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INCLUSION COMPLEXES OF MOLECULAR TRANSITION METAL HOSTS

The Ohio State University

Ph.D. 1985

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INCLUSION COMPLEXES OF MOLECULAR TRANSITION METAL HOSTS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy in the Graduate School of
The Ohio State University

by

Thomas Joseph Meade, M.S.

* * * * *

The Ohio State University

1985

Reading Committee:

Dr. Daryle H. Busch

Dr. Devon W. Meek

Dr. Alan G. Marshall

Approved by

Advisor
Department of Chemistry

To Karen: Who, in boundless love, has
endured and sustained me.

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VITA

June 30, 1957.....Born, Rochester, New York
May, 1979.....B.S., Arizona State University
September, 1979-.....Graduate Teaching Associate
September, 1981.....The Ohio State University
May, 1982.....M.S., The Ohio State University
September, 1981-.....Graduate Research Associate
August, 1985.....The Ohio State University
August, 1985.....Ph.D., The Ohio State University,
.....Columbus, Ohio

PUBLICATIONS

- T.J. Meade, D.H. Busch, "Inclusion Complexes of Molecular Transition Metal Hosts", Progress in Inorganic Chemistry, Stephen J. Lippard, Ed., 1985, 33, 59-127.
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FIELD OF STUDY

Major Field: Chemistry

Specialization--Inorganic Coordination Chemistry
Professor Daryle H. Busch, Advisor

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CHAPTER ONE

INCLUSION COMPLEXES OF MOLECULAR TRANSITION METAL HOSTS

INTRODUCTION

The analogy between host-guest complexes and enzyme-substrate complexes has directed much attention to host-guest chemistry. The "host-guest" label was coined by D.J. Cram and J.M. Cram in the early 1970's and a "host-guest" complex may be defined simply as a complex between organic compounds that simulates the substrate selectivity of enzymes⁶⁹. Such interactions imply a phenomenon described as "molecular recognition". Since the guest assumes a site within the host during host-guest complexation, the concave surface of a host compliments the convex surface of a guest⁷⁸, or as Cram has stated, "a host is characterized by its employment of converging binding sites while a guest incorporates diverging binding sites". "Inclusion complex formation" may be thought of as occurring when a host includes a guest without covalent bond formation.^{247,268a} The binding forces that are present in such complexes are recognized as van der Waals attractions, ion pairing, hydrogen bonding, metal ion to ligand attractions, and/or π acid to π base attraction, along with hydrophobic and solvent liberation driving forces. References 24, 35, 37, 70, 78, 88, 156a, 156b, 165, and 267 are useful reviews of this rather large subject.

The well known clathrates,^{5,64,122,153,187,225,325a} zeolites,³² and intercalated derivatives of graphite and transition metal chalcogenides,^{23,98,101,135,228} are examples of solid state inorganic host-guest complexes, while the cyclodextrins,^{24,247,267} crown ethers,^{152,328} ionophores,^{104,239} cryptands,^{166,169} and related structures are molecular organic hosts^{129a}. Only the latter, the systems based on molecular (more or less) organic hosts will be treated here. While this host-guest chemistry is a fundamental realm of great novelty and importance in its own right, a great impetus to study this field has been the need and desire to understand enzyme substrate binding through use of models. Host-guest complexes provide the opportunity to study the various possible modes of interaction mentioned above and to learn about the regio- and stereospecific interactions that may accompany inclusion complex formation. The roles of such interactions in catalytic rate enhancement are also of vital interest in such studies.

While a great deal of work from many laboratories has been applied to organic guest-host chemistry, systems containing transition metal hosts have received much less attention. The traditional approach to host-guest chemistry lacks the ability to model metalloenzymes in which a metal atom is critical to the enzyme function. It is our purpose to review the current status of the field of molecular host-guest chemistry for those systems in which a transition metal atom is incorporated into the structure of the host molecule. In order to proceed, it is first necessary to consider the essential elements of host-guest chemistry in general, such as the design, synthesis, and applications of host-guest complexes, and to become acquainted with the most common families of molecular hosts.

HOST-GUEST CHEMISTRY IN GENERAL

An effort is made here to briefly familiarize the reader with the literature on organic host-guest complexes. While the review is not complete, it provides useful background and introduces a number of significant systems within which much of the fundamental chemistry of the field has been studied.

Cyclodextrins. The cyclodextrins are probably the most intensively studied class of host molecules and five notably excellent reviews have summarized this rather large field.^{24,247,265a,267,290} Cyclodextrins were the first host compounds to be recognized as possessing selective molecular recognition capabilities¹⁰⁷ and are a class of cyclic oligomers of glucose. The so-called α -, β -, and γ -cyclodextrins are composed of 6, 7, and 8 glucose units, respectively. They are very soluble in water and form inclusion complexes with a wide variety of guest species.^{31,54,106,124a,135a,172,184,193,220a,302} The general structure and preparation of α -cyclodextrin is shown²⁴⁹ in Figure 1.

Figure 1. (a) Preparation of cyclodextrins. (b) Structural representation of α -cyclodextrin. (c) Structural representation of α -cyclodextrin.

These short cone-shaped molecular cylinders are about $8.5\text{\AA}$ high. The internal diameter of α -cyclodextrin is $4.5\text{\AA}$ and the depth of the void is $6.7\text{\AA}$. The cavities are lined on both rims with hydroxyl groups. The interior of the cavity is hydrophobic while the outside is hydrophilic. It has been confirmed via crystallographic studies that the central cavities of α - and β -cyclodextrin contain 2 and 9 water molecules, respectively.¹⁸⁴ Upon inclusion complex formation with a guest molecule, the water molecules are then displaced.²⁴⁸ The x-ray crystal structures of several inclusion complexes of cyclodextrins have also been reported.^{125,125a,125b,125c,126,140,143,144,189,190,227} Cyclodextrins are capable of catalyzing many types of reactions.^{188,267,298,306,317} The hydrolysis of phenyl esters is an example of this activity and a pictorial representation of the process is given^{225a,247,318} in Figure 2.

Figure 2. The cyclodextrin catalyzed hydrolysis of phenyl acetate.

Usually, the cyclodextrins form one-to-one host/guest complexes; however, one-to-two host/guest complexes are known as well.^{127,298a,302} Dissociation constants for one-to-one inclusion complex formation by many cyclodextrin systems²⁴⁹ are of the order of 10^{-2} to 10^{-4} M⁻¹.

Attention has been directed toward several proposed binding forces and thermodynamic parameters that may be responsible for the inclusion complex formation of cyclodextrins with guest molecules. These include the release of both conformational strain energies and high energy water molecules from the cavity, hydrogen bonding, van der Waals forces, and hydrophobic interactions. The measurement and discussion of these phenomena as they relate to host-guest complexation have been reported in detail elsewhere.^{25,26,84,85,119,181,194,195,240a,275,313,329a} Although it is likely that all of these phenomena play a role in the binding of a substrate within the cavity of a cyclodextrin, the most significant may be the van der Waals and hydrophobic interactions.^{195,275} This is primarily due to the fact that the interaction takes place in aqueous solution. With this in mind, Tabushi has estimated the relative magnitude of the hydrophobic interaction on the basis of thermodynamic relationships²⁷⁵ (Figure 3).

Figure 3. Species that must be considered in a thermodynamic analysis of host-guest complex formation.

Kinetic studies of the host-guest binding of cyclodextrins have been carried out by conventional titration and relaxation techniques, as well as by phosphorescence quenching.^{8,52a,243,276} By using a fluorescent guest (sodium 1-anilino-8-naphthalene-sulfonate; 1,8-ANS), a number of association constants have been determined by observing shifts in the fluorescent spectra.^{66b,297} The intensities are very sensitive to changes in the dielectric constant or polarity of the medium. Such data have been interpreted as indicating that a guest goes from the polar medium into the apolar confines of the host. For cases where the guest absorbs ultraviolet or visible light, inclusion complex formation can be followed by simple titration with cyclodextrin.^{63,85,109,233,315,316} Calorimetric, conductivity, polarographic, NMR, ESR, and circular dichroism techniques have also been exploited in the characterization of guest binding.^{20,27,45,83,105,113,123,128,146,149,181,182,197,202,231,232,314}

In the final analysis, it is the expectation of rate enhancements and selectivity in reactions that attracts much interest to this chemistry. The rate enhancements observed for the catalysis of reactions by cyclodextrins are rather low. It has been suggested that this occurs because the cyclodextrins stabilize the ground states of the reacting guest molecules more efficiently than they stabilize the transition states.³⁴ Since the cavity of the cyclodextrin is open at both ends and not completely nonpolar, an included guest is not completely immobilized when bound. High concentrations of guest are also required to saturate the cavity. These factors and others have led, more recently, to the modification of cyclodextrins in order to freeze out rotational degrees of freedom in the transition state.³⁰⁶ A number of studies have been

concerned with the addition of flexible and rigid caps to one end of the cyclodextrin cylinder^{36,38,39,268,269,277,279,282,283,288,289,292,297a} (Figure 4). This makes the cavity more shallow but it also increases

Figure 4. (a) The concept of a capped cyclodextrin. (b) The concept of a capped cyclodextrin. (c) Capped and doubly capped cyclodextrin.

the fraction of the surface area of the cyclodextrin cylinder walls that is hydrophobic and this has been shown to enhance the binding of guests remarkably.^{38,247,290} An illuminating example of this result has been provided by Tabushi. The association constant for 1,8-ANS with β cyclodextrin is 58 and, upon addition of a terephthalate cap, it becomes 640. Finally, with a diphenylmethanedisulfonate cap the association constant was found to be 1300.^{267,297} A novel host molecule has been prepared that has two hydrophobic binding sites and has been named duplex cyclodextrin.^{108a,280} On the basis of these studies and others, Breslow and

collaborators and Tabushi and collaborators have constructed models of several enzymes, such a ribonuclease, transaminase, lipase, carbonic anhydrase, and rhodopsin using modified cyclodextrins.^{39,40,271,278,281,294}

Finally, attention has been directed to the conformational changes that accompany complexation with cyclodextrin hosts. These studies may provide models for the structural changes that are induced in enzymes upon substrate binding, and may help elucidate those important properties in enzyme catalysis.^{109,139a,248,249a,270} An example of just such a process occurs with a modified cyclodextrin, as shown in Figure 5.

Figure 5. Conformational change induced by inclusion complex formation.

Association constants for several guests were increased as a result of the presence of the cap and it was concluded that a conformational change around the chromophoric moiety of the cyclodextrin takes place during guest inclusion.²⁷⁰

Cyclophanes. Cyclophanes are simply macrocyclic compounds containing benzene nuclei as ring members²⁵⁶ (Figure 6). There exists a large body of literature on the synthesis, characterization, and properties of numerous types of cyclophane systems that is not

Figure 6. Examples of cyclophane structures.

applicable to the discussion of host-guest complexes and are treated elsewhere.^{90,91,112,115,124,130,160,163,204,223,245,255,259,295} Organometallic complexes of the [2n]cyclophanes have been summarized by Boekelheide.³⁰ Although first noted by Stetter and Roos²⁶⁰ in 1955, inclusion complex formation by this class of host molecule has been the subject of intense study^{284,295} only since about 1976. Vogtle et al. have synthesized neutral molecules whose cavities are capable of selective inclusion of uncharged organic guest molecules.^{319,322} Cram and co-workers synthesized macrocyclic polyether derivatives of [2.2]paracyclophane and measured the association constants of their complexes with several alkali metal ions.^{133,305} At this point it should be emphasized that such metal derivatives have long been recognized as coordination compounds and that they should be considered independently from the discussion of host-guest complexation.

A great deal of work has been done on the functionalization of cyclophanes with the goal of producing catalysts and enzyme models and two recent reviews have summarized much of this work in detail.^{220,297} Several design strategies have been employed for the synthesis of

cyclophanes as host molecules. On the one hand, efforts have been directed at designing the macrocycle in such a way as to promote the maximum cooperativity between structurally incorporated functional groups, which may preclude the need for a "pocket" for the binding of a substrate.²²⁰ Alternatively, attention has been focused on para- and azaparacyclophanes which satisfy the most fundamental requirement for the hydrophobic interaction. These are water solubility and the presence of a hydrophobic domain in which a guest can reside.^{220,297}

Tabushi has pioneered the work on water soluble cyclophanes, and others have more recently synthesized these types of host molecules.^{1,2,147,229a,272,274,293,296,297,305a} Solubilization of a cyclophane in water may be effected by achieving a hydrophobic-hydrophilic balance in the design of the cyclophane. Murakami has synthesized para- and azaparacyclophanes which contain amide nitrogens as structural components. Some of these compounds possess long alkyl chains as appended groups^{215,219} (Figure 7a). These host molecules provide a deeper hydrophobic cavity and consequently have the ability for a selective induced fit binding mechanism for various types of more bulky guests (reference 220 and references therein). These hosts have also shown a high degree of substrate specificity as a result of the geometrical constraints that the cavity provides.

Murakami has described three basic modes of incorporation of a guest into macrocyclic cyclophane host. These include the penetration mode,²²⁰ and the face-to-face mode,²¹³ as shown in Figure 8. The penetration mode is exemplified by the incorporation of polymethylene

Figure 7. Inclusion complexes of cyclophanes.

Figure 8. Modes of incorporation of guest into a cyclophane host.

(a) Penetration mode. (b) Face-to-face mode.

chains into the cavity of [20]paracyclophane, which has dimensions of between 4.4 and 4.8Å. In contrast, data indicates that the hydrophobic association of substrates with [10.10]paracyclophane does not involve inclusion of the guest into the cavity,²²⁰ but rather a different mechanism, such as the induced-fit mode.

As discussed for the cyclodextrins, the hydrophobic guest binding of water soluble cyclophanes may be demonstrated spectroscopically,^{1,2,89,272,274,298} as well as by surface tension methods, and fluorescence spectroscopic studies. X-ray analyses have confirmed the 1:1 nature of these inclusion complexes²²⁹ (Figure 7b). NMR has also been used to study the conformational changes induced by the host-guest interaction.^{291,297} Detailed kinetic information has been obtained on the rate of inclusion complex formation using temperature jump and spectroscopic techniques.^{212,218,273,297} It has been determined that inclusion of a guest proceeds rapidly for most hydrophobic substrates; however, as expected, when more bulky substituted groups are used, the formation and decomposition of the host-guest complex is retarded. It is generally believed that hydrophobic interactions are responsible for guest inclusion in the cyclophane systems and that the binding of hydrophobic guests is accompanied by significant conformational changes induced by the host-guest interaction.^{90,148,203a,297b}

Crown Ethers. A third class of organic host-guest complex involves the so-called crown ethers, a field generated by the innovative synthesis of Pedersen.²³⁶ Examples are shown³²⁸ in Figure 9. This area contains a great deal of both coordination chemistry and host-guest chemistry. Only the more common host-guest complexes and a few model systems will be discussed.

Figure 9. (a) A number of crown ethers. (b) Template synthesis of the crown ethers.

Vogtle has suggested the general terms coronand for the free host and coronate for the host-guest complex.³²⁷ The crown ethers and the cryptands (vide infra) are related in structure, properties, and chemical behavior to the natural and neutral ionophore antibiotics exemplified by valinomycin and nonactin.^{104,239} These antibiotics affect the uptake and transference of ions through a lipophilic medium.

The synthesis²³⁶ of the basic [18]crown-6 host is accomplished by using the template effect.^{43,102,304} An example of a few host complexes and a typical synthesis is shown in Figure 9.³²⁸ Structural modification of the crown ethers is rather easily accomplished and is therefore a major advantage in attempts to apply crown host-guest chemistry to more selective complexes and models.²⁴⁰ Modification of the periphery of the cyclic crowns and of the noncyclic polyethers (podands) has been the target in many laboratories. Efforts have yielded chiral crown ether molecules, as well as the attaching of large side arms thereby increasing the steric bulk near the binding site^{21,22,51,73,80,87,99,132,157,164,168,171,178,323} (Figure 10). Unsaturated crown ethers, crown ethers possessing low symmetry, or crown ethers having photoresponsive properties, have all been studied recently.^{150,234,252,253} Although the majority of the compounds of this type contain only oxygen donors, sulfur and nitrogen atoms have been substituted for oxygen in many cases.^{28,179,237} In fact, there is a large body of literature on the many macrocyclic ligands containing nitrogen and/or sulfur donors.^{152,154,199} It is concerned with coordination chemistry and has little to do with host-guest chemistry. The progress of the field of host-guest complexes of crown ethers has

Figure 10. Chiral crown ethers.

been well summarized in excellent reviews.^{82,139,156,164,240a,324,328} The strategy behind the design of host-guest molecules is responsive in part to studies using space filling molecular models (e.g., CPK models) which help indicate the complementary relationships between a host and a guest. These indications have been confirmed by the results of crystal structure determinations on examples of the crystalline complexes themselves and have established molecular models as a powerful tool in the prediction of the nature of the host-guest complexation phenomenon.^{19,95}

Several derivatives of the [18]crown-6 macrocyclic polyethers have been designed to take advantage of their special complexing properties. In addition to coordination and transport of alkali metal ions,^{52,164,178} for which they are best known, studies with crown ethers

have been directed toward catalytic modification of primary ammonium salts,¹⁵¹ and complexing such guest molecules as uncharged substituted hydrazines,³²⁰ aromatic amines and phenols,^{321,325} alcohols and water,^{52,326} and molecular halogens.^{235,224} The tridentate binding of many guests is exemplified by the complexation of primary ammonium salts, (Figure 11); however, the binding of alkali metal cations, such as K^+ and Rb^+ , is appreciably stronger. It is significant that in many crown ether hosts (many chiral crowns as well) a cavity develops only when the host-guest complex is formed (Figure 11).^{82,186} Several types of this reorganizational scheme have been recognized for various kinds of host molecules.⁷²

Figure 11. Conformational changes accompany coordination or inclusion complex formation.

An interesting example of the complementary placement of binding sites in a host is given by the molecule to which the colorful name "jaws" has been assigned^{81,303} (Figure 12). Since the 1,1'-dinaphthyl units are chiral and rigid, the binding sites are positioned in such a way as to impose special constraints relative to each other. The efficiency of such complexes in chiral recognition has been well documented.^{81,82,164,168,263} These complexes use chiral recognition to separate, by extraction, the enantiomers of racemic amino acids and amine salts. They have been covalently bound to polystyrene resins in order to produce chromatographic separations.⁷⁹ This discrimination of the host between guest molecules is of substantial importance to the design of more selective catalysts and inclusion complexes.

Binding free energies for the inclusion complexes of crown ethers have been measured and found to be dependent on the relative sizes of the cavity and the guest. The better the match in size, the greater the binding energy. The ammonium ion is particularly well suited for complexing by a tripodal arrangement of hydrogen bonds. Data are summarized in reference 82.

The application of these crown ether host molecules are numerous but among the most important are chemical synthesis, catalysis, facilitated transport, and chiral recognition,^{50,168,244} where guests may be selectively varied and modified by complexing to the crown ether and where the reaction itself may not take place in the absence of the host.

Figure 12. The host named "jaws" and suitable substrates.

Cryptands. The cryptands were developed by Lehn and are a class of macrobicyclic, macrotricyclic, and polycyclic ligand systems bearing nitrogen bridgeheads, but otherwise resembling crown ethers^{164a,166,167,169,174,175,176} (Figure 13). They are selective in the formation of inclusion complexes and those complexes are very stable. The inclusion complexes are called cryptates. These complexes are similar in nature to those of crown ether hosts, and studies have been directed toward some of the same goals. The stability and selectivity of the complex may be intimately controlled through the ligand structure by increasing or decreasing the size of the cavity and by regulating the nature of the binding sites. Synthetic receptor molecules have been

Figure 13. Cryptands of spherical (a, b, i) , ellipsoidal (d, e) and cylindrical dimension (h) and with different donor sets (c, f, g).

synthesized to selectively bind a given set of substrates (i.e., to function as molecular carriers) and to contribute to the understanding of the geometric and energetic factors that control molecular recognition and association in host-guest complexes. These goals are in addition to the potential use of the substances in anion activation, salt solubilization, and phase transfer catalysis.⁵³ A number of excellent reviews deal exclusively with cryptand/cryptate systems.^{88,165,166}

The synthesis of the cryptands is more difficult than that of the crown ethers because of their bicyclic structures and increased numbers of steps in their synthesis.¹⁷⁵ The coordination chemistry of the cryptands shows important properties of the host. The result of cryptate formation with an alkali metal or alkaline earth ion^{67,97} is the inclusion of a cation into the molecular cavity of the cryptand. As stated previously, the x-ray structures of these hosts do not show the presence of a cavity in the absence of a metal ion or guest. Instead these cavities are produced by the "folding outward of their inward parts during complexation of a guest,"⁸² (Figure 14). Alternatively, the guest may displace solvent which had previously organized the host.⁸⁸ The overall geometry of these molecules has a pronounced

Figure 14. Reorganization of a cryptand upon coordination to potassium ion.

effect on the stabilities of host-guest complexes and coordination complexes.^{164,166} For example, the K^+ complex of a cryptand may be 10^5 times as stable as a similar crown ether complex and 10^4 times more stable than complexes of the natural ionophores; this is known as the cryptate effect.¹⁶⁶ The selectivities of these systems are intimately related to the cavity size and the number of binding sites. The large size and spherical nature of the cryptates and the presence of the cations inside the molecular cavity (Figure 14) have been confirmed by crystal structures and by Stokes' radii from conductivity measurements.^{200,208}

Those macropolycyclic structures that possess two receptor sites and can include two metal cations or guest molecules are known as dinuclear cryptates^{117,170,173} (Figure 15). They may form cryptates with transition metal cations, such as Cu(II), Co(II), and Zn ions in their bridged macrobicyclic structures (Figure 16).²¹⁰

Spherical macrotricyclic cryptands that possess a tetrahedral recognition site show remarkable binding properties in the formation of ammonium cryptates^{118,158} (Figure 17). Optically active macrobicyclic and macrotricyclic ligands have been synthesized in order to function as chiroselective molecular receptors, differentiating between optical antipodes of some given substrate^{116,177,163} (Figure 18). These complexes have been shown to be capable of complexing and transporting chiral molecular cations, as well as anions, although the chiral discrimination appears to be weak. Further, these complexes display a metallo-receptor model behavior where the binding of an anionic substrate is dependent on the prior binding of a metal cation.^{11,170}

Figure 15. Successive formation of mononuclear and binuclear cryptates by a cylindrical macrotricyclic ligand.

