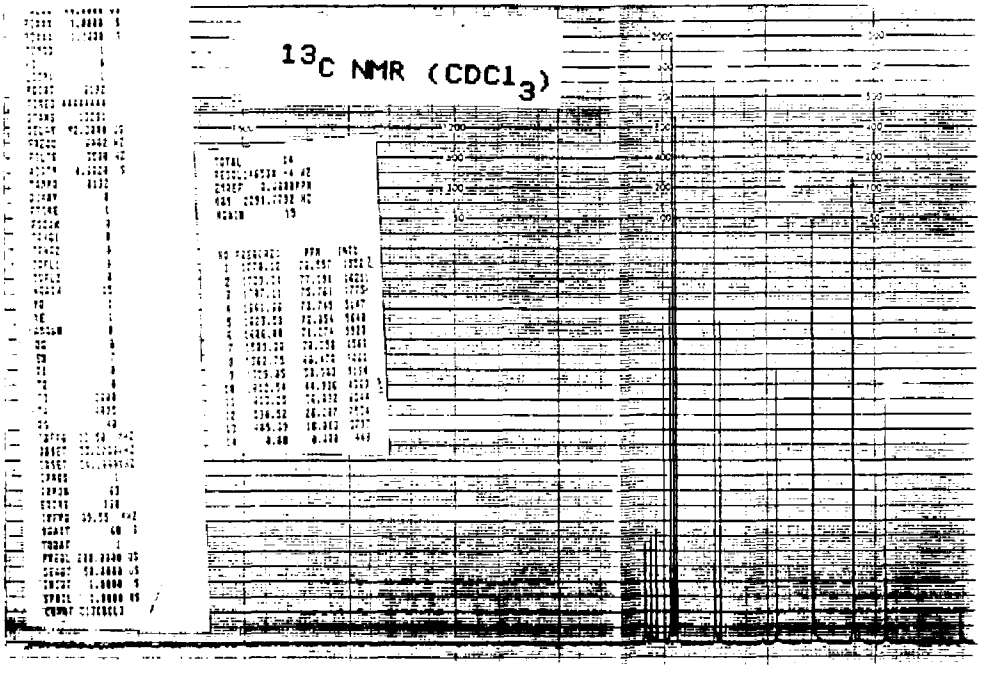


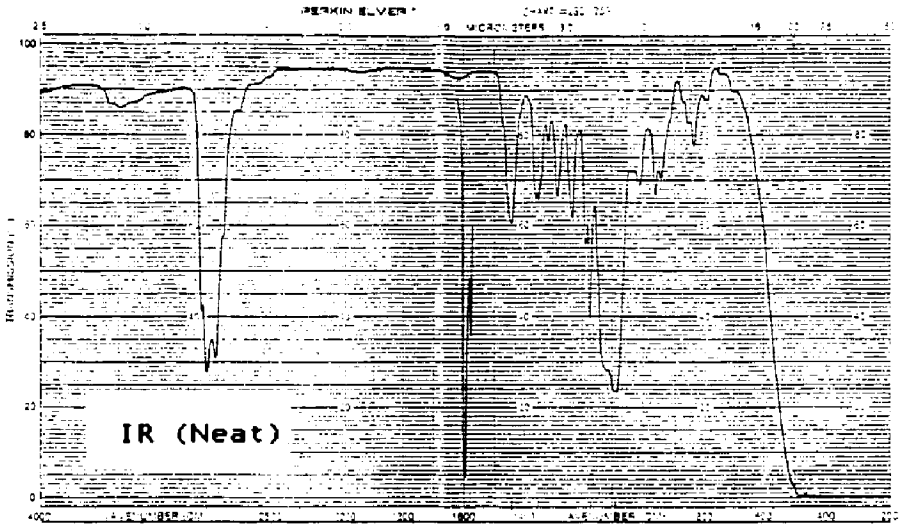
IR (CCl_4)

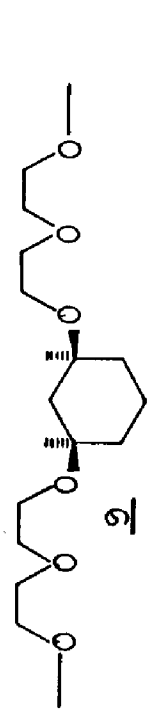




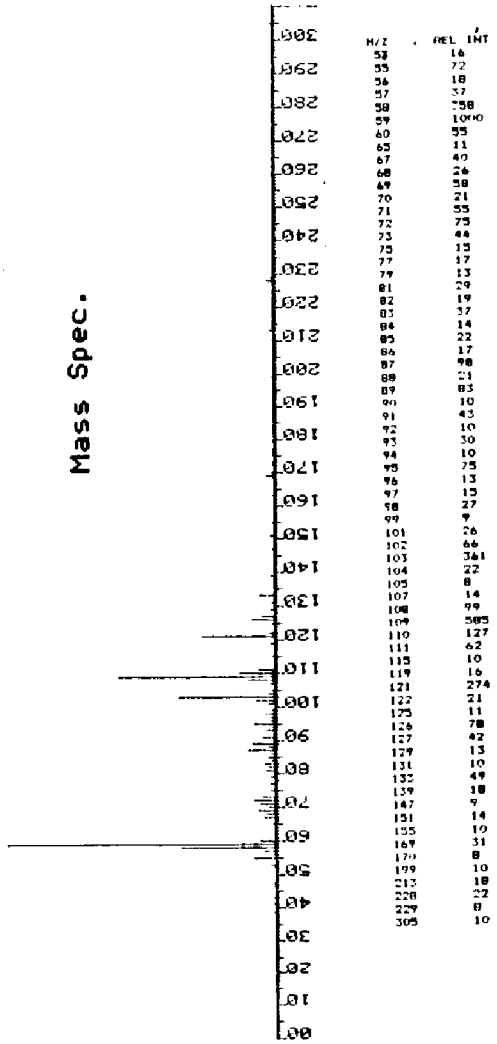
9







Mass Spec.



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69	58
70	21
71	55
72	75
73	44
75	15
77	17
79	13
81	29
82	19
83	57
84	14
85	22
86	17
87	98
88	21
89	83
90	10
91	43
92	10
93	30
94	10
95	75
96	13
97	15
98	27
99	9
101	26
102	66
103	341
104	22
105	8
107	14
108	99
109	585
110	127
111	42
115	10
119	16
121	274
122	21
125	11
126	78
127	42
129	13
131	10
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147	9
151	14
155	10
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199	10
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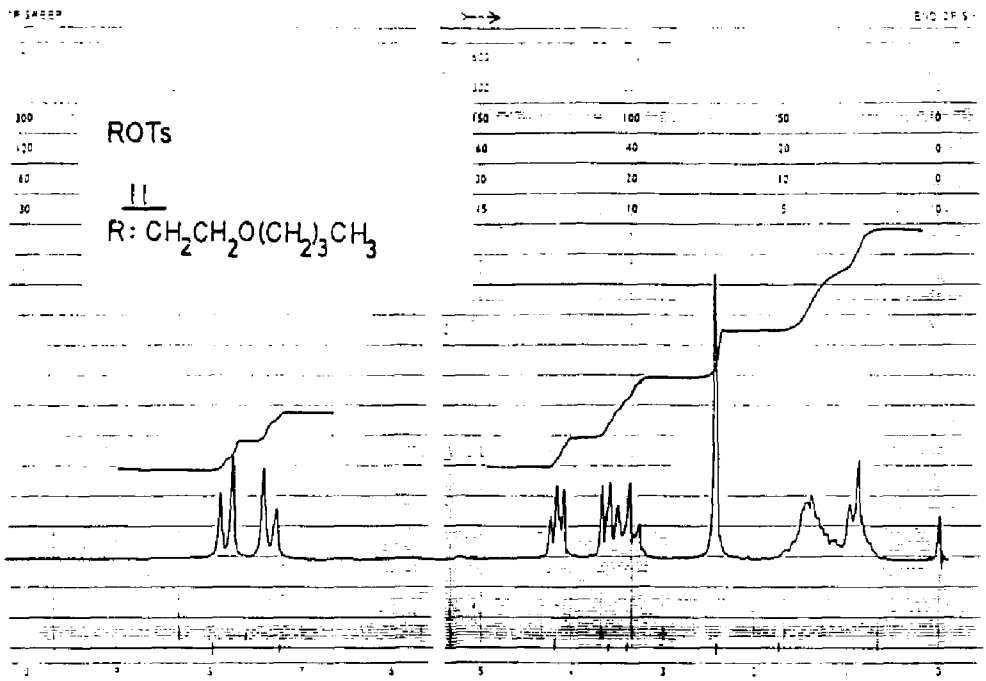
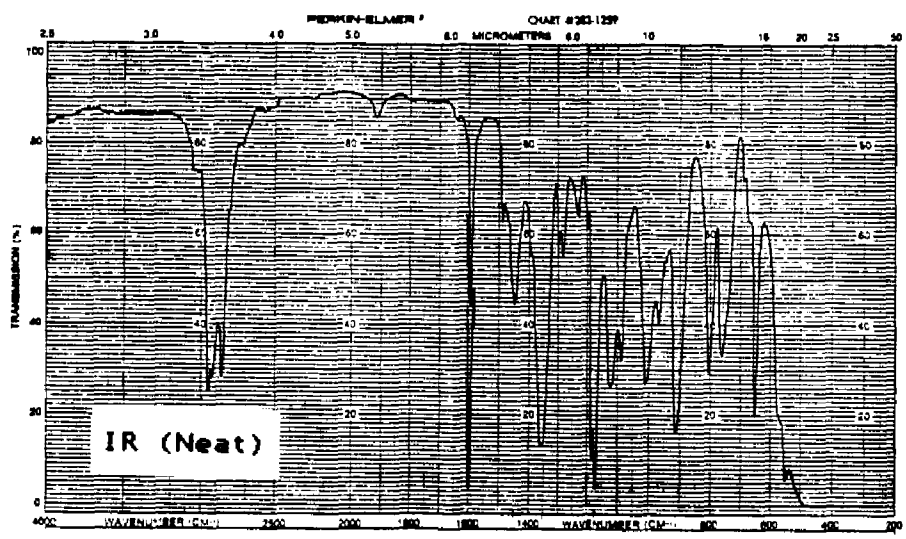
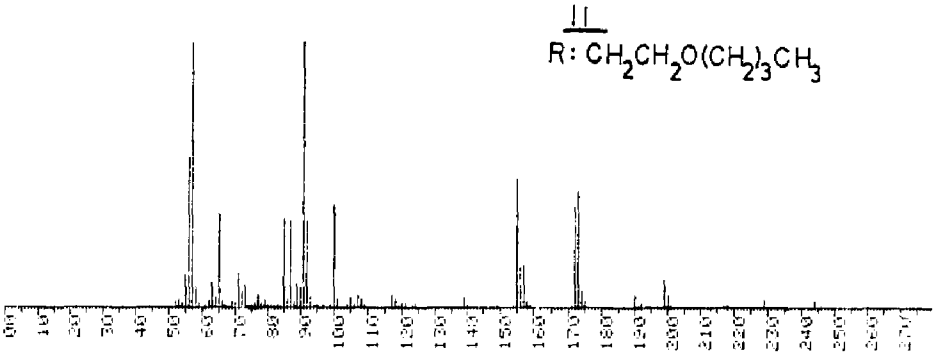
228	22
229	8
305	10



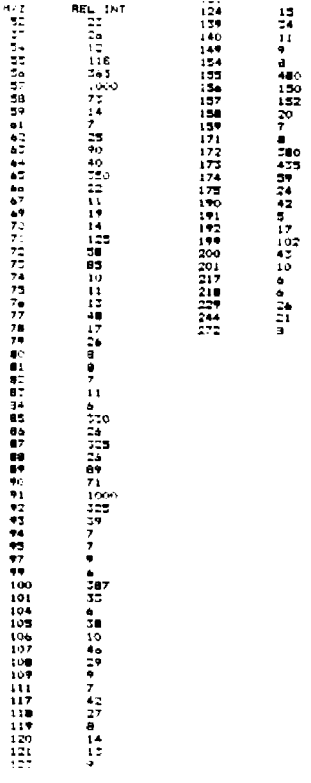
^1H NMR ($CDCl_3$)

