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Use of the [2+2] macrocyclization in the synthesis of macrocyclic imines

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USE OF THE [2+2] MACROCYCLIZATION IN THE SYNTHESIS OF MACROCYCLIC IMINES.

by

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A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1994

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Executive Officer

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Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

USE OF THE [2+2] MACROCYCLIZATION IN THE SYNTHESIS OF MACROCYCLIC IMINES.

by

CLAUDE E. BRATHWAITE

Advisor: Professor Valeria Balogh-Nair

The [2+2] macrocyclization of dicarbonyl and diamine moieties were applied to the synthesis of metal-free macrocyclic imines. This method also permitted systematic syntheses of sidearm derivatives. In the design and syntheses of macrocycles, one was not limited to the syntheses of imines, as the procedure was equally efficient in the synthesis of amides. This extension of the [2+2] cyclization to the synthesis of the more hardy macrocyclic amide expanded even further the potential uses of this macrocyclization process. The metal-free nature of the synthesis brought with it enormous flexibility and application possibilities.

Sidearm derivatized macrocycles enable the building of function specific macrocyclic systems such as chiral, lipophilic, coordinative, photoactive, polymeric, and responsive macrocyclic imines; they have all been synthesized by this methodology. Because of the similarity in cavity size in the series of imine and amide macrocycles synthesized, and the flexibility of sidearm derivatizations, the solubility, association, cation and guest binding behavior of the macrocycles can be modified at will. Increased flexibility in the type of macrocycle to be synthesized is also achieved by the choice of the dicarbonyl moiety used in the synthesis. Sidearm derivatization to yield anthracenyl macrocyclic imines, produced macrocycles that possessed not only the ability to coordinate cations, but also took advantage of the photochemical, association and luminescence properties of the anthracenyl moiety.

All new compounds were characterized by spectroscopic studies. Fluorescence and ^{1}H nmr spectroscopy were used to probe the self-association properties of selected macrocycles. Monolayer formation and cation recognition at the water/air interface by the sidearm derivatized macrocycles demonstrated the potential of these macrocyclic imines in the construction of supramolecular assemblies. FAB mass and uv/vis spectroscopies employed to explore the cation binding demonstrated the ability of these macrocycles to bind Ni^{2+} ions, hence the oxidation chemistry of two selected macrocycles were explored to develop oxidation catalysts and nucleic acid cleaving agents.

Dedicated to my mother, Mrs. Brenda Scotland and to the loving memory of Sarah-Jane 'Dee Dee' Elizabeth Spencer (1914-1991).

Acknowledgements

I would like to express my thanks to Dr. V. Balogh-Nair for providing more than the guidance, freedom and tools to pursue this endeavor.

I also want to thank Drs. V. Balogh-Nair and M. Fishman for their counsel and support throughout my studies.

I also wish to thank Dr. L. Mars for conducting the monolayer studies, and Dr. S. Simms for his assistance in conducting the DNA experiments. Special thanks to Mr. R. Pal and Mr. H. Schimatz for mass spectroscopy and glass blowing services respectively.

Preface

The scope of the work presented is not limited to the synthesis of macrocyclic imines, but focuses on the uses and properties of these macrocyclic systems once synthesized, together with the general potential of both the macrocycles and the methodology for further applications. Host-Guest, supramolecular and aspects of Macrocyclic chemistry deemed to be pertinent to the work presented are given special attention to demonstrate the relevance of the work undertaken. I have tried as much as possible to give the most current and relevant references that pertain to the subject under discussion.

Claude Brathwaite

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Chapter 1: Background

Pedersen's synthesis of the crown ethers in 1967,[1] ushered in a new field of chemistry, that even twenty six years later, remains at the forefront of modern organic chemistry. The importance of this discovery, and subsequent development of its vast potential, was recognized when in 1987, the Nobel prize in chemistry was awarded to Pedersen, Cram, and Lehn for their contributions to this field.[2]

Early work on macrocyclic chemistry was focused on the synthesis of crown ethers of various sizes, and the structurally related aza-, thio-, and aromatic analogs, and improvements in the synthetic methodologies employed. Exhaustive studies on the cation complexing abilities of the crown ethers, cryptands and spherands soon followed, along with equally intense efforts on the synthesis of calixarenes, cyclophanes, and cyclodextrin and porphyrin analogs.[3] The complexation abilities of macrocycles have been utilized extensively in analytical chemistry, and are also partially responsible for their importance in enzyme catalysis, energy transduction processes, materials science, and membrane mimetic chemistry.[4]

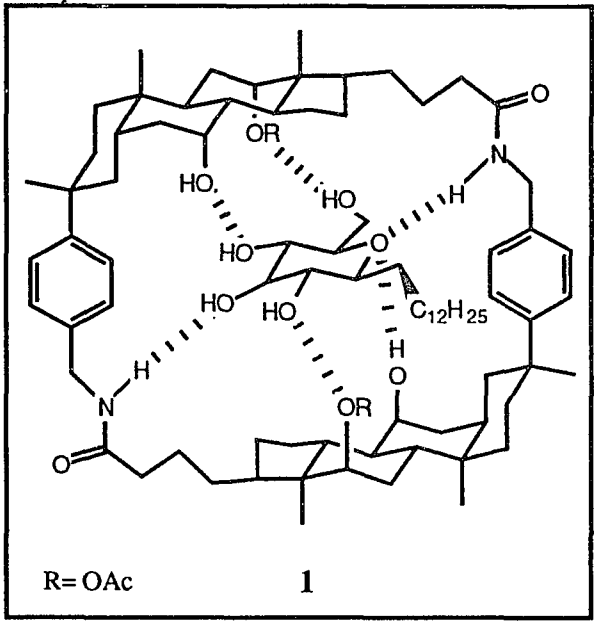
The field of macrocyclic chemistry has been benefited tremendously from the progressive fusion between the biological and chemical sciences.[5] The intensified study of chemical interactions involved in host-guest chemistry, i.e., molecular recognition, utilizes the preformed cavity of the host, designed specifically for a particular guest moiety, to enhance our understanding of basic chemical interactions. Artificial enzyme systems, self-replicating systems, DNA specific cleavage and recognition agents, and self-assembling constructs, all employ molecular recognition principles.

In nature, relatively simple starting materials form a plethora of complex structures, e.g., the genetic code is derived from nucleotide bases, and protein structures from amino acids. Base pairing in nucleic acids, local structural motifs of genetic material, three dimensional structure of proteins, the compartmentalization and organizational structure of the cell, signal transduction (i.e., second messengers), enzyme specificity, the activity of genes, and immune response, all employ molecular recognition and host-guest chemistry principles which are cardinal to essential life processes. Delineation of these complex molecular forces responsible for the formation of these structures points to some very basic chemical interactions present, not only at the molecular level but also at the larger macroscopic level.[6] This encompasses the macrocyclic concept under the heading of supramolecular chemistry which is primarily concerned with the application of a number of basic chemical principles to construct larger macroscopic systems, some of which directly mimic nature.

1.1. Host-Guest Chemistry and Molecular Recognition.

The non-covalent chemical interactions involved in molecular recognition processes are electrostatic interactions, hydrogen-bonding, van der Waals forces, aromatic π stacking interactions, and hydrophobic/hydrophilic interactions. Predominance of one of these forces will in some cases play the major role in determining the extent of the molecular interaction, and/or type of host-guest complex formed. However, in numerous systems evidence can be seen that these basic interactions combine to determine the overall characteristics of the molecular system. The complementary nature of these interactions in most instances depend on the chemical environment of the system. For example, in aqueous systems, the hydrogen bonding abilities of the interacting moieties are minimized and the hydrophilic and Coulombic interactions are maximized. In other cases, the molecular recognition can be just size dependent, (induced fit), or as sophisticated as stereodifferentiation, or as elegant as the self-replicating systems, and self-assembling systems, of Rebek and Stoddart respectively. Selected examples of synthetic host-guest systems and preorganized assemblies in which molecular recognition plays a key role are discussed below:

Hydrogen bonding between the amide bonds of the macrocycle **1**, and four glucosidic hydroxyl groups permits the complexation of glucosides by the cholic acid cyclodimer.[7] The complexation properties of other steroid-based systems, such as the water soluble oligomeric cholesterophanes, are now explored to generate novel synthetic ionophores



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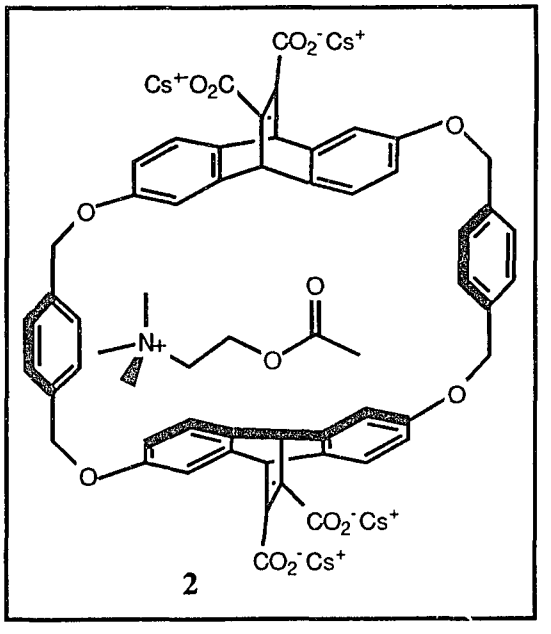
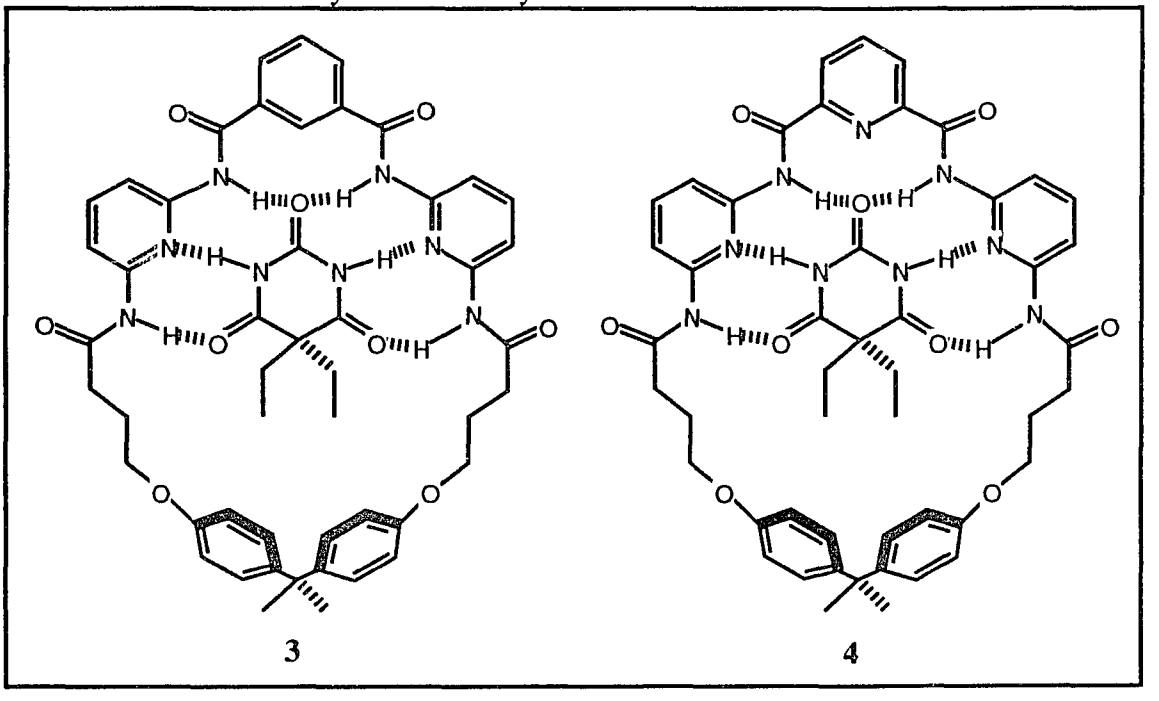


2

The cyclophane **2**,[8] has proven to be a versatile tool in the understanding of molecular recognition interactions and catalysis. In aqueous media, **2** has the ability to bind ammonium ions such as in acetylcholine. The driving force responsible for the binding interactions is the hydrophobic effect in conjunction with the cation-π interaction between the ammonium ion and the aromatic π system of the cyclophane. The rate acceleration observed in the S_N2 reactions of **2** can be understood using this model. Hence there is a significant charge separation in S_N2 transition states, such transition states can be stabilized by cation-π interactions of the substrate with **2**. Thus, since acetylcholine binding sites are known to contain aromatic amino acid residues, synthetic receptors, such as **2**, can provide alternative methods to evaluate and understand the role of the π system interactions not only in molecular recognition processes, but also in enzymatic transamination reactions.

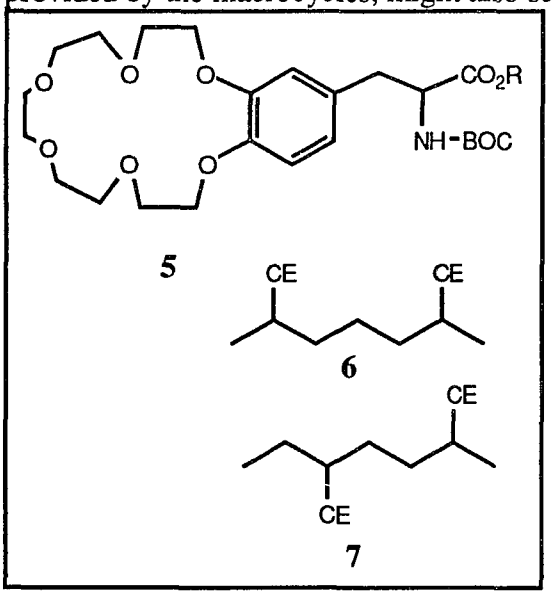
The crystal structures of **3** and **4** show that the 'correct fit' of host and guest is facilitated by the complementary hydrogen bonding interactions of the barbiturate, and the amide functionalities of the macrocycle.[9] ^1H nmr complexation studies demonstrated that this 'correct fit' mechanism operates also in solution. Urea derivatives and dicarboxylic acids can also be bound by these macrocyclic amides.

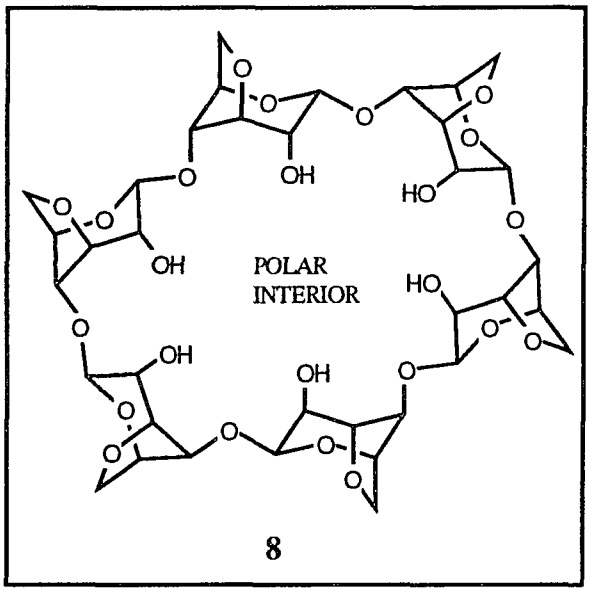


3 **4**

Bis-macrocycles, shown in **6** and **7**, use the peptide backbone, derived from **5**, to position the crown ethers (CE) at periodically spaced intervals, at fixed spatial orientations, and at fixed distances.[10] The α-helix conformations of the peptide backbone is used as the controlling element for supra-structure generation. Cation selectivity and

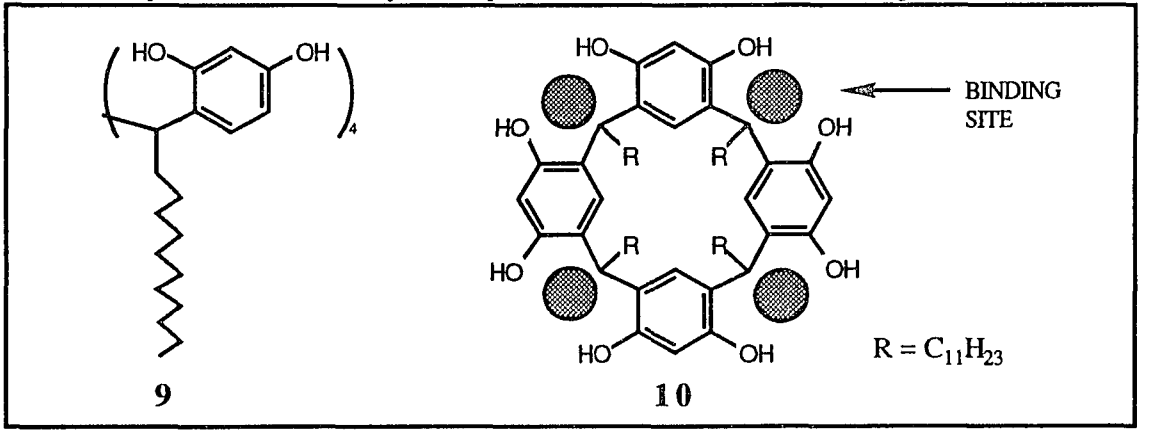
linear recognition properties for diammonium ions were displayed by these macrocyclic structures. It is expected that these structures designed with multiple complexation sites, provided by the macrocycles, might also serve as artificial ion-channels.





The recent synthesis of the per-3,6-anhydro cyclodextrin, **8**, is an important development in cyclodextrin host-guest chemistry.[11] This modified system has a cavity that is, in contrast to the usual case, is hydrophilic, because of the free hydroxyl groups lining the inside of the cyclodextrin cavity. Solubility, conformational mobility and guest binding properties of the cyclodextrins are therefore changed drastically.

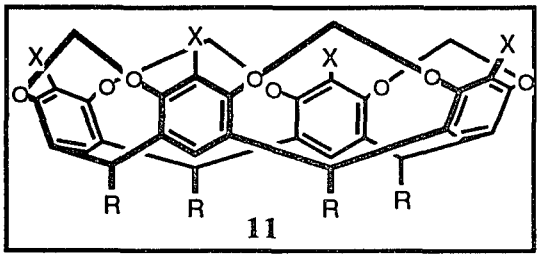
The cyclotetramer **9**,[12] prepared by the condensation of dodecanal and resorcinol, shows complexation selectivity for aliphatic diacids and fructose over glucose. The torus



shaped cavity, schematically represented by **10**, displays molecular recognition properties as a direct result of the cooperative nature of the four complexation sites of the macrocycle. In the case of the aliphatic diacids, an induced fit linear recognition model can be invoked to explain the discriminating effect observed. The cis disposition of the

hydroxyl groups in fructose versus the trans orientation in glucose is responsible for the selectivity observed in the binding of sugars by **9**.

Linkage of the free phenolic groups in cyclotetramers such as **9** by an intervening methylene, (or other bridging groups), produces the rigidified basket shaped carcerands **11**.[13] Further linkage through the **X** functionalities produce the hemicarcerands **12**.



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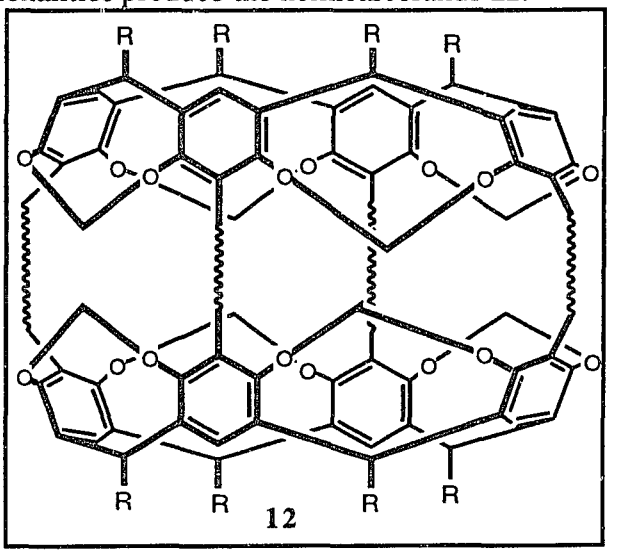
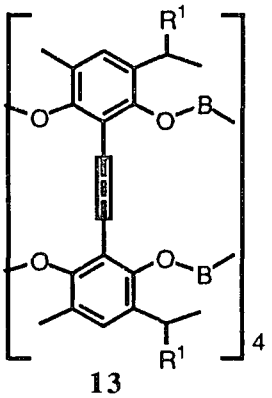


12

By varying the nature and/or number of linkage groups (**X**) an enormous variety of macrocyclic structures can be generated,[14] each capable of binding structurally diverse guests. For example, the macrocyclic imine hemicarcerand **13a** forms host-guest complexes with a whole array of polar, aromatic, and organometallic compounds.[15]



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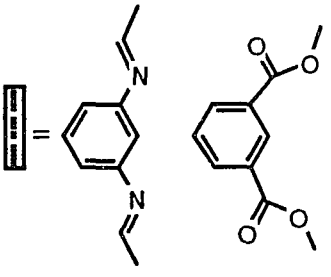
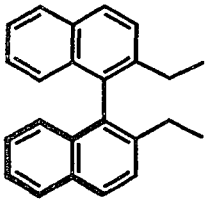


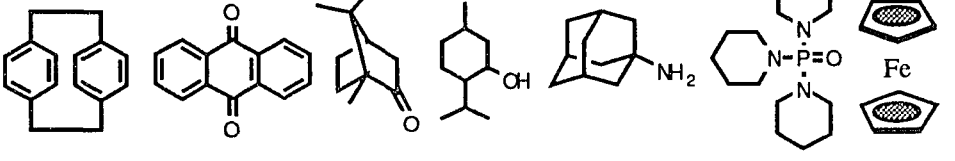
13a

13b



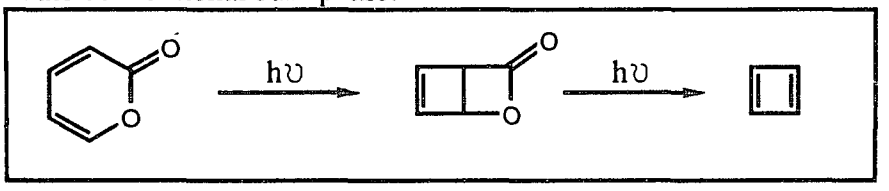
13c

Guests of (**13a**):



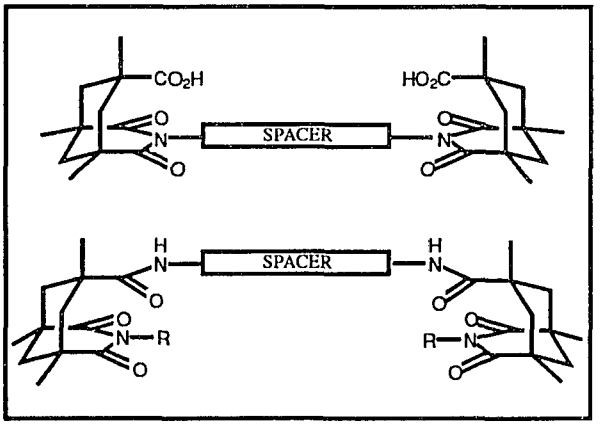
Entry and egress of guest molecules into and from the hemicarcerands is regulated by the constrictive binding of the hemicarcerand.[16] The ability to '*release and capture*" by the

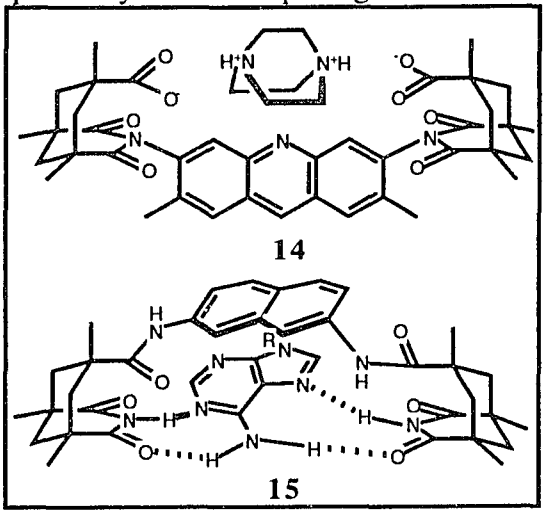
host is determined predominantly by the size and shape of the guest molecule. Thermal perturbation of the macrocycle is needed to overcome the steric constraints of the linkage groups, and thus allow '*entry and release*' of the guest. In the case of some carcerands the guest is confined so tightly that only destruction of the cavity's structure, by hydrolysis, can release it. This concept of constrictive binding was harnessed to generate cyclobutadiene photochemically from the ∝-pyrone-hemicarcerand complex,[17] and was detected at 60°C by ^{1}H nmr spectroscopy (Scheme 1). It can be postulated that the 'innerphase' of the hemicarcerands acts as a stabilizing novel chemical environment, distinct from the conventional bulk phase.



Scheme 1.

Departing from the use of the macrocyclic cavity, where enzyme-like convergence of the functional groups is difficult to achieve, but nevertheless, retaining the preorganized cavity as the model to study molecular recognition, transport, and catalytic properties, Kemp's acid derivatives have proven to be powerful alternatives.[18] Because the acid functionalities are locked into a triaxial conformation, derivatization of them produces amide, ester, or imide functionalities at fixed distances and orientations (Scheme 2). Compounds **14** and **15** are representative examples of synthetic receptors generated from



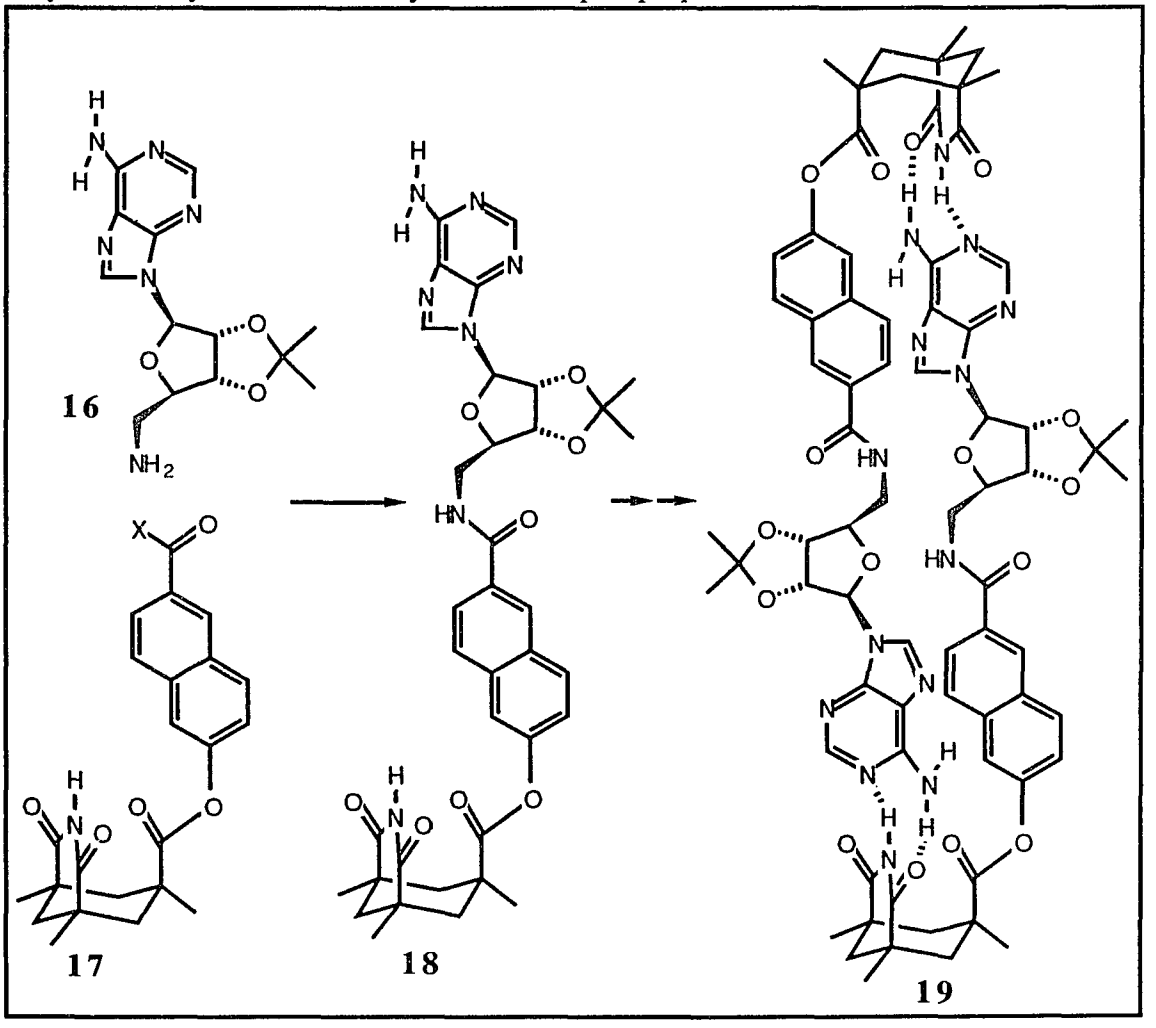


Scheme 2.

Kemp's acid derivatives. The carboxylic acid functionalities in the cleft of **14** bind the complementary basic nitrogens of DABCO, but amines of appropriate basicity that do not fit the cleft are bound weakly if at all. In the receptor mimic **15**, highly efficient binding of adenine derivatives is assured not only by Watson-Crick and Hoogsteen types of base

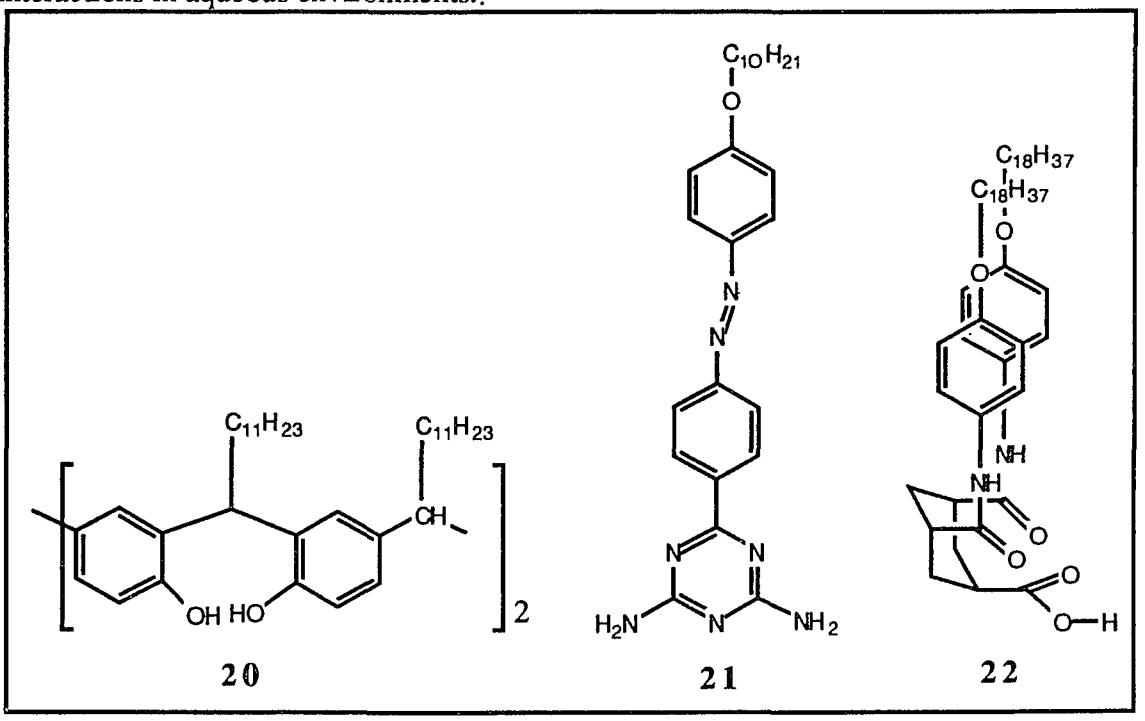
pairing, but also by simultaneous π-stacking interactions with the planar aromatic spacer group.

Self-replication using **16** and **17** clearly displays features of molecular recognition at work (Scheme 3).[19] A combination of hydrogen bonding and π stacking interactions of the triacid derivatives, positions the reactive moieties in **16** and **17** into close proximity. Once reaction has occurred to form **18**, binding of **16** and **17** to **18** again places the reactive functionalities in close juxtaposition. In effect, the product of the first reaction sequence "acts as a template for its own formation, and thereby exhibit autocatalysis".[19] The interactions present in the dimer **19** are such that it dissociates to allow the reaction sequence to repeat itself. Use of the molecular clefts and tweezers as the preorganized *foci* for molecular recognition interactions have been explored by many other researchers to synthesize systems with catalytic and transport properties.[20]



Scheme 3.

In biological systems, recognition at cell surfaces play important roles in immunology, molecular transport, and regulatory processes. To understand successfully, to model, and to exploit these properties of biological systems, the evaluation of Coulombic as well as non-Coulombic molecular recognition interactions in organized media are extremely important. To mimic these biological interactions, the recognition properties of the polar head groups in **20**, **21**, and **22** have been evaluated previously in non-polar organic media.[21] Moreover, **20**, **21** and **22** formed monolayers with molecular recognition properties which were also useful to evaluate hydrogen bonding interactions in aqueous environments..



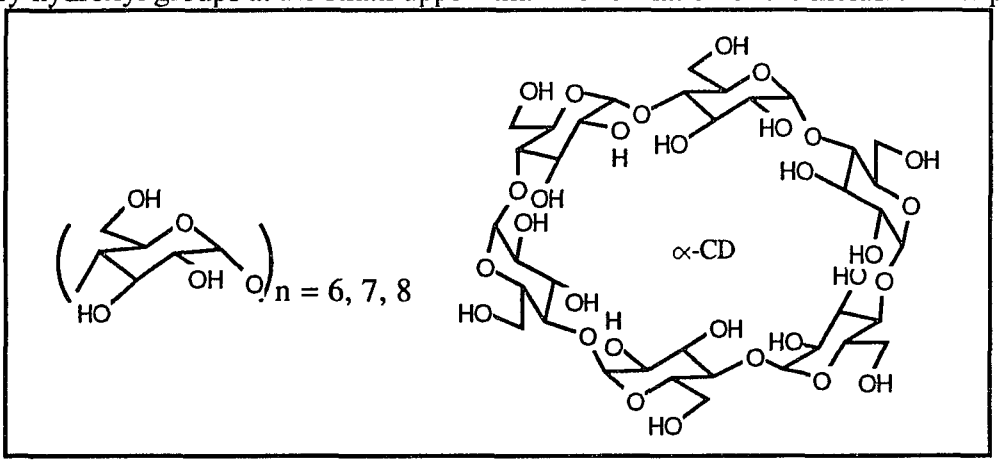
20 **21** **22**

1.2. Macrocycles as enzyme mimics.

Enzymes function under conditions that are largely hydrolytic, therefore it is important that model systems which are to be used as enzyme mimics have the ability to function in aqueous environments. Moreover, in a substantial number of enzymes, the active sites by contrast are hydrophobic in nature and display molecular recognition characteristics that can be readily mimicked by macrocyclic systems. Cyclodextrins, calixarenes, cyclophanes, crown ethers, and porphyrins have all been explored as possible enzyme mimics.

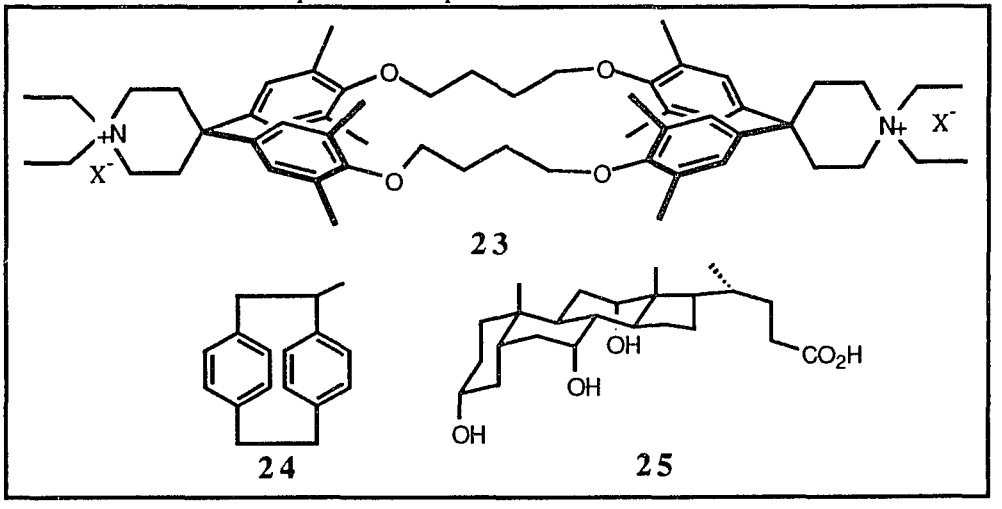
Cyclodextrins, (CDs), are cyclic oligomers of (∝)-D-glucopyranose. The alpha-, beta- and gamma-CDs are composed of 6, 7, and 8 glucose units respectively, linked by a

∝-1,4 glycoside bond (Scheme 4). The torus shaped CD cavity possesses a hydrophobic interior flanked by polar secondary hydroxyl groups situated at the large bottom rim, and primary hydroxyl groups at the small upper rim. The formation of the inclusion complexes

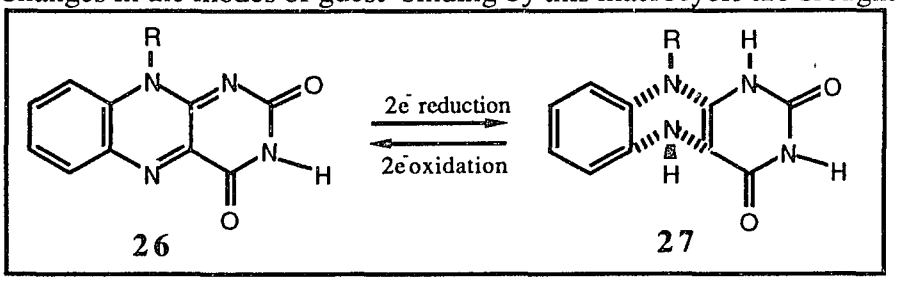


Scheme 4.

complexes with CDs is driven primarily by the hydrophobic effect, and to a lesser extent, by hydrogen bonding and dipole interactions. Selective functionalization of CDs, fine-tunes their binding and catalytic properties,[22] which makes possible the synthesis of CD-based ribonuclease, transaminase, aldolase, NADH, and metallo-enzyme mimics.[23] Influence by CDs over chemical transformations extends beyond their use as enzyme mimics; stereoselective reductions, epoxidations, and ring openings in a stereoselective and regioselective manner, are some of the chemical transformations influenced by the CDs.[24] The binding of organic substrates by cyclophanes is also driven predominantly by the hydrophobic interaction of the guest with the apolar cavity of the cyclophane.[25] The complexation of the cyclophane, **24**, and the steroid, **25**, by **23**, illustrates the range of substrates that can be complexed in aqueous solutions.

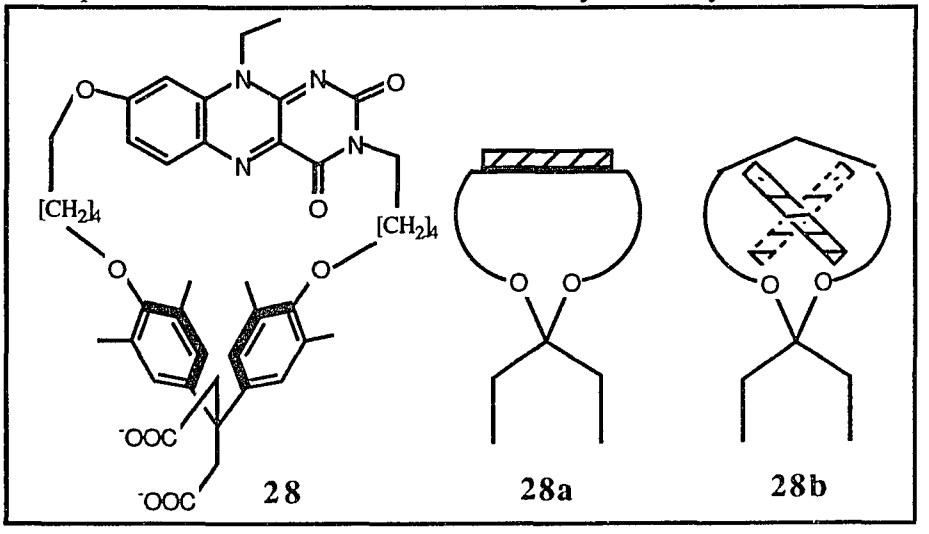


Flavin coenzymes are important in a number of biochemical processes. At the center of the enzymatic activity is the redox chemistry of the planar isoalloxazine moiety, **26**, and the structural changes accompanying its interconversions with the butterfly-shaped, reduced form, **27**. The flavinophane, **28**, may be an ideal macrocyclic coenzyme mimic.[26] Changes in the modes of guest binding by this macrocycle are brought about by



26 **27**

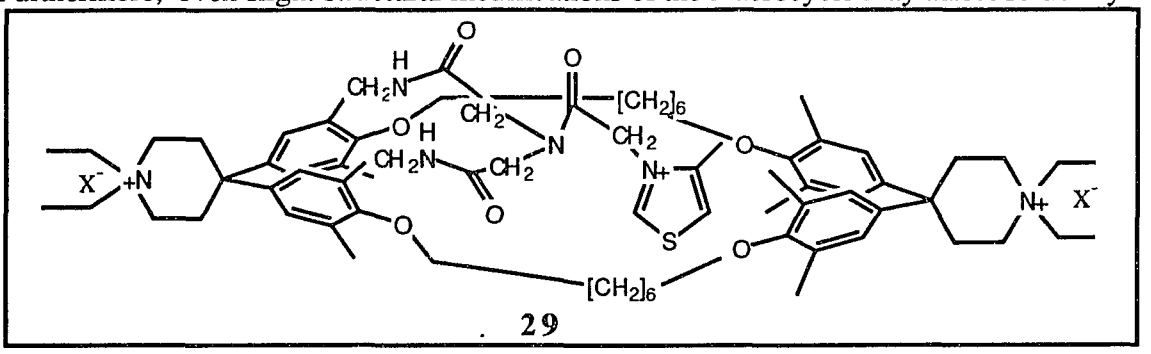
the shape changes resulting from the redox conversions of its flavin moiety. Thus, in the oxidized form, **28a**, the size of the apolar macrocyclic cavity is smaller and the flavinophane has the ability to self associate, hence binding of a naphthalene guest is possible only at the outside, by π stacking of the naphthalene and the planar isoalloxazine moiety. In the reduced form, **28b**, the angular nature of the macrocycle increases the size of apolar cavity and eliminates the self-associating properties of the flavinophane, and therefore the naphthalene is bound inside of the macrocyclic cavity.



28 **28a** **28b**

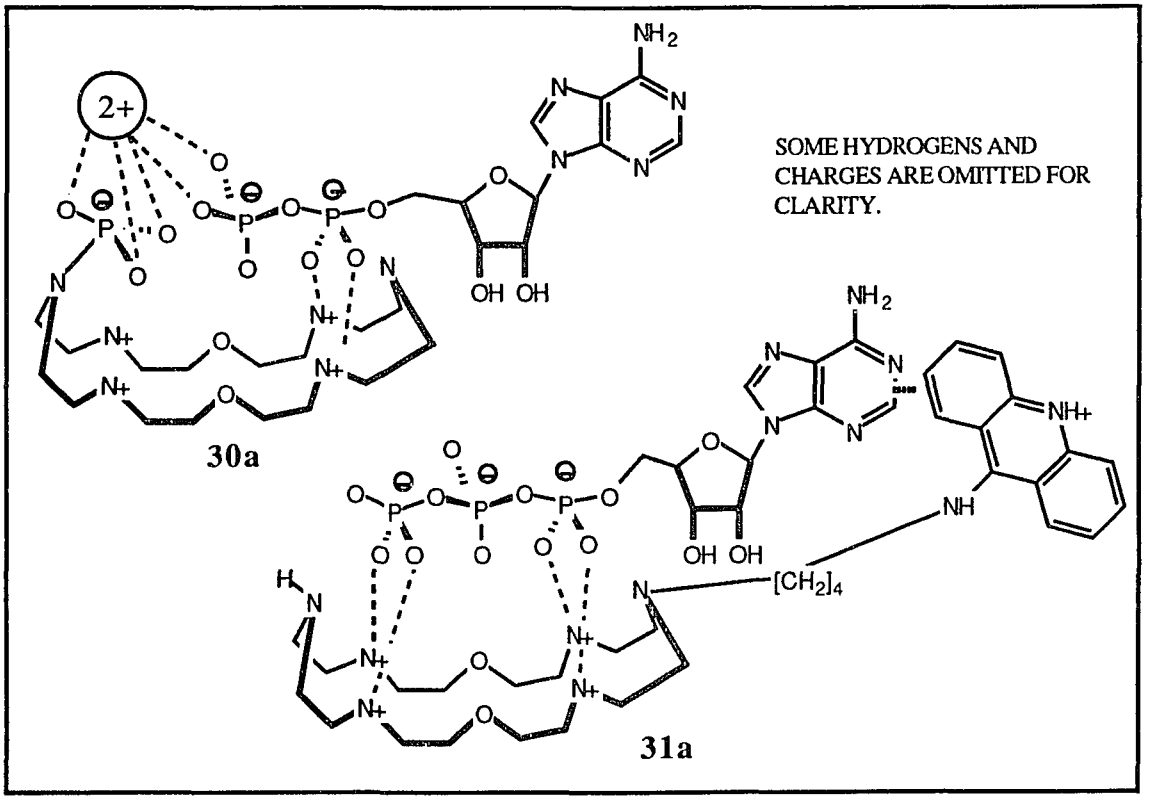
Thiamine pyrophosphate is a cofactor in numerous enzyme catalyzed reactions involving carbon-carbon bond formation. Benzoin condensation for C-C bond formation was used to test cyclophane, **29**, containing a macrobicyclic triazolium ring, and it was found that as a turnover catalyst it was much more efficient than the non-macrocyclic thiazolium derivatives.[27] The above examples demonstrate that appending or integrating a cofactor or prosthetic group into the macrocyclic construct is one of the most useful synthetic methodologies to mimic enzymatic activity. The catalytic properties of

macrocyclic systems can also be altered by modifying the reaction conditions. Furthermore, even slight structural modifications of the macrocycle may affect solubility



29

under lipophilic/hydrophilic conditions, conformational mobility and/or crucial binding properties. Cations may induce association of the macrocycle and substrate or inhibit other possible pathways of the reacting system. Illustrations of some of these effects are seen in the catalytic properties of the ligand **30** and its derivatives.[28] With an acridine pendant arm attached to **30**, as in **31**, ATP hydrolysis to ADP is catalyzed more efficiently. Addition of Ca^{2+} ions to the reaction system of the unmodified ligand **30**, on the otherhand, allows the formation of a ternary complex from which catalytic synthesis of ATP can occur. Only the intermediates responsible for the catalytic activities observed, **30a** and **31a**, are shown here.



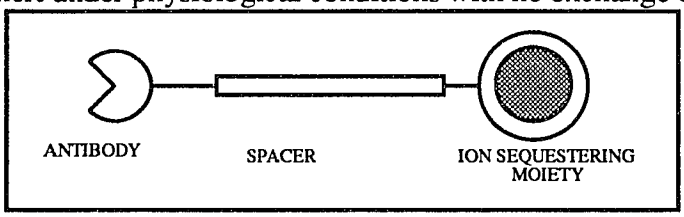
30a

31a

1.3. Macrocycles in medicine.

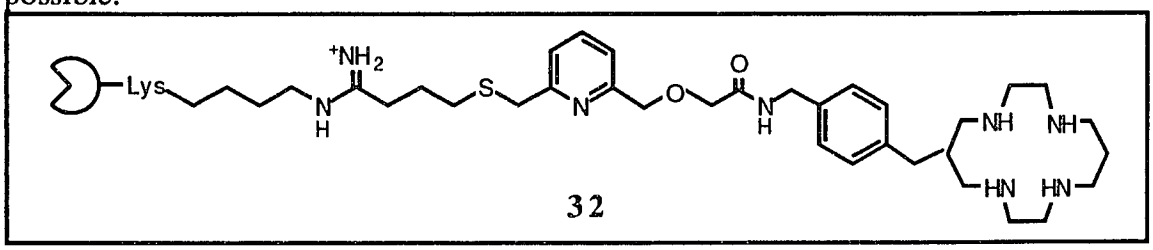
Utilization of antibody technology, combined with the well characterized ion binding, and molecular recognition properties of macrocycles, may result in successful alternatives to conventional medical treatments and diagnostic procedures. In particular, the specificity of tumor targeting and fluroimmunoassay methods, using monoclonal antibodies (MCAs), could eventually replace the radioimmunoassays.

Chemical structures specific to the cell membranes of cancerous cells, or a particular cell type can be used as antigens against which MCAs can be produced. Linkage of the MCAs to an ion sequestering moiety, e.g., a radioisotopically labeled macrocycle complex, results in a ligand that is cell specific (Scheme 5).[29] The sequestering agent chosen for the radioisotope must have the ability to form stable complexes that are kinetically inert under physiological conditions with no exchange of the radioisotope for



Scheme 5.

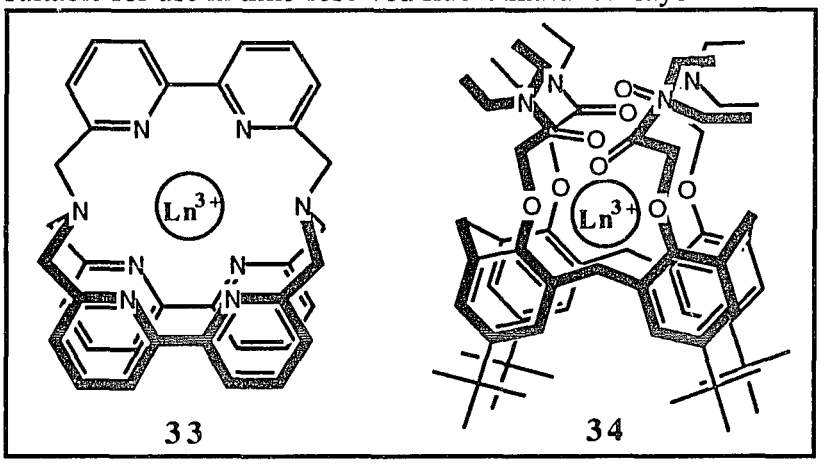
the Ca^{2+}, Na^{+} or other cations that are prevalent in the body. In addition, the sequestering agent chosen, e.g., the tetraazamacrocycle in **32**, must have other functionalities to which attachment to the MCA can be made. Adaptations of this methodology of tumor targeting for drug delivery and photodynamic therapy, where specificity is problematic, may be possible.



32

An antenna for photoreception, coupled to a luminophoric cation is fundamental in the design of probes which have potential uses in fluoroimmunoassays. It is from this antenna that efficient energy transfer to the cation must occur to produce a highly luminescent species. Encapsulation of the cation enhances the efficiency of the energy transfer to it by minimizing its radiationless decay, and also by preventing the decay of the excited "antenna" species by direct emission. The "antenna"-cation complex is protected from solvent molecules that would facilitate radiationless decay/direct emission, hence it is

stable in aqueous media. Lanthanide complexes of the cryptand **33**,[30] (one member of a large family of similar cryptands), and the calixarene **34**,[31] absorb efficiently in the UV via the macrocyclic ligand, and emit in the visible, via the lanthanide cation, thus display properties suitable for use in time-resolved fluoroimmunoassays.



33 34

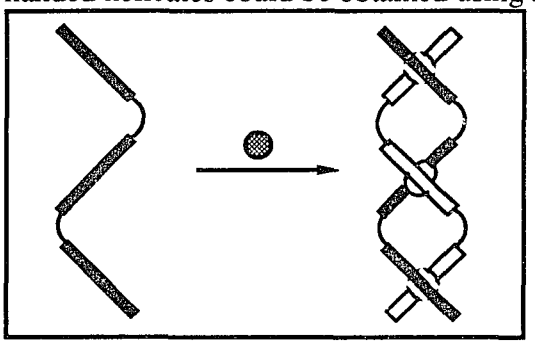
2. Supramolecular chemistry.

In nature, the assembly of biological components into ordered structures occurs routinely and are important in, among others, the regulation of enzyme activity, recognition processes, and gene expression. The interrelation between structure and function in nature creates an intricate balance from which the control over structure and hence function can be precisely modified. Basic understanding of this balance leads to, in essence, the mimicry of a large number of natural processes and the construction of new materials whose functions are cntrolled by structure design.

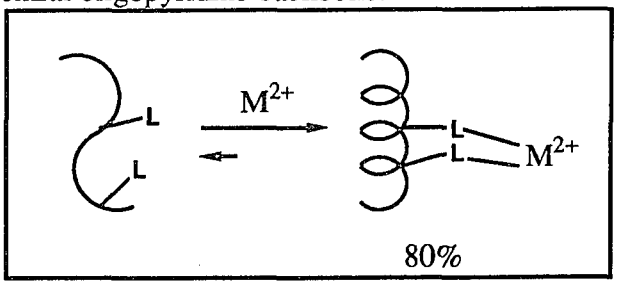
2.1. Cation induced assembly.

Bis-polydentate ligands form complexes of double-helical geometry, the nucleohelicates, in the presence of the appropriate cation. This happens when the cation is too small to fill the bonding cavity to yield a planar complex, instead the coordination requirements of the cation are satisfied when two coordinating sites on independant molecules arrange themselves in a helical array, and the ligand strands wrap around three (Scheme 6), four, five, or more metal ions. Thus, quinque-pyridine, sexi-pyridine and 2,2'-bipyridine derivatives have been used to assemble supramolecular nucleohelicates.[32] Nucleoside derivatives of the 2,2'-bipyridine, such as **35**, also form

deoxyribonucleohelicates on the addition of Ag^+ and Cu^+ cations,[33] and left and right handed helicates could be obtained using a chiral oligopyridine backbone.[34]

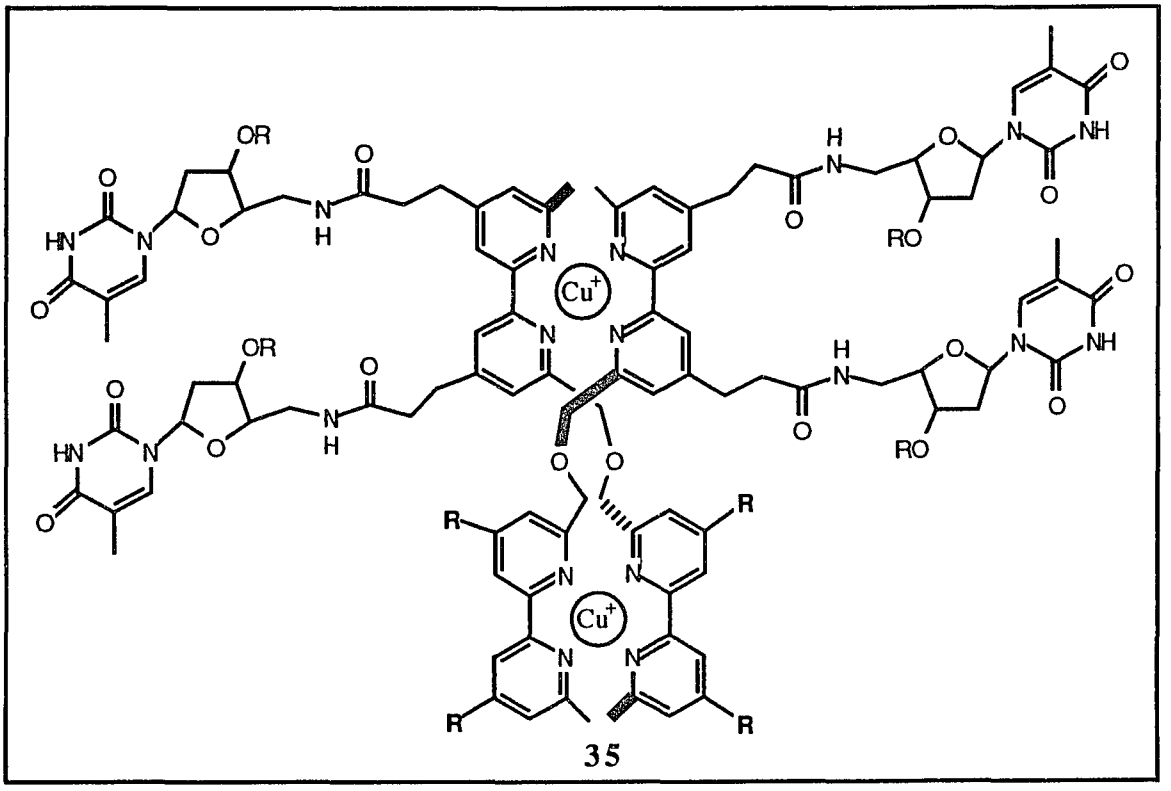


Scheme 6



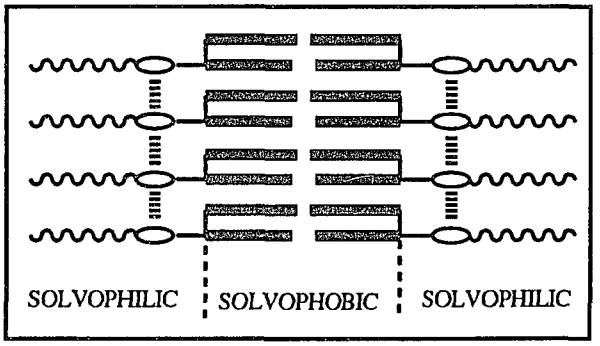
Scheme 7

Some cations are known to influence the ∝-helical structures of polypeptides, and the tertiary structures of proteins, and nucleic acid conformations. To gain control over these processes a useful strategy is to introduce metal ligating residues into the backbone of the biopolymer. These residues can form "crosslinks" that selectively stabilize the folded form thereby affecting the position of coil-to-helix equilibrium. To illustrate, up to 80% conversion from random coil to the ∝-helical arrangement of an 11-residue peptide was accomplished using Cd^{2+} ions (Scheme 7).[35] The complexation of Ru^{3+} by pyridine and bipyridine polypeptide derivatives have been used to assemble peptide bundles.[36]

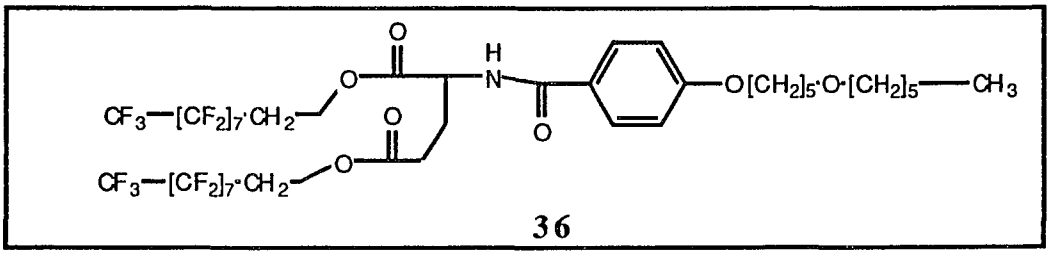


2.2. Self-assembly.

In aqueous systems, self-association of amphiphilic molecules into micellar and bilayer structures is largely dependant on the hydrophobic effect. The formation of bilayer membrane structures in organic solvents are not driven by the hydrophobic effect and are rare. The spontaneous assembly of **36** into bilayer structures (Scheme 8) in hexane and methylene chloride is driven by the self-associative behavior of the solvophobic and solvophilic moieties present in each molecule.[37] Thus, the associative properties of the fluorocarbon tails that serve as solvophobic units enables a group of these molecules to form highly organized, bilayer type structures. The presence of organized chromophoric units in these structures gives rise to exciton coupled CD spectra of high intensity that permits monitoring their formation.

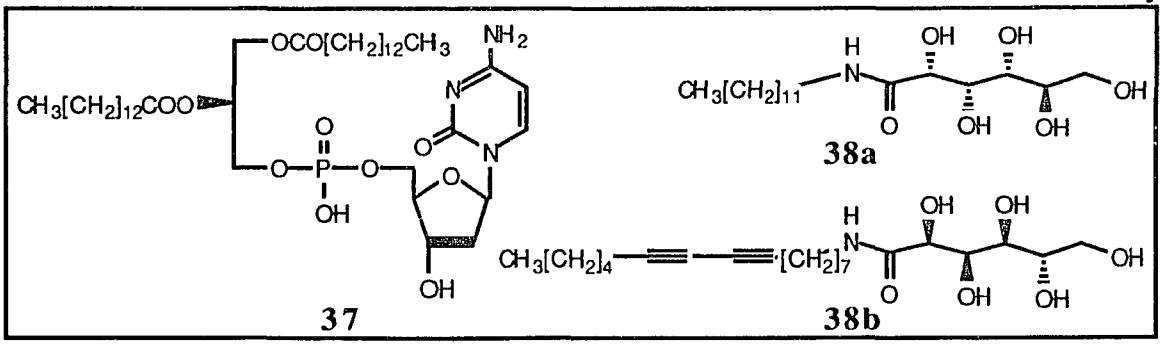


Scheme 8.



36

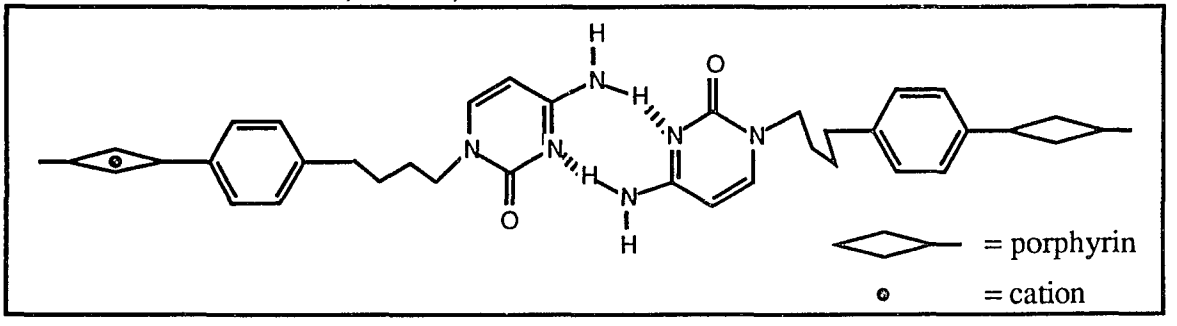
Phospholipid-nucleoside conjugates combine in one ligand two chemical entities that self-associate into superstructures similar to DNA.[38] Base stacking and the inward orientation on association of the hydrophobic tail, contribute to the curvature and stability



37 **38a** **38b**

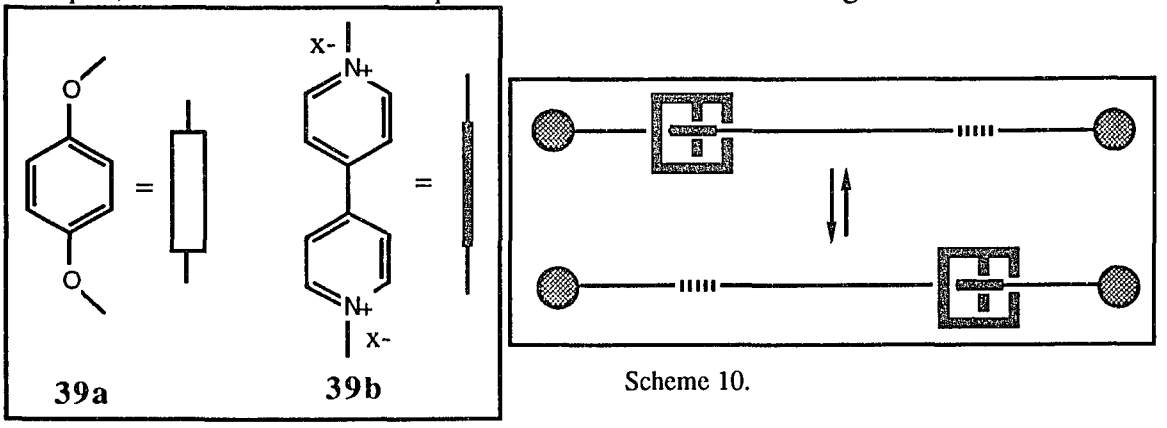
of the superhelical right handed strands formed by **37**. Amphiphiles such as **38** form micellar fibers and cloth-like aggregates spontaneously that are held together by the hydrophobic effect and amide hydrogen bond chains.[39] Electronmicrographs revealed that the micellar rods and "cloths" are composed of helical structures that aggregate into bundles which then form tubes of several micron length. The diameter of the tubules appears to depend on headgroup composition and the chiral headgroups also control curvature and handedness in these supramolecular aggregates.

Aside from their emerging importance in medicinal chemistry, nucleoside derivatized, macrocyclic and acyclic compounds, serve as useful model systems for the study of supramolecular chemistry. Base pairing abilities of the purines and pyrimidines are used as pendant arm recognition handles to drive the association characteristics of these systems. Long-range energy and electron transfer processes are being studied using supramolecular assemblies such as the one illustrated in Scheme 9.[40] The assembly of molecular tapes, liquid crystalline arrays, directed co-crystallization and solution state supramolecular structures were achieved using two (Scheme 9) or three point hydrogen bonding interactions of nucleosides, amides, and imides.[41]



Scheme 9.

Stoddart *et al.*[42] had shown that crystalline donor-acceptor complexes can be formed by crown ethers derived from bisparaphenylene units such as **39a**, and dications such as Paraquat, **39b**. Face-to-face complex formation results from charge transfer interactions

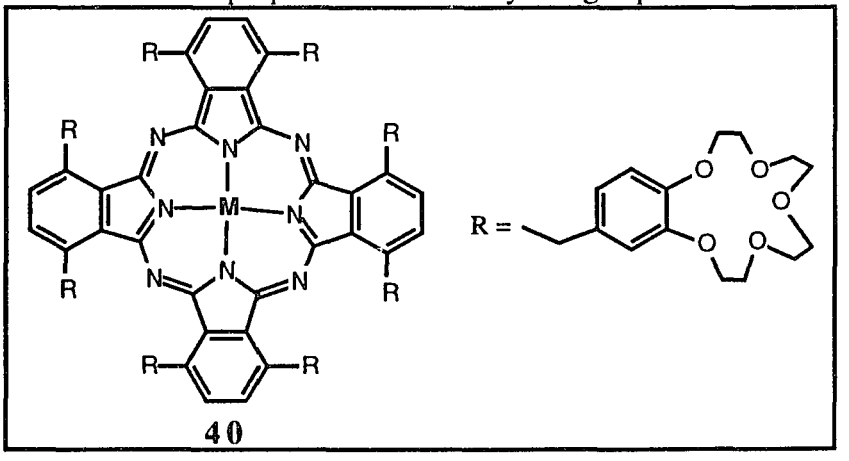


Scheme 10.

between the π-electron rich hydroquinol units and the π-electron deficient bipyridinium moieties. This type of molecular interactions was exploited in the synthesis of novel supramolecular systems by integrating the self-assembling donor/acceptor moieties into synthetic schemes as templates to guide the construction of catenanes and rotaxanes.[42,43] Self-assembly of the rotaxane like molecular shuttles (Scheme 10) can be monitored using low temperature ^{1}H nmr studies revealing the movement of the macrocycle at a rate of 500 times per second between the two extremes of the rotaxane.

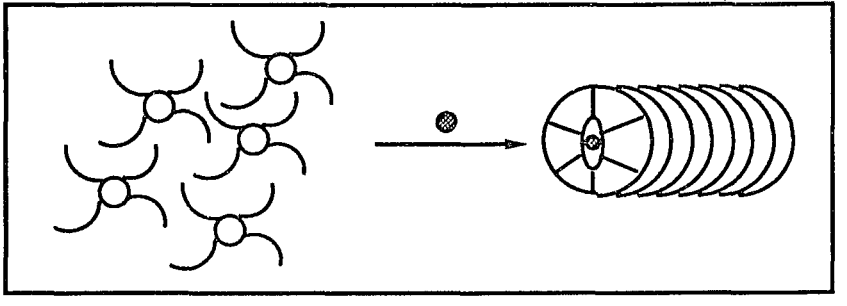
2.3. Macrocyclic liquid crystals.

Phthalocyanines, (PCs), and porphyrin macrocycles have been extensively employed to produce liquid crystalline materials.[44] The electronic, redox, and structural properties of the liquid crystals formed using PCs can be modulated by the choice of the coordinating metal ions. In addition, PCs derivatized with macrocycles, e.g., crown ethers, on the periphery of the PC core, as in **40**,[45] possess the ability to stack, form sandwich dimers and aggregates on the addition of metal ions. The formation of channel like structures by PCs and their ion-conductance properties are currently being explored.



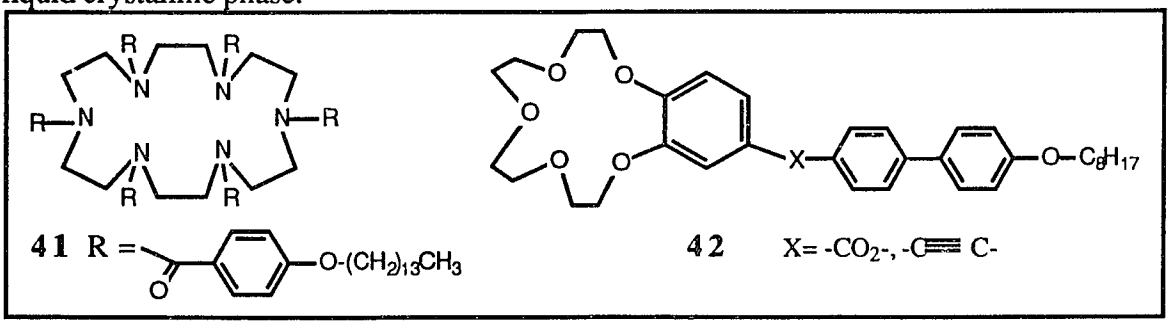
40

Columnar mesophases have been obtained using the macrocyclic ligand **41** only in the presence of Ni^{2+} cations[46] (Scheme 11) because the metal-free macrocycle is too flexible to



Scheme 11

display liquid crystalline properties. However, complexation to Ni^{2+} cations forces the macrocyclic ligand to adopt a highly rigid conformation required for the formation of a liquid crystalline phase.