Figure 16. A dinuclear dioxxygen binding cryptate.

Figure 17. Tetrahedral binding site in an ammonium ion binding cryptate.

Figure 18. A chiral cryptand.

Recently, Lehn has defined a new subclass of cryptands called speleands.⁴⁴ Described as polar binding subunits operating in conjunction with hydrophobic shaping components, they are "hollow" in nature and have flexible bridges which permit adjustment of cavity height (Figure 19).

Figure 19. Examples of ligands called speleands.

Cavitands. It is useful to make a distinction between those complexes which undergo significant host reorganization upon complexation with a guest (crown ethers, cryptates, cyclophanes, etc.) and those that have permanent or preorganized cavities. Cram and co-workers have recently developed synthetic organic hosts that possess enforced cavities large enough to accommodate simple molecules and ions. They are called "cavitands" to describe their unique properties.^{71,74a,75,78,121,131,311} The spherands and hemispherands are specific classes of cavitands and pictorial representations along with representations of crystal structures are given in Figures 20 and 21.^{9,76,77,207}

Figure 20. Cavitands are molecules having permanent cavities. Spherands are cavitands with fixed cavities and relatively rigid walls.

Figure 21. Hemispherands are cavitands with partially rigid walls.

In the spherand, the six oxygen atoms point inward, in an octahedral fashion, with their unshared electron pairs lining the cavity. The stability and selectivity of the spherands for alkali metal ions is the highest seen to date.²⁰⁷ The importance of the enforced cavity, or preorganization, of the molecule was further evidenced by a comparison of the free energies of complexation for a straight-chain adduct versus a spherand, where the generalization was realized that "the larger the number of host ligating sites that are organized for maximum binding prior to complexation, the higher the free energy of complexation".^{68,78,82,180} Many types of spherands have been synthesized, varying in cavity size and shape and several host molecules have been synthesized that contain only cyclic urea binding sites.²²⁶ Some are capable of relieving enforced electron-electron repulsions when binding to cations.⁷⁴ A meaningful comparison has been made between the free energies of complexation of picrate guests with (1) hosts that have no enforced conformational organization (crown ethers), (2) hosts that have partially enforced conformations (hemispherands), and (3) hosts with totally enforced conformations (spherands). These results are further evidence for the generalization quoted above. This preorganizational effect is of critical importance in the design of premier host molecules.

METHODS FOR THE STUDY OF TRANSITION METAL HOST-GUEST COMPLEXES

Due to the inherent similarities in the nature of inclusion complex formation, regardless of the specific kind of synthetic host, techniques used in the detection of transition metal inclusion complexes and the

measurement of their association and dissociation constants have mimicked those already developed in the study of organic host complexes. Bender and Komiyama²⁴ have summarized a number of these techniques as applied to the cyclodextrin inclusion complexes; however, they have been exploited in the study of several other classes of host complexes, as has been discussed above. These techniques include NMR spectroscopy, ultraviolet and visible absorption, and fluorescence spectroscopic techniques, ESR spectroscopy, the use of spin labels, titrations, polarographic measurements, circular dichroism spectra, and, of course, x-ray crystallography. The following brief discussion characterizes some of the appropriate techniques for the detection and characterization of inclusion complexes in species having transition metal atoms as parts of the host molecules. Only brief mention will be given to techniques that have been heavily reviewed in discussions of organic host-guest complexes unless the importance of the measurement warrants further attention.

Nuclear magnetic resonance has been extensively used in the detection of the formation of inclusion complexes, as well as the measurement of their binding constants. As is true of unmodified cyclodextrins, cyclodextrins that are bound to transition metal atoms possess protons that protrude into the cavity. Proton NMR spectra^{24,149,254} can be applied to the study of these protons in order to detect the formation of inclusion complexes. These protons are anisotropically shielded and thus shifted upfield as guest molecules invade the host. The protons on the cyclodextrin that are not directed into the cavity are shifted only to a small extent. This technique has

proven extremely useful in a number of studies with several different host molecules.

Carbon-13 chemical shift values for six unique cyclodextrin carbon atoms have been shown to vary as a function of guest concentration¹¹⁴ during the formation of an inclusion complex. The observed chemical shift value may be expressed as follows:

$$\delta_{\text{obsd}}^i = \delta_H^i \frac{H}{H_t} + \delta_{GH}^i \frac{GH}{H_t}$$

where H = the concentration of free host; GH = the concentration of the inclusion complex; H_t = the total concentration of host; δ_H^i = the chemical shift of carbon atom c^i in the absence of a guest, and δ_{GH}^i = the chemical shift of carbon atom c^i in the host-guest complex. The association constant for inclusion complex formation can be defined as follows:

$$K = [GH]/[G][H]$$

A Benesi-Hildebrand analysis provides a value for the equilibrium constant, where the equation to be solved is

$$\frac{\Delta\delta}{\Delta\delta_M} = \frac{KG_t}{1+KG_t}$$

Here G_t is the total guest concentration and $\Delta\delta_M$ is the maximum chemical shift (saturation value) for a particular resonance. The distance between carbon c^i and the guest molecule is then a function of the total change in chemical shift as shown below:

$$\Delta\delta_M = \delta_{GH}^i - \delta_H^i$$

It is then possible to qualitatively infer the geometry of the host-guest species through a spatial analysis of all of the $\Delta\delta_M^i$ values.

The effect of a paramagnetic metal ion on the spin lattice, or longitudinal, relaxation rates of protons on a guest molecule has been used to determine the approximate distance from the transition metal atom to those protons.²⁰³ The paramagnetic contribution to the longitudinal relaxation rate is give by the relationship

$$1/T_{1p} = (1/T_1) - (1/T_1)_0$$

where $(1/T_1)$ and $(1/T_1)_0$ are the relaxation rates measured in the presence and absence of the paramagnetic host, respectively. The relaxation rates are measured by a pulsed sequence that begins with a 180° pulse to invert the population of aligned spins, followed by several regularly space 90° sensing pulses. This is commonly described as an inversion-recovery experiment.^{120,203} It yields rate data from which the relaxation time is calculated.^{162,203}

The paramagnetic contribution to the relaxation rate obeys the equation below.^{29,257}

$$1/pT_{1p} = q/(T_{1M} + \tau_M) + 1/T_{os}$$

The quantity p is the ratio of the concentration of host to that of guest. The second term reflects the outer sphere effect of the

paramagnetic center and is assessed by measuring the effect on species that cannot act as guests toward the host in question. The number of guest molecules bound to the host at saturation of the equilibrium is q . τ_M is the chemical relaxation rate and this term would dominate if the rate determining process were the exchange of the complexed guest with the guest that is free in solution. So long as the magnetic (τ_{1M}) dominates, and there is no covalent interaction between the guest and the host, the Solomon-Bloembergen (S-B) equation²⁵⁸ can be used in a conveniently simple form.

$$r(\text{\AA}) = C[pT_{1p} \left(\frac{3\tau_c}{1+3.9 \times 10^{13} \nu_I^2 \tau_c^2} + \frac{7\tau_c}{1+1.71 \times 10^{19} \nu_I^2 \tau_c^2} \right)]^{1/6}$$

This form of the S-B equation provides an estimate of the distance between the paramagnetic center, within the host, and any given proton on the guest. It is only necessary to determine τ_c , the correlation time, in addition to the quantities already mentioned and this is readily done so long as data can be obtained at two or more spectrometer frequencies, ν_I .

Fluorescence measurements have been heavily used in the study of host-guest complexing. For example, 1-anilino-8-naphthalenesulfonate (1,8-ANS) has been used to demonstrate that inclusion complex formation occurs with transition metal modified cyclodextrins.^{277,284,295} While simply dissolved in an aqueous solution, 1,8-ANS exhibits only weak fluorescence but marked enhancement is observed when it is complexed within the cavity of the host molecule.^{103,254,277} As has been pointed out, this is consistent with the behavior of 1,8-ANS when it is

dissolved in apolar solvents.²⁹⁵ Again, these results suggest that the guest has been moved from the external polar medium into the relatively nonpolar environment of the cavity within the host. Dissociation constants have been calculated from measurement of the fluorescence intensity.^{24,103,277}

Electronic absorption spectra have also been used to detect transition metal host-guest interactions in solution and such measurements have been widely used in the determination of the related reaction rates and dissociation constants.^{160,196,214,215} Circular dichroism spectra have revealed conformational changes upon addition of a guest into a solution containing a cyclodextrin having an appended porphyrin.²⁰⁵

In those rare but interesting cases where a guest is coordinated between two metal ions within a host molecule, ESR spectra are uniquely informative. ESR spectra show the presence or absence of antiferromagnetic coupling between the two paramagnetic centers in such cases.^{66,141,265} X-ray studies provide ultimate demonstration of the presence of guests within the host in the solid state and this has been of particular significance for systems involving guest molecules bridging between pairs of metal atoms, as is discussed below.

TRANSITION METAL CONTAINING HOSTS AND THEIR INCLUSION COMPLEXES

Host-guest complexes that possess a transition metal incorporated directly into the host ligand open the door to much new chemistry ranging from the modeling of metalloenzymes to the development of new kinds of transition metal catalysts. Recalling that host species accommodate guest species without covalent bond formation, the transition metal in host species is, by definition, not necessarily

involved in the binding of the guest. Consequently, any vacant coordination sites on the metal remain unoccupied during inclusion of a guest and are therefore available for coordination to other molecules, such as dioxygen. The exciting possibility may then be realized of selectively placing some guest molecule in close proximity to an activated site. The presence of the transition element may also exert rather large effects on the binding of substrates to the host. When it functions in this way, the transition metal ion confers a sort of "double recognition" capability on the host compound. It follows that the metal ion may affect both the fundamental processes of inclusion complexation and catalytic action of these unusual substances.

Transition Metal Modified Cyclodextrins. As indicated earlier, disappointing results have been obtained in attempts to mimic enzyme functions with cyclodextrins. The observed catalytic activity of the cyclodextrin itself was minimal.^{37,267} The addition of a transition metal ion has yielded more promising results.

Breslow provided an early example of transition metal host-guest chemistry in attempts to model metalloenzymes and solve the problem of the low catalytic activity of cyclodextrins. He modified the structure of cyclodextrin (Figure 22) in order to combine the catalytic ability of a nickel solvolytic catalyst with the regioselective substrate binding of a hydrophobic cavity.^{33,41} A chelating ligand was attached to the cyclodextrin by ester exchange. Nickel(II) was then allowed to coordinate to this moiety and a second ligand, 2-pyridinecarboxaldoxime, was also added to the metal ion. The proposed structure of the catalyst-substrate complex is shown in Figure 23.

Figure 22. A catalyst using both a cyclodextrin (CD) and a metal containing functional group.

Figure 23. The catalyst-substrate interaction for an artificial enzyme based on a substituted cyclodextrin chelated to a metal ion.

The compound was shown to be an effective catalyst for the hydrolysis of certain esters. *p*-Nitrophenyl acetate was hydrolyzed by the nickel complex with a rate acceleration of greater than 10^3 times that of the uncatalyzed rate. As Figure 23 shows, the *p*-nitrophenyl group enters the cyclodextrin cavity, thereby bringing its ester group into close proximity to the oxime group of the externally appended metal complex. The oxime displaces the *p*-nitrophenyl group from the acetate. Subsequently, the resulting acetylated oxime is catalytically hydrolyzed by the nickel(II) ion.

Inhibition studies add support to this explanation. The nickel ion catalyzed hydrolysis of the acetylated oximes is not affected by the presence of cyclohexanol. However, the catalytic hydrolysis of *p*-nitrophenyl acetate by the nickel-cyclodextrin catalyst is competitively inhibited by cyclohexanol which, presumably, competes for the cavity. 8-Acetoxy-5-quinolinesulfonate, a molecule that is too large to enter the cavity, was found to be substantially less reactive toward the catalyst and its rate of hydrolysis was not inhibited by cyclohexanol. The acceleration attributable to the hydrophobic binding of the aromatic group was only modest and it was concluded that increased rigidity in later designs might freeze out some of the rotational degrees of freedom and improve this contribution. Greater rate enhancements were observed for the copper(II) complex.

Tabushi and co-workers have provided striking insight into the roles a metal ion can play in facilitating the binding of a guest within the cavity of a host molecule.^{268a} They successfully modified cyclodextrins with flexible caps²⁸⁶ composed of polyamine ligand groups that are capable of chelating to metal ions, as shown in Figure 24. Complexes

Figure 24. Promotion of hydrophobic anion binding by a cationic cap on a cyclodextrin; (a) and (b), substituents on cyclodextrin; (c)-(e), metal ions used in cap; (f)-(m), anions studied as guests.

were formed with Zn^{2+} , Cu^{2+} , CO^{2+} , and Mg^{2+} . Formation constants for coordination of metal ions to these cyclodextrin-polyamine ligands were quite similar to those with the corresponding parent polyamines. These compounds are the subject of a Japanese patent.²⁸⁵

The presence of the metal ion-containing cap on the cyclodextrin conferred rather special host-guest binding abilities on the cyclodextrin.^{276a} Hydrophobic anionic guests are especially strongly bound because of the combined effect of the hydrophobic interaction and the electrostatic attraction of the anion for the cationic cap. The various anions studied are also shown in Figure 24. For example, the binding of adamantan-2-one-1-carboxylate by these metal-containing species is 330 times that by β -cyclodextrin. The presence of the two interactions within a single host-guest complex constitutes a double recognition phenomenon and the authors have separated the respective free energy contributions (Figure 25).^{276a} They suggest that these results may

Figure 25. Contributions of coulombic and hydrophobic interactions to the binding energy of inclusion complexes involving hydrophobic anions.

eventually lead to multiple recognition sites, thereby imitating the more complicated biological processes; however, details of the mechanism of this multiple recognition are still uncertain.

This structural design has been used to produce polymeric cyclodextrin derivatives. Polyalkyleneamines, such as triethylenetetramine, were used to attach the cyclodextrin to a polystyrene support, as shown in Figure 26.²⁸⁷ These cyclodextrin polymers form metal complexes when

Figure 26. A polymer supported cyclodextrin: a polyamine bridge is used.

treated with aqueous solutions of metal salts. The product is especially useful for extracting organic anions from aqueous solution.

A bifunctionalized cyclodextrin has been equipped with a transition metal ion in order to produce a novel carbonic anhydrase model^{266,275a,277} (Figure 27). This complex incorporates the following recognized

Figure 27. A functionalized cyclodextrin complex that has been used as a carbonic anhydrase model.

features of carbonic anhydrase: a hydrophobic pocket, Zn^{2+} bound to imidazole and located at the edge of the hydrophobic pocket, and additional, favorably placed basic groups.

The results of kinetic studies on the rate of formation of carbonate showed that each of the structural features listed above contributes to the catalysis. Thus, the metal-free species is less effective than the zinc complex in promoting the formation of carbonate. It is also true that the histamine complex of zinc is not so effective a catalyst as the zinc-histamine derivative of cyclodextrin. The secondary amine groups are believed to make a positive contribution as well, because the corresponding species in which imidazole is directly bound to the cyclodextrin produces a catalyst that is ten-fold less active. The better catalyst produces a rate that is 83 times that observed for the formation of carbonate from CO_2 in the presence of the bis(imidazole)zinc complex; however the enzyme is still some 10^7 times more effective. From the standpoint of this review, this is an excellent example of substrate binding of a small molecule by host-guest complexation.

Matsui and co-workers reported a novel catalyst having two neighboring cyclodextrin cavities.¹⁹⁶ It is derived from a cyclodextrin to which an ethylenediamine moiety has been covalently attached. When two of these ligands are chelated to a single copper(II) ion, the two cyclodextrin cavities are arrayed on opposite sides of the coordination sphere of the copper ion (Figure 28). Therefore, an appropriate substrate, such as furoin, could be bound with its terminal groups in the two opposing cavities but with the center-most part of the

Figure 28. Proposed inclusion complex utilizing two cyclodextrin moieties organized by chelation of their appended groups to a single copper(II) ion.

molecule exposed to the action of the metal ion. Studies on the equilibrium behavior of this ligand- Cu^{2+} system, revealed that the 1:1 complex was rather more greatly preferred over the 2:1 than would be expected, suggesting that steric effects may operate against the latter.

The 2:1 complex is more effective as a catalyst for the oxidation of furoin to furil than either the free ligand, ethylenediamine, or the copper(II) complex of ethylenediamine. The rate dependence on complex formation showed a saturation effect reminiscent of Michaelis-Menten kinetics. Accordingly, a dissociation constant for inclusion complexation of 2.6×10^{-3} M and a rate constant of 1.1 min^{-1} were calculated. These results suggest an acceleration by a factor of about 20.

Cyclohexanol acts as an inhibitor, an observation consistent with the requirement for the substrate to enter the cavity of the cyclodextrin in order to be activated. The addition of Cu(II)(en)_2 led to an appreciable decrease in the catalytic rate. From this it was suggested that two of the cyclodextrin ligands may be required within a single complex in order to produce the most effective catalysis. This is based on the possibility that some of the mixed complex would be formed and that its presence accounts for the retardation. Since the enolate anion

has been implicated in the oxidation of acyloins, it was suggested that the intricate complex of Figure 28 stabilized this anion, although it was recognized that the copper ion might be involved in the oxidation.

In addition, the same group reported a retardation of the hydrolysis of organic phosphates by a cyclodextrin-copper(II) complex.²⁰⁵ The active species is a 1:2 complex of α - or β -cyclodextrin with Cu^{2+} . The reactions proceed via formation of an adduct followed by nucleophilic attack by a hydroxyl group within the cavity.

Cyclodextrins with Appended Porphyrins. Several reports have appeared on attempts to combine the well known oxygen carrying ability of the porphyrins with the host-guest capability of the water soluble cyclodextrins. The products should be very interesting models of the natural oxygen carriers and they might function as catalysts for a variety of reactions. Water solubility has been a limitation of the obvious hemoglobin models, such as the picket fence or capped porphyrins.^{12,55,59,100}

Porphyrin esters have been linked through the primary OH groups of the cyclodextrin and the carboxyl groups of the porphyrin. Such species have been suggested for use as synthetic dioxygen carriers in artificial blood.¹⁶¹ The flexibly linked derivative^{117a,159} of porphyrin and cyclodextrin shown in Figure 29 was designed as a water soluble model dioxygen carrier; however, the iron complex showed no affinity for O_2 . The addition of guests to aqueous solutions of the compound showed diverse conformational changes as revealed by the circular dichroism spectra. It was proposed that this species might be a useful model for substrate induced conformational changes in enzymes. Similarly, a

Figure 29. The appending of a porphyrin to a cyclodextrin.

recent Japanese patent application reveals that iron protoporphyrin IX can be attached by a single chain to cyclodextrin³¹² and these porphyrin derivatives resemble Tabushi's flexible cap and thus open the possibility of enhanced hydrophobic binding coupled to the kinds of redox chemistry that heme proteins promote.

Iron protoporphyrin IX itself has been reported to bind to the methylated and acetylated derivatives of β -cyclodextrin.²⁵⁴ These species form as 1:1 adducts via inclusion of the hydrophobic hemin ring, containing the vinyl groups, in the plane of the cyclodextrin on the side of the secondary OH groups. These associations were characterized by their fluorescence and proton NMR spectra. In an interesting contrast of binding behavior, it has been shown the 1-substituted 2-methylimidazoles that are included in the cavity of α -cyclodextrin will form stable pentacoordinate complexes with iron(II) protoporphyrin IX.¹⁰³ The imidazole within the inclusion complex competed effectively with simple imidazole for complexation with the iron. The iron derivative of the inclusion complex is reported to form an O₂ adduct at -30°C.

Transition Metal Modified Cyclophanes. Murakami has synthesized derivatives of [20] and [10.10] paracyclophanes (Figure 30) with coordinated Zn^{2+} and Cu^{2+} ions, with the specific goal of achieving enzyme-like activity in the catalysis of ester hydrolysis.^{211,214-217} The species are designed to coordinate to a metal ion while retaining nucleophilic groups in the vicinity of the substrate binding site (the cavity within the cyclophane). The contrasting behavior of the various [20]cyclophanes provides good evidence for multiple roles on the part of the catalyst as it acts to hydrolyze p-nitrophenylhexadecanoate (PNPP). The metal ion coordinates to the cyclophane through the appended imidazole. Its role is to polarize the carbonyl group of the hydrophobic ester as the latter is held in close proximity by hydrophobic binding within the cavity. The oxime group serves as the nucleophile and attacks the carbonyl carbon (Figure 31). The reactivity of the oxime group in this process is surprisingly high; however, the reaction is essentially stoichiometric since the product of acyl transfer to the oxime function of the paracyclophane does not undergo rapid deacylation.

The [10.10]paracyclophane of Figure 30 is characterized by one appended imidazole groups from each of the benzene rings. In the presence of copper(II) ions this substance is an effective catalyst for the hydrolysis of p-nitrophen esters of long chain carboxylic acids. The role of the pair of appended imidazoles is critical to the kinetic behavior since the corresponding species with only one imidazole group merely reacts to form the acyl derivative and stops at that point. Further, when there is only one imidazole group, Cu^{2+} inhibits the

Figure 30. Modified cyclophanes that bind metal ions.

Figure 31. Proposed mechanism of hydrolysis of an ester by the copper(II) complexes of a modified cyclophane.

acylation reaction rather than promoting catalysis. The compound having two imidazoles is truly catalytic in the presence of copper(II). Cu^{2+} assists acyl transfer from the hydrophobically bound substrate to one of the imidazole groups with an apparent second order rate constant of $1.3 \times 10^3 \text{M}^{-1}\text{s}^{-1}$ in ethanol-dioxan-water at 40° and an ionic strength of 0.1 (KCl). The imidazole-bound Cu^{2+} ion also promotes the deacylation of the second imidazole with a rate constant $> 10^{-3}\text{s}^{-1}$. In a plausible reaction scheme, coordination of the carbonyl group to the metal ion is believed to facilitate both of the acyl transfer steps. Of course the substituted p-cyclophane also functions by hydrophobic binding of the substrate within the cavity and by presenting the appended nucleophile to the electrophilic carbonyl carbon. Thus the copper(II) complex acts in three ways as it catalyzes the hydrolysis of the p-nitrophenyl ester.