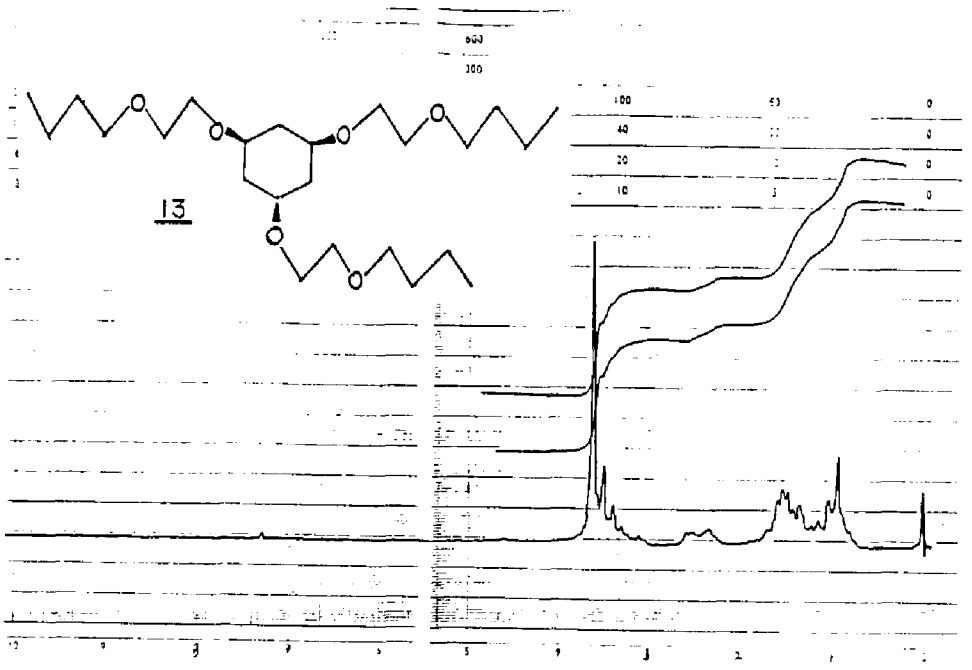


ROTs

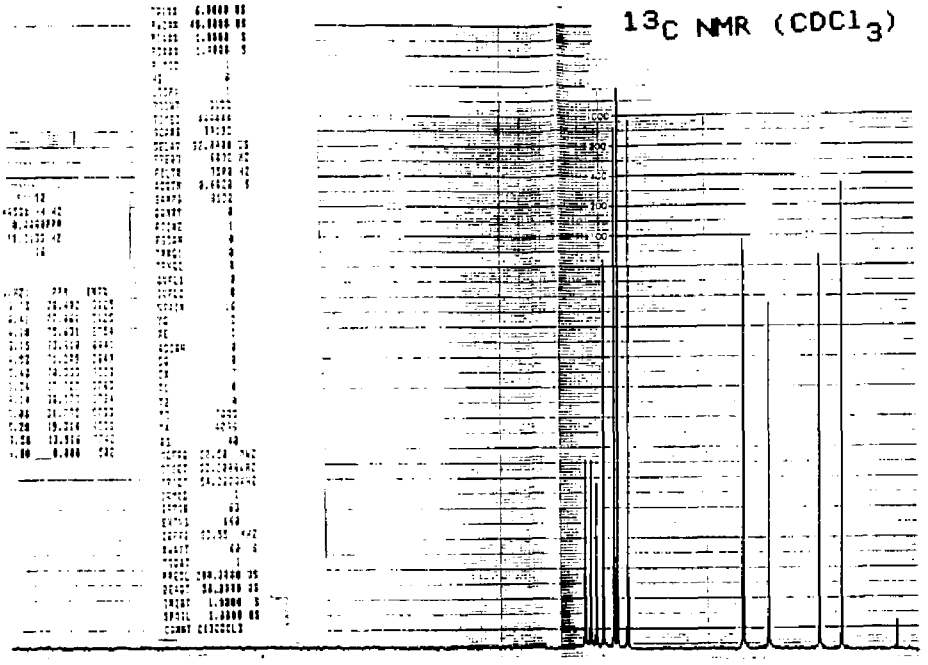


Mass Spec.



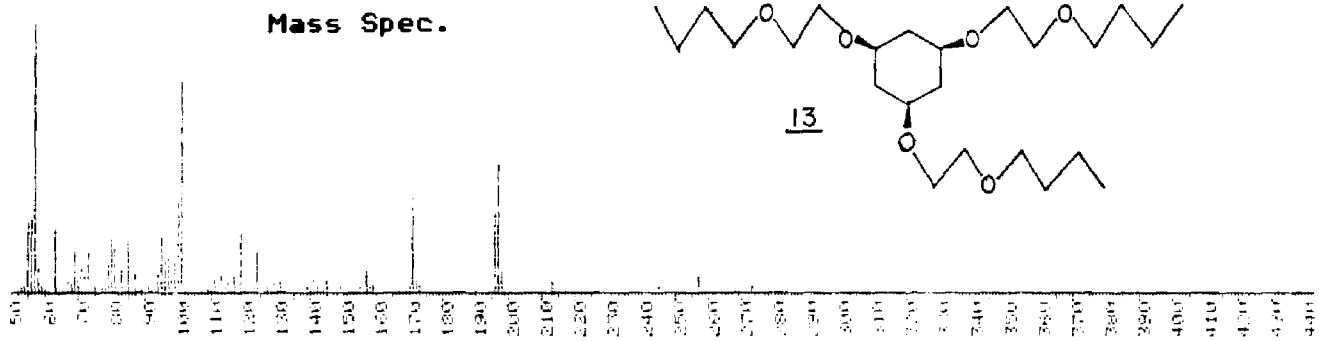


^{1}H NMR ($CDCl_3$)



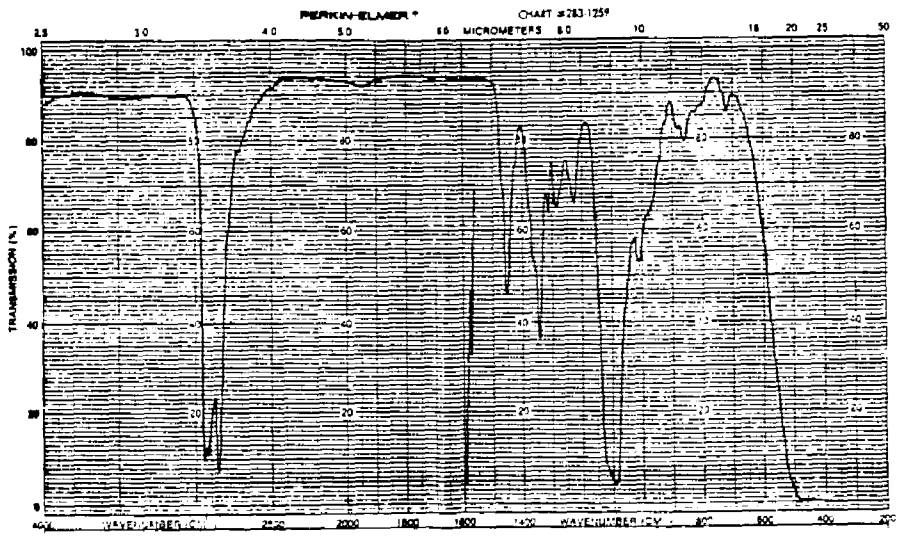
^{13}C NMR ($CDCl_3$)

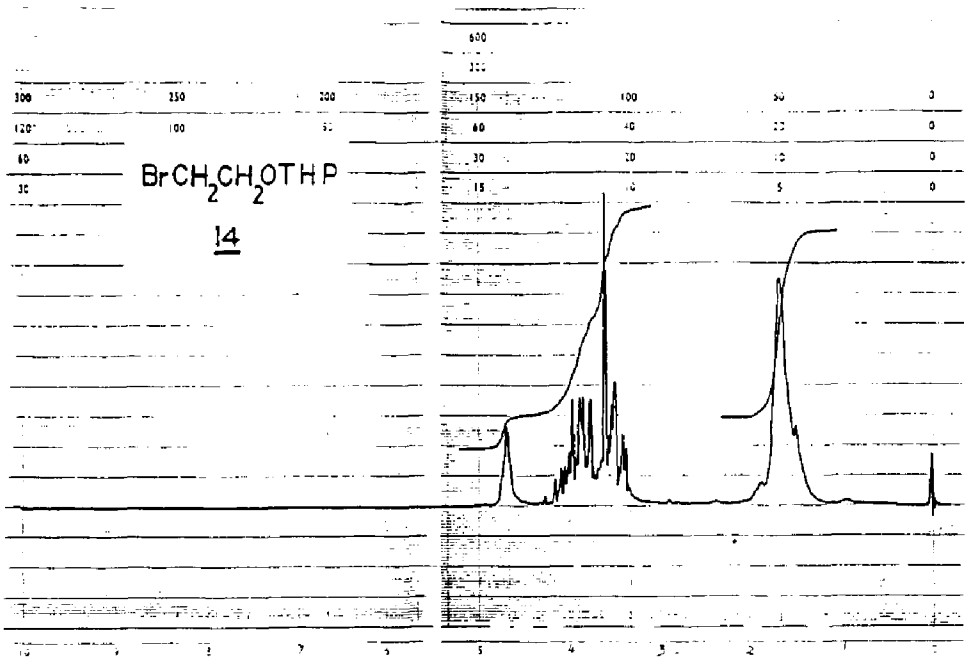
Mass Spec.



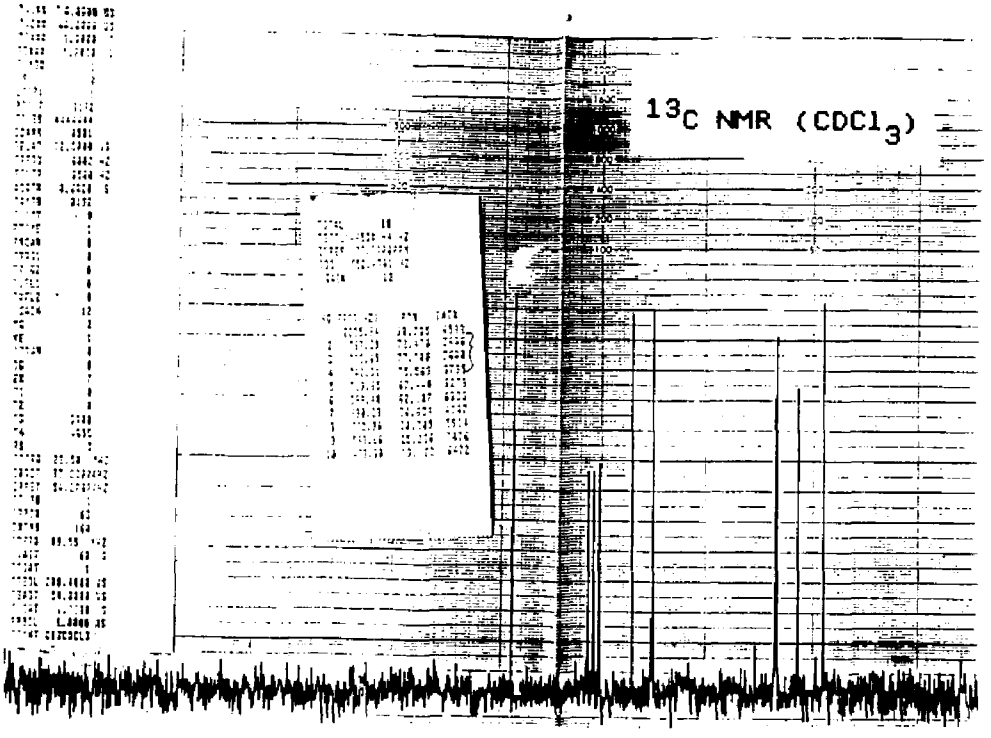
13

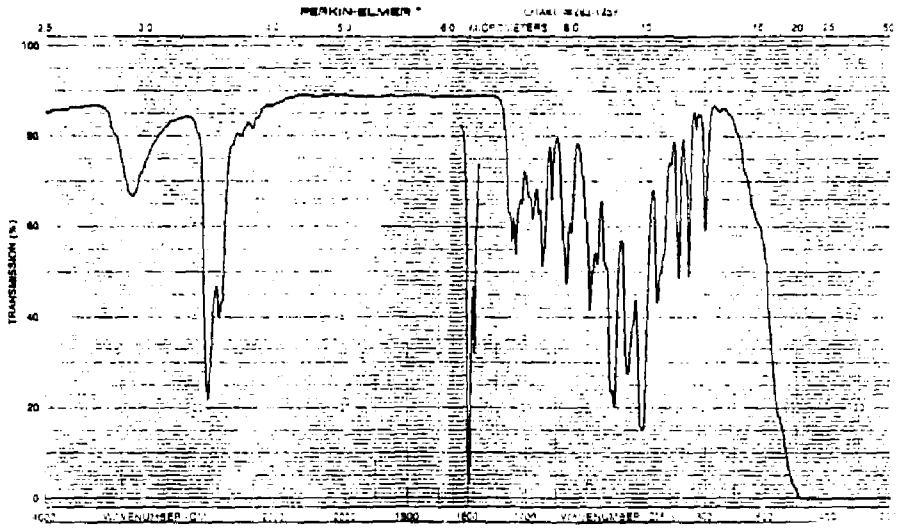
IR(Neat)





^{1}H NMR ($CDCl_3$)