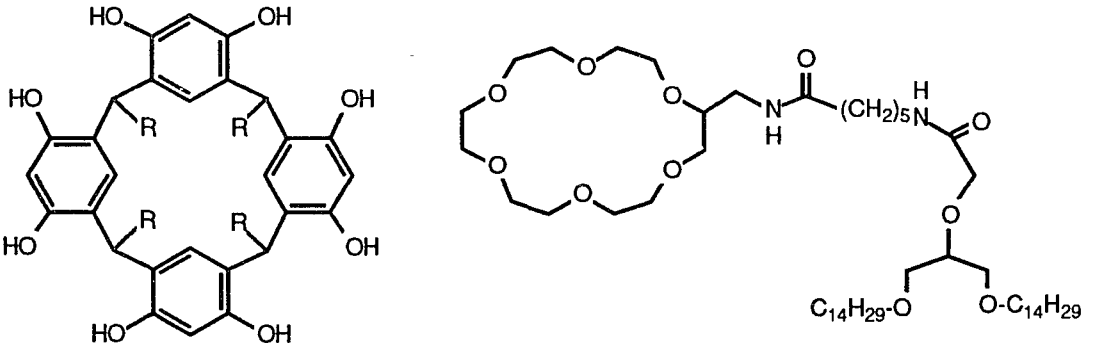
Crown ether derivatives of the type **42**[47] display a nematic liquid crystalline phase and the corresponding 4'-cholesteryl derivative exhibits a cholesteric phase instead. The conformational rigidity of the crown ether moiety in **42** was found to be the crucial factor responsible for this behavior since more flexible analogs (e.g., 18-crown-6) show no mesophases.

2.4. Macrocyclic monolayers and LB systems.

Supramolecular assemblies of monolayers and Langmuir-Blodgett films (LBs) derived from macrocycles are ideal to exploit the supramolecular properties of the organized media and the molecular recognition properties of macrocycles. The term 'molecular recognition' here is meant to include the host-guest interactions of macrocycles as well as their ionophoric, catalytic and electrochemical properties. The resulting properties of the supramolecular systems under investigation may be unique, amplifications of many of the preexisting properties or a mirror image of the properties in non-organized media. Application of these properties are envisaged in the fabrication of novel eletronic and biosensing devices, and in the elucidation of molecular recognition processes at the cell surface.

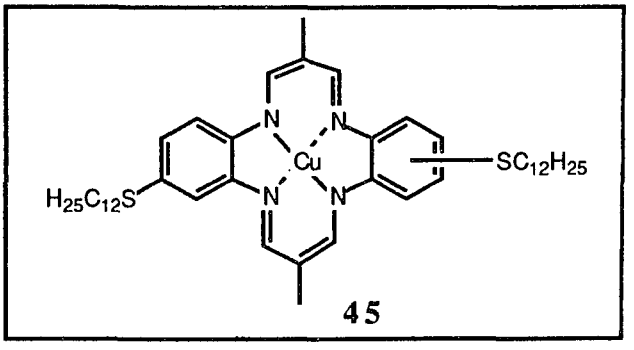
Monolayers of phthalocyanines, crown ethers, cyclodextrins, calixarenes, porphyrins and polyamides have been prepared.[48] Tin oxide electrodes modified with monolayers of macrocycle **43**, showed concentration and guest dependent electrode responses for a number of sugars.[49] The selectivity towards the sugars of the modified electrode was different from the extraction ability of **43** for these sugars, instead it was related to the lipophilicity of the sugars and their conformations in water. Modification of a tin oxide electrode with **44** produced a semiconductor sensor that displayed surface conductance

changes for alkali metal and alkaline earth metal ions of the order similar to the ion-complexation ability of 18-crown-6 in water.[50]



43 R = $C_{11}H_{23}$ **44**

Appearance of a novel, red-shifted absorption band and the characteristics of surface pressure-area isotherms obtained when the copper complex of the amphiphilic dibenzotetra-aza[14]annulene, **45**,[51] was inserted into LB fims pointed to a stacked orientation of the macrocyclic ring perpendicular to the water surface with the aliphatic chains pointing away from the water. Electrical conductivity in the semiconductor range and the sensitivity to reactive gases and liquids indicated the usefulness of the LB films of **45** for sensor applications.



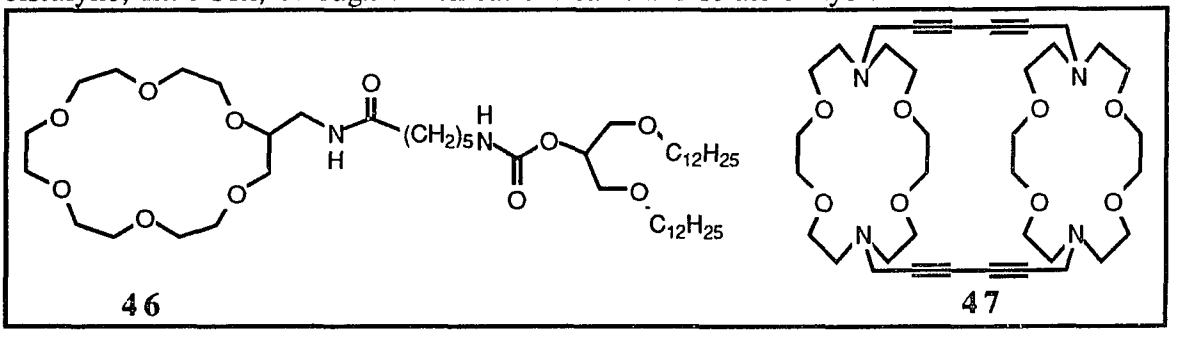
45

3. Membrane mimetic chemistry.

A number of model systems have been synthesized to mimic both the structural and transport properties of cell membranes. In most cases, the general structure consists of an ion sequestering moiety linked in some fashion to a lipophilic hydrocarbon chain.

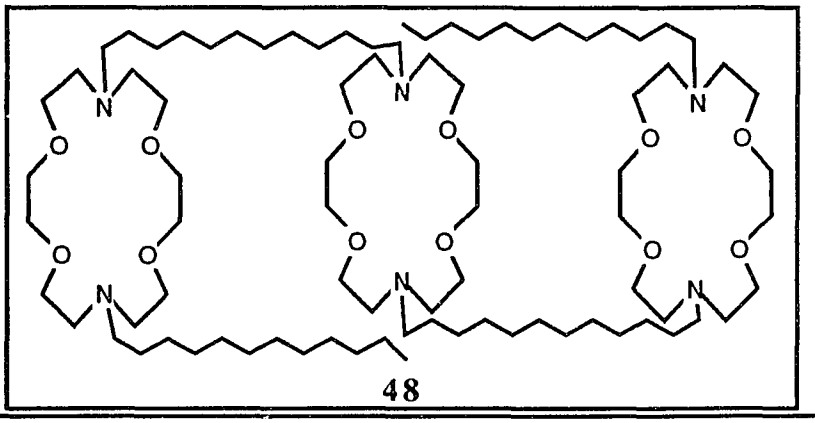
Single, large unilamellar vesicles formed by **46** displayed greater stability compared to phosphatidyl choline vesicles.[52] Electrophoretic mobility studies conducted with various cations paralleled the trend showed by 18-crown-6, which indicated that the vesicles are organized with the crown ether moieties at the outer layer. End-on-end combination of the

rigid ditopic macrocycle, **47**,[53] may serve as possible ion channel by providing a cistulyne, 'little box,' through which cations can traverse the bilayer.



46 **47**

The insertion of **48** in phosphatidylcholine vesicles resulted in an enhancement of the transport of Na^+ ions.[54] Cation transport in this case is believed to occur via the formation of an ion channel through which the cations hop from macrocycle to macrocycle until they cross the bilayer of the vesicle. The mechanism is reminiscent of the ion transport process in gramicidin.



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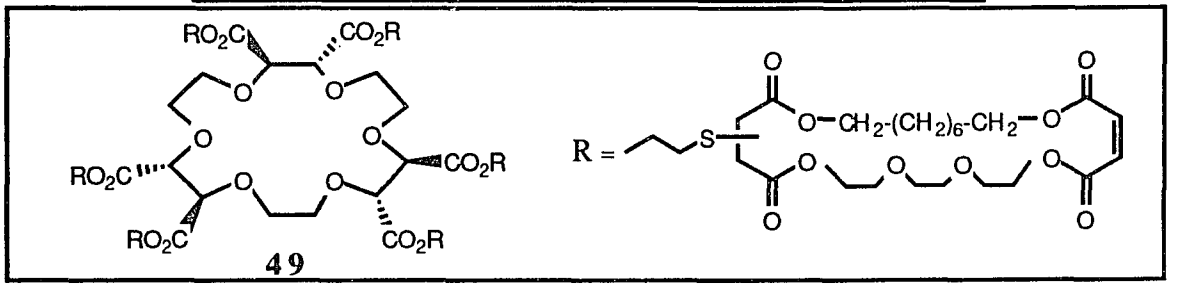
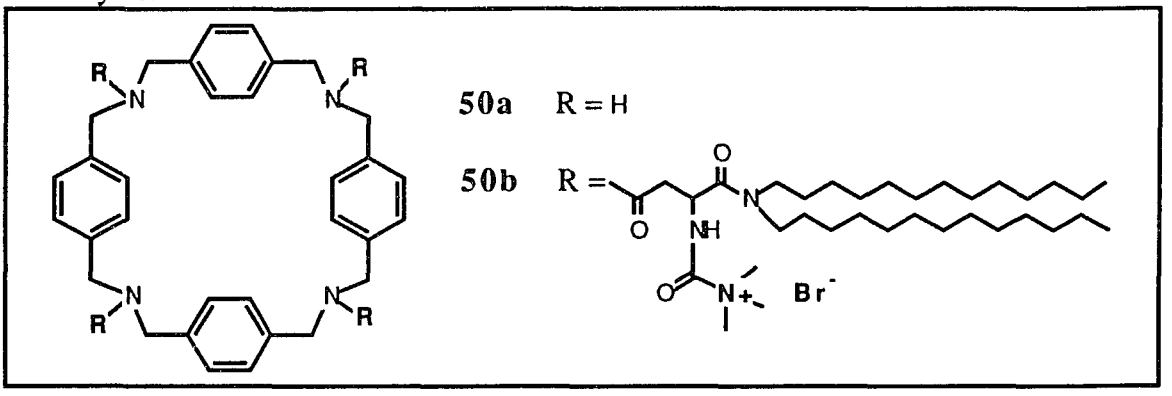


49

Another interesting biomimetic ion channel structure was synthesized by inserting a crown ether of the type **49** into bilayer vesicles.[55] Building channel walls on the crown ether framework above and below the plane of the macrocyclic ring positions the crown ether moiety in the midplane of the lipid bilayer anchoring the 'coordinating tube,' that enables cations or small molecules to pass. This unimolecular ion channel forms stable unilamellar vesicles in the presence of detergents and natural and artificial channel

compounds; however, the cation transport rate is strongly dependent on the presence of the glycol spacers in the channel walls' structure.

Attachment of hydrophobic chains to the tetraaza-[3.3.3.3]paracyclophane skeleton, **50a**, expands the apolar volume and hence the size of the guest that can be bound by induced fit host-guest complexation.[56] The water soluble octopus cyclophanes, such as **50b**, developed by Murakami,[56] form multiwalled bilayer vesicles whose guest binding capabilities of the macrocycles remain unaffected despite the aggregation behavior of the macrocycle.



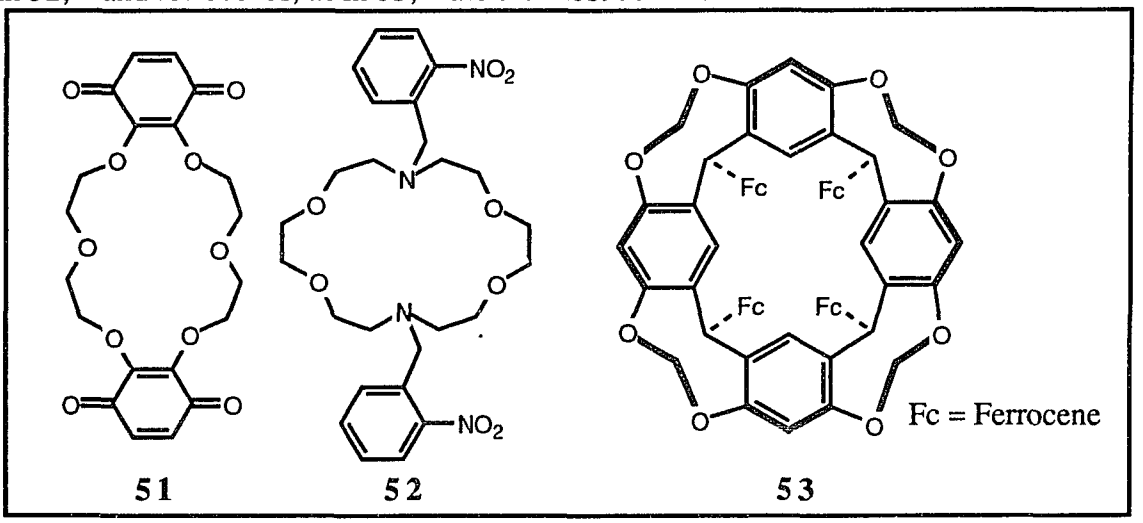
4. Responsive macrocycles.

Interest in the design and synthesis of responsive macrocyclic systems, is mainly geared towards their possible use as biological probes, in the construction of molecular switches, and as indicators. Responsive macrocycles utilize the guest binding ability of macrocycles combined with properties of a reporter moiety that is responsive to a particular stimulus. Selective binding of guest molecules by the macrocycle also needs to be translatable into observable changes in the optical or spectroscopic properties of the system. To be efficient, changes in the electronic absorption, fluorescence, conformational mobility, optical or redox properties of the system must be unambiguously related to the presence of a particular entity or a physical/chemical condition.

4.1. Redox responsive macrocycles.

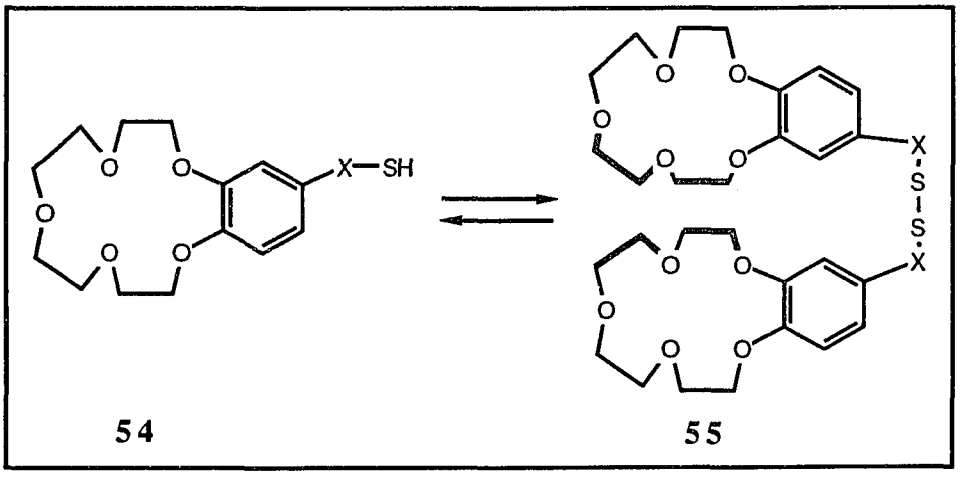
Changes in the electrochemical properties of redox active functionalities incorporated into/linked to macrocycles are utilized to produce redox responsive probes.[57] These changes are manifested as perturbations in the binding properties of the macrocycles, and

as shifts or multiple cyclic voltammetric waves. Quinones, as in **51**,[58] nitrobenzenes, as in **52**,[59] and ferrocenes, as in **53**,[60] are the most common redox active moieties used.



51 **52** **53**

In biological systems, thiol and disulfide functionalities play important roles in cofactor binding, enzyme catalysis, maintenance of the three dimensional structural integrity of proteins, and immunology. Conversion of the thiol to the disulfide functionality, and the reverse process, have been used to produce macrocyclic systems that are redox switchable.[61] Crown ether derivatives **54** and **55** display ion selectivities that are a function of the binding cavity size available in the reduced and oxidized forms of the ligand.

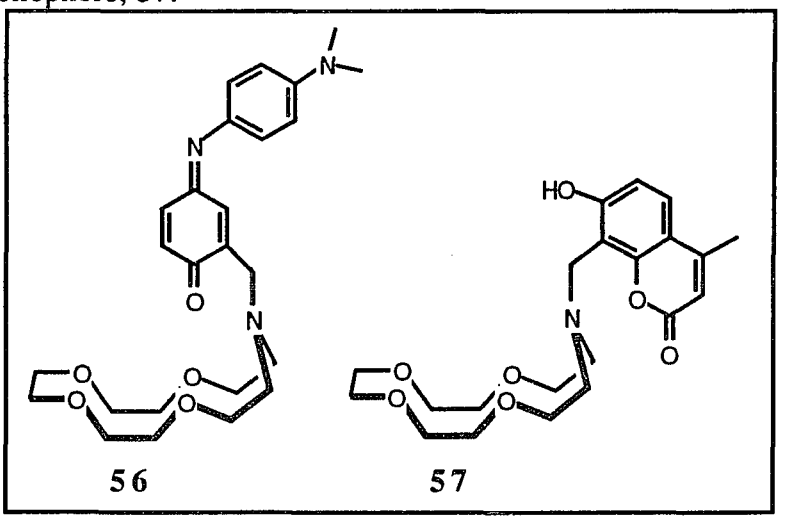


54 **55**

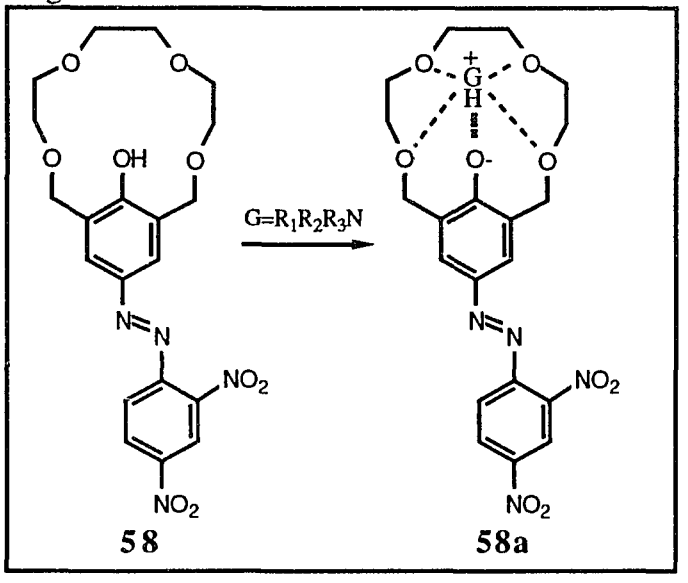
4.2. Guest responsive macrocycles.

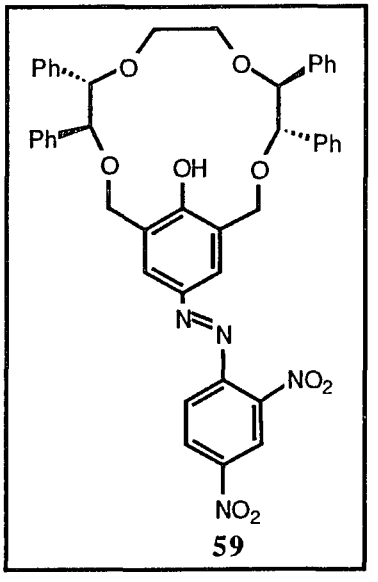
In many cases, the binding of guests to the cavity of the macrocycle induces changes in the spectroscopic properties of the ligand.[62] In **56**, guest binding is signalled by changes in the electronic absorption spectrum of the macrocycle, whereas in **57** the

response is seen in the fluorescence emission spectrum, hence two functionally different systems could be constructed from the same macrocycle. In general terms, the greater the interaction of the guest molecule, in this case cations, with the macrocyclic moiety, the greater is the observable change in the spectroscopic properties of the chromoionophore, **56**, or fluoroionophore, **57**.[63]

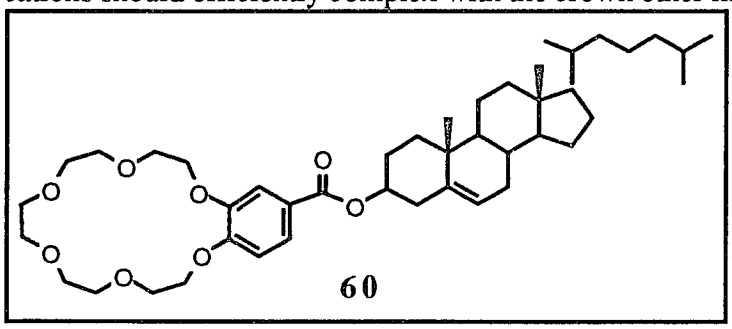


The anions of proton-ionizable ligands, the acerands, such as **58**, form salt complexes or "saltexes," such as **58a**, with organic ammonium ions with concomitant changes in their absorption spectra.[64] These absorption changes are of sufficient magnitude to permit to distinguish among primary, secondary, and tertiary amines by monitoring the absoption changes observed upon saltexation. Chiral chromoacerands, such as **59**, yield diastereomeric saltexes that are useful as color indicators of the absolute configuration of chiral amines.[65]



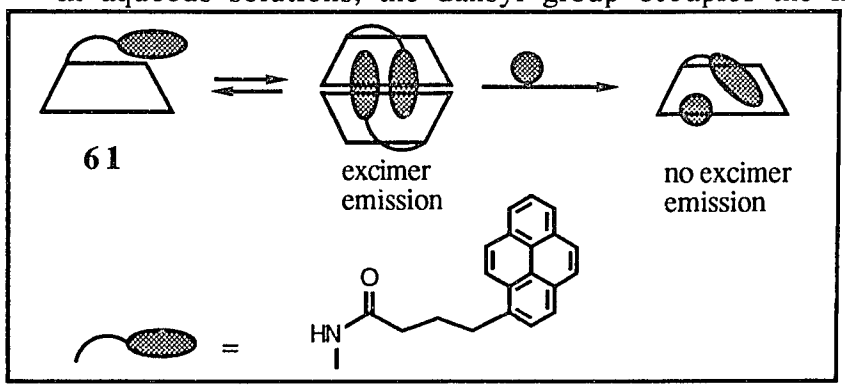


Chirality recognition could be visually monitored in cholesteric liquid crystals containing the steroidal crown ether, **60**.[66] On addition of (R)- or (S)-mandelates, the helical pitch of the liquid crystals, and hence their color, changed in an enantioselective manner. While the magnitude of the wavelength shifts observed depend on the chirality of the counteranions, the mandelates, to observe these shifts, it requires that the accompanying cations should efficiently complex with the crown ether moieties.



60

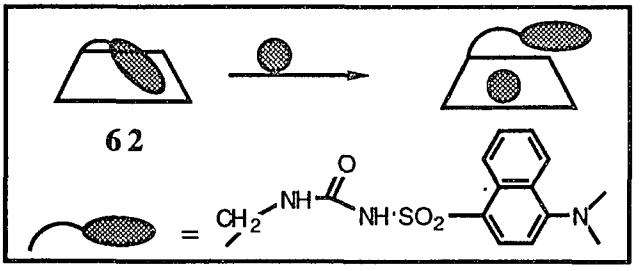
Movement of chromophoric or luminophoric groups on guest binding can result in changes in the absorption or luminescence properties of guest responsive systems. In solution, pyrene derivatized β and ϒ-CDs, **61**, form dimers; the two pyrene units of the dimer interacting to result in excimer fluorescence at 470 nm (Scheme 12).[67] Guest binding induced dissociation of the dimer leads to the reduction of excimer emission and concomitant increase of the monomer fluorescence at 378/396 nm. Therefore, these systems can be employed as sensors to detect and quantitate guest substances by determining changes in the excimer/monomer intensity ratios. In the case of a dansylated β-CD, **62**,[68] in aqueous solutions, the dansyl group occupies the interior of the



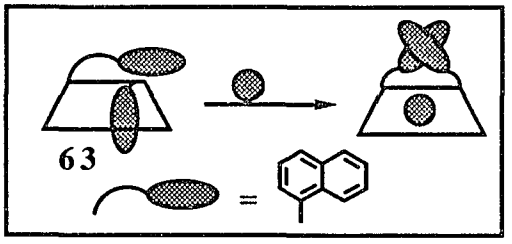
Scheme 12.

hydrophobic CD cavity, and the system fluoresces at 535 nm. On guest binding, the dansyl moiety is displaced into the aqueous medium, resulting in reduction of its fluorescence intensity (Scheme 13). But, with the disubstituted naphthalene derivative, **63**,[69] one naphthalene unit is located inside the CD cavity and the other, outside the cavity resulting in monomer emission only. Binding of guests, such as cholic acid or borneol,

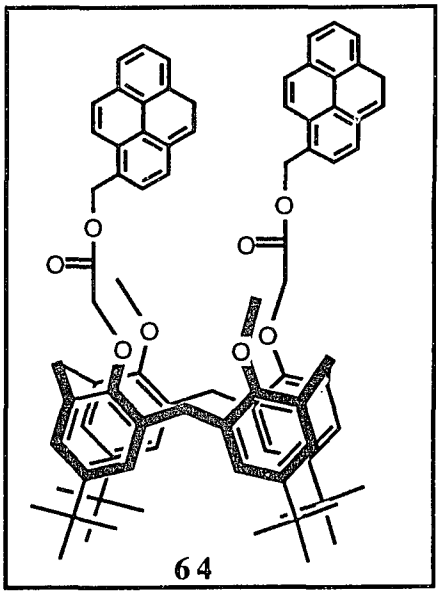
which displaces the naphthalene unit from the cavity, results in excimer emission at 410 nm generated by the naphthtalene units, now located proximally, in the aqueous phase (Scheme 14). Pyrene derivatized calixarene, **64**,[70] could also be used to signal guest binding which forces the pyrene units apart resulting in a decrease of the excimer emission intensity at 480 nm.



Scheme 13

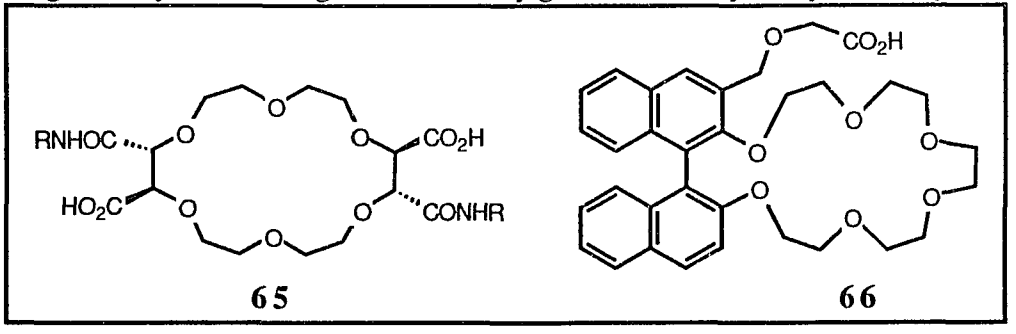


Scheme 14

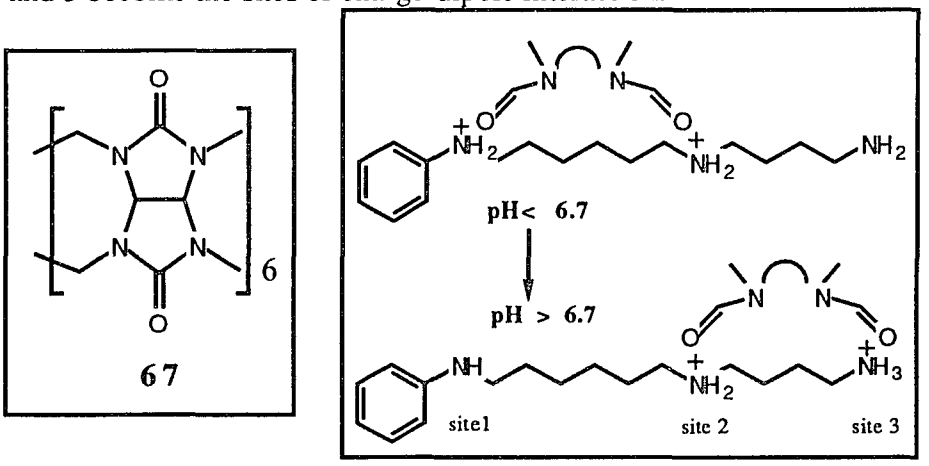


4.3. pH responsive macrocycles.

Crown ether derivatives **65** and **66** containing ionizable carboxyl moieties are typical examples of macrocyclic carriers that mediate pH-dependent cation transport.[71] At a low pH, protonation reduces the ion binding capacity of the macrocycles, while at a high pH it is enhanced. Control of the ion complexation properties of the macrocycles is accomplished by the incorporation of one or more proton-ionizable groups projecting towards the interior or the exterior in the macrocyclic cavity, or located on the periphery of it. Curcurbituril, **67**, synthesized by condensation of urea, glyoxal and formaldehyde,[72] forms a rigid cavity ressembling CD where only guests of strictly complementary structure



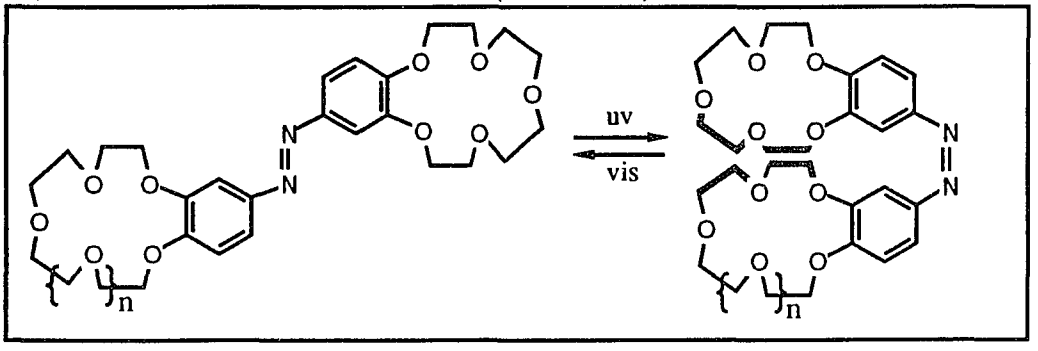
can be complexed. Thus, curcurbituril binds primary ammonium ions (Scheme 15) in a highly site-selective manner: at pH<6.7 binding occurs at sites 1 and 2, whereas at pH>6.7, 2 and 3 become the sites of charge-dipole interaction.



Scheme 15.

4.4. Photoresponsive macrocycles.

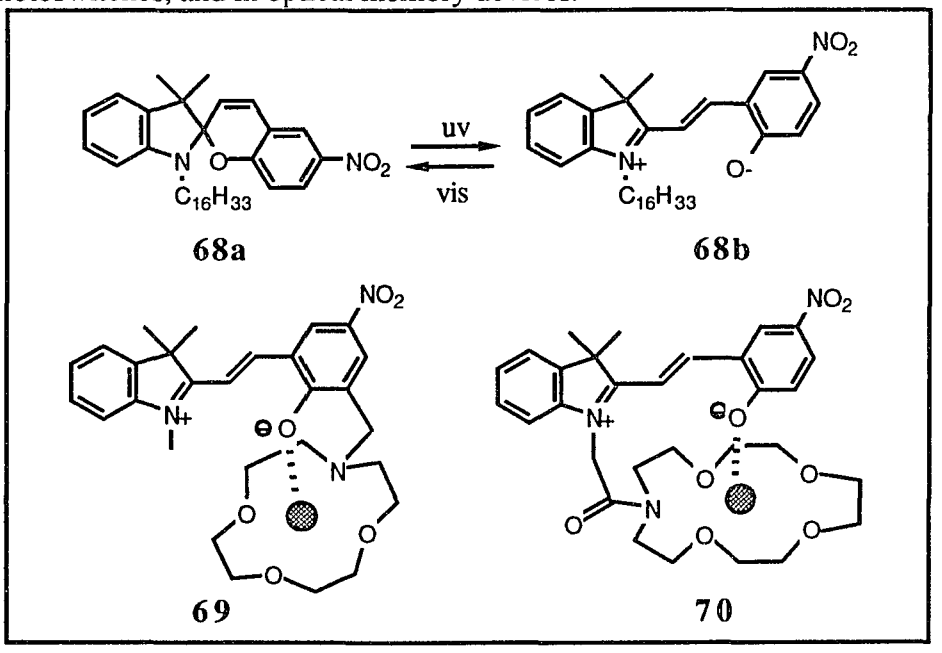
The photochemical isomerization of the azobenzene functionality has been thoroughly explored by Shinkai in the development of photochromic crown ethers[73] such as ditopic azobenzene crown ethers, azocryptands, and photochromic polymeric azobenzene crown ethers. The molecular motion inherent in light-induced the cis-trans isomerization, enables "butterfly crown ethers" to bind preferentially larger cations in the cis form, and smaller ones in the trans form (Scheme 16).



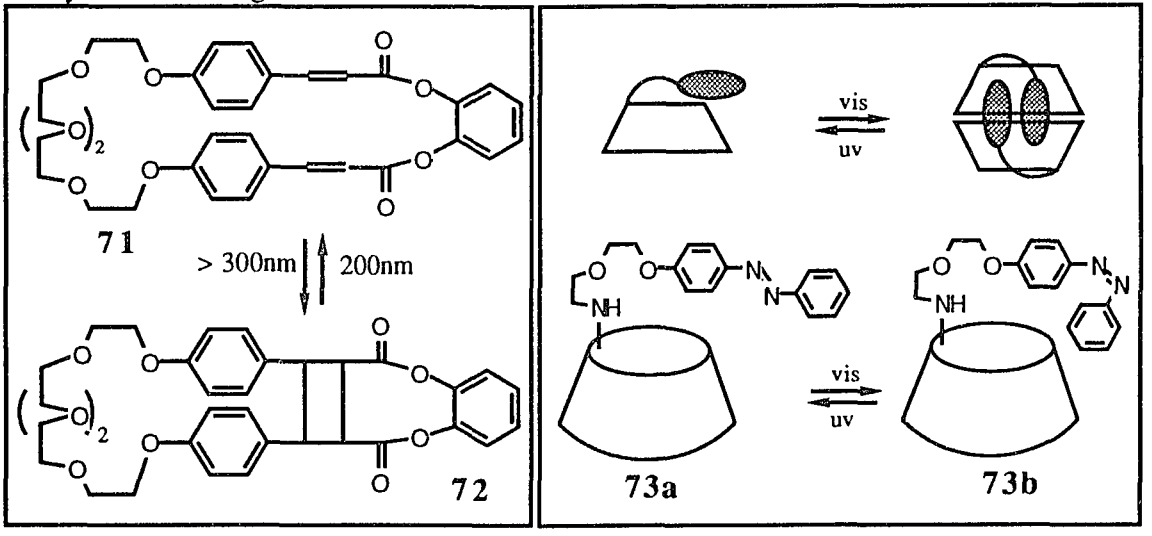
Scheme 16.

The photoinduced potential changes observed when photochromic spirobenzopyrans **68**[74] were incorporated into membranes led to the development of photoresponsive membranes,[75,76] containing the crowned spirobenzopyrans, **69** and **70**. In the case of spirobenzopyran **68a**, uv irradiation induced ring opening to the more stable, zwitterionic merocyanine form, **68b**. But with the macrocyclic analogs, complexation to

alkali metal cations alone induced the ring opening of the spiropyrans to merocyanines **69** and **70**, accompanied with a red shift in the absorption maxima. Therefore, the crowned spirobenzopyrans may find applications as sensors for biologically important alkali metal ions, as photoswitches, and in optical memory devices.



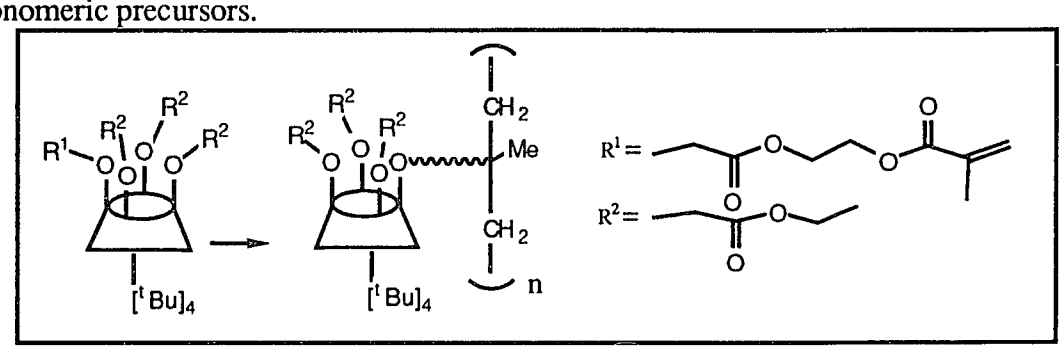
Cation selectivity, controlled via an intramolecular [2 + 2] cycloaddition, was achieved using the macrocycles **71** and **72**;[77] photochemical transformation to the cyclobutane derivative **72**, results in the deformation of the crown ether ring, which then loses the complexation and selectivity properties for K^+ and Rb^+ cations. In **73**, trans to cis isomerization facilitates molecular association to the dimeric form.[78] Photoisomerization to the trans isomer forces the disruption of the dimer and frees the CD cavity to bind with guest molecules.



5. Polymeric macrocycles.

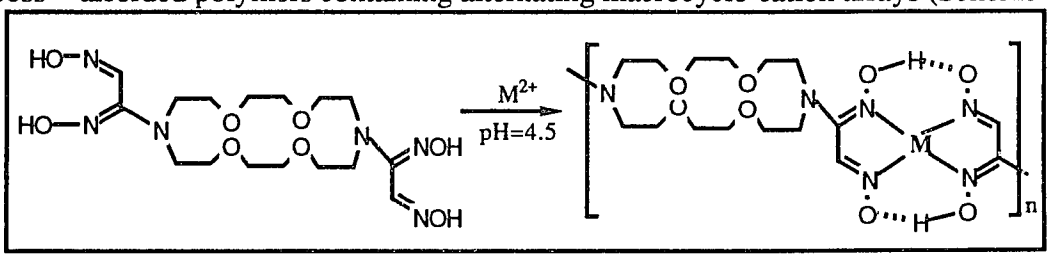
Polymeric macrocyclic systems possess unique structural, catalytic, separation, photochemical, electrochemical, and complexation properties that may prove to be very important in the development of new materials. To test this, polymeric phthalocycanine,[79] porphyrin, [80] and crown ether [81] macrocycles have been synthesized.

The synthesis of polymeric calixarenes[82] (Scheme 17) was straightforward once well established methodologies were at hand for the synthesis and derivatization of their monomeric precursors.



Scheme 17

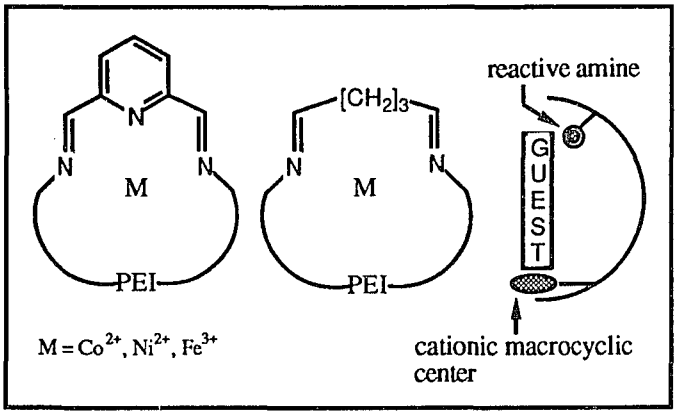
Pendant arm complexation of Ni^{2+} or Cu^{2+} ions to bis-dioximes via a 'cascade' process[83] afforded polymers containing alternating macrocycle-cation arrays (Scheme 18).



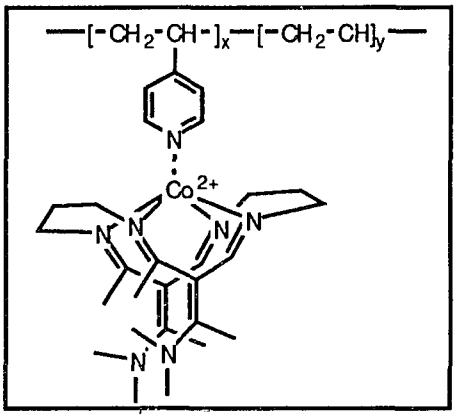
Scheme 18

Condensation of polyethylene imine (PEI), that contains ca. 25% primary amines, with dialdehydes or diketones in the presence of cations yielded hydrophobic, polymeric macrocyclic imines (Scheme 19).[84] In these polymers the guests are complexed by interacting with the cationic macrocyclic centers and reactive amine functionalities. Catalytic properties in ester deacylation studies are displayed by a number of these complexes. Macrocyclic imines, of the 'lacunar cyclidene' variety, when complexed to copolymers of 4-vinylpyridine (Scheme 20), form stable oxygen adducts,[85] hence their high potential in the mimicry of cytochromes and oxygen transport proteins.

New methodologies for the synthesis of chiral polymeric crown ethers, and polyrotoxane systems of threaded α-cyclodextrins, and the use of porphyrins in the construction of two-dimensional polymers were recently reported.[86]



Scheme 19



Scheme 20

6. Macrocyclic Imines.

Metalloenzymes are ubiquitous in nature. Hemocyanin, the oxygen carrier of molluscs and arthropods, consists of a dinuclear copper center, the catalytic center of cytochrome P-450 consists of an iron porphyrin complex while dopamine β-hydroxylase, ureases, and tyrosinase possess two cationic centers at the active site. Photosystem II, on the other hand, consists of a tetranuclear manganese center. Synthetic mimicry of these biological systems is important in the development of artificial enzymes, new materials, and solar energy conversion devices.

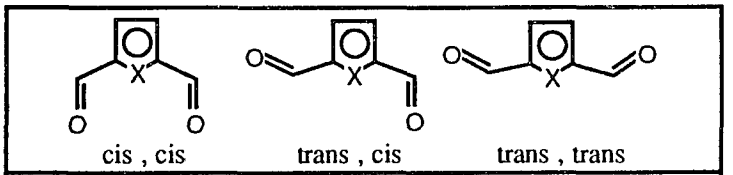
In cytochrome P-450, the iron center is reduced then reoxidized to a hypervalent oxidation state. Therefore, while designing ligands that are to serve as models of the metalloenzymes, consideration must be given to the changes in the oxidation states that occur at the metallocenter. Stabilization of these changing oxidation states is best accomplished by employing a ligand capable of conformational mobility while at the same time retaining its coordinative properties, so that the differing oxidation states can be accommodated with a minimal distortion of the ligand. The pre-organized structure of flexible macrocyclic imines could fulfill these requirements making them suitable to mimic metalloenzymes.

6.1. Syntheses.

Until recently, macrocyclization via the template directed [2+2] condensation of dicarbonyls with diamines was the usual route to prepare macrocyclic imines. Absence of the cation template led to the formation of unidentifiable, polymeric materials. From the beginning, alkaline earth metals were used extensively as templating agents.[87] Smaller

transition metals were found to be ineffective in generating the [2 + 2] macrocyclic entities, giving instead the [1+1] macrocyclic imines.[88] Larger cations, e.g., Pb^{2+} or Ba^{2+}, yield dinuclear imino macrocycles.[89] The preparation of mononuclear transition metal complexes of [2+2] macrocyclic imines relied heavily on the transmetallation of the preformed alkaline metal complexes of the macrocycles or on the transmetallation of the preformed, kinetically labile [2 + 2] lanthanide complexes.[90] The introduction of exogenous ligating groups into the lateral units of aliphatic diamines or using 2,6-diformyl phenol derivatives afforded polynuclear transition metal complexes of the macrocyclic imines.[91]

Metal-free macrocyclic imines would provide versatile building blocks for construction of whole arrays of novel macrocycles with functionalities derivable from the imines. However, at the initiation of the work presented here, there were no adequate methods to synthesize them. While this work was in progress, a conformer distribution study of heteroaromatic dialdehydes, potential head groups in the imino macrocycles, was reported (Scheme 21).[92] Since the *cis-cis* conformers are ideally oriented to undergo [2+2] cyclizations, the extent to which they are present in solution can be employed to predict the propensity of heteroaromatic headgroups to yield metal-free imino macrocycles in solution. Thus, 2,6-pyridinedicarboxaldehyde having only small amount of *cis-cis* conformer is expected to undergo [2+2] cyclization only to a negligible extent, whereas pyrrole and thiophene headgroups with the 80% *cis-cis* content would be the best candidates.

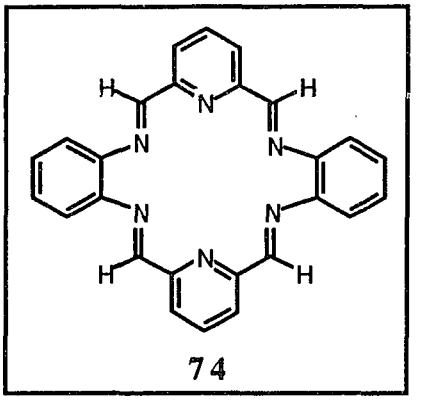


	X			
	N	NH	O	S
c , c	<5%	80%	50%	80%
t , c	5%	20%	25%	20%
t , t	95%	---	25%	---

Scheme 21.

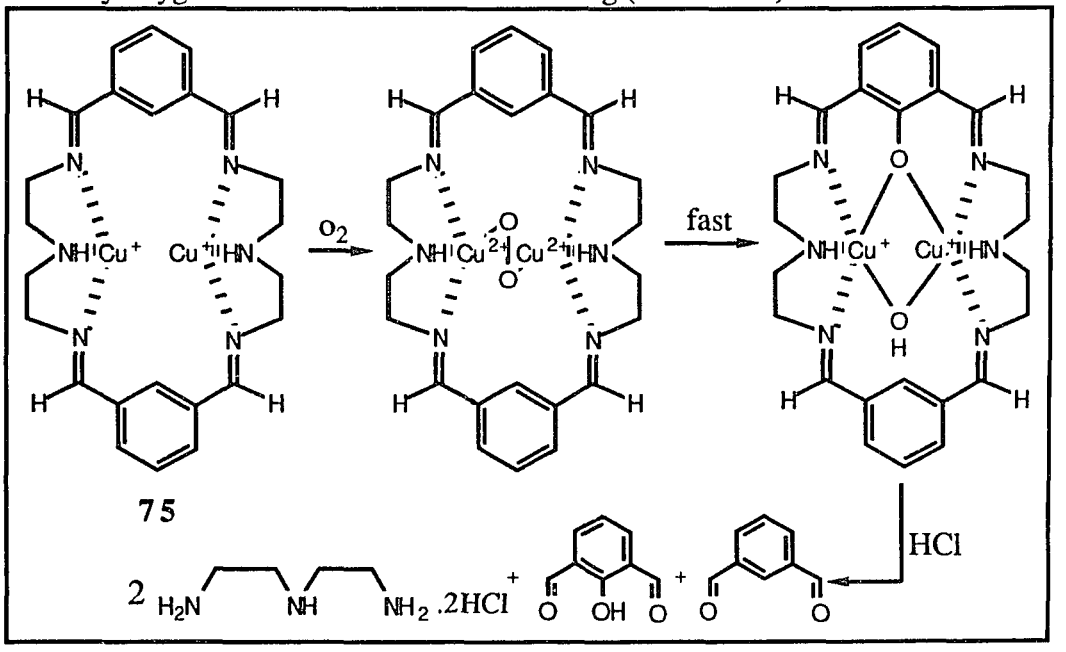
The first report of a metal free macrocyclic imine that utilized pyridine as the head group appeared in 1986.[93] Template directed [2+2] cyclization, metal ion exchange and

the competitive complexing properties of the imine and 18-Crown-6 for potassium ions were used to produce the metal free macrocyclic imine **74**. Evaluation of the complexation properties of this ligand with a variety of cations has now become possible, as well as direct comparison of the coordinating ability of the imino group to cryptands, spherands and crown ethers could be made.[94]



74

In 1989, the first report of a macrocyclic tyrosinase model, the binuclear Cu^{+} macrocyclic imine complex, **75**, was published.[95] Similar to tyrosinase and dopamine-β-hydroxylase, the complex **75** inserts oxygen by forming a peroxo-bridged Cu^{2+} species, followed by oxygen insertion into the aromatic ring (Scheme 22).

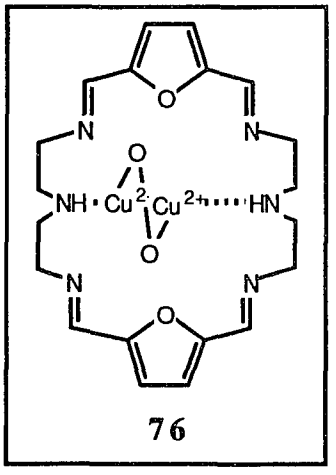


75

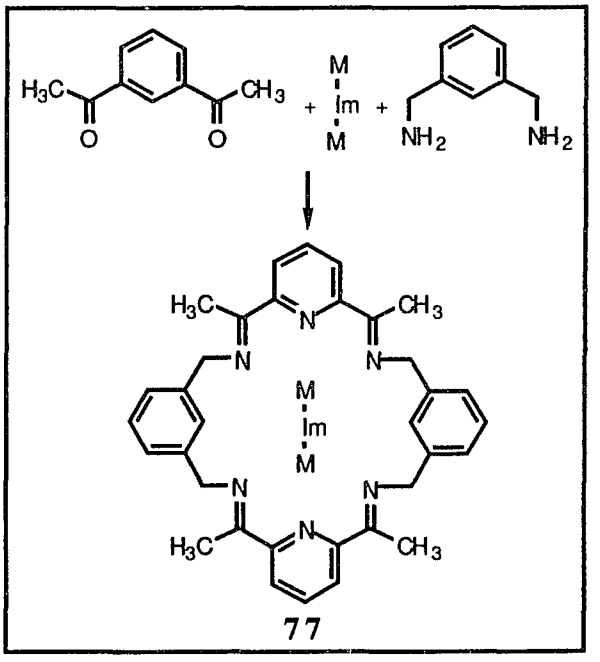
Scheme 22.

Substitution of the benzene rings in **75** by furans prevents aromatic hydroxylation.[96] Oxygen uptake and uv/vis studies indicate that rapid oxygen absorption by the binuclear complex yields peroxybridged Cu^{2+} species, **76**. However, the latter, unlike the analogous species obtained in the case of **75**, **76** yields only degradation

products. These examples, tyrosinase model **75**, and oxygen carrier **76**, demonstrate the versatility of macrocyclic imines that can control reaction pathways by providing rigid ligands with highly preorganized structures.



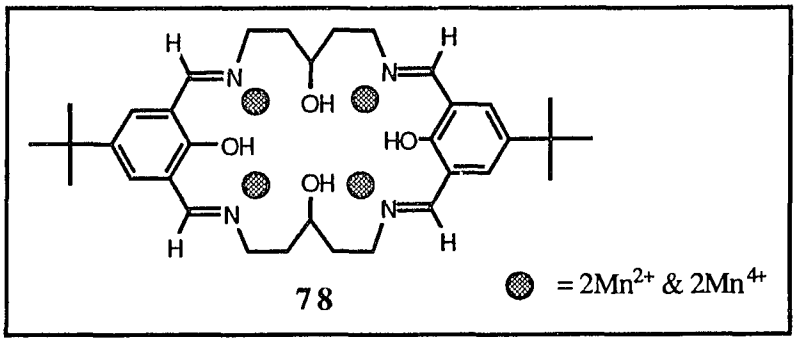
76



77

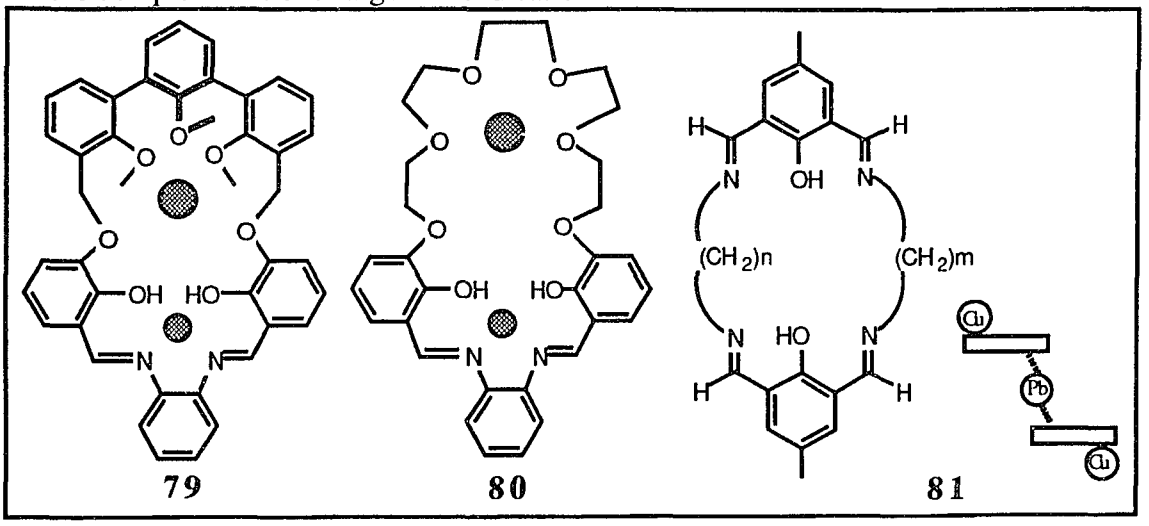
In order to develop synthetic mimics of nickel containing ureases, preorganization of two metal centers (M) by a bridging imidazol unit, (Im), was employed to effect a "template" synthesis[97] of the macrocyclic imine complex, **77**.

Polynuclear macrocyclic imines, i.e., which possess more than two metal centers, were synthesized from 2,6-diformylphenol derivatives and aliphatic diamine building blocks via the template directed methodology[98] The number of metal centers that could be introduced into the macrocyclic cavity was determined by the chain length and number of coordination sites available on the diamine employed.[99] The tetra-manganese complex of the macrocyclic imine **78**, is a photosystem II mimic,[100] but analogs of **78** with zinc, copper, and nickel centers to study electron transfer processes, could also be prepared in a similar manner.[101]



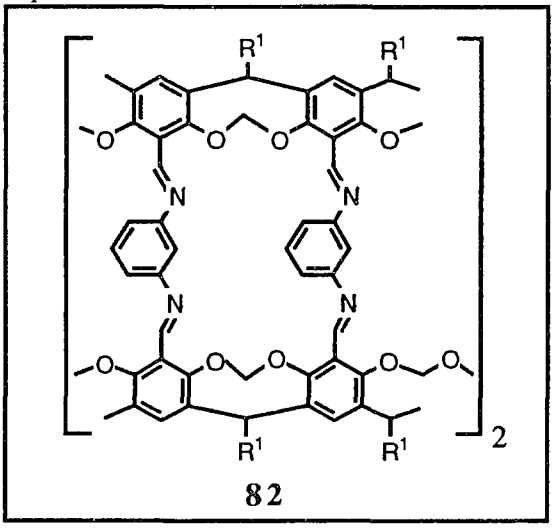
78

Heterodinuclear complexes in which metal centers of different characteristics were inserted into the same macrocyclic cavity by combining salophene building blocks with hemicarcerand, in **79**, and with crown ether, **80**, moieties were synthesized to serve as models for metalloproteins like superoxide dismutase and peptidases.[102] To form heterocationic complexes using **81**, the free cavity of each macrocycle serves as a perch for the complexation of a larger second cation.[103]



79 **80** **81**

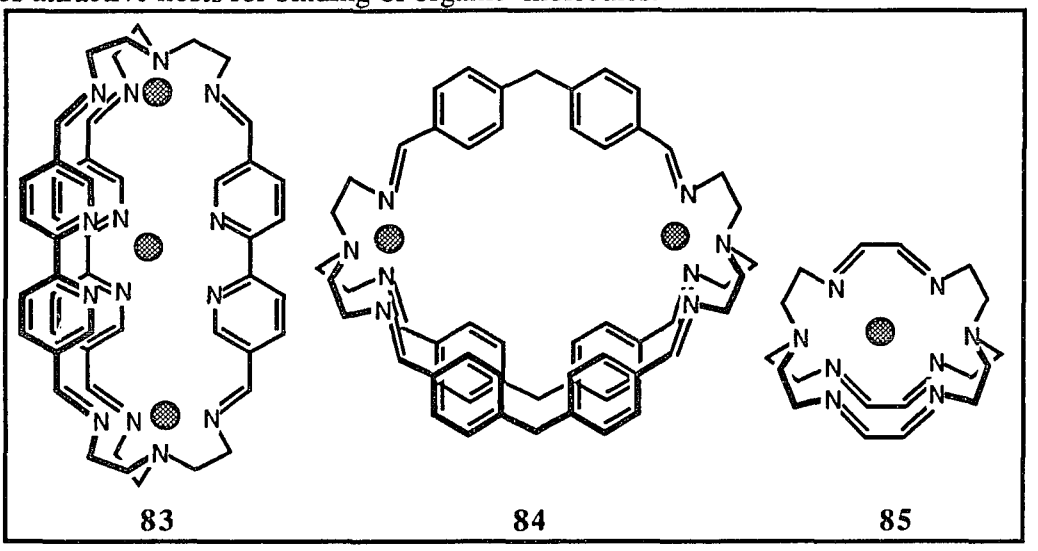
Beyond its direct use in the synthesis metalloenzyme mimics, macrocyclization by the formation of an imine bond is also useful in the synthesis of other macrocyclic systems. For instance, in the synthesis of the hemicarcerand **82**, Schiff base moieties were used as linker groups.[14f]



82

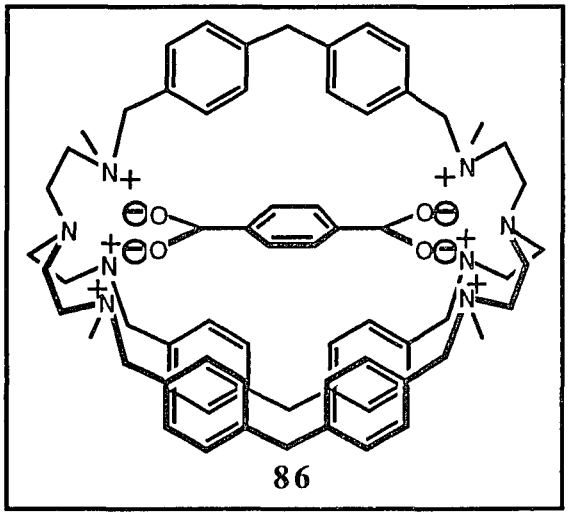
Macrocyclization via [3+2] condensations of dicarbonyls with triamines is the most direct way to synthesize macrobicyclic Schiff base cryptands such as **83-85**.[104] Numerous other macrocycles of this type that utilize pyridine, furan, pyrrole, phenol and ferrocene and even carotenoid type dialdehydic moieties have been reported.[105] The

stability of the complexes formed can be directly attributed to the increased coordinative ability of the cryptand ligand. Cavity size and cation center interspace are controlled by the dicarbonyl used in the [3+2] condensation as in **83-85**; The cavity size makes these imines attractive hosts for binding of organic molecules.

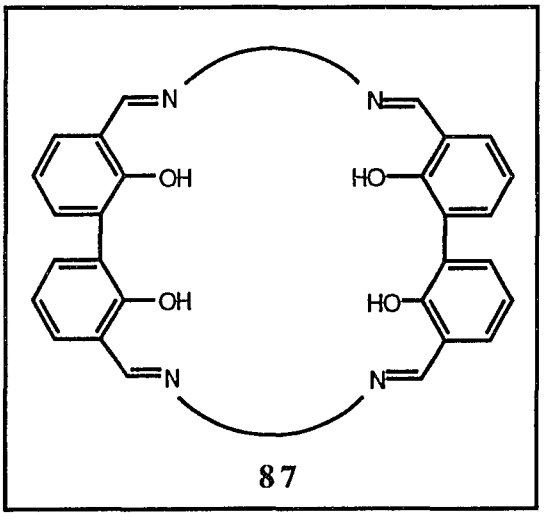


83 **84** **85**

Reduction of the hexa-imine macrocycle, **84**, to the protonated amine produced yet another macrocycle, **86**, which is capable of linear molecular recognition properties for anions.[106]

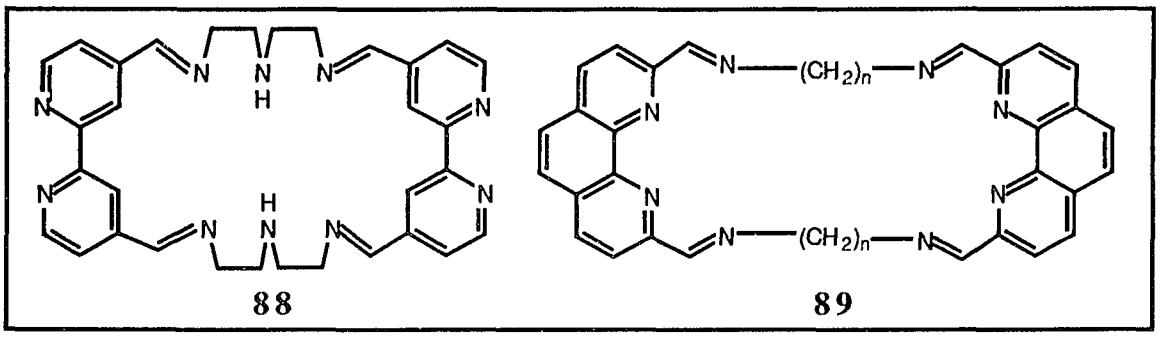


86



87

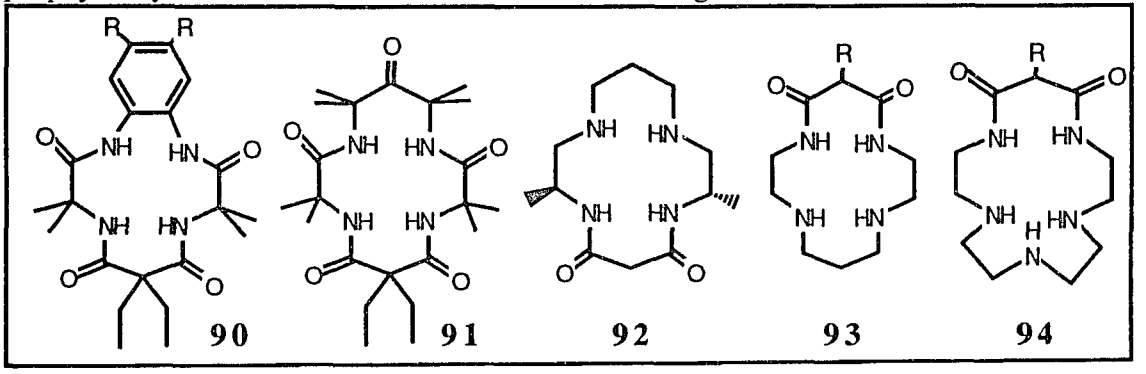
The bisbiphenyl macrocyclic imine, **87**, was synthesized by a template directed synthesis using boron.[107] The macrocyclic cavity has eight possible sites for guest interaction via hydrogen bonds in addition to the inherent chirality of the biaryl moiety. In addition to the internal macrocyclic cavity, two additional cationic binding or interaction sites are possessed by **88**.[108] The assembly of **88** and **89** into supramolecular arrays, or multiple cationic complexes may be possible, producing unique photochemical and/or electrochemical properties.



7. Macrocyclic Cytochrome P-450 Mimics.

Cytochrome P-450 enzymes are involved in the oxidation of endogenous and exogenous substrates, detoxification, lipid biosynthesis, and polyaromatic hydrocarbon activation.[109a] Mimicry of P-450 activity in stereoselective and regioselective fashion during alkene epoxidation and cleavage, and aromatic and aliphatic hydroxylation reactions will have numerous applications in synthetic organic chemistry. Porphyrin ligands have been used extensively[109b] among the macrocyclic systems studied so far as oxidation mimics. Cyclophane capped and 'picket fence' porphyrins mimic the oxidation properties of cytochrome P-450.[110] Cyclodextrin sandwiched,[111] cyclodextrin linked,[112] and cyclodextrin capped porphyrins,[113] have been shown to mimic the oxygenation activity of metalloenzymes. Photocatalytic enantioselective oxidation was also achieved using a porphyrin linked cyclodextrin.[114] Transition metal Schiff base salen complexes of iron, cobalt, manganese, and nickel in conjunction with external oxidants have been used extensively to mimic the oxidation properties of P-450.[115]

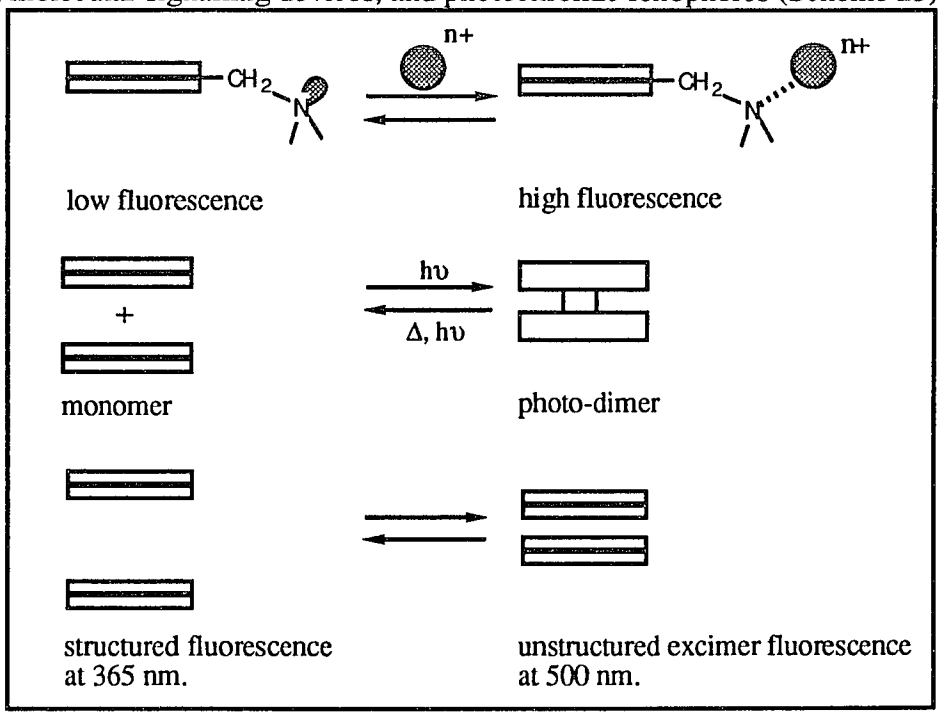
Formation of a hypervalent metal-oxygen species is a common intermediate in both the mimics and the natural P-450 systems. The strong donor capacity of the amide functionality, its stability, and flexibility, make it an excellent alternative to the rigid porphyrin systems. The amides **90-94** can stabilize higher oxidation states of some



transition metals by adopting a distorted square planar or square pyramid conformation.[116] Stereo- and regioselective epoxidations, double bond cleavage and hydroxylation can be effected with the use of square planar Ni^{2+} complexes of the macrocyclic amides **92-94**.[117]

8. Anthracenyl macrocycles.

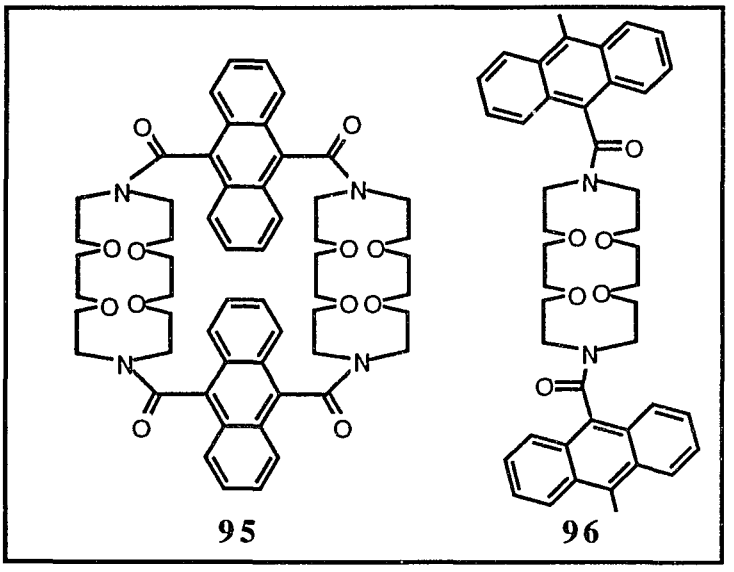
Anthracenyl macrocycles by virtue of their luminescence properties and the presence of cavities to bind guest molecules, have high potential to function as molecular probes, molecular signalling devices, and photochromic ionophores (Scheme 23). Among



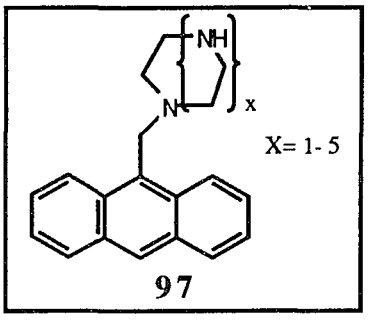
Scheme 23.

the most successful applications are: Anthracenophane cryptands, **95** and **96**, have been used as lipid phase transition sensitive, fluorescent probes to study the thermodynamic and kinetic properties of lecithin membranes.[118] Intense, chelation enhanced fluorescence (CHEF) effects (20-190 fold) were observed upon protonation or complexation with transition metals of anthrylazamacrocycle, **97**, even in 100% aqueous solution.[119] The explanation for the strong enhancement is that on electronic excitation, the unavailability of the benzylic nitrogen lone pair in **97** either through protonation, or through chelation, results in reversion to the ground state not by photoinduced electron transfer (PET) pathway, but via fluorescence. Other anthracenyl macrocycles synthesized recently serve

as anion and pH sensitive indicators, and as fluorescent sensors for biologically important alkali cations.[120]

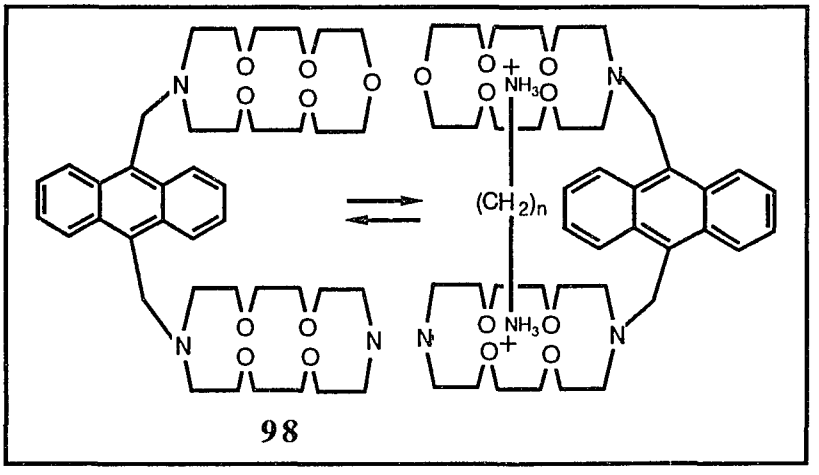


95 96



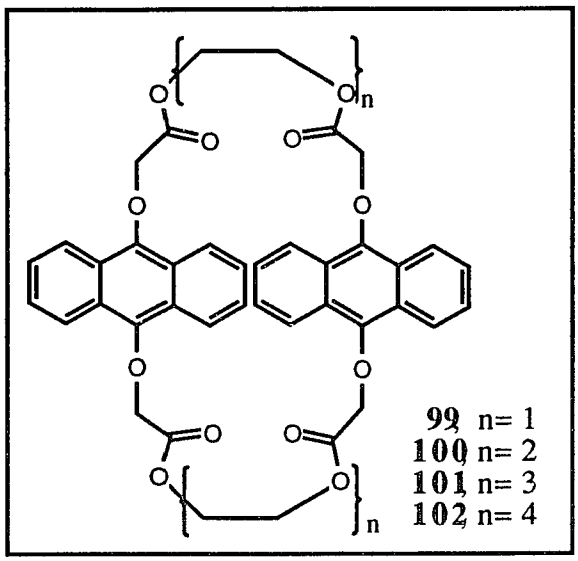
97

Fluorescence "off-on" signalling for alkanediammonium ions is displayed by crown anthracenophanes of the type **98**.[121] Upon binding, the alkanediammonium guest acts as a molecular trigger to turn on the fluorescence, but only when both nitrogens are protonated.