A model (Figure 32) has been demonstrated for NAD-dependent alcohol dehydrogenase that contains a zinc ion as an essential co-factor.²¹⁵

Figure 32. A substituted cyclophane designed as a zinc ion dependent alcohol dehydrogenase model.

The enzyme catalyzes the conversion of carbonyl compounds into alcohols and the model has been tested using the activated ketone, hexachloroacetone, as a substrate. [20]Paracyclophane provides the skeleton for

the enzyme model and the hydrophobic binding site for the substrate. 1,4-Dihydronicotinamide is appended from the aromatic ring of the cyclophane and 2-pyridinecarboxylic acid is attached by an amide linkage to the opposite side of the cyclophane. The pyridinecarboxylate group is present to bind to a metal while the dihydronicotinamide provides the reducing power. The zinc complex of this substituted cyclophane is indeed catalytic and a maximum acceleration by a factor of 7 is observed. This is judged to be quite a good demonstration of the effectiveness of the model since the catalyst has no specific affinity for the substrate even though the catalytic activity depends, presumably, on coordination of the carbonyl oxygen atom to the zinc. A complicated behavior is observed because the coordination of the zinc to the dihydronicotinamide group stops the catalytic action. Thus, the catalytically active species is the complex in which two of the large ligand molecules are bound to a single zinc ion and this particular complex is not the main component in solution.²¹⁴

Vaulted Transition Metal Macrocyclic Complexes. Busch and co-workers have designed and synthesized a new family of host molecules, called vaulted complexes for the purpose of mimicking the ternary (enzyme:dioxygen:substrate) complex of cytochrome P-450.^{299,300} Figure 33a represents the structure as a flat projection while Figure 33b indicates its three-dimensional structure. These species are cationic and contain the positively charged metal ion coordinated to four nitrogen donor atoms and incorporated into one wall of the permanent void that has been provided to accommodate a substrate molecule. The actual incorporation of the metal binding site into the parent structure is a

Figure 33. Structures of the vaulted macrobicyclic complexes.
 (a) Flat representation of the structure. (b) Three-dimensional representation of the structure.

novel feature of these compounds. They share with the spherands the presence of a permanent void that exists in the absence of any guest molecule.

These structures were derived from an intensely studied family of lacunar dioxygen complexes^{136-138,261,262} in order to provide a coordination environment that would guarantee the ability to bind dioxygen. The structures of the lacunar complexes are shown in Figures 34a and 34b. As all the structures in Figures 34 and 35 show, the ligands are macrobicycles. Template reactions³⁰⁴ are employed in both ring closure steps with nickel(II) serving as the templating metal ion. The iron(II) and cobalt(II) complexes are produced by coordination to the free ligand after it is liberated from the nickel(II). The modification to the lacunar ligands to produce the vaulted macrobicyclic ligands is shown in Scheme 1.³⁰⁰ The deep saddle shape that was well established in studies on the lacunar complexes was preserved in the

Figure 34. Structures of the lacunar macrobicyclic complexes.
 (a) Flat representation of the structure. (b) Three-dimensional representation of the structure.

structures of the vaulted complexes. Further modification to the parent structure is readily made by variations in the groups labeled R^1 , R^2 , and R^3 in Figure 34.

X-ray crystal structure determinations^{138,300} establish the general structural features and reveal a number of unusual aspects. Figure 35 shows two views of the vaulted complex having an anthracene bridge, R^1 . Both the presence and magnitude of the commodious cavity are apparent. It tapers in dimensions from $8.24\text{\AA} \times 8.95\text{\AA}$ at the grand opening to $7.26\text{\AA} \times 6.57\text{\AA}$ at the opposite, smaller entry. Surprisingly, in the hydrophobic environment of the solid crystal, a guest molecule has been accommodated. The host molecule provides a hospitable environment by rotating its piperazine rings so that the nitrogen atom of the acetonitrile can enjoy six nearly ideal van der Waals contacts with hydrogen atoms (Figure 36), while aligning the π system of the nitrile group with that of the anthracene ring. Doubtless, the acetonitrile would reverse its orientation in an aqueous solution where the polar solvent would provide better solvation of the polar nitrile nitrogen.

Scheme 1

Figure 35. X-ray structure of the anthracene bridged vaulted macrobicyclic complex of nickel(II).

Figure 36. Mode of association between guest acetonitrile and host.

The chloride salts of the vaulted complexes have good water solubility and hydrophobic binding is expected to be mainly responsible for host-guest interaction in that solvent.^{195,275,301} This is augmented in certain cases by the release of high energy solvent molecules upon host-guest complexation, a pattern of behavior that parallels that of the cyclodextrins.^{275,300,301} The characterization of the solution behavior of these substances has been based on NMR studies.

As described above, Laufer¹¹⁴ has shown that chemical shift values can be used to identify guest-host complexation, to estimate equilibrium constants for inclusion-complex formation, and to obtain structural information. Carbon-13 NMR studies were directed toward demonstration of these processes for the vaulted host cations.³⁰¹ The nickel(II) complexes were used because a diamagnetic host is required for these measurements. Specific site isotopic enrichment studies provided definitive assignment of a number of resonances and these were used in equilibrium studies. NMR titrations, in which the concentration of guest was incremented (Figure 37), revealed (a) each carbon atom of the host has a characteristic response to the addition of guest, and (b) all changes in chemical shifts show the saturation behavior expected of equilibrium processes. Thus the specific interaction associated with inclusion complexation was demonstrated.³⁰¹ With guest molecules having larger hydrophobic groups than ethanol, the binding constants were essentially constant, but the smaller groups appeared to bind more weakly, suggesting that a minimum hydrophobic bulk is required for host-guest complexation to occur. The variation of the bridging group of the host with more or less hydrophobic bulk, or other changes in the extent

* The $\Delta\delta$ values for carbon atom B coincide with the values for carbon atoms N or C.

Figure 37. NMR titration of a vaulted host with the guest butanol in D₂O solution, using carbon 13 chemical shift data.

of the hydrophobic walls of the host, should affect the association constant for the inclusion process, as has been seen with capped versus noncapped cyclodextrins²⁶⁷ (vide supra). Efforts are underway to elucidate these relationships. For example, Figure 38 contains an additional

Figure 38. Structure of the doubly bridged, vaulted host compound.

bridge (macrotricyclic) and this is expected to produce enhanced binding.⁶² In addition, extending the size of the void has been accomplished with the use of 4,4'-bipiperidine as the riser, and this has allowed for the incorporation of larger substrates.¹⁹⁸

In view of the presumed hydrophobic binding of guest to host in the vaulted systems, the behavior in solvents other than water is of critical importance. NMR chemical shift studies were therefore carried

out in the solvents acetonitrile, acetone, and nitromethane. No variation of chemical shift values was observed and this indicates that inclusion complex formation depends on the solvent water for these host compounds; i.e., the interaction is hydrophobic in nature.

An additional result of much interest comes from the NMR chemical shift studies. The variation of chemical shift with structure makes it clear that the entry of the hydrophobic host into the void is accompanied by the departure of water molecules that are hydrogen bonded to the nitrogen atoms of the bridge. The chemical shift pattern very closely parallels that associated with the deprotonation of organic amines^{209,250} but the effect is smaller, as would be expected for hydrogen bonding.³⁰¹

A second powerful NMR technique has been applied to the study of the vaulted macrobicyclic host systems. The diamagnetic nickel(II) ion was replaced by a paramagnetic copper(II) ion ($S = 1/2$) and the resulting host cation was used in spin-lattice relaxation time (T_1) measurements on the NMR signals of the protons of various guest molecules.¹⁶² With the copper(II) ion in place, entry of a guest into the cavity assures that the metal ion can operate on it, in this case the strong magnetic field of the metal ion acts to relax the orientation of the nuclear dipole of the proton. The technique is discussed in the section on methods. The ultimate results from such studies provide structural information on the inclusion complex. These studies confirmed the saturation of the host-guest equilibrium; the Cu^{2+} -proton distances calculated are independent of guest concentration in the region chosen for study. A number of supporting measurements have been

made to obviate some of the inherent uncertainties or difficulties of the method.^{162,198} Temperature dependence showed that T_1 was not determined by chemical exchange, which was expected to be very fast. Tetraalkylammonium ions were chosen as target molecules that would be unable to enter the cavity because of their positive charges and these did indeed show relatively small effects due to the paramagnetic copper(II) ions. In order to provide counter examples of another critical kind, lacunar complexes having very small cavities were substituted for the vaulted host cations; again, the effect of the paramagnetic copper(II) ion on a guest (n-butanol) was relatively small.

The structural information derived from T_1 measurements on inclusion complexes of the vaulted macrobicyclic hosts has confirmed the occurrence of the process and shown, at least approximately, the orientation of the guest within the host cavity. For many alcohols (e.g., methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol, and others), the alkyl group is substantially closer to the metal center than is the hydroxyl group, as required by hydrophobic interaction. Further it appears that the OH group is in about the same place in all cases and that it remains in the solvent sheath. Thus the image emerges that the hydroxyl group is solvated and remains in the solvent sheath that encompasses the host cation and that the hydrophobic portion of the small molecule simply protrudes into the permanent void. Even bulky substituted phenols partially enter the cavity, showing strongly oriented binding (Figure 39). These data show most emphatically that the guests do not coordinate to the metal ion and suggest that the inclusion complexing is indeed driven by hydrophobic interactions.

Figure 39. Orientation of bound 2,6-dimethylphenol within the cavity of the vaulted host. Note that the OH remains solvated and hydrophobic extremity lodges in the molecular void.

An important consequence follows from the conclusion that such guest molecules as alcohols and phenols are bound by hydrophobic forces and do not coordinate to the metal ion. It must be true that the binding site at the metal ion is not taken by the guest molecule and barring blockage by solvent, the metal ion site remains available for coordination to other ligands. As indicated above, these vaulted macrobicycles were designed as models for the ternary complex of cytochrome P-450. That ternary complex involves hydrophobic binding of a substrate to the enzyme and the coordination of dioxygen to the iron atom of the heme group. Clearly, it should be possible to bind both dioxygen and a substrate to the iron derivative of the vaulted macrobicyclic ligand (Figure 40).

The iron (II) and iron(III) complexes of these host ligands have been prepared and it has been shown that the iron(II) atom does indeed bind to dioxygen.⁶² It has also been shown that the iron, and certain

other transition elements, can be activated by some reagents with the result that substrates can be oxidized.

Figure 40. Model of the ternary complex for cytochrome P-450.

Binuclear Transition Metal Complexes as Coordinating Hosts.

Systems that possess the ability to bind a guest molecule inside their cavities by coordination, rather than noncovalently, are considered here as a separate class of transition metal inclusion complexes. The intense interest in recent years in the design, synthesis, and coordination chemistry of model compounds of biomolecules requiring more than one metal site (e.g., hemerythrin, hemocyanin, tyrosinase, cytochrome c oxidase) has resulted in a number of specialized binuclear metalloenzyme models, with emphasis on binding and activating dioxygen and on multielectron processes. Lippard has summarized design requirements for effective bimetallic systems: (a) fixed metal sites, (b) stability, (c) coordinate unsaturation, and (d) accessible sites.¹⁹² While the goal of some of these studies is the binding of small

molecules, such as O_2 and CO within the confines of a cavity, this is specifically not a matter of interest to the present review. Our purpose is to point out those cases in which molecules are simultaneously involved in inclusion complexing and in coordination to metal ions. In these cases we will recognize that the interaction that stabilizes the inclusion complex is coordination.

The imidazolate bridge of a bimetallic model system for superoxide dismutase, studied by Lippard and his associates,^{65,65a,66,66a,192,192a,264,265} illustrates this class of compound. As Figure 41 indicates, the

Figure 41. Coordination as a binding mode for an inclusion complex of an imidazolate ligand.

imidazolate is contained within the cavity created by the binucleating ligand but it is held in this position by the coordination to two metal ions. This type of model system exploits an interesting and novel feature of internally coordinated guest species that bridge metal centers. ESR spectroscopy will reveal whether or not the guest bridging ligand is displaced by some other ligand. If the new ligand does not bridge, the magnetic interactions between the two copper atoms would disappear. It was shown that the bridging imidazolate is displaced by

SCN⁻ in analogy to the behavior of dicopper superoxide dismutase.²⁶⁵ This conclusion was confirmed by x-ray structural analysis. In contrast, azide does not displace the bridging group, a result that is also in accord with the behavior of superoxide dismutase.

A similar mode of binding has been observed for 4,4'-bipyridine within the cavity of the tricyclic face-to-face compartmental ligand whose structure is given in Figure 42. The crystal structure of the nickel(II) complex showed a void large enough to accommodate the 4,4'-bipyridine and the cobalt(II) complex containing the guest ligand has been isolated and characterized.¹⁴¹ ESR spectra showed that the cobalt(II) centers in the inclusion complex are magnetically coupled, as a result of the mediation of the bridging base. Upon addition of a stronger base (n-methyl imidazole), the ESR spectral pattern returned to that for uncoupled metal centers. This confirms the displacement of the bridging ligand from the cavity.

A family of macrocyclic polyamine Schiff base ligands, synthesized by Nelson et al., act as hosts toward a variety of bridging ligands, such as hydroxide, alkoxide, halide, azide, thiocyanate, pyrazolate, imidazolate, and pyrazine.^{93,94,221} The structures of the ligands and their azide and imidazolate inclusion complexes are shown in Figure 43. The wide range of intramolecular bridge distances is made available by varying the separation of the metal centers through changes in ligand structure.²²¹ The bridging systems have been characterized by magnetic susceptibility measurements, x-ray structure determinations, and ESR spectroscopy. Template strategies were employed in ligand syntheses⁸⁶ using ketones and aldehydes of pyridine, furan, and thiophene.²²¹ Ring

a

b

Figure 42. (a) Structure of compartmental binuclear complex showing extensive void that can accommodate 4,4'-bipyridine. (b) Proposed structure of 4,4'-bipyridine bridged binuclear complex. B is the guest 4,4'-bipyridine.

a

b

c

d

Figure 43. Binucleating macrocyclic Schiff base ligands and their inclusion complexes with imidazolate and azide.

sizes have been varied from 18 to 30 atoms in the case of the pyridyl containing ligands. The 18- or 20-atom ring systems have cavities that are only large enough to accommodate single atom bridges between metal atoms; e.g., hydroxide or end-on bound azide.²²¹ This conclusion is based on infrared spectral data and magnetic evidence for weak antiferromagnetic coupling between the two copper(II) ions.⁹⁴ The 24- and 28-membered rings can include multi-atom bridging guests such as imidazolate and pyrazine²²¹ (Figure 43c). Weak antiferromagnetic exchange is again observed. The 30-membered ring ligand is more flexible and is reported to be capable of adapting to the formation of mononuclear complexes in addition to the binuclear derivatives. The azide bridged inclusion complex derived from this ligand is shown in Figure 43d.⁹³ It is stated that only a very weak antiferromagnetic interaction between the Cu^{2+} ions is apparent. The furan derivatives exhibit a different coordination chemistry because the oxygen atoms do not coordinate to the copper ions.

The importance of general synthetic routes and the power that can accompany variations in ligand structure in the design of model systems, particularly where host-guest complexation is involved, served as a motivation for studies by Bulkowski and co-workers.¹⁹¹ They have synthesized bicyclic hexamine 'open-face' macrotricycles having constrained orientations of the coordination spheres as indicated by Figure 44.^{42,191} The substrate (guest) is bound by bridging between the two metals using σ orbitals associated with a square planar array of bonds. Changing the length of the bridging group B-B can exert substantial effects on guest binding.

Figure 44. (a) Representation of a bimetallic complex having oriented vacant orbitals. (b) A specific example of the same general structure as (a) and with a guest ligand bridging between the two metal ions.

Agnus et al. have developed synthetic models of type 3 copper proteins using 1,3-diaza-4,10,16,22-tetrathiacyclotetracosane.^{3,4} Azide ions bridge the pairs of copper(II) ions within the macrocycle (Figure 45) and the diamagnetism of the compound indicates very strong

Figure 45. Azide bridged model of type 3 copper proteins.

antiferromagnetic coupling.³ Pyrazole will also bridge between the metal ions, but this large organic molecule is essentially out of the cavity (Figure 46).

Figure 46. Type 3 copper model system having pyrazole bridge.

PROSPECTIVE TRANSITION METAL HOST COMPOUNDS

Although the extent of previous investigations on inclusion complexation with transition metal host compounds (and ions) remains rather limited, there are many transition metal complexes, especially macrocyclic derivatives, whose structures clearly indicate the possibility of their serving in this role. The following is a brief introduction to some of those complexes that may exhibit the ability to act as hosts in the inclusion complexation process and is not intended to review the chemistry that has already been realized with them. The usual motivation for the synthesis of these complexes has been to provide steric encumbrance about the oxygen binding site in a cobalt or iron complex. Numerous reviews are available on substituted porphyrins and on oxygen complexes.^{60,145,201,241,307,308} This brief presentation of prospective transition metal hosts is intended to show representative examples and is by no means complete.

Modified Porphyrins. There exist many literature reports on synthetic porphyrins that fit the general criteria for acting as hosts for inclusion complexation. The strapped porphyrins constitute the largest number of known examples, a number of which are shown in Figure 47.^{16,18,47,49,92,110,111,230,230a,309,309a,310,331} They are macrobicycles, having a second ring in addition to the porphyrin ring. Two synthetic schemes exist for the synthesis of strapped porphyrins: (a) addition of the strap, or bridge, to an existing porphyrin or porphyrin complex, and (b) the bridge forming components are built into reagents that are later used in the formation of the porphyrin ring. Both are illustrated in Figure 48.^{13,14,14a,18}

Figure 47. Examples of strapped porphyrins.

Figure 48. Synthetic schemes for the preparation of strapped porphyrins. (a) Addition of the strap to a porphyrin. (b) Formation of the porphyrin with the strap in place.

A wide range of bridging groups has been used in strapped porphyrins. They range from simple linear aliphatic chains¹⁶ through aromatic groups such as naphthyl and anthracene moieties,¹⁴ quinones,^{110,111} and cyclophanes,^{92,230,309,310,331} to heteroatom-containing species like diaminothiazolesulfide⁴⁹ and crown ethers.⁴⁷ Double straps, one above and one below the plane of the ring, have been appended to porphyrins^{17,18} (Figure 49).

Figure 49. Doubly strapped porphyrins.

The principal shortcomings of most of these species as hosts for inclusion complex formation are associated with the motivation that led to their design. The relatively flexible arms holding the straps above the porphyrin and the dominant flat structure of the porphyrin combine to produce relatively small cavities that, like many of the known host molecules, tend to collapse in the absence of a guest. When investigations are focused on the binding of organic guests, for example as possible substrates for autoxidation, it will help to introduce rigid 'risers' to separate the roof of the strap from the porphyrin and provide a substantial permanent cavity between the two.

The second matter that must be addressed is the mode of binding of the guest. Since porphyrins are neutral and very limited in their water solubility, it is not obvious that hydrophobic interactions will be among the most useful binding modes. The compound in which a crown ether is suspended above the porphyrin (Figure 47c) provides both coordination and hydrogen bonding as promising interactions to generate host-guest complexing. Other examples exist (see Figure 47) in which heteroatoms in the strap may aid in the binding of the guest. In future studies, attention will surely be given to strategic placement of such groupings.

Capped porphyrins are interesting candidates for the role of host in inclusion complexes (Figure 50).^{6,7,12,14a,185} The observation by

Figure 50. Examples of capped porphyrins.

Basolo et al.^{100,183} that Baldwin's capped metal porphyrins show some tendency to interact with a second axial ligand, suggests that the second ligand goes, at least partially, into the pocket. Depending on the balance of repulsions against attractions, the cap could enhance the binding of an axial ligand. On the other hand, crystal structure determinations have shown that the cavities are indeed quite small. It is suspected that the tendency of the bridge to collapse onto the porphyrin reduces the dioxygen affinities of these compounds. The quinone capped porphyrin shown in Figure 50b may be able to accommodate sizeable guest molecules. The center to center distance between the two rings is $10\text{\AA}$.¹⁸⁵ In contrast, Ibers has pointed out that the structure of the $\text{FeCl}(\text{C2-cap})$ (Figure 50a)²⁴⁶ is very similar to the free ligand and that the cap-to-porphyrin separation in this molecule (about $4\text{\AA}$) is even too small to accommodate carbon monoxide or dioxygen in the cavity. In solution this separation must increase by 1 to $1.5\text{\AA}$ since the complex does bind small molecules. The synthesis of the capped porphyrins is indicated in Figure 51.¹³

Collman and co-workers^{57,58} have recently synthesized sterically encumbered hemoprotein models called 'pocket' porphyrins, Figure 52. These species have one relatively large opening into the cavity created by the presence of an unsymmetrically bound cap. They may provide the best general structural type for host-guest complexes among the substituted porphyrins known to date.

The geometry of face-to-face metalloporphyrins makes them interesting in the present context. They differ from the examples previously cited in this section in that two metal ions flank the cavity

Figure 51. Synthesis of a capped porphyrin.

Figure 52. The pocket porphyrin.

(Figure 53).^{46,48,56,61,96,108,222} Also, studies have indicated a characteristic distance between metal ion centers depending on the

Figure 53. Structures of face-to-face porphyrins.

external bridging groups. This suggests that the existing structures may be relatively rigid and the void may be a permanent one. However, as in most of the cases mentioned above, the cavity is a small one in the known examples (center-to-center distance from 4.2 to 6.4 Å). The small separations between porphyrin rings were built into the structures because they were designed to bridge such small species as peroxide.