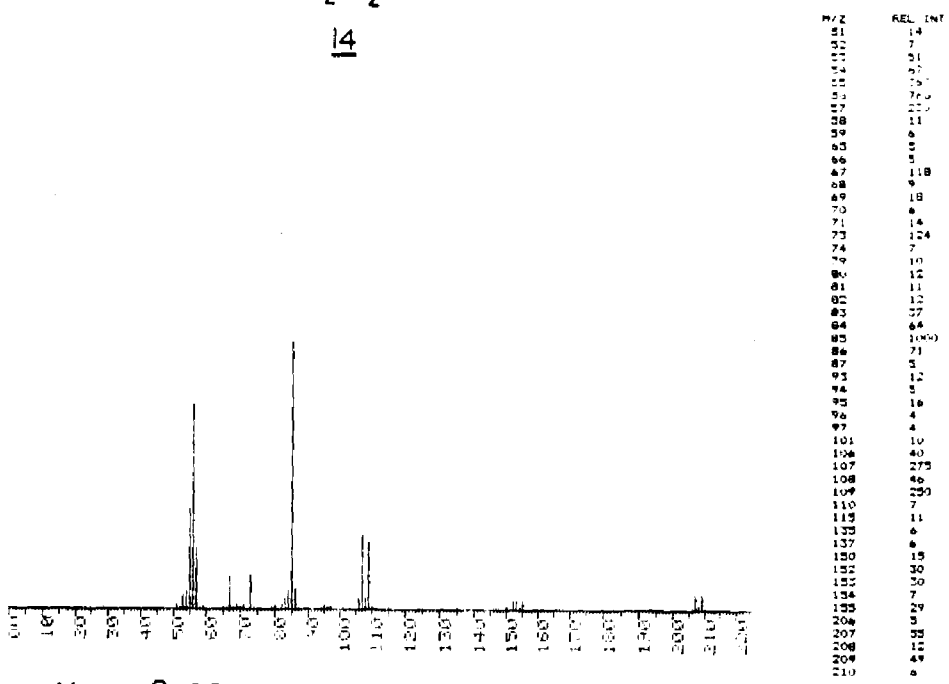




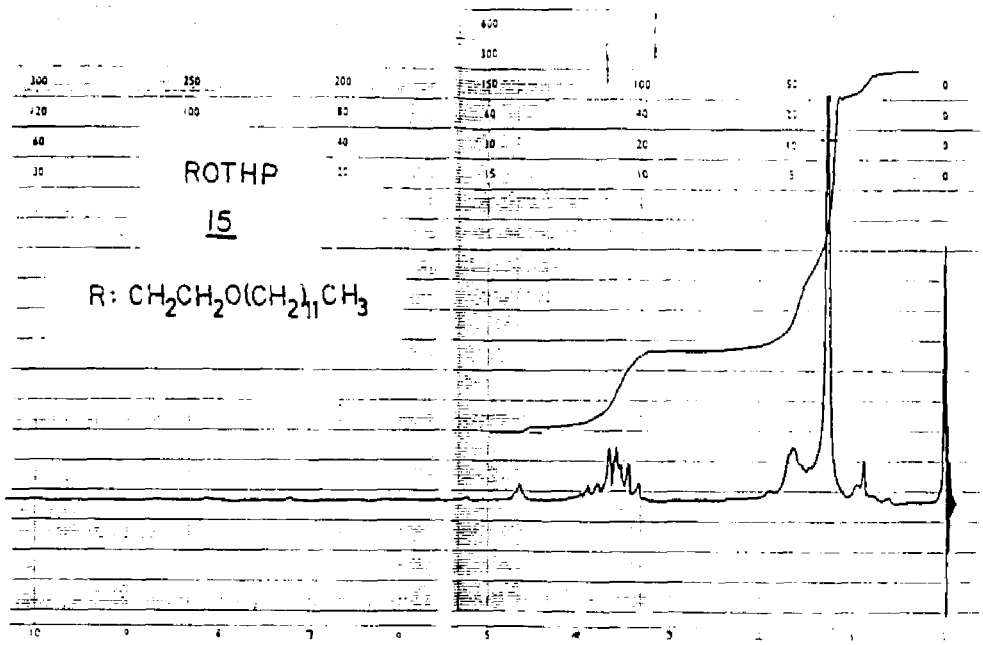
IR (Neat)

$BrCH_2CH_2OTHP$

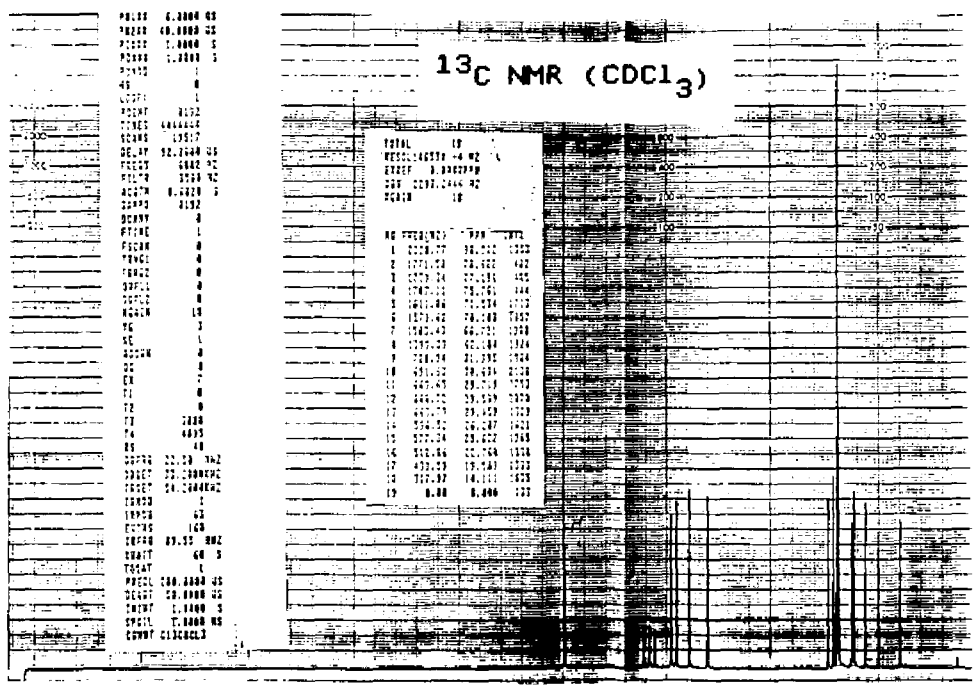
14



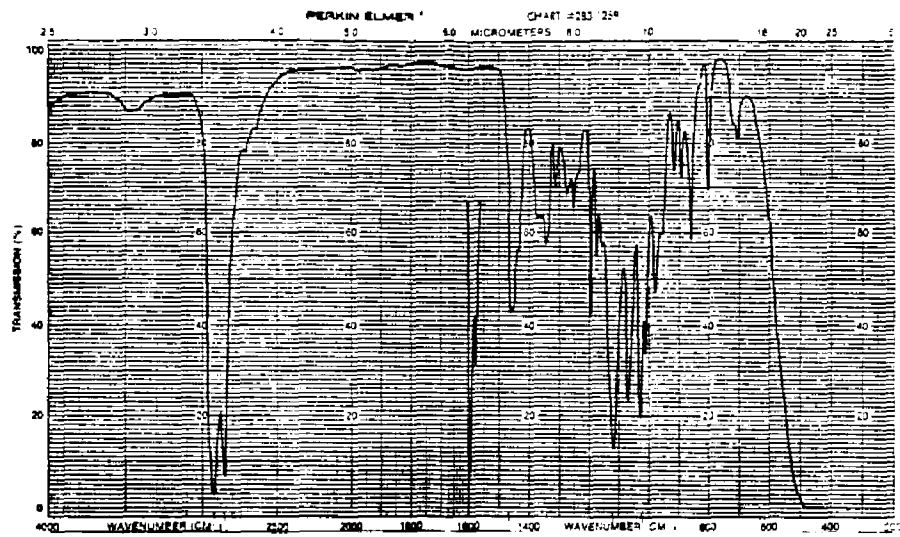
Mass Spec.



^{1}H NMR ($CDCl_3$)



IR (Neat)

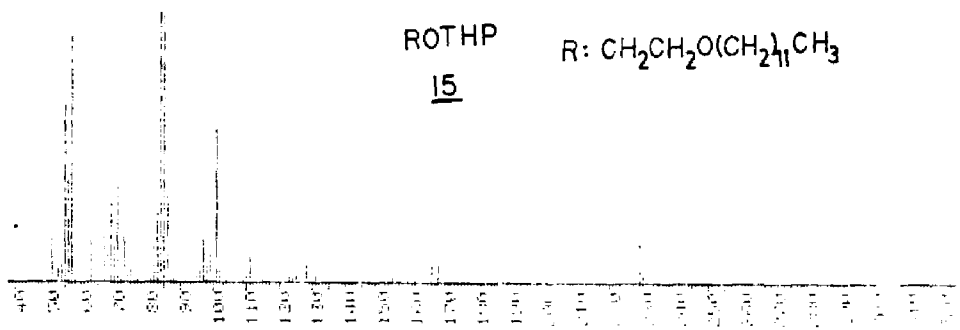


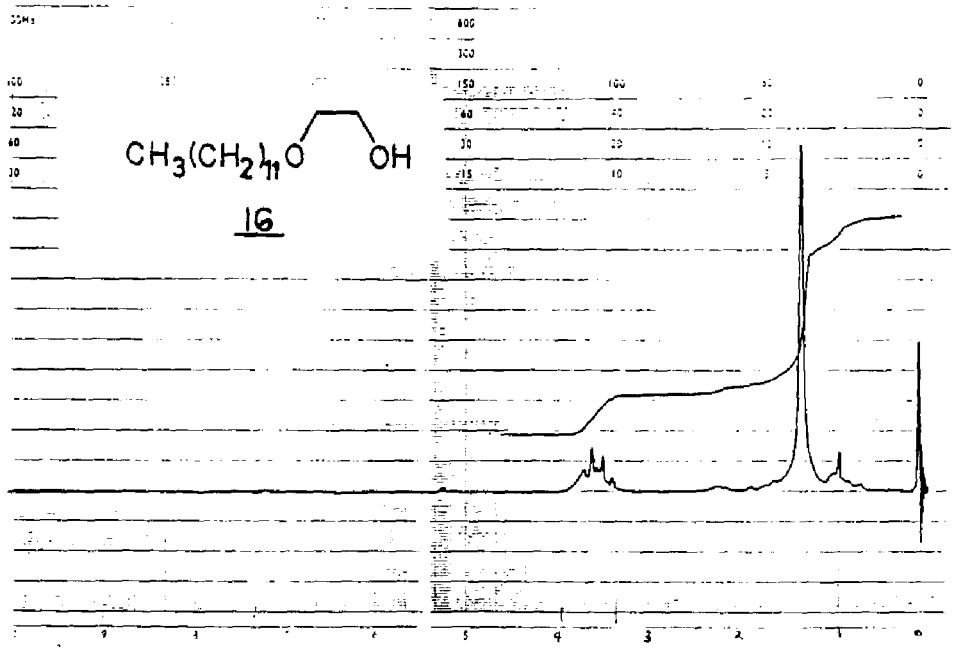
ROTHP

15

R: $CH_2CH_2O(CH_2)_{11}CH_3$

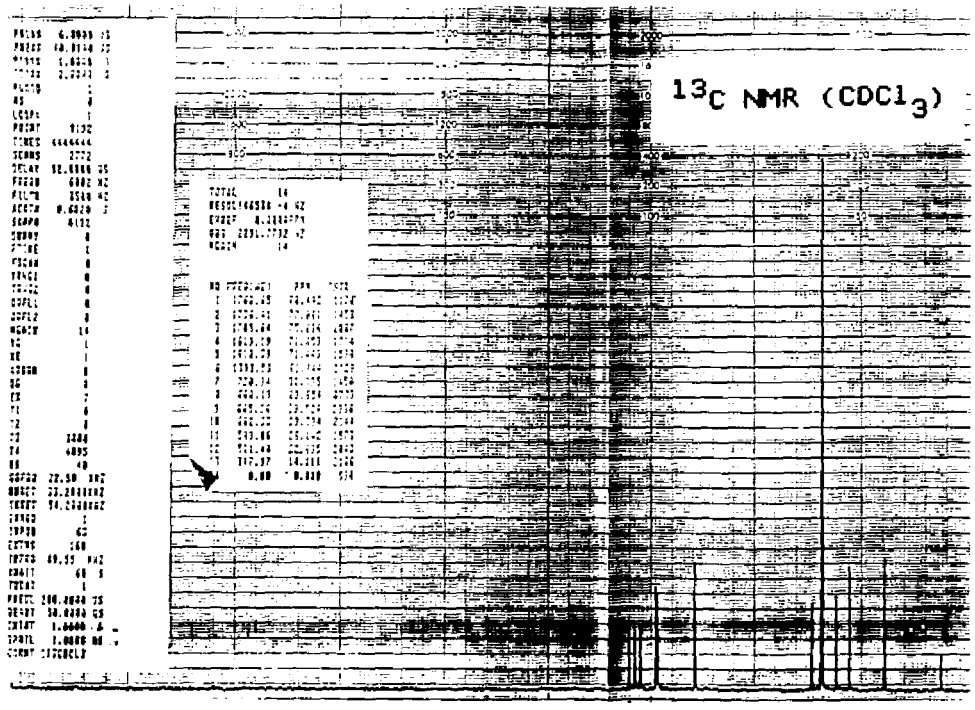
Mass Spec.