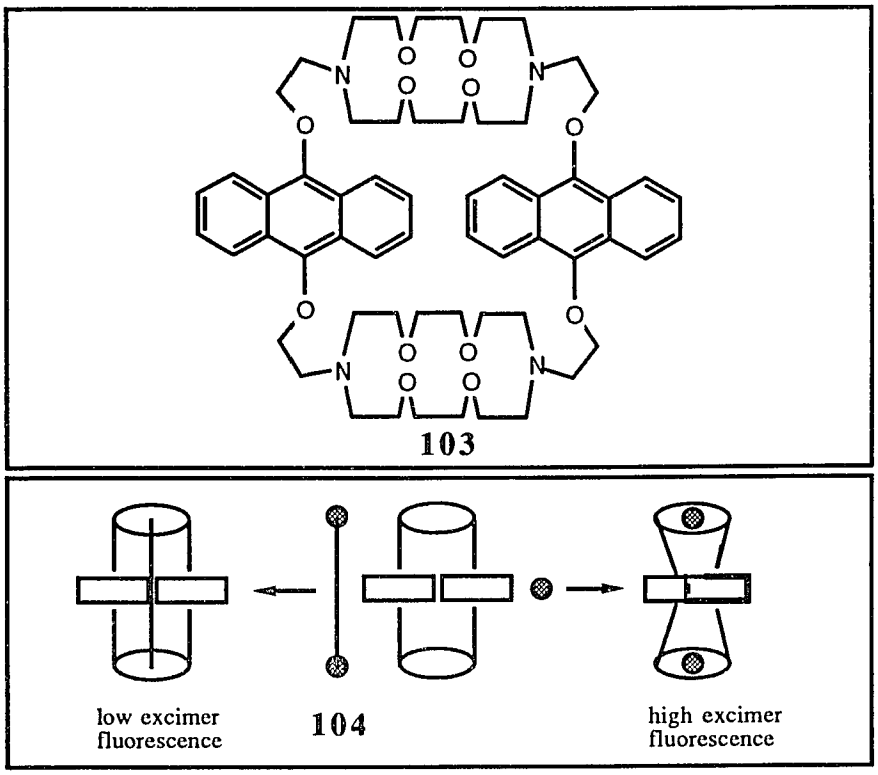


98

The fluorescence spectrum of anthracenyl derivatives is also useful in assessing the solid and solution state conformational properties of anthracenyl macrocycles.[122] Close juxtaposition (stacking orientation) of two anthracene moieties results in unstructured excimer fluorescence at ca. 500 nm. Solution and solid state conformational properties of **99-102** were determined by evaluating the monomer and excimer emissions, and by X-ray data. The molecular recognition properties of **103** can be readily followed by monitoring the emission characteristics of the system.[123] This metal free ligand displays the characteristic structured fluorescence of the anthracene moiety in

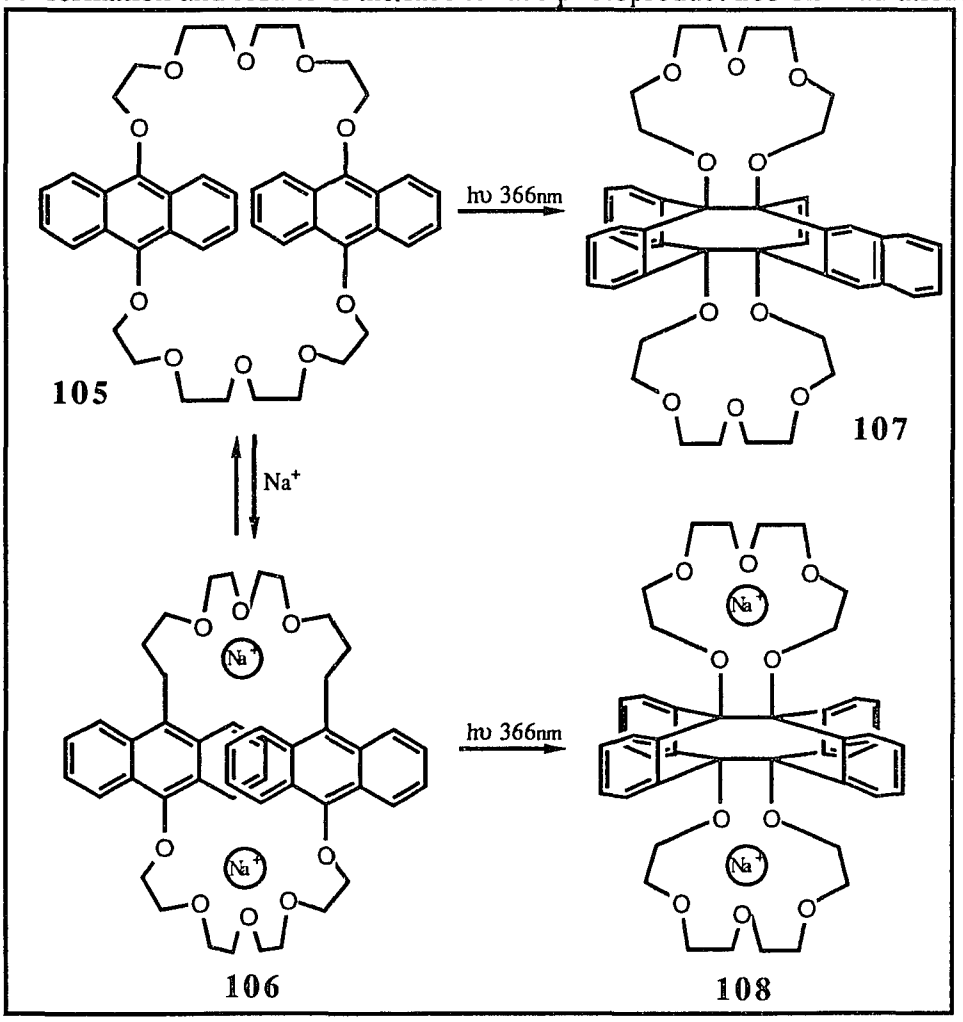


addition to the structureless band at 530 nm. On the addition of the Rb^+ cation, complexation forces the anthracene moieties to move closer to each other (Scheme 24), and the fluorescence spectrum is dominated by the excimer emission. On the addition of the alkanediammonium ion, **104**, the crown ether units serve as suitable hosts for the cationic end groups, while the intervening methylene units separate the anthracene units, resulting in the structured emission to be maximized.



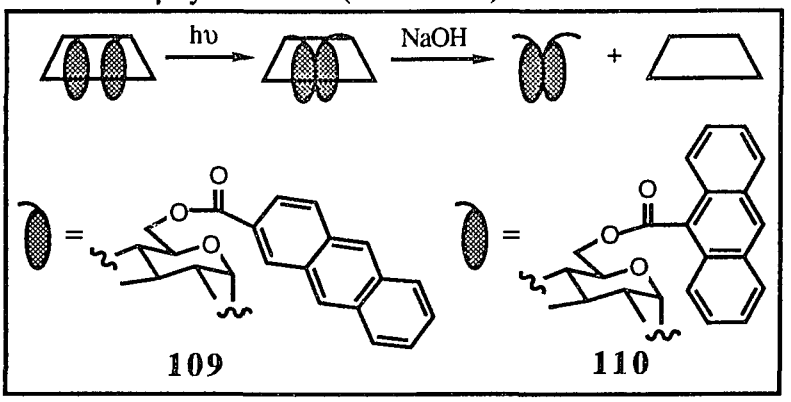
Scheme 24.

In solution, both the characteristic structured monomer and the unstructured excimer emissions are observed for the metal free ligand, **105**.[124] On the addition of sodium cations, the excimer fluorescence at 570 nm predominates at the expense of the monomeric emission. Complexation of sodium ions by the ligand forces the anthracene rings to lie in a parallel orientation facing each other, resulting in the excimer emission observed. The photochemical reactivity of **105** can be modified by the addition of Na^+ ions. Irradiation of **105** yields the photocyclomer **107**, but on addition of Na^+ ions to **105,** the rigid 2:1 complex, **106,** is formed, which positions the anthracene rings in face to face conformation and results in the face to face photoproduct **108** on irradiation.



Stereo and regio control over photochemical transformations can be achieved in enclosed cavities, in organized media, and in the solid state.[125] Stereochemical and regiochemical control during photochemical transformations was achieved by Ueno using disubstituted anthracene γ-cyclodextrins **109** and **110**.[126] The product distribution

profile is dependent on solvent polarity, the presence of a guest molecule, and the substitution pattern of the γ-cyclodextrin (Scheme 25).



Scheme 25.

9. Macrocycle-DNA interactions.

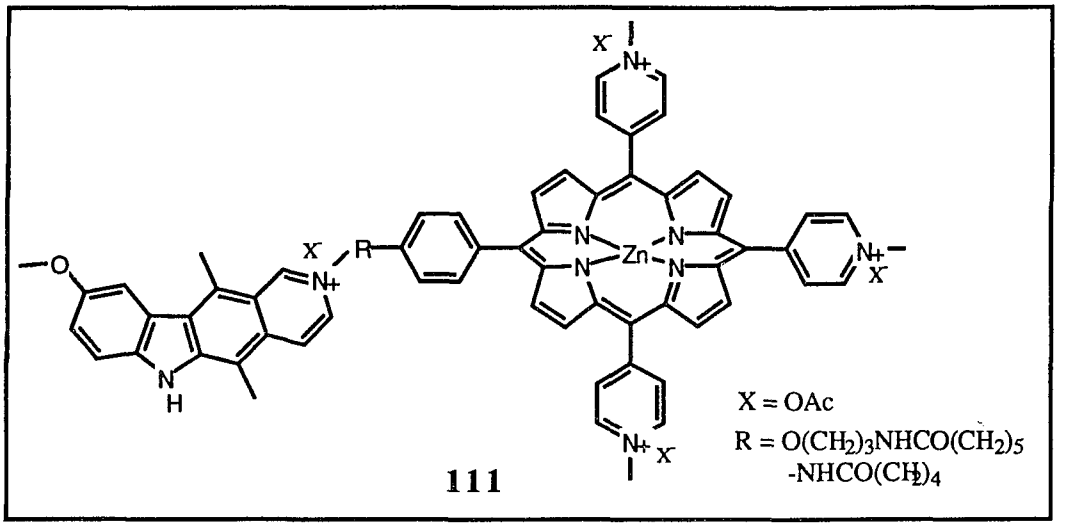
Site specific DNA recognition and cleavage agents will have future application as new tools to probe DNA' structure and in the development of novel therapeutic agents.[127] Noncovalent interaction of DNA with a probe can be thought of as the interaction of the host, DNA, with its guest, the probe. In the design of the probes, a combination of electrostatic, hydrogen bonding and π stacking interactions must be evaluated to permit the fine-tuning of the probe-nucleic acid interactions and to achieve site specificity.

Chemical probes for local DNA structures have been designed by Barton.[128] Chiral phenantroline-Ru^{3+} probes were shown to distinguish, and selectively cleave the Z and B forms of DNA. Site selective and sequence selective cleavage of DNA can also be accomplished by the footprinting and triple helix formation methodologies developed by Dervan.[129] Tethering the reactive center, to a known groove binder, intercalator, or sequence specific oligonucleotide, results in selective binding, and cleavage of DNA. The selective cleaving abilities of propargylic and allenic sulfones have also generated considerable interest.[130]

Macrocycles designed to interact with DNA have been synthesized and representative examples will be given below. Their mode of interaction with DNA may vary from an essentially Coulombic type, to multiple binding modes, in which intercalation, groove binding, and Coulombic interaction all do play roles.

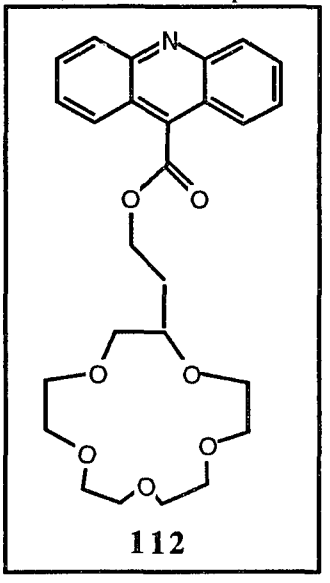
Cationic porphyrins have previously been shown to bind and cleave DNA.[131] The porphyrin conjugate **111**,[132] shows superior binding ability compared to other porphyrin

probes. Thus, binding of the ellipticine moiety to DNA by intercalation, and binding of the anionic phosphate backbone with the cationic porphyrin moiety by electrostatic interactions, produces a ligand with superior DNA binding abilities, in addition to being a photoactivatable DNA cleaver.

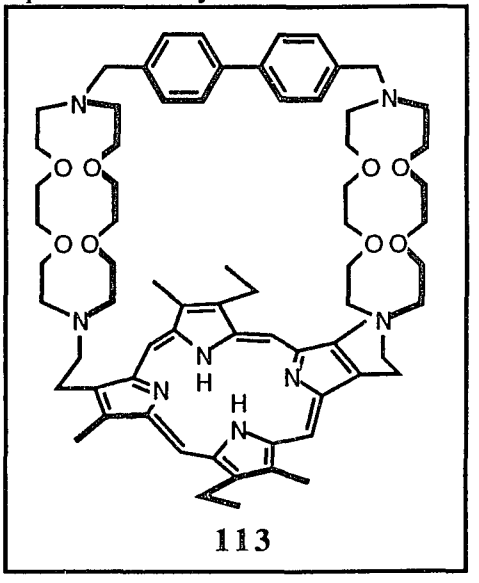


111

The acridine derivatized crown ether, **112**, does not interact with DNA in the absence of cations. However, upon addition of Na^+ or K^+, in a manner analogous to that of cationic porphyrins, the anionic DNA backbone interacts with the cationic macrocyclic ligand. In addition, the acridine part of the probe binds by intercalation.[133]



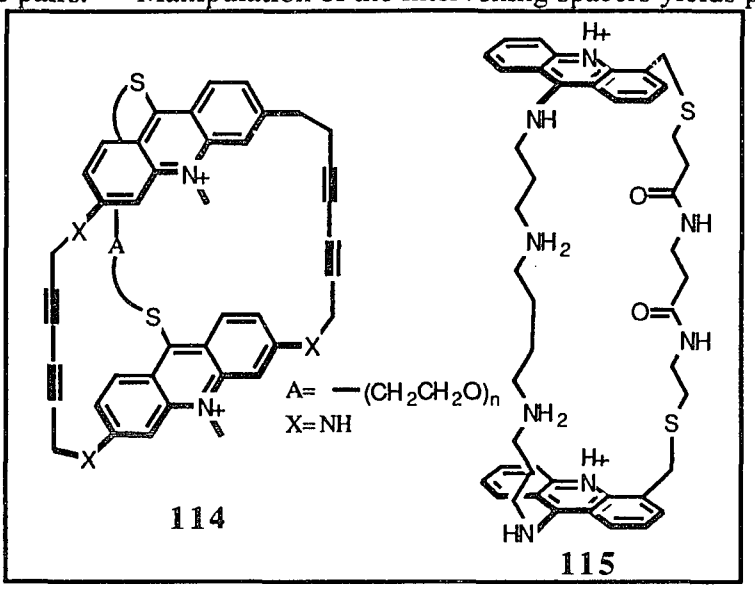
112



113

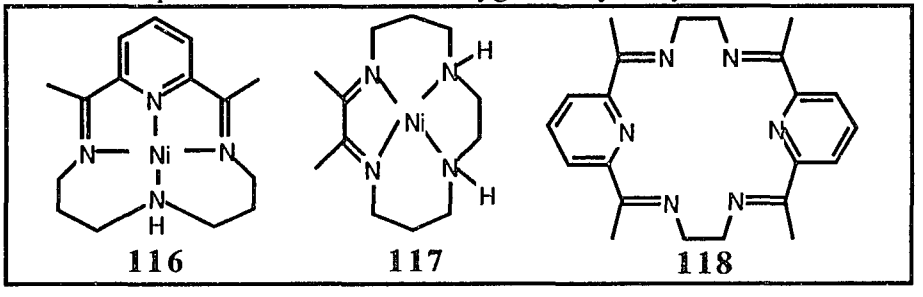
In the macro-tetracyclic ligand **113**, two levels of specificity are achieved by sandwiching the porphyrin moiety in a cryptand cage structure.[134] First, single stranded polynucleotides are bound in preference to the double stranded polynucleotides by **113**. Secondly, the steric bulk of **113,** forces binding in duplex DNA to occur at the large major groove.

Macrocyclic bisintercalands, **114** and **115** contain two sites, that bridge contiguous base pairs.[135] Manipulation of the intervening spacers yields probes that may



be major or minor groove binders, single strand as opposed to double stranded DNA binders, or specific for a particular base sequence via Hoogsteen type hydrogen-bonding interactions triple helix formation.

Square planar Ni^{2+} complexes of the macrocyclic imine **116**, and the cyclam **117**, selectively cleave DNA at guanine residues.[136] Higher oxidation states of nickel and its binding by the easiest oxidizable of the bases, guanine, are the major contributors to the observed DNA base specific nicking. Guanine residues, made accessible through the formation of loops, mismatches, duplex termini, and bulges are also cleaved selectively by **116**. The macrocyclic imine can thus be used as a probe for secondary DNA structures. For the lanthanide^{3+} complex of **118**, selective catalytic cleavage for RNA over DNA is not dependent on the production of reactive oxygen or hydroxyl radicals.[138]



Macrocycles consisting of oligodeoxynucleotides have been recently shown by Kool to recognize and stabilize DNA by triple helix formation.[139] The catalytic properties of nucleic acids may eventually become an integral part of these macrocycles and should add to the repertoire of macrocycles that interact and cleave nucleic acids.

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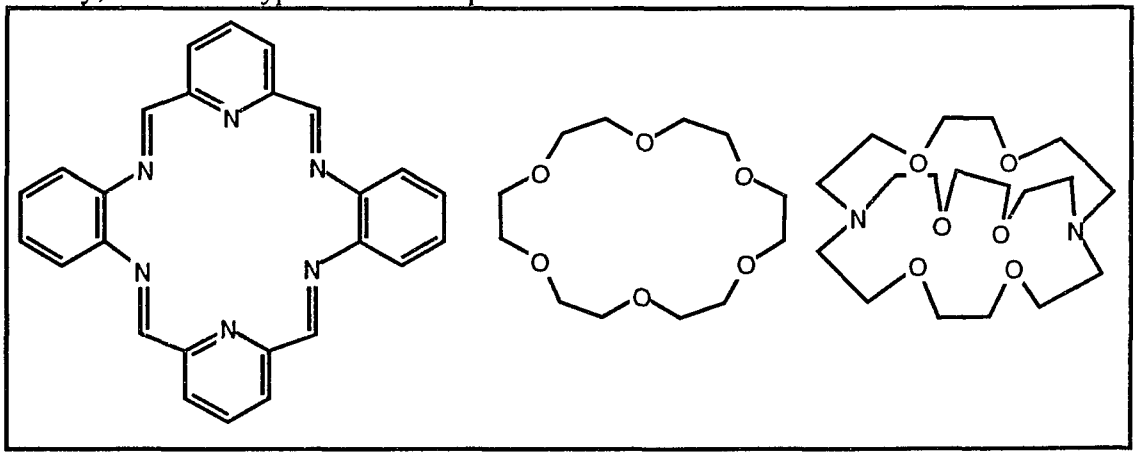
Chapter 2: Results and Discussion

2.1-Macrocyclic Imines:

An analysis of the existing literature on macrocycles clearly shows that the field is dominated by crown ethers, cyclodextrins, porphyrins, cryptands, cyclophanes, and calixarenes There is an acute need for the syntheses of novel macrocyclic systems which may serve as more useful alternatives to these macrocyclic systems. In doing this, derivatization must be readily accomplished, while at the same time, maintaining the basic macrocyclic structures.

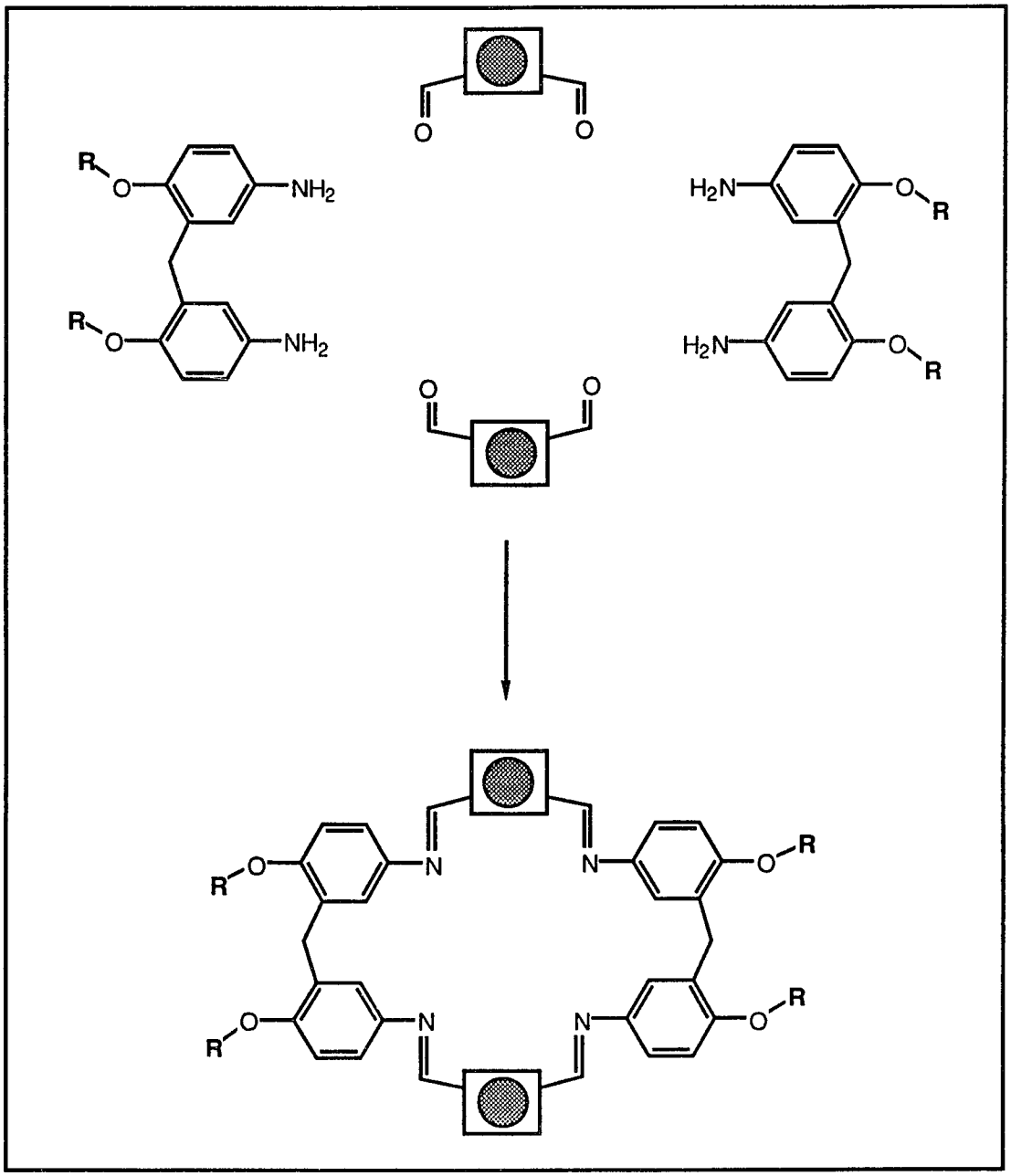
The imine nitrogen is a superior ligand compared to the ether oxygen, or amino nitrogen for cation complexation. The superior complexing ability of the tetra-imine for potassium ions, compared to the crown ether and cryptand derivatives, is entirely due to the near permanent dipole nature of the imino functionalities of the ligand.[1] Complete encapsulation of the cation by the ligand is a secondary factor in determining complex stability, when the cryptands are compared to the imine.



Apart from being an excellent functionality for cationic complexation, a considerable number of organic reactions can be performed on the un-coordinated imino functionality. Two basic reactions are, oxidation to the oxaziridine, and reduction to the secondary amine. In addition, there is no methodology available, at present, in the literature to prepare in a systematic fashion, metal-free sidearmed macrocyclic imines.

With metal-free macrocyclic imines now readily available via the facile [2+2] macrocyclization (Scheme 1), the study of the cation-ligand interaction is not limited to the

use of cations that can act as templates in the synthesis, or on ligands that can undergo transmetallation reactions. Solubility properties of the macrocyclic imines could also be modified by sidearm derivatization. From this, it affords one the unique opportunity



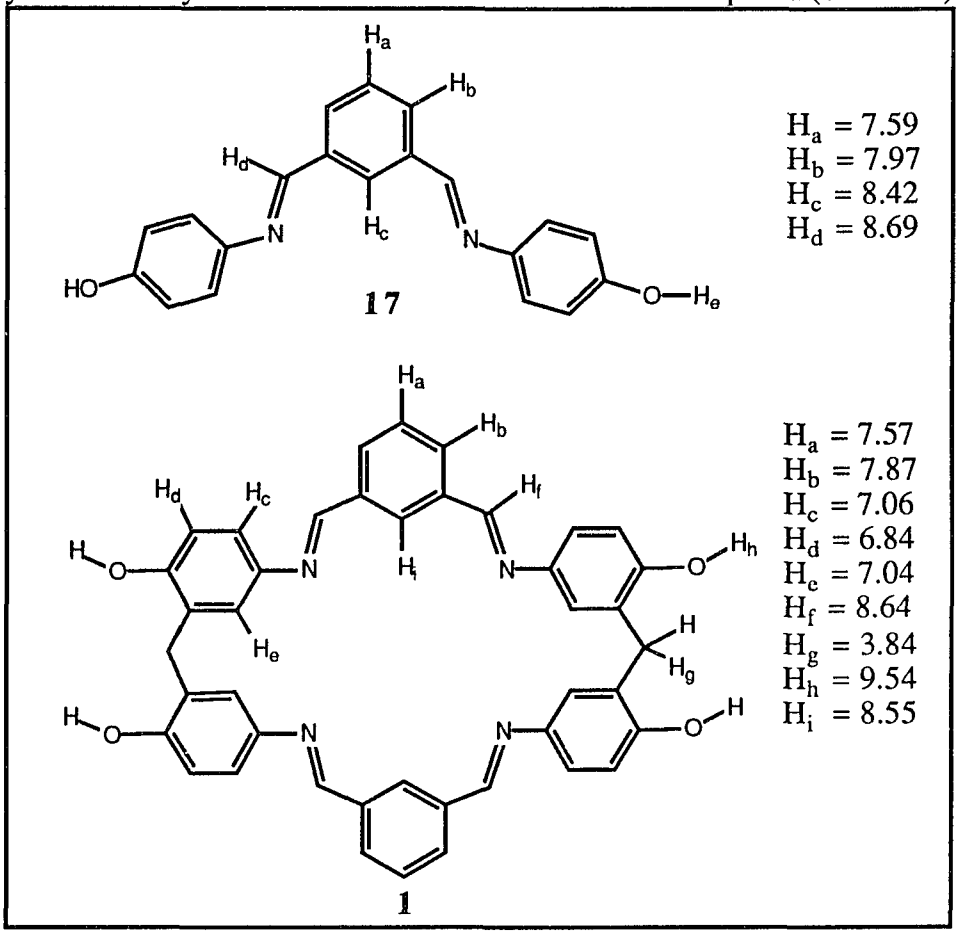
Scheme1. General [2 + 2] assembly of metal-free macrocyclic imnes.

of looking at the molecular recognition properties of the macrocyclic metal-free imine cavity in both polar and in apolar environments. The usefulness of the sidearm derivatization in this authors view, lies in chameleon like behavior of the macrocycle on

derivatization, that displays properties useful in processes from enzyme catalysis to material science.

The direct synthesis of metal-free macrocyclic imines has been limited to the use of dialdehydes that in solution are found to be in the *cis, cis* conformation. In Scheme 1, the preorganization of the amino functionalities is believed to be partially responsible for the success of the [2+2] macrocyclization assembly. Thus, the general feasibility of the assembly is no longer dependant exclusively on the dialdehyde conformation, but on the diamine.

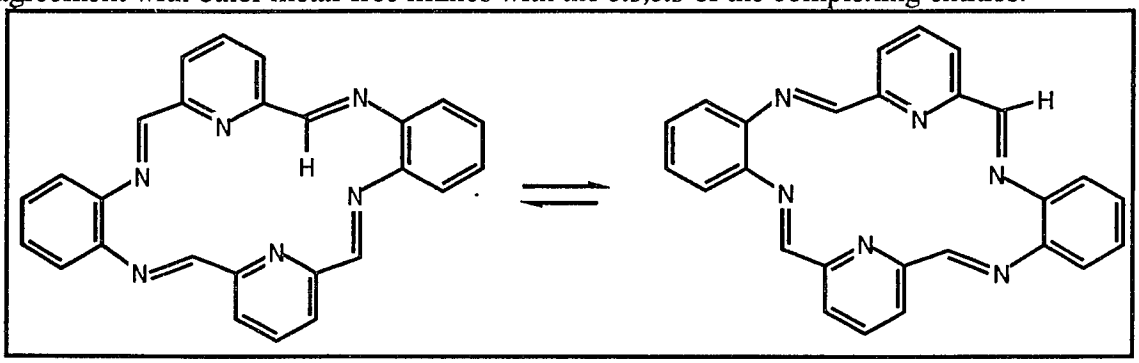
Using **1** as a prototype, and comparing it to the podand, **17**, some definitive conclusions can be made about the structural nature of the macrocycle. The idea of looking at the macrocyclic imines as two complexing entities linked by methylene bridges is partially confirmed by the near identical nature of their ^{1}H nmr spectra (Scheme 2).



Scheme 2. ^{1}H nmr comparison of **1** and **17**.

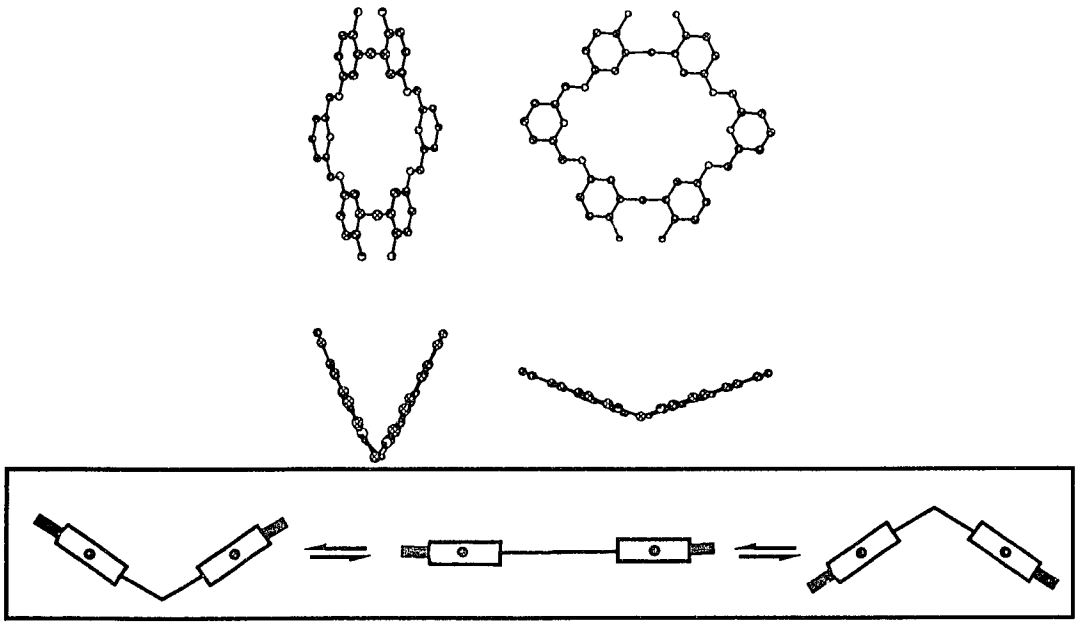
It is known that some pyridine derived metal-free macrocyclic imines exist in solution state as equilibrated mixtures of *cis* and *trans* conformers.[2] In solution, the tetraimine, (Scheme 3), exists as an ellipsoid equilibrated mixture, with the imine adopting

a *trans, cis* conformation at each pyridine head group. In such a conformation one imine proton is buttressed against the lone pairs of two nitrogen atoms, resulting in a average spectrum of the two conformers. The net result is seen in the ^1H nmr shift of the imine proton, which is observed at 9.3 ppm. The imine resonances around 8.6 ppm are in agreement with other metal-free imines with the *cis,cis* of the complexing entities.



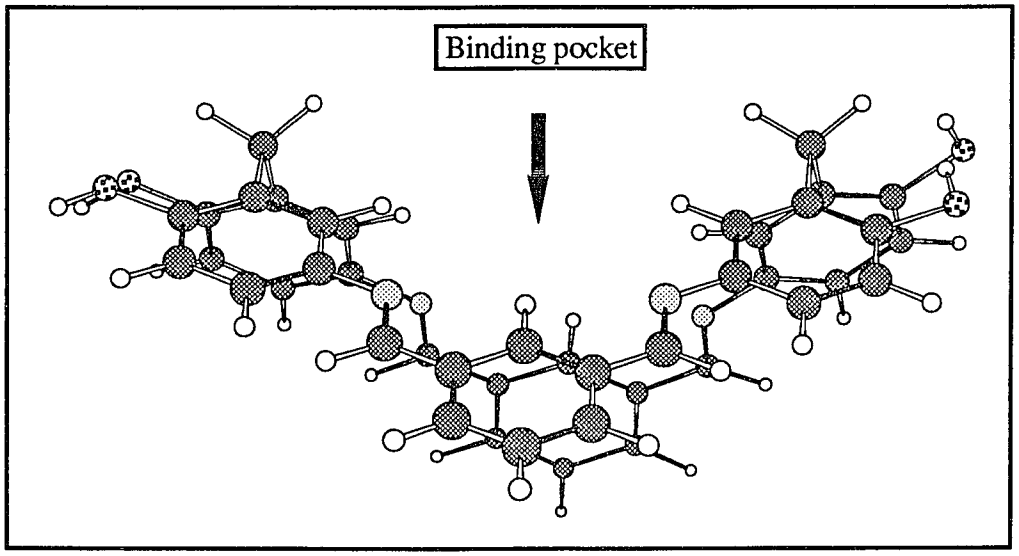
Scheme 3. Conformational equilibrium of metal-free macrocyclic imine.

Type 1 and 2 macrocycles, are in a state of conformational equilibrium similar to that exhibited by some calixarenes.[3] The ring flip around the intervenening methylene unit, results in a single ^1H nmr resonance at 4.0 ppm, at room temperature for the two methylene protons. The flexibility of the macrocycles also lends itself to exploitation in guest (cation) binding. As the macrocyclic cavity is not rigid, the two intervening methylenes create a hinge effect around the macrocyclic core. In going from the 'V' shaped conformer to the inverted 'V' conformer, (Scheme 4), passage may be possibly through an almost circular 'O' conformer, or as in the case of the calixarenes, it may involve other intermediate conformers.



Scheme 4. Conformational equilibrium present in type 1 and 2 macrocycles.

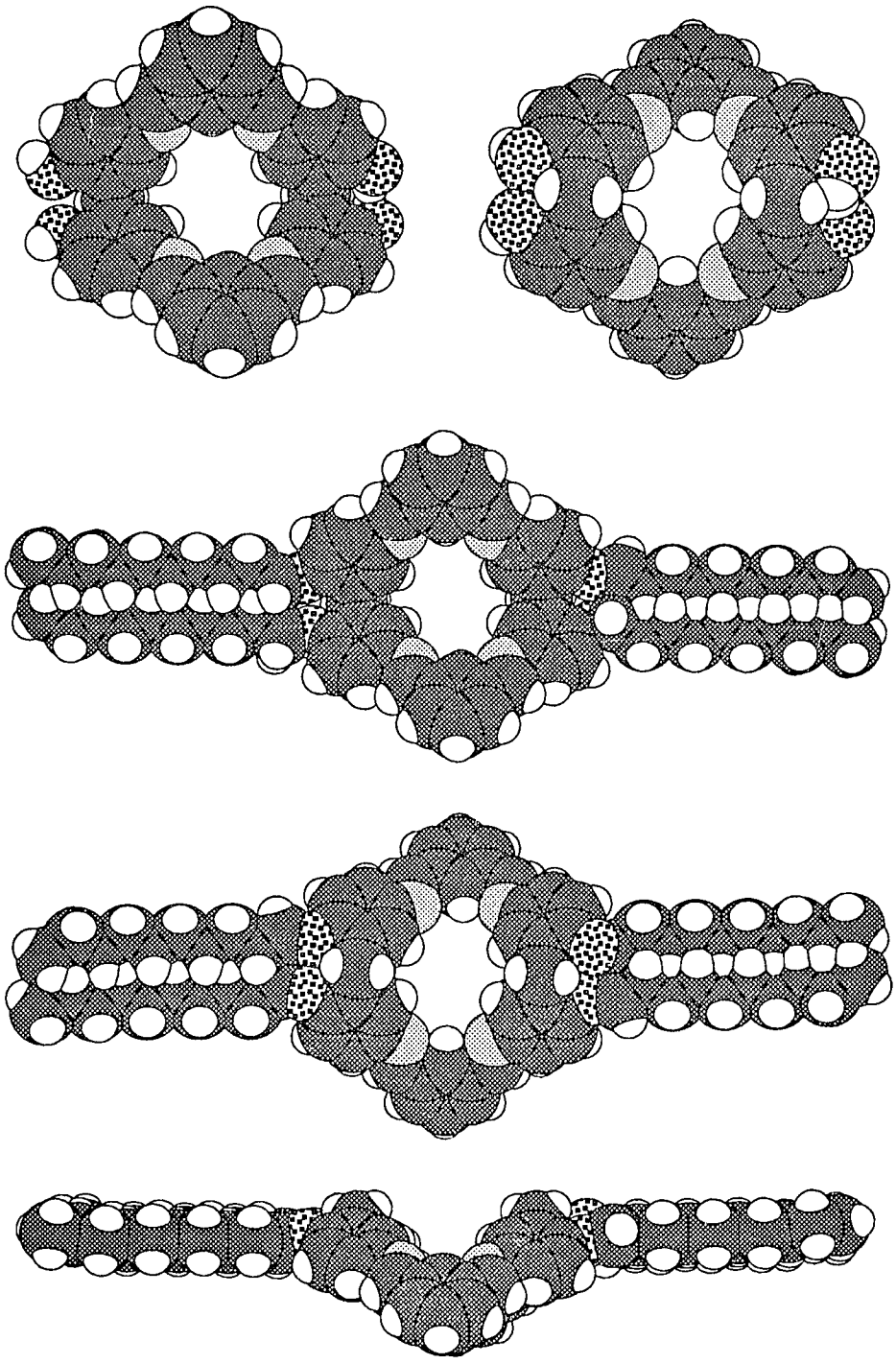
Again using **1** as a prototype, one can consider the central macrocyclic core as two halves of a cut bagel linked by two methylene hinges. From CPK models, fully extended, the macrocyclic core for both type 1 and 2 will have the imino functionalities positioned into the central cavity (Scheme 5). The cavity size is at a maximum with a diameter of ca. 8 Å. In the 'V' form, the size of the macrocyclic cavity is at its minimum, with the imino functionalities lining the binding pocket, about 6 Å deep.



Scheme 5. Binding core of macrocyclic imines.

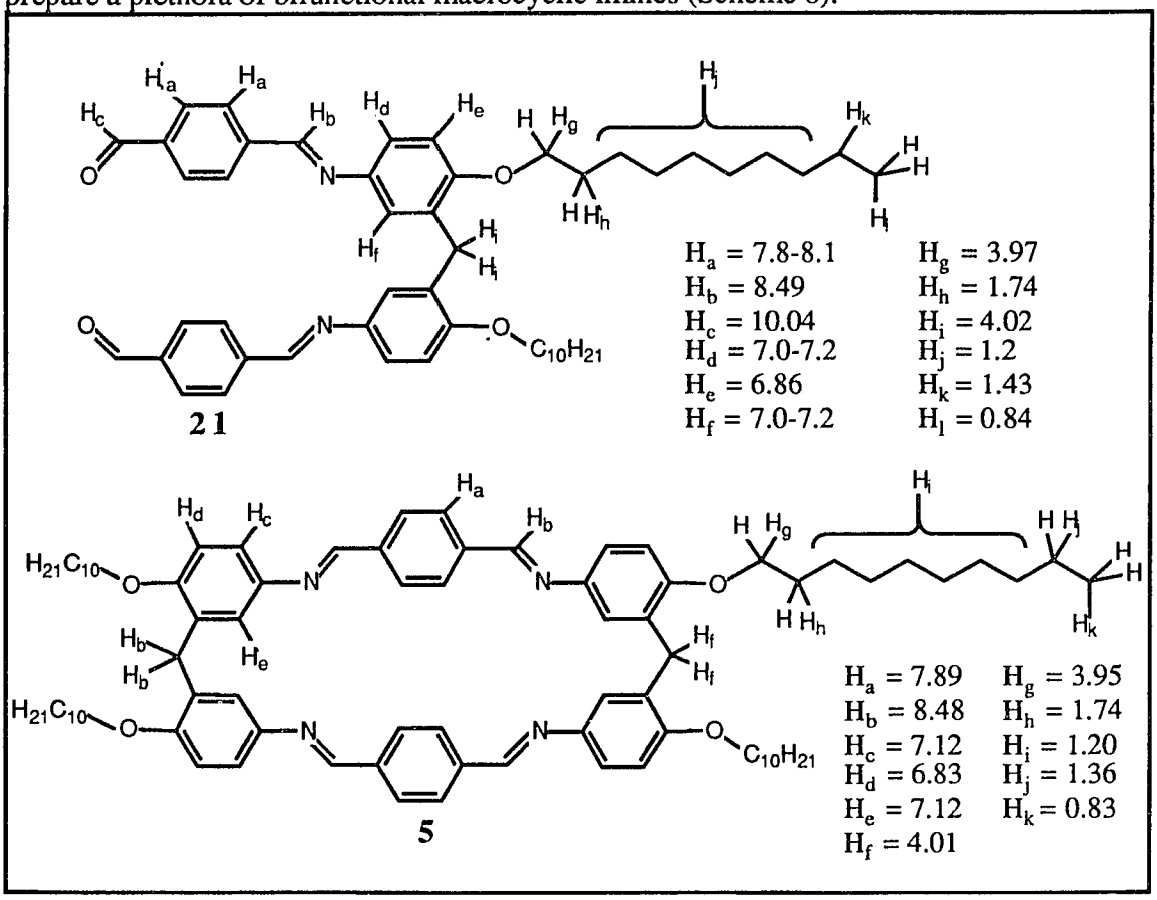
For the type 2 macrocyclic imines, with the decyl aliphatic chains fully extended a span of about 40 Å is expected (Scheme 6). It should be possible to regulate the molecular dimensions of the macrocyclic imine by changes in the polarity of the environment. In nonpolar media, the hydrocarbon chain should be fully extended whereas in polar media, the chains should fold into or over the macrocyclic core. The binding of lipophilic guests in polar environments could be accomplished by the creation of the apolar volume formed by the C-10 hydrocarbon chains around the binding pocket.

The podand, **22**, allows us to gain further insight into some of the structural characteristics of the imines, and can also serve as an intermediate from which other macrocyclic imines can be synthesized. In **22**, only one of the methylene hinges are present, and surprisingly there are no major differences in the ^{1}H nmr spectrum of **22**, and that of the macrocyclic analog **58**. The symmetry elements seen in the macrocycles are also present in the podand, thus leading one to infer that macrocyclization proceeds with little or no apparent structural reorganization (Scheme 7). The ring flip alluded to earlier is also



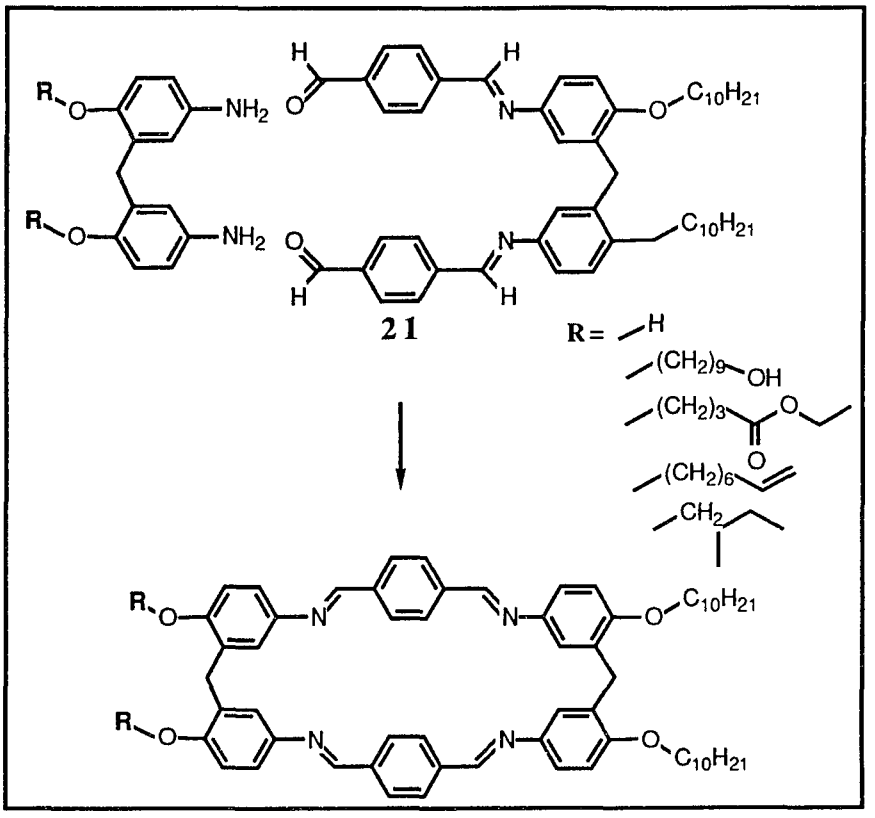
Scheme 6. CPK models of **1** and **4**.

evident; condensation of the dialdehyde podand with other diamines may be used to prepare a plethora of bifunctional macrocyclic imines (Scheme 8).

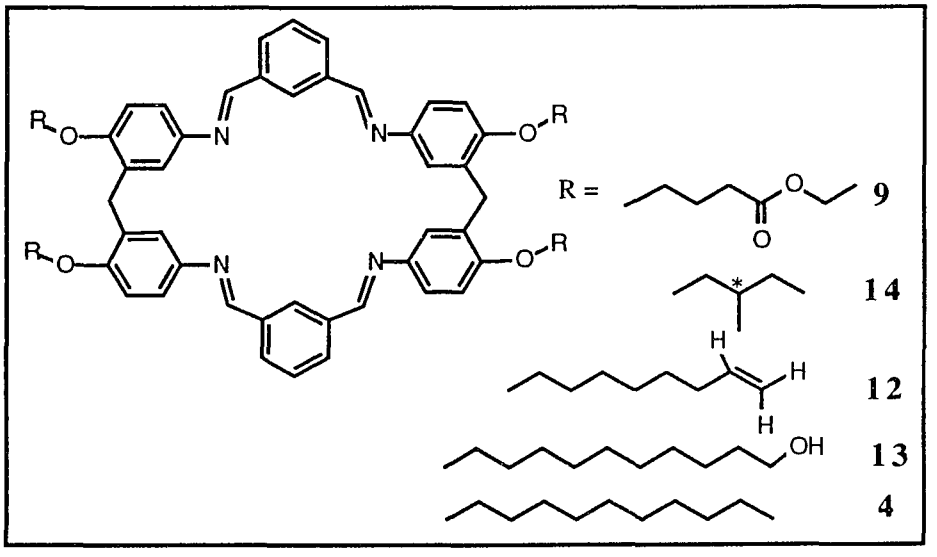


Scheme 7. ^1H nmr comparison of podand **21** and macrocycle **5**.

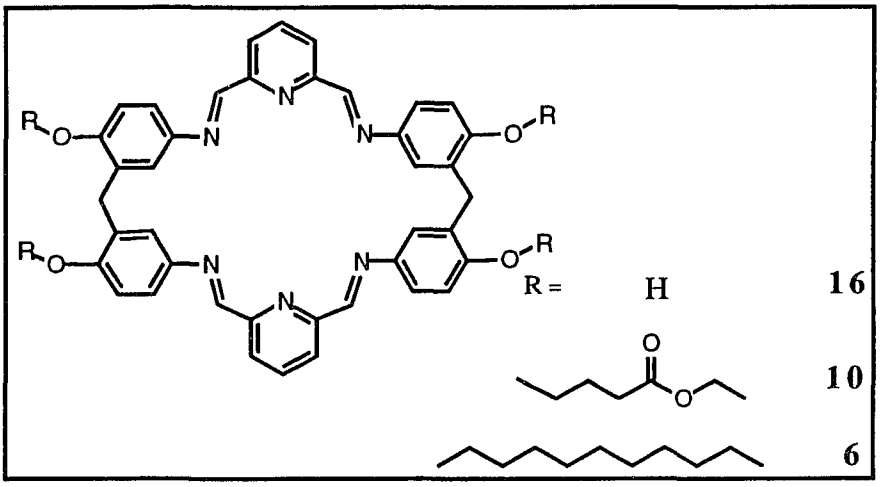
The versatility of this [2 + 2] methodology in the assembly of macrocyclic imines was established by the synthesis of other macrocyclic systems with sidearm coordination sites, chiral substituents, assembly foci, and functionalities that can undergo further transformations (Scheme 9 to 13).



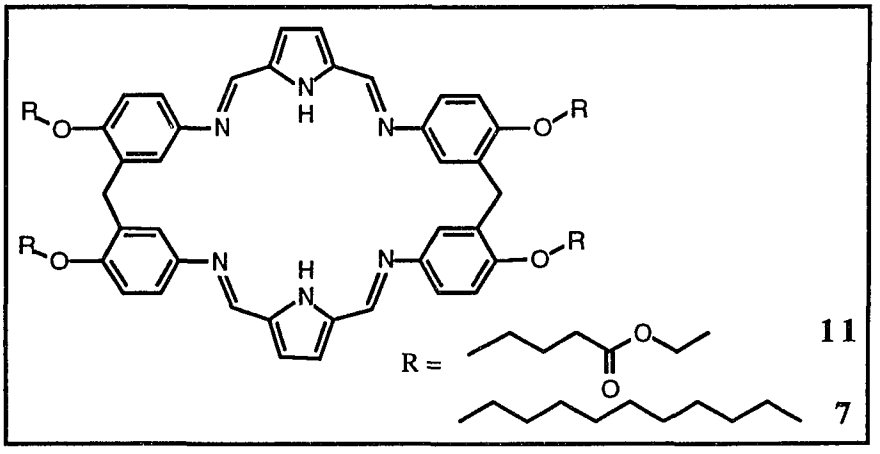
Scheme 8. Proposed general method to prepare difunctional macrocyclic imines.



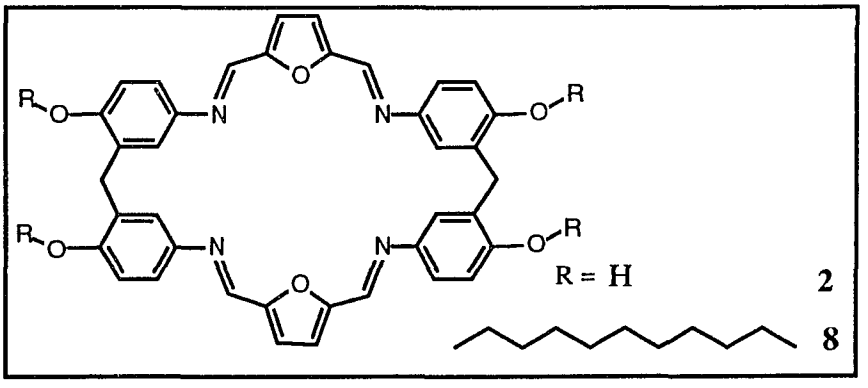
Scheme 9.



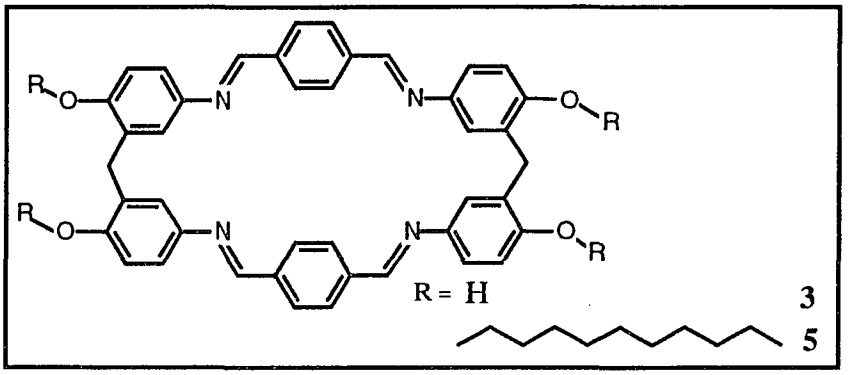
Scheme 10.



Scheme 11.



Scheme 12.



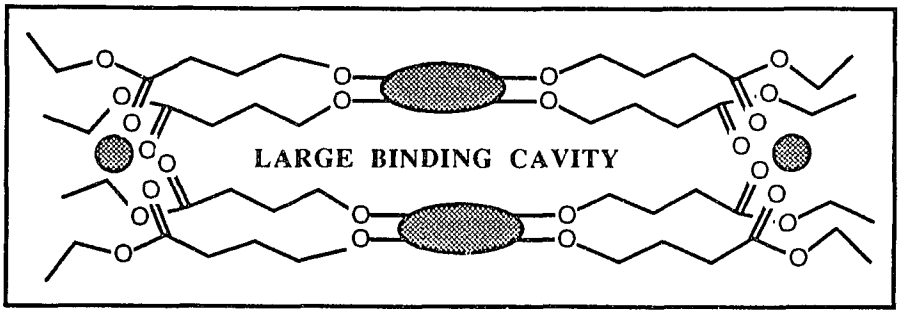
Scheme 13.

Preservation of the macrocyclic core, while allowing for alterations on the periphery, is one of the major reason for the permeation of the macrocyclic concept in virtually every aspect of modern chemistry. Earlier interest in sidearm derivatization of macrocycles was almost exclusively focussed on fine-tuning the cation binding/discriminating ability of them. Presently, sidearm derivatization of macrocyclic systems are done in the context of functionalizing the macrocyclic entity itself. That is, to transform it into an enzyme mimic, a guest responsive sensor, a redox responsive sensor, pH indicator, a photoresponsive ligand, a liquid crystal, mesogen or conducting polymer, or a vehicle used to study basic biophysical/biochemical processes.

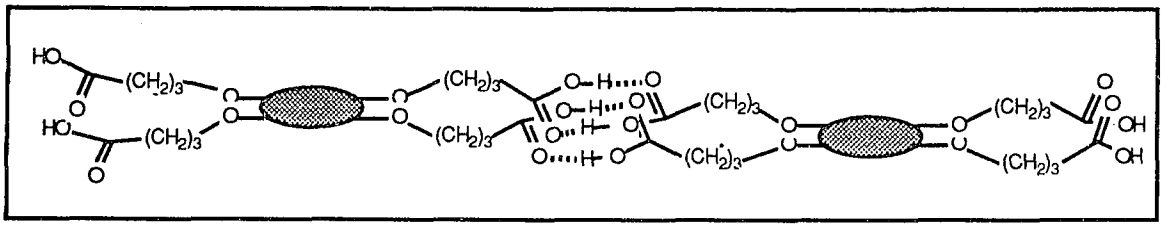
A delicate balance between cation binding and ligand flexibility can be achieved by both the type 1 and type 2 macrocyclic imines. The two intervening methylene units allow for ligand reorganization or conformational adjustments to accommodate various cations. This ability to be highly coordinative, but not restricted in a rigid preorganized manner, will prove to be extremely important if these imines are to stabilize hypervalent cationic centers in functioning as oxidation catalysts.

Apart from demonstrating the versatility of the sidearm derivatization methodology, the ester functionality and the terminal alkene moieties are excellent synthons for other sidearm-derivatized macrocyclic imines.

The use of the ester functionality is two fold. The functionality is itself highly coordinative, and can be used to bind cations or other guest molecules, in a cooperative manner that produces larger binding cavities (Scheme 14). In addition, hydrolysis of the esters would produce macrocyclic imines that should be soluble in polar environments, and at the same time be highly complexing because of the acid group (Scheme 15). The hydrogen bonding ability of carboxylic acids are currently used in the fabrication of liquid crystals.[4]



Scheme 14. Using complexing sidearms to generate larger binding cavities.

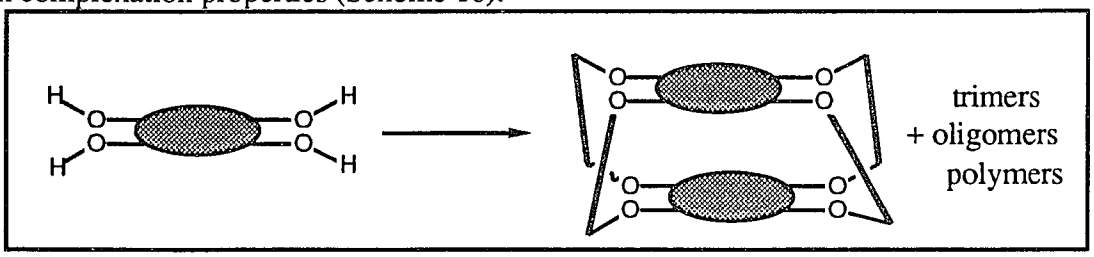


Scheme 15. Self-association of acid derivatives.

The lipophilic terminal alkene, **12**, can serve as a stepping stone to other macrocyclic systems. The coordination ability of the alkenyl group with cations can be used as the assembling foci for the construction of supramolecular systems, alone or in tandem with the hydrocarbon chains. Oxidation of the alkene to the epoxide, acid or its hydroxylation reactions are yet to be explored. We found that all these transformations can be done at the nitrophenol stage, prior to the macrocyclization, thereby avoiding the possible decomposition of the macrocyclic imine ring under more drastic chemical environments.

Some general comments should be made here concerning the differences inherent in each macrocycle, resulting from the dialdehydes used in the assembly. Higher complexation ability will undoubtedly be achieved with the choice of pyridine as the head group as opposed to the furan or isophthalaldehyde. This change in complexing ability also brings with it small changes in the overall size of the cavity. Substitution at the pyrrole nitrogen, hydrogen bonding interactions, or the polymerizability of the pyrrole moiety itself, and the recent reports of pyrrolic macrocyclic imines used as anion binders,[5] introduce new dimensions into the binding characteristics of the macrocyclic cavity. For the terephthalaldehyde derived macrocyclic imine, the elongated, as opposed to the circular cavity creates a host that may be best suited for the binding of small molecules by molecular π stacking interactions or intermolecular π interactions.

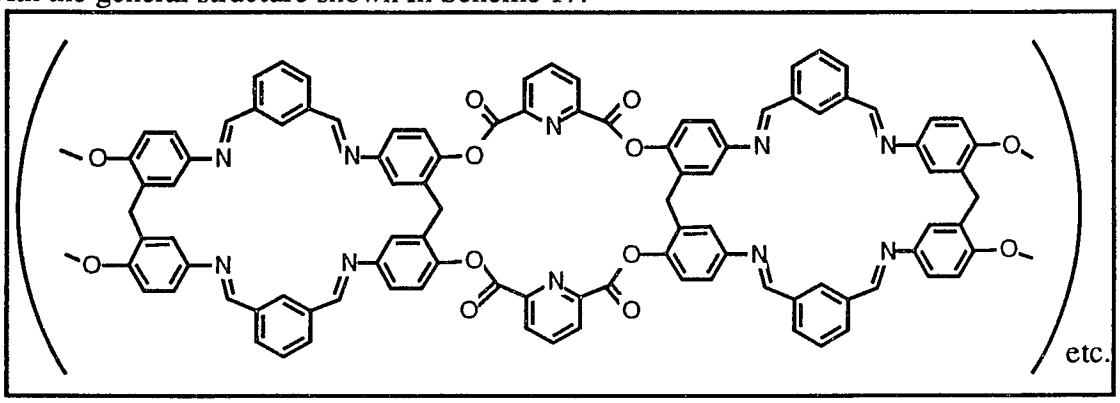
Type 1 macrocyclic imines, in addition to the macrocyclic cavity, possess four complexing/reacting phenolic sites. Reaction with the appropriate base and alkylating agent could be used to produce dimeric, or new polymeric macrocyclic imines with catalytic and ion complexation properties (Scheme 16).



Scheme 16. Alkylation, oligomerization and polymerization of type 1 macrocyclic imines.

The imine-K^+ complexes of **1** and **2** were produced using K_2CO_3. Analysis of the ^1H nmr and UV-VIS data revealed that the macrocyclic cavity is not disrupted under basic conditions. The relatively large potassium cation interacts with the macrocycle via the phenolic sites, not by the imine functionality of the macrocyclic cavity.

Stability of the macrocyclic cavity under basic conditions and the free macrocyclic cavity may be useful in the construction of heterocationic oligomers or polymeric material with the general structure shown in Scheme 17.

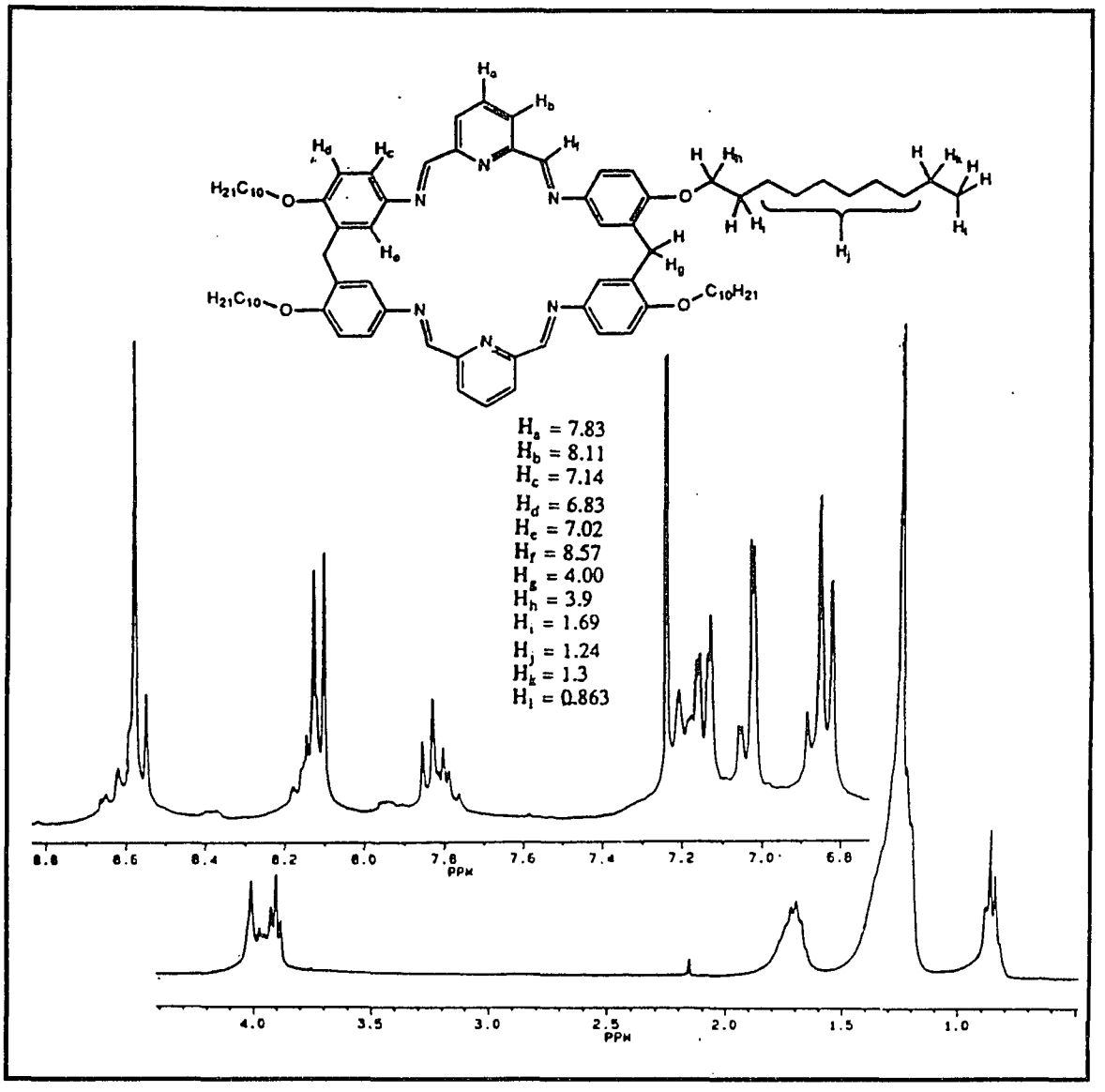


Scheme 17. Proposed model for macrocyclic polymers with two binding sites.

The chiral calixarenes of Shinkai are closely related to **14**.[6] For the calixarenes, the interaction of the chiral chromophoric macrocycle and achiral guests, or the interaction of the macrocycle with chiral guests was evaluated by CD spectroscopy. The imine **14**, is also chromophoric in addition to being chiral and there is every reason to believe that the basic properties of the macrocyclic core in **14** will be similar to that of the other macrocyclic imines synthesized. With this in mind, it is conceivable that the conformational mobility of the core can be exploited not only to indicate the degree of mobility in the macrocycle itself but also as a molecular signalling system. Host-guest interactions

displayed by ligands, that are not observable by conventional means, can be evaluated quite easily by CD spectroscopy. In addition, although the macrocyclic cavity remains unchanged, the S, S, S, S tetrasubstituted macrocyclic cavity could display novel electronic or optical properties in the solid state, in the form of thin films, or monolayers.

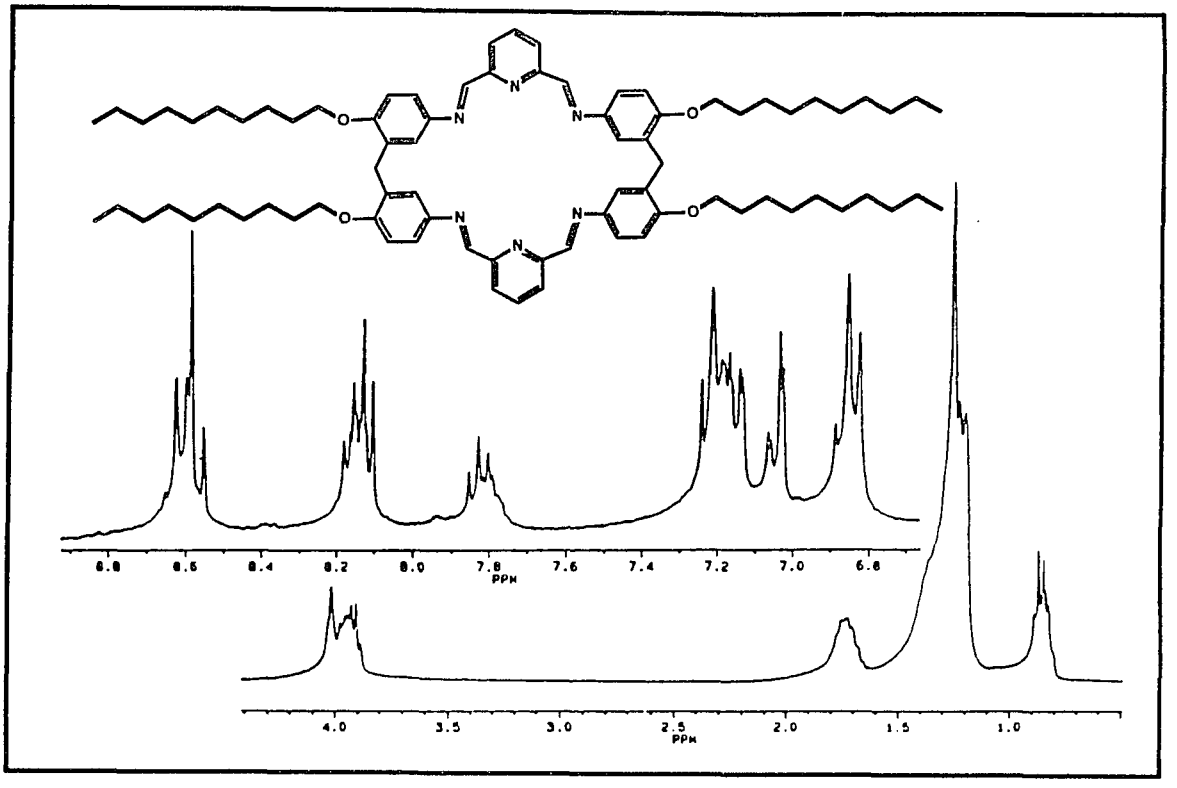
To demonstrate the self-associative properties of the macrocyclic imines, a ^{1}H nmr concentration study was conducted using **6**. At a concentration of 1.2 x10^{-2} M, the aromatic resonances from the pyridine head group, the diphenyl methane and the C-10 alkyl chains are well resolved (Scheme 18).



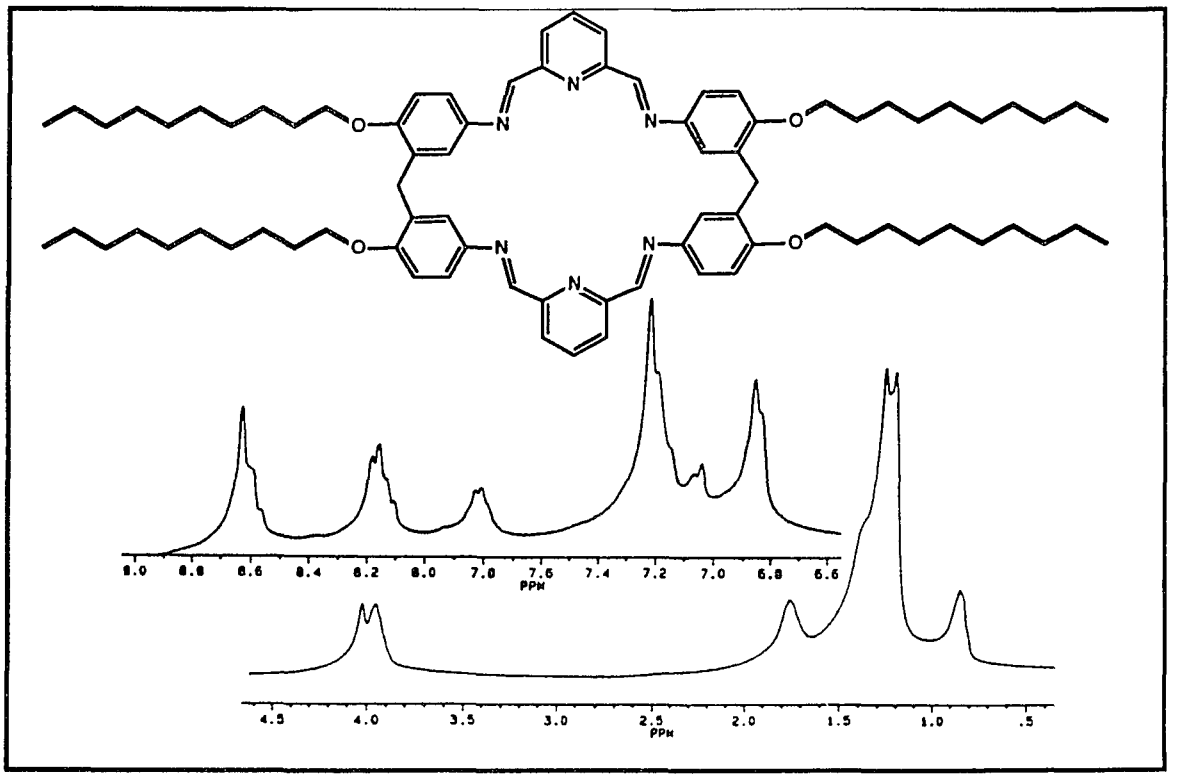
Scheme 18. ^{1}H nmr spectrum of **6** (1.2 x10^{-2}M, $CDCl_3$).