Schiff Base Compounds. The well-known structural and synthetic versatility of Schiff base complexes provides an alternative route to the design of potential transition metal host systems. As early as 1925, work on salen derivatives (Figure 54) had opened the

Figure 54. (a) Usual structure of "salen" complexes derived from linear diamines. (b) Possible trans structure of salen complex derived from long-chain diamines.

possibility of producing a cavity, or lacuna, in the vicinity of the coordination site that contains the metal atom.^{238,251} These compounds were prepared by the condensation of salicylaldehyde with long chain diamines. Salen and its analogs have involved α , ω -diaminoalkanes having polymethylene groups ranging from 2 to 12 carbon atoms.^{129,142,329} In the case of the shorter polymethylene chains, the nitrogen atoms are in cis positions. However, when the nitrogens are trans, as in Figure 54b, the polymethylene chain forms a bridge above the metal atom. In several cases, the compounds were reported to be polymers, but the long chain diamine derivatives of 5-chloro-2-hydroxybenzophenone have been reported to give monomeric complexes with nickel(II).²⁰⁶

Well characterized examples of salen complexes having cavities were developed by Martin et al. (Figure 55).^{10,134} These so-called 'fly over' ligands used diamines that both forced a trans configuration on the imine nitrogens of the Schiff base and contained naphthalene risers

Figure 55. (a) Structure of the salen derivative containing a "fly over" ligand. (b) X-ray structure of the two nonequivalent molecules of the nickel(II) complex of a "fly over" ligand.

that lifted the bridge substantially above the metal ion site. Thus, in contrast to many of the porphyrin derivatives and in analogy to the spherands, the complexes contain a permanent cavity. The crystal structure of the nickel(II) complex of one of the fly over ligands clearly shows this cavity (Figures 55b and 55c).¹⁰ The crystal contains two nonequivalent molecules and the dimensions and details of the structures of the cavities differ somewhat between the two.

The first strapped macrocycle to be synthesized was not a porphyrin derivative but a condensation product of a long chain diamine with the anhydrotetramer of o-aminobenzaldehyde called TAAB (Figure 56a).¹⁵⁵

Figure 56. (a) Early strapped TAAB complex indicating coordination by the central heteroatom. (b) Strapped TAAB complex having a cavity.

The first derivatives involved straps having heteroatoms at their centers and their coordination to the metal ion was envisioned, although uncertainty was expressed. More recently a simple polymethylenediamine has been put in place as a strap (Figure 56b),³³⁰ showing that these compounds can indeed generate structures that might act as transition metal hosts. Analogously, straps have been synthesized on a bis(α -dioxime)cobalt complex, where the bridge spans cis positions (Figure 57).^{15,242}

Figure 57. The strapped α -dioxime.

CONCLUSIONS

The incorporation of transition metals into the architecture of host molecules is well demonstrated by the pioneering work that has been reported to date. A number of special binding interactions can be provided by incorporation of a metal ion; for example, addition of an electrostatic component to the guest affinity and, more obvious, use of coordination as a means of guest binding. Special advantages accrue to the study of the host-guest phenomena because of the differing properties of the various metal ions that may be incorporated into the metal binding site. That ion may be diamagnetic or paramagnetic, thereby increasing the variety of experiments that can be applied. The metal ion may serve any of many catalytic roles, especially the promotion of electrophilic processes or participation in redox reactions. The metal ion effect can be closely coupled to other promotional aspects of a multifunctional catalyst in transition metal host molecules. Use of the hydrophobic binding mode and proximal

nucleophiles to augment the electrophilic promotion of a reaction by a metal ion serves to illustrate this. Roles that remain to be demonstrated include such popular themes as the activation of dioxygen in the presence of a bound substrate, the production and utilization of an unsolvated nucleophile, and the use of conformational change to cycle between stages in which a site is protected from the solvent and stages where the site is exposed to solvent. In the limit, one can visualize doing highly oxygen and moisture sensitive chemistry within a protected cavity in a complicated host molecule that is otherwise exposed to ambient conditions.

ADDENDUM

The mechanism of CO₂ hydration via a carbonic anhydrase model consisting of a bifunctionalized cyclodextrin Zn(II) complex²⁶⁶ has been amended.^{275a} The free histidine cyclodextrin complex was shown to rapidly convert to the corresponding carbamate, effectively reducing the catalyst concentration. The active site of the model complex (see Figure 27) evidently contains a third coordinating imidazole and was concluded to be essential to the catalysis of CO₂ hydration.

A novel transition-metal-host complex has recently been prepared which exploits two distinct host mechanisms.^{156c} Between the silicate layers of monomorillanite, the authors have successfully incorporated dimers of a 1:1 complex of Cu(II) and a modified β -cyclodextrin. The layers of silicate function as a host for the Cu(II)-cyclodextrin complex while the cyclodextrin serves as a host for other substances.

It is proposed that these compounds will act as an immobilized artificial enzyme as well as models of membrane enzymes.

Metal rotaxane complexes^{229c} are compounds consisting of rings that are "threaded" by long chains with end groups that are sterically encumbered as to prevent them from being extruded from the ring. The rings in these complexes are α - and β -cyclodextrin, while the threads are diamino-alkane-cobalt(II) complexes.^{229b} Studies involving inclusion phenomena and nonbonded interactions of rotaxane metal have been proposed.

The incorporation of an Ru(II)(bpy)_3 moiety into a covalently linked strap over a Zn-porphyrin complex has been synthesized to study luminescence behavior and electrochemical properties of the interaction between two photochemically active centers.^{123a} Although the distance between the metal centers is 4Å, appropriate ligand design with host-guest complexation in mind could produce a host complex with several novel properties. These complexes would certainly be quite different in nature than the more traditional face-to-face porphyrin dimers.

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CHAPTER TWO
HYDROPHOBIC, REGIOSPECIFIC GUEST BINDING BY TRANSITION
METAL HOST COMPLEXES HAVING PERMANENT VOIDS AS REVEALED
BY FT-NMR RELAXATION STUDIES

ABSTRACT

The family of macrobicyclic ligands called vaulted cyclidenes was designed to model the ternary complex formed by cytochrome P-450 in its reaction cycle, thereby establishing new structural features for coordination catalysts. Thus, it is necessary for these complexes to simultaneously bind dioxygen by coordination to a chelated metal ion, and bind an organic molecule by host-guest complexing using hydrophobic interactions. We report here a detailed study of the host-guest complexing behavior of the vaulted cyclidene complexes. The copper(II) complexes of the vaulted cyclidene ligands have been prepared in order to study inclusion complexing by NMR relaxation techniques. Extensive experimental justification has been provided for the calculation of distances from the relaxation rates. Three FT-NMR spectrometers operating at different frequencies gave essentially identical results. Outer sphere effects were shown to be small. Temperature dependence studies showed that the relaxation process is not chemical exchange limited. The conditions for saturation of the host-guest equilibrium

were determined experimentally. Structures having very small or no cavities show, by counter-examples, the effects of the permanent void. This unusually well controlled application of a well known, sometimes maligned, technique has yielded remarkable structural information about the inclusion complexes that exist in solution. Alcohols and phenols enter into inclusion formation in a regiospecific manner. They extend their hydrophobic components into the cavity of the vaulted cyclidene complex, leaving their hydrophilic OH groups immersed in the solvent sheath that surrounds the host ion. The cavity is adequate to completely enclose the hydrocarbon moieties of all of the alcohols we studied with the result that their OH groups are, in all cases, at about the same distance from the copper atom. Phenols assume the same orientation but are too large to be engulfed by the small cavity. Solvent data are consistent with the expectation that a single water molecule is coordinated on the side of the copper opposite that of the cavity. These results support the credibility of the vaulted cyclidene systems as ternary complex models.

INTRODUCTION

Transition metal host-guest chemistry is being exploited with increasing frequency as a means of dictating the placement of organic substrates in purposeful proximity to a metal atom (Figure 58).¹ The unique properties of the resulting complexes lend themselves well to the study of a wide variety of chemical phenomena, ranging from catalysis and enzyme modeling, through various aspects of facilitated transport,

Figure 58. The concept of inclusion complex formation with a copper containing host suitable for relaxation studies.

to the study of host-guest chemistry in general.^{1a,2} Consequently, the number of studies involving inclusion complexes and host-guest phenomena has increased rapidly during the past several years. The cyclodextrins,³ crowns,⁴ cryptands,⁵ cavitands,⁶ cyclophanes,⁷ and others all constitute well documented families of hosts. The fundamental interactions between certain enzyme complexes and their substrates have been attributed to host-guest complexing, mainly involving hydrophobic driving forces.^{1a,3a,3d,8}

We have reported the design and synthesis^{9,10} of a family of transition metal-containing, molecular host species, that can serve as components in a credible model of the ternary complex of cytochrome P-450.^{11,12} Evidence has also been presented for their ability to form inclusion complexes.¹³ The ligands in these complexes belong to a broad family of ligands that have been called cyclidenes and the particular

adaptation of that family that forms host-guest complexes is called the vaulted cyclidene structure (Figure 59). A distinctive feature of the cyclidenes is the ease with which superstructures can be constructed above their primary coordination spheres by bridging reactions. As Figure 2a,b shows, bridging produces a large persistent void in the vicinity of one of the axial binding sites of the metal atom.^{9,10,13} Large voids have been designed into the structures of the vaulted cyclidenes for the inclusion of organic guest molecules. The smaller voids characteristic of the lacunar cyclidene complexes (Figures 59c and 59d), are only big enough for coordination of such small molecules as O₂ and CO to the metal atom.¹⁴⁻¹⁷

Studies of the carbon-13 chemical shifts, using the diamagnetic nickel(II) derivatives, have shown that metal complexes of these vaulted macrobicyclic ligands do indeed function as hosts for a variety of alcohols and phenols.¹³ The observed changes in chemical shifts that accompany inclusion complex formation are consistent with a model that involves the displacement of water molecules from the cavity by the incoming guest. The dependence of this inclusion complex formation on solvent and on structural parameters, especially of the host molecule, indicates that the driving force for the reaction is hydrophobic in nature.¹³

In this report we describe the detailed characterization of the inclusion complex formation between the vaulted cyclidene complexes and a range of guest molecules by application of paramagnetic relaxation techniques. These studies use a paramagnetic metal ion, copper(II), coordinated within the parent macrocycle of the host to relax the protons of the guest molecule. A preliminary report has appeared.¹⁸

Figure 59. Structures of the vaulted and lacunar macrobicyclic cyclidene complexes: (a) flat and (b) three-dimensional representation of the vaulted complexes; (c) flat and (d) three-dimensional representation of the lacunar complexes.

Protons and other magnetic nuclei undergo relaxation by interacting with, and exchanging magnetic energy with, their magnetic environment. Since protons are weak magnets and because of the large difference in the tumbling frequency of small molecules and the Larmor precession frequency of protons, the transfer of magnetic energy takes place at a slow rate. The relaxation rates of the protons of water and other small molecules are therefore slow.¹⁹ The much stronger magnets represented by unpaired electrons are three orders of magnitude more effective at increasing the relaxation rates of protons within small molecules. The effects of paramagnetic metal ions on spin lattice, or longitudinal, relaxation rates ($1/T_1$) of protons have been exploited extensively in the study of such properties of enzymes as their conformations and the placement and orientation of bound substrates in solution.¹⁹⁻²² The definition of T_1 , and a schematic representing the inversion recovery method used to measure them is in Figure 60. Because the application of this technique permits the estimation of the distances in solution between the paramagnetic center and individual atoms of the molecule under study, it provides the opportunity to obtain exceptional insight into the space relationships associated with host-guest binding. We offer here the first detailed application of this technique to the formation of inclusion compounds using molecularly discrete hosts that incorporate a paramagnetic ion within the walls of their cavity.

The theory of the dependence of the longitudinal relaxation time, T_1 , on electron spin-nuclear spin interaction was first developed by Solomon, Bloembergen, and others.²³⁻³⁷ The Solomon-Bloembergen equation

Inversion Recovery Method

T_1 : SPIN-LATTICE or LONGITUDINAL RELAXATION TIME

Redistribution(Boltzmann) of the populations in the higher to lower energy states from an interaction of a nuclei with the surrounding magnetic dipoles (lattice).

or

it simply serves as a measure of the rate at which a spin system comes into equilibrium with its environment during energy transfer.

Figure 60. Inversion recovery method for measuring T_1 .

describes the rate of spin-lattice relaxation of a nucleus in a molecule bound in the proximity of a paramagnetic ion (Equation 1).

$$\frac{1}{T_{1m}} = (2/15) \frac{s(s+1)\gamma_I^2 g^2 \beta^2}{r^6} \frac{3\tau_c}{1+W_I^2 \tau_c^2} + \frac{7\tau_c}{1+W_g^2 \tau_c^2} + (2/3) \frac{s(s+1)A^2}{h^2} \left(\frac{\tau_e}{1+W_s^2 \tau_c^2} \right)$$

The first term in Equation 1 represents the distance dependent dipolar component, while the second term is a hyperfine contact component.¹⁹ The other parameters are defined as follows: r is the length of the vector from the paramagnetic ion to the relaxing nucleus; τ_c is the correlation time for the process that modulates the dipolar interaction, and τ_e is responsible for the time dependence of the hyperfine contact term.^{19,23} The present case of molecular host-guest complexing is especially convenient to treat because there is no covalent interaction between the guest, whose protons are being studied, and any atom in the host which contains the paramagnetic center. Consequently, the hyperfine term can be eliminated. Because the purpose of the measurement is to obtain distance information, the simplified expression is rearranged in a form solved for internuclear distance and further simplified by evaluating constants (Equation 2).

$$r(\text{\AA}) = C T_{1m} \frac{3\tau_c}{1+(3.94 \times 10^{13} \nu_1^2 \tau_c^2)} + \frac{7\tau_c}{1+(1.71 \times 10^{19} \nu_1^2 \tau_c^2)} \quad 1/6 \quad (2)$$

The coefficient C in Equation 2 is a composite of many physical constants dependent on the nature of the relaxing nuclei and the paramagnetic center.^{15,18} For Cu^{2+} interacting with protons, C has a value of 539.¹⁹

The correlation time, τ_c , is given by Equation 3.

$$1/\tau_c = 1/\tau_r + 1/\tau_s + 1/\tau_m \quad (3)$$

The rotational correlation time is τ_r ; τ_s is the electron spin relaxation time, and τ_m is the mean residence time of the guest in the first coordination sphere of the host.¹⁹ The fastest of these processes makes the greatest contribution to τ_c . It is known that τ_s for Cu(II) is of the order of 10^{-8} sec and therefore cannot be the dominant contributor.²² τ_c can be determined experimentally by the measurement of T_1 at two or more frequencies;²⁸⁻³³ this determination will be discussed later.

For any given moiety, the contribution to the observed relaxation rate due to the presence of a paramagnetic ion, $1/T_{1p}$, is given by Equation 4.

$$\frac{1}{T_{1p}} = \frac{1}{T_1} - \frac{1}{T_1}_o = \frac{pq}{\tau_m + T_{1m}} + \frac{1}{T_1}_{os} \quad (4)$$

$(1/T_1)_o$ is the relaxation rate determined in the absence of the paramagnetic ion and p is the molar ratio of the paramagnetic sites to diamagnetic sites. $(1/T_1)$ is, of course, the relaxation rate measured in the presence of the paramagnet. T_{1m} is the magnetic relaxation time,

and T_{os} is the outer sphere or bulk contribution to the measured relaxation rate. For a fast exchange process, the quantity $T_{1m} \gg \tau_m$; then $T_{1m} = pT_{1p}$ (if $q = 1$ and $(1/T_1)_{os}$ is negligible) and the paramagnetic contribution to the relaxation rate is magnetically determined. Equation 5 incorporated these relationships and is the form used for distance calculations associated with our experiments.^{19,20}

$$r(\text{\AA}) = C p T_{1p} \frac{3\tau_c}{1+(3.94 \times 10^{13} \tau_c^2)} + \frac{3\tau_c}{1+(1.71 \times 10^{19} \tau_c^2)}^{1/6} \quad (5)$$

The use of the dipolar component of the Solomon-Bloembergen relationship, as described here, for the calculation of internuclear distances involves a number of assumptions and these are treated below.

RESULTS AND DISCUSSION

Justification for Dipolar Model. Use of the dipolar component of the Solomon-Bloembergen equation in order to quantify the reductions in T_1 values observed in the presence of paramagnetic ions requires experimental justification for those specific cases where one might hope to make use of this relatively simple model.¹⁹ The assumptions requiring justification are (1) the hyperfine contribution to the relaxation process must be negligible; (2) the outer sphere contribution, $(1/T_1)_{o.s.}$, must be small; (3) $(1/T_{1p})$ must not be exchange limited; and (4) an accurate value of the dipolar correlation time, τ_c , must be determined.¹⁹ Certain other relationships must also be demonstrated. Among these is the assumption that the host-guest

equilibrium is saturated and the assumption that guests actually do enter the cavities of vaulted cyclidene complexes when the cavities are sufficiently large. Direct evidence for hydrophobic interaction is also desirable.

In earlier studies involving the use of the Solomon-Bloembergen equation,¹⁹⁻²² the hyperfine contributions to the relaxation process were assumed to be negligible. This was especially true for systems involving Cu(II) and high-spin Mn(II). Although some doubt has been expressed³³ about the validity of neglecting the hyperfine term in those cases, little importance can be expected for the hyperfine contribution to interactions in the non-bonded situation that applies to host-guest associations wherein hydrophobic interactions are dominant. Since the guest molecule is not bonded, either directly or indirectly to the copper atom, no transfer of spin density can occur between these moieties. It follows that the systems described in this report are ideally suited for use of this simplified mode.³⁴

The magnitude of the outer sphere, or bulk susceptibility, contribution $(1/T_1)_{os}$ to the relaxation data has been determined experimentally. The relaxation data obtained for the tetramethylammonium ion and for the symmetrically solvated 1,4-dioxane and 1,4-butanediol molecules at the same mole ratios (p) used for the study of organic guests are shown in Table 1. Because of the large size and the positive charge of the tetramethylammonium ion, it is considered highly unlikely that this species could enter the cavity and act as a guest. Also, the miscibility of dioxane and butanediol with water does not make these solutes candidates for host-guest complexing by hydrophobic

Table 1

Relaxation Times (T_1 , sec) for the Determination of the Outer Sphere or Bulk Susceptibility Contribution to the Measured T_1 of Guests with Host

M = Cu, R = tetramethyl-p-xylene (T = 304K)

Guest=Tetramethylammonium ion:^b $(\text{CH}_3)_4\text{N}^+$ ($p = 1.4 \times 10^{-3}$)^a

$(T_1)_O$, sec	10.22 ± 0.20
(T_1) , sec	10.16 ± 0.20
r (Å)	>17

Guest=1,4-dioxane^b ($p = 1.10 \times 10^{-3}$)^a

PROTONS	1,4-dioxane
$(T_1)_O$, sec	8.51 ± 0.50
(T_1) , sec	7.95 ± 0.50
r (Å)	>14

Guest=1,4-butanediol^c ($p = 1.15 \times 10^{-3}$)^a

PROTONS	$\alpha(\text{CH}_2)$	$\beta(\text{CH}_2)$
$(T_1)_O$, sec	$3.52 \pm .16$	$3.24 \pm .1$
(T_1) , sec	$3.46 \pm .1$	$3.20 \pm .1$
r (Å)	>11	>11

a. $p = \frac{[\text{host}]}{[\text{guest}]}$

b. $\nu = 300 \text{ MHz}$

c. $\nu = 500 \text{ MHz}$

interactions. The results given in Table 1 demonstrate that the effect of the paramagnetic complex on the measured T_1 values for these species is extremely small. Consequently, the calculation of distances is not justified because of the uncertainties inherent in the small differences between the T_1 values measured in the presence and absence of the paramagnetic center. Further, the distances that are crudely estimated from these data far exceed the values for all true guests. The smallness of the effect both confirms that this relaxation is induced by an outer sphere "bulk" relaxation phenomena for these species and provides an indication of the magnitude of the bulk effect in this system. This effect is intrinsically present in all experiments of this type and adds to the relatively large, more specific relaxation arising from the host-guest association. For the relaxation data involving organic guests, this outer sphere effect is calculated to be negligible when compared to the magnitudes of the specific effects and the experimental errors (ca. 1%).

In order to verify the assumption that the measured T_1 values are magnetically determined, it is necessary to show that they are not exchange limited (τ_m , see Equation 4). Rationally, one expects hydrophobically driven host-guest complexation to be very rapid, and experimental verification can be straight forward through measurements on the temperature dependence of the rate process. In principle, such chemical processes as inclusion complex formation will proceed more rapidly at higher temperatures while magnetically determined processes may show an inverse temperature dependence; i.e., the rate may decrease as the temperature increases. Thus, a decrease in the observed $1/T_{1p}$

value with an increase in the temperature supports the assumption we have made.^{19,22,35} Such measurements have been made on two systems involving the host of structure I and the guests n-butanol and 2,6-dimethylphenol. As the data in Table 2 show, the value of $1/T_{1p}$ decreases as the temperature increases, indicating that the process is not exchange limited.^{22,35}

An accurate means of determining the value of τ_c for the ligand is also required. The frequency (ν_1) dependence of T_{1p} is one of the most accurate and direct means of measuring τ_c .^{19,36,37} T_{1p} values of several guests were measured at three frequencies (200, 300, and 500 MHz) and τ_c was evaluated using simultaneous equations. The best value obtained from our measurements is 1.2×10^{-10} s, from a range of 10^{-11} to 10^{-10} .