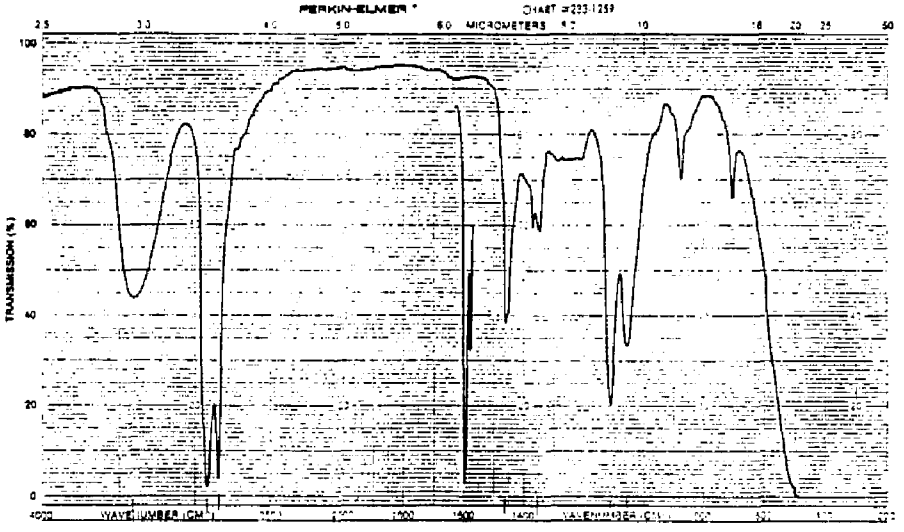


16

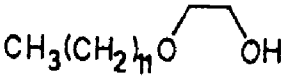
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)



IR (Neat)



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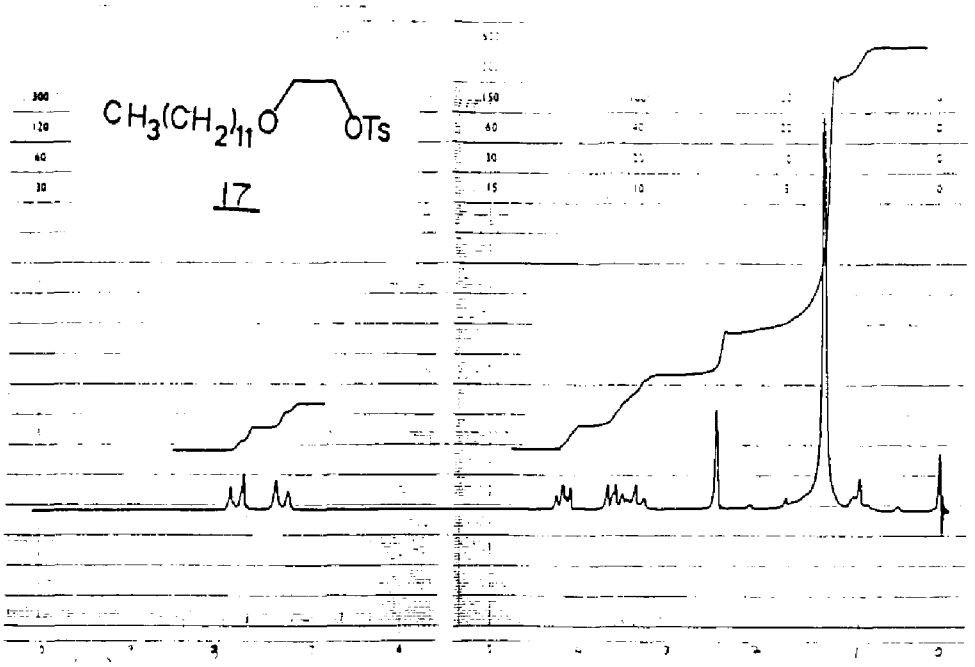
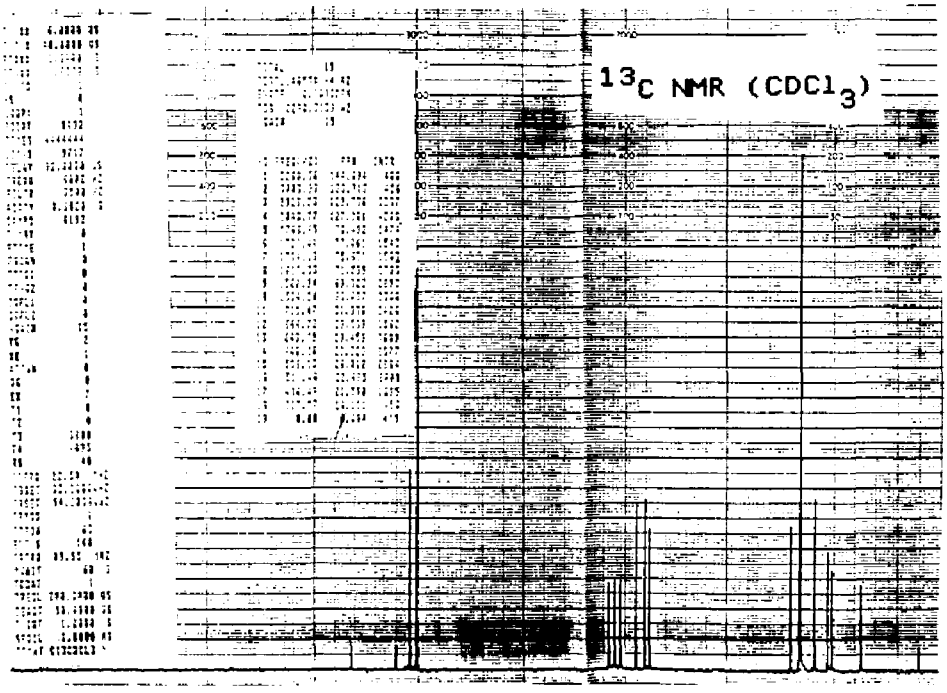


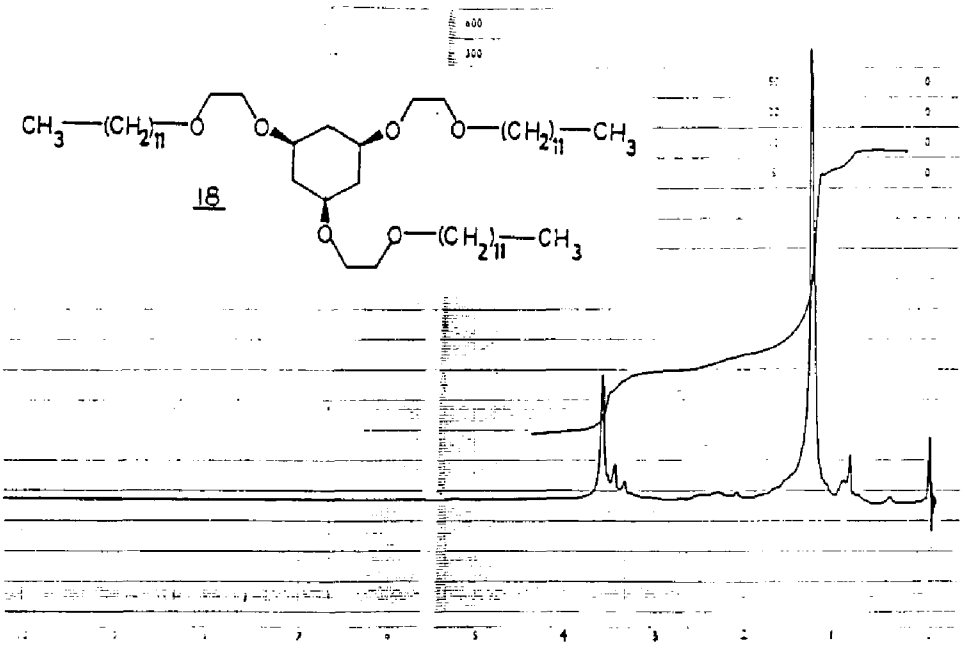
^{1}H NMR ($CDCl_3$)



IR (Neat)

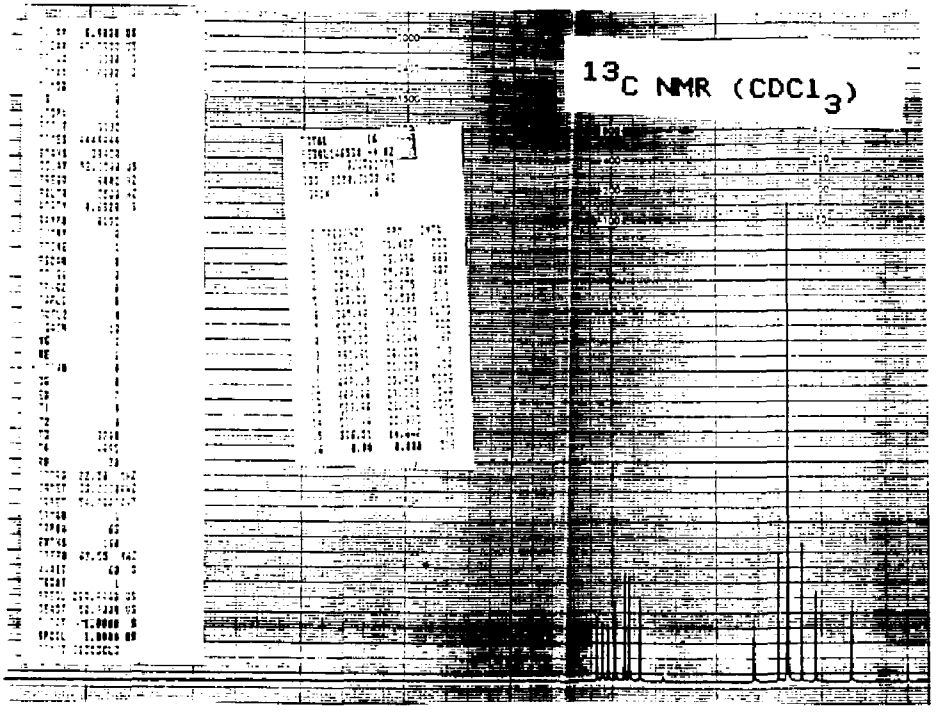
17

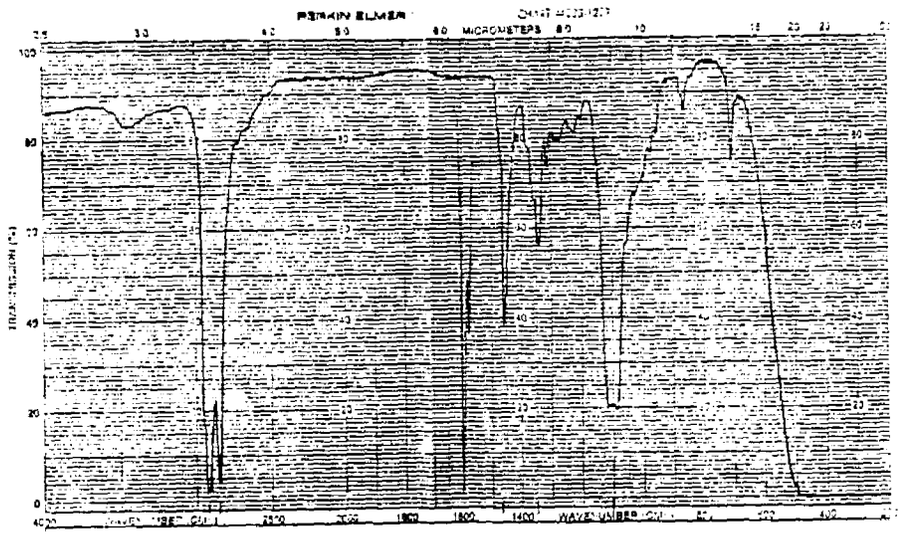
Mass Spec.