However, at a concentration of 4.5 x10^{-2} M, multiple resonances and peak broadening are observed for all resonances, and is indicative of a number of chemical species being present in solution. A dramatic difference was seen in the resonances corresponding to the six methylene units and the terminal methyl resonances. The largely singular resonance from the methylene units seen in Scheme 18 is now seen as two additional resonances, at higher field, indicating a more hydrophobic environment. The broadened triplet in Scheme 18, is now clearly observed as two overlapping triplets (Scheme 19).

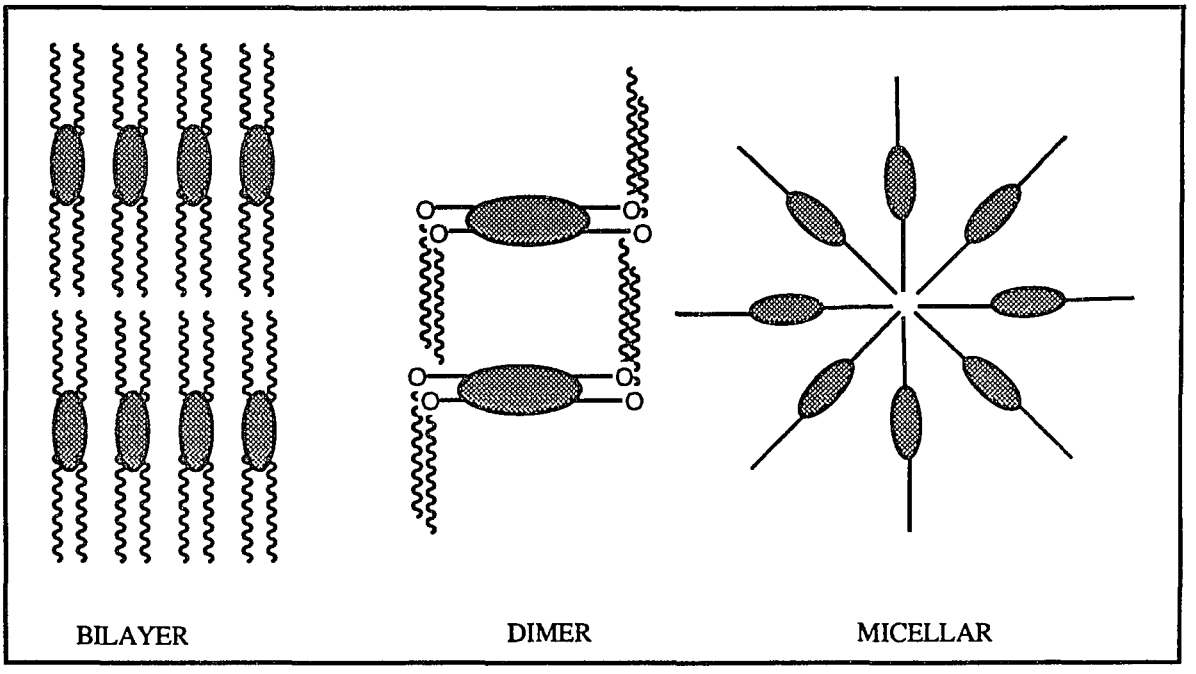
At even higher concentration severe peak broadening occurs on all proton resonances and two observations are clearly seen. First, the solution remained free from solid particles, and secondly, there are now two distinct resonances for the six methylene units. Micellar, bilayer or dimer formation by the macrocycle could account for the two differing environments experienced by the methylene units. In each case methylene units buried in the hydrophobic pocket could be accounted for at 1.20 ppm, and the signal at 1.25 ppm belonging to methylene units exposed to the solvent (Scheme 20).



Scheme 19. ^{1}H nmr of **6** (4.5 x10^{-2} M, $CDCl_3$).



Scheme 20. ^1H nmr of **6** (9 x10^{-2}M, $CDCl_3$).

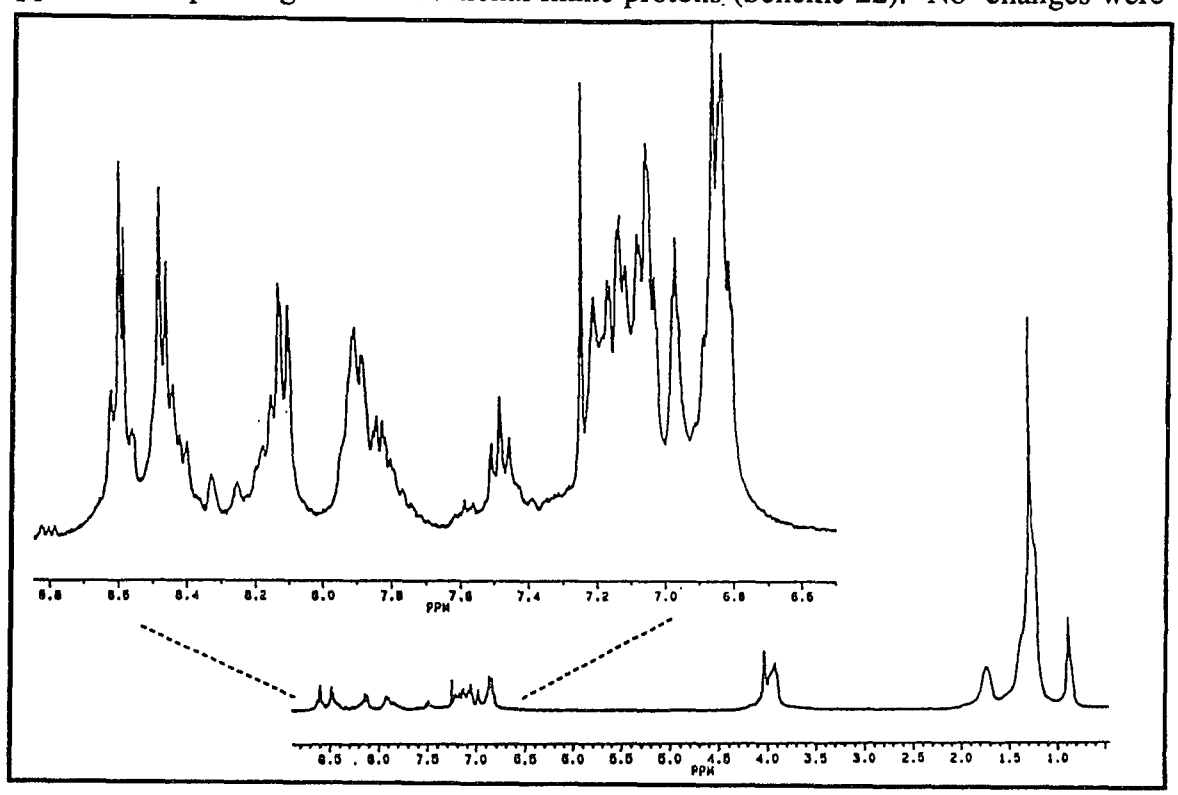


Scheme 21. Possible modes of self-association by **6**.

The second explanation which is necessary to augment the argument given earlier takes into account the equilibrium, (i.e 'V' to inverted 'V'), present in the macrocycles.

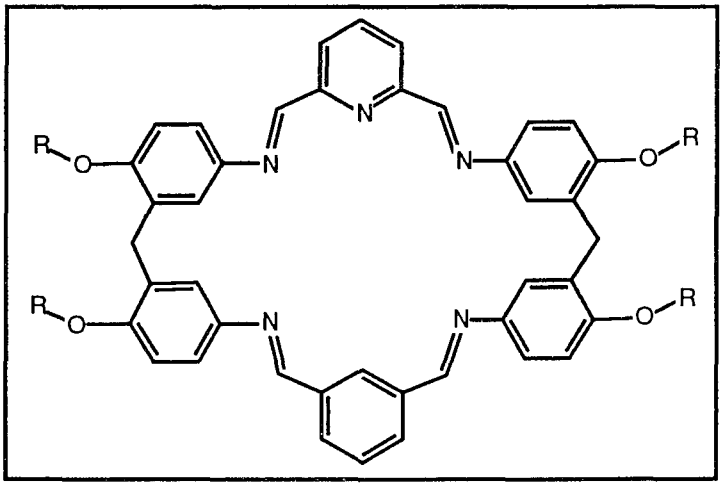
The self-associating behavior, into structures shown in Scheme 19, slows down this interconversion resulting in the broadened spectra observed. At higher concentrations of the macrocycle, the hydrophobic tails present in the macrocycle induce association into an organized structure in which the tails of the macrocycle are buried in a hydrophobic environment. The association of the hydrophobic tails essentially 'pins' them and reduces the ability of the macrocycle to interconvert from the 'V' to the inverted 'V' conformer. The two results of these effects are the severe peak broadening of all resonances and the upfield shift seen in the resonances of the six methylene units.

To explore further the self-assembling properties of the type 2 macrocyclic imines and to test the possibility of generating supramolecular structures by the association of differing imino cores, studies were done using **9**, **10**, **4** and **6**. For each macrocycle, all resonances are well resolved in both the aromatic and aliphatic regions. Mixing and retaking the ^{1}H nmr spectrum of an equimolar mixture, the resulting spectrum was not the sum of the two isolated macrocycles. Broadening was seen for all resonances corresponding to the aliphatic protons. The intervening six methylene units showed no shift to lower ppm values, indicating that the chemical environment (as far as polarity is concerned) is unaffected by whatever process is occuring. Two additional resonances appear, corresponding to two additional imine protons (Scheme 22). No changes were



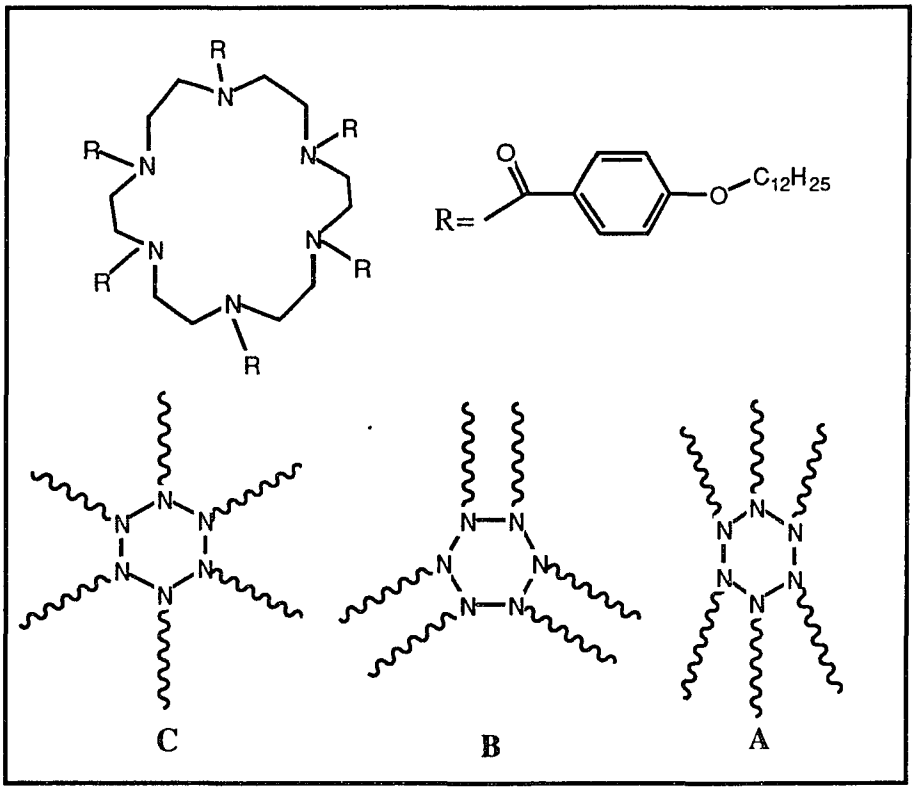
Scheme 22. ^{1}H nmr of equimolar mixture of **6** and **4**.

seen in the head group protons and phenyl resonances of the diamino component. No changes were also seen on diluting the mixture. Combinations of **4** and **9**, and **10** and **6**, failed to produce any of these effects. In these instances, the macrocyclic cores are the same, and the sidearms different. Differing head groups with identical sidearms also do not produce the effect seen. One basic question has to be asked. Why is the effect only seen for mixtures with the head groups derived from pyridine and isophthalaldehyde and identical sidearms? At this point one can only speculate that either a transamination process to produce the imine shown in Scheme 23, or a unique association/recognition process, dependant on associations such as that shown in Scheme 24.



Scheme 23. Product of transamination in macrocyclic imines.

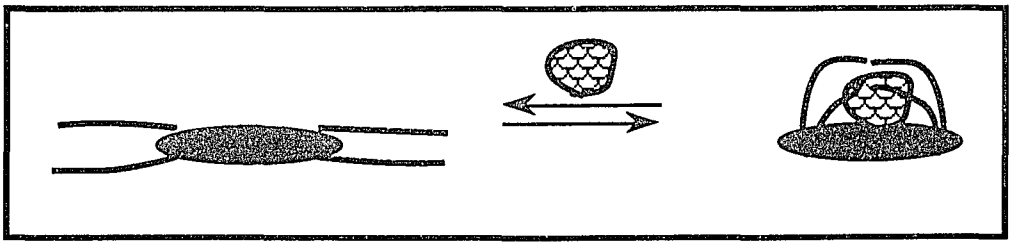
As the methylene unit linking the two complexing motifs remains unaffected, one may safely assume that the rotations around the methylene unit continues throughout the process. From Scheme 23, a macrocycle of this structure should show the largest difference, in ^{1}H nmr, when the sidearms are different. The association responsible for these changes could be dependant only on the similarity in dimensions of the macrocycles involved. In each case where they are observed, both macrocycles are identical except for the head group. This slight difference has no effect on the size or shape of the molecules. In the hexacyclam (Scheme 24), molecular modelling studies, using MacroModel, showed that the conformer A, with all the hydrocarbon chains associated together was more stable than B or C.[6] If intramolecular chain association does operate in the macrocyclic imines, it should also follow that intermolecular chain association may also be operating. On mixing, because of the similar dimension of the macrocycles, a second equilibrium is set up, due to the association of two differing macrocycles, that have no way of distinguishing self from non-self. This could change the overall conformational mobility of individual macrocycles resulting in the effects observed.



Scheme 24.

The solubility of **4** in chloroform is considerably less than that of **6**. At the saturation point for **4**, the pyridine analog does not display any self-association properties detectable by ^1H nmr. A saturated solution of **1** in DMSO also did not display these self-association properties. It is important to note that in the two cases looked at to date, (**6** and **8**), the studies were done in an organic apolar environment, ($CDCl_3$).

The effects observed for **6** and **8** conform with the expected tendency of these molecules to self-associate primarily because of the lipophilic hydrocarbon chains. The hydrophobic effect seen in numerous macrocyclic and acyclic systems is in this case not responsible for the effects seen. It is not unprecedented that the polarity of the environment can be utilized to control not only guest binding but self-association. In polar hydrophilic media, the natural tendency of the lipophilic macrocycles would be to fold inward over the cavity, (Scheme 25), as opposed to the extended model that operates in apolar media.

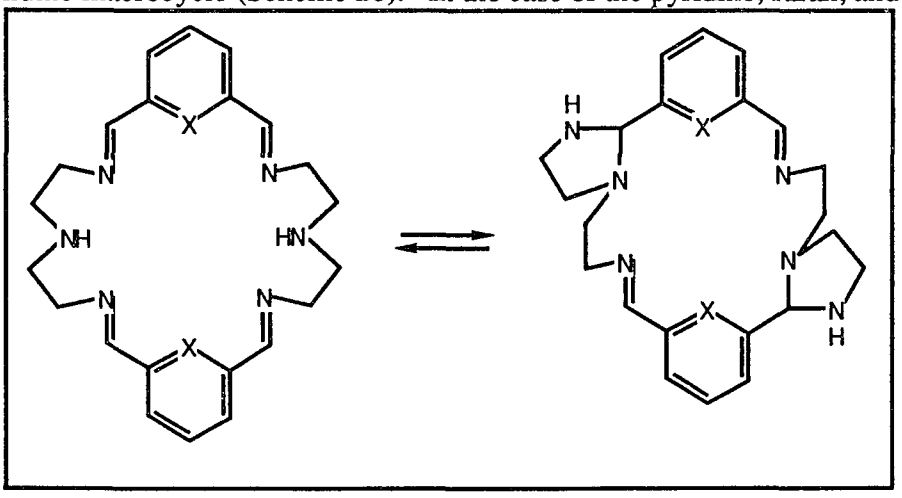


Scheme 25. Control of molecular binding properties by polarity of medium.

2.2-Anthracenyl macrocyclic imines:

Metal-free macrocyclic assembly of imines using the procedure devised by Lehn have been exploited to produce a number of macrocyclic imines derived from diethylene diamine and triethylene triamine.[8] Earlier work done on the imines synthesized were focussed exclusively on the redox properties, protonation, oxygen binding and transport properties, cation binding, and the oxidation properties of these complexes, and the reduced derivatives.

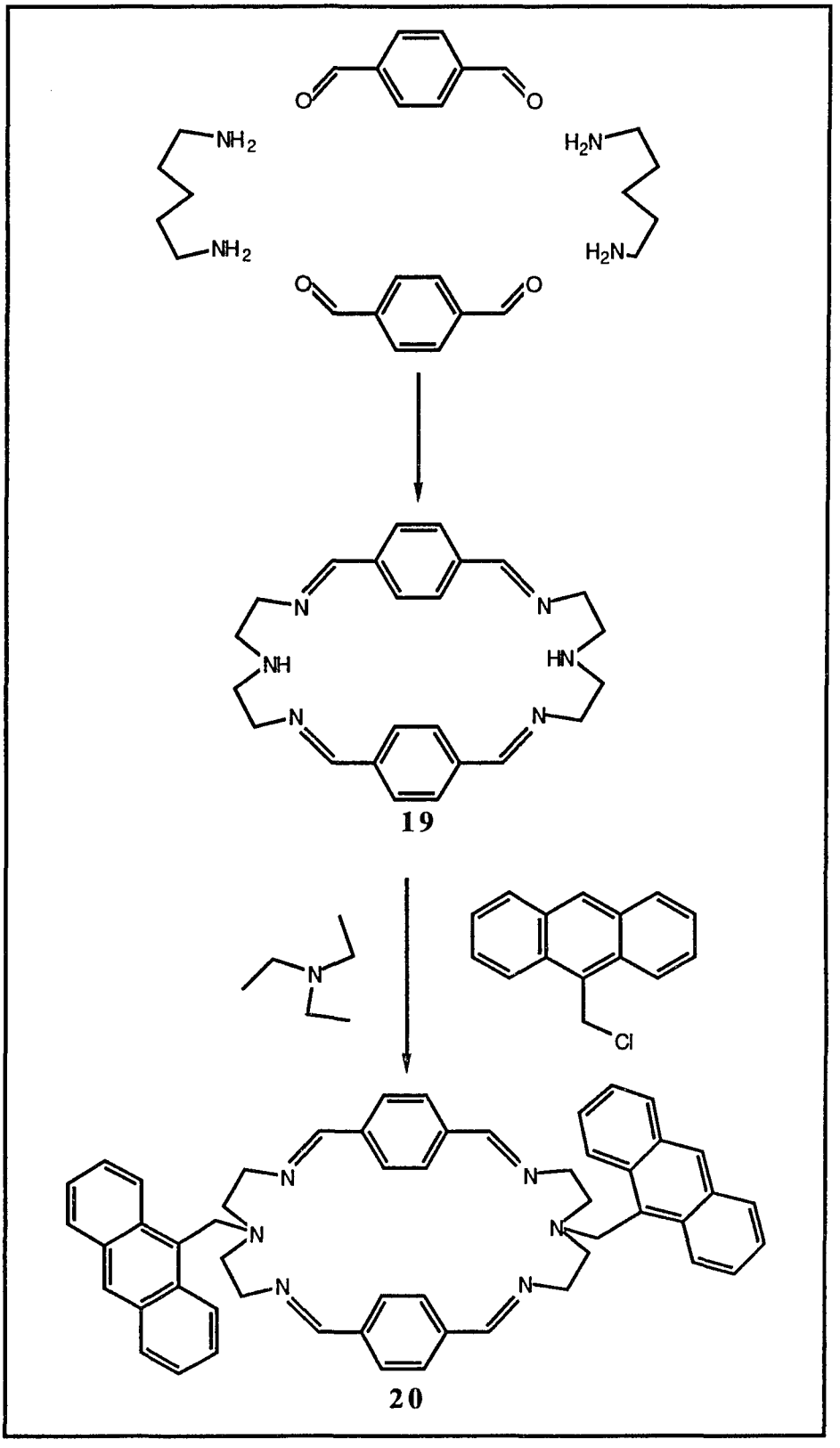
A number of these [2+2] macrocyclic imines derived from diethylene diamine, at room temperature, exist as a mixture of the macrocyclic tetraimine and the diimine diimidazolidine macrocycle (Scheme 26). In the case of the pyridine, furan, and isopth-



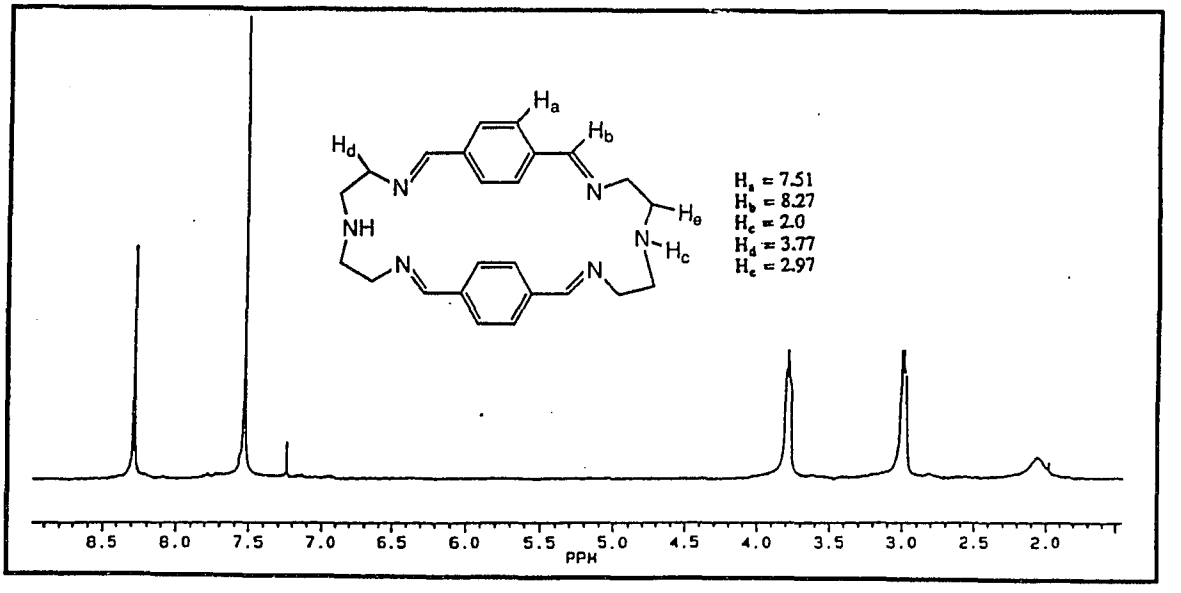
Scheme 26. Solution state isomeric equlibrium of tetraimines.

alaldehyde derived macrocycles, the removal of this abiguity is achieved by the formation of the cationic complexes. This however reduces the nucleophilic nature of the nitrogen lone pair, which is now occupied with the complexation of the metal ion. It should also be noted that the heteroatom in the dialdehydes used plays no role in the binding of cations. The success of the synthetic scheme, (Scheme 27), depends on the availability of the nitrogen lone pair, and the absence of the equilibrium shown in Scheme 26.

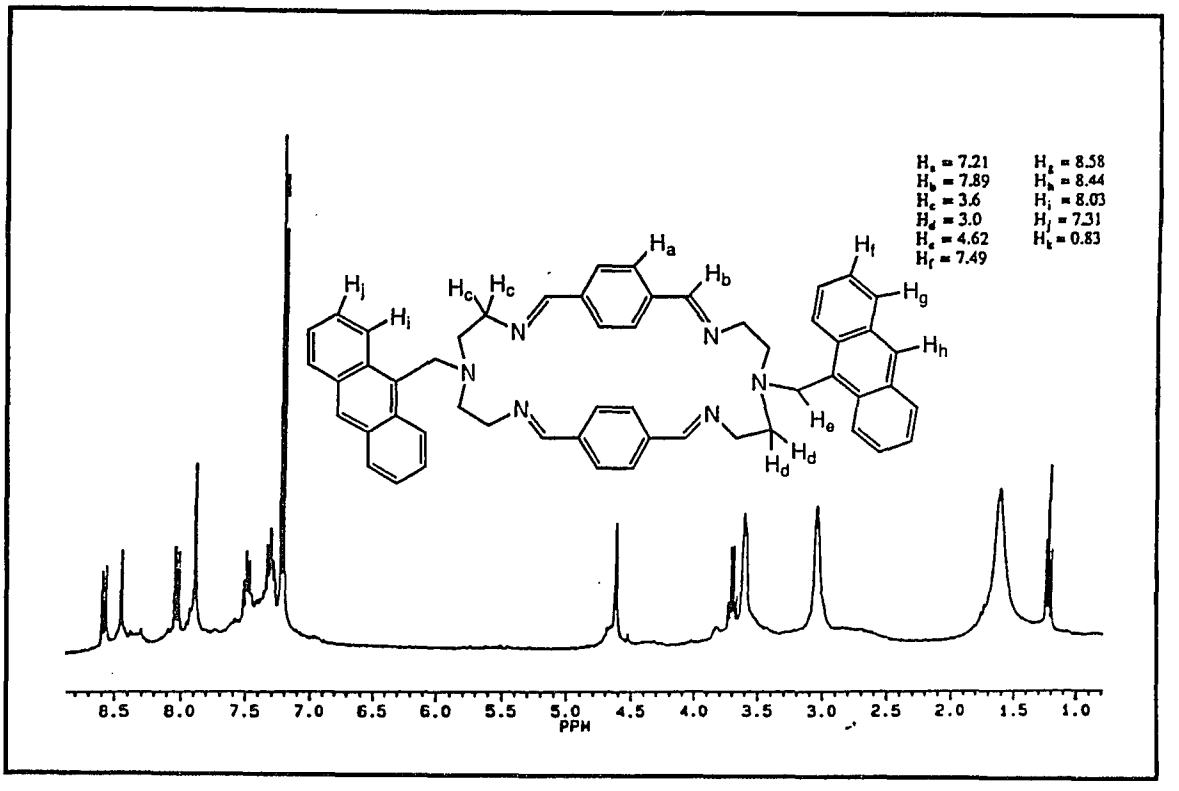
The equilibrium that exists in solution, (Scheme 27) is not displayed by **19**. ^1H nmr analysis of **19** in $CDCl_3$ shows the existence of only one species in solution; the macrocyclic imine (Scheme 28). Removal of this ambiguity in **19** is conducive to the synthesis of a family of disubstituted macrocyclic imines.



Scheme 27. Assembly of anthracenyl macrocyclic imines.



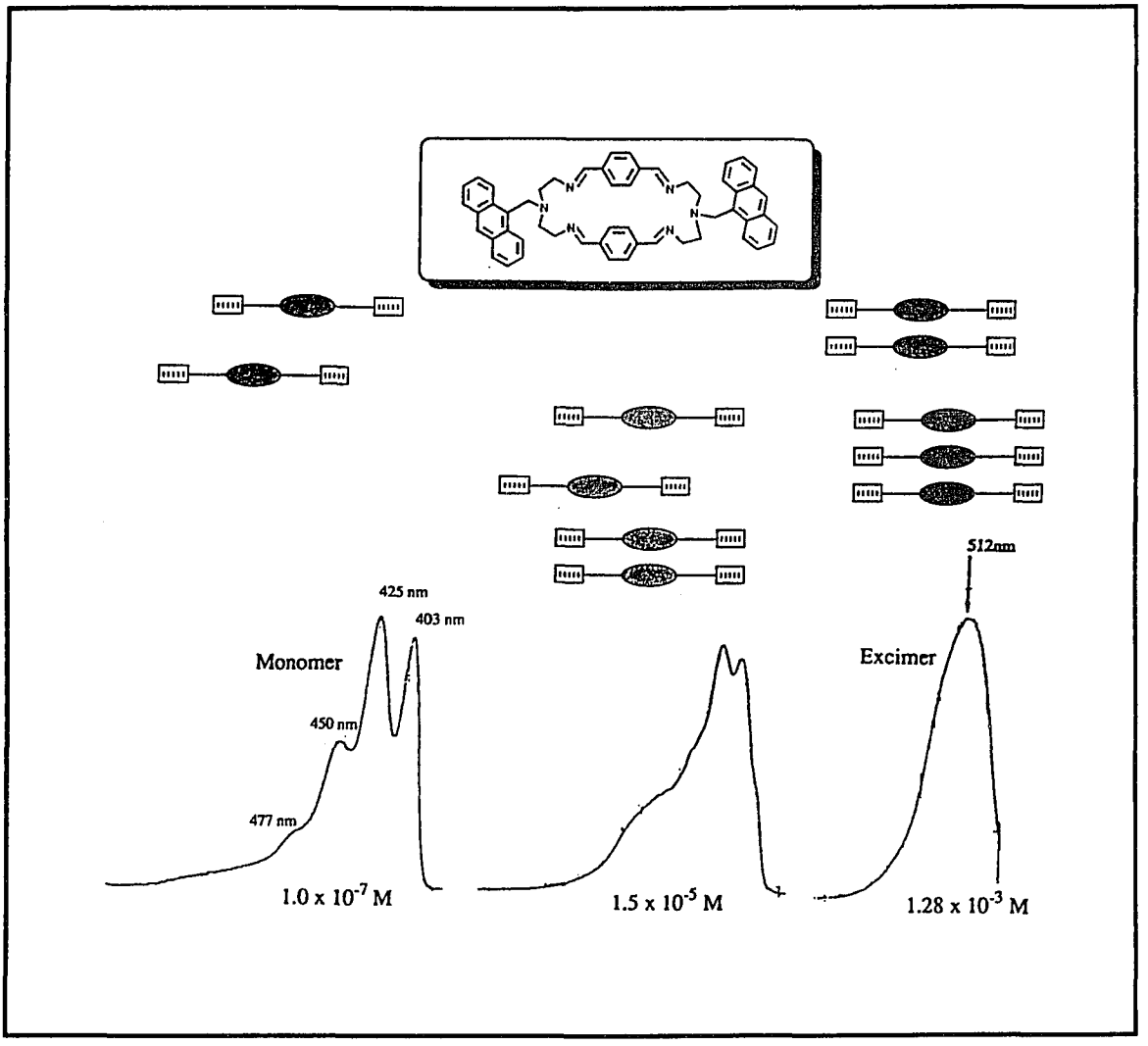
Scheme 28. ^{1}H nmr spectrum of **19**($CDCl_3$).



Scheme 29. ^{1}H nmr spectrum of **20**($CDCl_3$).

The associative properties of the anthracenyl macrocycle, **20**, was evaluated by fluorescence spectroscopy (Scheme 30). At low concentration, (< $1x10^{-7}$ M), the emission spectra is a well resolved. On increasing the concentration, there is the progressive shift from the structured emission, to that of the unstructured excimer emission completely

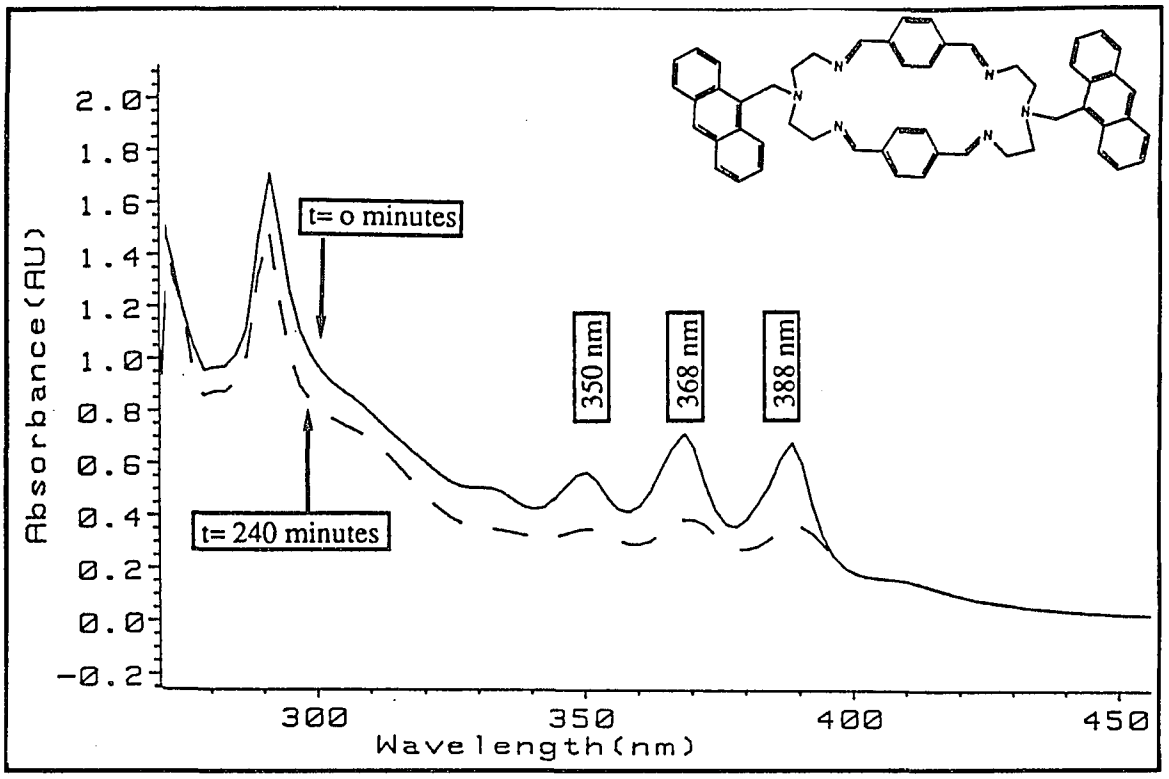
dominating the spectra. Self-association of the imine would account for the emission spectra observed.



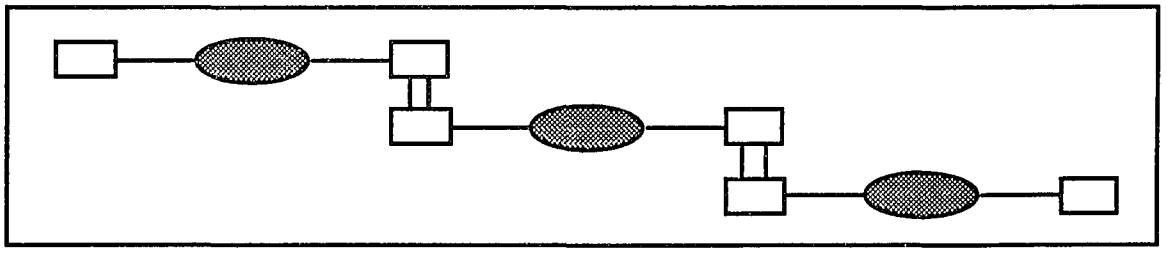
Scheme 30. Self-association of **20** followed by fluorescence spectroscopy.

The concentration at which the ^{1}H nmr spectrum was measured, 1.28×10^{-3} M, is in the range at which the excimer emission completely dominates the fluorescence spectra. Increased understanding of the association is gained by examining the ^{1}H nmr spectrum. Subtle changes are revealed in the spectrum when the precursor macrocyclic imine and the anthracenyl derivative are compared. The upfield shift seen in the aromatic protons of the benzene moiety going to 7.21 ppm in the anthracenyl derivative, compared to 7.51 ppm in **19**, along with the deshielding of the imine proton (7.89 ppm), is a result of self-association (Scheme 29 and 30).

Photoactive behavior was also displayed by **20** (Scheme 31). The concentration at which the irradiation was done (> 350 nm), is a concentration range where the emission spectra is dominated by the structured monomeric emission of the anthracene unit. The insoluble solid produced is in keeping with other reports of a head to tail polymer (Scheme 32).[9a]



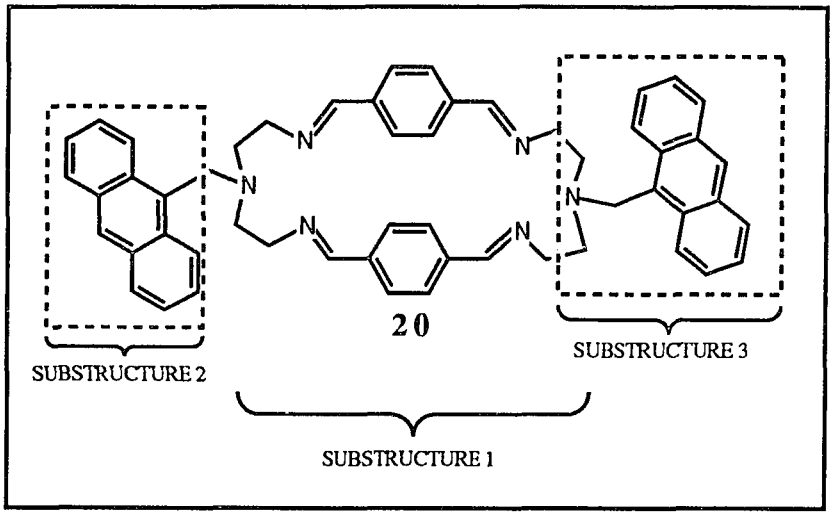
Scheme 31. Irradiation of **20**, (<350 nm, $CHCl_3$).



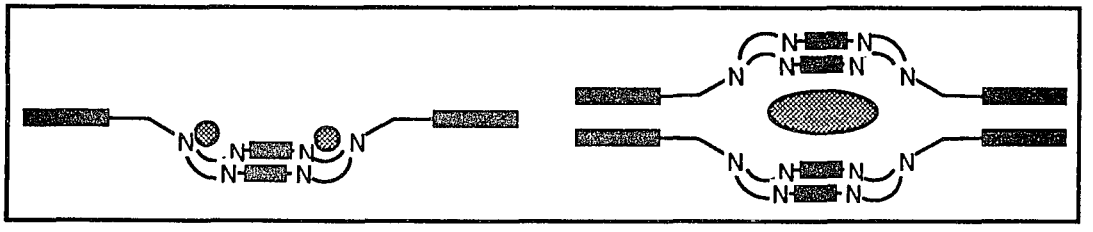
Scheme 32. Schematic representation of photochemically generated macrocyclic polymer.

The anthracenyl macrocyclic imine can be subdivided into three distinct structural entities with each substructure having common to it a number of distinct chemical properties (Scheme 33). The macrocyclic core, (substructure 1), has two distinct binding cavities for guest interaction. The anthracenyl moiety (substructure 2), can be exploited for its photochemical and associative properties.[9b-f] Substructure 3, is basic in the construction of molecular signalling systems.[10]

Intermolecular association of **20**, produces a large binding cavity of eight imino functionalities that are potential coordinative sites. The large cavity should allow for the binding of larger cations, multiple cationic species or organic molecules (Scheme 34). The formation of such a π stacked dimer can be monitored by the appearance of the structureless excimer fluorescence.



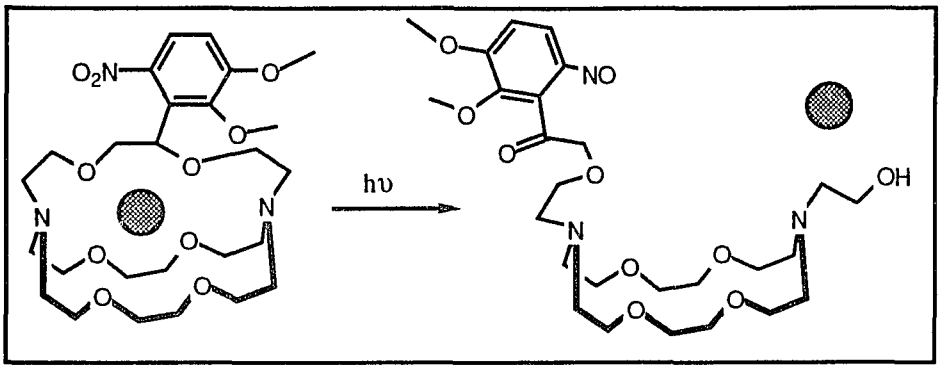
Scheme 33. Substructure representation of **20**.



Scheme 34. Molecular self-association to control binding cavity size.

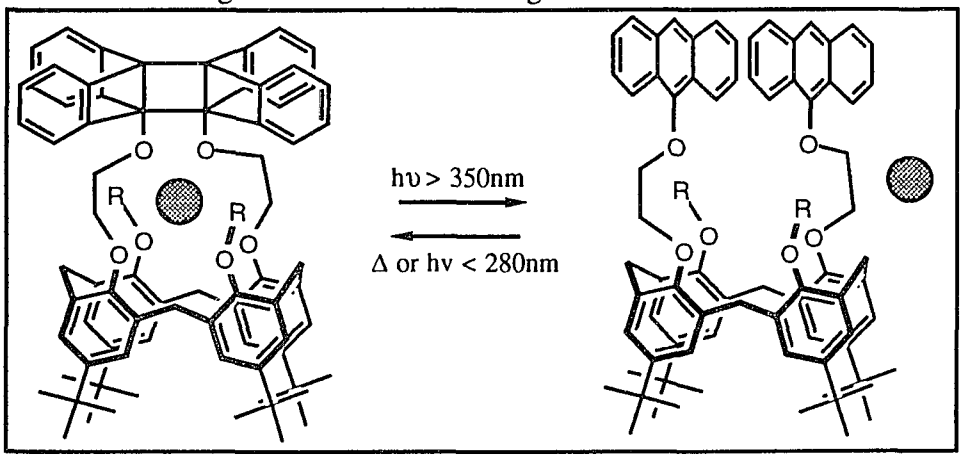
An available lone pair on nitrogen in a benzylic position to a large aromatic chromophore, in this case anthracene, have been exploited by Da Silva [10] and Czarnik [11] to produce molecular probes, macrocyclic and non-macrocyclic, that are cationic, anionic and pH responsive. This is the first report of macrocyclic probes of this type that utilize the imine functionality as the guest interacting foci.

More recently, Skinkai, [12] and Lehn, [13] departing from the use of the azobenzenes as the photochemical switch, have utilized the nitrophenol cryptand derivative, (Scheme 35) and the anthracenyl calixarene (Scheme 36), to exert photocontrol over cation binding and release using macrocycles.

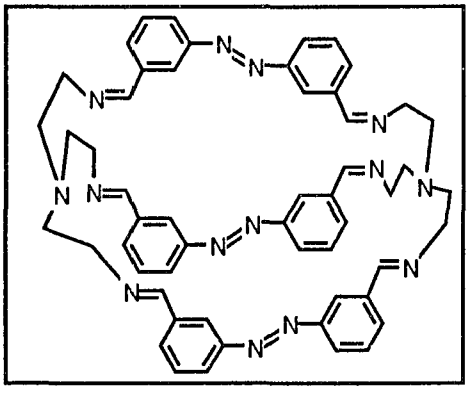


Scheme 35. Cation release controlled by photo cleavable cryptand.

To this author's knowledge, **20** represents one of two photoactive metal-free macrocyclic imines synthesized. The other, product of a [3+2] cyclization, was recently reported by Vogtle.[14] Here, the photochromic behavior of the azo moiety is used to control cavity size and the binding characteristics of the ligand.



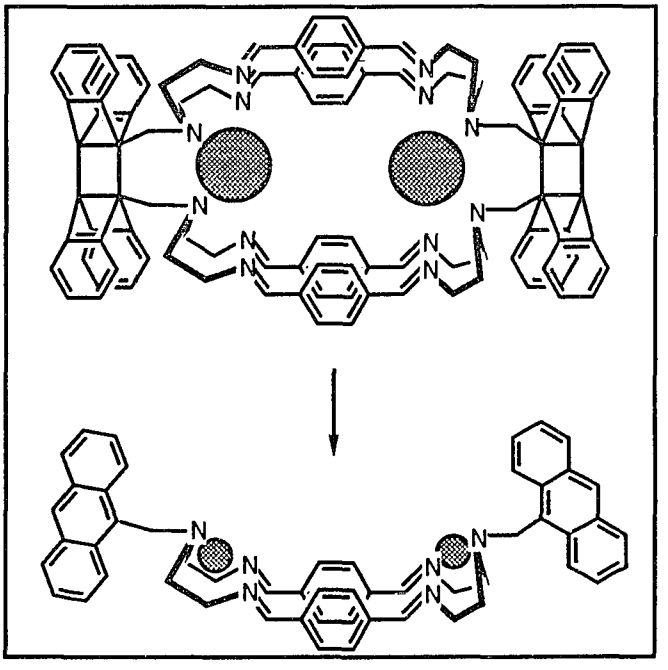
Scheme 36. Photocontrol of ion binding via an anthracenyl calixarene.



In **20**, properties basic to the cryptand, calixarene and the imine above are combined in one ligand. At our disposal are the associative properties of anthracene unit to

define cavity size along with cation binding and photoactive properties. A common scenario would be association of **20** into the dimer, for the binding of larger guests, followed by the photochemical generation or disruption of the dimer when necessary. In the monomeric form, the ligand has available two small binding cavities. One can now envisage the cation selectivity/binding of the macrocyclic system modulated by molecular association and photoswitching. The dimeric imine for large cations or guests, and the monomeric imine for small cations or molecules (Scheme 37).

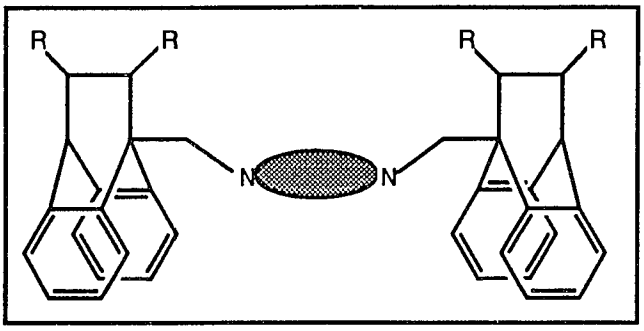
The photoactive macrocyclic imine may be advantageous over the more commonly explored macrocycles because of the fact that the imine binding site in the macrocycle remains undisturbed throughout either polymerization or dimerization. Secondly, to reiterate, the imine functionality is a superior complexing moiety, compared to the crown ethers and cryptands. In addition, we now have the luxury of controlling the photoproduct by varying the degree of self-association.



Scheme 37. Proposed photocontrol over guest binding using **20**.

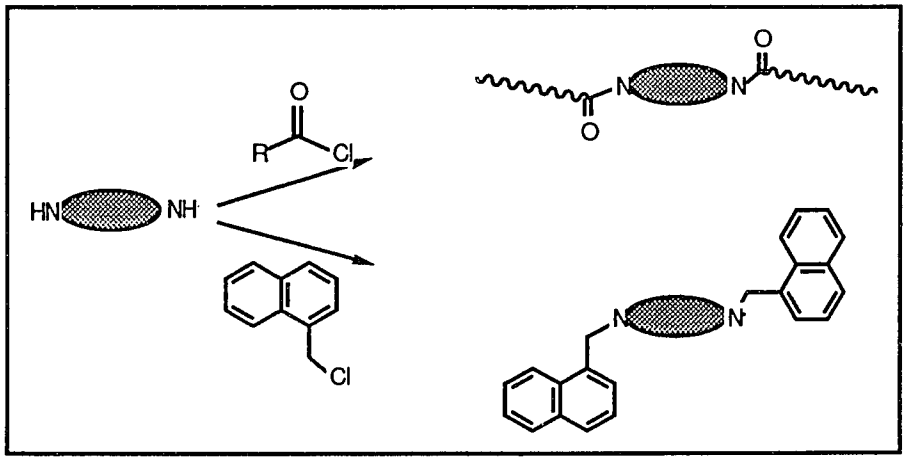
There are a number of other chemical transformations that are yet to be explored using **19** and **20**. Each is related to the reactions of the anthracenyl sidearm or the substitution at the secondary nitrogen.

Diels Alder cycloaddition of activated alkenes to anthracenes is well known. Similar cycloadditions can be used to provide further derivatization around the macrocyclic core (Scheme 38), to give non-photoactive polymers and lipophilic macrocyclic imines.



Scheme 38. Cycloaddition reactions of anthracenyl macrocyclic imine.

Substitution at the secondary nitrogen, (Scheme 39), is possible with a variety of sidearms. As stated earlier, the success of the entire process depends on the availability of the nitrogen lone pair to participate in substitution reactions under reactions conditions that do not destroy the macrocyclic imine ring.



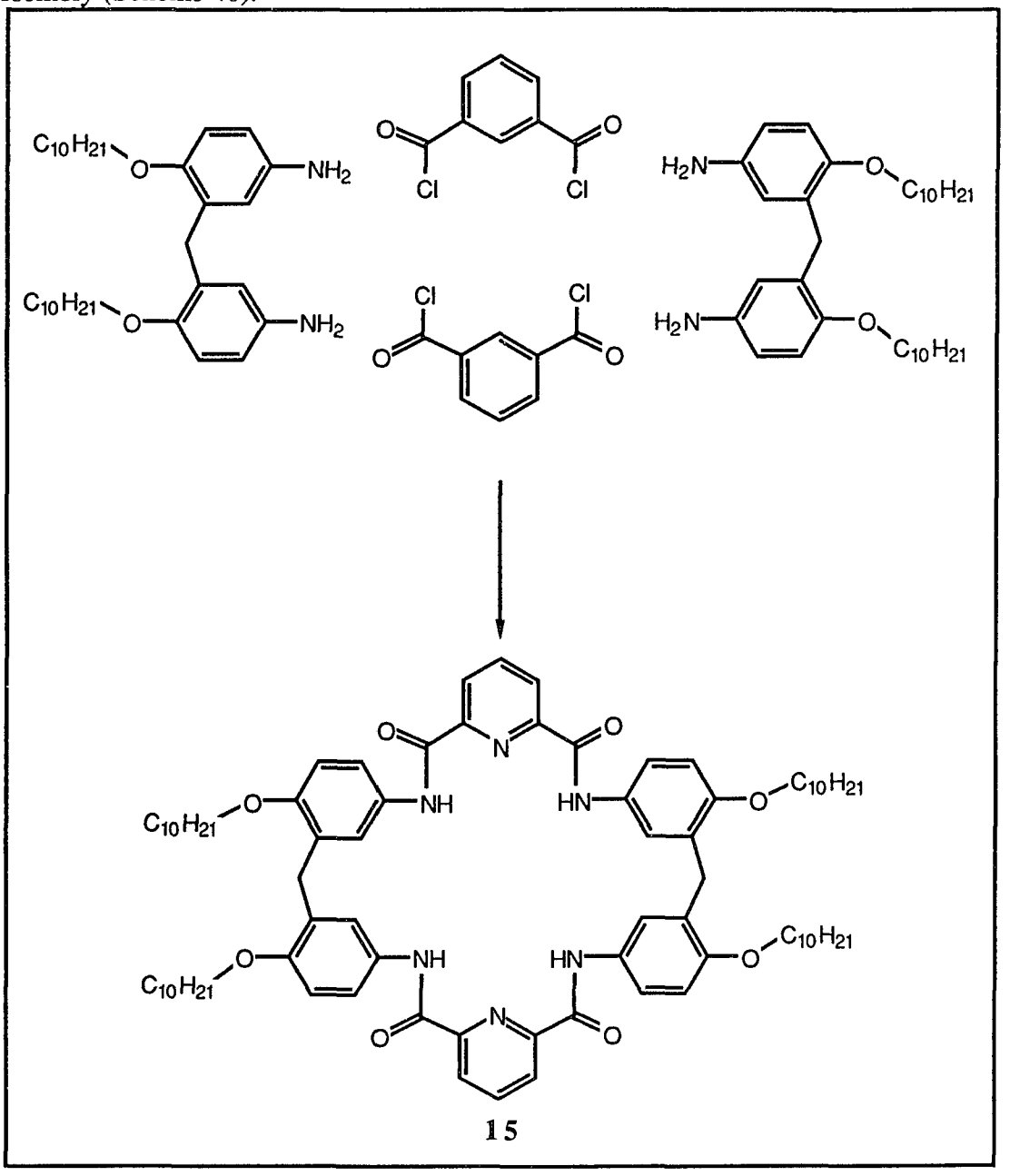
Scheme 39. Sidearm derivatization of **19** to produce disubstituted macrocyclic imines.

Anthracenyl moieties or naphthyl moieties can be used as recognition handles for other macrocycles such as cyclodextrins. This recognition of the pendant arm can be utilized to produce multicomponent arrays, supramolecular structures, to mask or control the photochemistry, or cycloaddition chemistry of the anthracene unit.

In both **19** and **20**, the necessary functionalities that are responsible for the cation binding are retained by the macrocycles. The metal-free nature of both ligands gives one great flexibility in the choice of cations selected to study the binding, oxygen binding, transport, and oxidation properties. Cation doped polymeric materials may find applications in catalysis, oxygen binding, and optical memory devices. The anthracenyl moiety present in the ligand makes it quite versatile with potential uses in supramolecular chemistry, oxygen binding and transfer, photo-responsive/switching devices, as a DNA binding and nicking agent, in chemical sensor technologies and material science.

2.3-Macrocyclic amides:

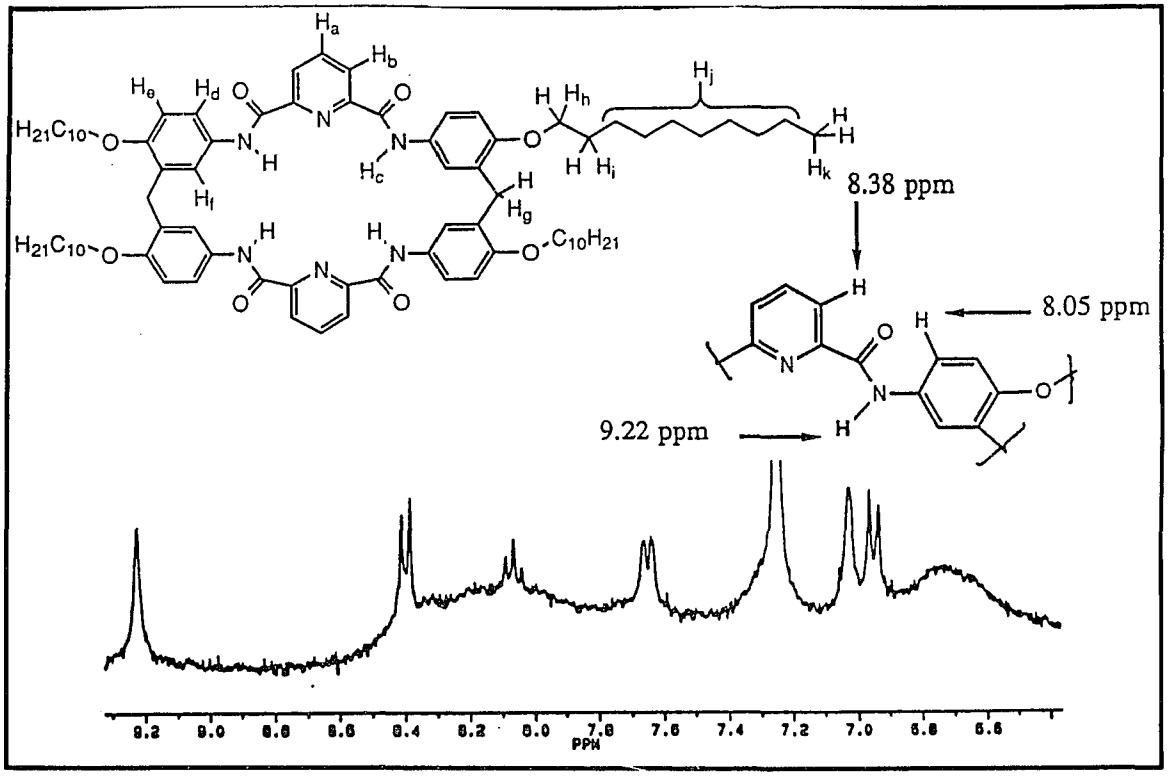
The methodology established for the synthesis of macrocyclic imines (type 1 and 2), can be extended to the synthesis of macrocyclic amides via the [2+2] macrocyclization assembly (Scheme 40).



Scheme 40. [2+2] assembly of macrocyclic amides.

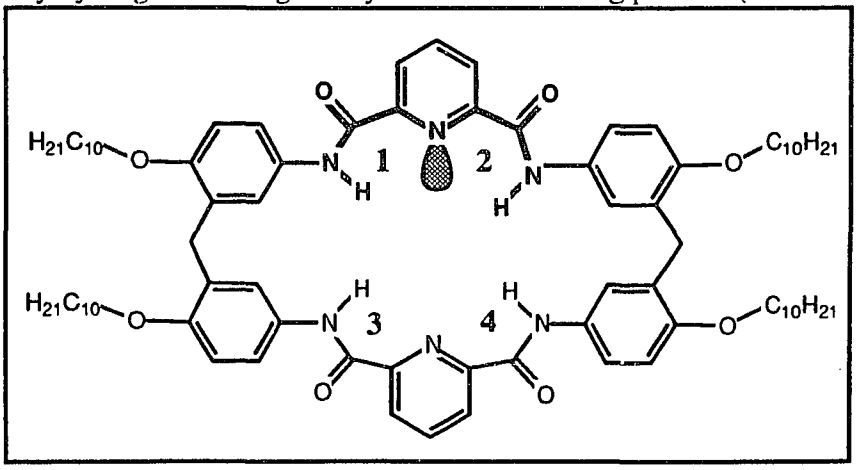
From the ^{1}H nmr spectroscopic data, a considerable amount of insight into the structure of the ligand is possible. The amide proton at 9.2 ppm indicates that the proton is

not hydrogen bonded to the pyridine nitrogen (Scheme 41). The planar nature of the amide bond also positions the carbonyl bond in close proximity to $\mathbf{H_d}$, and this is reflected as a downfield shift, (when compared to the analogous imine at 6.9 ppm), to 8.05 ppm.



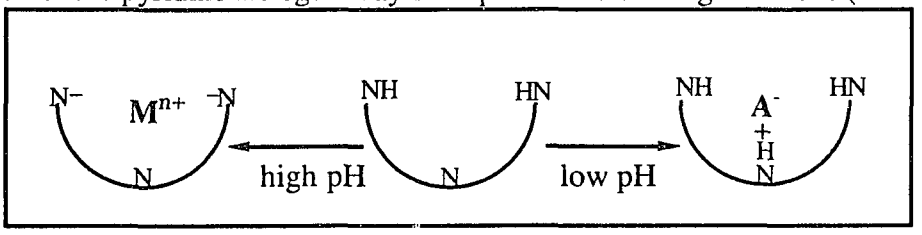
Scheme 41. Partial ^{1}H nmr of macrocyclic amide, **15**.

Further comparison, by CPK analysis, of the macrocyclic amide to the analogous imine, reveals that they are structurally similar, differing only in the functionality of the macrocyclic core. In **15**, the macrocyclic core is now '*sticky*', defined by the complementary hydrogen bonding ability of the four binding pockets (Scheme 42).



Scheme 42. Potential binding sites of **15**.

Macrocyclic amides presents to us yet another handle to control the guest binding properties of the macrocyclic cavity. The amide linkage compared to the imine is extremely stable under more forcing chemical conditions. At high pH, the macrocycle should become highly coordinative via the deprotonation of the amide nitrogen, whereas at low pH, protonation of the pyridine nitrogen may even permit the binding of anions (Scheme 43).



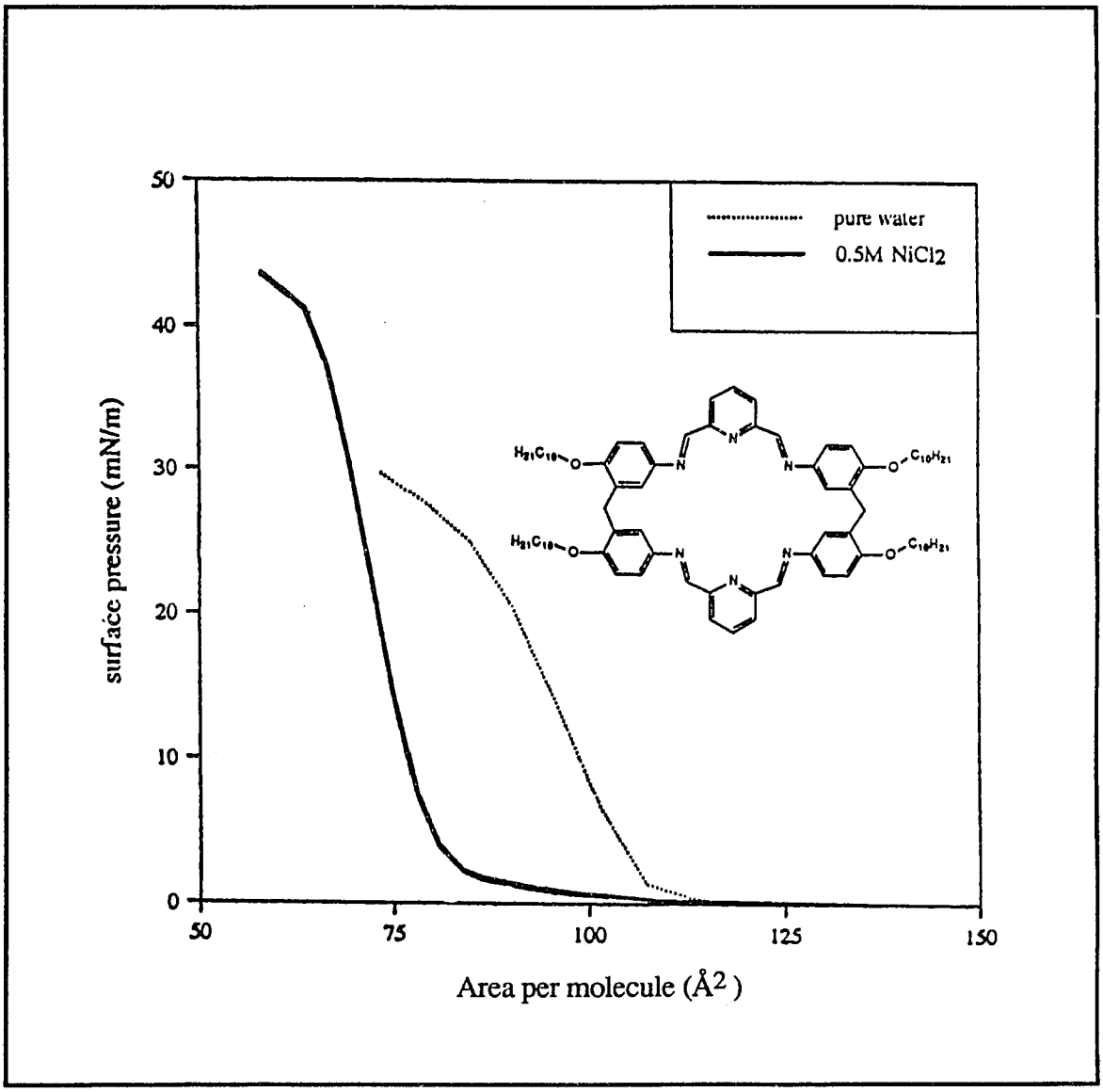
Scheme 43. pH control of guest binding.

One can also envisage the methodology used in the synthesis of **15** extended to the synthesis of other macrocyclic amides differing only in the choice of the dicarbonyl head group or the sidearm.

2.4-Monolayer formation:

Structurally, the lipophilic macrocyclic imines, and amides are set up to form monolayers and by extension, Langmuir-Blogdett (LB) films. Here, one can envisage, the macrocyclic imine or amide functionalities positioned into the aqueous subphase, and the hydrocarbon chains extended at the water/air interface. The molecular recognition capabilities of the macrocycle could also be evaluated by monitoring the effects of substrates such as cations or acids added to the subphase.

Preliminary experiments using **6** indicate an arrangement in which the macrocyclic core resides at the water/air interface with the aliphatic chains extended

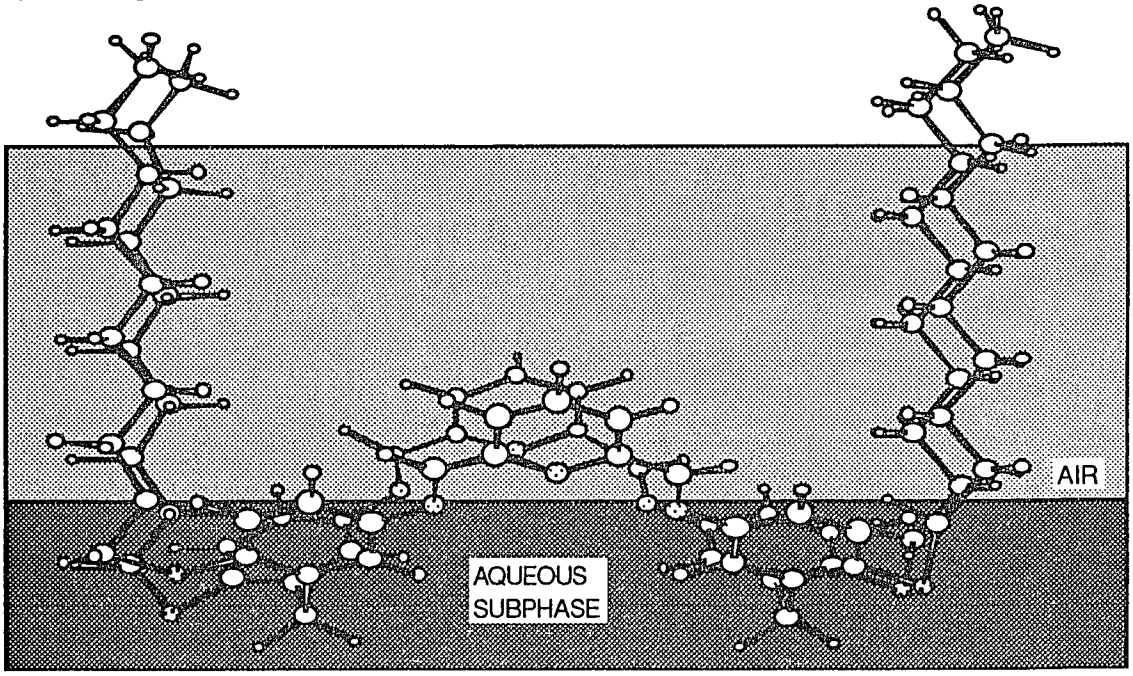


Scheme 44.Π-Area isotherms of **6**.

upwards (Schemes 44 and 45). It is fair to conclude that due to the similarity in structure of **6** and the other lipophilic macrocycles, they too by extension can form monolayers. From these monolayers, LB film construction may also be possible.

On comparing the isotherm obtained in pure water, to that where Ni^{2+} ions are added to the subphase, the ability of the macrocycle to form monolayers was not affected. Moreover, there are differences in the isotherms related to the stability of the monolayer formed, the molecular area, and the shape of the isotherm.

Isotherms obtained in the absence of nickel show a collapse pressure of 30 mNm^{-1}, compared to 45 mNm^{-1} with nickel added to the aqueous subphase. Extrapolating to zero pressure, the area in the absence of nickel to the subphase was about 110 $Å^2$ and 81 $Å^2$ in the presence of nickel. With no nickel present in the subphase, one sees formation of the monolayer taking place over a wider range of molecular areas. With nickel in the aqueous subphase, the generation of the condensed phase takes place over a smaller range. Complexation of nickel cations by the macrocycle at the interface occurs from a conformation of the macrocyclic head group that is conformationally restricted and occupies a smaller area. This restriction is absent in pure water, where, the ring flip occurs, and there are numerous molecules at various conformational states, the condensed phase is highly compressible over a wider range of pressures.

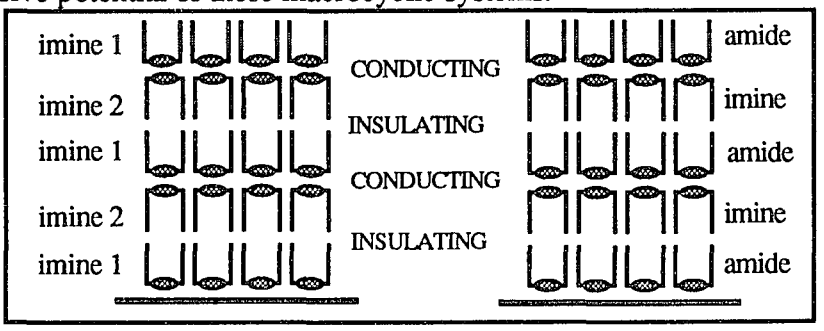


Scheme 45. Proposed models for monolayer formation and subphase interaction using **6**.