Equation 5 is based on the assumed saturation of the equilibrium relating the paramagnetic center and the molecule undergoing examination. In order to assure that the host-guest equilibrium is saturated, determinations were made at different concentrations of guest. If the equilibrium is saturated the distances calculated should be identical, within experimental error, regardless of concentration. The results shown in Table 3 reveal that as $p = [\text{host}]/[\text{guest}]$ is varied, the distances calculated are independent of excess guest present only below an upper limit of $p = 10^{-3}$. It must be realized that the value of p , as it appears in the Solomon-Bloembergen equation, is a mole ratio and not a mole fraction. For ratios ranging from around 1/1000 to ratios in the vicinity of 1/10,000, the distances are constant, well within experimental error. However, when the ratio of host to guest falls below 1/100,

Table 2

Temperature Dependence of Relaxation Rate ($1/T_{1p}$, sec^{-1}) with Host I
($\nu = 300 \text{ MHz}$)

Guest=2,6-dimethylphenol ($p = 1.54 \times 10^{-3}$)

<u>Protons</u>	<u>T,K =</u>	<u>$1/T_{1p}$, at T Kelvin</u>		
		<u>291</u>	<u>304</u>	<u>314</u>
CH ₃		0.381	0.0724	0.0261
meta		0.439	0.132	0.0676
para		0.817	0.218	0.1413

Guest=n-butanol ($p = 1.18 \times 10^{-3}$)

<u>Protons</u>	<u>T,K =</u>	<u>$1/T_{1p}$, at T Kelvin</u>		
		<u>274</u>	<u>304</u>	<u>314</u>
α		0.0389	.0193	0.0164
β		0.0619	0.0491	0.0261
γ		0.0663	0.0574	0.0469
δ		0.1905	0.1087	0.1029

Table 3

Saturation^a of the Host-Guest Equilibrium
 as Determined by T₁ Measurements^b
 Host = Host I; Guest=n-butanol; T = 304K

<u>Host:Guest (p)</u>	<u>r; Å Calcd. for the Indicated Protons</u>			
	<u>α</u>	<u>β</u>	<u>γ</u>	<u>δ</u>
(1.23 x 10 ⁻¹)	13.7	13.3	12.6	11.9
(1.23 x 10 ⁻²)	12.9	11.2	10.5	10.2
(1.18 x 10 ⁻³)	9.0	7.7	7.4	6.6
(7.89 x 10 ⁻⁴)	8.9	7.6	7.4	6.6
(1.24 x 10 ⁻⁴)	8.8	7.9	7.6	6.5

a. Note that the calculated values for r become constant as saturation is achieved.

b. $\nu = 500$ MHz

Table 4

Relaxation Data^a for the n-butanol guest in the Presence of
 Host I in Acetonitrile Solvent

<u>Protons</u>	<u>α</u>	<u>β</u>	<u>γ</u>	<u>δ</u>
(T ₁) ₀ ,sec	7.63 ± .1	6.45 ± .08	6.65 ± .1	6.26 ± .01
T ₁ ,sec	6.81 ± 0.2	6.11 ± 0.15	6.18 ± 0.2	5.77 ± 0.1
r,Å	9.1	10.1	10.5	9.4

[Host] = 6.85 x 10⁻⁵

[Guest] = 5.47 x 10⁻²

a. $\nu = 500$ MHz

the distances calculated are erroneously high and concentration dependent. This result reflects the rather low binding constants of the host-guest complexes.

As Equation 4 shows, it is necessary to either determine or assume the ratio of host to guest molecules within a single inclusion complex, q . We have assumed that the host:guest ratio, q , for the inclusion complex is equal to 1. On the basis of molecular models and from x-ray structural data for the host complex,⁹ this conclusion is a reasonable one. Although one guest molecule, in the size range we have investigated, may reside comfortably in the cavity of this host, a second guest of the same kind is sterically precluded from entering the same cavity.

The action of water as a solvent is unique, particularly in its relationships to organic solutes.^{1a,1b,3a,3d,7b,7c,8,13} The collection of interactions that are described as hydrophobic are a part of the uniqueness and we have asserted that this is the driving force responsible for host-guest complexation in the systems of immediate interest. In order to provide support for this view, acetonitrile was substituted for water as the solvent in a number of T_1 experiments. If hydrophobic interactions are essential to the inclusion complex formation under study, then the process should not occur in acetonitrile solutions. Table 4 summarizes the relaxation data for host I and the guest n-butanol. The very long distances calculated from the relaxation data indicate that the host-guest complexing is not taking place. The very small difference between T_1 and $(T_1)_0$ indicates that the n-butanol guest does not enter the cavity of the host. These data support the

requirement for water as the solvent and the assumed hydrophobic driving force.

Relaxation Rate of Water. Since water is the required solvent for this particular inclusion complex formation, the effect of the paramagnetic Cu(II) host complex on the spin lattice relaxation rate of water is of interest. The results of carbon-13 NMR chemical shift studies¹³ of the host-guest association between our vaulted cyclidene complexes and small organic molecules have been rationalized on the assumption that the entry into the cavity by most host molecules is accompanied by displacement of water molecules from that lacuna. These included water molecules were assumed to be hydrogen bonded to the piperazine nitrogen atoms.^{9,13} This model suggests a further role of water that might relate to relaxation.

The paramagnetic relaxation rates of water were determined under four separate conditions. (1) The relaxation rate of the pure solvent was measured as a standard; (2) the rate was measured for water containing dissolved host I; (3) the rate was measured in the presence of host I plus methanol ($6.18 \times 10^{-2}\text{M}$); and (4) the rate was measured in the presence of host I plus n-butanol ($5.48 \times 10^{-2}\text{M}$) was determined. The results have been summarized in Table 5. The value of 61.7 seconds indicates the upper limit of the relaxation rate obtained for pure degassed water in these laboratories. When host I is added to the solution, the T_1 of the water protons is significantly reduced, 42.9 sec, because of the approach of water molecules to the paramagnetic Cu(II) center. When methanol is introduced into the solution, the value obtained for the relaxation rate of the water protons is, within

Relaxation Times^a for Water Under Several Conditions (T = 304K)

<u>Host</u>	<u>Guest</u>	<u>p (or conc.)</u>	<u>T₁,sec</u>
None	None	---	61.7 ± 0.9
I	None	6.48 x 10 ⁻⁵	42.9 ± 0.5
I	MeOH	1.54 x 10 ⁻³	43.5 ± 0.5
I	n-BuOH	2.5 x 10 ⁻³	48.1 ± 0.5

a. $\nu = 300$ MHz

experimental error, unchanged from the value measured when the paramagnetic host alone was present. Finally, when n-butanol is introduced as the guest, there is a reproducibly measureable increase in T₁ value and the number moves toward that for pure water.

The data are totally consistent with the suggestions made by Takeuchi^{9,13} on the basis of carbon-13 chemical shift studies. The substantial reduction in the T₁ for water in the presence of the paramagnetic host merely indicates that some of the water molecules are close to the copper(II) ion. Of course, this might involve any of several different mechanisms. However, the fact that the value of T₁ increases upon addition of n-butanol to this solution suggests that the positions of some water molecules have been moved further from the copper(II) center. This is consistent with the earlier conclusion that the presence of the guest (n-butanol) causes displacement of water molecules from the cavity. The experiment in which both host I and methanol are present reinforces this conclusion. Takeuchi found that methanol gave no detectable chemical shift effects and concluded that the small methyl group did not protrude deeply enough into the cavity to displace the hydrogen bonded water molecules. This is confirmed by the failure of methanol to measureably affect the T₁ value for water. When the

relaxation data for host I and water (T_1), and the value of water itself (T_1)₀, are inserted into the Solomon-Bloembergen equation a distance of 3.3Å is obtained from Cu to a hydrogen on a proposed axially coordinated water molecule, corresponding to a distance of 2.8Å for Cu to the oxygen of water. This result may be viewed schematically in Figure 61 and has been tabulated for $q = 1$ and $q = 2$. The Cu-OH₂ distance for the case $q = 2$ is abnormally high, and therefore it is assumed $q = 1$. This result is well within the reported x-ray data ranges of water molecules axially coordinated to Cu.³⁸

Variation of Guest Compound. The proton-Cu(II) internuclear distances calculated from the paramagnetic relaxation rates of a series of aliphatic alcohols shows very clearly that a hydrophobic host-guest association is taking place. The complex of structure I served as the host complex for these experiments, while the guest alcohol was varied according to Table 6 (see also Table 10). A stacked plot from an inversion recovery pulse sequence (180° , τ , 90°) is shown in Figure 62b. The guest is n-propanol while the host is host I. The plot shows τ values increasing along the y axis and ppm along the x axis. The individual protons relax at a rate which is a function of their distance from the Cu²⁺ center. At the five second delay value, the methyl group of n-propanol has already inverted, while the protons of the methylene carbon adjacent to the OH group of n-propanol have not inverted, clearly indicating that protons of the methyl group are closer to the Cu²⁺ center while the proton on the carbon atoms adjacent to the OH are farther away. In Figure 62a, a T_1 curve is shown for protons of n-propanol. The x axis is the τ or delay value, while

Figure 61. Results for the distance calculation of the presumed coordinated water.

Table 6

Calculated Distances for Various Protons
in Several Alcohols for Host I^{a,b}

Alcohols	(Å) ^c			
	α	β	γ	δ
CH ₃ OH	8.6			
CH ₃ CH ₂ OH	8.4	7.5		
CH ₃ CH ₂ CH ₂ OH	9.0	8.2	7.5	
CH ₃ CH ₂ CH ₂ CH ₂ OH	9.0	7.7	7.4	6.6
Avg.	8.8 ± 3	7.8 ± 3	7.5	6.6
t-(CH ₃) ₃ COH	-	7.4		
i-(CH ₃) ₂ CHOH	9.2	8.2		
CH ₂ =C-CH ₂ -OH CH ₃	9.0	- (7.2)	7.6	
Overall Avg.	8.9 ± 2	7.8 ± 3	7.4 ± 1	(6.6)

a. Data U 300 MHz and T 304K using a Bruker WM300 spectrometer. (T₁) and (T₁)₀ values are reported in supplemental material.

b. [Host] = 6.48 x 10⁻⁵M; [Guest] = 10⁻²M.

c. From Equation 5, using a measured value of τ_c = 1.2 x 10⁻¹⁰ sec.

a. T_1 curve

b. stack plot

Figure 62. Stacked plot and T_1 curve for the guest n-propanol and host $[\text{Cu}\{3,6\text{-durene}(\text{CH}_2\text{-piperazine})_2\text{clcyidene}(\text{Cl})_2\}]$.

the y axis is intensity. As the slope of the curve increases, T_1 decreases. The data show that the orientation of the associated guest molecule is regiospecific. The hydrocarbon moiety of the guest alcohol protrudes into the cavity while the hydroxyl extremity remains exposed to the solvent. The hydroxyl or hydrophilic end of the guest is consistently found at the greatest distance from the copper ion. Further, this distance is approximately constant for the whole array of alcohols, a fact that suggests that the OH is embedded in the solvent sheath. For the six alcohols, methanol, ethanol, n-propanol, isopropanol, 2-methyl-2-propen-1-ol, and n-butanol, the distances to the OH groups and the position of the carbon atoms are very closely related. The alkyl group of each of the alcohols inserts into the hydrophobic void of host I to the depth that is required by its chain length. The α -carbon adjacent to the OH group is furthest from the interior of the cavity and at approximately the same distance from the copper nucleus in all cases. At these locations the hydroxyl groups are able to maintain effective hydrogen bonding with the water molecules of the solvent bulk.

The spatial relationships are illustrated in Figure 63 which was created using the computer program named ChemGraph. The coordinates of the atoms composing the host molecule were obtained from the previously reported⁹ crystal structure, modified to the durene roof from the anthracene roof. The distances between the guest protons and the metal atom are those given by the relaxation studies reported here. Figures 63a, 63b, and 63c are both side views of the inclusion complex between host I and n-butanol. Figure 63a provides a space-filling representation of the structure while 63b and 63c make it easy to distinguish

Figure 63. Inclusion complex between host I and n-butanol guest.

between the host and guest by successively reducing each of them to a stick representation. Figures 63d, 63e, and 63f are similar illustrations, but the viewer is looking directly into the cavity. Outstanding features implied by these drawings are: (1) The n-butanol is so located that it blends into a fairly smooth outline that may be circumscribed about the inclusion complex; this may be taken as modeling the solvent sheath. (2) The OH group protrudes into the solvent sheath. (3) The n-butanol is nicely accommodated near the top of the void, leaving room for the binding of dioxygen (in the cases of the corresponding iron and cobalt complexes). (4) The piperazine rings that constitute the side walls of the cavity have rotated sufficiently to accommodate the n-butyl group, but they are closed to such an extent that a nest-like site is formed.

While the details of these features are more suggestive than factual, certain of them are unequivocal. The guest does indeed occupy the top sector of the cavity, leaving room for dioxygen to bind to the metal atom. The presence of this guest reduces the cavity volume into the range of the usual lacunar complexes and this will affect dioxygen binding. The OH group is indeed inserted into the solvent sheath and the alkyl group extends into the hydrophobic cavity. A very intriguing and highly plausible relationship that is suggested has to do with a detail of the inclusion complex structure. This is the indication that the guest is positioned so that the solvent sheath is a smoothly curving surface. If this relationship is substantiated, it may have significance to the general subject of solute solvent interactions.

Data have also been obtained using substituted phenols as the guest species in inclusion complexes with host I. A similar behavior for the binding of the phenol within the confines of the hydrophobic void of the host has been observed. The hydrophobic end of the phenol extends into the cavity, while the hydrophilic OH group remains directed out into the solvent water (Figure 64, Table 7) (see also Table 10). As Figures 64a - 64d show, the phenol does not nearly enter the cavity to the extent that n-butanol does, however, it is binding with the same preferred orientation seen previously. Similarity to the n-butanol case is apparent in the way the phenol lies across the entry of the cavity. It effectively smooths out the contour represented by the hydrophobic exterior of the vaulted cyclidene structure.

The behavior described here clearly demonstrates that the guest species is not coordinated to the metal atom through the OH group of the alcohol or the phenol. If this were the case, the distances calculated for the host-guest association would be reversed with the protons nearest OH also nearest the Cu(II). Further, it may be concluded that inclusion complex formation is hydrophobically driven and that, barring blockage by solvent, the metal ion site remains available for coordination to other ligands such as dioxygen.

Variation of Host Compound. Replacement of the durene group forming the roof of host I with anthracene gives host II. Studies on inclusion complex formation between host II and alcohols and substituted phenols reveals results closely similar to those described above, Table 8. The distances calculated for the internuclear separation between

Figure 64. Inclusion complex between host I and 2,5-dimethylphenol guest.

Table 7

Relaxation Times for Guest Molecules with Host (I) (T = 304K)

Guest=2,6-dimethylphenol^a ($p = 1.54 \times 10^{-3}$) T = 304K

<u>Protons</u>	<u>Me</u>	<u>Meta</u>	<u>Para</u>
(T ₁) _O ,sec	4.08 ± 0.09	9.45 ± 0.20	7.88 ± 0.13
(T ₁),sec	3.15 ± 0.13	4.20 ± 0.06	2.90 ± 0.10
r, Å	7.6 ± 0.4	6.8 ± 0.1	6.1 ± 0.1

Guest=3,5-dimethylphenol^a ($p = 1.78 \times 10^{-3}$)

<u>Protons</u>	<u>Me</u>	<u>Ortho</u>	<u>Para</u>
(T ₁) _O ,sec	2.41 ± 0.08	13.78 ± 0.35	8.80 ± 0.35
(T ₁),sec	1.91 ± 0.04	3.86 ± 0.04	5.27 ± 0.36
r, Å	7.1 ± 0.1	6.9 ± 0.1	6.6 ± 0.1

Guest=2,5-dimethylphenol^b ($p = 2.50 \times 10^{-3}$)

<u>Protons</u>	<u>ortho-methyl</u>	<u>Meta</u>	<u>Ortho+Para</u>	<u>Meta-methyl</u>
(T ₁) _O ,sec	3.01±0.05	6.39±0.08	9.25±0.07	3.20±0.05
(T ₁),sec	2.01±0.03	2.81±0.02	3.58±0.10	1.64±0.05
r, Å	6.6±0.10	6.2±0.2	6.4±0.2	5.8±0.1

a. $\nu = 300$ MHzb. $\nu = 500$ MHz

Table 8

Variation of Host: (A) Effect of Closing the Cavity,
(B) Effect of Absence of Bridge

Guest=2,6-dimethylphenol ($p = 3.33 \times 10^{-3}$)

A.	Host	Protons	(CH ₃) avg.	Para H	Meta H avg.
T=304	Lacunar Complex ^a	(T ₁) _O ,sec	3.69±0.05	8.11±0.15	9.45±0.2
	R ¹ = (CH ₂) ₄	T ₁ ,sec	3.54±0.06	7.92±0.08	9.19±0.06
		r, Å	>12	>14	>14
T=304	Vaulted Complex ^a	(T ₁) _O ,sec	4.08±0.09	9.45±0.20	7.88±0.13
	R ¹ =duryl=Host I	T ₁ ,sec	3.15±0.13	4.20±0.06	2.90±0.1
		r, Å	7.6±.4	6.8±.1	6.1±.1

Guest=n-butanol ($p = 2.48 \times 10^{-3}$)

	Lacunar Complex ^a		α	β	γ	δ
T=304	R ¹ =(CH ₂) ₄	(T ₁) _o ,sec	6.62±.10	5.5±.10	5.40±0.10	6.33±0.10
		T ₁ ,sec	5.66±.15	4.70±.10	4.40±0.10	4.40±0.15
		r ₁	9.7±0.20	9.2±.20	9.4±0.20	8.3±0.20

Guest=n-butanol ($p = 6.90 \times 10^{-4}$)

T=304	Vaulted Complex ^a	α	β	γ	δ
	R ¹ =Anthracene=Host II				
	(T ₁) _O ,sec	5.60±0.15	5.48±0.05	6.22±0.20	6.11±0.10
	T ₁ ,sec	4.35±0.13	4.25±0.10	4.20±0.10	4.01±0.04
	r,Å	7.8±0.2	6.8±0.2	6.5±0.2	6.3±0.1

B. Host^b

T=304, unbridged, T = 304K
R¹ = R² = R³ = Me

Guest=n-butanol ($p = 4.62 \times 10^{-3}$)

Protons	α	β	γ	δ
(T ₁) _O ,sec	6.16 ± 0.03	5.64 ± 0.02	5.99 ± .04	5.73 ± .05
T ₁ ,sec	4.17 ± 0.10	3.84 ± 0.02	3.85 ± 0.1	3.69 ± 0.05
r, Å	8.6 ± 0.2	8.5 ± 0.1	8.3 ± 0.1	8.3 ± 0.1

a. ν = 300 MHz

b. ν = 500 MHz

the Cu(II) atom and the protons on the guest are generally a few tenths of an Angstrom shorter for host II. However, an identical pattern is found showing the specific orientation of the guest with its hydrophobic portion protruding deeper into the cavity and the hydrophilic portion extending outward into the solvent sheath. The enhanced hydrophobic region afforded by the anthracene as opposed to the durene roof appears to be barely significant.

These studies have been designed on the premise that inclusion complex formation is facilitated by the presence in the host of a permanent void of appropriate dimensions. A critical counter example involves the use of lacunar complexes¹⁴⁻¹⁶ having very small cavities that are not expected to be capable of binding even such small organic molecules as the alcohols and phenols used as guests in these studies. The data shown in Table 8 reveal that the effect of the paramagnetic center of the Cu(II) lacunar complex, having only a tetramethylene bridge (Figure 2)¹⁴ on the relaxation times of the protons of 2,6-dimethylphenol, is very small. Again, the uncertainties in the small differences between T_1 values made in the presence and absence of the copper complex impair the calculation of distances. Further, the distances that can be estimated are large when compared to those observed for the vaulted host. It is certainly clear that the substituted phenol is too bulky to enter the cavity of the tetramethylene-bridged Cu(II) lacunar complex. Significantly, these data also indicate that the guest is not within the first coordination sphere of the host complex for that would have placed the protons much nearer to the metal ion. In contrast to this result are those very large reductions in the T_1 vs. T_{10} seen

for the vaulted host I (included in Table 8 for comparison), which clearly indicate inclusion of the guest within the host species. Similar results are observed when n-butanol is used as the guest (Table 8); however, the effect of diminishing the cavity is less extreme. This is in keeping with the smaller size of the guest n-butanol. The data suggest that the butyl group may tend to lie along the entry to the small cavity where the CH_3 group might even penetrate to a small extent.

Further clarification of the role of the cavity provided by such hosts as I and II follow from the use of an unbridged complex as a possible host. The relaxation data (Table 8) indicate some moderate non-regiospecific association may take place. These data certainly show that there is no preferred orientation of the guest species. A major feature of the structure of the unbridged host complex is a deep, saddle-shaped conformation. The guest might occupy the cleft of the saddle. It appears that the guest resides at the approximate location assumed by the α -protons in the vaulted complexes as described earlier. Thus the most distant guest proton in the inclusion complexes of hosts I and II is at about the same distance from the copper(II) as are all the guest protons in the case of the unbridged host, confirming the importance of the cavity in promoting inclusion complexation and in producing regiospecific interaction.