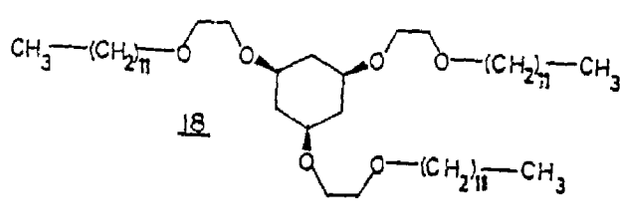
18

^{1}H NMR ($CDCl_3$)

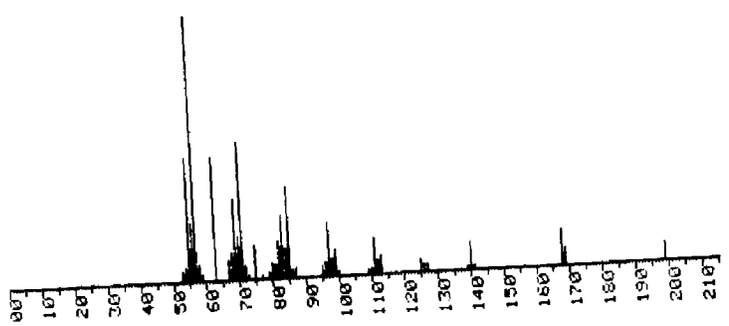




IR (Neat)



18



Mass Spec.

M/Z	REL INT
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55	466
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57	1000
58	56
59	24
63	469
67	73
68	103
69	303
70	164
71	518
72	50
73	17
75	123
77	16
79	20
80	59
81	52
82	139
83	239
84	110
85	342
86	32
87	38
95	34
96	52
97	203
98	68
99	94
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109	18
110	22
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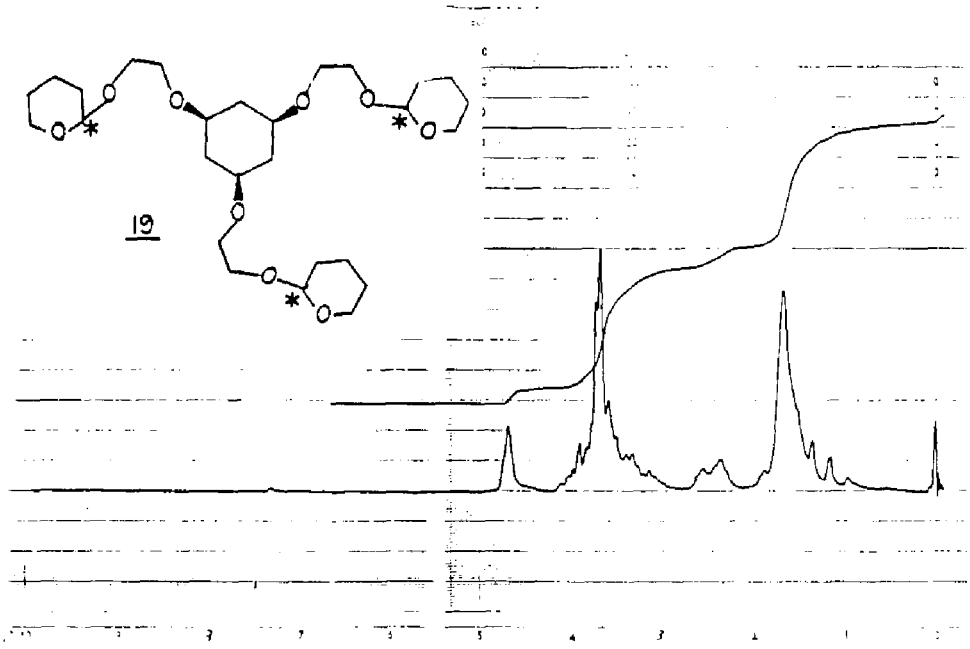
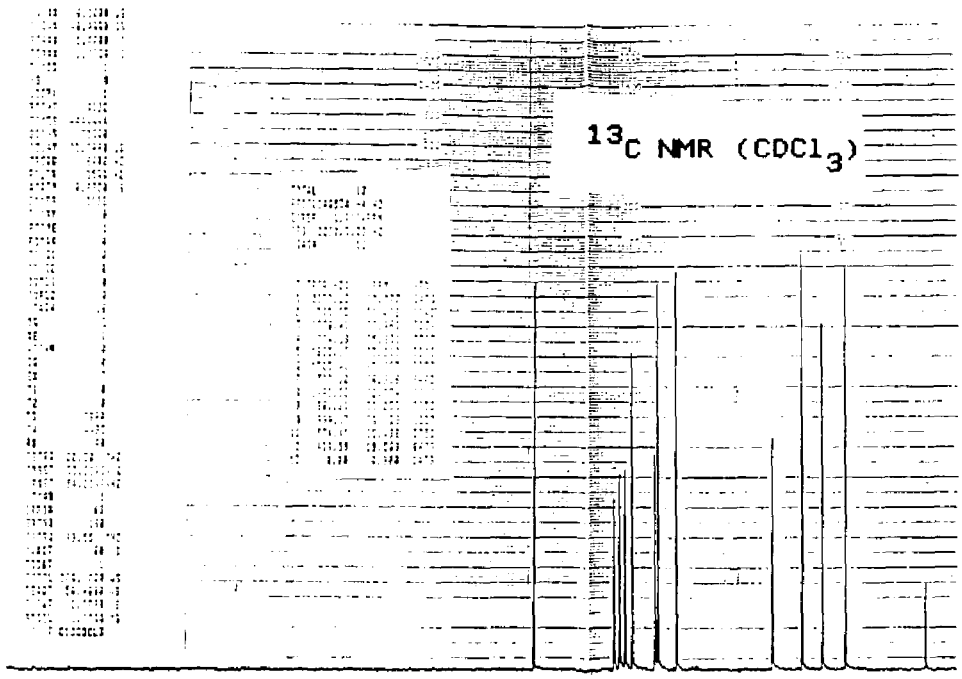
199	68



19

^{1}H NMR ($CDCl_3$)

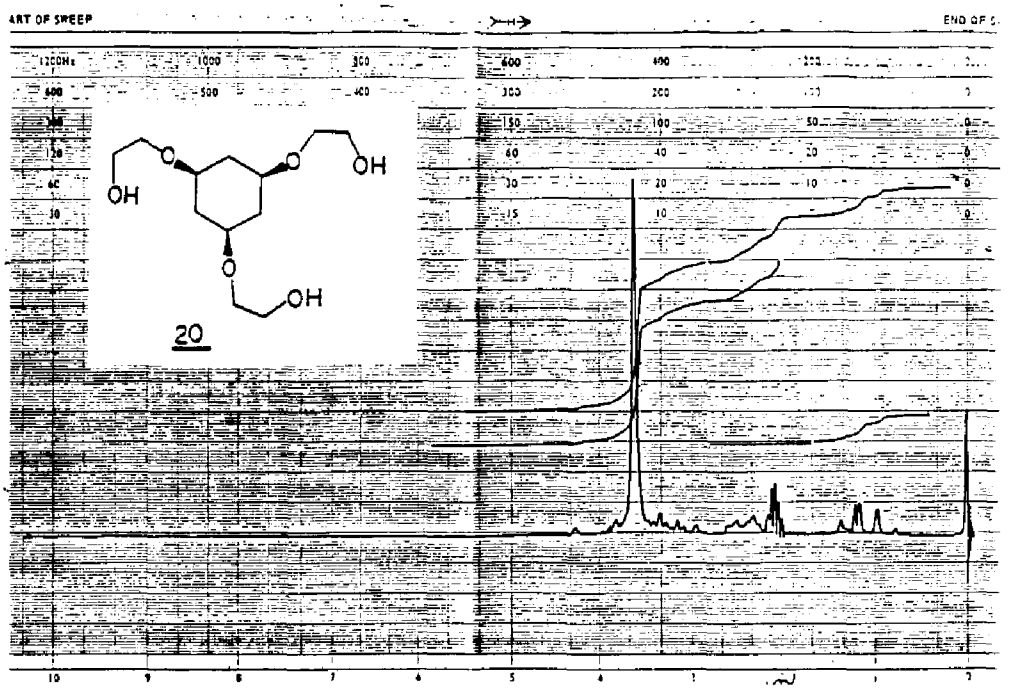


^{13}C NMR ($CDCl_3$)

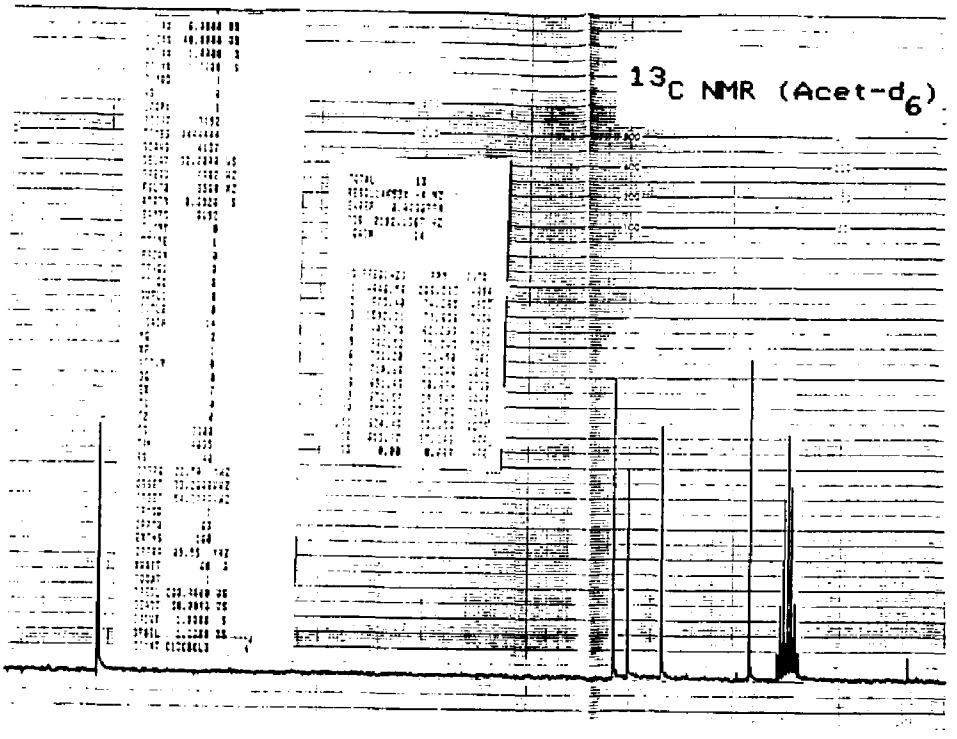
IR (Neat)

19

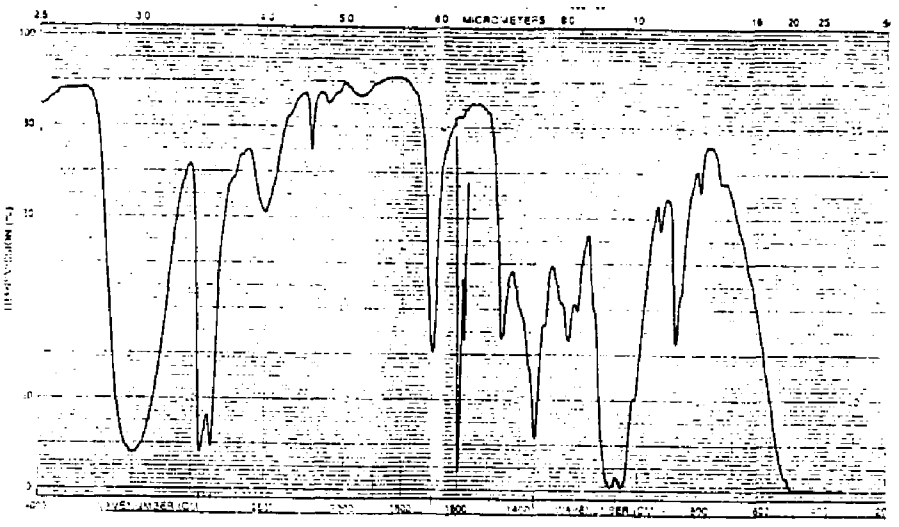
Mass Spec.