It is fair to conclude that the results establish molecular recognition at the interface by the macrocycle for cations and that the complexation of nickel cations increases the

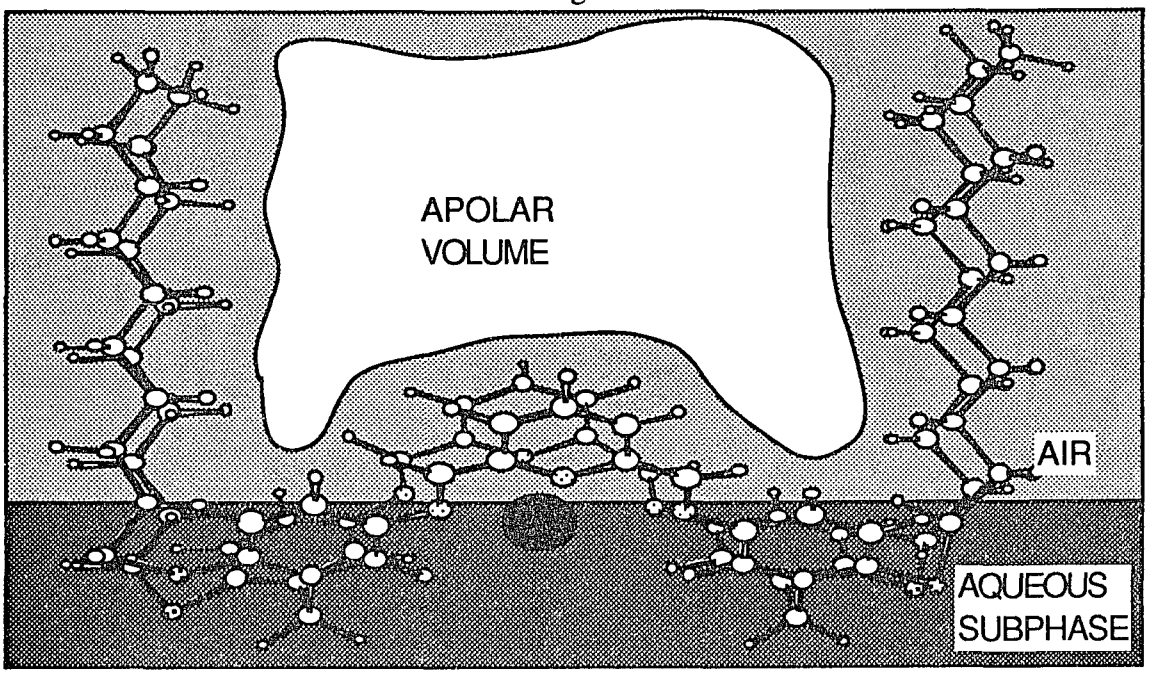
stability of the monolayer. Recognition may not be limited to imine/cation interactions but should be applicable to amides and other substrates.

The similarity in structure of the imines and amides should allow for the fabrication of LB films composed of mixed monolayers of imines and amides. Alternating layers of differing imines and imine-amide combination are also possible reflecting the cationic binding properties. There are numerous LB film constructs that these macrocycles could be used in to produce new material with unique electrical and chemical properties (Scheme 46). The enormous flexibility in the choice of the head group or the tail and the functionality, (i.e imine or amide), present in the macrocycles is the prime driving force for the explosive potential of these macrocyclic systems.



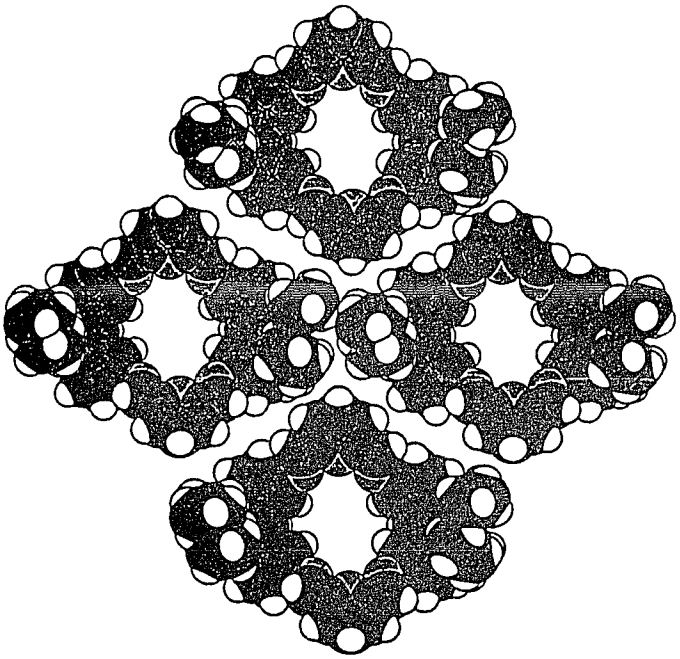
Scheme 46. LB film constructs using lipophilic imines and amides.

The apolar volume, (Scheme 47), formed by monolayer formation can also be utilized as hosts for the inclusion of other larger substrates.

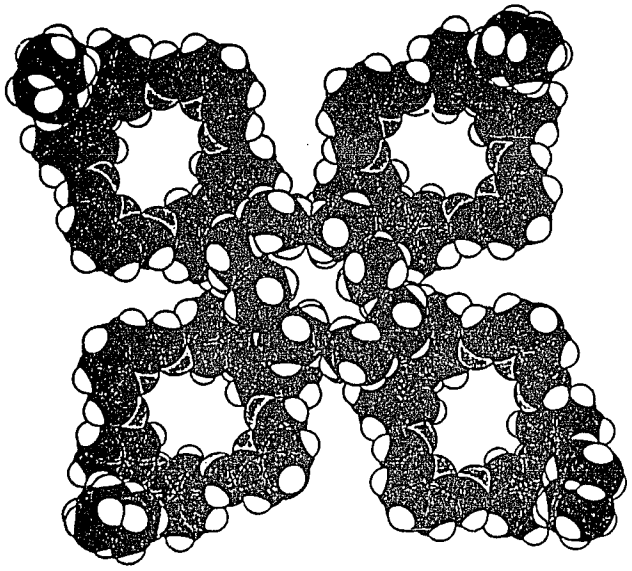


Scheme 47. Use of the apolar volume for additional Host-guest interactions.

Two arrangements of the macrocycle at the interface are clearly envisioned. In **A**, the hydrocarbon tails of two adjacent molecules are positioned end on end in a linear manner. On the other hand, in **B** the association of the eight hydrocarbon tails would produce in addition to the apolar cavity a second a apolar channel (Scheme 48).



A



B

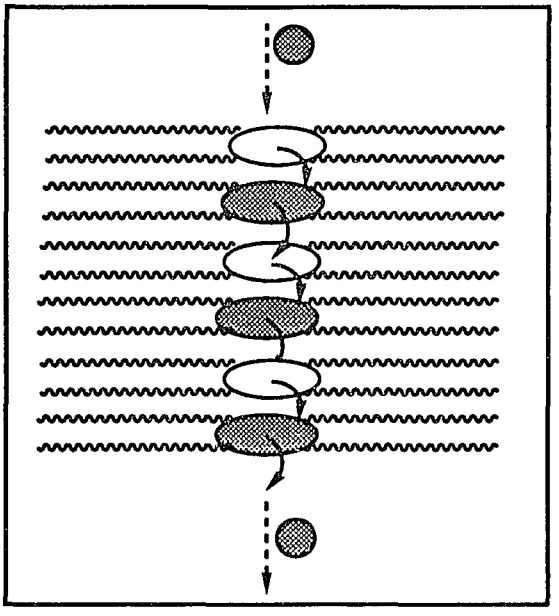
Scheme 48.Packing arrangement of monolayer formed by **6.**

2.5-Supramolecular structure formation:

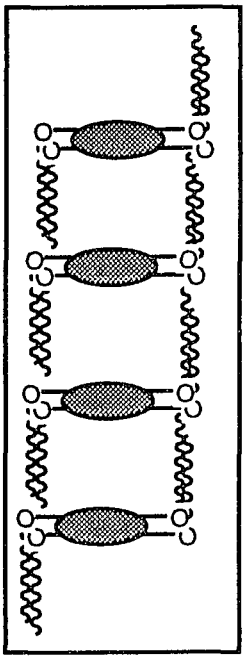
Membrane mimetic chemistry:

Gramicidin and amphotherin are two examples self-associating systems that form channels to transport cations.[15] The proposed mechanism of cation transport via ion channels formation of gramicidin, envisions the cation 'hopping' from one complexing site to the next until it traverses the bilayer structure of the membrane. Complexation and decomplexation processes account for the 'site hop' and cation movement. In amphotherin more than two molecules are thought to be involved in the association process. Common to both systems, is the positioning of the hydrophobic portions of the assembly oriented in such a way that they are placed in contact with the interior of the cell membrane. The polar ion-interacting moieties line the interior of the channel that is formed.

Lipophilic macrocyclic imines that self-associate may be utilized to form ion channels in a manner similar to the naturally occuring systems discussed above. Using **6** and **15** to illustrate, it is clear that the macrocyclic core in each molecule is conserved, however by changing the head group or the ring forming functionality, (amide and imine), modulation of differing complexing abilities at the core of the macrocycle may be effected (Scheme 49 and 50). The greatest challenge however rests with chosing the appropriate sidearm to force the ligands to assemble as shown.

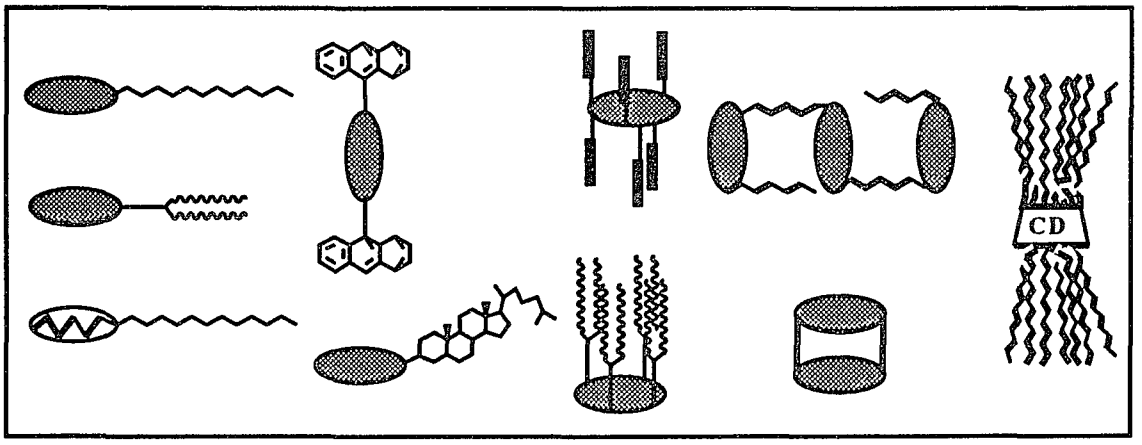


Scheme 49. Ion channel formation using **6** and **15**.



Scheme 50. Ion channel formation using **6**.

Membrane mimetic chemistry is replete with lipophilic crown ethers, cyclophanes and cryptands. The current report by Lehn using cyclodextrins is one of the few variations away from this theme.[16] Lipophilic macrocyclic imines are conspicuously absent from this considerable body of literature. A common feature seen in all of the macrocycles shown is the macrocyclic core appended to a lipophilic moietiy (Scheme 50). Type 2 macrocyclic imines **4**, **6**, **7**, **8** and **20**, all satisfy this one common property.

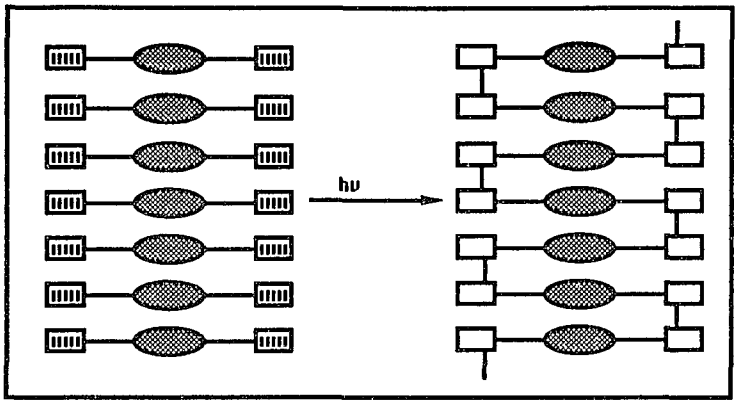


Scheme 51. Lipophilic macrocycles commonly used in membrane mimetic chemistry.

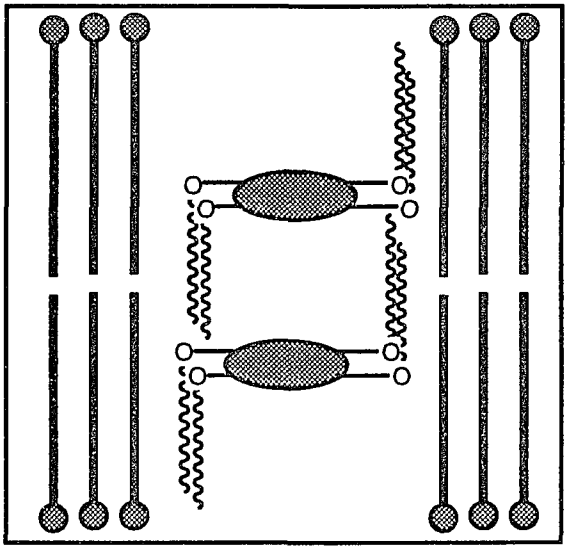
One potential use of **20** is in the fabrication of ion channel-like structures that can be photochemically activated or deactivated into supramolecular structures (Scheme 52). In such an arrangement, the ionophoric center of the imine would be positioned along the central cavity of the supramolecular structure, and once formed, then be temporarily fixed by a cascade photo-polymerization.

Excimer fluorescence produced by the association of pyrene, dansyl or anthracenyl moieties have been used to study membrane morphology.[17] Control over membrane structure can be achieved using polymerizable functionalities incorporated into the membrane structure.[18] Both of these important properties can be met using anthracenyl macrocyclic imine.

It is conceivable that orientation of the polar macrocyclic head group on integration into membrane structures would occur with the head group positioned in the same manner as the lipid amphiphiles, and the hydrocarbon chain positioned into the lipophilic interior of the membrane. On the other hand, it may take place by dimerization of the C-10 macrocyclic imines spanning approximately 40 Å; roughly the length of the bilayer of membranes (Scheme 53). Replacing the C-10 lipophilic chain with the oxyethylene units or other complexing moieties of similar length should allow for further expansion of the macrocyclic imines in membrane mimetic chemical studies.



Scheme 52. Photochemical control over ion-channel formation.

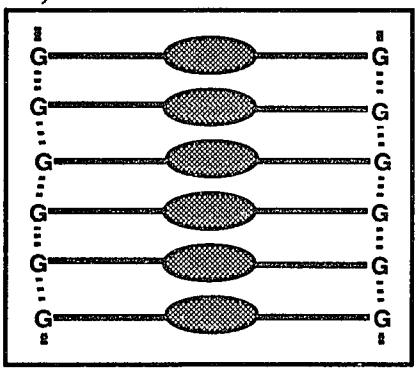


Scheme 53. Orientation of dimeric macrocyclic imine integrated into membranes.

Supramolecular arrays

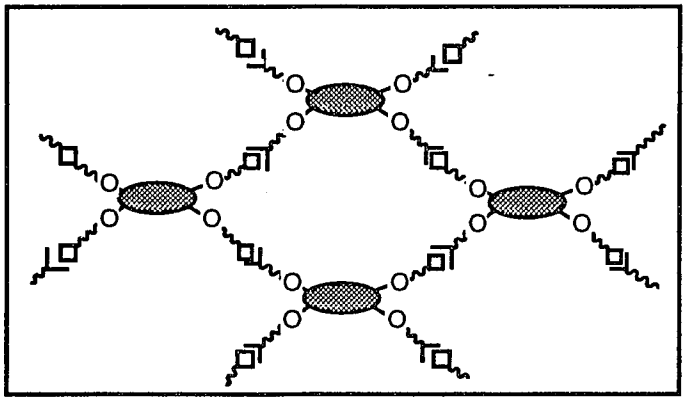
Supramolecular structure formation into fibers, cloths, superhelical structures, dendrites and molecular arrays, are well within reach using the [2 + 2] assembly utilized in the synthesis of type 1 and type 2 macrocycles. Placing moieties that interact by inter and intra molecular hydrogen bonding, π stacking interactions or Coulombic interactions, at each of the four linkage sites could be used to construct supramolecular assemblies. In such arrangements, the macrocyclic cavity may be placed in a fixed position (Scheme 54). Molecular arrays of the macrocyclic imines could be produced using pendant arms such as the purine or pyrimidine bases or phenanthroline (Scheme 55). In the first case the potentially liquid crystalline molecular array would be produced by the A:T or C:G hydrogen bonding interactions of the bases. A cation induced assembly or hydrogen

bonding foci could be used to produce photochemically/electronically active or liquid crystalline arrays (Scheme 56).

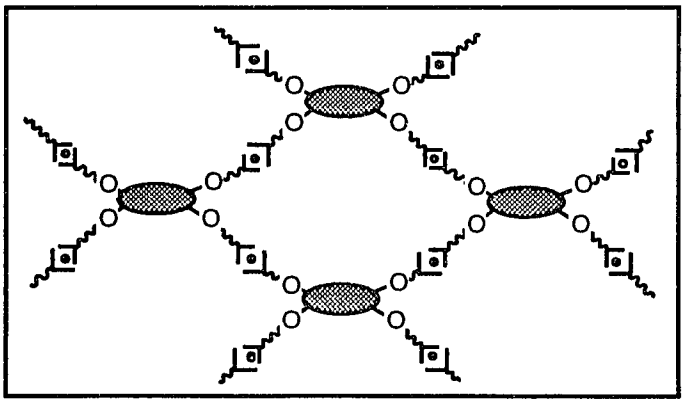


Scheme 54. Intermolecular interaction of sidearm in the production of supramolecular arrays.

The assembly of helical bundles of peptides, are also within reach using the [2 + 2] macrocyclization assembly.[19] Derivatization of the diamine or dinitro, followed by assembly, (the functionality of macrocylization is variable) would produce ion channels, peptide bundles or other highly ordered supramolecular structures. Macrocyclic imines or amides tethered to monoclonal antibodies and proteins are also within reach.[20]



Scheme 55. Molecular arrays by complementary hydrogen bonding interactions.



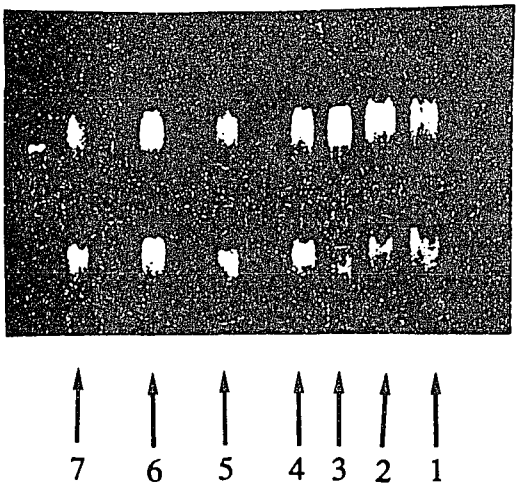
Scheme 56. Guest induced assembly into supramolecular structures.

2.6-Macrocycles as oxidative DNA cleavers/Oxygen transfer catalysts:

The ability of macrocyclic ligands to complex nickel cations in the +2 and the hypervalent oxidation states is paramount in their success as oxidation catalysts and nucleic acid cleavers. The restrictive flexibility, conformational mobility, and coordinative ability of the type 1 and 2 macrocyclic imines, and their recognition/binding properties for the nickel cation make promising candidates from which to explore the oxidative chemistry of nickel.

Preliminary experiments done to explore the DNA cleaving and catalytic potential were conducted using **1** and **4** in the presence of Ni(II) cations. Oxone and Clorox were used as the terminal oxidant for the DNA cleaving and alkene oxidations, respectively.

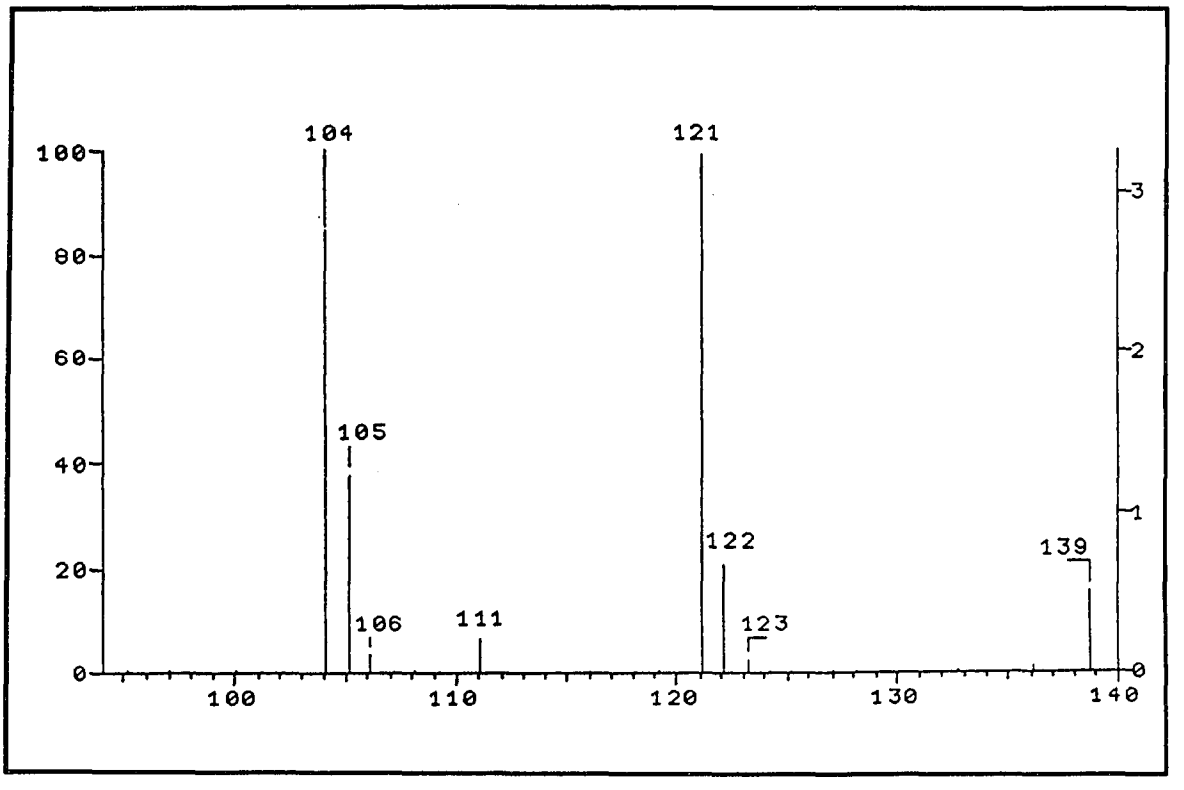
A supercoiled plasmid was used to test the DNA cleaving ability of the macrocycle. Incubation of the plasmid with **1** produced a gel electrophoresis profile indicative of DNA 'nicking' (Scheme 57). The increase in the intensity of bands B after the incubation is consistently reproducible and does occurs in the absence of the macrocycle. Complete conversion from A to B did not occur possibly due to the hydrolysis of the macrocycle under hydrolytic aqueous conditions.



LANE	DNA	Ni^{2+}	[O]	C=N
Lane !	+	+	+	-
Lane 2	+	+	-	+
Lane 3	+	-	-	-
Lane 4	+	+	+	+
Lane 5	+	+	+	+
Lane 6	+	+	+	+
Lane 7	+	+	+	+

Scheme 57. Oxidative cleavage of supercoiled DNA using **1**.

Oxygen transfer experiments with **4** using styrene, to examine its oxidative potential were conducted in a CH_2Cl_2/H_2O mixture in the absence of a phase transfer catalyst. Immediately after addition of the oxidant to the mixture of **4** and $NiCl_2.6H_2O$, a brown/black solid formed that was insoluble in CH_2Cl_2 or water. This observation was reported earlier using bipyridine nickel complexes as the oxidation catalysts.[21] The precipitate or the formation of products did not occur in the absence of Ni^{2+} cations or the macrocycle. Complete conversion of the styrene was observed by TLC analysis. Mass spectral analysis of one isolated product gave a m/z 121, a gain of 17 units possibly due to hydroxylation (Scheme 58).

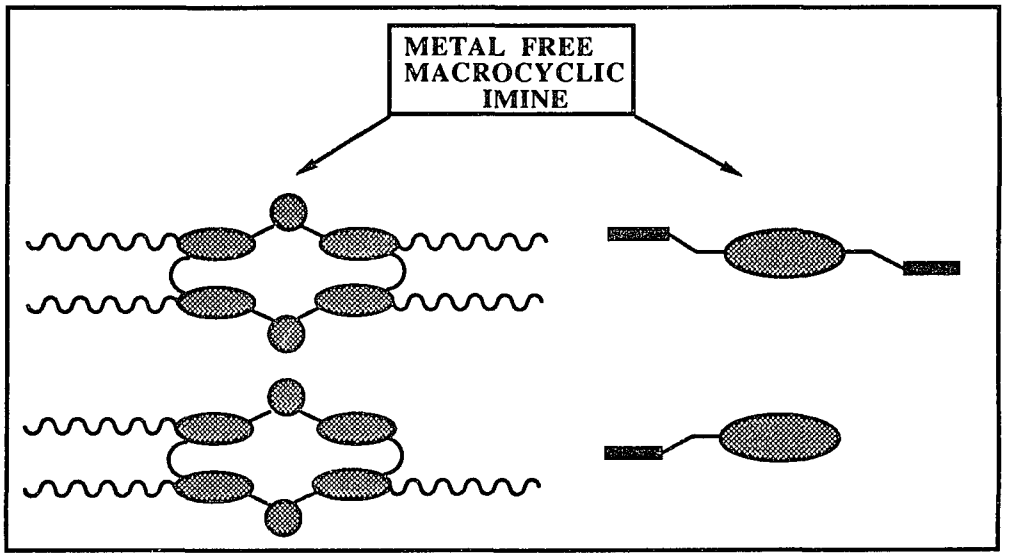


Scheme 58. Mass spectrum of styrene oxidation isolate.

2.7-Mass Spectroscopy

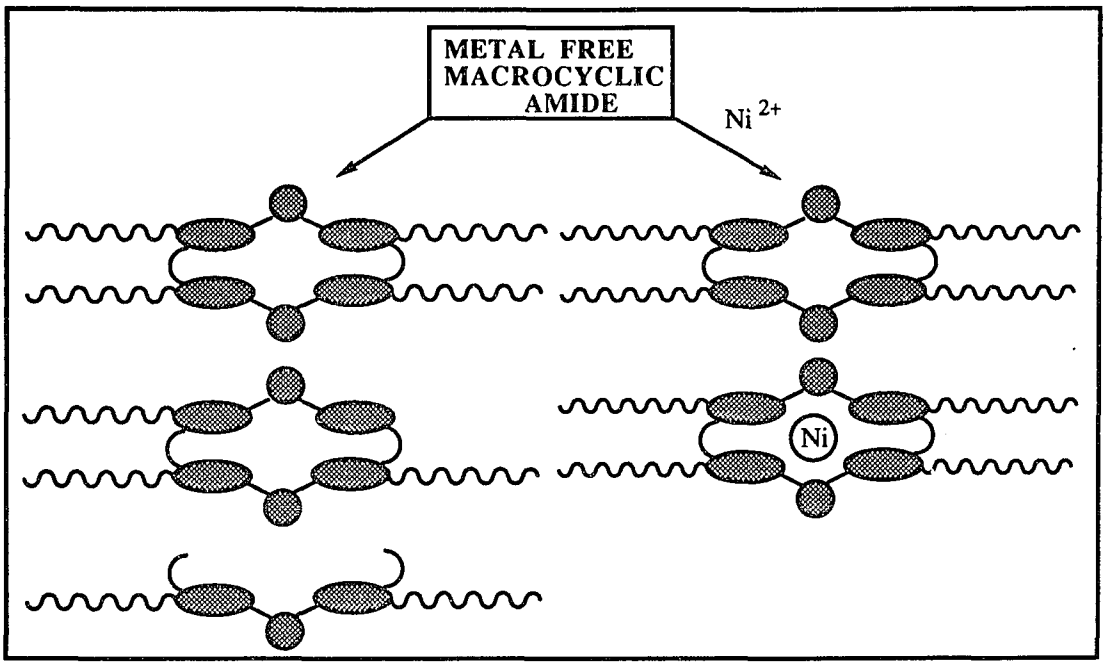
Increasingly, mass spectroscopy is becoming one of the primary methods used to characterize macrocycles and their host-guest adducts.[22] The ion discrimination properties of crown ethers in solution, and gas phase have been determined by mass spectroscopic analysis.[23]

Electron impact, (EI), analysis of macrocyclic imines (cation complexes or metal free) in most cases produce the metal free macrocycle as the molecular ion, or macrocycle derived decomposition and reaction products. Macrocyclic imines as a group have been studied primarily by Vigato, reporting on the EI and FAB fragmentation patterns in the presence of cations or metal-free ligands.[24] For the imines reported here, EI analysis failed to produce observable molecular ions. FAB analysis on the other hand gave results consistent with the earlier studies. A brief summary of the general fragmentation pattern of the metal-free imines, and some examples are shown in Scheme 59 and 61-63 respectively.



Scheme 59. General FAB-MS fragmentation pattern of macrocyclic imines.

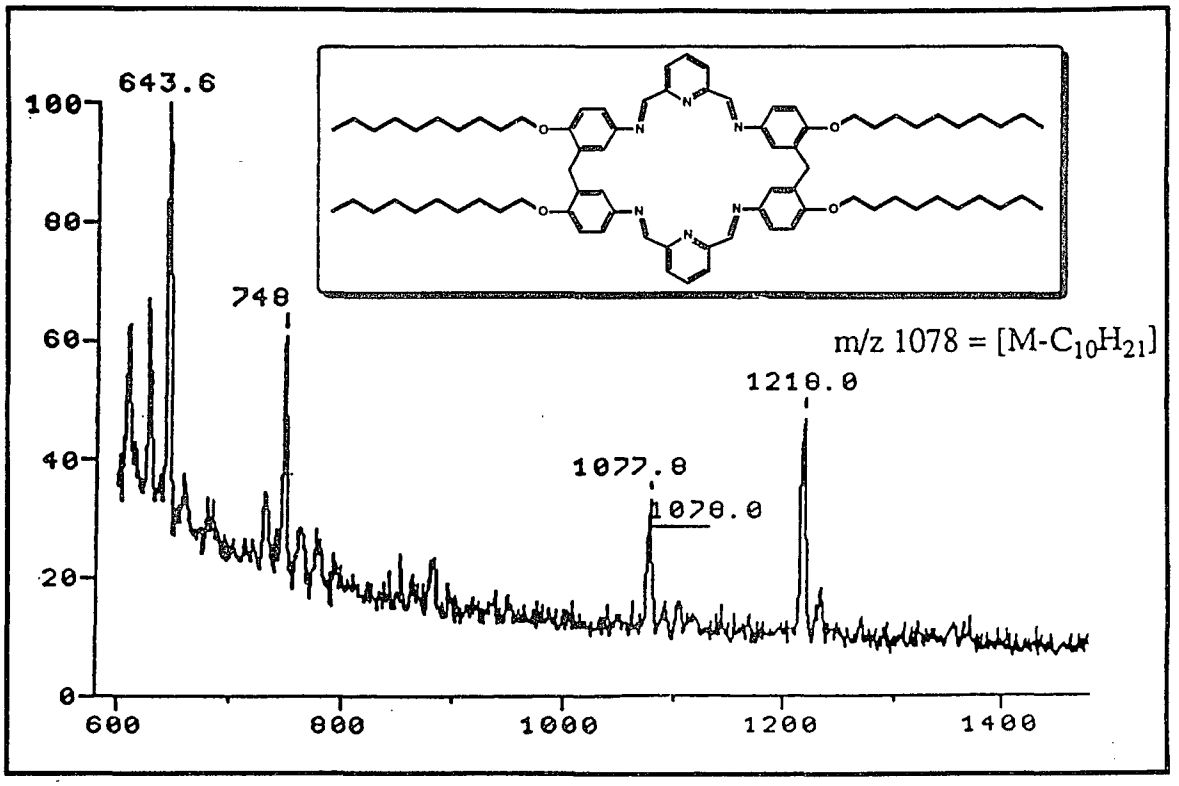
A similar pattern, (Scheme 60), was observed for the macrocyclic amide, **15**. Evaluation of the guest binding properties of the ligand was done using $NiCl_2$ (Scheme 64-66). In the case of the preformed complex, both the free ligand and the Ni-**15** complex were observed. With the metal-free ligand, on adding $NiCl_2$ to the NBA matrix, the fragmentation pattern observed was similar to that of the preformed complex. Other matrices will have to be explored to evaluate the utility of this technique to evaluate solution state host-guest properties of the macrocyclic imines and amides.



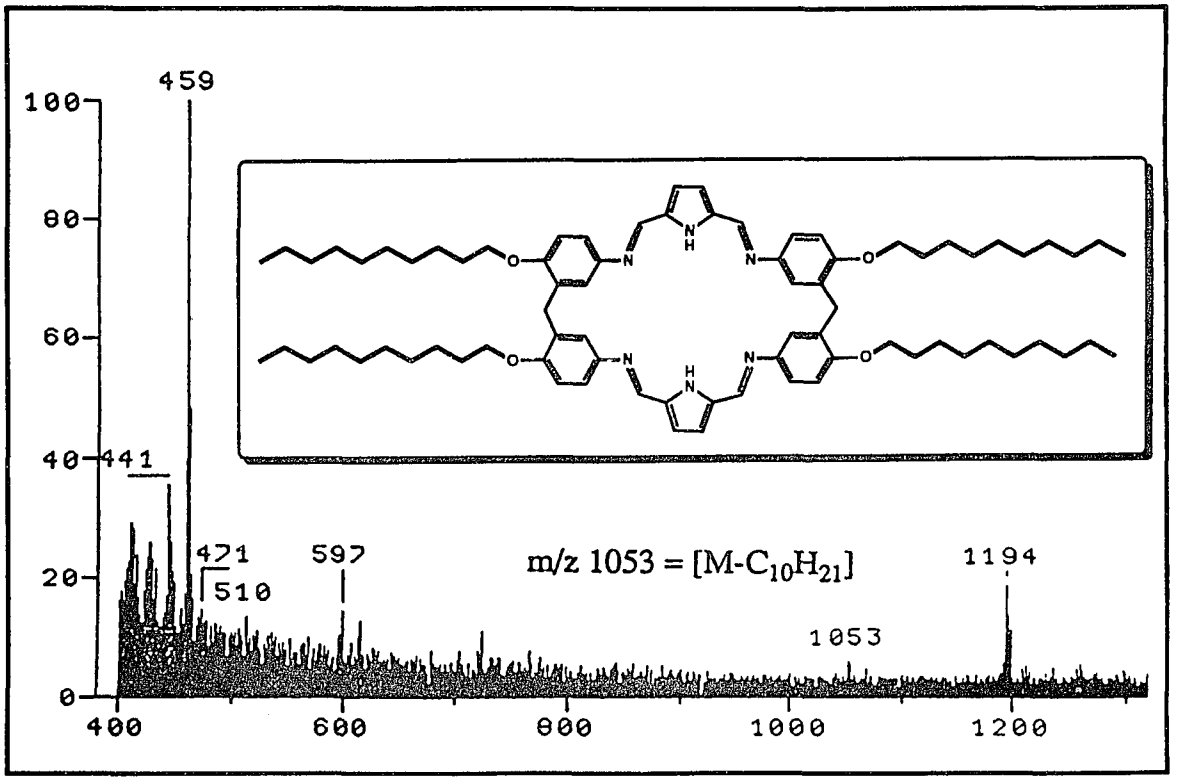
Scheme 60. General FAB-MS fragmentation pattern of **15**.

If rapid complexation occurs on the addition of guest molecules, and this preserves the macrocyclic cavity, it may be possible to finetune the procedure for use in characterizing not only the macrocyclic imines but their molecular recognition characteristics as well.

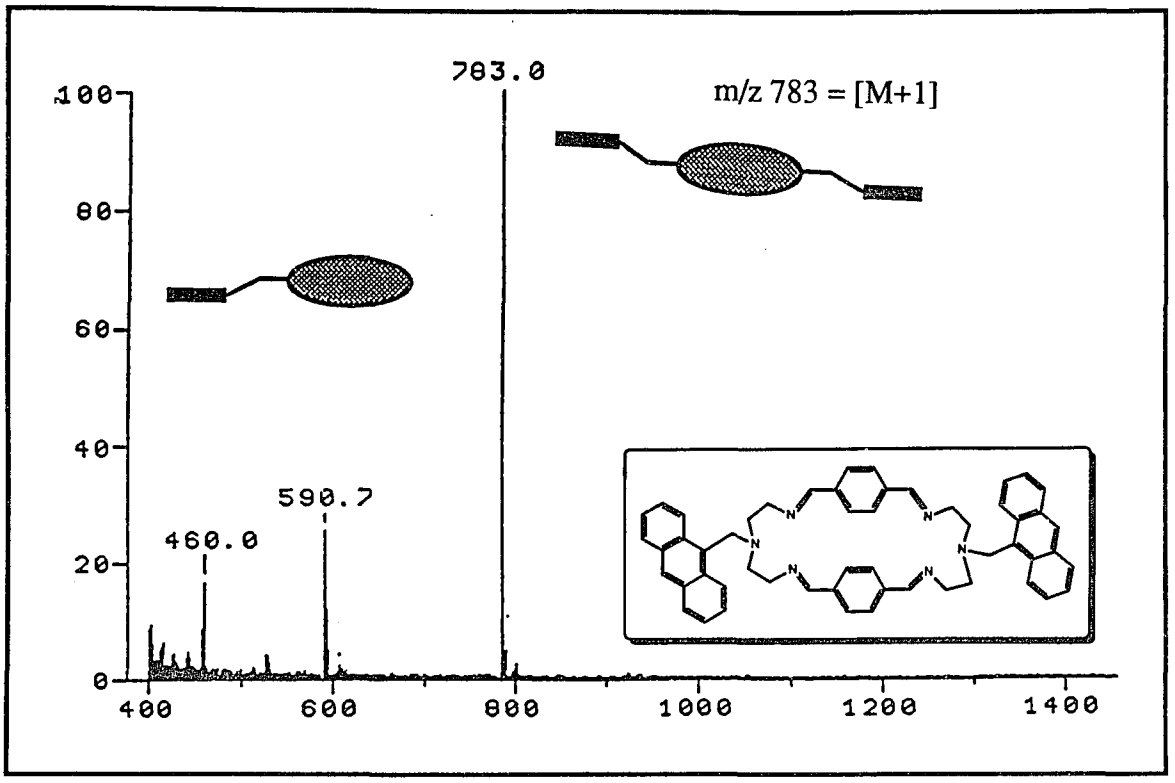
Some general observations were made while conducting the FAB studies. To enhance the quality of spectra obtained and increase the likelihood that the molecular ion will be observed, acidic additives are often added to the matrix. For the macrocyclic imines, this was not the case and probably resulted in disruption of the imine linkage. It was also observed that the solubility of the macrocycle in the matrix or a matrix/solvent combinations also effects the appearance of an observable molecular ion. Matrices such as trifluoroethanol may be advantageous over NBA.[25] For a number of the substances it is known that reactions do occur during the FAB experiment which can not only obscure the pertinent process being evaluated but now becomes a time dependent process.



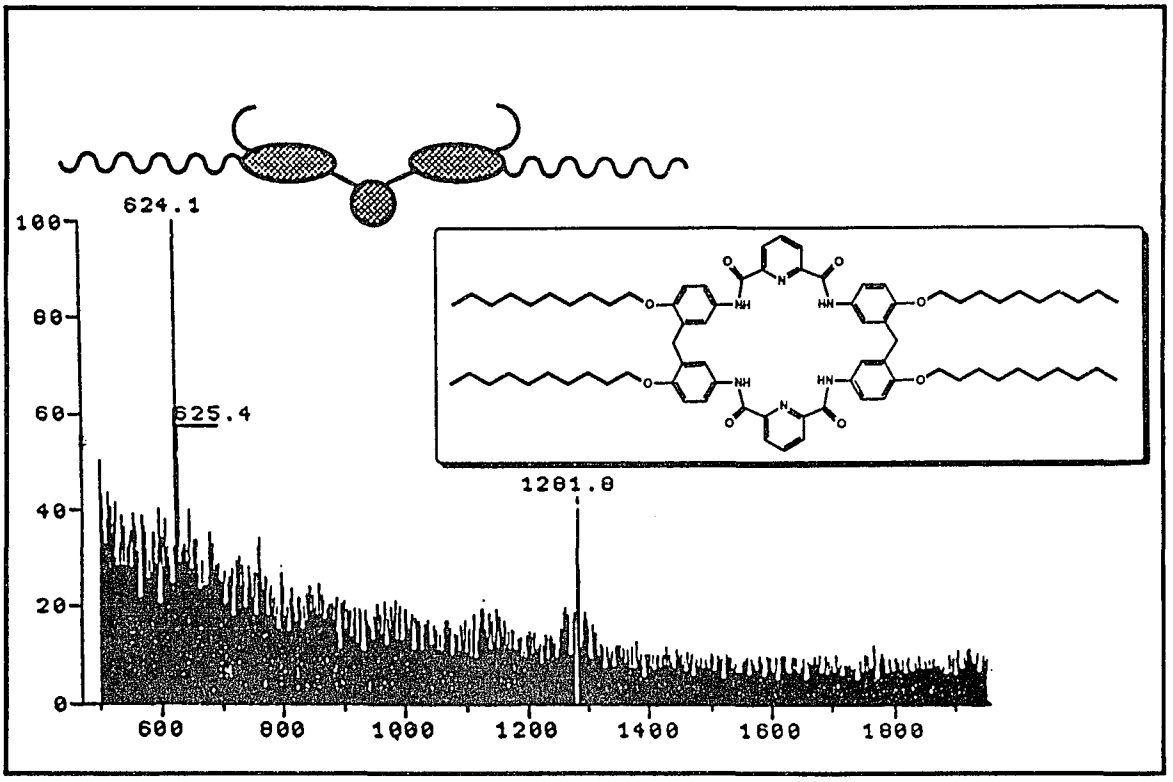
Scheme 61. FAB-MS spectrum of **6**.



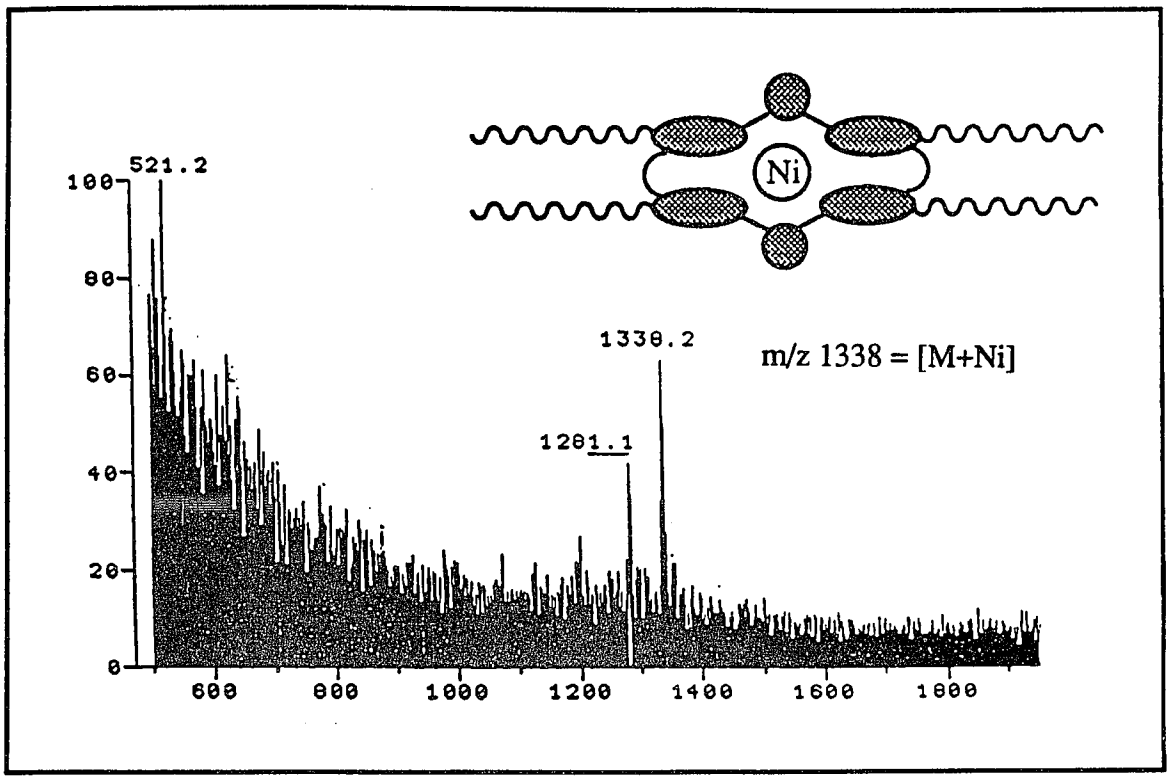
Scheme 62. FAB-MS spectrum of **7**.



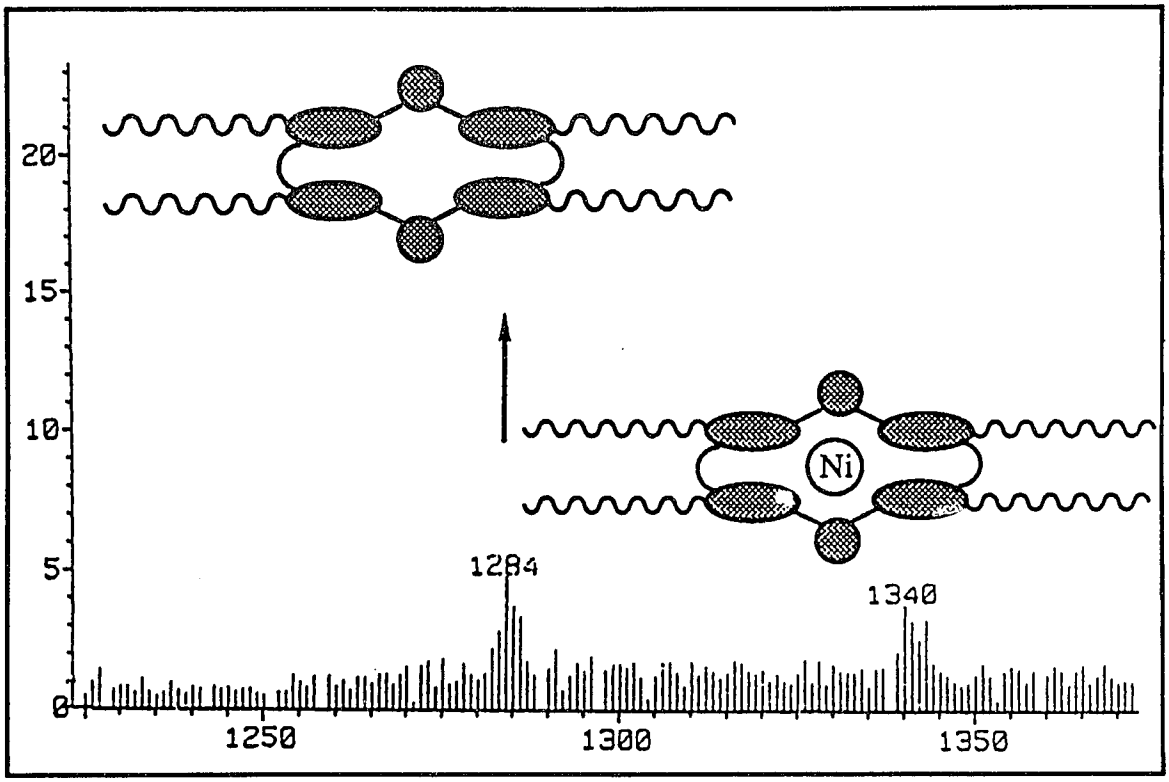
Scheme 63. FAB-MS spectrum of **20**.



Scheme 64. FAB-MS spectrum of **15**.



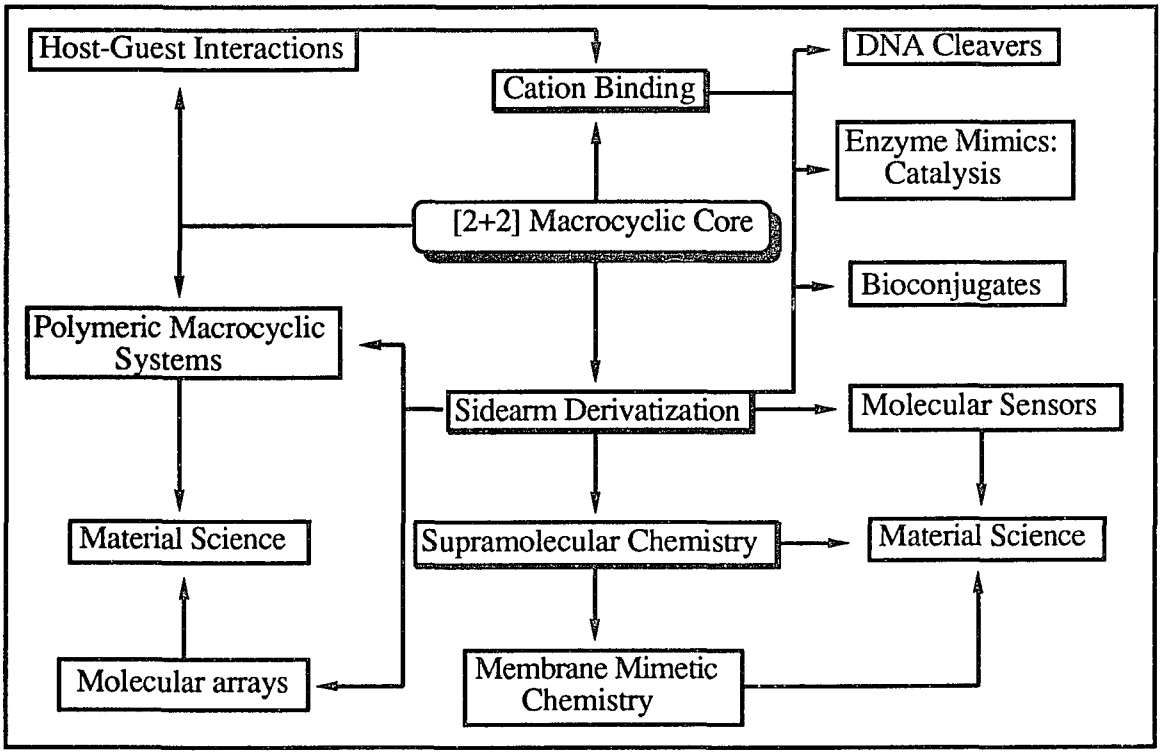
Scheme 65. FAB-MS spectrum of 15 + $NiCl_2$.



Scheme 66. FAB-MS spectrum of 15-Ni complex.

3-Conclusion:

The most important outcome of the work we have presented here is that the facile [2+2] addition opens a number of avenues, hitherto not accessible. Three fundamental reasons for the broad potential of this work are the metal-free nature of the macrocycles, sidearm derivatization, and the cation binding ability of the macrocyclic cavity. Combinations of these, so far, has allowed us to study a number of important aspects; furthermore, future applications of them will have equally significant impact. The salient aspects of this work, and its impact in other areas in the future studies, are succintly presented in a chart form in Scheme 67.



Scheme 67. Diverse application of the[2+2] macrocyclization.

The metal-free nature of the macrocyclic cavity presents a binding site to probe Host-Guest interactions with small molecules, cations such as nickel, and also transition metals of similar size. Focusing on nickel, the binding of the cation by the macrocycles is an important step in exploiting the oxidation properties of the nickel cations in the development of artificial enzymes and nucleic acid cleaving agents. Sidearm derivatization of the cavity can be employed to not only to fine-tune the aforementioned properties, but also to expand their use in the construction of bioconjugates.

The stability of the macrocyclic cavity under basic conditions combined with the presence of four phenolic hydrogens at the rim, enables the construction of polymeric macrocycles from these unique macrocyclic monomers. The conformational mobility of the macrocyclic core, the electronic properties of of the cation complexes,and its oxidation and photochemical properties, all will become integrated in the polymeric material. The large choice of sidearms that can be attached at the four phenolic sites also introduces the possibility of using these macrocyclic cores in the construction of 2D polymers.

The most important outcome of our work is, probably, the sidearm derivatization of the macrocyclic core. The supramolecular properties of sidearm derivatized lipophilic macrocycles which we have demonstrated, portend the feasibility of producing a plethora of supramolecular structures specifically designed to have desired properties. As was in the case with the polymeric macrocycles, it will be possible to retain as well as to fine-tune the properties of the macrocycles in the supramolecular systems generated from them. This, in turn should lead to optimized oxidation and photochemical properties, and to the development of better DNA cleaving agents and molecular sensors.

One field which has not yet been explored, but which could benefit significantly from the present work, involves material science. Exerting true control over the outcome of the making of unique materials is best achieved starting from the origin in the present case, the macrocycle. The versatility of the macrocycle has been established since their discovery over two decades ago by the intensive scientific exploitation, that is intensifying further, as the applicability of the macrocycle constantly expands. The products of [2+2] cyclizations presented, and the potential for numerous others makes the procedure one of the most promising one for future exploration in material science.

The complementary relationship of virtually every branch springing from the [2+2] macrocyclization, each serving to utilize existing properties by combining and building on others, steers towards the creation of even more diverse and broader use of the [2+2] macrocyclization.

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Chapter 3: Experimental

All chemicals were purchased from Aldrich Chemical Co. and used as such.
Solvents used were from Fischer Scientific unless otherwise stated.
Formaldehyde, NH_4Cl, $NiCl_2.6H_2O$, K_2CO_3 were also from Fisher Scientific.
Anhydrous solvents were purchased from Aldrich Chemical Co.
Ethidium bromide, agarose, and borate buffers were from Sigma Chemical Co.
Zinc dust was from Mallinckrodt Chemical works.
Deuterated nmr solvents were from Aldrich Chemical Co.
^1H and ^{13}C nmr spectra were recorded using a Bruker 300 MHz spectrometer.
Water supression was done using the PRESAT water suppression microprogram.
Fluorescence spectra were run using a Perkin Elmer LS-5 spectrofluorometer.
UV-VIS spectra were recorded using an Hewlett Packard 8452A spectrophotometer.
Finnigan SSQ-70 was used to obtain the EI, CI and FAB mass spectral data.
Energy minimizations were done on an IRIS INDIGO 4000 graphic station using the program MacroModel (W.C. Still, Columbia University).

Abbreviations used for energy minimized CPK models:

BEN13H	**1**
BEN13C10	**4**
BEN14H	**3**
BEN14C10	**5**
MACANTH	**20**
PYRC10	**6**
FURC10	**8**
PYRAMIDE	**15**
PYRRC10	**7**
PYRRESTER	**11**

Group identification of macrocycles:
Type 1: phenolic [2+2] macrocyclic imines- **1, 2, 3, 16,**
Type 2 : alkyl substituted [2+2] macrocyclic imines- **4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,**

3.1. Synthesis of 2, 2'-methylenebis(4-nitrophenol): [1]

13.9 g (0.1 mol) of 4-nitrophenol was placed along with 2.5 ml of water into a three necked flask. The flask was then heated to 70°C in an oil bath until the 4-nitrophenpl dissolves. A mixture of 5 ml of 40% formaldehyde and 12 ml of concentrated sulfuric acid was then added under stirring. The temperature was raised to 130°C. A greenish solid began to appear at about 30 minutes of heating. The stirring was continued for another two hours. The precipitate was transferred to a sintered glass funnel and was washed thoroughly with 500 ml of water and was allowed to dry (90 % yield).

3.2. General procedure for the synthesis of bisnitrophenyl ethers, e.g., 2,2'-methylenebis(4-nitrophenyl decylether):

A reaction flask was charged with 1.0 g 2, 2'-methylene bis(4-nitro phenol), 3.4 mmol, 10 g anhydrous K_2CO_3, (72 mmol) and 25 ml anhydrous DMF. The mixture was heated to 60°C and was stirred 12-16 hours at which time 1-chlorodecane was added. Stirring was continued for another 12 hours. The mixture was then allowed to cool to rt, and was filtered through a sintered glass funnel. The solvent was removed from the filtrate under reduced pressure and the ether was isolated by trituration in ethanol.

3.3. General [2+2] cyclization procedure: [2]

In a mixture of 10 ml THF, 20 ml EtOH and 5 ml of water, 0.35 mmol of 2,2'methylenebis(4-nitrophenyl decylether was dissolved. To this solution 2 mmol of NH_4Cl and 30 mmol of zinc dust were added while stirring. The reaction mixture was maintained at 50°C for 30 minutes and stirring was continued for one hour at room temperature. The mixture was cooled to rt, and was filtered through a sintered glass funnel. The residue was washed with 15 ml of EtOH, and the combined solvents were removed at reduced pressure. The grey brown solid that remained was taken up in 25 ml of ethanol and to this solution of the diamine, 0.28 mmol of the appropriate dialdehyde was added and the mixture was stirred for 16 hours. The precipitated macrocycles were isolated by trituration in ethanol.

3.4. Synthesis of podands

Preparation of 17, 18 and 21:

To 0.300 mmol of 4-amino phenol in 25 ml of ethanol was added 0.140 mmol of pyridine 2, 6 dicarboxaldehyde or isophthaldehyde and the solution stirred for 3-5 hours. The diimines, (**17** and **18**), were isolated by trituration with ethanol (100 % yield).

To 0.875 mmol of terephthalaldehyde in 25 ml of ethanol was added 0.175 mmol of 2, 2' methylene bis(4-amino phenyl decylether, (obtained from the reduction of 2,2'methylene bis(4-nitrophenyl decylether), in 20 ml of ethanol. The solution was stirred 5 hours and the product, **21**, was isolated by trituration with ethanol. A five fold excess of the dialdehyde is required to eliminate [2+2] macrocyclization to the tetraimino macrocycle giving instead **21**.

3.5. Synthesis of **15**: [2]

In a mixture of 10 ml THF, 20 ml EtOH and 5 ml of water, 0.35 mmol of 2,2'-methylenebis(4-nitrophenyl decylether) was dissolved. To this solution with stirring was added 2 mmol of NH_4Cl and 2 g (30 mmol) of zinc dust. The reaction mixture was kept at 50°C for 30 minutes and stirring was continued for another hour room temperature. The reaction mixture was filtered, and the residue washed with 15 ml of ethanol. The combined solvents were removed at reduced pressure. The grey brown solid was dried further *in vacuo* at rt for an additional 16 hours. To the solid was added 25 ml of anhydrous CH_2Cl_2, and 0.1 ml of triethylamine (dried on 4A molecular sieves). The solution was transferred to a reaction flask containing 0.28 mmol of 2,6-pyridinedicarbonyl dichloride and the mixture was stirred for 16 hours. At this time 40 ml of methanol was added and CH_2Cl_2 was removed at reduced pressure at room temperature. Precipitation of the grey-brown macrocyclic amide, **15**, occurred on the removal of the methylene chloride. The remaining methanol was removed by decantation. The precipitated macrocyclic amide was triturated further with two 10 ml portions of methanol (50-55 % yield).

3.6. Synthesis of **19**: [3,4]

Di amino ethylene triamine (0.8 ml, 7.5 mmol) was dissolved in 125 ml of acetonitrile, and to this solution was added under stirring phthalic dicarboxaldehyde (1 g, 7.5 mmol), in 200 ml of acetonitrile over a period of two hours. The solution was stirred for an additional 12 hours, during which white crystals began to form. The reaction mixture was filtered, and the solid was washed with 50 ml of acetonitrile and allowed to dry at rt (51 % yield).

3.7. Synthesis of **20**:

To **19** (100 mg, 0.25 mmol) dissolved in 50 ml of CH_2Cl_2 containing 0.5 ml of triethylamine, 9-(chloromethyl)anthracene (113 mg. 0.50 mmol) was added. The solution was stirred at room temperature for 12 hours, at which time 50 ml of methanol was added and the methylene chloride removed at reduced pressure at room temperature, to yield a

yellow-brown solid. From this solid, the anthracenyl macrocyclic imine was isolated by trituration with methanol (33 % yield).

3.8. Self-association studies:

3.8.1.

^{1}H nmr:

Compound **6** (6 mg) was dissolved in 0.4 ml of $CDCl_3$ (99.98 atom % D) that was prefiltered through a small basic alumina pad to remove traces of acid. Care was taken to ensure that the solution remained free of solid particles before the spectrum was taken. A more concentrated solution of **6**, 22 mg in 0.4 ml of $CDCl_3$,was prepared in the same manner. The ^{1}H nmr spectra of the two solutions were compared.

3.8.2.

Fluorescence studies:

A stock solution was made by dissolving 10 mg of **20** in CH_2Cl_2 and the solution made up to 10 ml. Dilutions were then made for the appropriate concentrations (1.28×10^{-3}, 1.5×10^{-5}, 1.0×10^{-7}).

3.9. Photo-irradiation studies:

A solution containing **20** (10^{-7} M) in CH_2Cl_2 was irradiated, (λ>350 nm), and the spectrum taken every 30 minutes.

3.10. Mass spectroscopy:

For FAB-MS analysis, the solid macrocycle was added to, and thoroughly mixed with the 3-nitrobenzyl alcohol (NBA) matrix. A red/yellow color developed in the NBA matrix. Alternatively, the macrocycle was dissolved in CH_2Cl_2 or DMSO and this solution mixed with NBA and 1 μl applied to the probe tip. Xenon was used as the gas at 8 eV. For CIMS analysis, NH_3 was used as the reagent gas.

3.11. Cation-macrocycle interaction:

1-K_2CO_3

Compound **1** (3 mg) was dissolved in tetrahydrofuran-d_8 (99.5 atom % D). To this was added 15 mg of solid K_2CO_3 and the solution allowed to stand for 14 days at rt. A dark precipitate formed. The ^{1}H nmr was taken of the supernatant. No resonances

corresponding to the macrocyclic imine were seen. THF was then removed and to the solid dimethylsulfoxide-d_6 (99.9 atom % D) was added. The ^1H nmr was then taken.

15-$NiCl.6H_2O$

To a solution of the amide, **15**, in 2 ml of THF was added 10 mg of $NiCl_2.6H_2O$. The solution was allowed to stand for 12 hours at room temperature, during which time a yellow precipitate formed. The THF was removed using a stream of nitrogen, DMSO added, and the absorbtion spectrum taken. UV-VIS spectroscopy was used to follow the complexation by taking the UV-VIS spectrum of the THF supernatant.

3.12. DNA cleavage studies:

Preparation of reaction mixture: [5]

To a solution containing 1 µl of PMG25, (5 Kd supercoiled plasmid obtained from Dr. S. Simms, (CCNY)), was added 1 µl of (6.0×10^{-3} M in DMSO), 1 µl of Ni (2.5×10^{-2} M $NiCl_2.6H_2O$ in H_2O), 1 µl of OXONE (0.162 M in H_2O) and 100 µl of TRIZMA buffer (pH=7). Reactions in which either the oxidant, nickel or the macrocycle was omitted were made in a similar manner using the prepared stock solution. A blank run containing only the supercoiled DNA was also preformed and used for comparison. All solutions were incubated at 37°C for 42 hours at which time 5 µl was removed from each for gel electrophoresis analysis.

Agarose gel preparation:

The agarose gel was prepared by adding 1g of agarose, (Sigma), in 100 ml of 0.5x TBE buffer and place in a microwave for 1-1.5 minutes. While cool to touch (50^0C), 10ug of ethidium bromide was added to the solution and poured into the imersion cell (Fisher), then allowed to set. The wells were loaded with 5ul from the reaction mixtures, 1ul of bromophenol blue and 2ul of TBE and allowed to run for 1.5-2 hours at a power setting of 100 Volts..

3.13. Monolayer studies:

All monolayer experiments were conducted within a Faraday box. Calcinated talcum powder was used to clean the surface and was removed using a glass tip connected to an aspirator. A 6.5×10^{-4} M solution of **6** was made by dissolving 8 mg of the macrocycle in 10 ml of chloroform. The solution was deposited on the aqueous phase using a

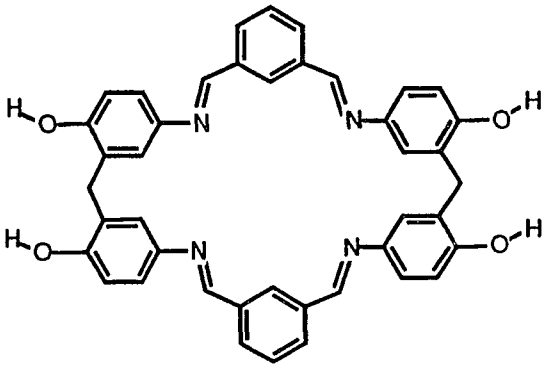
micrometer syringe and retained in a fused silica trough of 1.3 liter capacity. All measurements were done at 27^0C. Surface pressures were determined from surface tension measurements and followed the procedure of Rosano *et al.*[6]. A compression rate of $20A^2$/m/min was used.

3.14. Mixing studies of macrocyclic imines **6** and **4**:

Compound **4** (6 mg) was dissolved in 0.5 ml of acid-free $CDCl_3$ (99.98% atom D) and the ^{1}H nmr spectrum taken. The same process was then repeated for **6**. The contents of the two nmr tubes, (containing **4** and **6**), were then mixed and the spectrum taken. The ^{1}H nmr spectra for the isolated macrocycles and that of the mixed solution were then compared.

3.15. Molecular modelling studies using MacroModel.

The auxiliary computational chemistry program Batchmin was used to carry out all calculations. For the molecular mechanics calculations, a modified version of the MM2 force field (MM2*), was used for the energy calculations. In all calculations the effect of solvent was excluded. In each case, calculations started from an initial starting geometry that was planar.