In order to demonstrate the reproducibility of the relaxation data and, therefore, the calculated distances, experiments involving host-guest association were acquired at three spectrometer frequencies. Table 9 shows that the distances calculated from data obtained at 200, 300, and 500 MHz are the same, within experimental error, for host I and

Table 9

Frequency Dependence of Calculated Distances (T = 304K)

Host-Vaulted Complex^aR¹ = duryl = Host IGuest = n-butanol^b

		α	β	γ	δ
$\nu = 200$					
	(T ₁) _{o,sec}	5.30±0.08	4.95±0.02	5.95±0.4	6.18±0.1
	T _{1,sec}	4.71±0.10	3.90±0.1	4.18±.05	3.68±0.1
	r, Å	8.7±0.2	7.5±0.2	7.2±0.1	6.7±0.2
$\nu = 300$					
	(T ₁) _{o,sec}	5.70±0.1	5.33±00.18	6.25±0.2	6.20±0.1
	T _{1,sec}	5.05±0.1	4.22±0.05	4.6±0.04	3.71±0.1
	r, Å	8.7±0.2	7.5±0.2	7.3±0.1	6.6±0.1
$\nu = 500$					
	(T ₁) _{o,sec}	6.27±0.05	5.5±0.03	6.16±0.1	6.22±0.02
	T _{1,sec}	5.45±0.02	4.33±0.01	4.40±.03	3.61±.01
	r, Å	8.6±0.1	7.6±0.1	7.3±0.1	6.6±0.1

a. [Host] = 6.48 x 10⁻⁵b. [Guest] = 5.49 x 10⁻²

Table 10*

Relaxation Data and Calculated Distances from Tables 6 and 8

A. Guest = MeOH ($p = 1.04 \times 10^{-3}$) α

U = 200

$(T_1)_O, \text{sec}$	18.67 ± 0.75
T_1, sec	13.44 ± 0.30
$r, \text{\AA}$	8.7 ± 0.3

U = 300

$(T_1)_O, \text{sec}$	19.52 ± 0.9
T_1, sec	14.54 ± 0.2
$r, \text{\AA}$	8.6 ± 0.3

B. Guest = EtOH ($p = 1.92 \times 10^{-3}$) α β

U = 300

$(T_1)_O, \text{sec}$	14.46 ± 0.39	11.09 ± 0.22
T_1, sec	8.90 ± 0.37	6.43 ± 0.18
$r, \text{\AA}$	8.4 ± 0.5	7.5 ± 0.3

C. Guest = n-propanol ($p = 1.67 \times 10^{-3}$) α β γ

U = 200

$(T_1)_O, \text{sec}$	5.74 ± 0.15	6.32 ± 0.09	4.90 ± 0.1
T_1, sec	4.86 ± 0.03	5.04 ± 0.1	3.56 ± 0.1
$r, \text{\AA}$	8.8 ± 0.2	8.4 ± 0.1	7.6 ± 0.2

U = 300

$(T_1)_O, \text{sec}$	8.85 ± 0.20	8.65 ± 0.35	7.85 ± 0.10
T_1, sec	7.24 ± 0.14	6.8 ± 0.50	5.21 ± 0.11
$r, \text{\AA}$	9.0 ± 0.2	8.2 ± 0.5	7.5 ± 0.2

U = 500

$(T_1)_O, \text{sec}$	8.96 ± 0.02	8.49 ± 0.03	7.70 ± 0.05
T_1, sec	7.26 ± 0.02	6.54 ± 0.07	7.4 ± 0.09
$r, \text{\AA}$	8.9 ± 0.1	8.4 ± 0.1	7.7 ± 0.2

* Host I for all reported guests in Table X.

Table 10, continued

D. Guest = t-butyl alcohol ($p = 1.23 \times 10^{-3}$)
 β

$U = 300$

$(T_1)_{O,sec}$	4.28 ± 0.03
$T_{1,sec}$	3.34 ± 0.04
$r, \text{\AA}$	7.4 ± 0.1

E. Guest = i-propanol ($p = 1.90 \times 10^{-3}$)
 α β

$U = 200$

$(T_1)_{O,sec}$	15.48 ± 0.15	4.78 ± 0.18
$T_{1,sec}$	11.14 ± 0.20	3.81 ± 0.05
$r, \text{\AA}$	9.3 ± 0.2	8.2 ± 0.2

$U = 300$

$(T_1)_{O,sec}$	18.60 ± 0.7	5.20 ± 0.25
$T_{1,sec}$	13.55 ± 0.5	4.20 ± 0.07
$r, \text{\AA}$	9.2 ± 0.2	8.2 ± 0.2

F. Guest = 2-methyl-2-propen-1-ol ($p = 1.67 \times 10^{-3}$)
 α $\alpha (\text{CH}_3)$ $\beta (= \text{CH}_2)$

$U = 300$

$(T_1)_{O,sec}$	6.40 ± 0.04	7.36 ± 0.06	8.34 ± 0.05
$T_{1,sec}$	5.50 ± 0.07	5.65 ± 0.04	5.6 ± 0.06
$r, \text{\AA}$	9.0 ± 0.1	7.16 ± 0.10	7.58 ± 0.10

G. Guest = 3,5-dimethylphenol ($p = 1.78 \times 10^{-3}$)
methyl ortho para

$U = 200$

$(T_1)_{O,sec}$	2.28 ± 0.09	9.55 ± 0.06	7.04 ± 0.03
$T_{1,sec}$	1.82 ± 0.10	3.77 ± 0.08	3.30 ± 0.10
$r, \text{\AA}$	7.2 ± 0.2	6.8 ± 0.1	6.7 ± 0.2

$U = 300$

$(T_1)_{O,sec}$	2.41 ± 0.08	13.78 ± 0.35	8.80 ± 0.15
$T_{1,sec}$	1.91 ± 0.04	3.86 ± 0.041	5.27 ± 0.36
$r, \text{\AA}$	7.1 ± 0.1	6.90 ± 0.10	6.6 ± 0.1

$U = 500$

$(T_1)_{O,sec}$	2.96 ± 0.05	11.03 ± 0.02	8.29 ± 0.03
$T_{1,sec}$	2.31 ± 0.01	4.32 ± 0.07	4.01 ± 0.05
$r, \text{\AA}$	7.2 ± 0.1	6.8 ± 0.1	6.7 ± 0.1

Table 10, continued

H. Guest = 2,6-dimethylphenol ($p = 154 \times 10^{-3}$)

	methyl	meta	para
$U = 500$			
$(T_1)_O, \text{sec}$	4.08 ± 0.09	9.45 ± 0.20	7.88 ± 0.13
T_1, sec	3.15 ± 0.13	4.20 ± 0.06	2.90 ± 0.10
$r, \text{\AA}$	7.6 ± 0.2	6.8 ± 0.1	6.3 ± 0.1

$U = 500$			
$(T_1)_O, \text{sec}$	4.27 ± 0.03	9.71 ± 0.01	8.45 ± 0.05
T_1, sec	3.30 ± 0.01	4.41 ± 0.04	3.33 ± 0.02
$r, \text{\AA}$	7.5 ± 0.1	6.7 ± 0.2	6.3 ± 0.1

I. Guest = 2,5-dimethylphenol ($p = 2.50 \times 10^{-3}$)

	ortho-methyl	meta	ortho+para	meta-
methyl				
$U = 300$				
$(T_1)_O, \text{sec}$	3.26 ± 0.10	7.27 ± 0.15	9.88 ± 0.60	3.28 ± 0.11
T_1, sec	2.09 ± 0.04	3.17 ± 0.06	4.55 ± 0.11	1.65 ± 0.02
$r, \text{\AA}$	7.1 ± 0.2	7.0 ± 0.2	7.5 ± 0.1	6.4 ± 0.1
$U = 500$				
$(T_1)_O, \text{sec}$	3.01 ± 0.03	6.39 ± 0.05	9.25 ± 0.04	3.20 ± 0.03
T_1, sec	1.98 ± 0.03	2.71 ± 0.06	3.32 ± 0.04	1.63 ± 0.01
$r, \text{\AA}$	6.7 ± 0.2	6.2 ± 0.2	6.5 ± 0.2	5.8 ± 0.06

n-butanol. All other relaxation data obtained for the guest alcohols and phenols are found in Table 10.

Finally, in order to demonstrate that the cyclidene ligand itself is not contributing to the observed relaxation rates of the guest protons, several $(T_1)_0$ experiments were performed in the presence of a Ni^{2+} complex of ligand host I (dichloride salt). During all previous experiments mentioned, the $(T_1)_0$ value is simply the T_1 values of the guest in the absence of paramagnetic host. The results obtained for the relaxation rates of guest protons are within experimental error of those values measured in the absence of the Ni^{2+} diamagnetic host I.

CONCLUSIONS

The detailed studies reported here are based on the determination of longitudinal relaxation rates in systems designed for the fundamental study of a host-guest complexation reaction that was expected to be driven by hydrophobic interactions. Care has been taken to observe all reasonable precautions as described in the experimental section. Because hydrophobic guest-host complex formation involves no direct bonding between guest and host, relaxation effects should only involve dipolar contributions.

The use of the simplified Solomon-Bloembergen equation appropriate to this situation has been justified by testing all parameters. Outer sphere effects are small; the relaxation process associated with host-guest complexing is magnetically determined; and the host-guest equilibrium is saturated under conditions used. The validity of the model is also verified by the fact that essentially identical results

have been obtained with three different spectrometers operating at three different frequencies.

The hydrophobic character of the host-guest complexing is shown by the large relaxation rate effects observed for deuterium oxide solutions and the very small effects found for acetonitrile solutions. The assumption that the full relaxation effect of the vaulted complex requires entry of the guest into the cavity of the host is strongly supported by the small relaxation effects observed when the potential host has only a very small cavity. Further, closely related structures with no cavity show no regiospecific effects.

The distance data clearly show that the cavities of the vaulted complexes are large enough to accommodate small organic molecules. A regiospecificity is apparent from the orientations of the guests as they project into the cavities. The hydrophilic OH group is most distant from the copper(II) atom while the hydrophobic portion of the molecule protrudes into the cavity. In the case of the alcohols, the OH group is found at about the same distance from the paramagnetic center in all cases, presumably because it is embedded in the surrounding solvent sheath. The longer the alkyl group on the alcohol, the closer its hydrophobic terminus is to the copper atom. The cavities of the vaulted hosts are not big enough to encompass the substituted phenols studied here, but the orientation of the molecules mimics that of the alcohols, with the OH group exposed to the solvent. This persistent regiospecificity bears testimony to the hydrophobic nature of this example of inclusion complex formation.

It is, of course, gratifying to see that the alcohol and phenol guests are not coordinated to the metal ion. The relaxation behavior of the solvent suggests that a single water molecule is bound to the copper ion and this is expected to occur outside the cavity. These results indicate that the sixth coordination site of the metal atom that occupies the cyclidene macrocycle remains available within the cavity. This is particularly important since these ligands have been developed to permit simultaneous binding of an organic guest molecule and coordination of a dioxygen molecule.

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EXPERIMENTAL

Materials. Solvents and reagents used in the synthesis of copper(II) complexes were of reagent grade and were used without further purification unless otherwise noted.

Synthesis of Bridged Copper(II) Compounds.

(2,9,10,17,19,25,33,34-Octamethyl-3,6,13,16,20,24,27,31-octaazapentacyclo[16.7.7.2^{8,11}.2^{3,6}.2^{13,16}]hexatetraconta-1,8,10,17,19,24,26,31,-33-nonaenec⁴N)copper(II) Hexafluorophosphate, [Cu{3,6-durene(CH₂-piperazine)₂[16]cyclidene(PF₆)₂}. One gram (1.0 mmole) of [Ni{3,6-durene(CH₂-piperazine)₂[16]cyclideneN₄}(PF₆)₂ (see reference 8) was slurried in 50 ml of methanol. Dry hydrogen bromide gas was bubbled vigorously through the methanolic solution until a white precipitate was observed. The slurry was allowed to cool and the tetrabromide ligand salt was recovered by filtration, washed with small amounts of methanol, and dried in vacuo at room temperature. To a solution of 0.2 g (0.20 mmoles) of [H₄{3,6-durene(CH₂-piperazine)₂cyclideneN₄}]B₄ dissolved in 50 ml of hot methanol was added 0.12 g (0.40 mmoles) of copper acetate monohydrate and 0.080 g (0.48 mmoles) of sodium acetate-3-hydrate. The solution was allowed to stir and a solution of 0.15 g (0.36 mmoles) of ammonium hexafluorophosphate in ethanol was added. The reddish brown solid that formed almost immediately was recovered and recrystallized by dissolving

in acetonitrile and adding sufficient ethanol to induce crystallization. The crystals were ground to a powder and dried in vacuo overnight; yield, 0.07 g (64%). **Anal.** Calcd. for $\text{CuC}_{38}\text{H}_{60}\text{N}_8\text{P}_2\text{F}_{12}$: C, 35.87; H, 4.75; N, 8.81; Cu, 4.99. Found: C, 35.78; H, 4.88; N, 8.73; Cu, 4.98.

(2,17,19,25-Tetramethyl-3,6,13,16,20,24,27,31-octaazaheptacyclo-[20.7.7.6⁸,15.2³,6.2¹⁷,20.0⁹,14.0³⁷,42]hexatetraconta-1,8,10,17,19,24,-26,31,33,35,37,39,41-tridecaenek⁴N)copper(II) Hexafluorophosphate, $[\text{Cu}\{9,10\text{-anthracene}(\text{CH}_2\text{-piperazine})_2\text{cyclideneN}_4\}](\text{PF}_6)_2$. This reaction was performed in the same way as the preceding reaction using 0.6 g (0.6 mmole) of $[\text{Ni}\{9,10\text{-anthracene}(\text{CH}_2\text{piperazine})_2[16]\text{cyclideneN}_4\}](\text{PF}_6)_2$, (see reference 8); and 0.36 g (0.1 mmole) of copper acetate monohydrate and 0.24 g (1.44 mmole) of sodium acetate-3-hydrate and 0.45 g (0.08 mmole) of ammonium hexafluorophosphate; yield, 0.09 g (35%). **Anal.** Calcd. for $\text{CuC}_{42}\text{H}_{54}\text{N}_8\text{P}_2\text{F}_{12} \cdot \text{CH}_3\text{CN}, \text{H}_2\text{O}$: C, 48.77; H, 5.50; N, 11.64; Cu, 5.85. Found: C, 48.68; H, 5.57; N, 11.82; Cu, 5.45.

Synthesis of the Chloride Salts of the Copper(II) Complexes.

(2,9,10,17,19,25,33,34-Octamethyl-3,6,13,16,20,24,27,31-octaazapentacyclo[16.7.7.2⁸,11.2³,6.2¹³,16]hexatetraconta-1,8,10,17,19,24,26,31,-33-nonaenek⁴N)copper(II) Chloride, $[\text{Cu}\{3,6\text{-durene}(\text{CH}_2\text{piperazine})_2[16]\text{-cyclideneN}_4\}]\text{Cl}_2$. In an inert atmosphere glove box, one gram (1.0 mmole) of $[\text{Cu}\{3,6\text{-durene}(\text{CH}_2\text{piperazine})_2[16]\text{cyclideneN}_4\}](\text{PF}_6)_2$ was dissolved in 20 ml of acetone and 1.5 g (5.3 mmole) of tetrabutylammonium chloride, dissolved in 10 ml of acetone, was dripped slowly into the Cu(II) solution. A voluminous reddish precipitate formed immediately and was recovered and dried in vacuo; yield, 0.49 g (52%). **Anal.**

Calcd. for $\text{CuC}_{38}\text{H}_{58}\text{N}_8\text{Cl}_2 \cdot 2\text{HCl}$, $6\text{H}_2\text{O}$: C, 48.00; H, 7.69; N, 11.78; Cu, 6.68; Cl, 14.92. Found: C, 48.01; H, 7.37; N, 11.48; Cu, 6.37; Cl, 14.62.

(2,17,19,25-Tetramethyl-3,6,13,16,20,24,27,31-octaazaheptacyclo-[20.7.7.6^{8,15}.2^{3,6}.2^{17,20}.0^{9,14}.0^{37,42}]hexatetraconta-1,8,10,17,19,24,-26,31,33,35,37,39,41-tridecaene N_4)copper(II) Chloride, $[\text{Cu}\{9,10\text{-anthracene}(\text{CH}_2\text{piperazine})_2[16]\text{cyclideneN}_4\}]\text{Cl}_2$. The reaction was performed as the preceding reaction using 0.2 g (0.2 mmole) of $[\text{Cu}\{9,10\text{-anthracene}(\text{CH}_2\text{piperazine})_2[16]\text{cyclideneN}_4\}](\text{PF}_6)_2$ in 20 ml of dried acetone and 0.25 g (0.5 mmole) of tetrabutylammonium chloride dissolved in 10 ml acetone; yield, 0.039 g (22%). Anal. Calcd. for $\text{CuC}_{42}\text{H}_{54}\text{N}_8\text{Cl}_2 \cdot 6\text{H}_2\text{O}$: C, 55.21; H, 7.30; N, 12.28; Cu, 6.96; Cl, 7.76. Found: C, 55.34; H, 7.18; N, 12.20; Cu, 6.59; Cl, 7.90.

Physical Measurements. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The proton NMR spectra of the guest species, in the presence and absence of the paramagnetic Cu(II) host, were acquired at three different frequencies using Bruker WP200, Bruker WM300, Bruker AM500, and Nicolet NT500 MHz NMR spectrometers. Samples were allowed to equilibrate for 30 minutes at 304 K using a variable temperature control unit. Five-millimeter o.d. Wilmad Royal Imperial sample tubes, 528-PP, seven inches in length were used to contain the host-guest sample solutions. Aldrich Gold Label 99.96% hydrogen-2 deuterium oxide, low in paramagnetic impurities, was used as the solvent in all experiments. A 10 μl Hamilton syringe was used to prepare the host-guest solutions. The organic guest molecules used during inclusion complexation experiments were of spectrophotometric grade, Gold Label quality, purchased from Aldrich Chemical Company, and were used without further purification.

Experimental Precautions. (1) All glassware used in the study of the host-guest phenomena were soaked in 0.5M EDTA for 24 hours prior to use. (2) The deuterium oxide was low in paramagnetic impurities and degassed by freeze-pump thaw techniques on a vacuum line at 10^{-5} torr. Guest solutions were also degassed in this manner. (3) All samples for the study of the intramolecular association phenomena were prepared in an inert atmosphere glove box and sealed.

Procedure for Host-Guest Studies. (1) A stock solution of the host compound was prepared by accurately weighing an amount of the chloride salt of the host species and dissolving the complex in a 5 ml volumetric flask containing deuterium oxide (typically 1.5×10^{-2} M). (2) A 10 μ l syringe was used to deliver an aliquot of the stock host solution into a 2 ml volumetric flask containing D₂O and an accurately measured amount of the guest solution. The referenced solution was prepared in an identical manner, excluding the paramagnetic host complex. (3) Aliquots were then taken from each of the two 2 ml volumetric flasks and placed into the two 5 mm NMR sample tubes. (4) Measurement of T_{1p} was achieved by two sets of standard inversion recovery experiments obtained at each of three different frequencies. At least 12 different values of the variable delay parameter were used to determine accurately the relaxation times. The program used to calculate the T_1 values was from the Bruker library of software programs and the errors indicated in the table are standard deviations of the fit. The equation to which the points are fit is $Y = A_3 - A_2 \exp(-T/T_1)$, where:

A_3 = the normalized intensity of the largest point.

A_2 = the nucleus flip angle in units of $\pi/2$.

T = value.

The convergence limit was set to 1.0×10^{-5} , which provided a very accurate fit to the data.

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CHAPTER THREE
INCLUSION COMPLEX FORMATION INVOLVING A
NEW CLASS OF TRANSITION METAL HOST

INTRODUCTION

The field of host-guest chemistry is being increasingly exploited as a vehicle for the study of such phenomena as catalysis, enzyme modeling, and aspects of facilitated transport. Several intensively studied classes of hosts are cyclodextrins, cavitands, and cryptates.¹ Each of these host species undergoes inclusion complex formation where this interaction has been characterized by the absence of covalent bond formations.² Enzymes such as cytochrome P-450² exploit hydrophobic interactions as the driving force for enzyme-substrate binding³ and it is on these interactions that this and previous work in our laboratory have focused. It has recently been shown from x-ray crystallographic studies on cytochrome P-450 that there exists a hydrophobic region in the vicinity of the Fe atom of the porphyrin ring where the substrate is bound.⁴ This result has confirmed a great deal of work involving the type of substrate binding used by the enzyme.

The development by Takeuchi of the macrobicyclic ligands known as vaulted cyclidenes has provided the means by which the ternary complex of cytochrome P-450 may be modeled^{5,6,7} (Figure 65b). The complexes were shown to regiospecifically bind small organic molecules,^{8,9} while,

Figure 65. Three-dimensional representation of a) lacunar cyclidene, b) vaulted cyclidene, and c) supervaulted cyclidene.

at the same time, providing a vacant coordination site on the metal atom for the coordination of dioxygen. Previous work on the nickel(II) complexes of the vaulted cyclidene, using NMR chemical shift studies in aqueous solution, established that the transition metal complexes do indeed undergo host-guest association.⁵⁻⁷ The copper(II) complexes of the vaulted cyclidene ligands were prepared and inclusion complex formation was studied in greater detail by NMR relaxation techniques.^{8,9} The simplified dipolar form of the Solomon-Bloembergen equation was experimentally justified and then used to calculate distances from the Cu(II) atom within the cyclidene complex to the protons of the hydrophobically bound guest, using spin lattice relaxation data. These results confirmed the regiospecific binding of small organic guests and it was clearly evident that enough room remained in the pocket to coordinate dioxygen. From ChemGraph illustrations of the host-guest complex,¹¹ the guest was found to reside in the top part of the pocket formed by the cyclidene. The first vaulted cyclidene complexes were shape selective toward small rod-shaped molecules such as normal alcohols. Phenols associated but the larger aromatic ring was not engulfed by the void of the host.

In order to increase the size of the cavity of the vaulted cyclidene and allow it to accommodate even larger, and perhaps more interesting substrates or guests, the ligand has been redesigned, yielding the "super vaulted" cyclidene ligands. 4,4'-Bipiperidine has been substituted for piperazine as the riser (Figure 65c and Figure 66). This "raising of the roof" has provided a large cavity, as shown by x-ray crystallography. Relaxation experiments indicate that

$M^{2+} = \text{Cu, Ni}$

Figure 66. Flat representation of supervaulted cyclidene where

$M^{2+} = \text{Ni, Cu,}$ and $R^1 = 3,6\text{-durene}$ and $9,10\text{-anthracene}$.

substituted phenols are completely enveloped by the super vault cavity, in contrast to the vaulted cyclidene. Similar regiospecific binding of the guest has been observed, with the OH group remaining embedded in the solvent sheath, and it is clear that a vacant coordination site on the metal is available for binding dioxygen.

RESULTS AND DISCUSSION

The Design, Synthesis, and Characterization of the Nickel(II) and Copper(II) Supervaulted Cyclidene Complexes.

An essential design feature of the vaulted cyclidene complexes developed by Takeuchi⁶ is a large preformed cavity. This preformed cavity is in sharp contrast to the related structural features of several classes of organic hosts mentioned earlier (see Chapter 1). These include the crown ethers, cryptates, and many types of cyclophanes. The cavities in these hosts are recognized to be formed only during the course of host-guest complexation (see Figure 11). The vaulted complexes provided a preformed cavity which was shown to be capable of binding small organic guest species by a hydrophobic driving force in aqueous solution.⁷ In the lacunar and vaulted cyclidene structure, the NiN_4 plane functions as the floor of the void, while the piperazine risers are the walls, and the durene (or other organic groups) forms the roof. The supervaulted complexes are strictly analogous in all respects to the vaulted complexes with the exception that the walls are composed of 4,4'-bipiperidine moieties (Figure 66). This change has provided a much larger cavity, the consequences of which are discussed later.