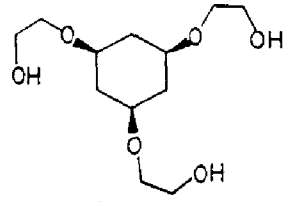
^{1}H NMR (Acet-d_6)



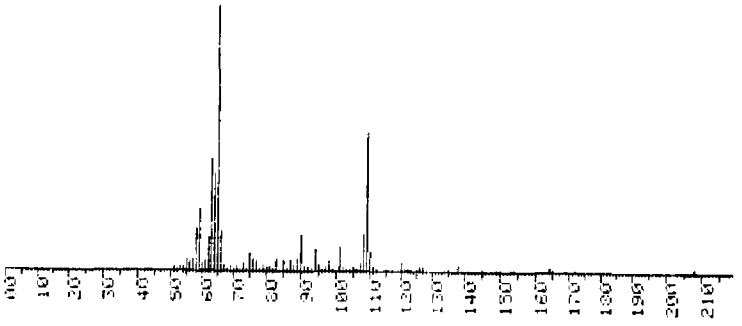
^{13}C NMR (Acet-d_6)



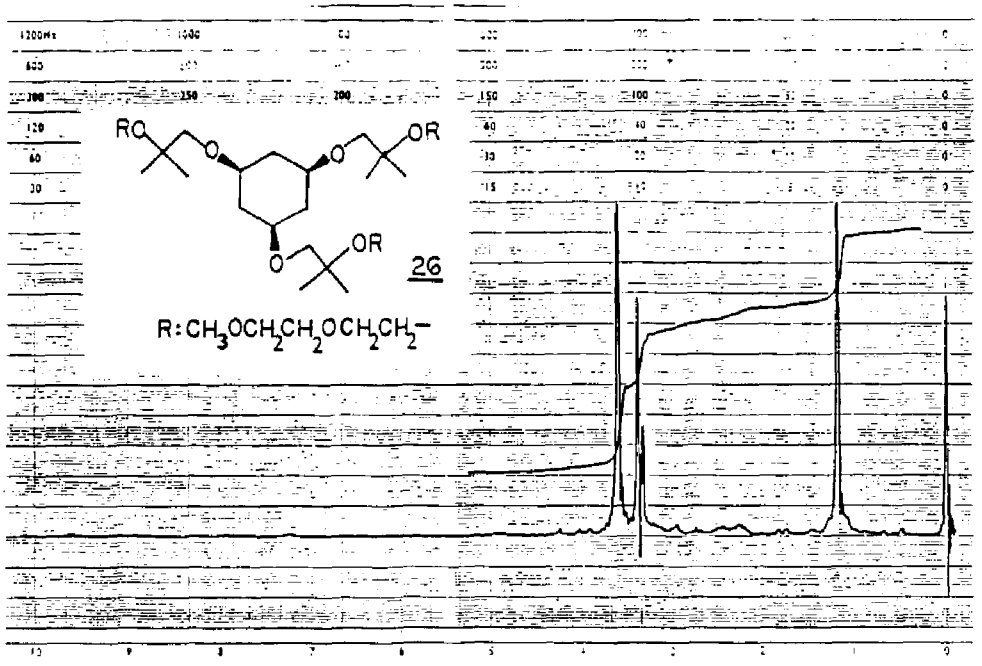
IR(Neat)



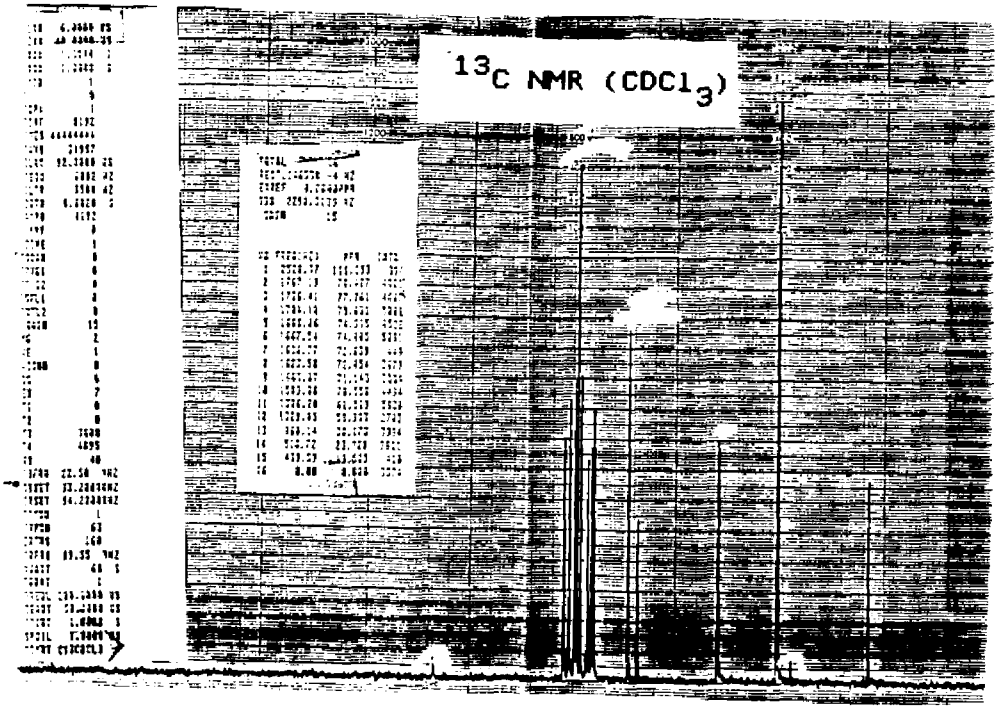
20

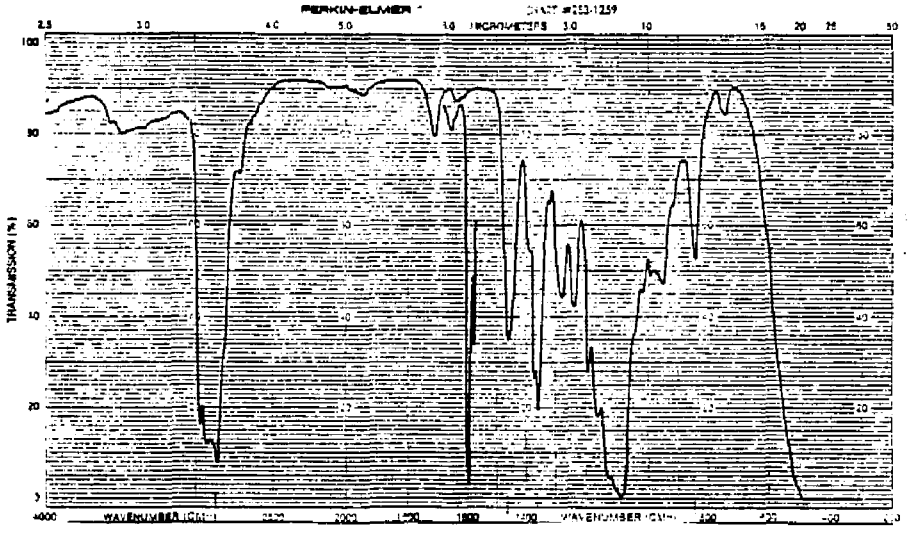


Mass Spec.

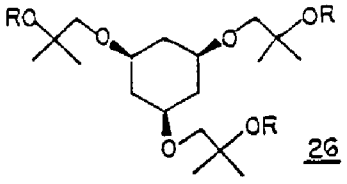


^{1}H NMR ($CDCl_3$)



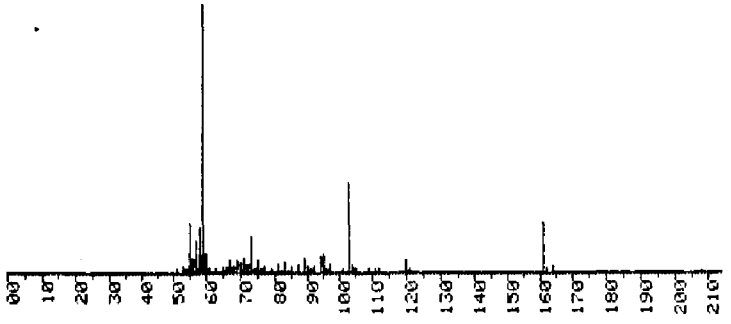


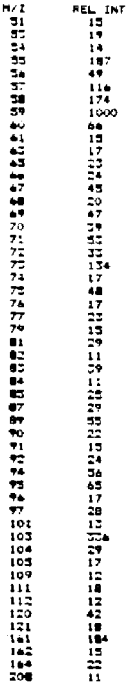
IR (Neat)



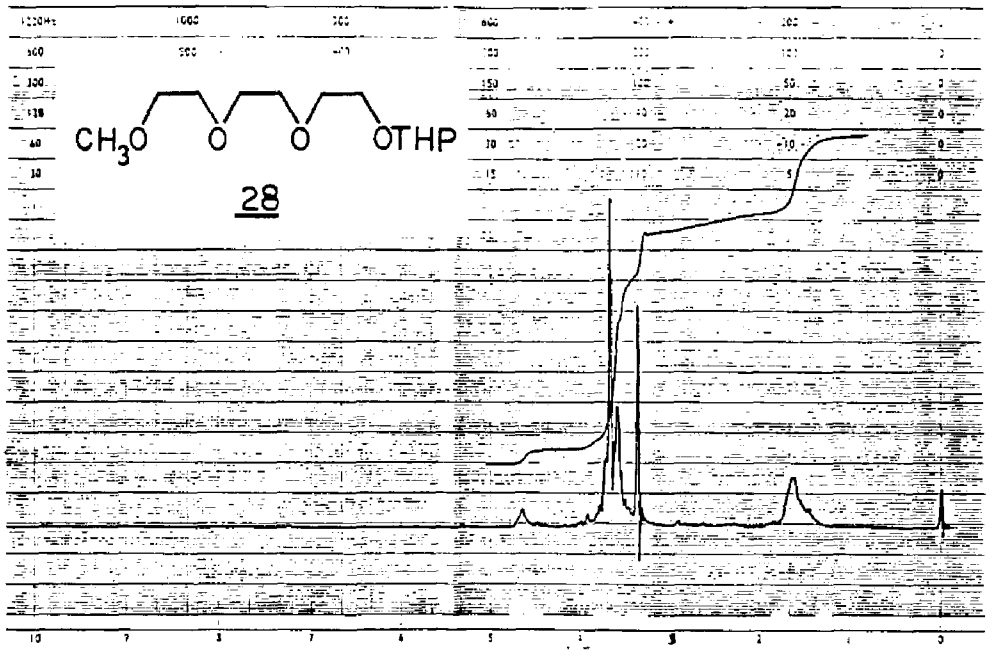
26

R: $CH_3OCH_2CH_2OCH_2CH_2-$



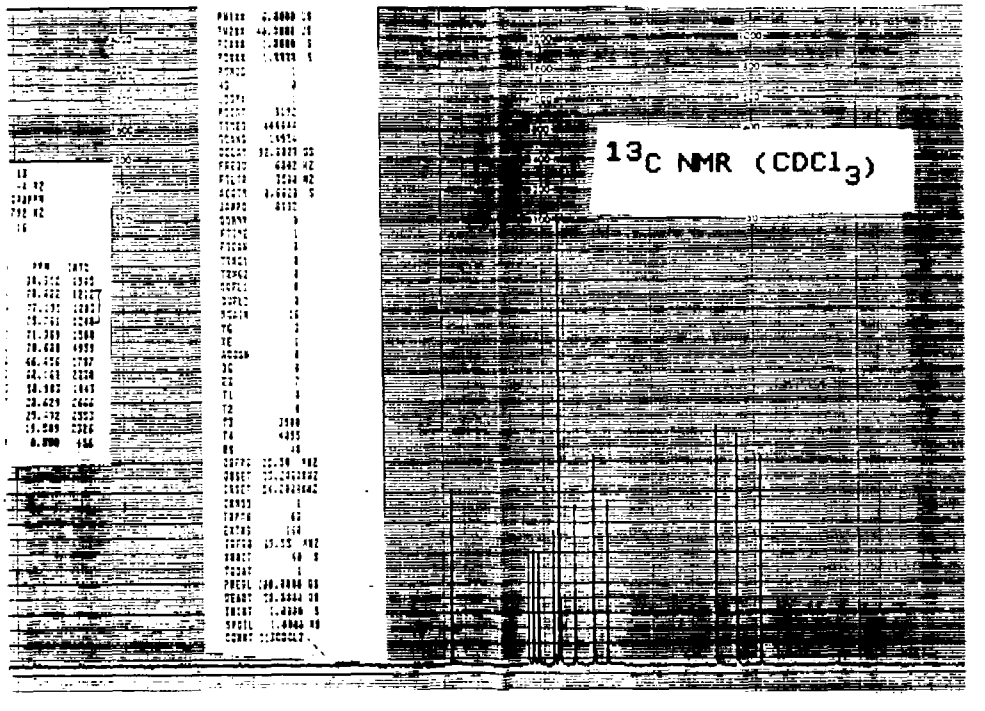


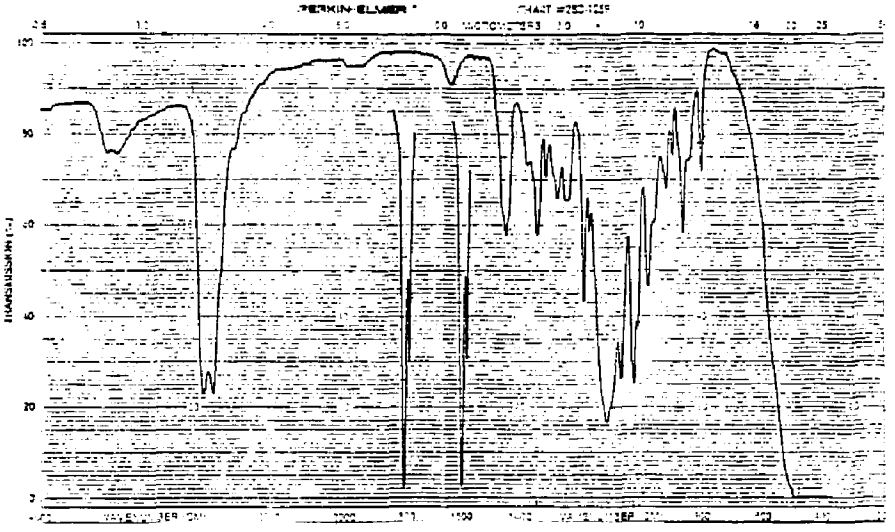
Mass Spec.