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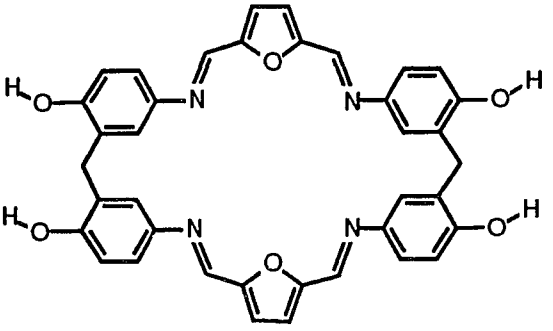

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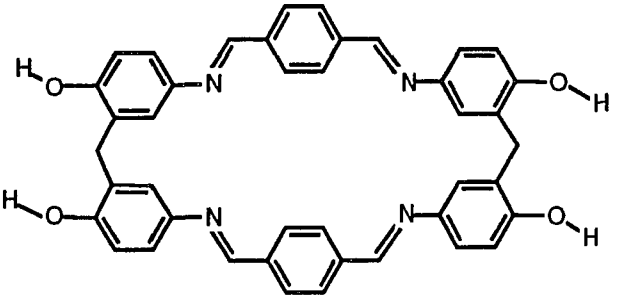

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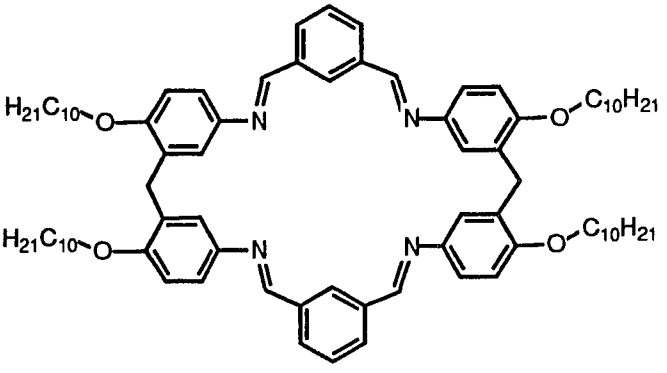

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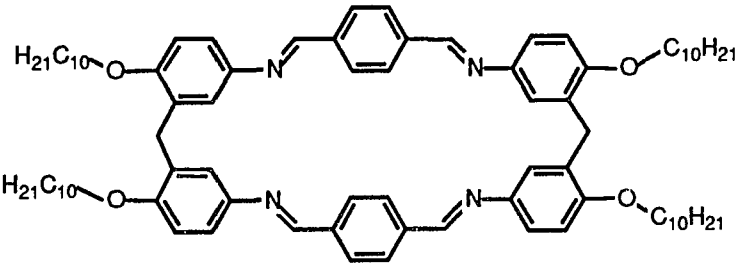

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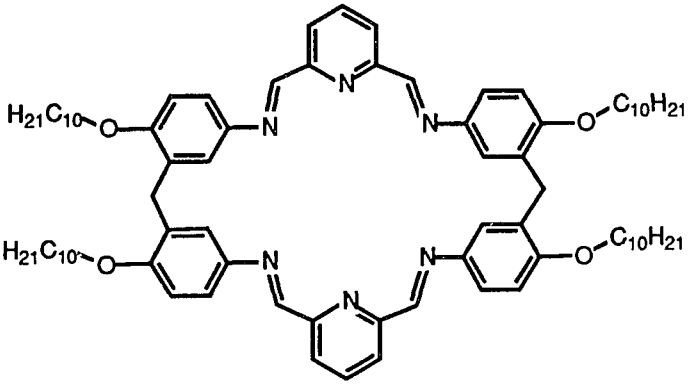

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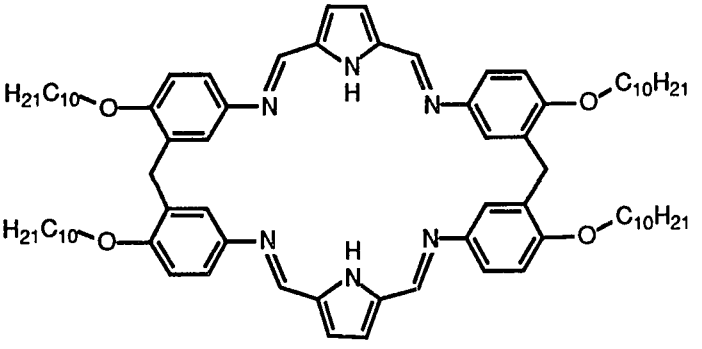

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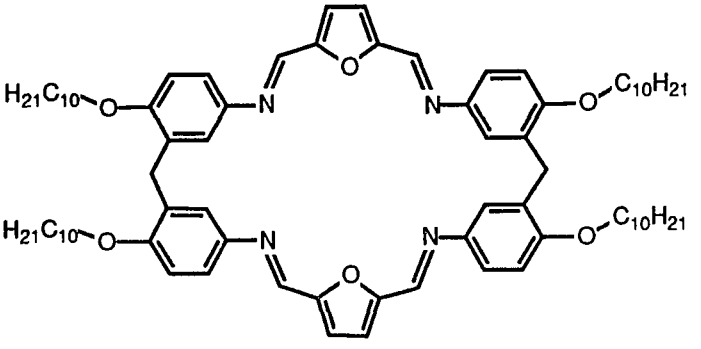

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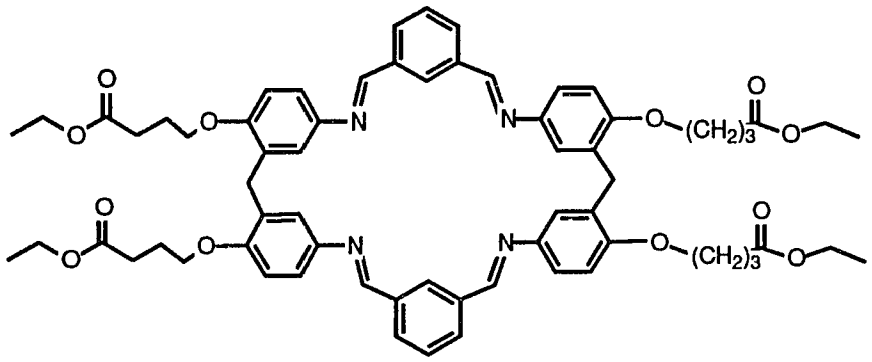

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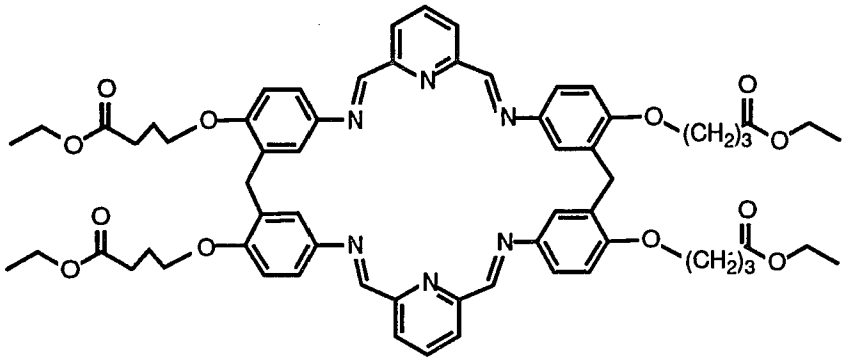

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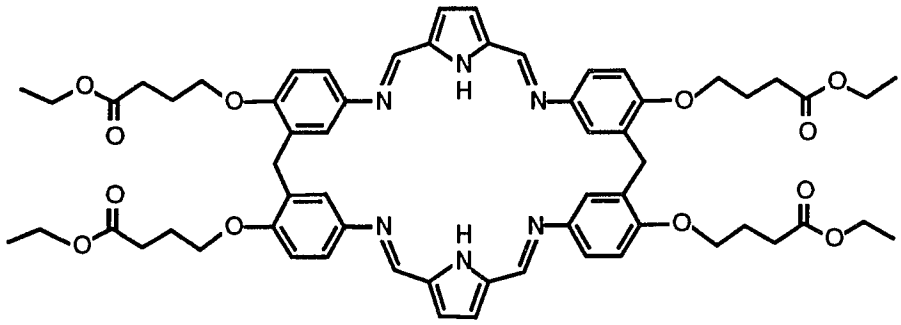

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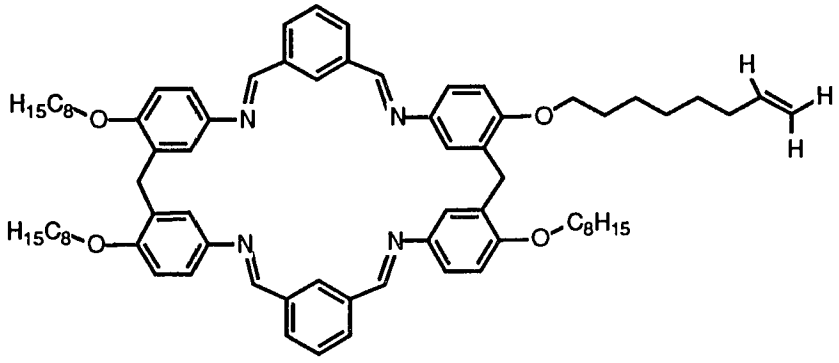

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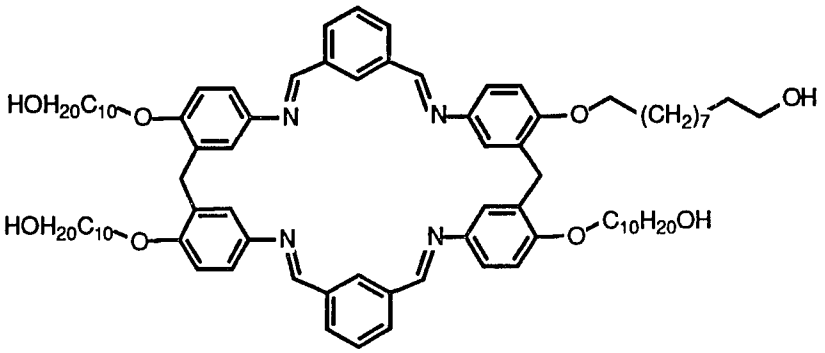

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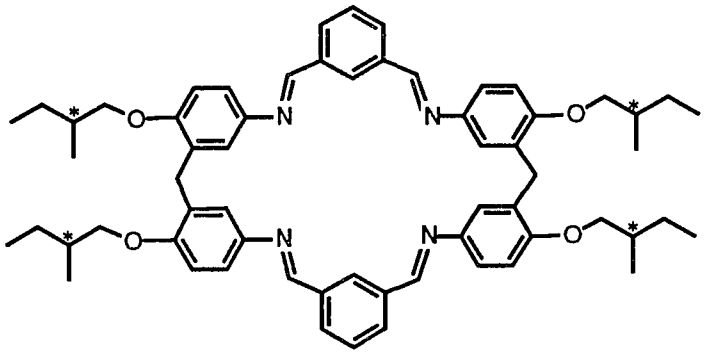

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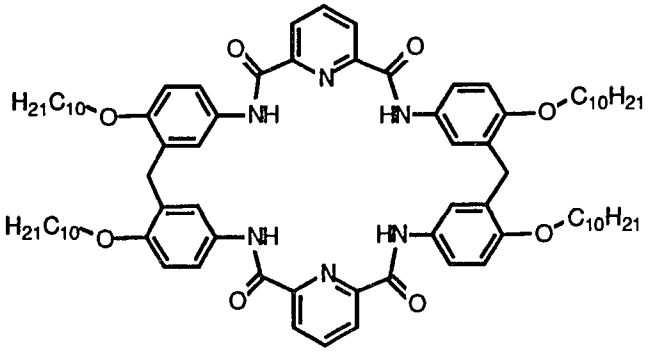

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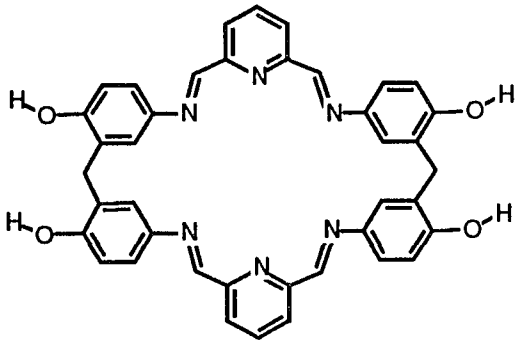

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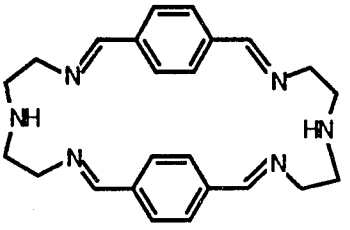

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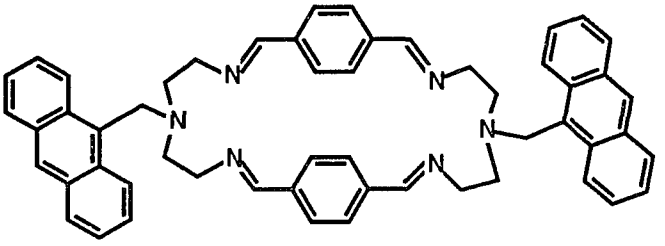

20 (33 %)

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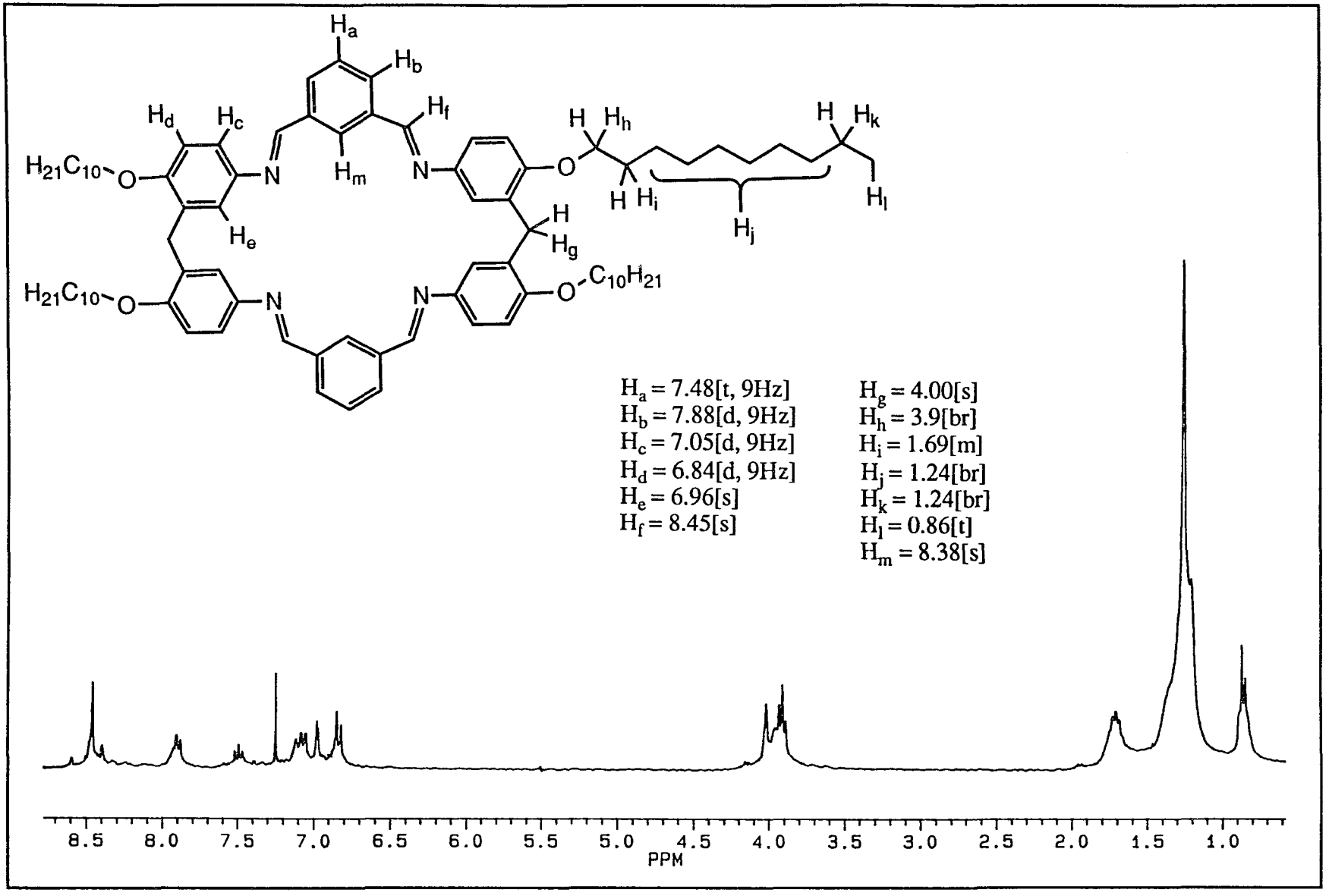
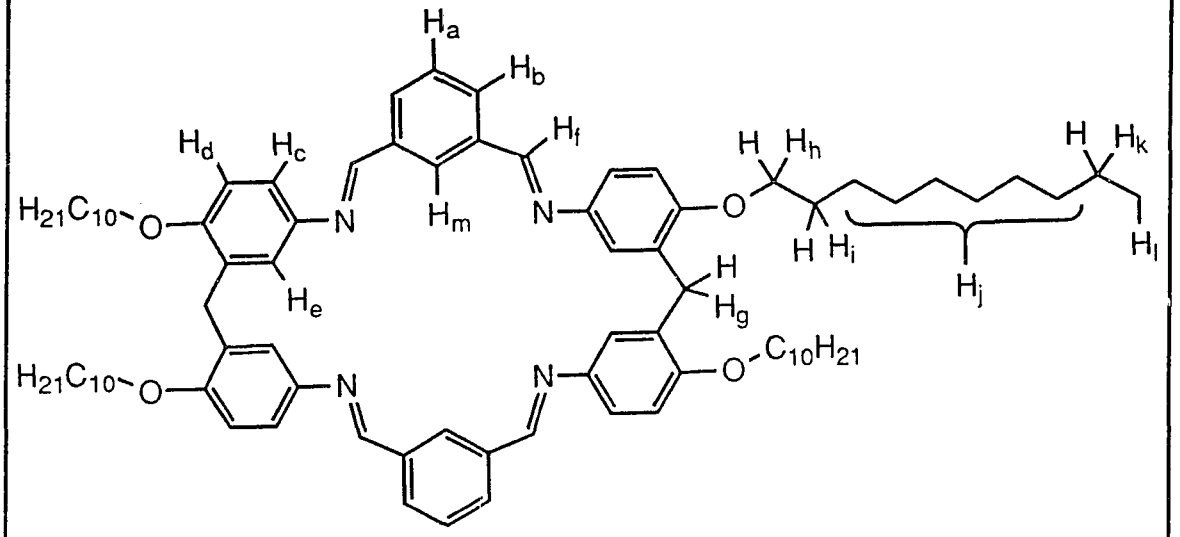
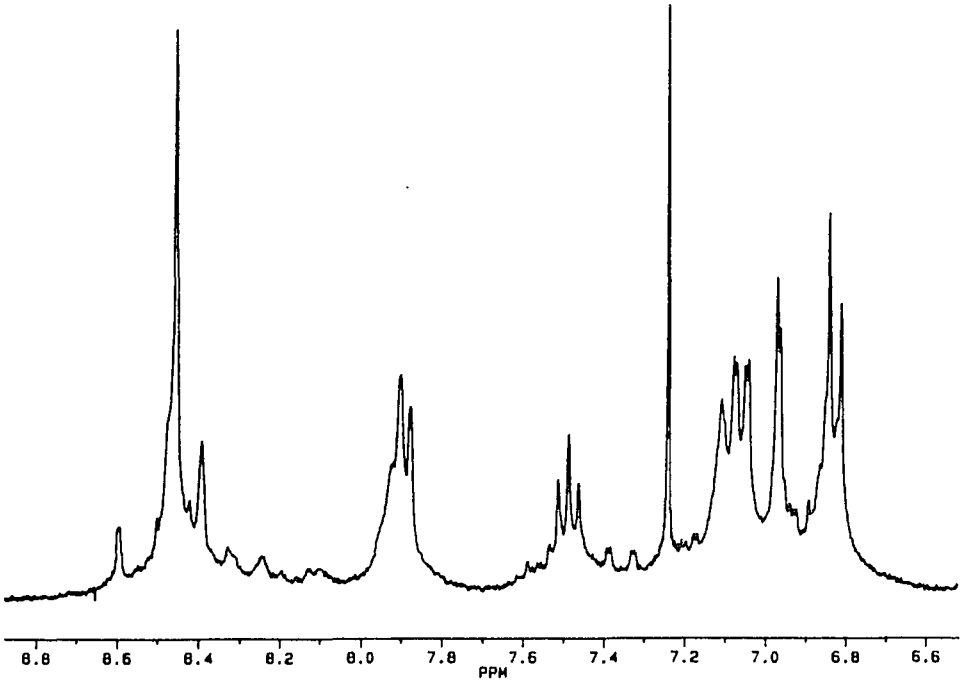
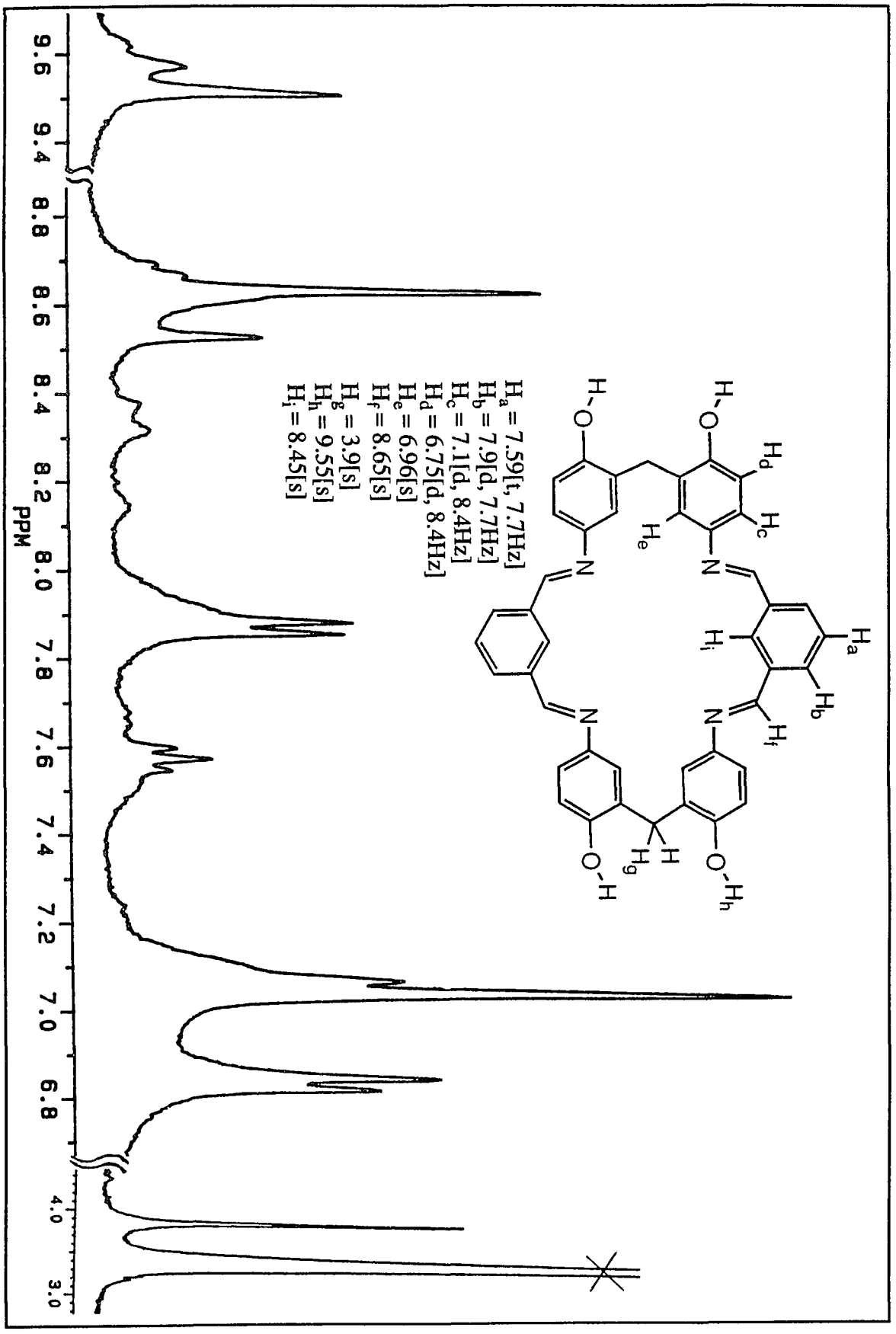

Ha
Hb
Hc
Hd
He
Hf
Hg
Hh
Hi
Hj
Hk
Hl
Hm
H21C10O
C10H21
N
O
Ha = 7.48[t, 9Hz]
Hb = 7.88[d, 9Hz]
Hc = 7.05[d, 9Hz]
Hd = 6.84[d, 9Hz]
He = 6.96[s]
Hf = 8.45[s]
Hg = 4.00[s]
Hh = 3.9[br]
Hi = 1.69[m]
Hj = 1.24[br]
Hk = 1.24[br]
Hl = 0.86[t]
Hm = 8.38[s]
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM

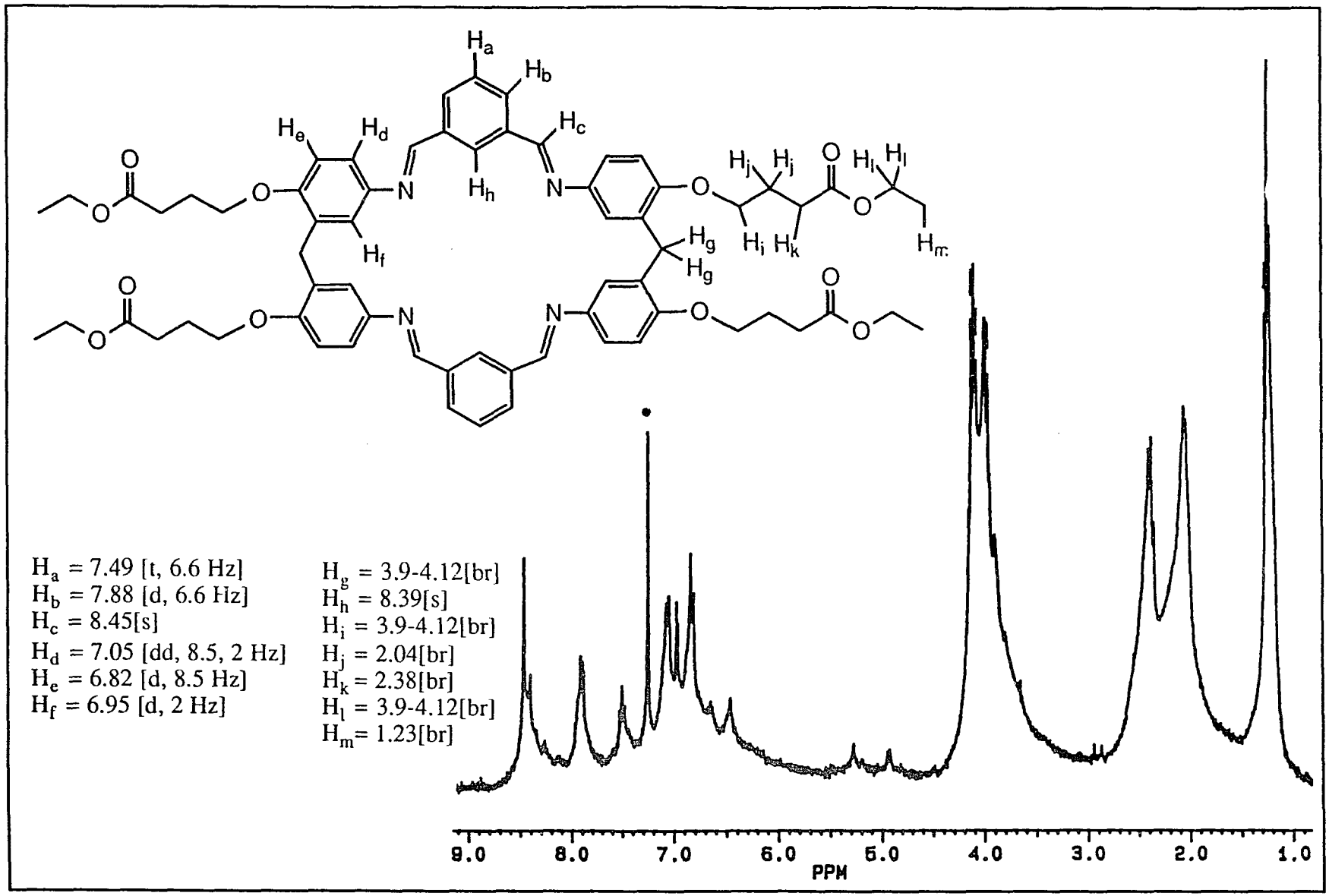


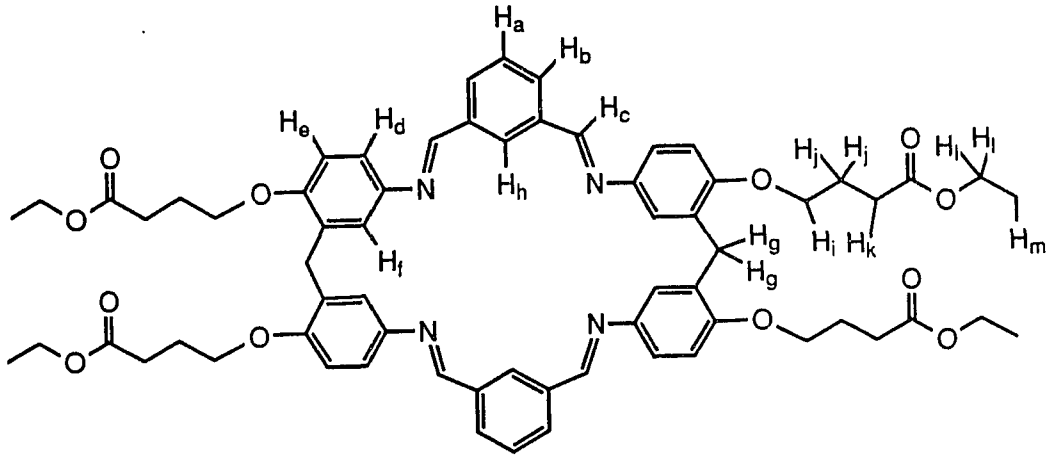
H_a = 7.48[t, 9Hz]
H_b = 7.88[d, 9Hz]
H_c = 7.05[d, 9Hz]
H_d = 6.84[d, 9Hz]
H_e = 6.96[s]
H_f = 8.45[s]

H_g = 4.00[s]
H_h = 3.9[br]
H_i = 1.69[m]
H_j = 1.24[br]
H_k = 1.24[br]
H_l = 0.86[t]
H_m = 8.38[s]



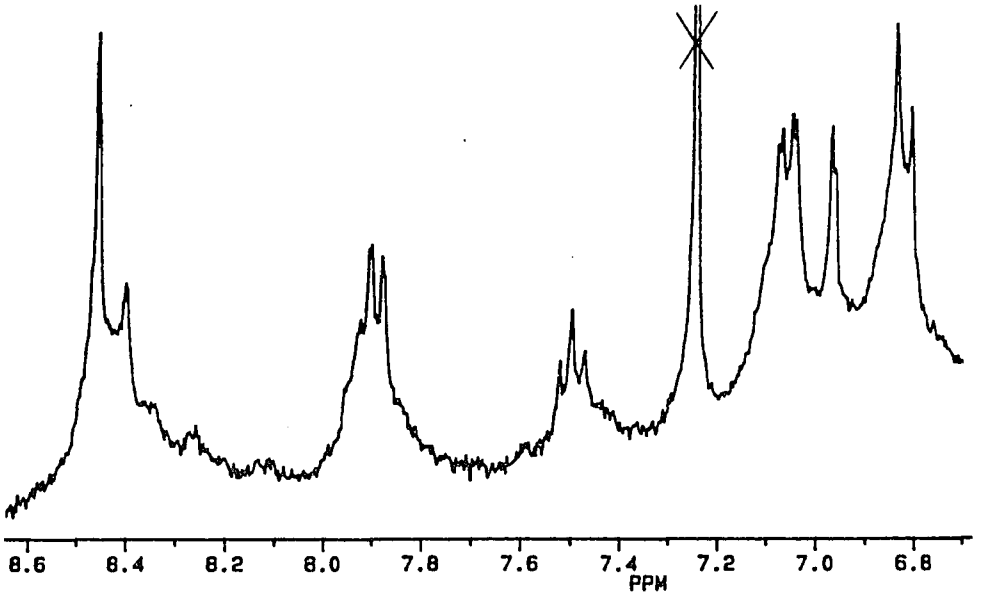

9.6
9.4
8.8
8.6
8.4
8.2
PPM
8.0
7.8
7.6
7.4
7.2
7.0
6.8
4.0
3.0
Ha = 7.59[t, 7.7Hz]
Hb = 7.9[d, 7.7Hz]
Hc = 7.1[d, 8.4Hz]
Hd = 6.75[d, 8.4Hz]
He = 6.96[s]
Hf = 8.65[s]
Hg = 3.9[s]
Hh = 9.55[s]
Hi = 8.45[s]
Ha
Hb
Hc
Hd
He
Hf
Hg
Hh
Hi
H
O
N

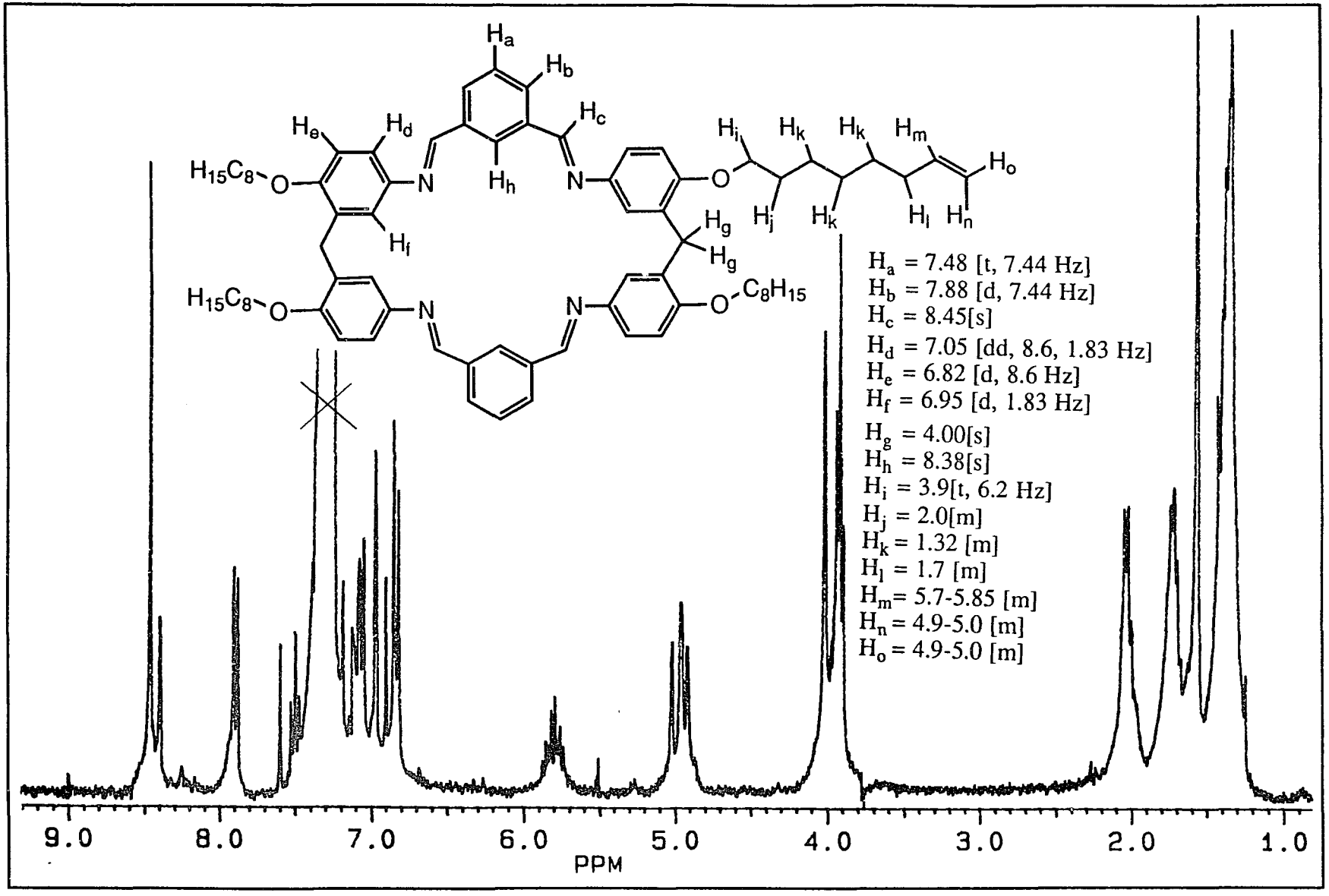

H_a
H_b
H_c
H_d
H_e
H_f
H_g
H_h
H_i
H_j
H_k
H_l
H_m
O
N
H_a = 7.49 [t, 6.6 Hz]
H_b = 7.88 [d, 6.6 Hz]
H_c = 8.45[s]
H_d = 7.05 [dd, 8.5, 2 Hz]
H_e = 6.82 [d, 8.5 Hz]
H_f = 6.95 [d, 2 Hz]
H_g = 3.9-4.12[br]
H_h = 8.39[s]
H_i = 3.9-4.12[br]
H_j = 2.04[br]
H_k = 2.38[br]
H_l = 3.9-4.12[br]
H_m= 1.23[br]
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

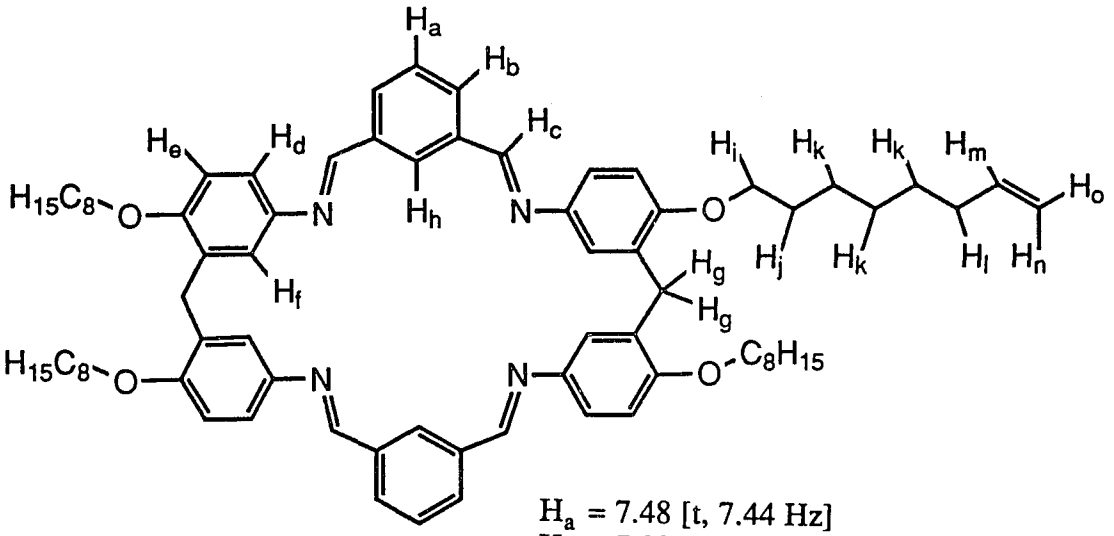


H_a = 7.49 [t, 6.6 Hz]
H_b = 7.88 [d, 6.6 Hz]
H_c = 8.45[s]
H_d = 7.05 [dd, 8.5, 2 Hz]
H_e = 6.82 [d, 8.5 Hz]
H_f = 6.95 [d, 2 Hz]

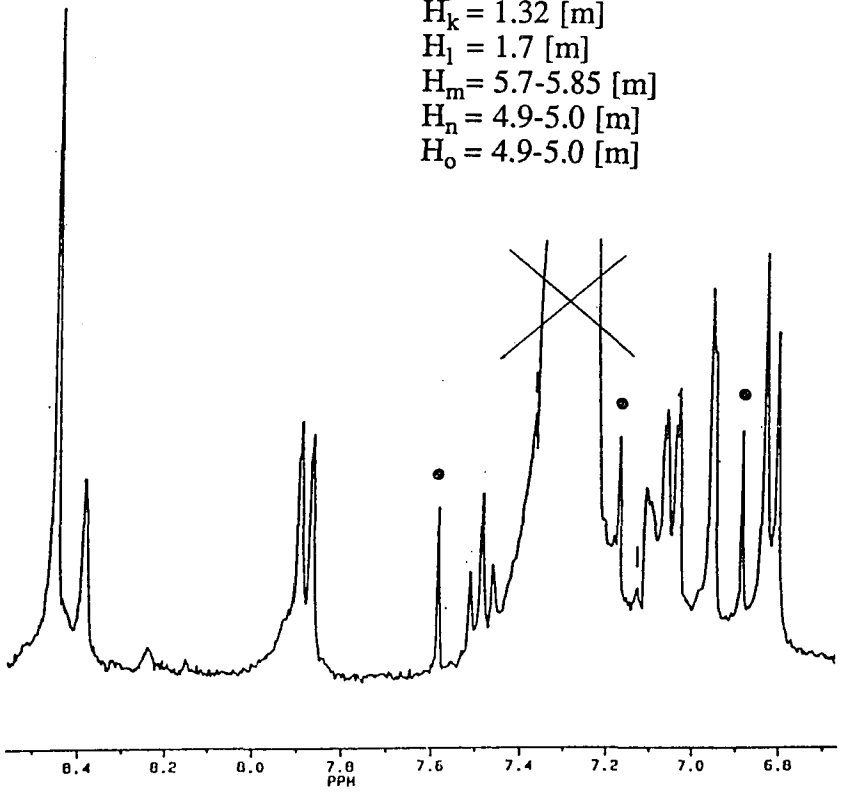
H_g = 3.9-4.12[br]
H_h = 8.39[s]
H_i = 3.9-4.12[br]
H_j = 2.04[br]
H_k = 2.38[br]
H_l = 3.9-4.12[br]
H_m = 1.23[br]

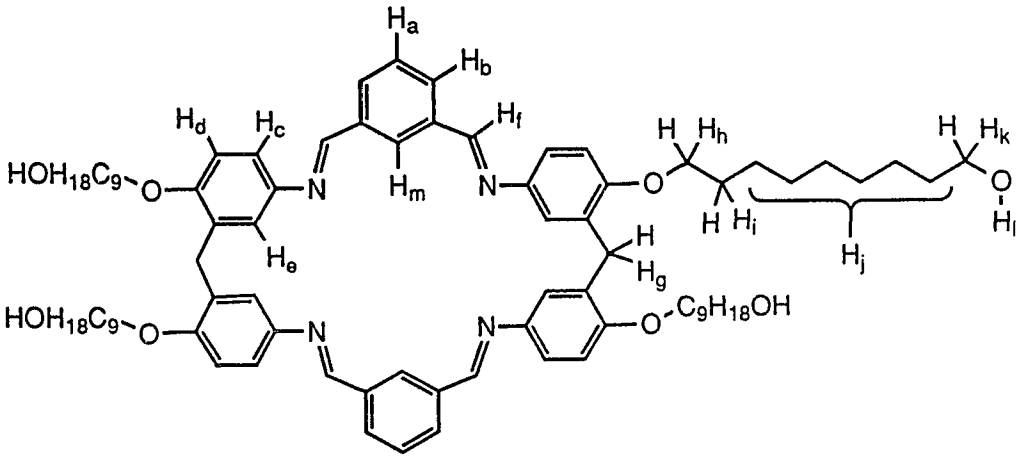



Ha
Hb
Hc
Hd
He
Hf
Hg
Hg
Hh
Hi
Hj
Hk
Hk
Hk
Hl
Hm
Hn
Ho
H15C8O
H15C8O
C8H15
N
N
N
N
O
O
O
Ha = 7.48 [t, 7.44 Hz]
Hb = 7.88 [d, 7.44 Hz]
Hc = 8.45[s]
Hd = 7.05 [dd, 8.6, 1.83 Hz]
He = 6.82 [d, 8.6 Hz]
Hf = 6.95 [d, 1.83 Hz]
Hg = 4.00[s]
Hh = 8.38[s]
Hi = 3.9[t, 6.2 Hz]
Hj = 2.0[m]
Hk = 1.32 [m]
Hl = 1.7 [m]
Hm= 5.7-5.85 [m]
Hn = 4.9-5.0 [m]
Ho = 4.9-5.0 [m]
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM



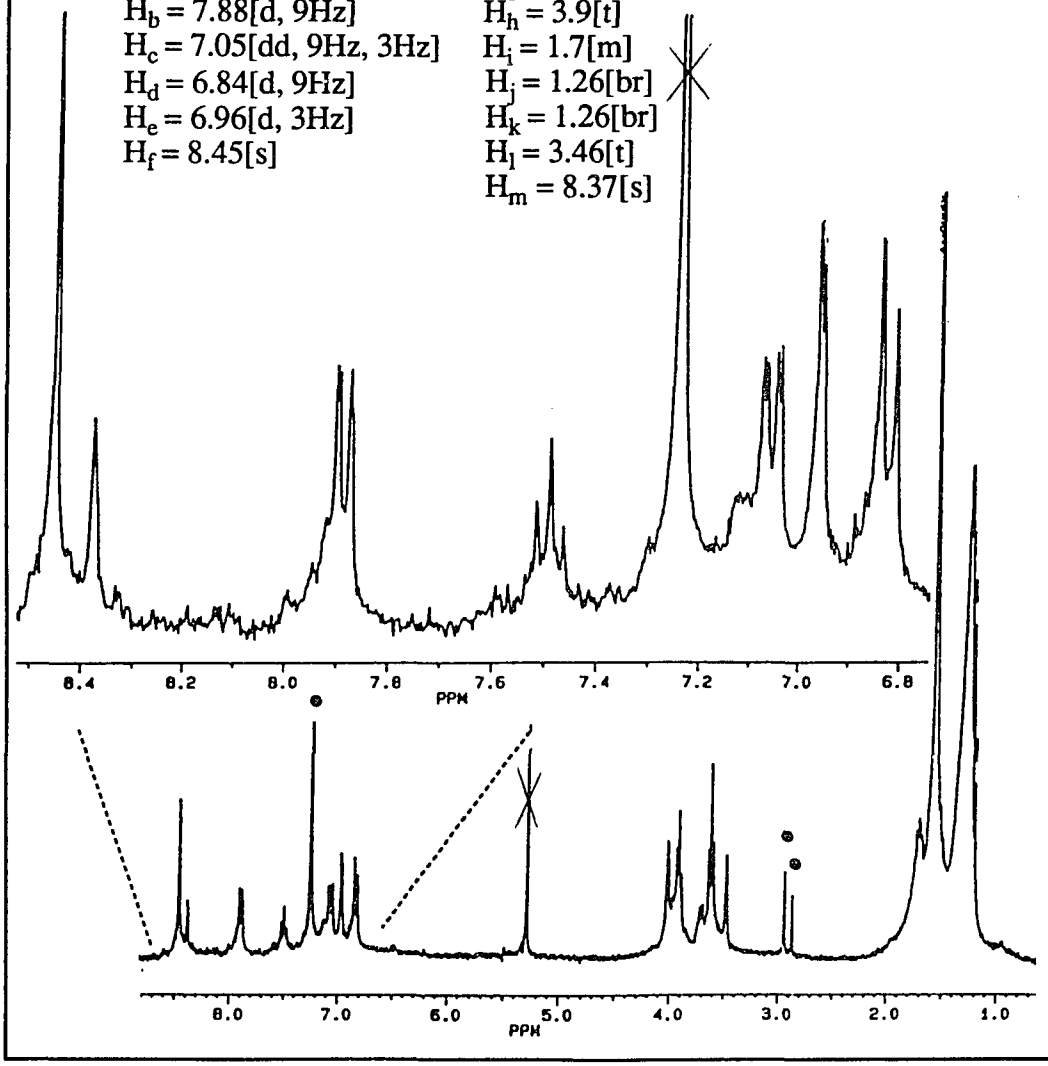
H_a = 7.48 [t, 7.44 Hz]
H_b = 7.88 [d, 7.44 Hz]
H_c = 8.45[s]
H_d = 7.05 [dd, 8.6, 1.83 Hz]
H_e = 6.82 [d, 8.6 Hz]
H_f = 6.95 [d, 1.83 Hz]
H_g = 4.00[s]
H_h = 8.38[s]
H_i = 3.9[t, 6.2 Hz]
H_j = 2.0[m]
H_k = 1.32 [m]
H_l = 1.7 [m]
H_m = 5.7-5.85 [m]
H_n = 4.9-5.0 [m]
H_o = 4.9-5.0 [m]

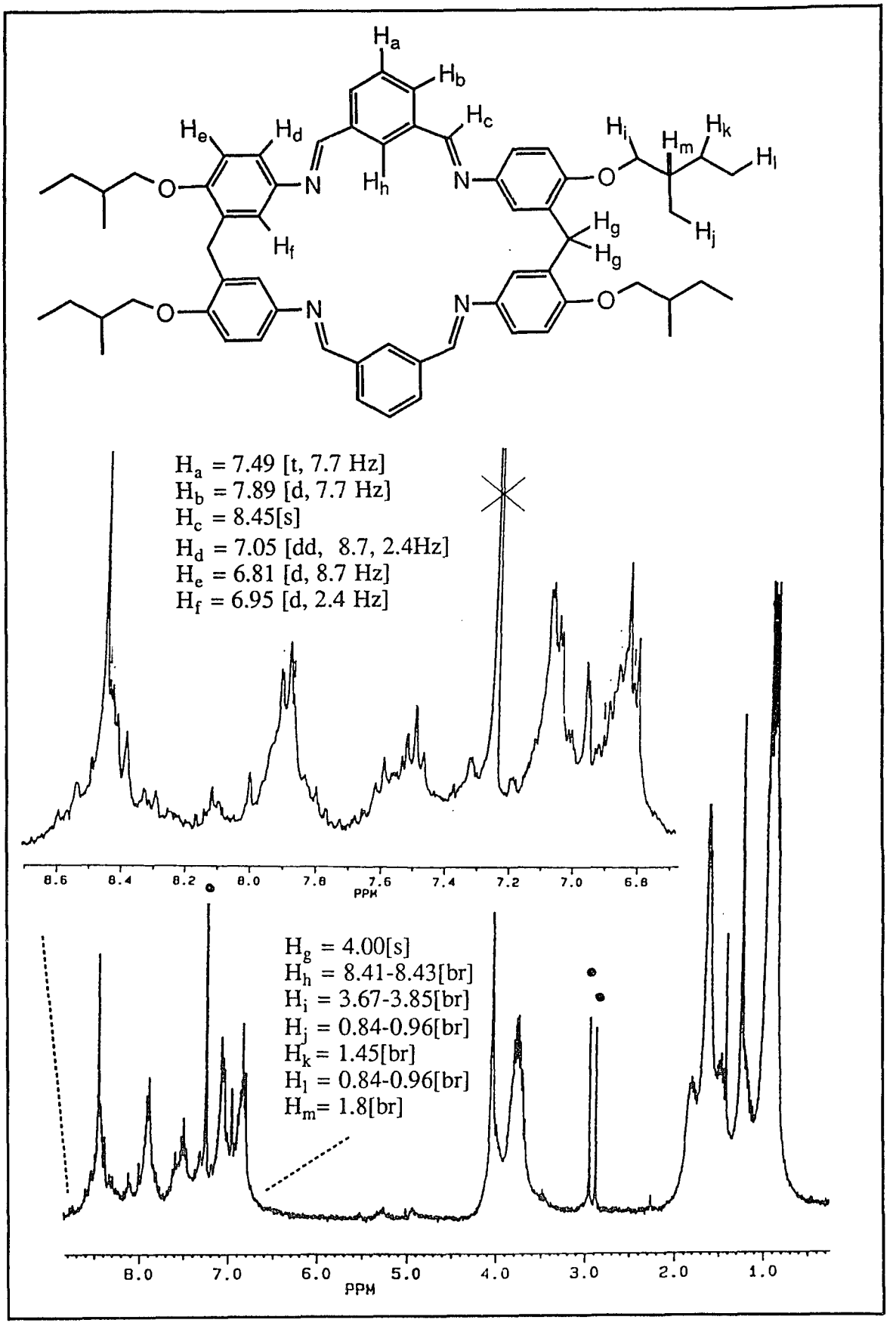


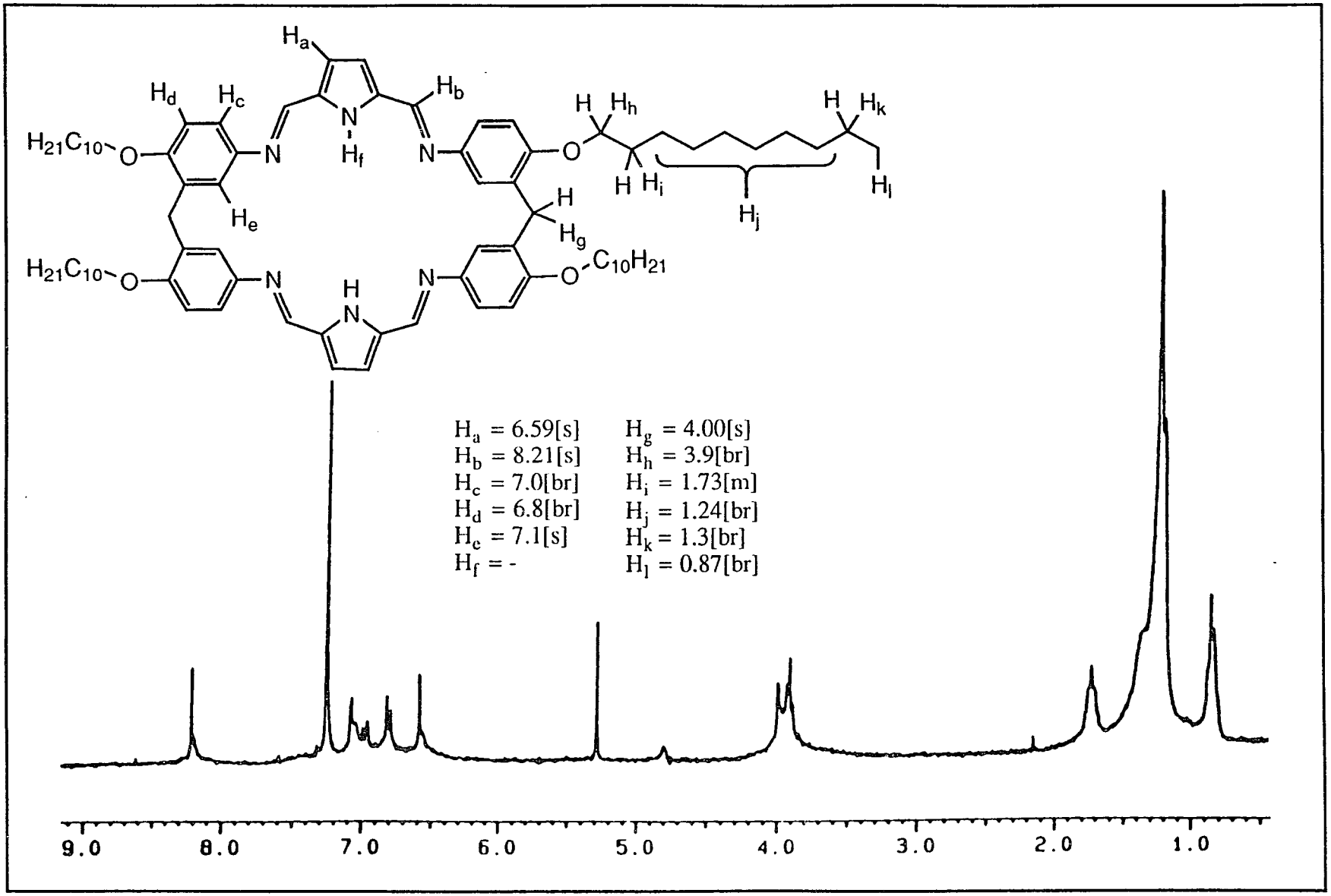


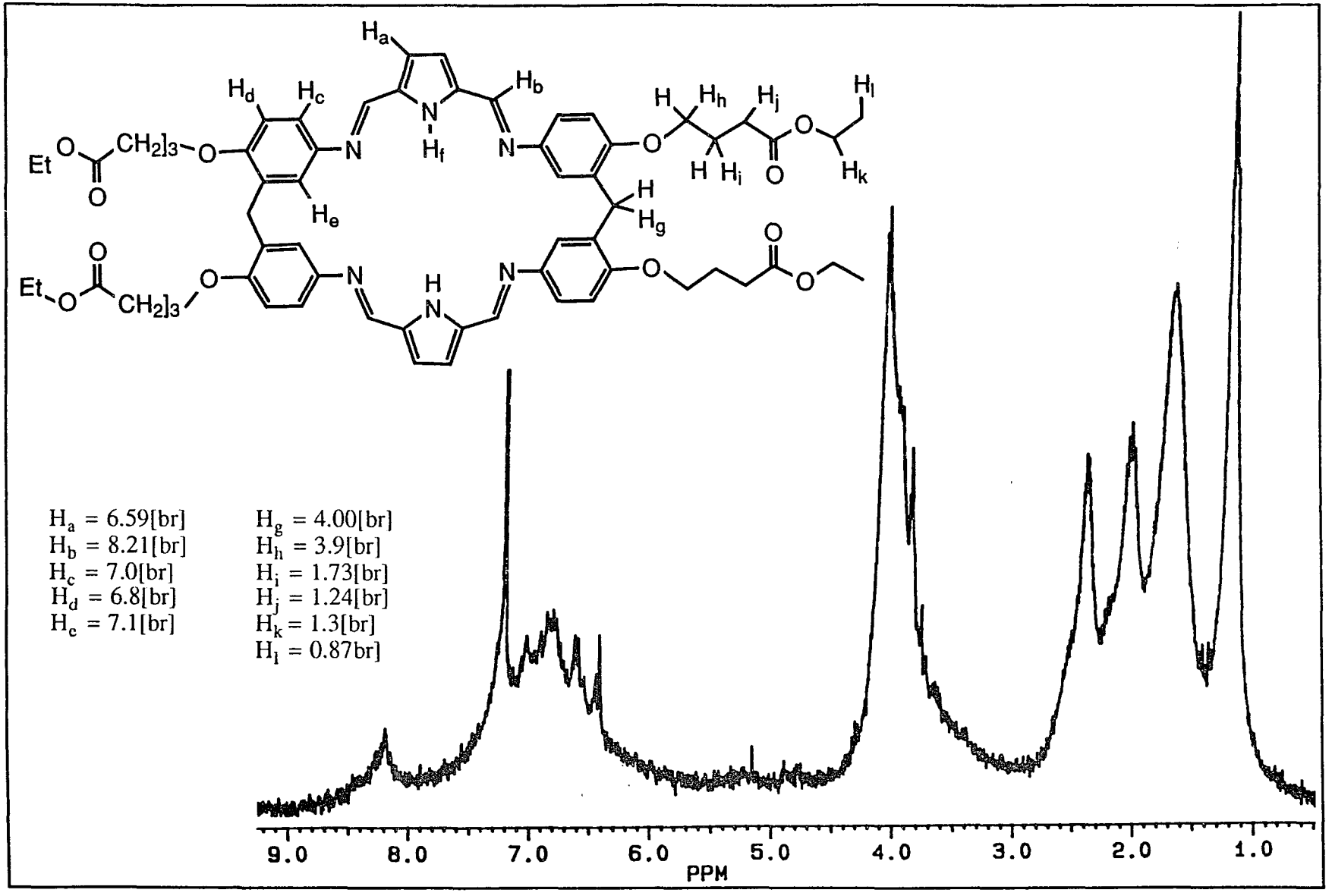
H_a = 7.48[t, 9Hz]
H_b = 7.88[d, 9Hz]
H_c = 7.05[dd, 9Hz, 3Hz]
H_d = 6.84[d, 9Hz]
H_e = 6.96[d, 3Hz]
H_f = 8.45[s]

H_g = 4.0[s]
H_h = 3.9[t]
H_i = 1.7[m]
H_j = 1.26[br]
H_k = 1.26[br]
H_l = 3.46[t]
H_m = 8.37[s]



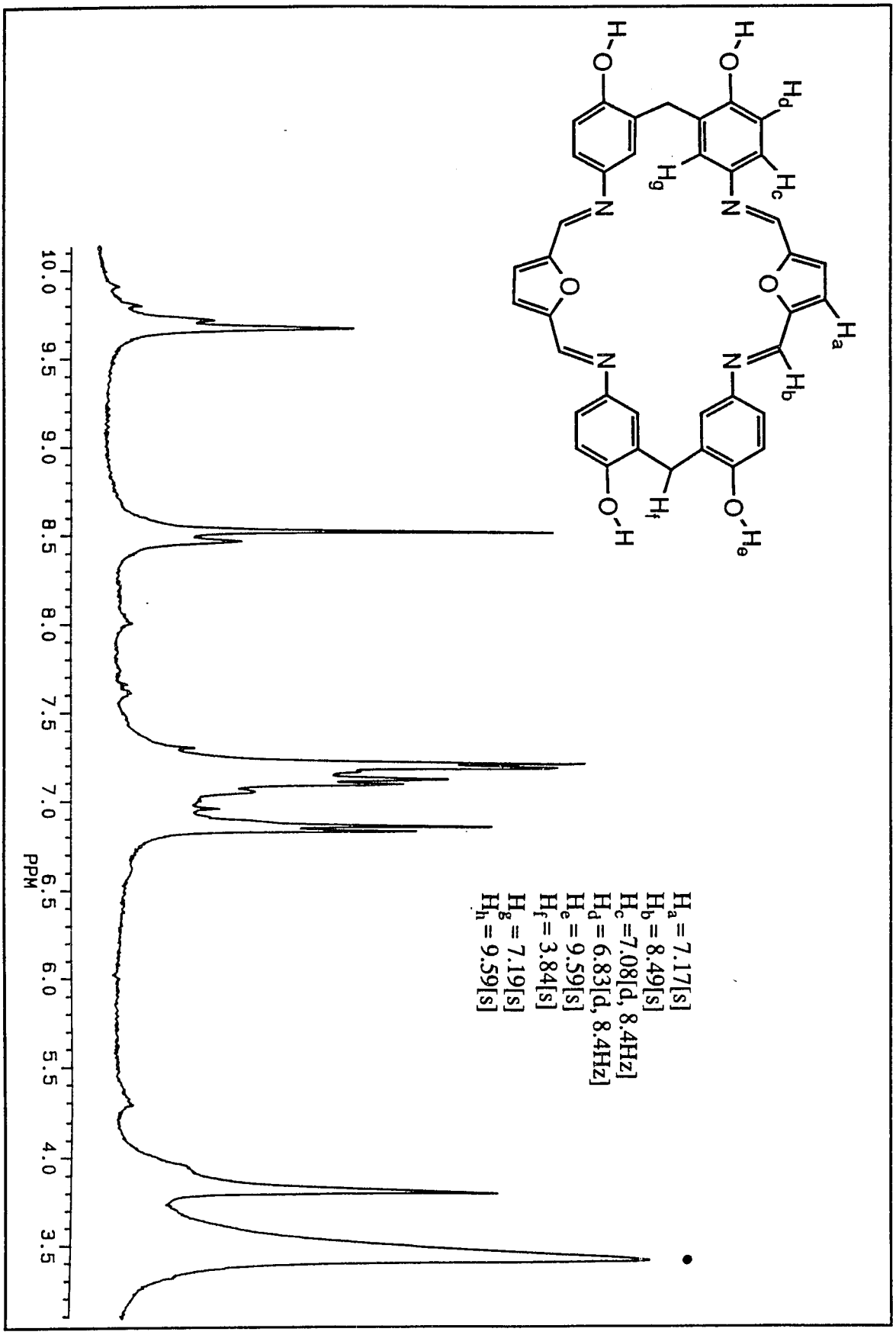

Ha
Hb
Hc
Hd
He
Hf
Hg
Hh
Hi
Hj
Hk
Hl
Hm
N
O
Ha = 7.49 [t, 7.7 Hz]
Hb = 7.89 [d, 7.7 Hz]
Hc = 8.45[s]
Hd = 7.05 [dd, 8.7, 2.4Hz]
He = 6.81 [d, 8.7 Hz]
Hf = 6.95 [d, 2.4 Hz]
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
PPM
Hg = 4.00[s]
Hh = 8.41-8.43[br]
Hi = 3.67-3.85[br]
Hj = 0.84-0.96[br]
Hk = 1.45[br]
Hl = 0.84-0.96[br]
Hm= 1.8[br]
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

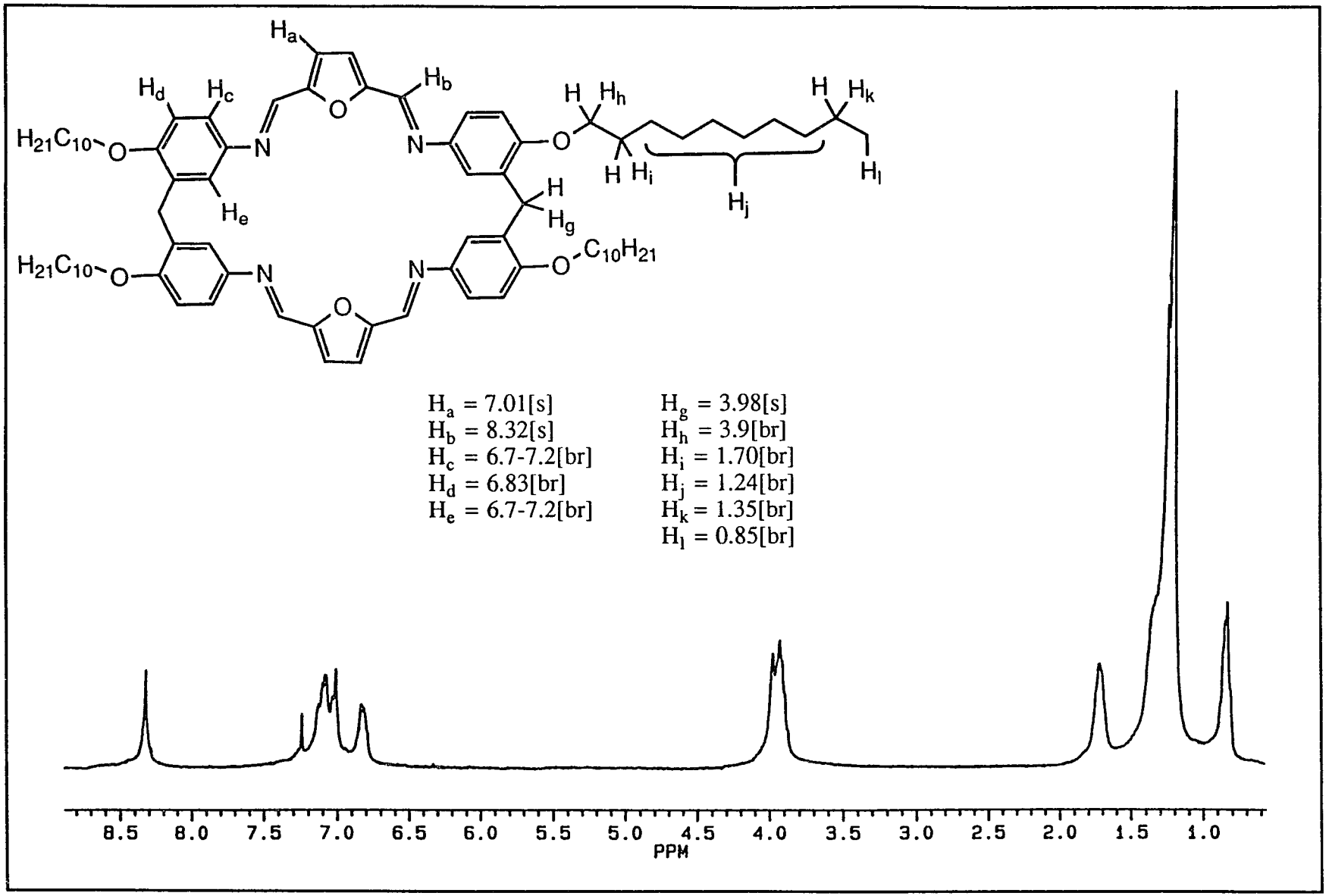

Ha
Hb
Hc
Hd
He
Hf
Hg
Hh
Hi
Hj
Hk
Hl
H21C10
O
N
H
C10H21
Ha = 6.59[s]
Hb = 8.21[s]
Hc = 7.0[br]
Hd = 6.8[br]
He = 7.1[s]
Hf = -
Hg = 4.00[s]
Hh = 3.9[br]
Hi = 1.73[m]
Hj = 1.24[br]
Hk = 1.3[br]
Hl = 0.87[br]
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0



H_a = 6.59[br]
H_b = 8.21[br]
H_c = 7.0[br]
H_d = 6.8[br]
H_e = 7.1[br]

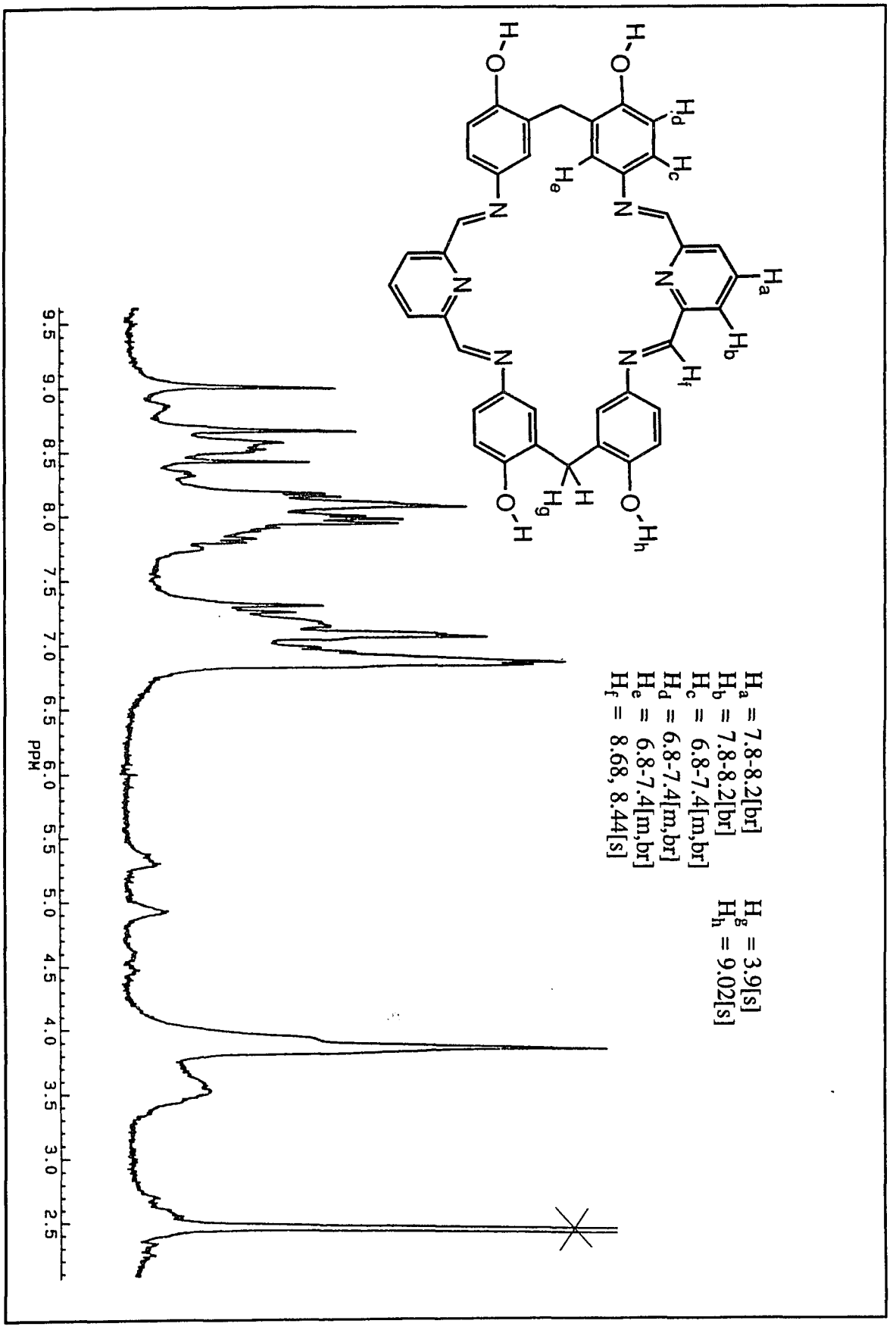
H_g = 4.00[br]
H_h = 3.9[br]
H_i = 1.73[br]
H_j = 1.24[br]
H_k = 1.3[br]
H_l = 0.87br]

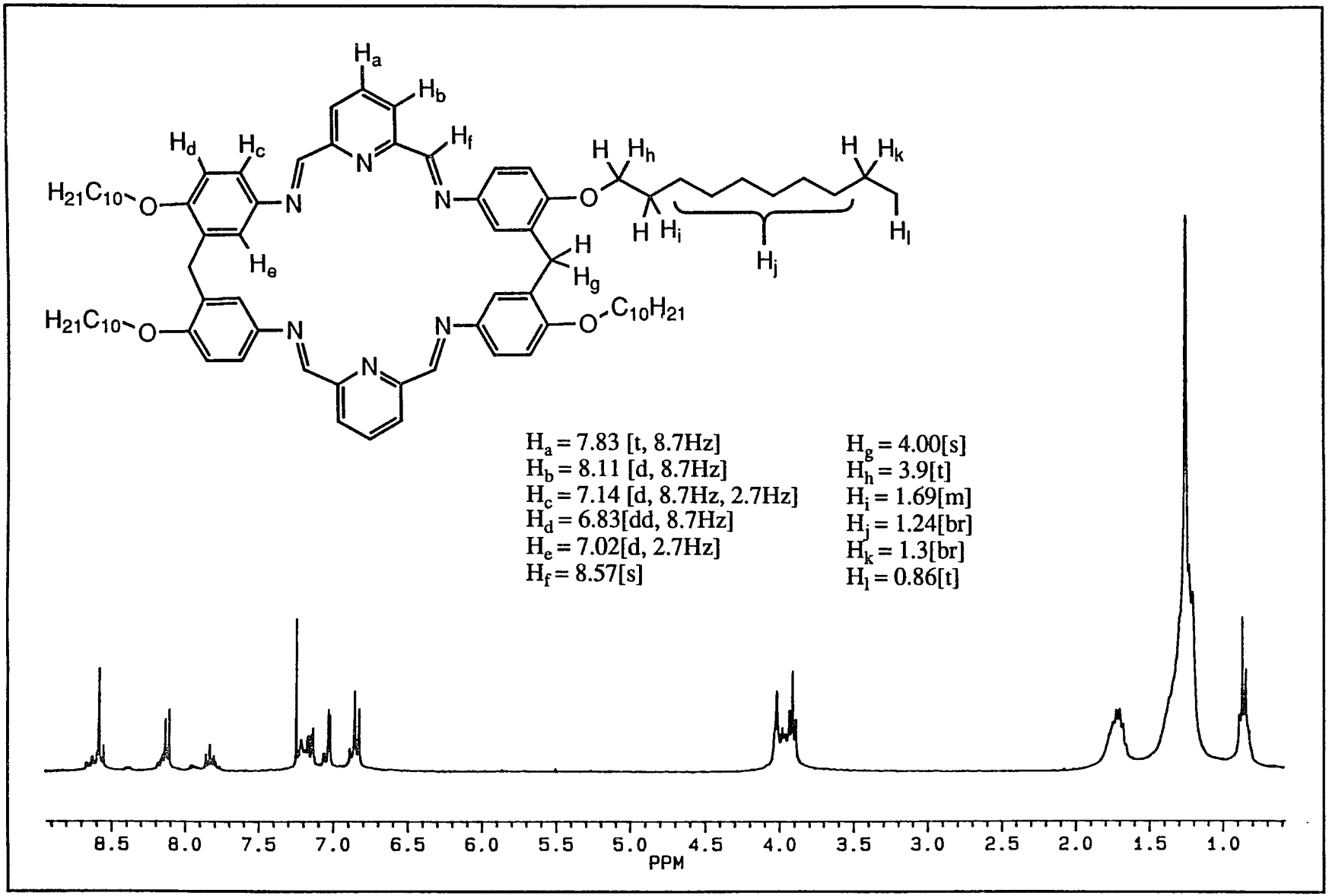

H_a = 7.17[s]
H_b = 8.49[s]
H_c =7.08[d, 8.4Hz]
H_d = 6.83[d, 8.4Hz]
H_e = 9.59[s]
H_f = 3.84[s]
H_g = 7.19[s]
H_h = 9.59[s]
PPM
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
4.0
3.5