The synthesis of the nickel(II) and copper(II) supervaulted complexes is outlined in Figure 67. The complexes are initially isolated as tetrahexafluorophosphate salts and metathesized to chloride salts after the nickel(II) has been removed and replaced by copper(II). The metathesis to the chloride salt provides a water soluble complex. Water is the solvent of choice so that the hydrophobic driving force may be exploited during inclusion complex formation. Several unsuccessful attempts were made to isolate the deprotonated bishexafluorophosphate salts of the materials. As described below, the amines adjacent to the bridging group (Figure 66) are sufficiently basic to remain protonated in the supervaulted complexes that have been isolated and characterized.

The nickel(II) intermediates and bridged supervaulted complexes were characterized by carbon-13, proton, and infrared spectroscopy, as well as by elemental analysis and electrochemistry. The carbon-13 NMR spectra of the intermediate, II, Figure 67, is shown in Figure 68. The majority of assignments made in the carbon-13 spectra have been based on prior ^{13}C enrichment and off-resonance studies of lacunar and vaulted cyclidene complexes.^{6,12} Therefore, changes in the ^{13}C spectra induced by the substitution of the 4,4'-bipiperidine into the parent cyclidene were easily detected and identified. As seen earlier for the vaulted complexes, the intermediate (II, Figure 67) possess mirror symmetry. It is of interest to note that carbon atoms M, P, N, and O (Figure 68) are equivalent pairs on the 4,4'-bipiperidine riser. This result indicates free rotation about the bond between carbon atom A and the adjacent nitrogen atom nitrogen. This is consistent with results obtained by Takeuchi for the complex having piperazine as the riser.⁶ The carbon-13

Figure 67. Synthetic scheme for the supervaulted Ni^{2+} and Cu^{2+} cyclidenes.

Figure 68. ^{13}C NMR spectrum of
 $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2[16]\text{cyclidene}\}](\text{PF}_6)_4$.

NMR spectrum of the bridged species (III) is shown in Figure 69. With the addition of the bridge, the rotation of the biperidine rings is stopped, as evidenced by the disappearance of the pair-wise equivalence of carbon atoms M, P, N, and O. In the region from fifty-seven to forty-five ppm (Table 11), the number of observed peaks increases from four (II) to at least seven (III). The expected seventh peak is attributed to Q, the methylene of the bridging durene. Although it is difficult to see in Figure 69, a blowup of the region reveals a shoulder at 57.7 ppm and displays the uniqueness of the four carbons labeled M, R, T, and P. The additional peaks are attributed to the loss of free rotation about the carbon-nitrogen bond. In the region from thirty-one to twenty-six ppm, a similar result is revealed. The previously pairwise equivalent carbon atoms of N and O are now seen to be a unique set of atoms, with addition of two peaks in that region. The carbon atoms K and L are unique and the proton coupled spectra of III reveals their positions (Figure 70, Table 11). The resonances at 40 and 37.7 ppm are split into doublets, indicating the single proton on each. Even at 500 MHz, the proton coupled signals of the other carbon atoms are too complicated to address; however, sufficient peaks are present to indicate the methylene character of each carbon resonance found in the regions from fifty-seven to forty-eight ppm and from thirty-one to twenty-six ppm.

In contrast to the dipositive charge on the vaulted cyclidene cations, the supervaulted complexes possess an overall 4^+ charge. This result was confirmed by elemental analysis and may be seen by examining the electrochemistry of the complex as shown in Figure 71. Scan A of Figure 71 represents the reversible $\text{Ni}^{\text{III/II}}$ couple of the isolated

Figure 69. ^{13}C NMR spectrum of
 $\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2, 6\text{-dur}[16]\text{cyclidene}\}(\text{PF}_6)_4$.

Table 11

Carbon-13 NMR Data for [Ni{Supervault[16]cyclidene}]
in CD₃CN. (Relative to 118.2(br) signal of solvent.)

R ¹	R ³	Chemical Shift (ppm)
-(unbridge)(II)	-	172.3, 167.8, 160.1, 111.4, 56.4, 52.8, 51.2, 48.2, 45.7, 39.7, 38.0, 30.3, 29.6, 26.6, 20.6, 19.3
3,6-durene(III)	Methyl	172.9, 167.6, 160.5, 138.1, 137.7, 128.7, 111.3, 56.9, 56.6, 55.3, 54.8, 51.8, 51.1, 48.2, 40.0, 37.7, 30.7, 30.0, 29.3, 28.3, 27.5, 20.6, 19.4, 17.9
9,10-Anthracene	Methyl	172.4, 166.9, 161.2, 133.3, 132.9, 132.1, 127.8, 127.1, 126.9, 56.7, 56.2, 55.5, 55.0, 54.9, 51.6, 40.2, 37.9, 31.9, 30.9, 30.2, 29.9, 29.4, 28.4, 20.5, 18.9, 17.8
3,6-durene	C ₆ H ₅	173.8, 168.4, 162.9, 137.2, 136.5, 134.5, 132.9, 131.5, 130.9, 130.4, 130.1, 113.5, 56.7, 55.7, 55.3, 54.6, 54.3, 53.0, 51.7, 40.4, 39.1, 31.5, 30.7, 30.5, 29.7, 29.2, 28.7, 21.0, 18.1, 17.8

Figure 70. ^{13}C NMR proton decoupled spectrum of $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_{2,3,6}\text{-dur[16]cyclidene}\}](\text{PF}_6)_4$.

Figure 71. Cyclic voltammogram for the $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_{23,6}\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_4$ at a Pt wire electrode vs. Ag/0.1M AgNO₃/CH₃CN: (a) in 0.1M TBAT/CH₃CN, (b) following addition of NaMeO, and (c) following addition of xs. 60% H⁺PF₆⁻.

supervaulted complex. By way of comparison, the scan for the $\text{Ni}^{\text{III/II}}$ couple for the vaulted cyclidene complex is highly irreversible. This result has been interpreted as arising from irreversible oxidation of the distant nitrogen atom of the piperazine ring.¹³ However, when the vaulted complex is protonated by the addition of HPF_6 , cyclic voltammetry reveals a reversible wave, in contrast to the behavior of the bipiperdyl adduct. After the initial scan (Figure 71a), a small amount of sodium methoxide was added and the resulting solution gave scan B. This irreversible wave is attributed to the irreversible oxidation of the distant nitrogen on the bipiperidine overlapping a second couple at lower potential due to $\text{Ni}^{\text{III/II}}$. Upon addition of HPF_6 , a reversible wave is again observed (Figure 71c), indicating that the nitrogen of the bipiperidine is again protonated and that the irreversible oxidation of the amine does not occur. In addition, the potential of the reversible wave of the protonated bipiperidine adduct is positioned at a lower potential than that for the analogous vaulted complex, probably because of the greater distance between the nitrogen and the metal center in the supervaulted case.

Replacement of the methyl group at the R^3 position with a phenyl group should enhance the hydrophobicity of the pocket. The synthesis and isolation of the phenyl substituted product were uneventful and followed the course for the vaulted systems outlined previously.¹⁴ The ^{13}C NMR spectrum of $[\text{Ni}\{\text{Ph}_2(\text{bipiperidine})_{2,3,6}\text{-dur[16]cyclidene}\}](\text{PF}_6)_4$ is shown in Figure 72. It may be noted that there is no overlap of resonances in the sixty to thirty ppm range and that every carbon atom is unique. The phenyl rings undoubtedly hinder any rotational motion of the bipiperidine rings that continue to be active after bridging.

Figure 72. ¹³C NMR spectrum of
[Ni{Ph₂(bipiperidine)_{2,6}-dur[16]cyclidene}](PF₆)₄.

Molecular models of the complex suggest that the lower ring (closer to the metal) of the bipiperidine risers are frozen, while the upper rings have very limited rotational freedom.

The synthesis and isolation of the copper(II) complexes with the supervaulted cyclidene ligands is smoothly carried out by removal of nickel ion with dry HBr and insertion of copper(II) with copper acetate and sodium acetate. The complexes were recrystallized and characterized by elemental analysis.

The ability of a host complex to undergo conformational change during host-guest complexation has been addressed in Chapters 1 and 2. It has been shown in the vaulted complexes that a priority of the piperazine rings accompanies the association of an acetonitrile molecule that is present in the crystal of the anthracene vaulted complex. From these results it is not unreasonable to expect that the bipiperidine walls of the supervaulted complex will be capable of pivoting to accommodate guests.

X-Ray Structure Determination of the Supervaulted Complex, $[\text{Ni}\{\text{Me}_2\text{-(bipiperidine)}_2\text{3,6-dur[16]cyclidene}\}](\text{PF}_6)_4 \cdot 2 \text{ Benzonitrile}$.

The Ortep diagram of the supervaulted complex is shown in Figure 73. As is evident from the diagram, the basic design features of the lacunar¹² and vaulted⁶ cyclidene complexes have been retained. The floor of the cavity consists of N_1 , N_2 , N_3 , and N_4 and has a square planar arrangement with all four Ni-N distances within 0.07 Å of 1.89 Å and N-Ni-N angles within 4° of 90°. Some selected bond lengths and angles are given in Tables 13 and 14. Coordinate and isotropic thermal parameters are given in Table 12. The cyclidene complex assumes the

Figure 73. Crystal structure and numbering scheme of
 $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2,3,6\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_4 \cdot 2 \text{ benzonitrile}.$

Figure 73, continued

Table 12

Positional Parameters for

	x	y	z	U
N1	1489(3)	6553(3)	4997(1)	59(2)*
P1	5135(6)	5548(5)	2249(3)	76(6)*
F11	4264	5158	2354	171(19)*
F12	6006	5937	2144	193(20)*
F13	5888	5129	2625	234(21)*
F14	4382	5967	1874	277(25)*
F15	5104	6301	2512	179(19)*
F16	5166	4794	1986	202(20)*
P2	0102(7)	1707(5)	1592(3)	096(7)*
F21	0055	0913	1346	166(17)*
F22	0148	2502	1838	140(14)*
F23	1009	1366	1938	172(17)*
F24	-0805	2049	1245	247(22)*
F25	-0607	1323	1793	228(24)*
F26	0810	2092	1391	210(22)*
P3	9296(8)	6427(7)	0810(4)	116(8)*
F31	10292	6857	0852	232(24)*
F32	8301	5997	0768	249(6)*
F33	9296	6021	0410	245(26)*
F34	9297	6832	1210	286(29)*
F35	8717	7166	0566	287(34)*
F36	9876	5688	1054	280(31)*
P4	4444(8)	1949(8)	0674(4)	118(9)*
F41	4330	1607	0248	249(24)*
F42	4558	2290	1100	280(27)*
F43	5550	1685	0829	394(39)*
F44	3338	2213	0519	305(30)*
F45	4144	1107	0798	336(38)*
F46	4745	2791	0550	346(37)*
N1	0552(15)	6214(13)	5212(6)	051(8)
N2	2230(17)	5600(15)	5229(8)	059(8)
N3	2492(17)	6871(15)	4794(7)	076(9)
N4	0831(19)	7553(16)	4795(7)	069(9)
N5	1819(17)	5870(15)	6496(7)	064(8)
N6	2548(16)	8977(14)	8107(7)	058(8)
N7	2586(18)	12037(15)	7113(7)	083(10)
N8	2609(24)	9541(20)	5328(10)	153(14)
C1	-0165(20)	5695(18)	5743(8)	054(10)
C2	0697(19)	5919(17)	5577(8)	047(9)
C3	1678(20)	5598(17)	5811(8)	041(9)
C4	2322(21)	5347(18)	5574(9)	051(10)

Table 12, continued

C5	2745(25)	5102(21)	4992(10)	071(11)
C61	2709(46)	5435(37)	4613(18)	101(20)
C62	3681(84)	5529(66)	4961(36)	101(20)
C7	2956(26)	6301(21)	4569(11)	093(13)
C8	2819(23)	7619(19)	4847(9)	081(12)
C9	2342(22)	8307(21)	4944(10)	086(12)
C10	1230(23)	8332(22)	4840(9)	092(12)
C11	0617(25)	9056(22)	4655(11)	103(14)
C12	-0287(21)	7528(19)	4577(10)	092(12)
C13	-0687(22)	6675(19)	4564(8)	081(11)
C14	-0562(17)	6288(17)	4996(7)	052(10)
C15	2064(21)	5369(17)	6236(8)	059(10)
C16	2586(19)	4576(16)	6386(8)	040(9)
C17	1459(18)	6720(16)	6397(7)	047(9)
C18	2022(22)	7315(18)	6728(8)	075(12)
C19	1960(21)	7107(16)	7159(8)	053(10)
C20	2365(22)	6198(17)	7246(9)	084(12)
C21	1832(20)	5632(17)	6914(8)	061(10)
C22	2525(20)	7665(16)	7495(7)	051(10)
C23	2303(21)	8582(18)	7394(9)	085(12)
C24	2816(23)	9124(21)	7729(9)	103(14)
C25	2793(22)	8099(16)	8234(9)	075(11)
C26	2318(23)	7508(21)	7878(9)	095(13)
C27	2966(20)	9547(16)	8456(8)	047(9)
C28	3018(26)	10420(21)	8321(9)	070(11)
C29	2147(22)	10888(19)	8223(9)	052(10)
C30	1231(24)	10651(21)	8353(10)	092(13)
C31	2120(23)	11601(21)	7969(9)	061(10)
C32	1155(25)	12129(20)	7883(10)	087(12)
C33	2966(21)	11798(19)	7872(9)	053(10)
C34	3919(19)	11393(18)	8050(8)	052(9)
C35	4829(22)	11728(20)	7974(9)	085(12)
C36	3936(22)	10693(17)	8291(8)	044(9)
C37	4923(21)	10223(17)	8449(8)	052(10)
C38	2802(23)	12395(20)	7537(9)	083(12)
C39	3325(26)	12067(23)	6938(10)	140(17)
C40	3082(25)	11814(20)	6511(10)	106(14)
C41	2714(23)	10920(20)	6475(9)	066(11)
C42	1908(21)	10836(19)	6658(8)	086(12)
C43	2220(25)	11165(21)	7086(10)	106(14)
C44	2440(25)	10661(21)	6043(10)	101(13)
C45	3248(25)	10729(23)	5853(10)	133(16)
C46	2884(35)	10447(27)	5389(13)	245(27)
C47	1898(23)	9396(21)	5551(9)	106(14)
C48	2176(21)	9665(16)	5989(8)	064(11)
C49	2919(28)	9033(24)	5134(12)	124(15)
C50	3914(25)	9252(24)	5036(11)	121(16)
CS100	8643(13)	4653(8)	1772(5)	137(17)
CS101	8640	4101	1464	139(17)

Table 12, continued

CS102	7733	3822	1187	168(19)
CS103	6829	4095	1218	160(19)
CS104	6831	4646	1527	161(19)
CS105	7738	4926	1804	108(14)
CS106	9566	4937	2054	154(18)
NS107	10320	5169	2285	188(17)
CS(2)110	4757(16)	7519(10)	0928(4)	110(14)
CS(2)111	5118	8101	0717	190(22)
CS(2)112	6089	8032	0706	190(22)
CS(2)113	6700	7380	0906	229(25)
CS(2)114	6340	6797	1117	258(29)
CS(2)115	5368	6867	1128	165(19)
CS(2)116	3768	7589	0939	169(19)
NS(2)117	2960	7647	0948	276(24)

Table 13

Bond Lengths (Å) for

[Ni{Me₂(bipiperidine)₂3,6-dur[16]cyclidene}](PF₆)₄·2C₆H₅CN

Ni-N1	1.185(25)	Ni-N2	1.891(23)
Ni-N3	1.860(28)	Ni-N4	1.885(25)
N1-C2	1.306(35)	N1-C14	1.506(29)
N2-C4	1.230(41)	N2-C5	1.507(48)
N3-C7	1.499(48)	N3-C8	1.291(39)
N4-C10	1.373(43)	N4-C12	1.508(36)
N5-C15	1.347(41)	N5-C17	1.471(35)
N5-C21	1.495(38)	N6-C24	1.502(44)
N6-C25	1.497(34)	N6-C27	1.481(33)
N7-C38	1.514(40)	N7-C39	1.377(51)
N7-C43	1.500(42)	N8-C46	1.518(55)
N8-C47	1.482(53)	N8-C49	1.235(56)
C1-C2	1.559(45)	C2-C3	1.450(35)
C3-C4	1.478(47)	C3-C15	1.438(37)
C62-C5	1.533(130)	C62-C61	1.503(109)
C62-C7	1.881(108)	C8-C9	1.404(48)
C9-C10	1.494(45)	C9-C49	1.458(49)
C10-C11	1.472(47)	C12-C13	1.491(45)
C13-C14	1.580(40)	C15-C16	1.488(37)
C17-C18	1.507(35)	C18-C19	1.564(43)
C19-C20	1.575(38)	C19-C22	1.481(34)
C20-C21	1.467(36)	C22-C23	1.538(39)
C22-C26	1.475(46)	C23-C24	1.443(40)
C25-C26	1.530(41)	C27-C28	1.505(43)
C28-C29	1.389(46)	C28-C36	1.411(50)
C29-C30	1.561(51)	C29-C31	1.449(45)
C31-C32	1.554(47)	C31-C33	1.387(49)
C33-C34	1.440(38)	C33-C38	1.471(44)
C34-C35	1.503(45)	C34-C36	1.406(40)
C36-C37	1.523(39)	C39-C40	1.464(48)
C40-C41	1.534(47)	C41-C42	1.488(50)
C41-C44	1.477(45)	C42-C43	1.498(43)
C44-C45	1.506(57)	C44-C48	1.657(42)
C45-C46	1.582(55)	C47-C48	1.599(41)
C49-C50	1.600(60)		

Table 14

Bond Angles (Deg) for

N1-N1-N2	67.4(11)	N1-N1-N3	177.3(9)
N2-N1-N3	90.1(11)	N1-N1-N4	94.3(11)
N2-N1-N(4)	175.4(9)	N3-N1-C14	88.1(12)
N1-N1-C2	127.9(17)	N1-N1-C14	124.1(17)
C2-N1-C14	107.8(23)	N1-N2-C4	123.3(23)
N1-N2-C5	120.6(20)	C4-N2-C5	116.1(25)
N1-N3-C7	123.6(20)	N1-N3-C8	119.3(24)
C7-N3-C8	117.1(29)	N1-N4-C10	128.2(20)
N1-N4-C12	117.8(19)	C10-N4-C12	113.9(24)
C15-N5-C17	123.8(24)	C15-N6-C25	107.8(24)
C24-N6-C27	117.9(23)	C25-N6-C27	111.4(19)
C38-N7-C39	118.7(24)	C38-N7-C43	112.0(25)
C39-N7-C43	107.7(28)	C46-N8-C47	105.6(35)
C46-N8-C49	127.0(49)	C47-N8-C49	127.4(35)
N1-C2-C1	124.0(21)	N1-C2-C3	118.7(27)
C1-C2-C3	115.7(23)	C2-C3-C4	116.4(23)
C1-C2-C15	128.9(29)	C4-C3-C15	114.0(23)
N2-C4-C3	124.5(25)	N2-C5-C61	115.7(36)
N2-C5-C62	112.7(51)	C61-C5-C62	61.3(50)
C5-H5a-C62	79.2(43)	C5-C61-C62	63.5(59)
C62-C61-C7	76.5(52)	C61-H61b-C62	83.8(66)
C62-H61b-C7	87.8(64)	N3-C7-C61	112.0(41)
N3-C7-C62	105.2(47)	C61-C7-C62	51.5(39)
C62-H7a-C7	95.5(39)	N3-C8-C9	127.2(33)
C8-C9-C10	121.2(28)	C8-C9-C49	120.7(30)
C10-C9-C49	118.1(32)	N4-C10-C9	111.3(29)
N4-C10-C11	121.8(26)	C9-C10-C11	123.1(31)
N4-C12-C13	111.3(24)	C12-C13-C14	115.0(23)
N1-C14-C13	105.4(22)	N5-C15-C3	115.9(24)
N5-C15-C16	119.9(24)	C3-C15-C16	123.7(26)
N5-C17-C18	111.7(19)	C17-C18-C19	113.8(24)
C18-C19-C20	104.6(24)	C18-C19-C22	115.5(24)
C20-C19-C22	110.9(20)	C19-C20-C21	112.3(20)
N5-C21-C20	115.7(24)	C19-C22-C23	113.4(20)
C19-C22-C26	112.6(25)	C23-C22-C26	106.6(25)
C22-C23-C24	113.5(23)	N6-C24-C23	113.5(27)
N6-C25-C26	111.4(22)	C22-C26-C25	116.8(28)
N6-C27-C28	112.4(22)	C27-C28-C29	117.3(31)
C27-C28-C36	117.5(28)	C29-C28-C36	125.2(30)
C28-C29-C30	123.5(29)	C28-C29-C31	115.1(31)
C30-C29-C31	121.3(26)	C29-C31-C32	113.5(30)
C29-C31-C33	118.9(27)	C32-C31-C33	127.1(29)
C31-C33-C34	123.6(28)	C31-C33-C38	115.1(26)

Table 14, continued

C34-C33-C38	121.0(30)	C33-C34-C35	119.7(26)
C33-C34-C36	116.7(27)	C35-C34-C36	123.6(24)
C28-C36-C34	117.8(25)	C28-C36-C37	125.0(26)
C34-C36-C37	116.7(23)	N7-C38-C33	116.1(26)
N7-C39-C40	118.9(28)	C39-C40-C41	107.7(29)
C40-C41-C42	110.0(29)	C40-C41-C44	108.4(28)
C40-C41-C44	115.5(25)	C41-C42-C43	112.2(25)
N7-C43-C42	112.2(28)	C41-C44-C45	116.6(27)
C41-C44-C48	111.4(27)	C45-C44-C48	101.4(28)
C44-C45-C46	113.0(29)	N8-C46-C45	113.7(34)
N8-C47-C48	119.4(26)	C44-C48-C47	111.8(24)
N8-C49-C9	122.6(38)	N8-C49-C50	117.9(34)
C9-C49-C50	118.8(35)		

saddle shape that is typical of this class of complex. The overall shape of the cavity is analogous to that of the vaulted complexes (see Figure 35), except that the distance from the NiN_4 plane to the center of the durene plane has increased from 8.35Å to 12.84Å. The additional height in the cavity is provided by the large bipiperidine risers and confirms the goal of the supervault synthesis; that is, to provide an even larger cavity for host-guest association. This ~4.5Å difference in height over the vaulted structure has had a crucial effect on the binding of guest molecules and is discussed in detail below.