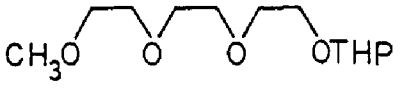
28

^{1}H NMR ($CDCl_3$)

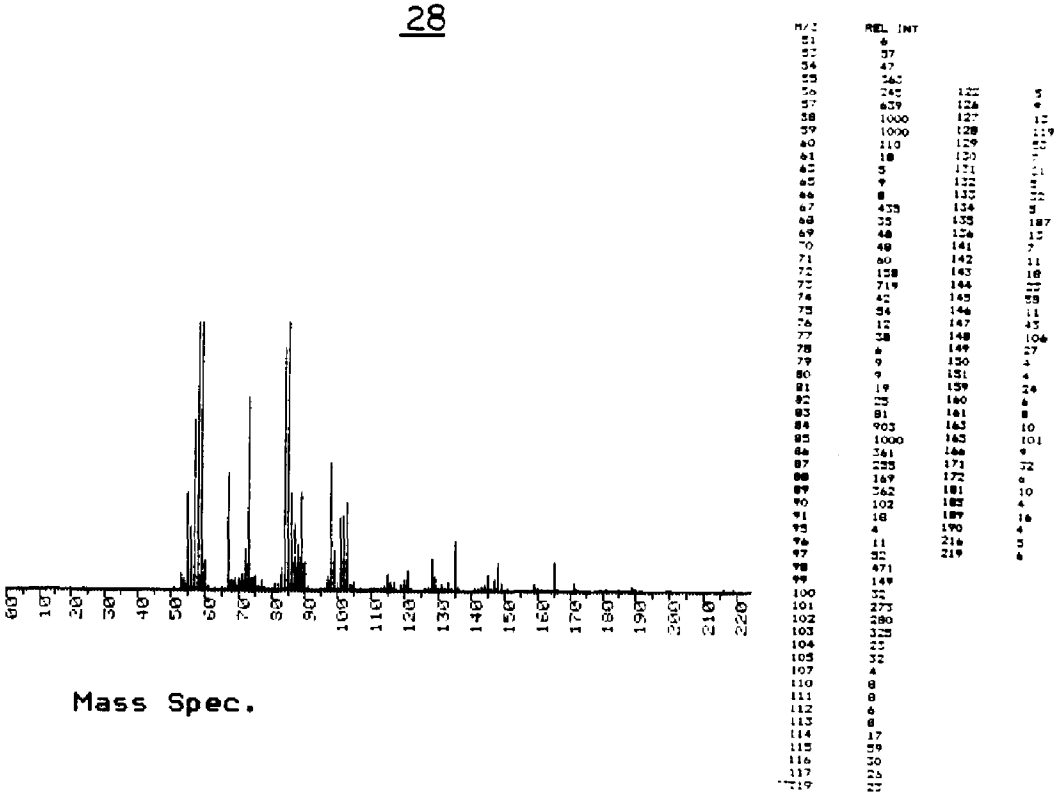




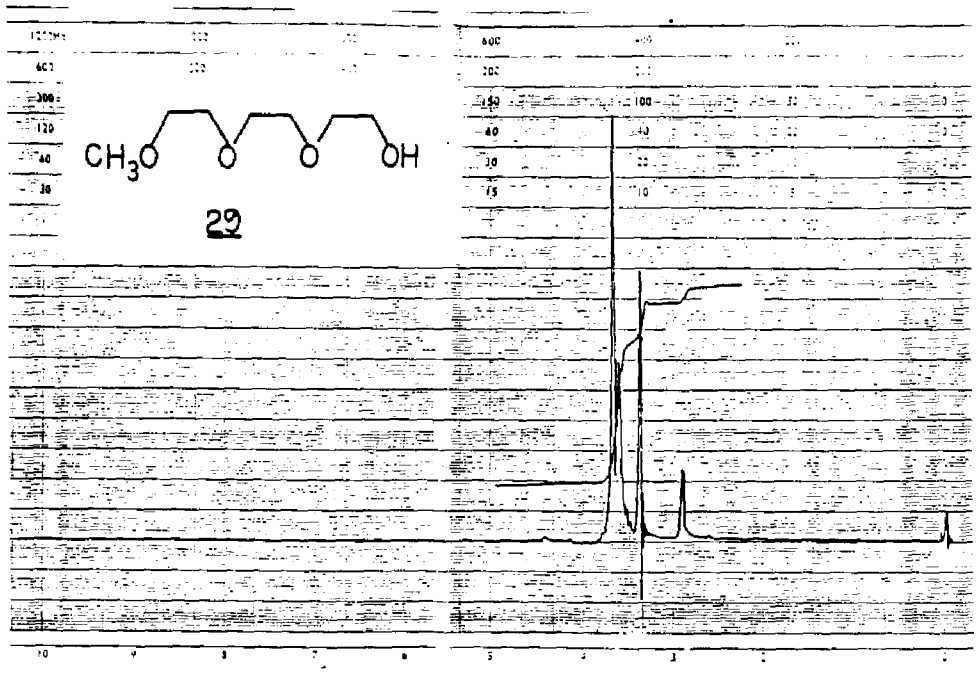
IR (Neat)



28

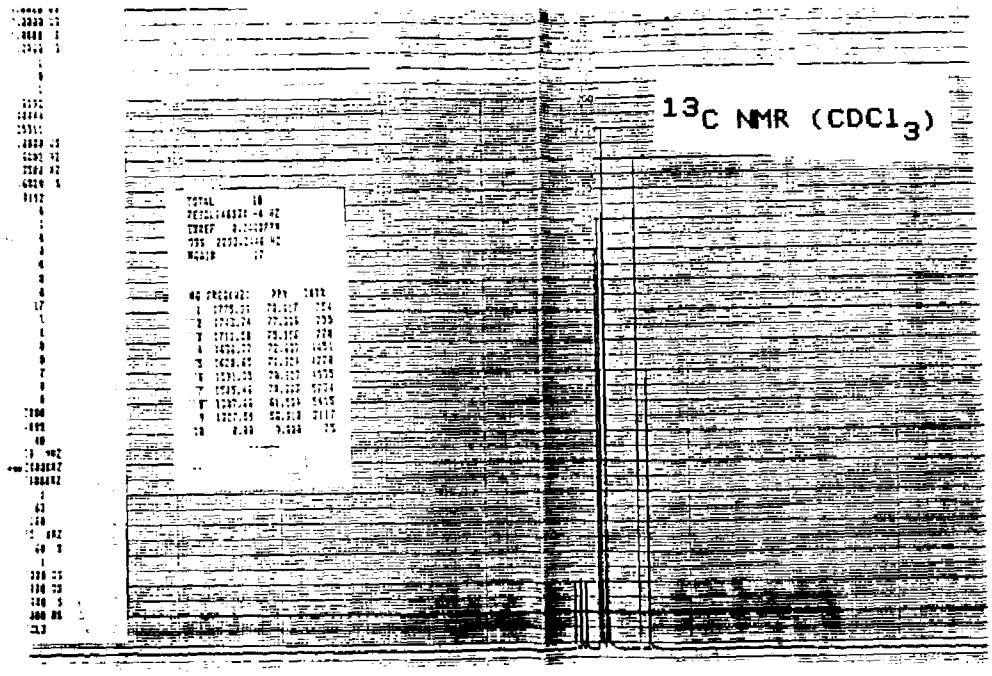


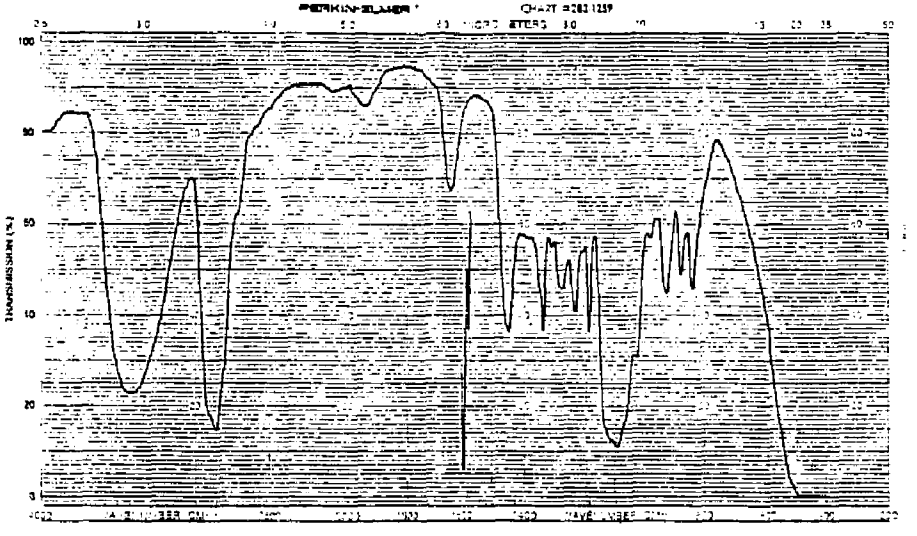
Mass Spec.



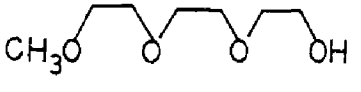
29

^{1}H NMR ($CDCl_3$)



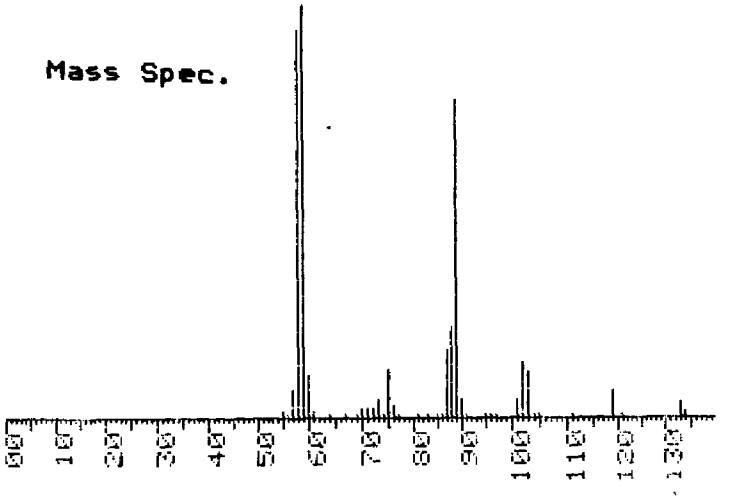


IR (Neat)