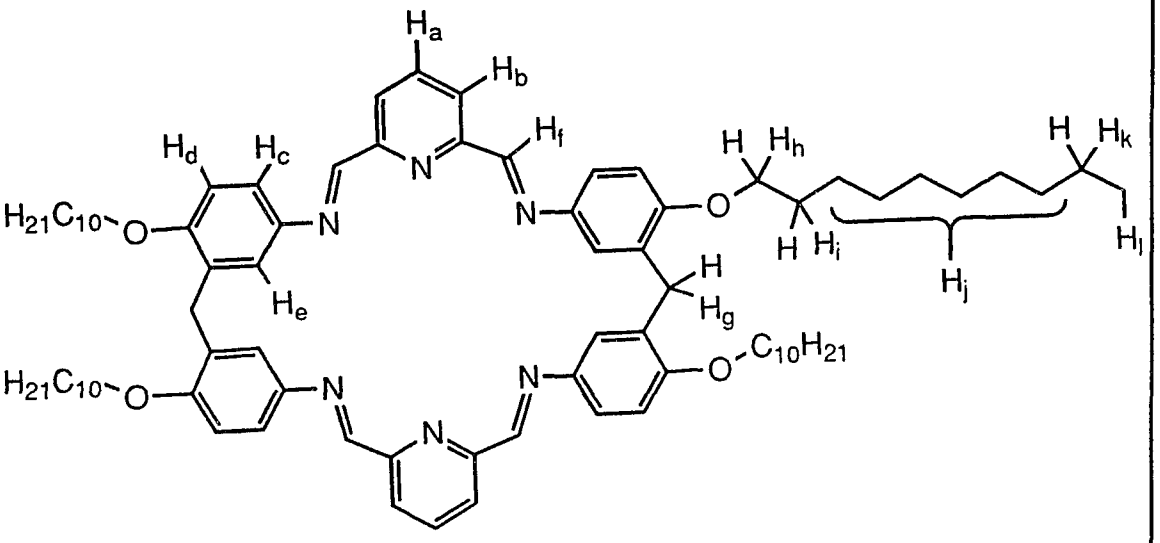


H_a = 7.01[s]
H_b = 8.32[s]
H_c = 6.7-7.2[br]
H_d = 6.83[br]
H_e = 6.7-7.2[br]

H_g = 3.98[s]
H_h = 3.9[br]
H_i = 1.70[br]
H_j = 1.24[br]
H_k = 1.35[br]
H_l = 0.85[br]

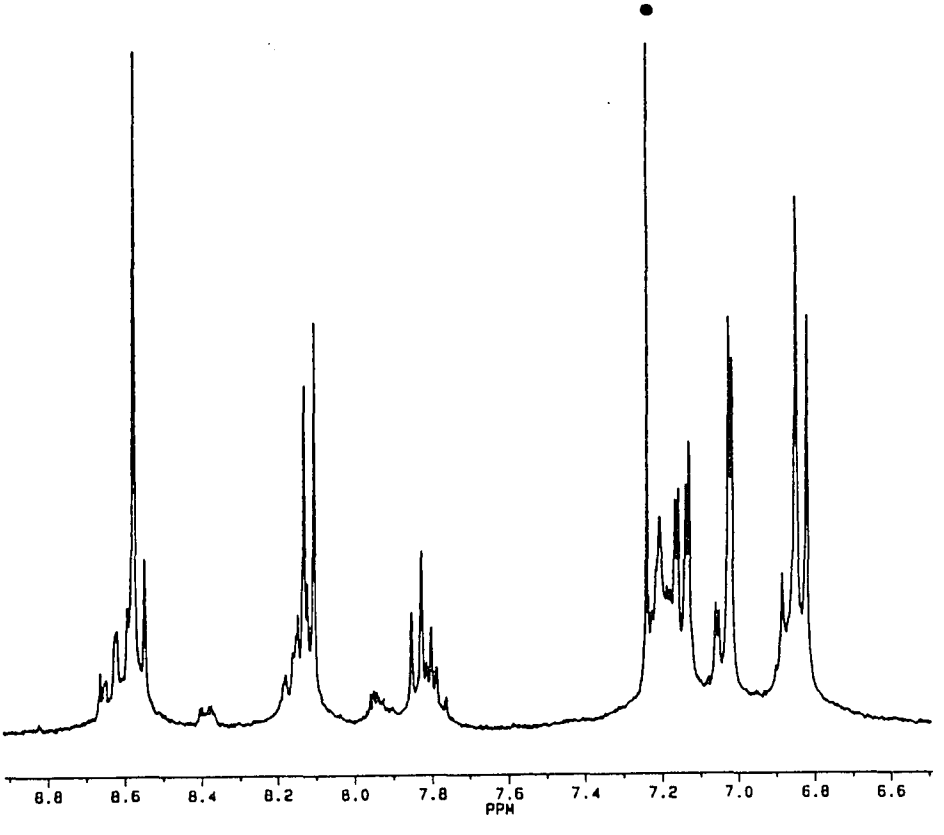

H_a = 7.8-8.2[br]
H_b = 7.8-8.2[br]
H_c = 6.8-7.4[m,br]
H_d = 6.8-7.4[m,br]
H_e = 6.8-7.4[m,br]
H_f = 8.68, 8.44[s]
H_g = 3.9[s]
H_h = 9.02[s]
PPM
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5

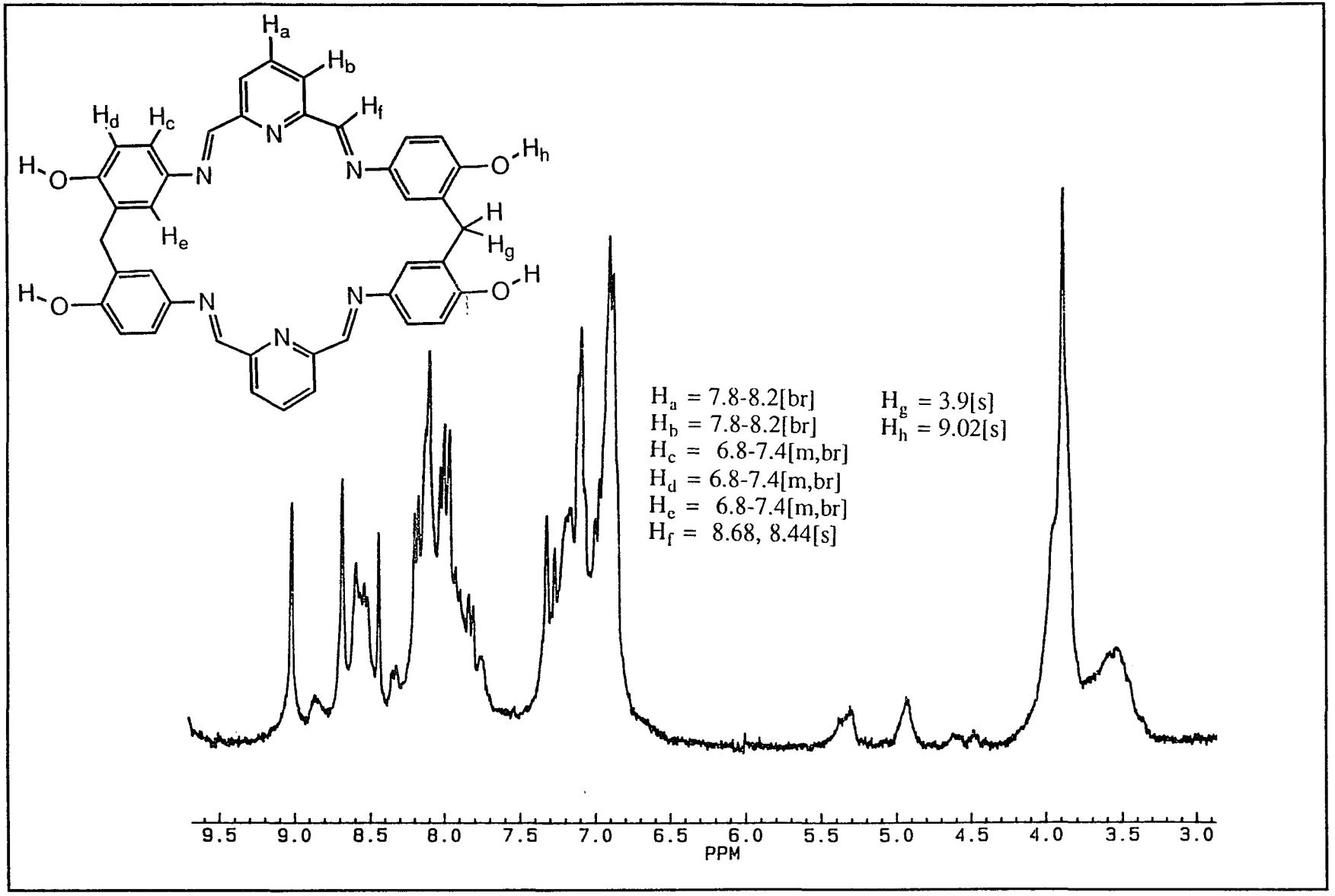

H_a
H_b
H_c
H_d
H_e
H_f
H_g
H_h
H_i
H_j
H_k
H_l
$H_{21}C_{10}$-O
$C_{10}H_{21}$
N
H_a = 7.83 [t, 8.7Hz]
H_b = 8.11 [d, 8.7Hz]
H_c = 7.14 [d, 8.7Hz, 2.7Hz]
H_d = 6.83[dd, 8.7Hz]
H_e = 7.02[d, 2.7Hz]
H_f = 8.57[s]
H_g = 4.00[s]
H_h = 3.9[t]
H_i = 1.69[m]
H_j = 1.24[br]
H_k = 1.3[br]
H_l = 0.86[t]
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM

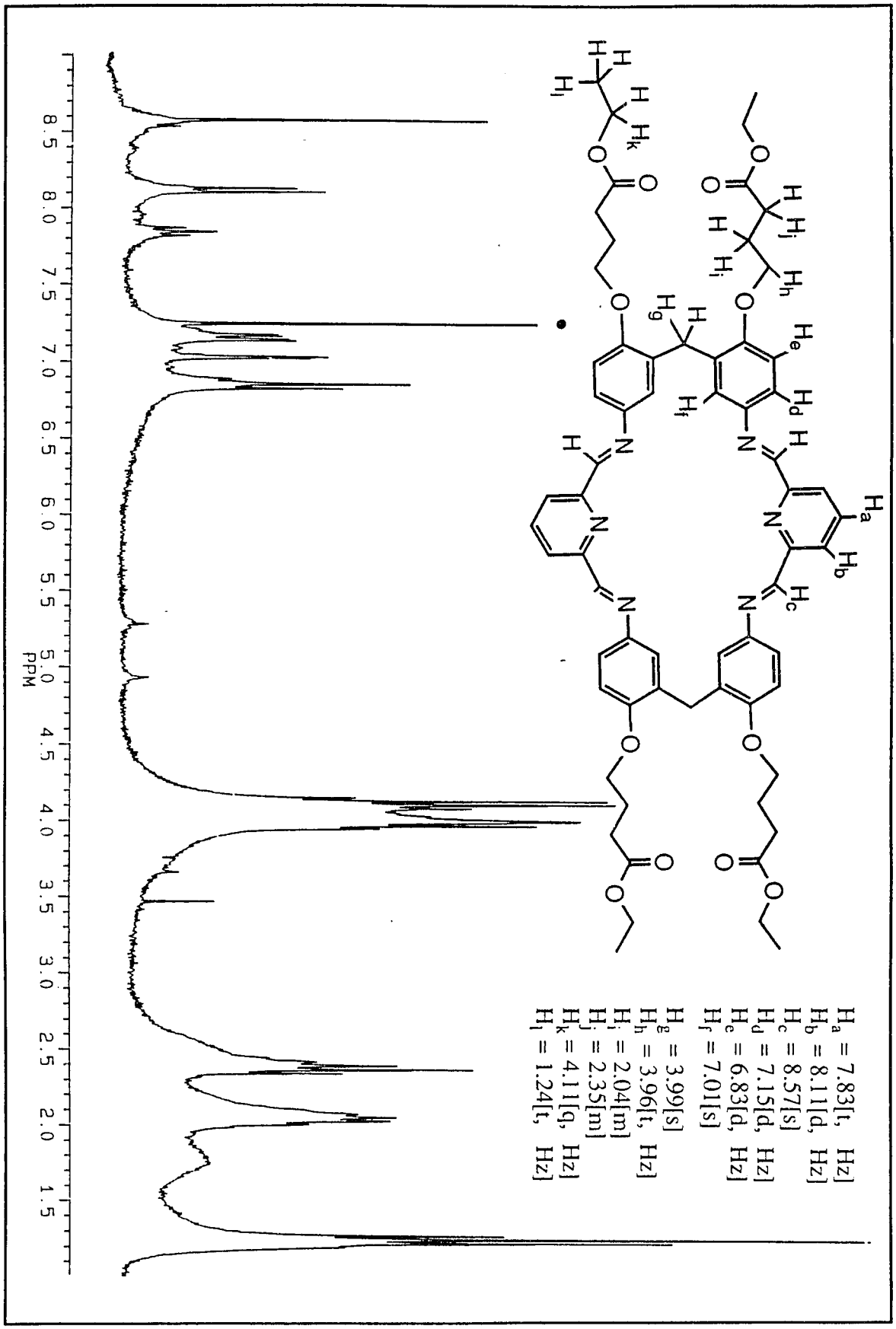


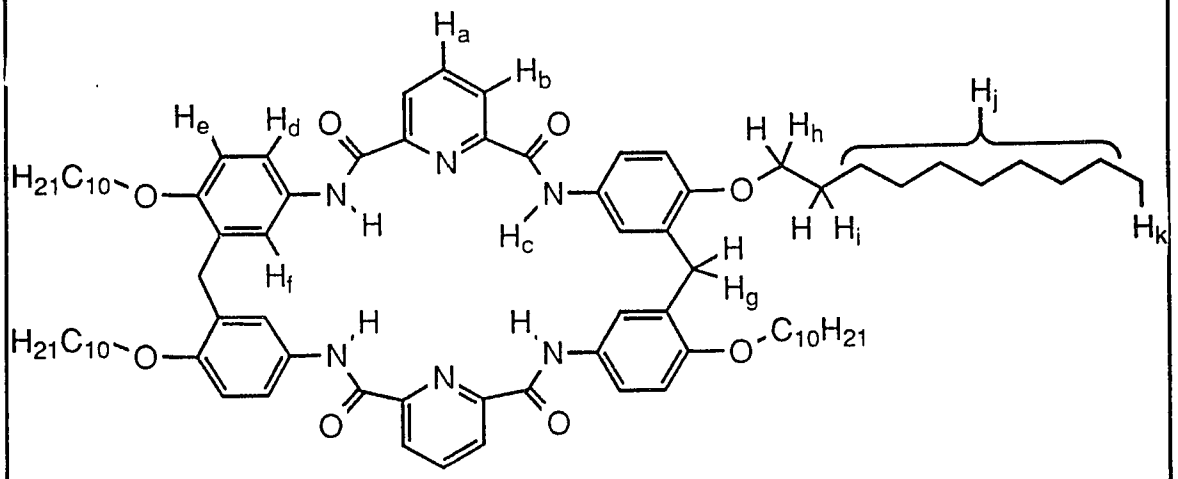
H_a = 7.83 [t, 8.7Hz]
H_b = 8.11 [d, 8.7Hz]
H_c = 7.14 [d, 8.7Hz, 2.7Hz]
H_d = 6.83[dd, 8.7Hz]
H_e = 7.02[d, 2.7Hz]
H_f = 8.57[s]

H_g = 4.00[s]
H_h = 3.9[t]
H_i = 1.69[m]
H_j = 1.24[br]
H_k = 1.3[br]
H_l = 0.86[t]



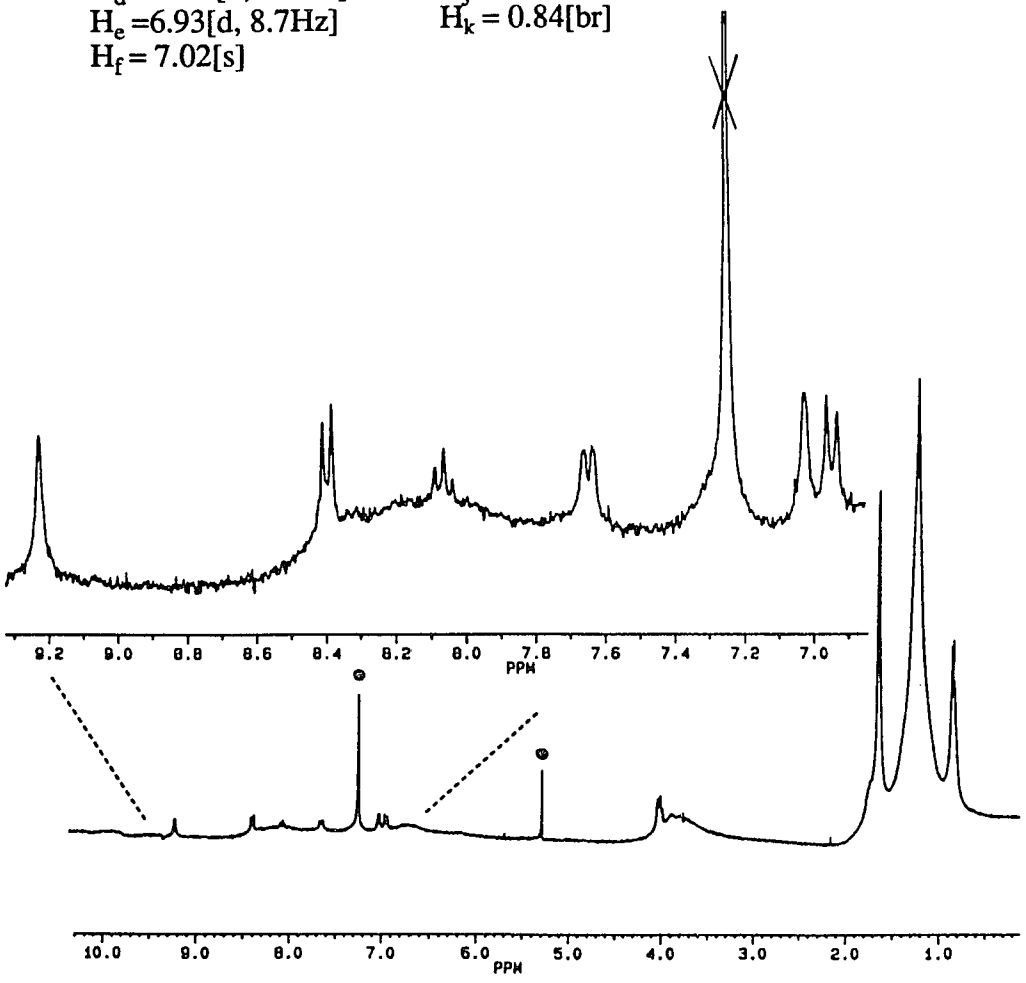

Ha
Hb
Hc
Hd
He
Hf
Hg
Hh
N
O
H
H_a = 7.8-8.2[br]
H_b = 7.8-8.2[br]
H_c = 6.8-7.4[m,br]
H_d = 6.8-7.4[m,br]
H_e = 6.8-7.4[m,br]
H_f = 8.68, 8.44[s]
H_g = 3.9[s]
H_h = 9.02[s]
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
PPM

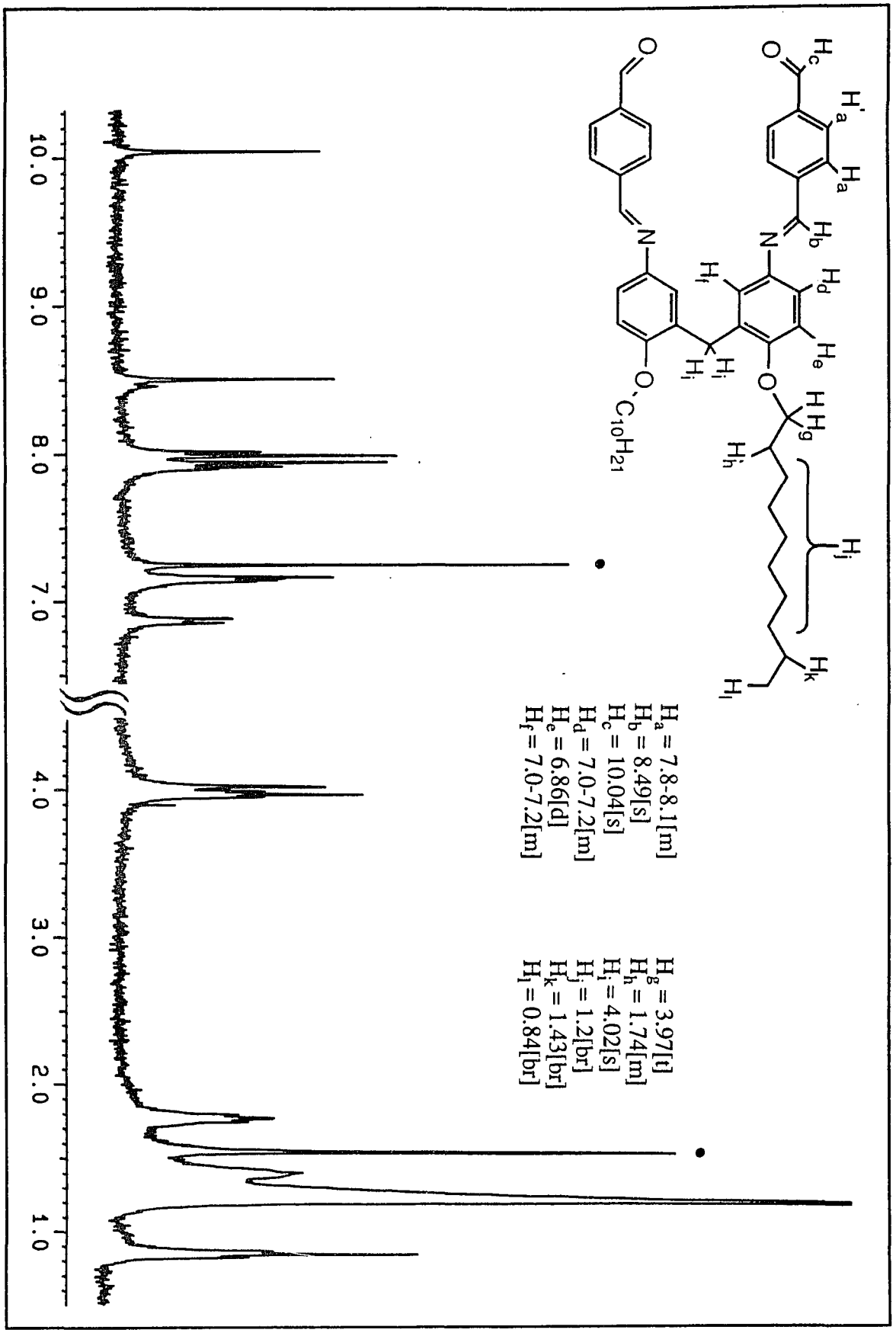

H_a = 7.83[t, Hz]
H_b = 8.11[d, Hz]
H_c = 8.57[s]
H_d = 7.15[d, Hz]
H_e = 6.83[d, Hz]
H_f = 7.01[s]
H_g = 3.99[s]
H_h = 3.96[t, Hz]
H_i = 2.04[m]
H_j = 2.35[m]
H_k = 4.11[q, Hz]
H_l = 1.24[t, Hz]
PPM
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5

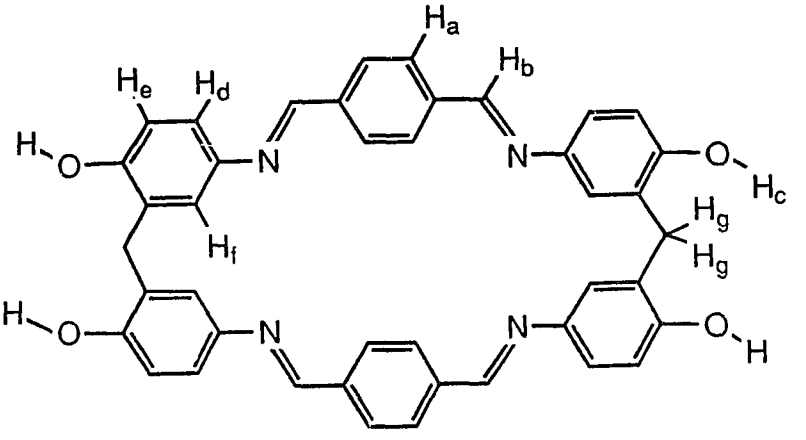


H_a = 8.05[t, 9Hz]
H_b = 8.38[d, 9Hz]
H_c = 9.22[s]
H_d = 7.64[d, 8.7Hz]
H_e =6.93[d, 8.7Hz]
H_f = 7.02[s]

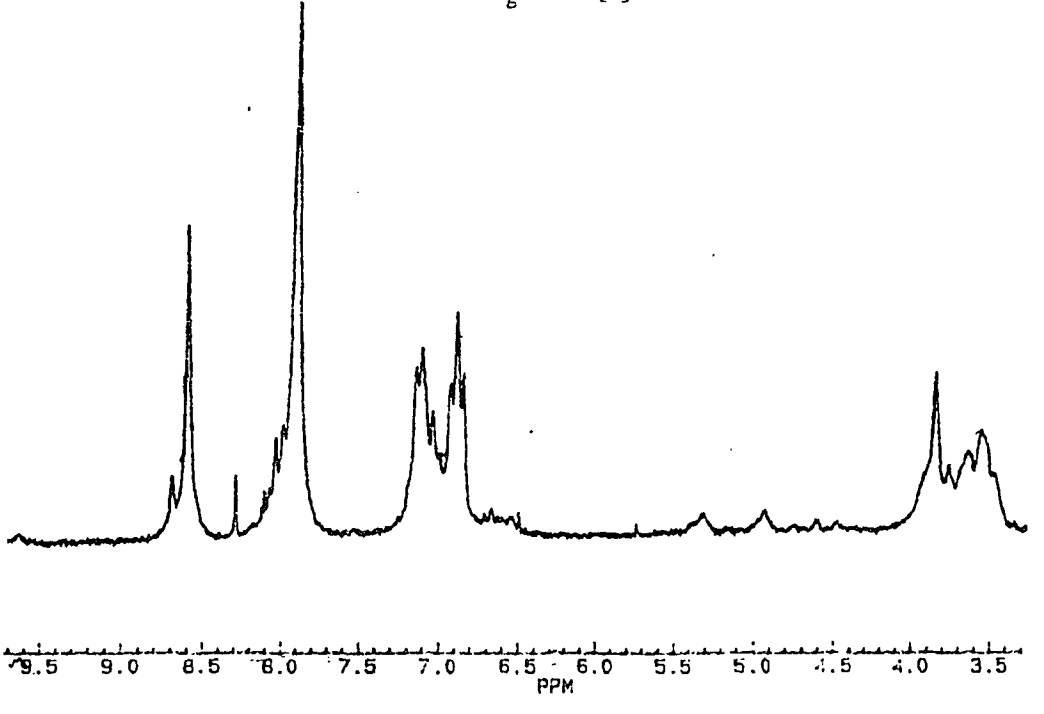
H_g = 3.5-3.9[br]
H_h = 3.5-3.9[br]
H_i = 1.8[br]
H_j = 1.22[br]
H_k = 0.84[br]

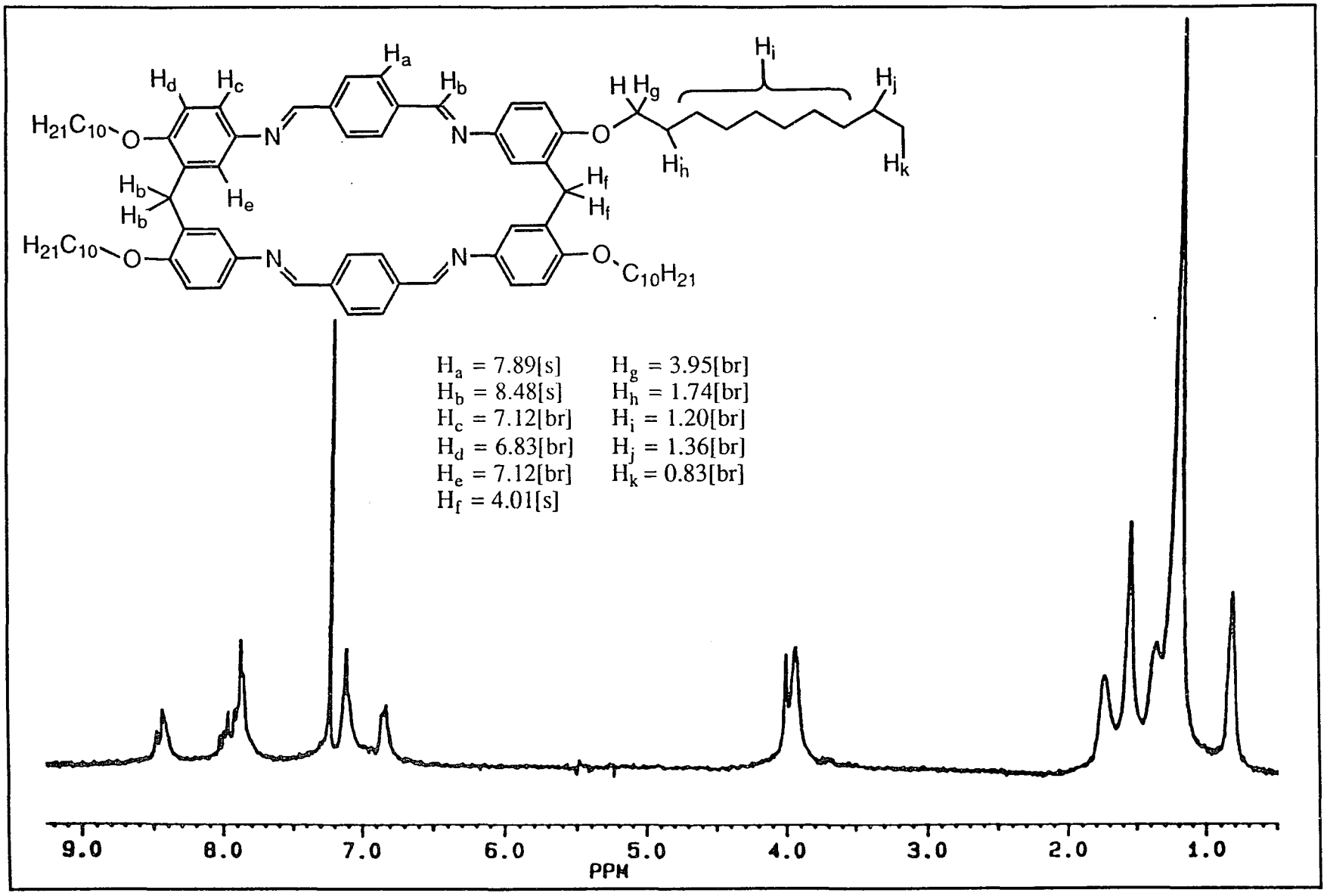


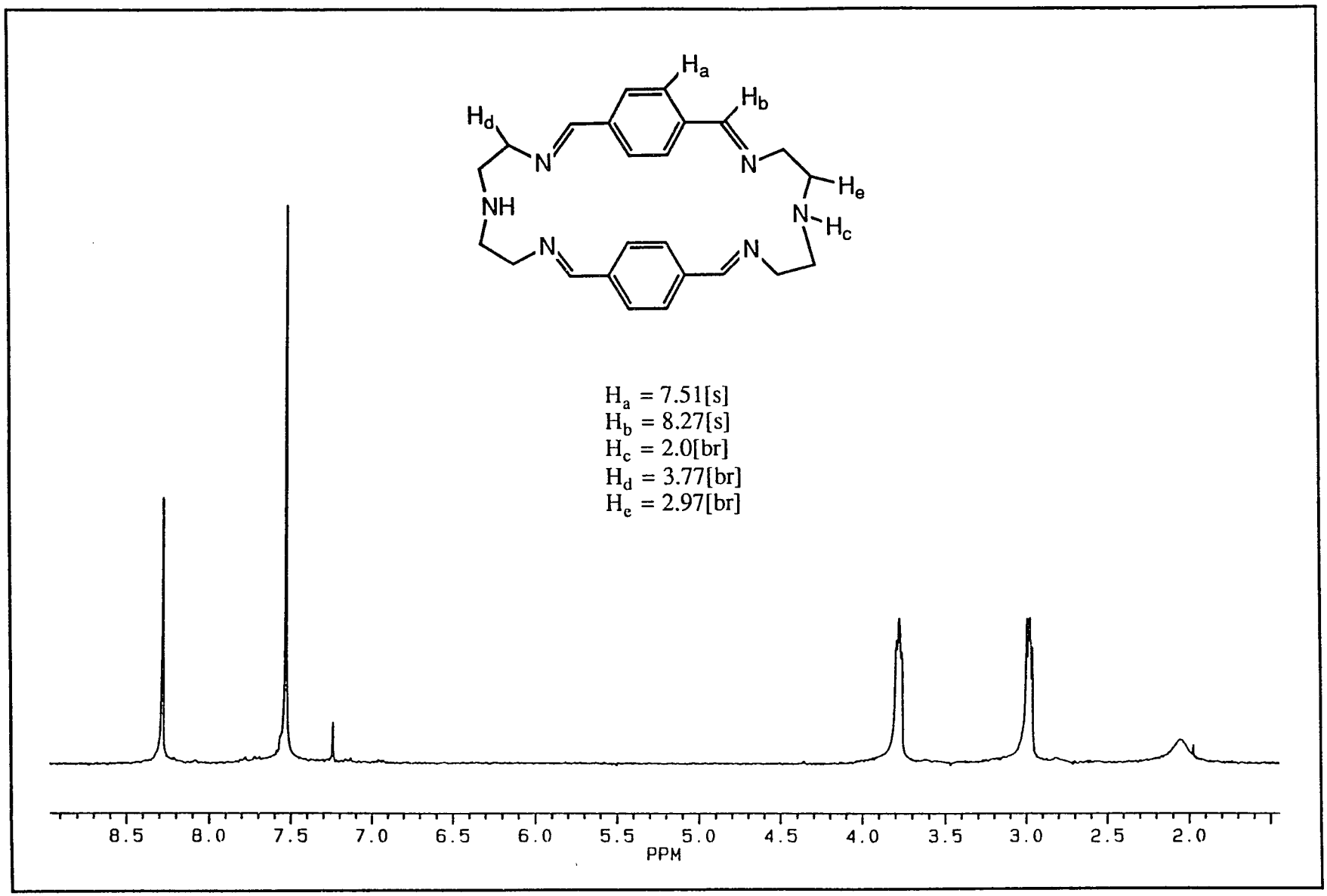

H_a = 7.8-8.1[m]
H_b = 8.49[s]
H_c = 10.04[s]
H_d = 7.0-7.2[m]
H_e = 6.86[d]
H_f = 7.0-7.2[m]
H_g = 3.97[t]
H_h = 1.74[m]
H_i = 4.02[s]
H_j = 1.2[br]
H_k = 1.43[br]
H_l = 0.84[br]
$C_{10}H_{21}$
10.0
9.0
8.0
7.0
4.0
3.0
2.0
1.0

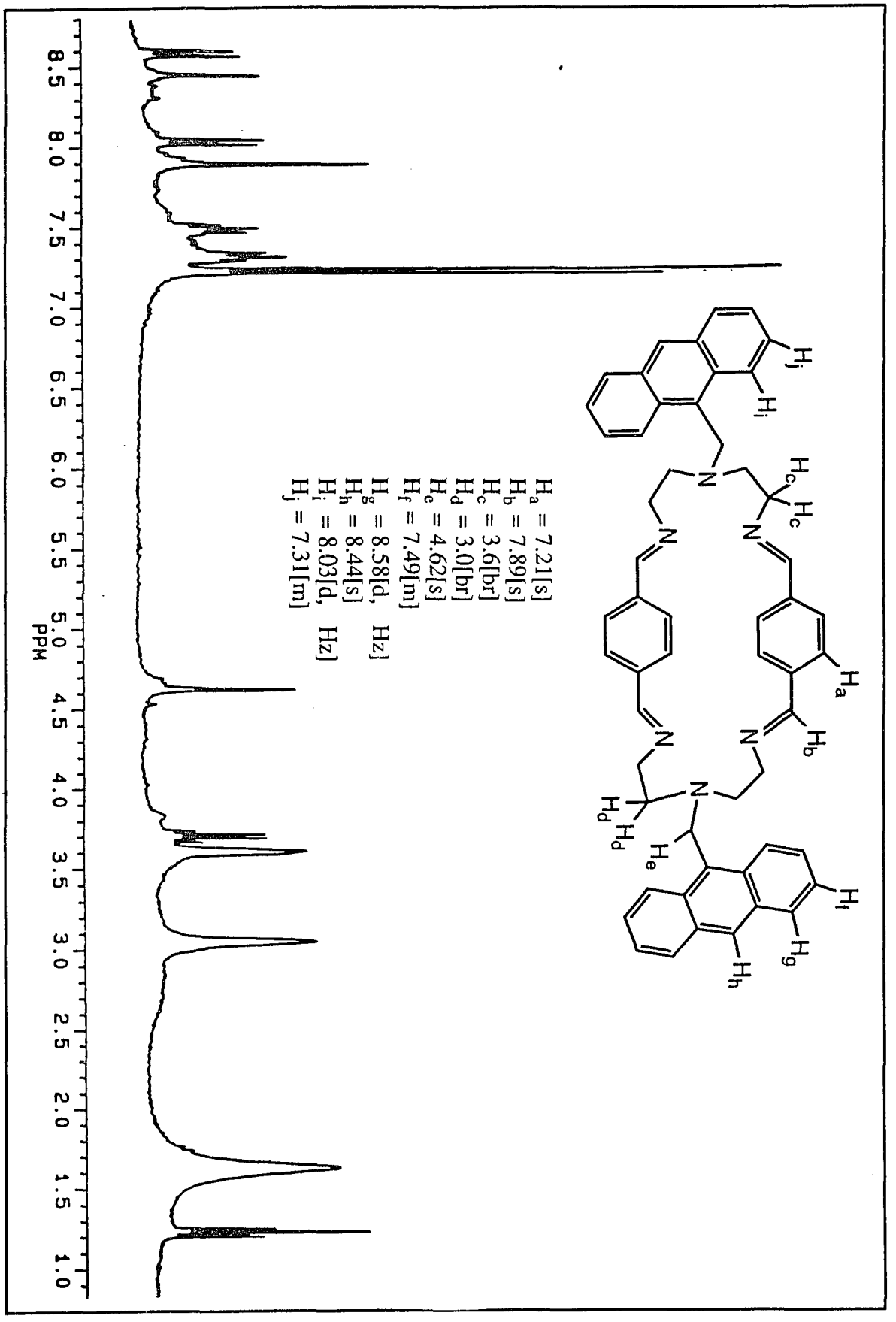


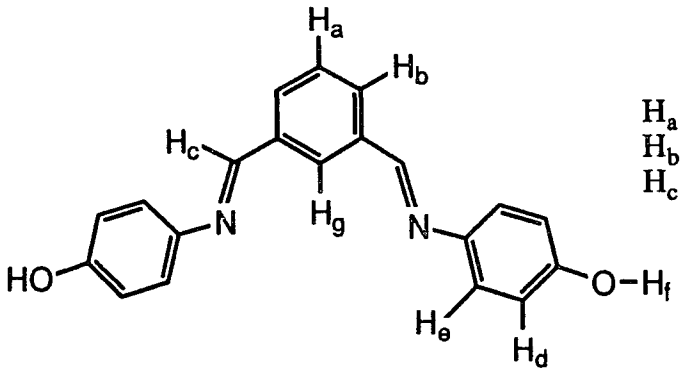
H_a = 7.93[s]
H_b = 8.6[s]
H_c = 9.65[s]
H_d = 6.8-7.3[m]
H_e = 6.8-7.3[m]
H_f = 6.8-7.3[m]
H_g = 3.9[s]




$H_{21}C_{10}$
O
H_d
H_c
H_a
H_b
N
H_g
H_i
H_j
H_h
H_k
H_b
H_e
H_f
$C_{10}H_{21}$
H_a = 7.89[s]
H_b = 8.48[s]
H_c = 7.12[br]
H_d = 6.83[br]
H_e = 7.12[br]
H_f = 4.01[s]
H_g = 3.95[br]
H_h = 1.74[br]
H_i = 1.20[br]
H_j = 1.36[br]
H_k = 0.83[br]
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

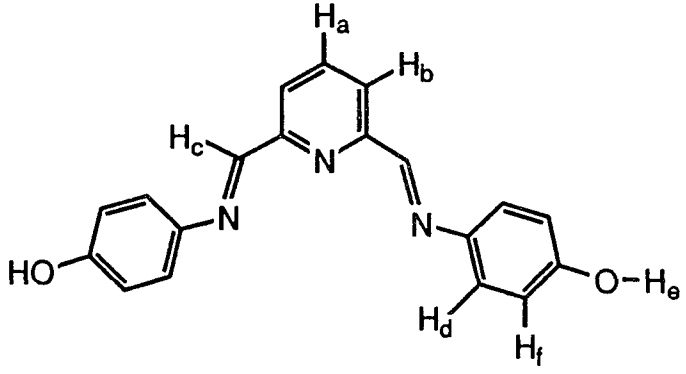

Ha
Hb
Hd
N
N
He
NH
N
Hc
N
N
Ha = 7.51[s]
Hb = 8.27[s]
Hc = 2.0[br]
Hd = 3.77[br]
He = 2.97[br]
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM


H_a = 7.21[s]
H_b = 7.89[s]
H_c = 3.6[br]
H_d = 3.0[br]
H_e = 4.62[s]
H_f = 7.49[m]
H_g = 8.58[d, Hz]
H_h = 8.44[s]
H_i = 8.03[d, Hz]
H_j = 7.31[m]
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM

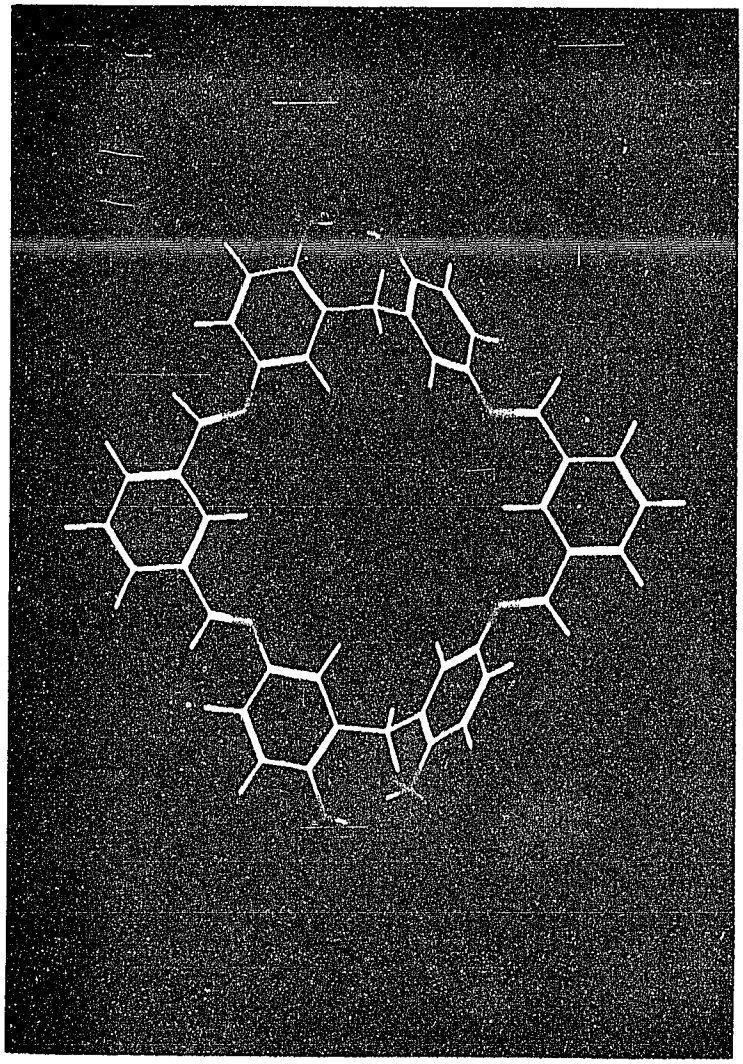


H_a = 7.59
H_b = 7.97
H_c = 8.42

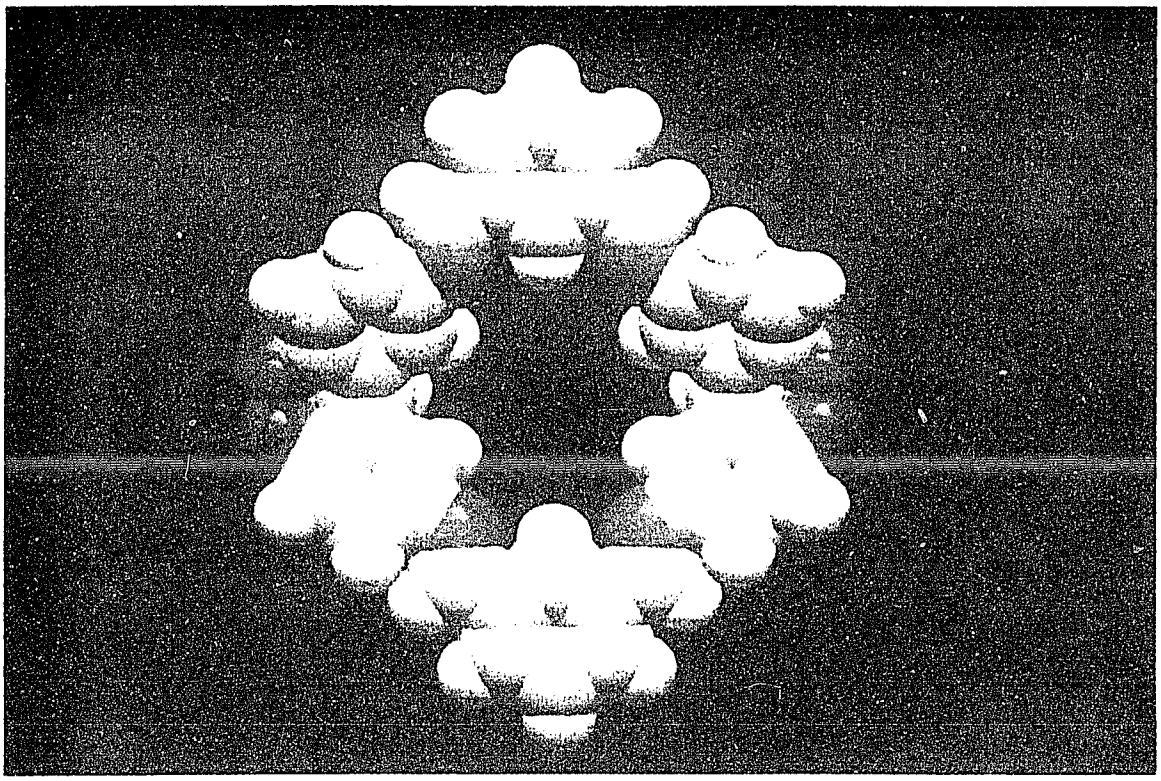
H_a = 7.59[t, 7.73Hz]
H_b = 7.97[d, 7.73Hz]
H_c = 8.69[s]
H_d = 7.24[d, 8.69Hz]
H_e = 6.81[d, 8.69Hz]
H_f = 9.6[s]
H_g = 8.42[s]

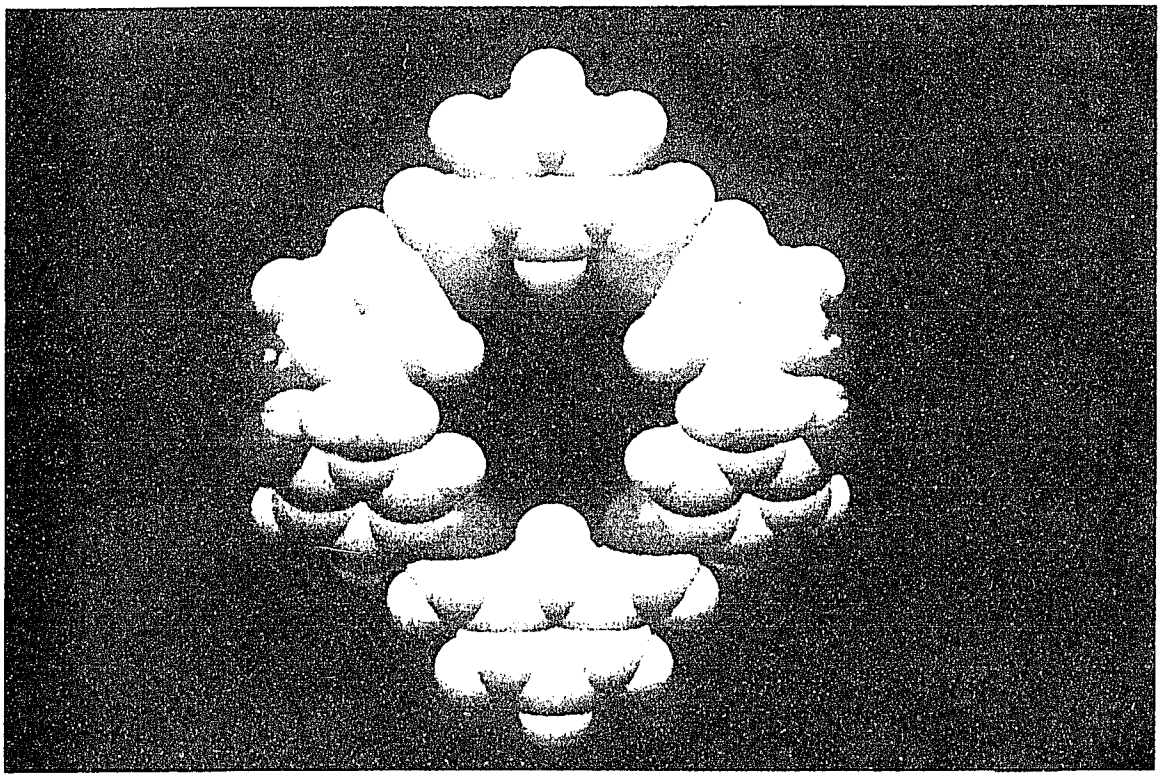


H_a = 8.03[t, 7.24Hz]
H_b = 8.18[d, 7.24Hz]
H_c = 8.67[s]
H_d = 7.33[d, 6.9Hz]
H_e = 6.82[d, 6.9Hz]
H_f = 9.68[s]

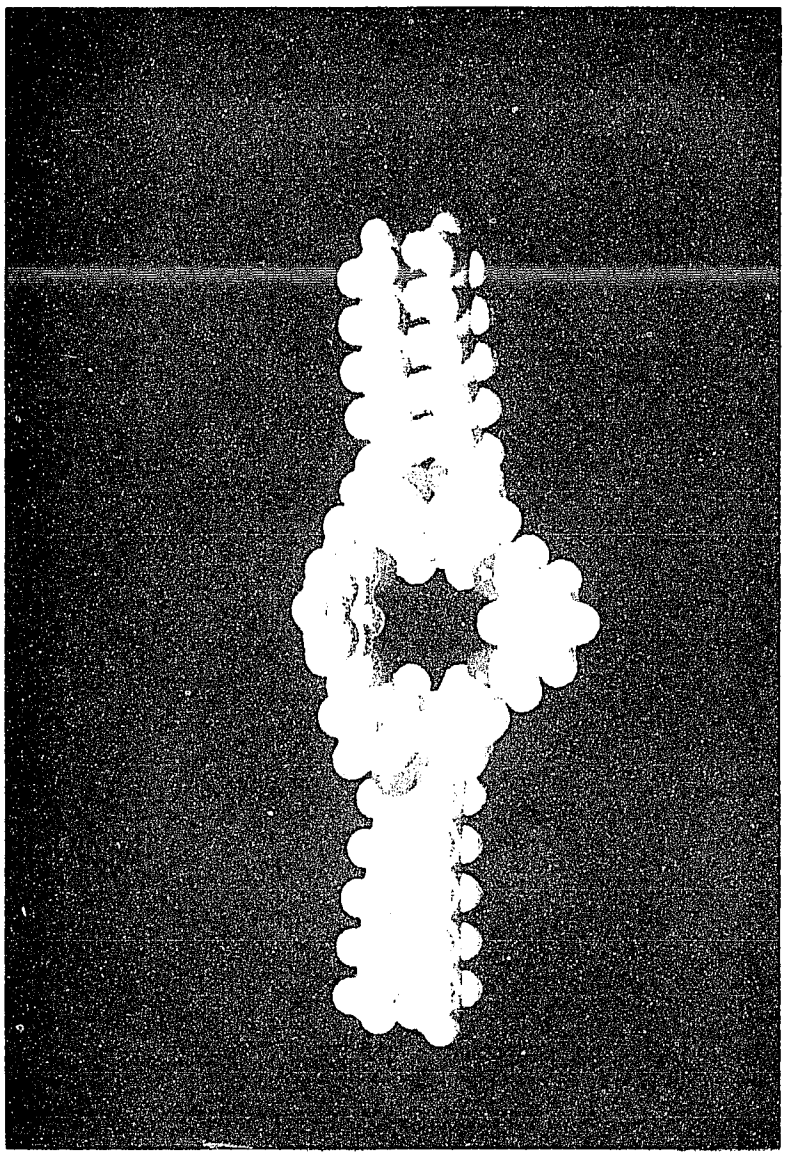


BEN13H

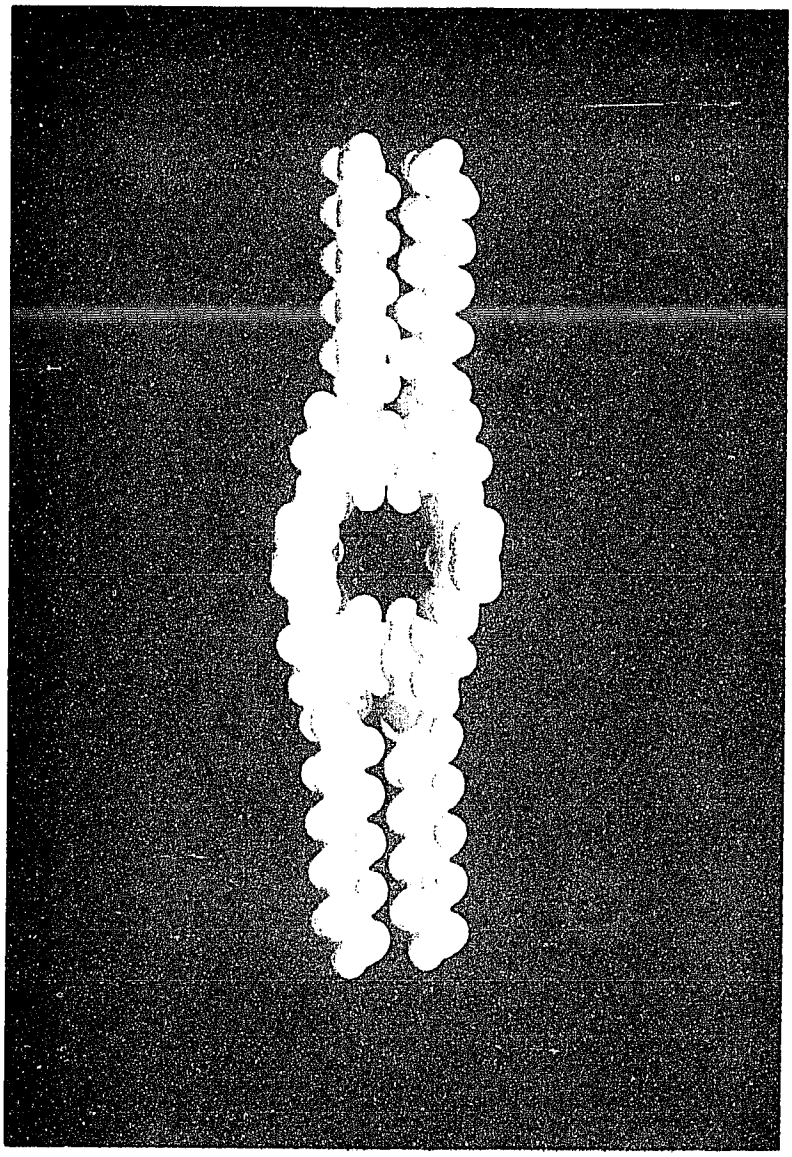




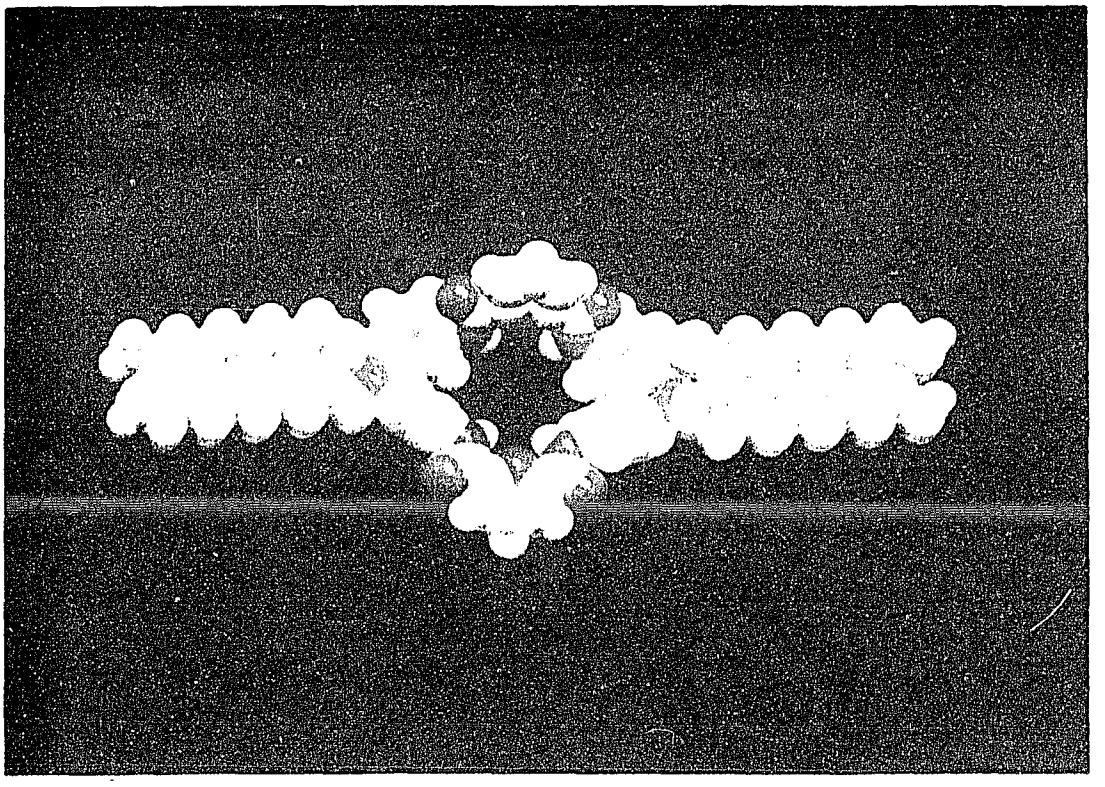
BEN13H

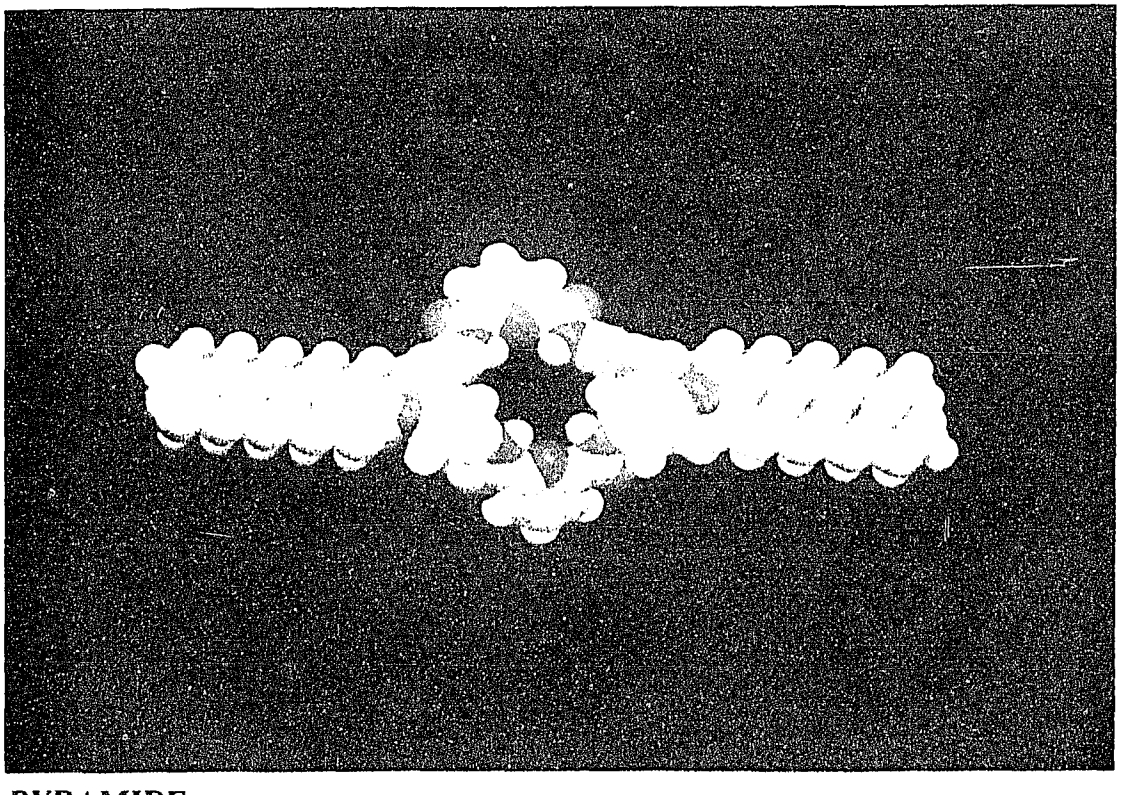


BEN13C10

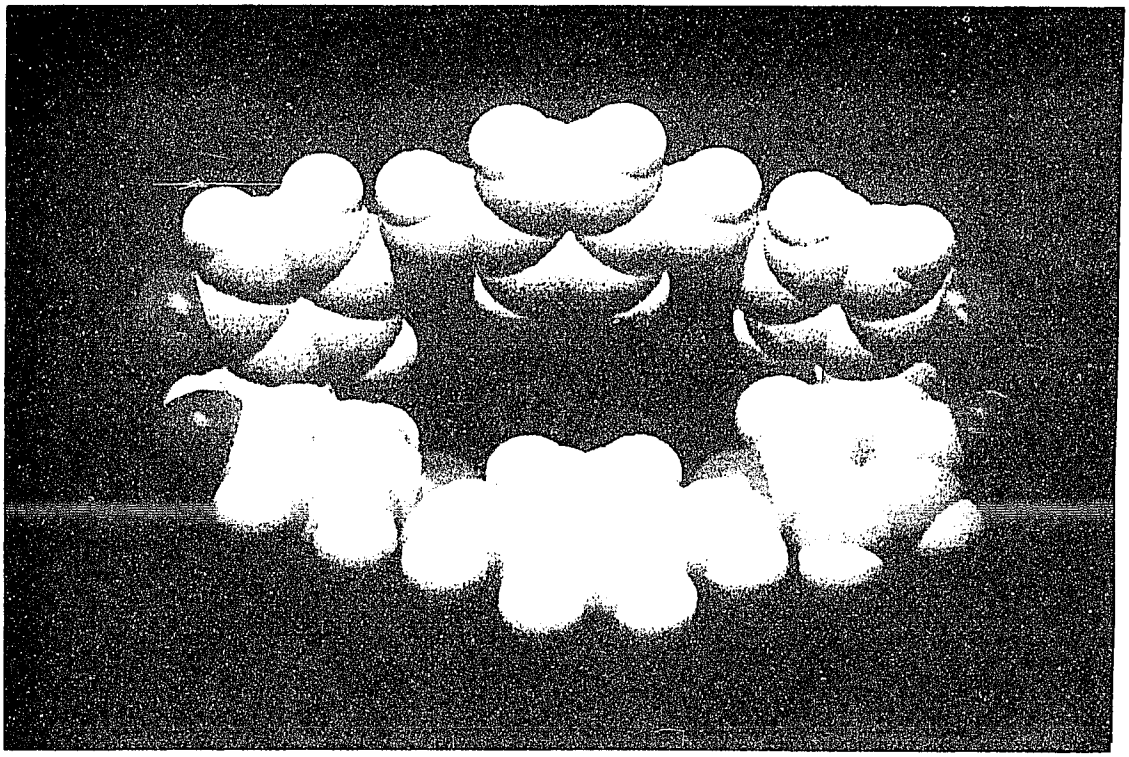


PYRRC10

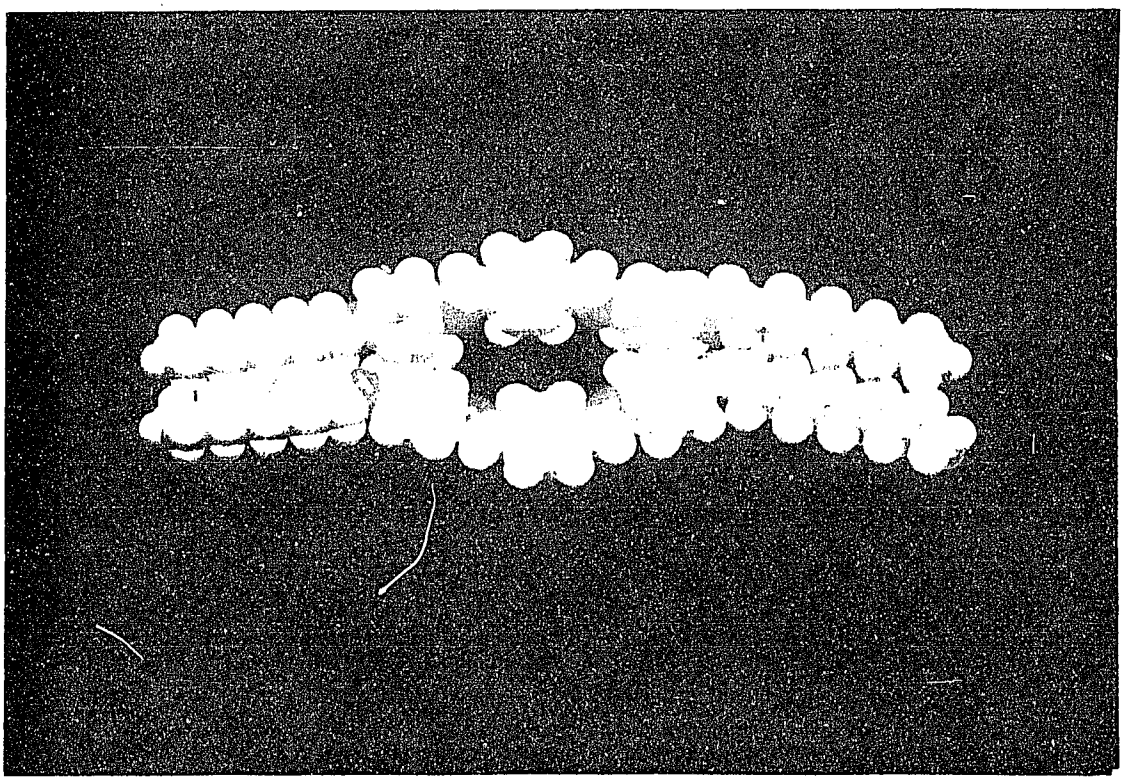




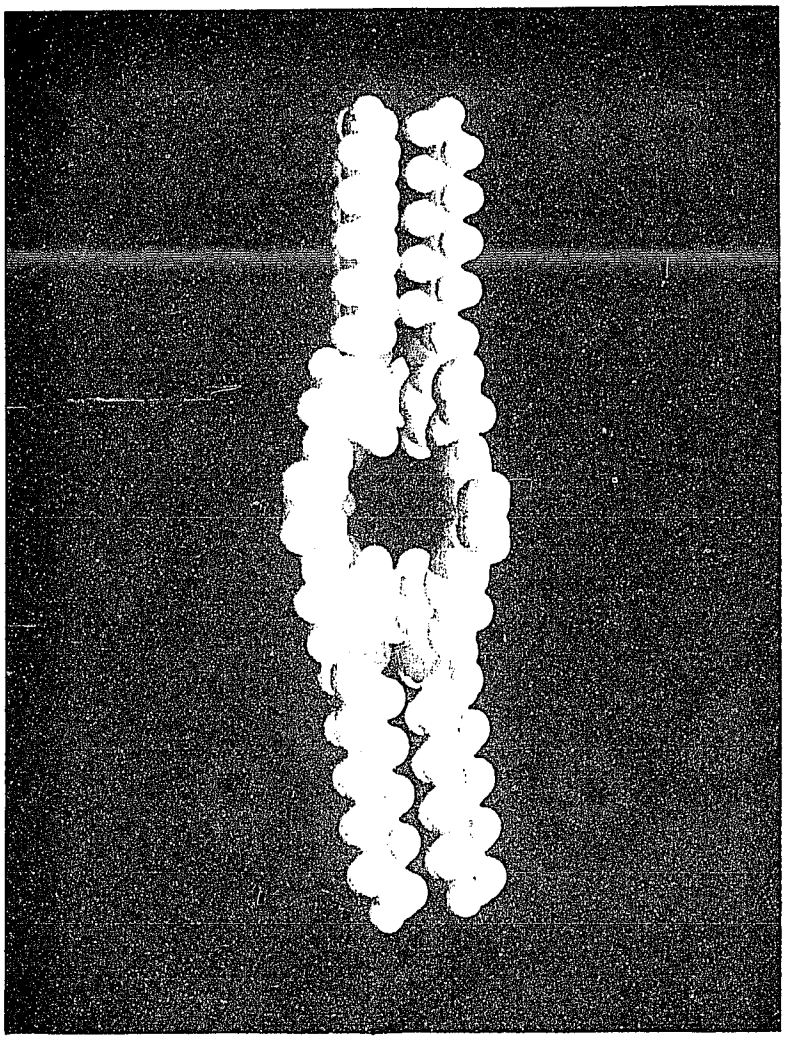
PYRAMIDE



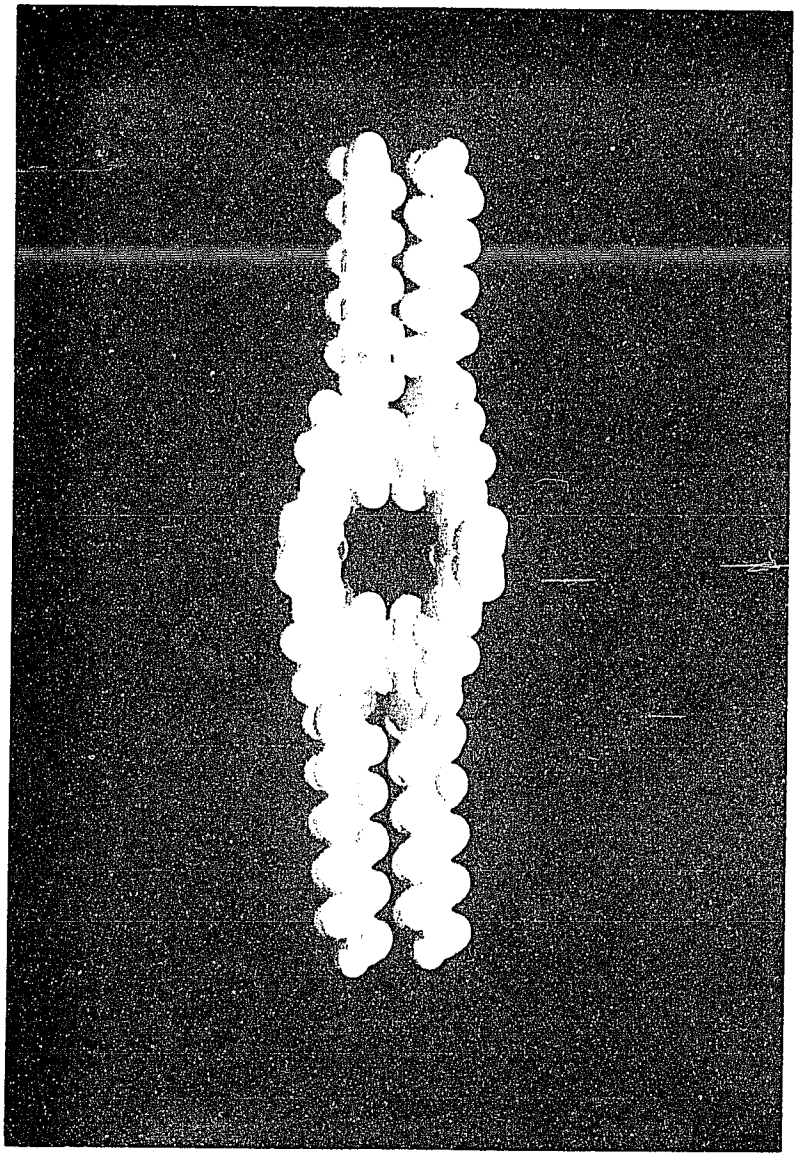
BEN14H



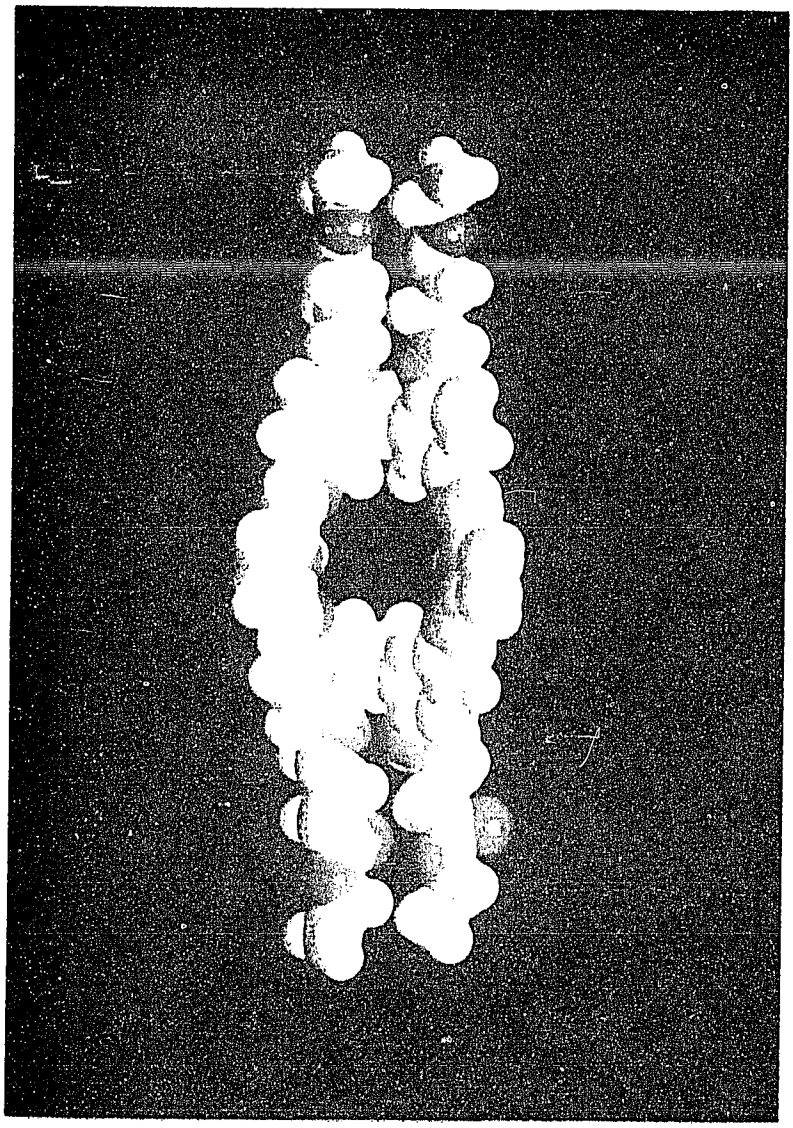
BEN14C10



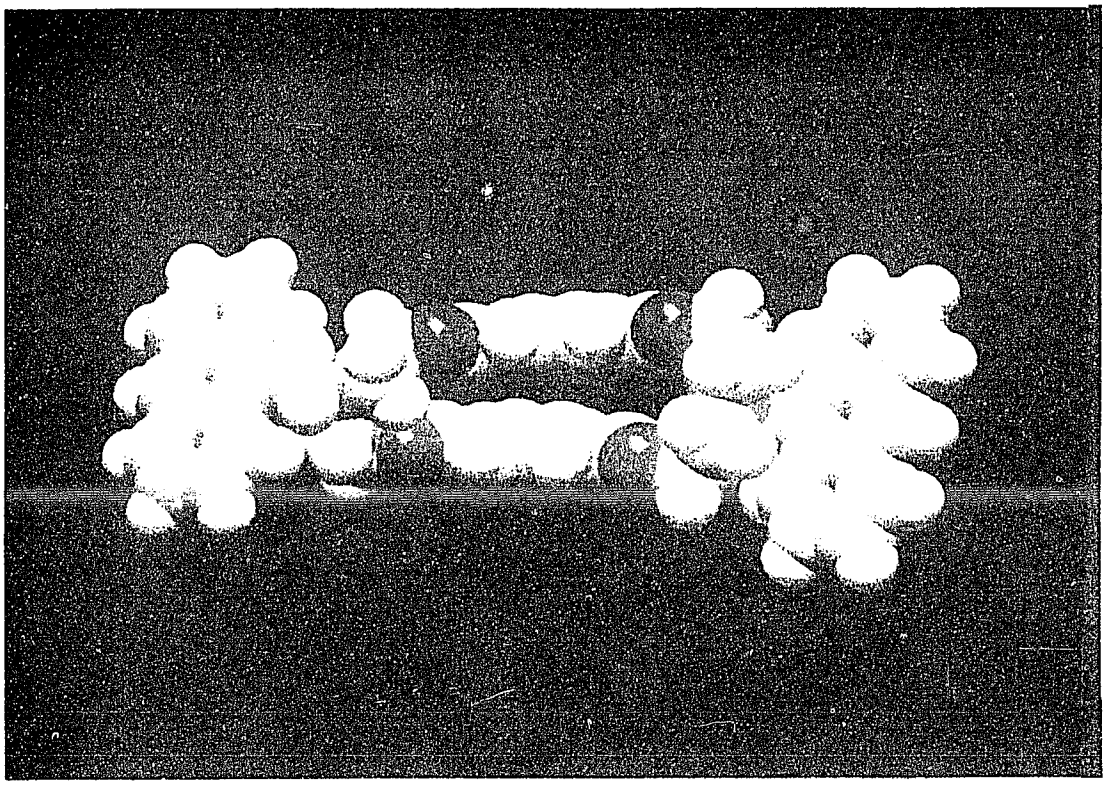
FURC10

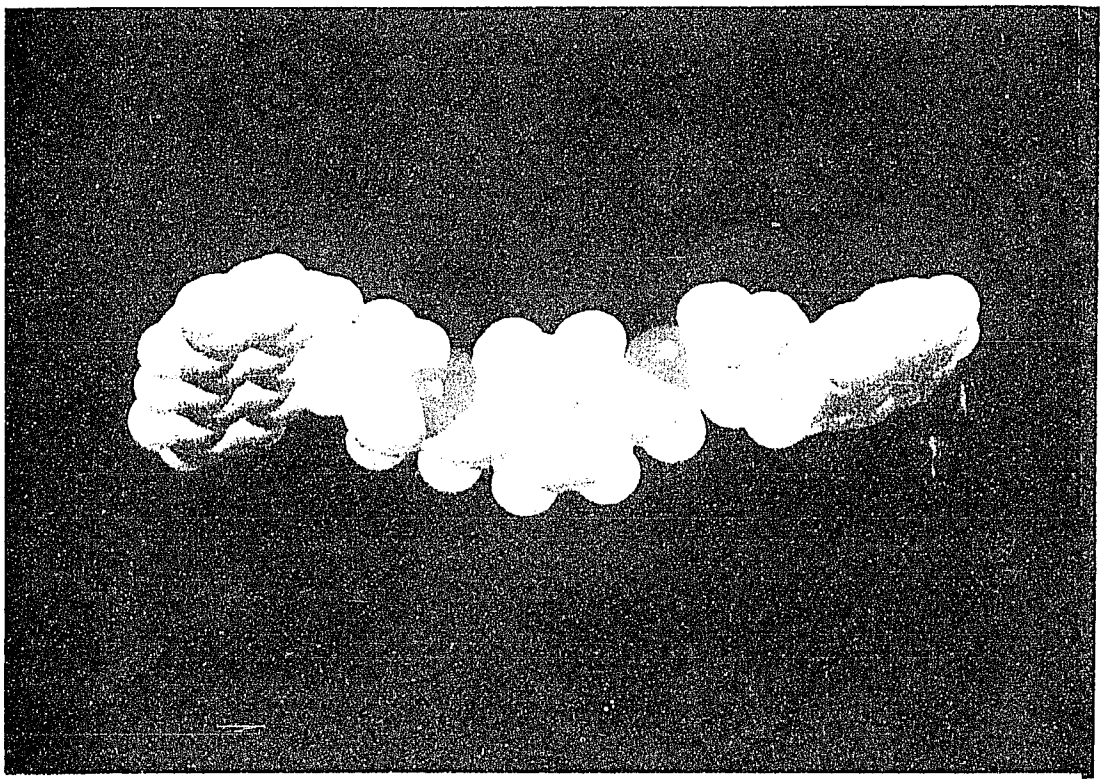


PYRRC10



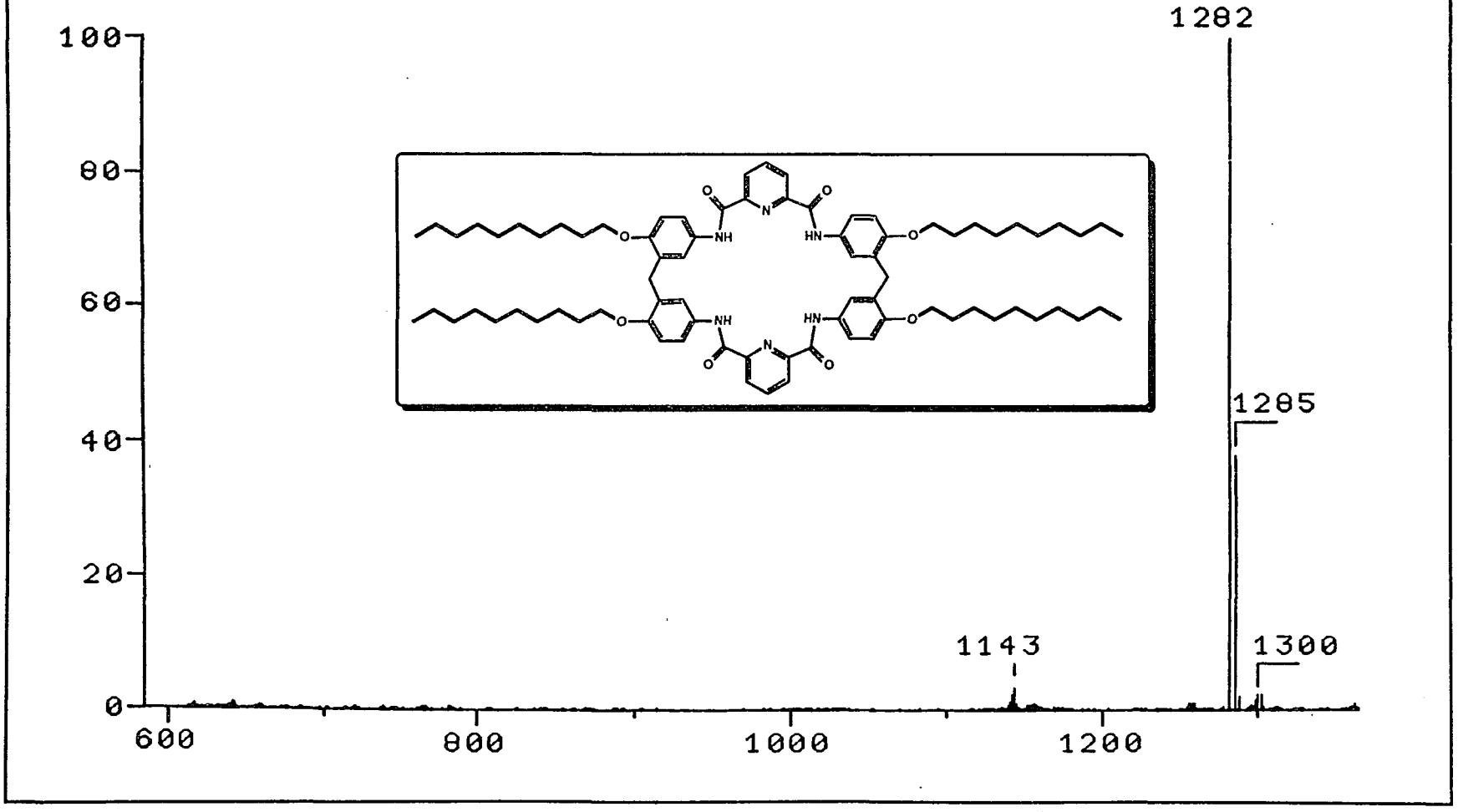
PYRRESTER



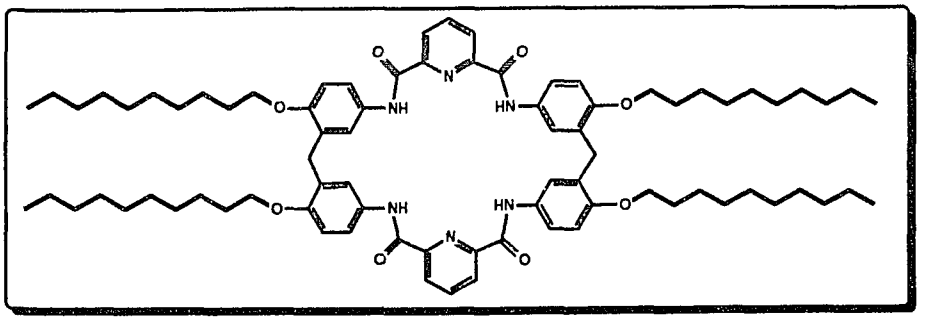


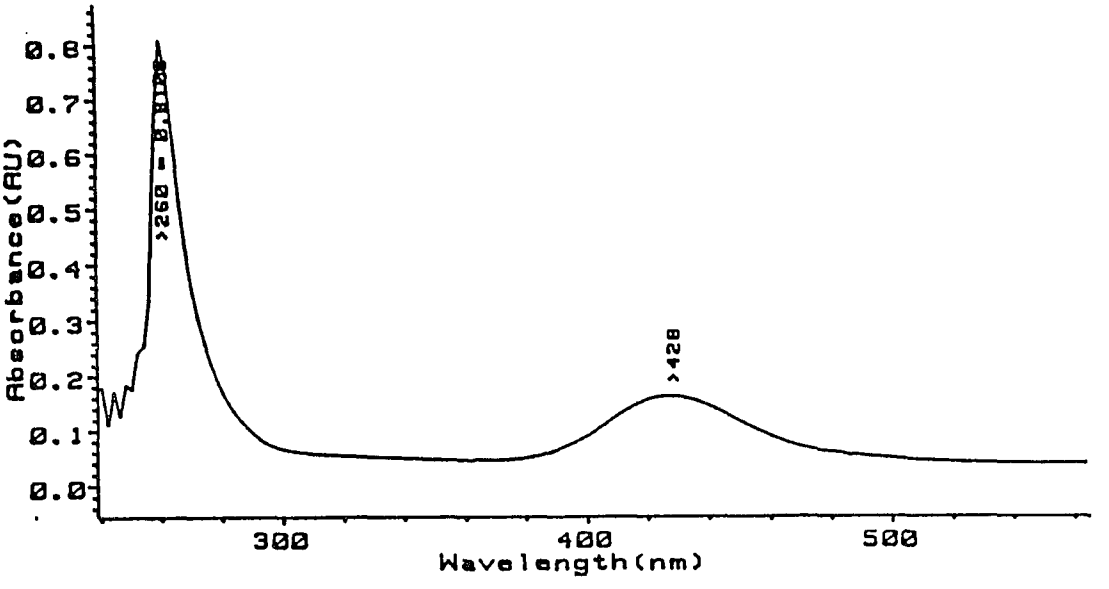
MACANTH

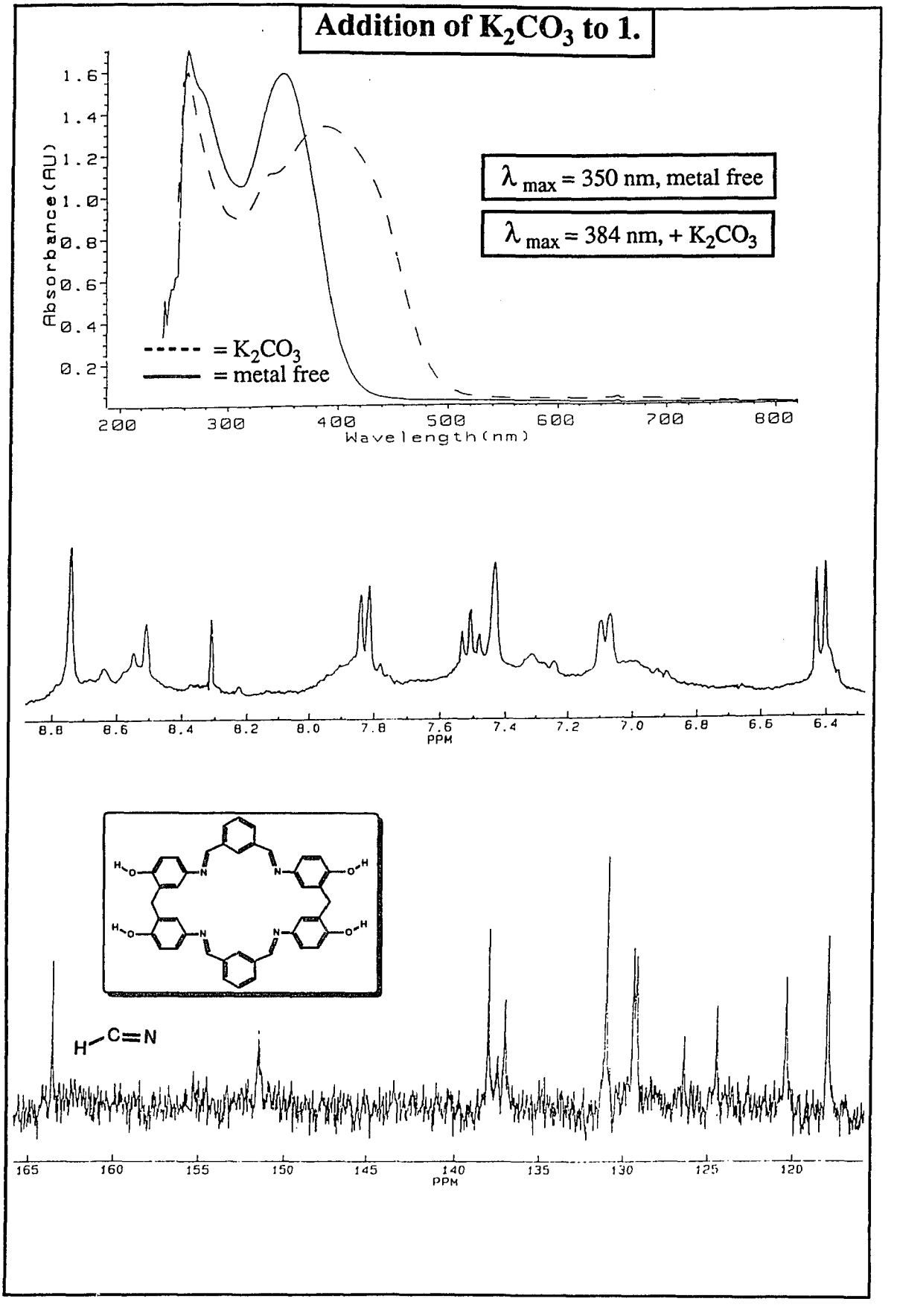
CI-MS spectrum of 15.



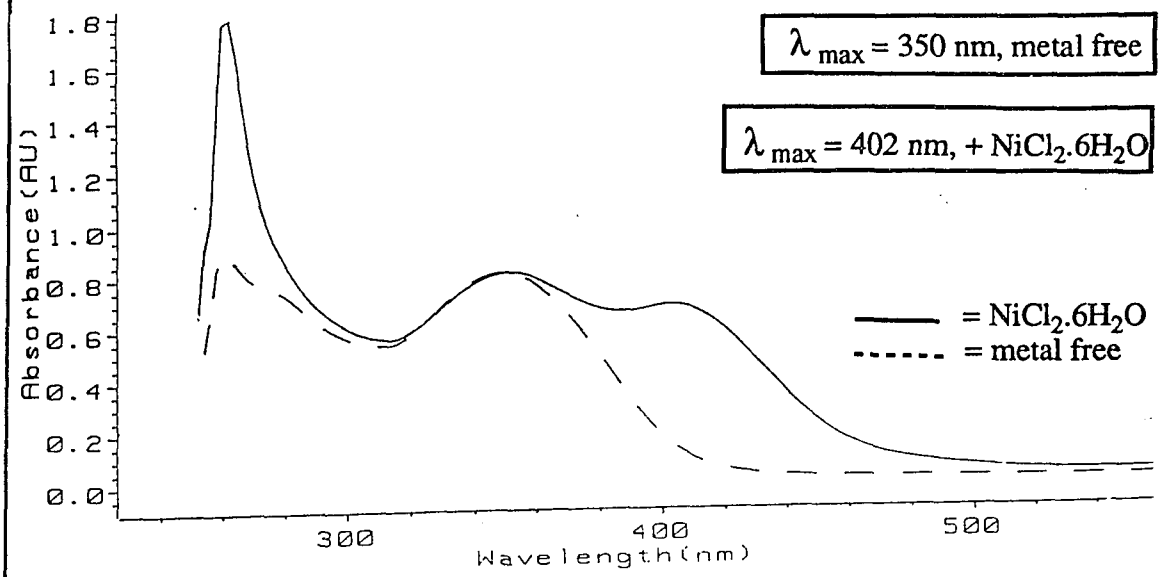
UV-VIS spectrum of 15-$NiCl_2.6H_2O$.

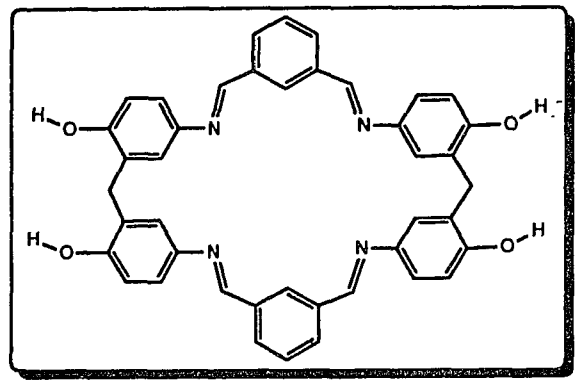


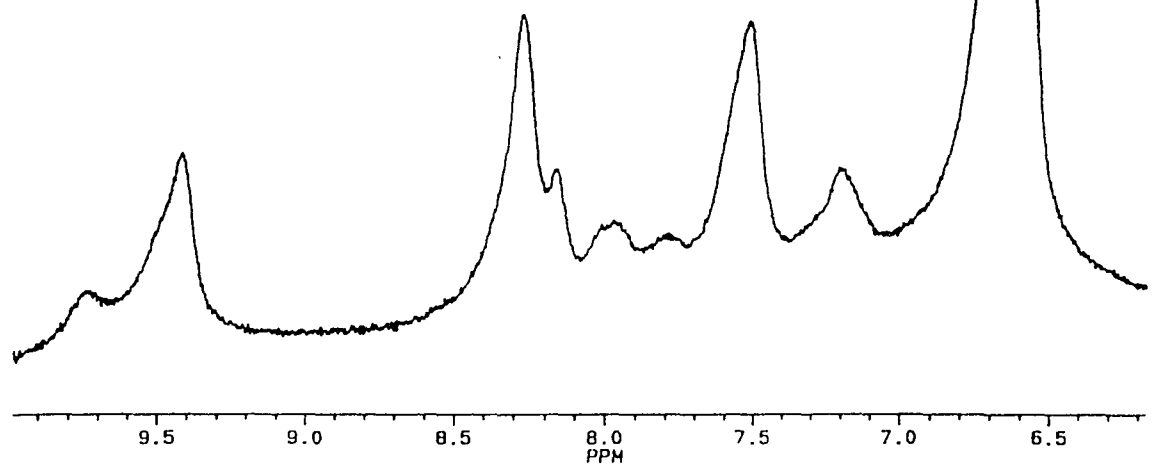



Addition of K_2CO_3 to 1.
λ_{max} = 350 nm, metal free
λ_{max} = 384 nm, + K_2CO_3
Absorbance(AU)
Wavelength(nm)
----- = K_2CO_3
——— = metal free
PPM
H–C=N
PPM

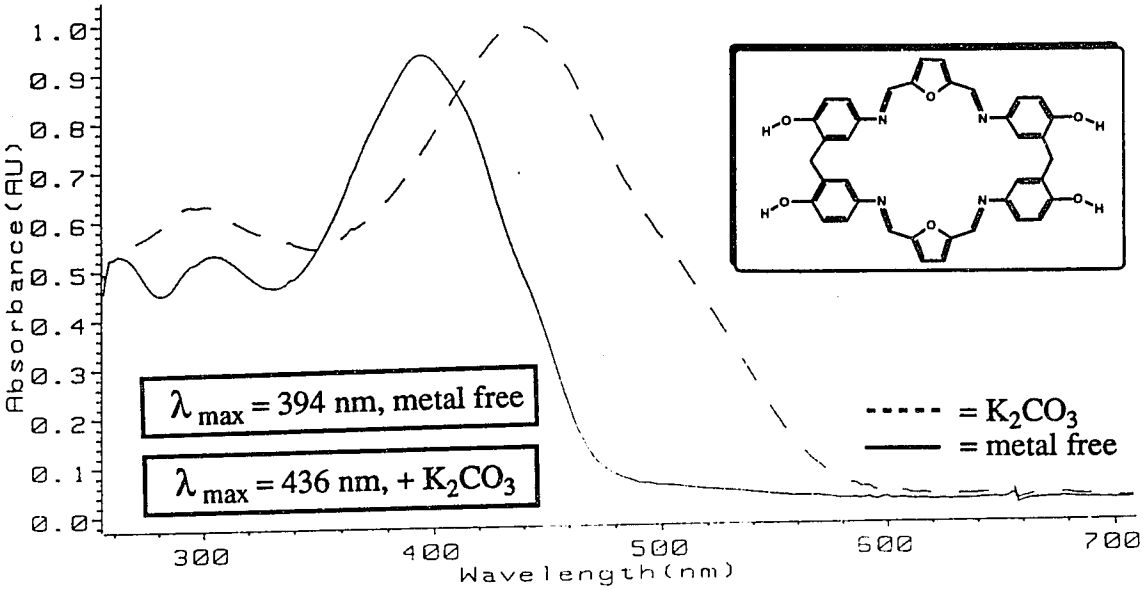
Binding of $NiCl_2.6H_2O$ to 1.

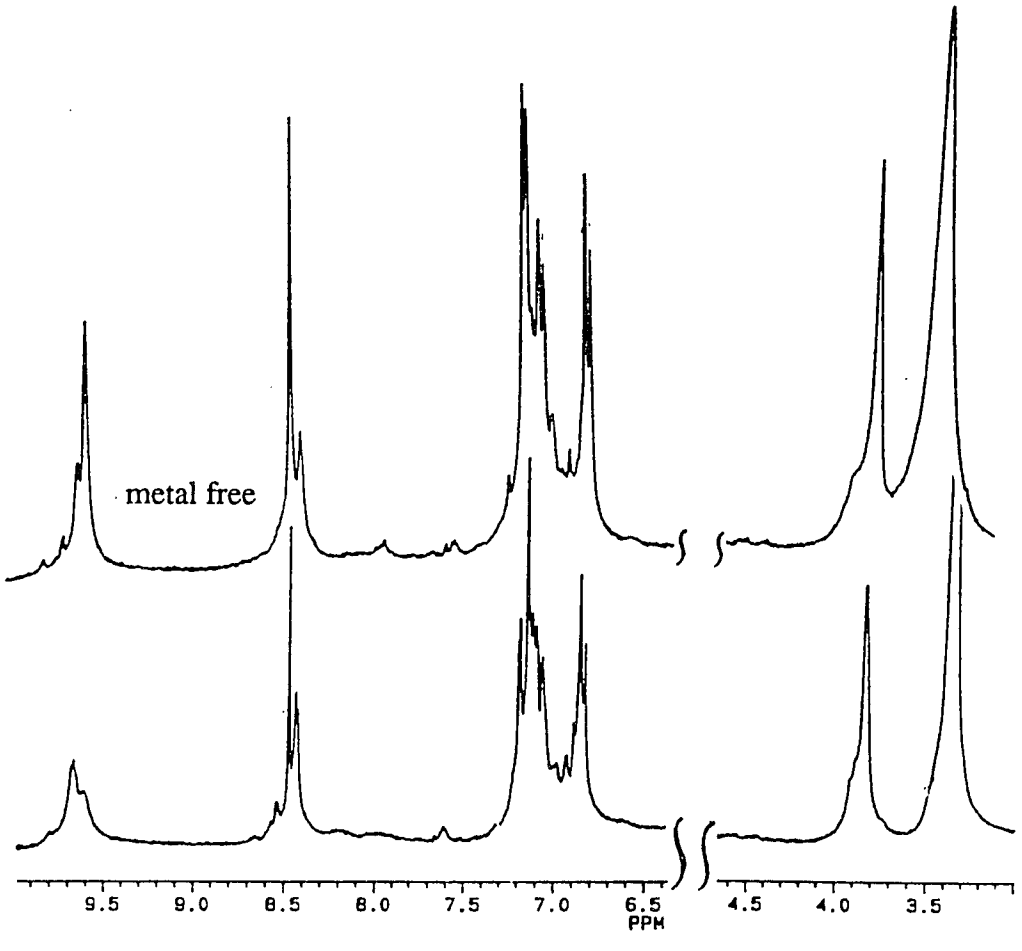






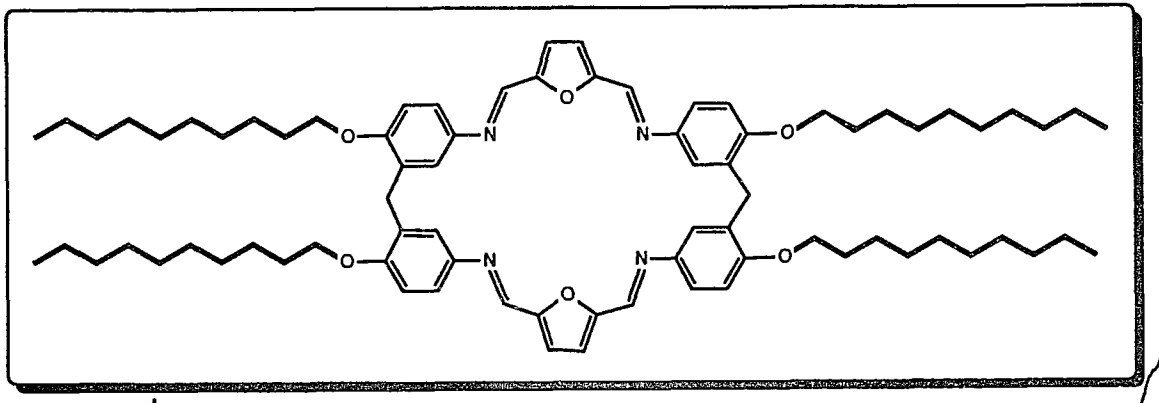
Addition of K_2CO_3 to 2.

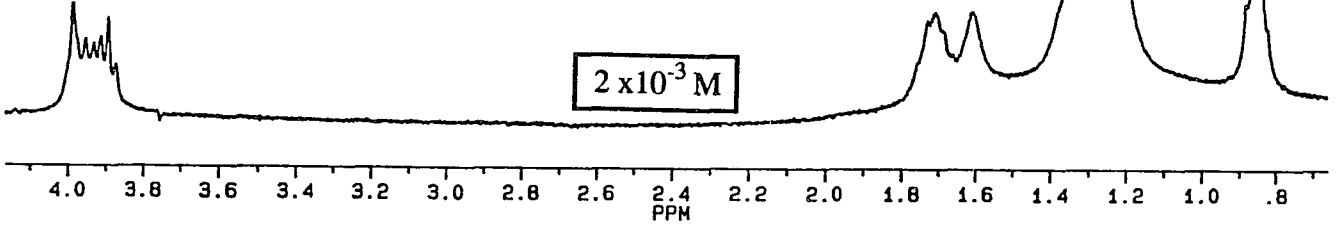


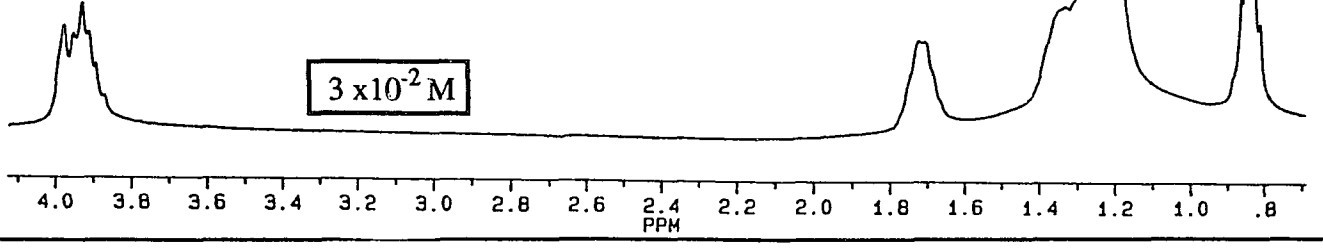


^{1}H nmr concentration study of 8.

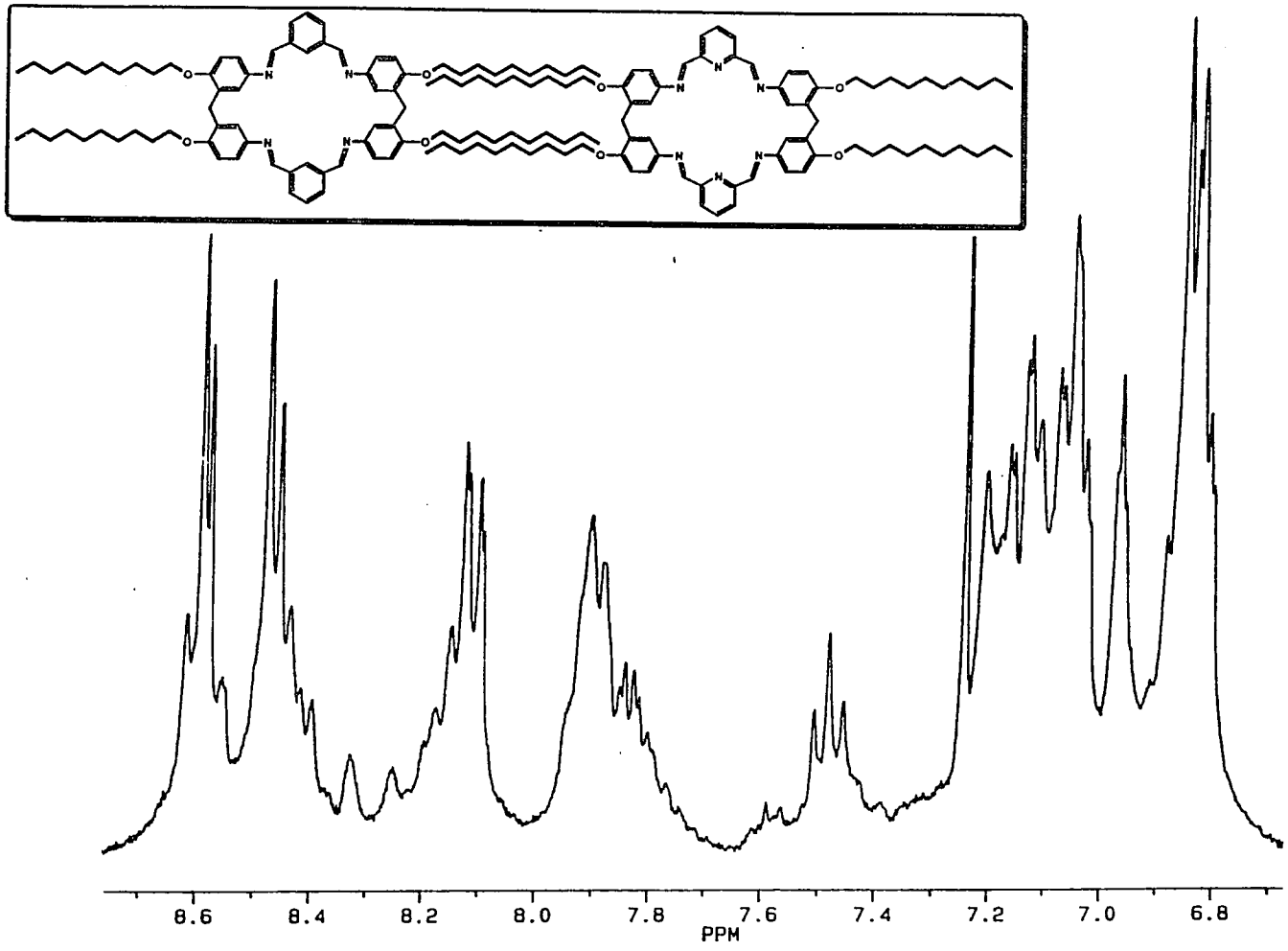
For the furan derived macrocycle, the six methylene units of the hydrocarbon chain illustrates association seen on increasing the concentration (lower spectrum). The shift to higher field is indicative of a more apolar enviroment.



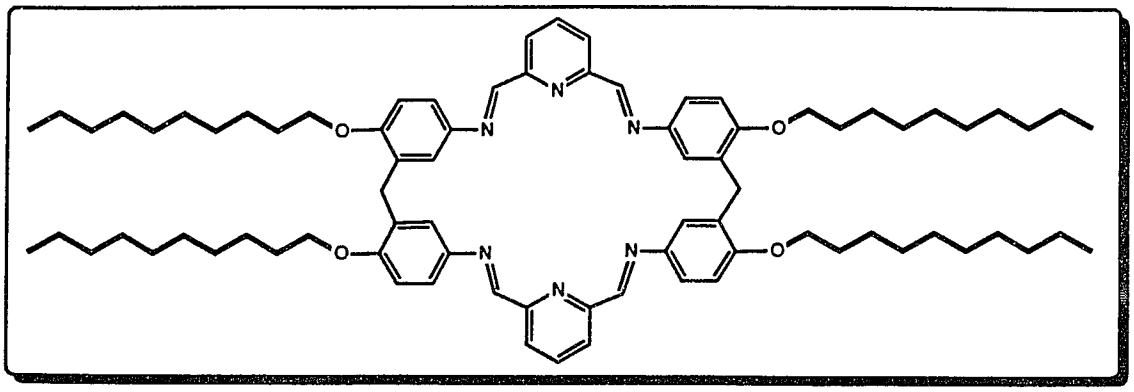


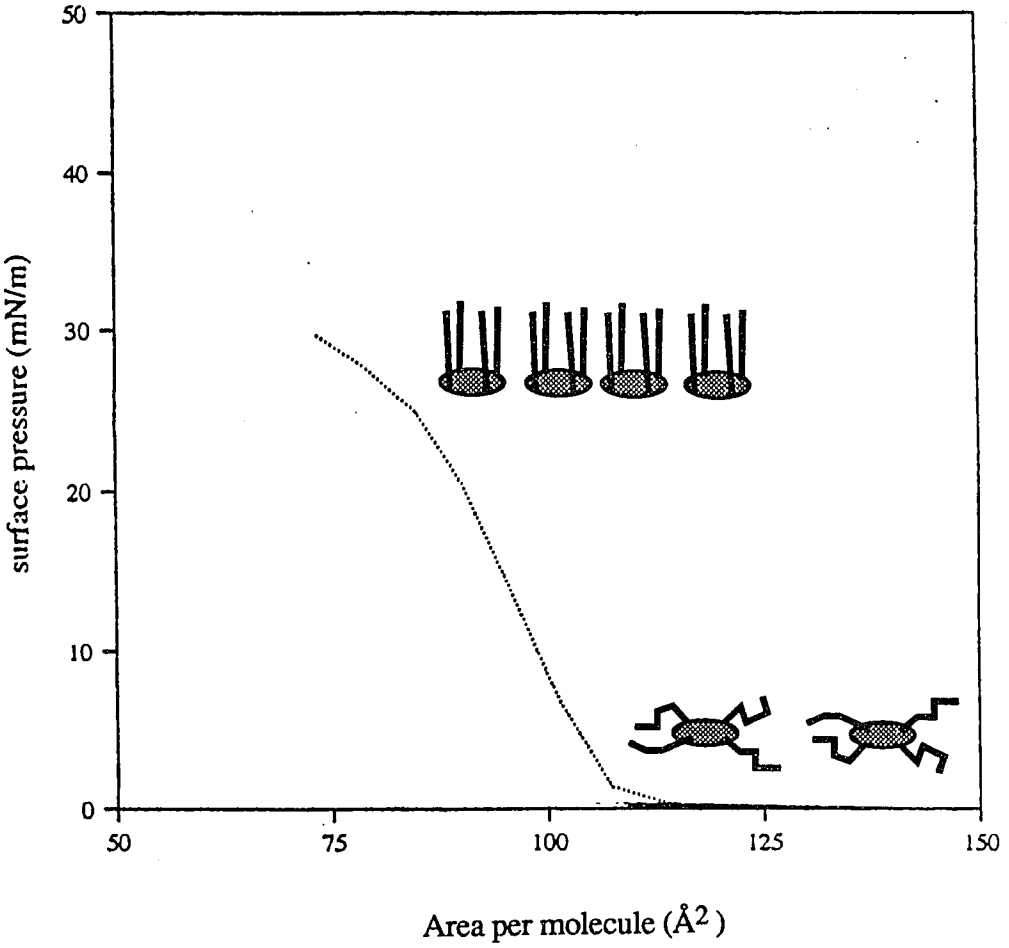


^{1}H nmr of an equimolar mixture containing 6 and 4.

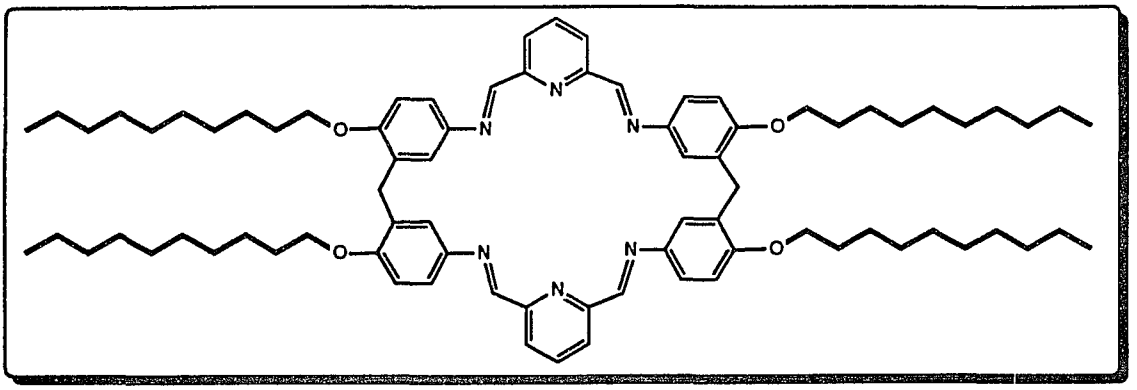


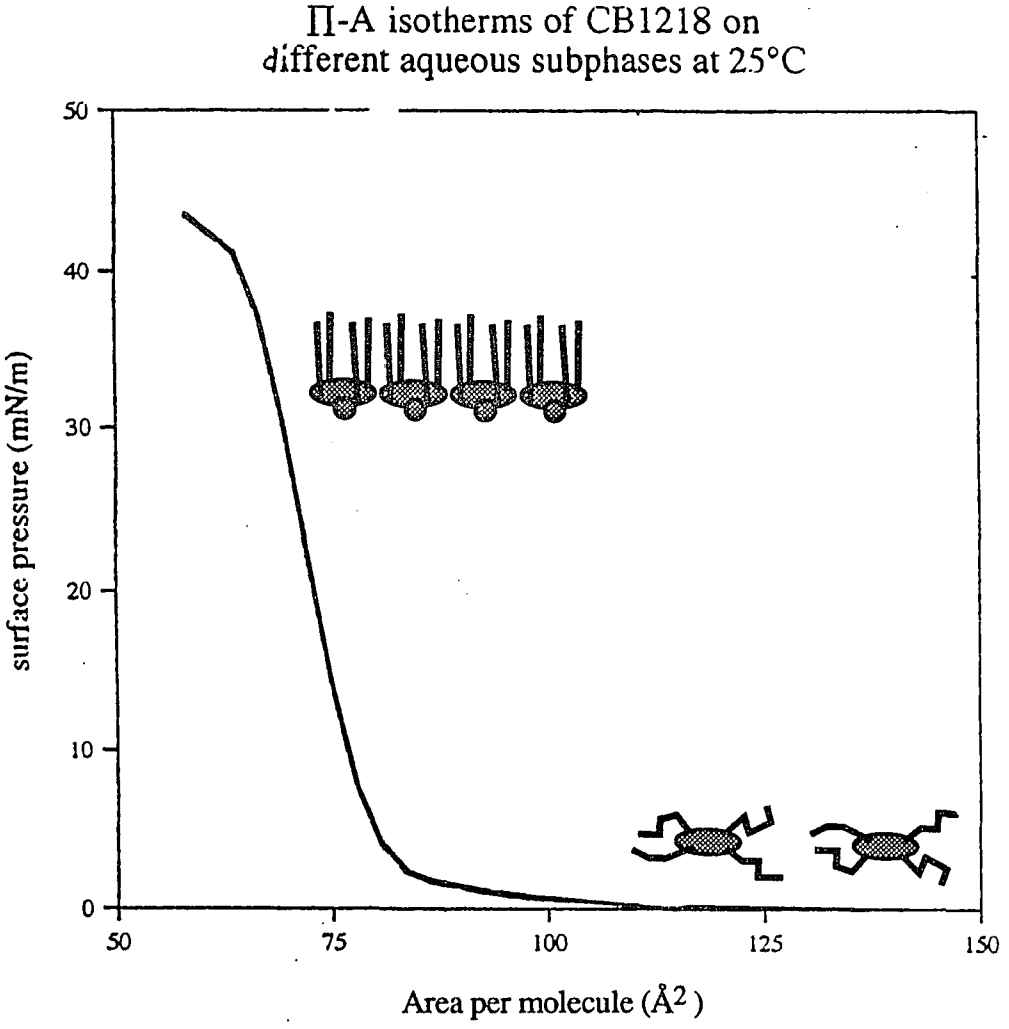
Π-A isotherm of 6 on pure water.



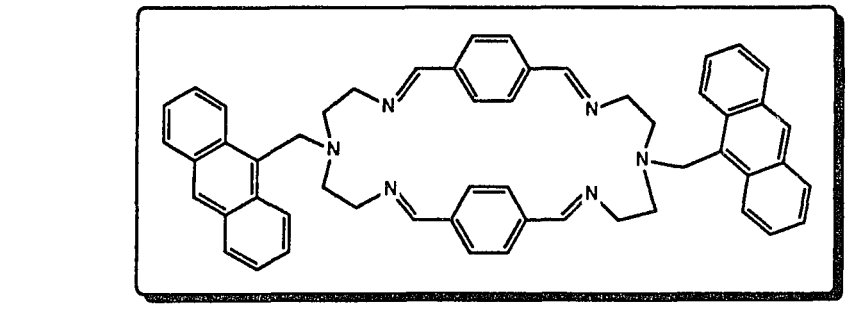


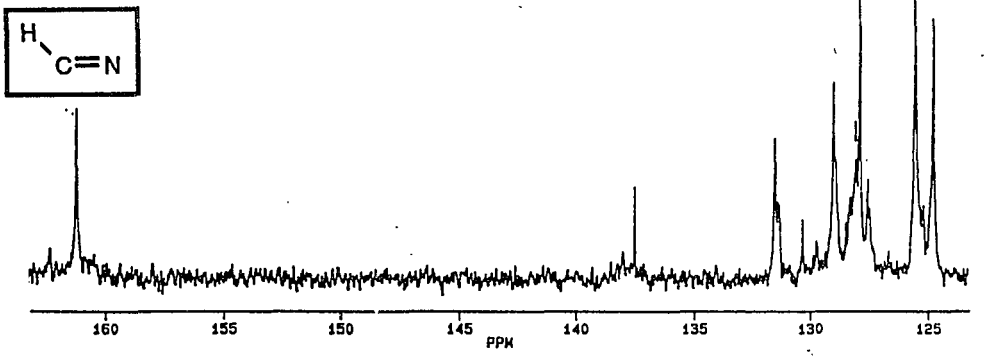
Π-A isotherm of 6 on 0.5M $NiCl_2$.

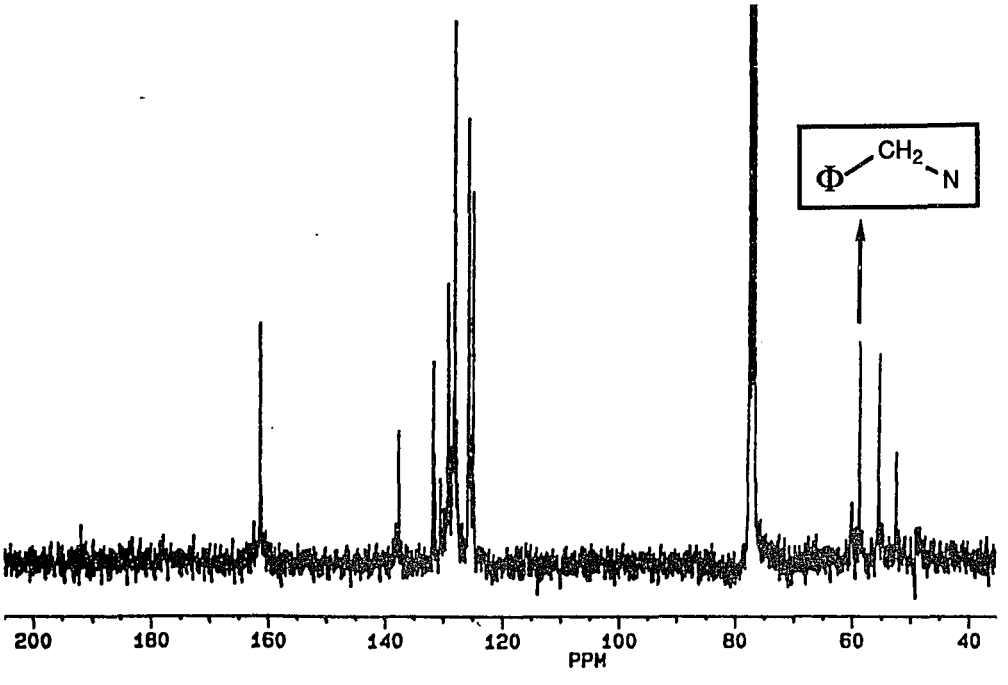




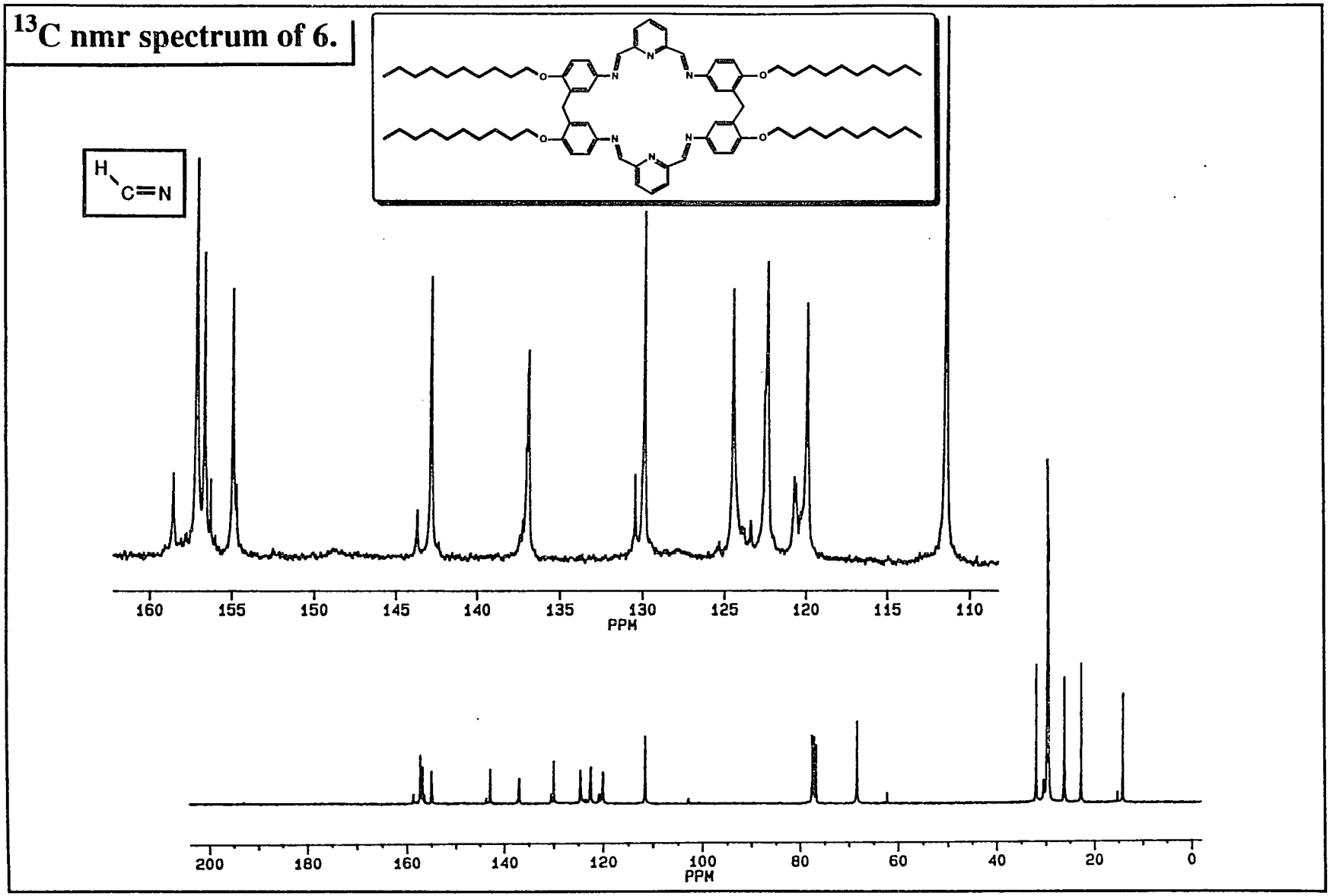
^{13}C nmr spectrum of 20.



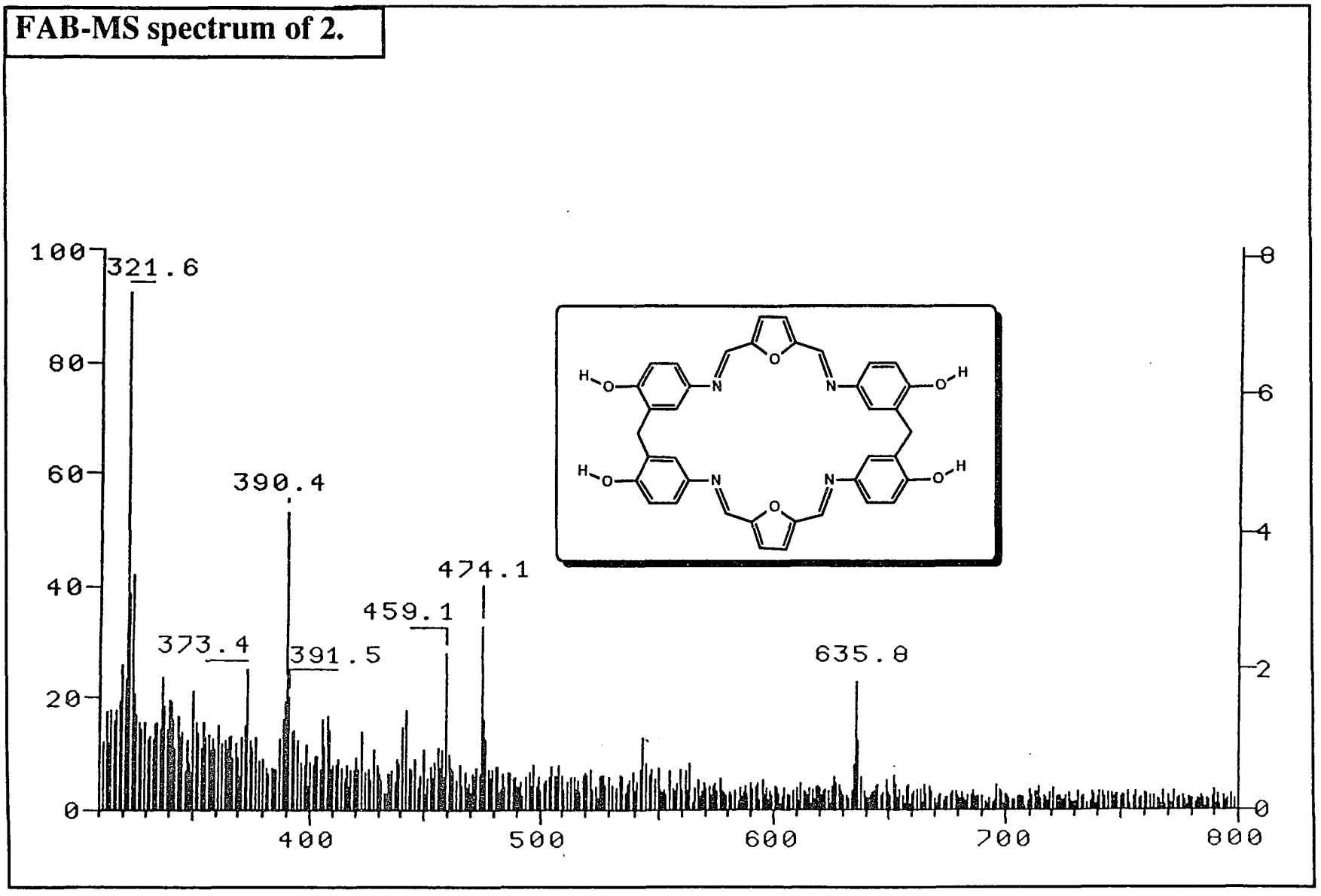




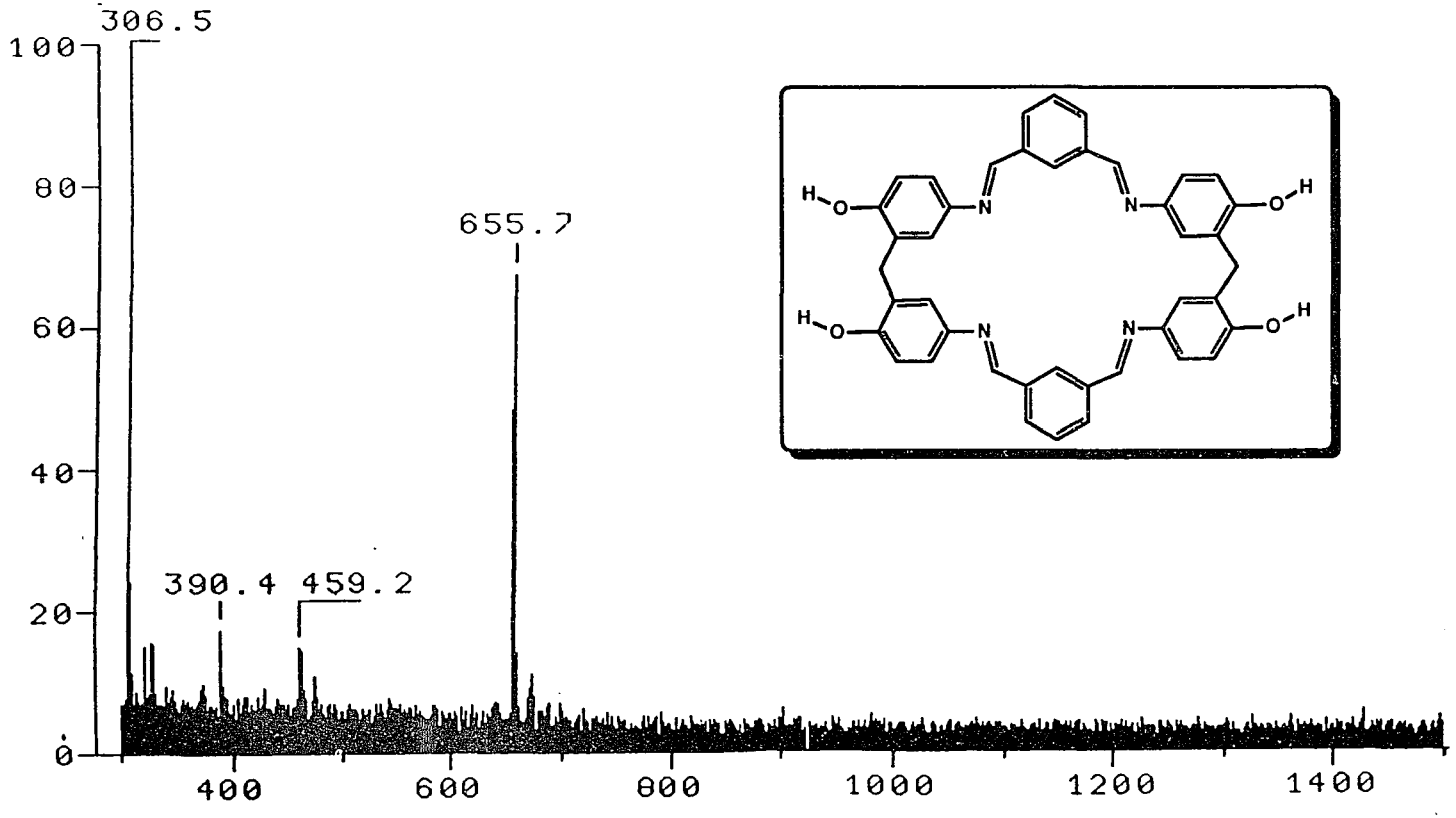
^{13}C nmr spectrum of 6.



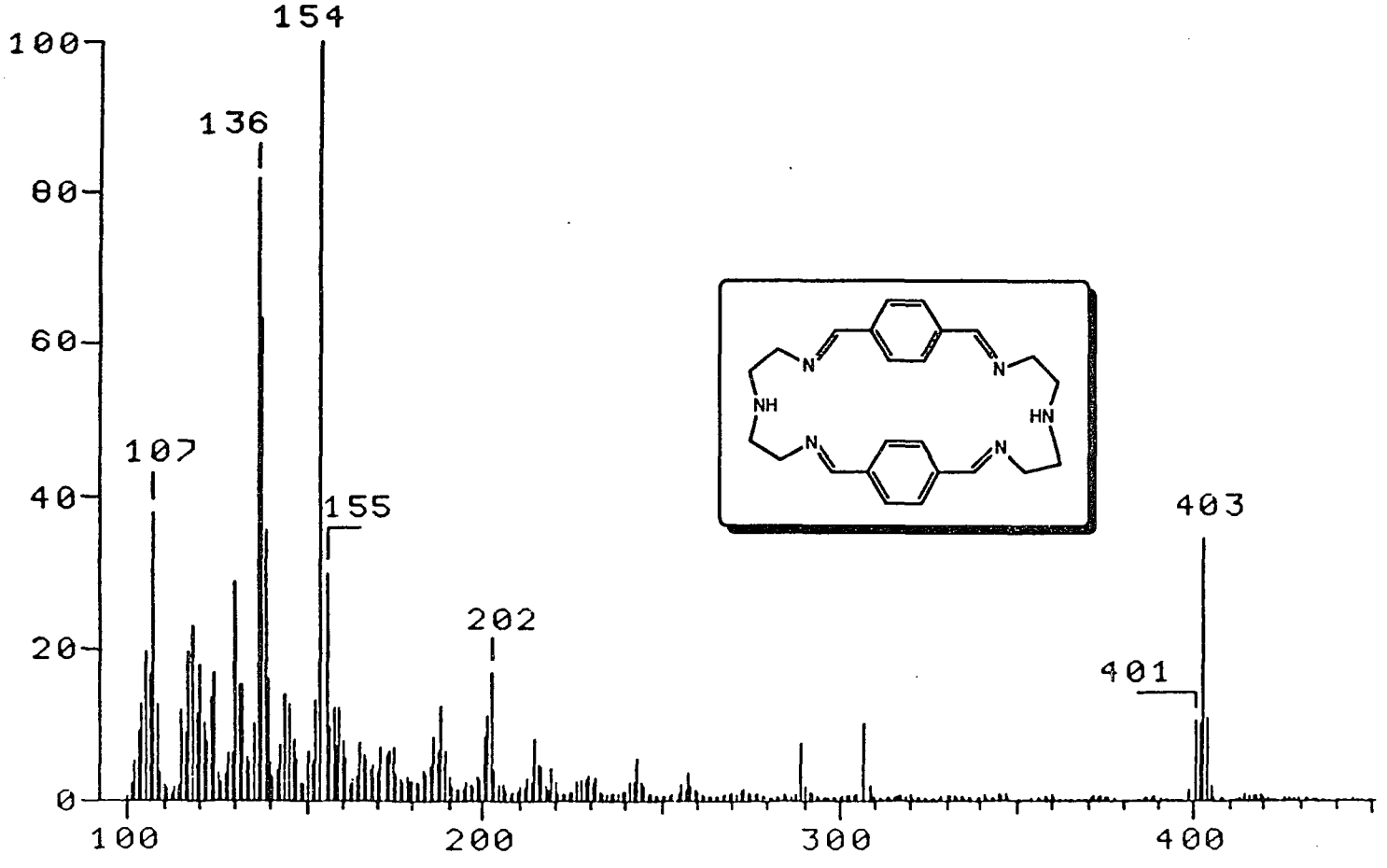
FAB-MS spectrum of 2.



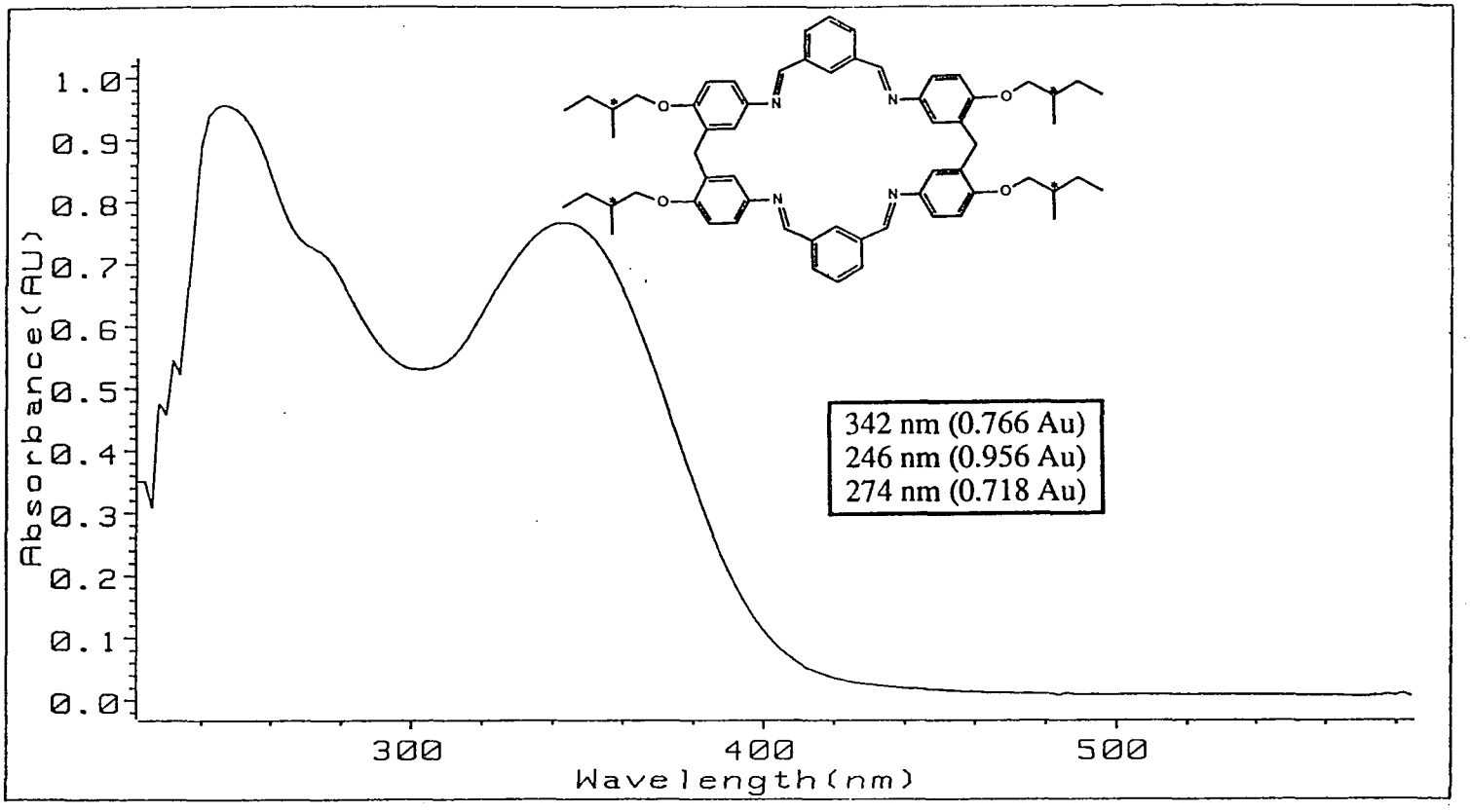
FAB-MS spectrum of 1.



FAB-MS spectrum of 19.



UV-VIS spectrum of 14 in CH_2Cl_2



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Chapter 1

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   b) Izatt, R, M., Chrisensen, J. J : *Synthesis of Macrocycles-The design of selective complexing agents*, John Wiley, New York, 1987.
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   e) Symposia in Print, *Pure & Appl. Chem.* 1989, **61**(9).

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   b) *Host-Guest Molecular Interactins: From Chemistry to Biology* (Ciba Foundation Symposium 158), Wiley, Chichester 1991.
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