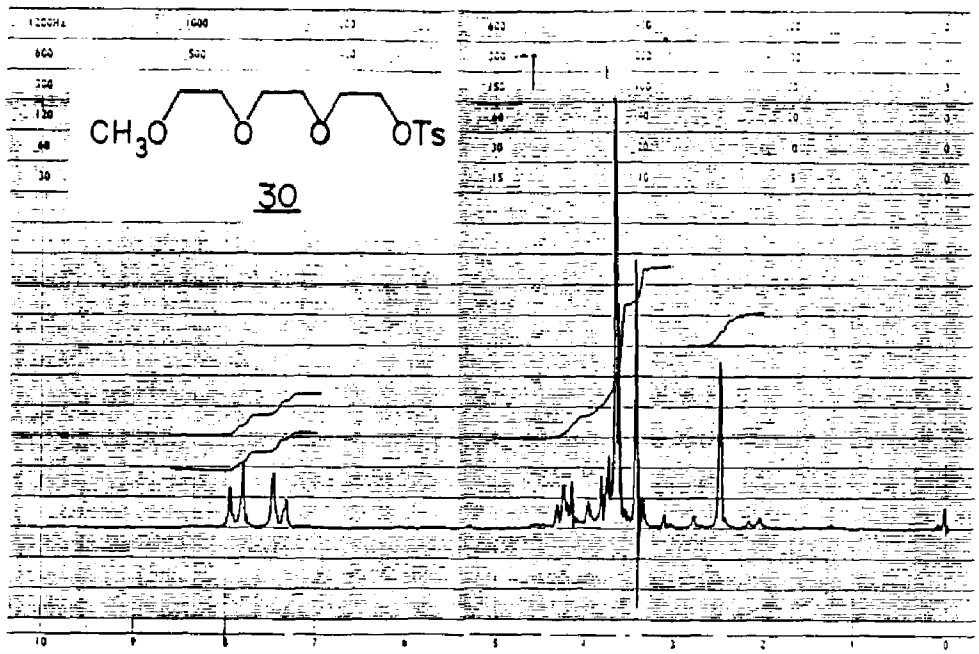


29

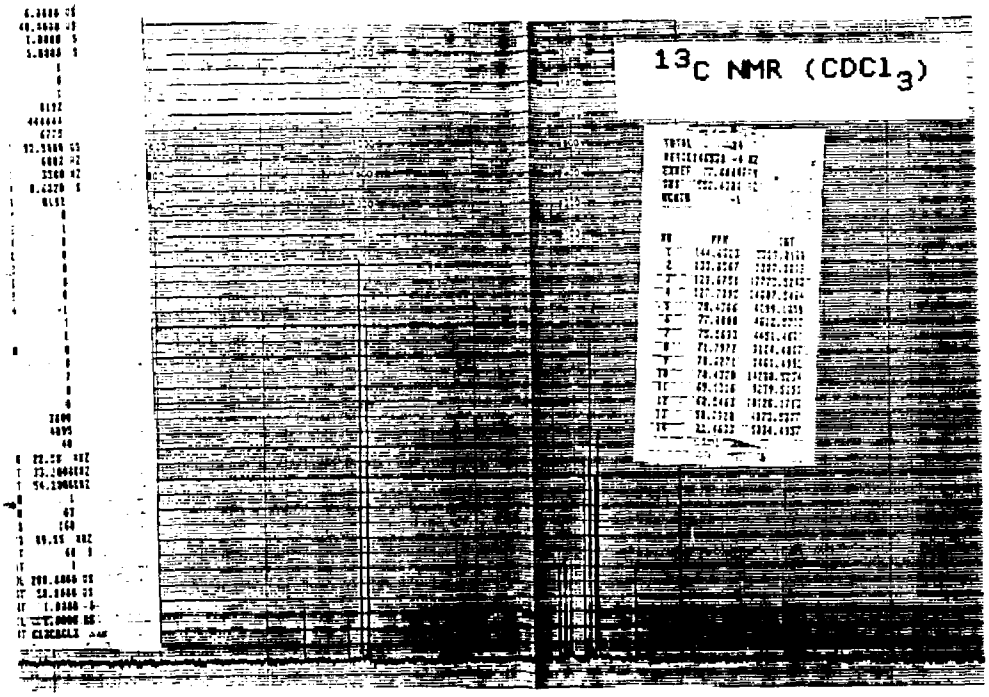
Mass Spec.



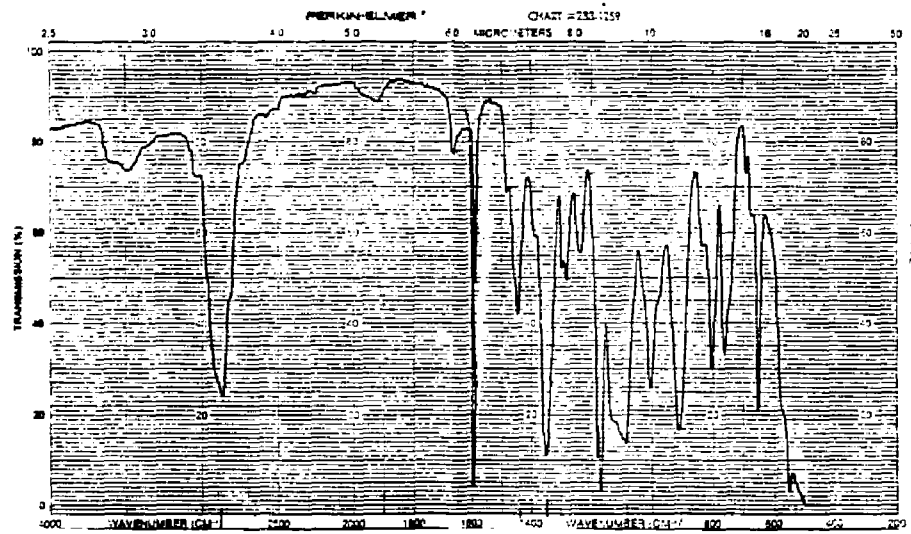
M.Z	REL INT
55	18
56	10
57	66
58	945
59	1000
60	103
61	16
64	4
67	6
69	10
70	21
71	20
72	22
73	46
74	5
75	116
76	27
77	8
81	5
83	7
85	10
86	8
87	162
88	223
89	767
90	46
91	8
95	4
96	4
97	6
101	43
102	132
103	112
104	10
105	6
111	5
119	66
121	7
133	37
134	13
149	6

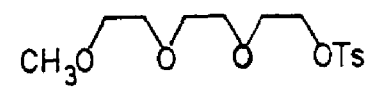


^{1}H NMR ($CDCl_3$)



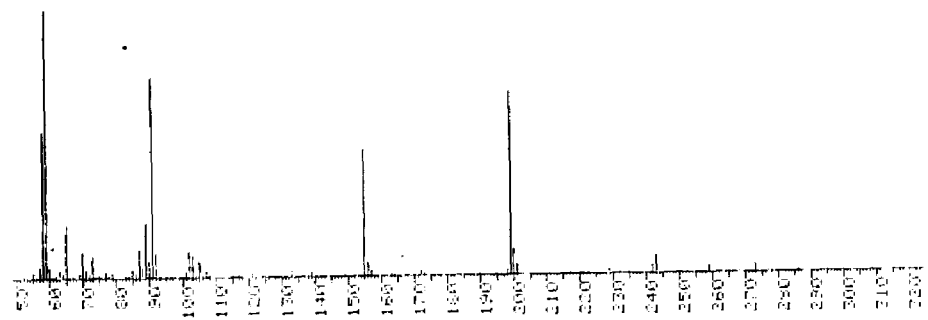
IR (Neat)

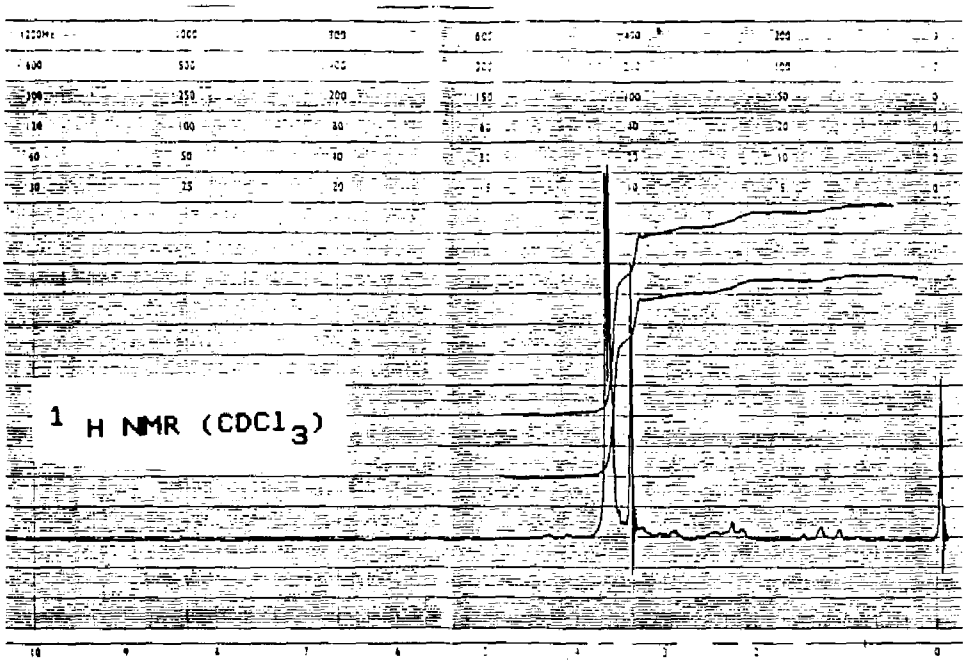


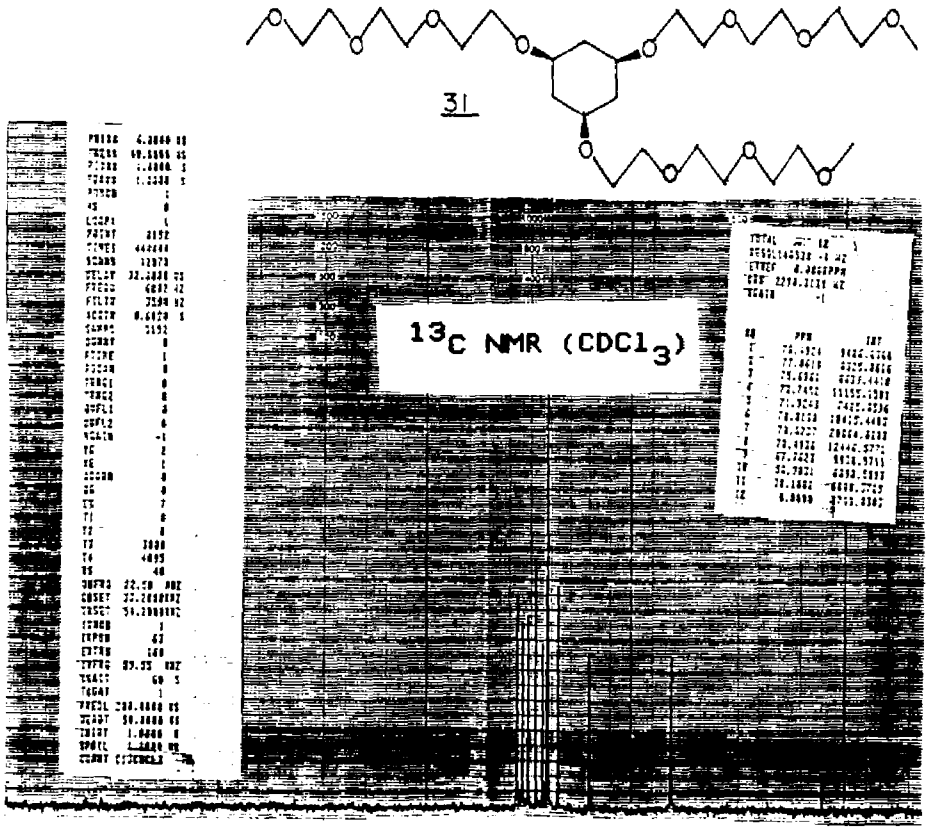


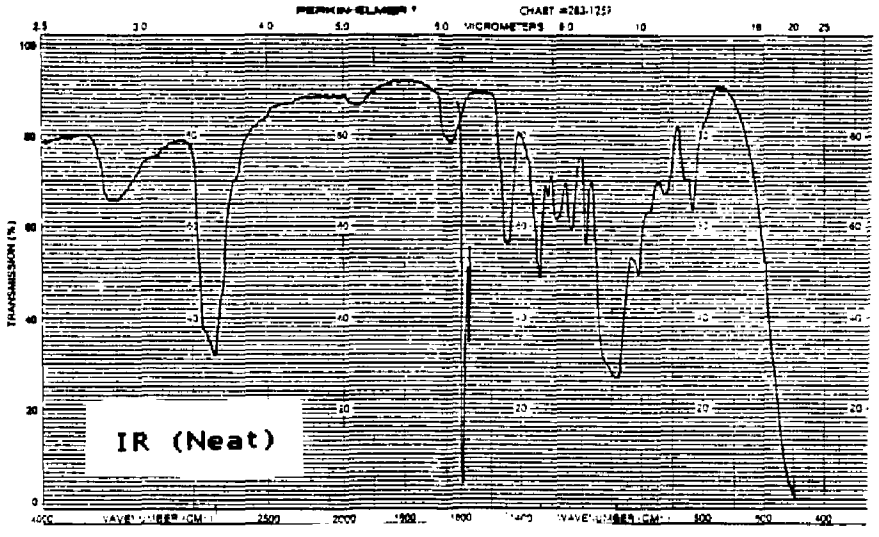
30

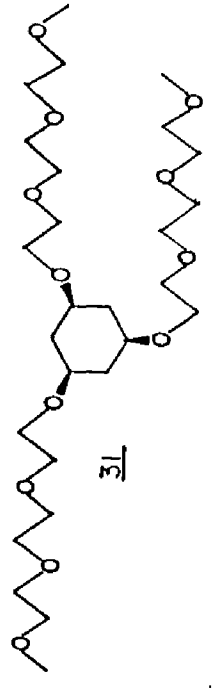
Mass Spec.




^{1}H NMR ($CDCl_3$)


31
^{13}C NMR ($CDCl_3$)





31

Mass Spec.

M/Z	REL INT
52	17
53	21
54	15
55	82
56	45
57	127
58	459
59	1000
60	41
63	18
65	14
67	40
68	24
69	47
70	67
71	55
72	312
73	82
74	15
75	18
77	16
79	35
80	19
81	81
82	19
83	71
84	28
85	141
86	185
87	135
88	46
89	84
91	26
95	31
96	56
97	41
98	18
99	15
100	15
101	55
102	69
103	168
104	24
109	20
111	22
112	18
113	19
115	19
116	31
121	14
123	14
125	14
129	102
130	138
131	26
153	28
141	14
147	27
165	29