The width of the cavity varies. The C3-C9 distance is 5.59Å and the C15-C49 distance is 7.39Å. The distance between the nitrogen atoms N5 and N8 on the bipiperidine rings (nearest the metal atom) is 7.50Å, while the nitrogen atoms N6 and N7, furthest from the metal atom, are 6.06Å. The largest portion of the cavity is the lower half and may explain why the included benzonitrile resides there. The bipiperidine rings are pivoted inward with a dihedral angle of 136.1° for the lower half and 142.5° for the upper half. An angle of 90° would result in the rings being strictly parallel to the plane of the macrocycle, while an angle of 180° would result in the rings being perpendicular to the plane of the macrocycle. It is evident from these results that the rings have pivoted so that the protons of the bipiperidine are residing toward the interior of the void.

In the vaulted anthracene structure (see Figure 36), an acetonitrile molecule was found to be internally associated within the confines of the void.⁶ The nitrogen atom of acetonitrile is within 2.97Å of the protons of the piperazine rings while its methyl group is directed away from the cavity.

It is clear from Figure 73 that a benzonitrile molecule has been accommodated in the cavity with the nitrogen end directed into the void. There is an additional benzonitrile molecule associated with solvent of crystallization. This interaction of an internal benzonitrile has been accommodated with no major conformational changes in the macrocycle or the bipiperazine rings (i.e., chair or boat). All that seems to have taken place is a pivoting of the bipiperazine rings in order to maximize van der Waals forces between the nitrogen and benzonitrile and the inner protons of the bipiperidine rings. In a polar solvent such as water, however, the orientation of the guest would be expected to be reversed. This conclusion is a natural consequence of the hydrophobic ring of benzonitrile seeking a hydrophobic environment while the polar nitrogen associates with the solvent water.

The packing diagram for the supervaulted complex, including two benzonitriles and four hexafluorophosphates, is shown in Figure 74. The bipiperidine rings have pivoted to accommodate the internal benzonitrile while the external benzonitrile is away from the pocket.

Inclusion Complex Formation with $[\text{Cu}\{\text{Me}_2(\text{bipiperidine})_2\}_3,6\text{-dur}[16]\text{cyclidene}]\text{Cl}_4$ and Organic Guests.

The results from the study of paramagnetic relaxation rates of guest protons using the Solomon-Bloembergen equation, have clearly shown that hydrophobic binding of the guest take place within the cavities of host vaulted complexes (Chapter 2). It has been proposed that major factors in determining the binding constants for inclusion complexes are the nature and match in size between the host and guest. For

Figure 74. Packing diagrams for
 $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_{23,6}\text{-dur[16]cyclidene}\}](\text{PF}_6)_4 \cdot 2 \text{ benzonitrile}.$

hydrophobic binding, an increase in the amount of hydrophobic surface area within the host that is available to the guest is expected to cause an increase in the binding constant. As stated earlier, guest inclusion of larger organic species, namely phenols, within the original vaulted complexes was not complete. The phenols studied were regiospecifically oriented; however, the majority of the ring was not contained within the cavity but lay across the entrance to the cavity,⁹ like a door, with the plane of the phenol parallel to the CuN_4 plane.

The increased size of the supervault cavity is ideally suited to accommodate a number of relatively large organic guests. The relaxation data and calculated distances for the guest 2,6-dimethylphenol and host III are shown in Table 15. By comparison with the results obtained for the same guest and the vaulted complex (Table 7), it is clear that supervaulted complex is far better able to accommodate the phenol. Instead of the phenol lying flat against the cavity entrance, as in the vaulted case, the ring of the guest lies deeply in the cavity and is oriented parallel to the bipiperidine walls, and its OH group is directed away from the cavity. These results are presented schematically in Figure 75. This illustration was generated using the computer program named ChemGraph.¹¹ The observed distances given in Table 15 are sixth power averaged distances for the equivalent protons present in the 2,6-dimethylphenol guest. From these observed average distances the distances of the guest shown in Figure 75 may be generated and are as follows: $\text{Cu-H}_{\text{meta}} = r_A = 4.23$, $r_B = 7.89$, and $r_{\text{Avg}} = 4.7$; $\text{Cu-H}_{\text{CH}_3}$: $r_A = 6.114$, $r_B = 9.50$, and $r_{\text{Avg}} = 6.7$. Figure 75a provides a space-filling representation of the structure, while 75b and 75c make it easy to distinguish between the host and guest by successively reducing

Table 15

Relaxation Times^a and Calculated Distances for the

Guest 2,6-Dimethylphenol with Host IV.

Guest = 2,6-Dimethylphenol ($P = 1.07 \times 10^{-3}$)^b

Protons	Me	Meta	Para
$(T_1)_0, ^c \text{sec}$	4.23 ± 0.02	9.72 ± 0.01	8.43 ± 0.03
$T_1, ^d \text{sec}$	2.78 ± 0.07	1.38 ± 0.18	1.89 ± 0.04
$r, \text{\AA}$	6.4 ± 0.2	4.8 ± 0.1	5.2 ± 0.1

a. Data at $\nu = 500$ MHz and T304K using a Bruker AM-500 spectrometer.

b. $[\text{Host}] = 5.25 \times 10^{-5} \text{M}$, $[\text{Guest}] = 4.91 \times 10^{-2} \text{M}$.

c. Longitudinal relaxation time in the absence of paramagnetic complex.

d. Longitudinal relaxation time in the presence of paramagnetic complex.

Figure 75. Inclusion complex between host III and 2,6-dimethylphenol guest.

each of them to stick representations. Figure 75e through 75g are similar side views of this inclusion complex. Some outstanding features may be seen from the illustrations. First, as in the case of the vaulted complexes, the host-guest complex possesses a fairly smooth outline that circumscribes the complex. This may be taken as modeling the solvent sheath. Second, the OH group clearly protrude into the solvent sheath where it is located.. Finally, the lower half of the bipiperidine ring has rotated to accommodate the guest, and the entire phenolic ring is accommodated by the host cavity.

Data has also been obtained for using substituted alcohols as the guest species in inclusion complexes with Host III. Using 3-methyl-phenethyl alcohol as the guest, there are five unique protons for which the T_1 may be measured in the presence and absence of the paramagnetic host. The results are presented in Table 16. The protons adjacent to OH group (α) are most distant from the Cu(II) center, while the β protons are the next furthest. Interestingly, it appears that the methyl group of the alcohol is closer to the metal center than is the meta proton. This details the orientational preference of the guest within the cavity of the host and gives an unusually complete view of the regiospecific nature of the inclusion phenomenon.

Another interesting phenomenon observed from 3-methyl-2-phenethyl alcohol may be seen from a stack plot of the guest itself (Figure 76). The protons in the region of 7.0 ppm display T_1 values that so differ enough to resolve a set of previously overlapping signals (Figure 77). In Figure 77, the top spectrum is that for a normal pulse width of four usec. The lower spectrum is that for a five second delay value from Figure 76, using the inversion recovery delay 180° , tau, 90° pulse

Table 16

Relaxation Times^a and Calculated Distances for the
Guest 3-Methyl-(2-phenyl)ethyl alcohol and Host IV

Protons	$\alpha(\text{CH}_2)$	$\beta(\text{CH}_2)$	Meta(H)	Methyl	ortho(H)
$(T_1)_0, \text{sec}$	2.63 ± 0.02	2.38 ± 0.01	6.88 ± 0.07	4.41 ± 0.02	7.27 ± 0.01
T_1, sec	2.22 ± 0.04	1.96 ± 0.05	2.94 ± 0.14	1.85 ± 0.18	4.28 ± 0.09
$r, \text{\AA}$	6.9 ± 0.1	6.6 ± 0.1	5.8 ± 0.2	5.3 ± 0.1	6.5 ± 0.1

a. $\nu = 500 \text{ MHz}$, $T = 304\text{K}$.

b. $[\text{Host}] = 5.25 \times 10^{-5}\text{M}$, $[\text{Guest}] = 5.50 \times 10^{-2}\text{M}$.

Figure 76. Stack plot of the inversion recovery sequence for
the guest 3-methylphenethyl alcohol.

Figure 77. ^1H spectra of the guest 3-methylphenethyl alcohol.
Top spectrum: normal acquisition with a four usec pulse width.
Bottom spectrum: Five second delay scan from an inversion
recovery pulse sequence.

sequence. The signal due to the two protons appears as a triplet during normal data acquisition; the signal is due to the para and ortho protons of the benzene ring. However, when the appropriate delay value is used, the triplet is resolved into the expected set of two doublets. Further, there is a remarkable difference in the respective T_1 values for the two protons, as can be seen by the recovery of the signal at higher field, while the lower field signal remains inverted.

Finally, the relaxation data for n-butanol as the guest with host III is given in Table 17. The distances calculated for this guest are remarkably similar to those obtained when the vaulted host complex was used (see Table 9). An identical regiospecific behavior is observed with the methyl group protruding into the cavity while the protons adjacent to the OH group indicate that the hydroxyl function is sticking out into the solvent. Since the distances for the vaulted and supervaulted hosts are essentially the same it is apparent that the guest has included the same conformation on the lower half of the bipiperidine ring system and that it is nested by this lower half of the riser.

CONCLUSIONS

As part of an ongoing effort to design and develop a new class of selective oxidation catalyst patterned after enzymes, the supervaulted complexes reported here represent a substantial refinement of inclusion complex formation studies in this laboratory. The experimentally justified technique of relaxation measurements for the determination of the precise nature of host-guest complexation has been successfully

Table 17
 Relaxation Times^a and Calculated Distances for
 the Guest n-butanol and Host IV.

Guest = n-butanol ($p = 9.60 \times 10^{-4}$)^b

Protons	α	β	γ	δ
$(T_1)_0, \text{sec}$	6.19 ± 0.03	5.47 ± 0.06	5.86 ± 0.01	6.11 ± 0.02
T_1, sec	5.44 ± 0.08	4.59 ± 0.15	4.76 ± 0.09	3.87 ± 0.06
$r, \text{\AA}$	8.3 ± 0.1	7.7 ± 0.1	7.5 ± 0.1	6.5 ± 0.1

a. $\nu = 500 \text{ MHz}$, $T = 304\text{K}$.

b. $[\text{Host}] = 5.25 \times 10^{-5}\text{M}$, $[\text{Guest}] = 5.49 \times 10^{-2}\text{M}$.

applied to these new complexes. Changing the dimensions of the transition metal host has dramatically changed its ability to bind larger substrates. Crystallographic data has confirmed the expanded cavity size and the nature of the supervaulted hosts. ^{13}C NMR has been used to characterize the complexes to infer the solution conformations of the host species. It is not surprising that the new supervaulted hosts bind organic guests in aqueous solution in much the same manner as their vaulted predecessors. Phenol guests are completely engulfed in the supervaulted complexes while they are only partially enclosed by the vaulted complexes.

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EXPERIMENTAL

Materials.

Solvents and reagents used in the synthesis of nickel(II) and copper(II) complexes were of reagent grade and used without further purification.

Synthesis of Nickel(II) Supervaulted Cyclidene Complexes.

[(2,12-Dimethyl-3,11-bis[1-(1-bipiperidine)ethylidene]-1,5,9,13-tetraazacyclohexadeca-1,4,9,12-tetraene- $\kappa^4\text{N}$) Nickel(II)] tetrahexafluorophosphate, $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2[16]\text{cyclidene}\}](\text{PF}_6)_4$. Five grams of $[\text{Ni}\{\text{Me}_2(\text{MeOEthi})_2[16]\text{cyclidene}\}](\text{PF}_6)_2$ was dissolved in 250 ml of acetonitrile and added dropwise over a period of four hours to a solution of 16.4 g of 4,4'-bipiperidine dihydrochloride and 18.9 ml of triethylamine in 700 ml of methanol. The reaction was allowed to proceed for an additional two hours with constant stirring. The volume of the solution was reduced to approximately 150 ml and excess 4,4'-bipiperidyl (confirmed via ^{13}C), was filtered, and discarded. The solution was reduced in volume to an oil, redissolved in 100 ml acetonitrile, and a solution of excess ammonium hexafluorophosphate in ethanol added. The mixture was allowed to stand overnight in a refrigerator and the solid that appeared was filtered and discarded. The solution was reduced in volume to approximately 10 mls and passed through a neutral alumina column with a 10% methanol/acetonitrile (u/v) solution as the eluent.

The solution was reduced in volume to an oil and dissolved in 50 ml of methanol. To the methanol solution of the product was added 50 ml of water and the voluminous yellow precipitate that immediately formed was collected and dried in vacuo. Yield: 2.1 gr, 50%. Anal. Calcd. for $\text{NiC}_{38}\text{H}_{62}\text{N}_8(\text{PF}_6)_4$: C, 35.39; H, 5.17; N, 8.69; Ni, 4.55. Found: C, 35.46; H, 5.31; N, 8.91; Ni, 4.67. When the isolation of this intermediate is not necessary, the following abbreviated procedure is appropriate.

Once the reaction described above is completed (~ six hours) the reaction mixture is reduced in volume to dryness, dissolved in a minimum of acetonitrile, and filtered. This dark red solution may then be used to proceed directly to the subsequent bridging reaction described below.

[(18,25-Dihydro-2,8,10,21,22,33,41,42-octamethyl-3,7,11,18,25,32,35,39-octaazaheptacyclo-[24.7.7.2^{20,23}.2^{11,14}.2^{15,18}.2^{25,28}.2^{29,32}]pentacont-2,7,9,20,22,33,34,39,41-nonaene- $\kappa^4\text{N}$)nickel(II)] tetrahexafluorophosphate, $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_{23,6}\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_4$. The oil obtained of $[\text{Ni}\{\text{Me}_2(\text{bipiperidineEthi})_2[16]\text{tetraeneN}_4\}](\text{PF}_6)_4$ was dissolved in 250 ml of acetonitrile and placed in a 250 ml pressure equalizing funnel along with 1.28 g of triethylamine. To a second 250 ml pressure equalizing funnel was placed 0.8 g (3.8 mmoles) of 3,6-bischloromethylidurene in 250 ml of acetonitrile. Both were dropped simultaneously over a period of three hours into a 1000 ml three-neck round-bottom flask containing 300 ml of boiling acetonitrile. The reaction was allowed to proceed at reflux for an additional three hours. The reaction mixture was reduced in volume, filtered, and passed down a neutral alumina column and the fastest moving yellowish band

collected. (It is frequently necessary to repeat the column step.) A solution of 2 g ammonium hexafluorophosphate was dissolved in 50 ml of ethanol and added slowly to the orange solution obtained from the alumina column. The solution was reduced to dryness and slurried in a 100 ml 50/50 (v/v) of methanol/water solution, filtered, and dried in vacuo. The yellow-orange solid was recrystallized from an acetonitrile/ethanol solution. **Anal.** Calcd. for $\text{NiC}_{50}\text{H}_{80}\text{N}_8(\text{PF}_6)_4 \cdot \text{CH}_3\text{CN}$: C, 42.39; H, 5.71; N, 7.61; Ni, 3.98. Found: C, 42.13; H, 6.00; N, 7.82; Ni, 3.65.

[(18,29-Dihydro-2,8,10,37-tetramethyl-3,7,11,18,29,36,39-43-octaazanonacyclo-[28.7.7.6²⁰,27.2¹¹,14.2¹⁵,18.2²⁹,32.2³³,36.0²¹,26.0⁴⁵,50]octapentaconta-2,7,9,20(50),21,23,25,27(45),37(1),38,43,46,48-tridecaene- $\kappa^4\text{N}$]nickel(II)] Tetrahexafluorophosphate, $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_{2,9,10\text{-anthra[16]cyclidene}}\}](\text{PF}_6)_4$. This reaction was performed by dissolving 0.5 g of 9,10-bischloromethylantracene in 200 ml of acetonitrile and heating the solution to reflux. The oil of $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2[16]\text{tetraeneN}_4\}](\text{PF}_6)_4$ was dissolved in 250 ml of acetonitrile along with 0.8 ml of triethylamine and dripped into the solution over a period of four hours. The reaction was allowed to proceed for an additional eight hours at reflux. The solution was reduced in volume to approximately 15 ml, filtered and passed down a neutral alumina column and the fastest moving band collected. This process was repeated and the product was recrystallized from acetonitrile/ethanol. **Anal.** Calcd. for $\text{NiC}_{54}\text{H}_{78}\text{N}_8(\text{PF}_6)_4 \cdot 2\text{CH}_3\text{CN}$: C, 42.70; H, 5.19; N, 7.38; Ni, 3.86. Found: C, 42.48; H, 5.01; N, 7.30; Ni, 3.66.

Synthesis of R³ = Phenyl, Supervaulted Cyclidene.

[(2,12-Dimethyl-3,11-bis[1-(1-bipiperidine)phylidene]-1,5,9,13-tetraazacyclohexadeca-1,4,9,12-tetraene- κ^4 N)nickel(II)] tetrahexafluorophosphate, [Ni{Ph₂(bipiperidine)₂[16]cyclidene}](PF₆)₄. A solution of 6.0 grams of [Ni{Me₂₃(MeOEthi)₂[16]cyclidene}](PF₆)₂ was dissolved in 250 ml of acetonitrile and added dropwise over a period of four hours to a solution of 17.2 g of 4,4'-bipiperidine dihydrochloride and 21 ml of triethylamine in 600 ml of methanol. The reaction mixture was reduced in volume to approximately 50 ml and filtered. No analytical data were acquired.

[(18,25-Dihydro-2,8,10,21,22,33,41,42-octamethyl-10,33-diphenyl-3,7,11,18,25,32,39-octaazaheptacyclo[24.7.7.2^{20,23}.2^{11,14}.2^{15,18}.2^{25,28}.2^{29,32}.]pentaconta-2,7,9,20,22,33,34,39,41-nonaene- κ^4 N)nickel(II)] tetrahexafluorophosphate, [Ni{Ph₂(bipiperidine)₂3,6-dur[16]cyclidene}](PF₆)₄. A solution of [Ni{Ph₂(bipiperidine)₂[16]cyclidene}](PF₆)₄ obtained as an oil in 200 ml of acetonitrile and 0.8 g of 3,6-bischloromethyldurene in 200 ml of acetonitrile were dropped simultaneously into a boiling reservoir of 200 ml of acetonitrile over a period of approximately three hours. The reaction mixture was allowed to react for an addition eight hours before cooling to room temperature. The value of the solution was reduced to about 15 ml, filtered, and passed through a neutral alumina column using acetonitrile as the eluent, and the fastest moving yellow band collected. A solution of excess NH₄PF₆ in ethanol was added to the solution and the rotary evaporated to a reddish orange oil. The oil was slurried in a 20% methanol/water (v/v) solution after twenty-four hours, filtered,

and dried in vacuo. The solid was recrystallized from an ethanol/acetonitrile solution. Anal. Calcd. for

Synthesis of Copper(II) Supervaulted Cyclidene Complexes.

[(18,25-Dihydro-2,8,10,21,22,33,41,42-octamethyl-3,7,11,18,25,32,35,39-octaazaheptacyclo-[24.7.7.2²⁰,23.2¹¹,14.2¹⁵,18.2²⁵.28.2²⁹,32]pentaconta-2,7,9,20,22,33,34,39,41-nonaene- κ^4 N)nickel(II)] tetrahexafluorophosphate, [Cu{Me₂(bipiperidine)₂3,6-dur[16]cyclidene}](PF₆)₄. Two grams of [Ni{Me₂(bipiperidine)₂3,6-dur[16]cyclidene}](PF₆)₄ was slurried in 100 ml of methanol and dry hydrogen bromide gas was vigorously bubbled through the solution for fifteen minutes upon which the solution went from a clear orange to green to blue. The reaction mixture was reduced in volume to an oil and dissolved in water and an excess of ammonium hexafluorophosphate added. The resulting voluminous whiteish precipitate was collected and dried in vacuo. 1.8 Grams (1.3 mmoles) of the free ligand was then slurried in 75 ml of hot methanol. 0.26 Grams (1.3 mmole) of copper acetate and 0.36 g (2.6 mmoles) of sodium acetate were slurried in 50 ml of hot methanol and added to the solution of free ligand. The resulting brick red precipitate was collected and recrystallized from acetonitrile/ethanol. The microcrystalline product was ground and dried in vacuo. Yield: 0.8 g (36%). Anal. Calcd. for CuC₅₀H₈₀N₈(PF₆)₄: C, 41.58; H, 5.63; N, 7.80; Cu, 4.18. Found: C, 41.37; H, 5.25; N, 7.79; Cu, 4.20.

[18,25-Dihydro-2,8,10,21,22,23,33,41,42-octamethyl-3,7,11,18,25,32,35,39-octaazaheptacyclo-[24.7.7.2²⁰,23.2¹¹,14.2¹⁵,18.2²⁵,28.2²⁹,32]pentaconta-2,7,9,20,22,33,34,39,41-nonaene- κ^4 N) copper(II)]tetrachloride,

$[\text{Cu}[\text{Me}_2(\text{bipiperidine})_2 3,6\text{-dur}[16]\text{cyclidene}]](\text{Cl})_4$. 1.0 Gram (0.7 mmoles) of $[\text{Cu}\{\text{Me}_2(\text{bipiperidine})_2 3,6\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_4$ and 0.97 g (3.5 mmoles) of tetrabutylammonium chloride were rigorously dried at 10^{-3} torr and taken into an inert atmosphere glove box. The copper complex was dissolved in 20 ml of previously dried acetone and the tetrabutylammonium chloride dissolved in 30 ml of dried acetone was dripped slowly into the copper(II) solution. The resulting voluminous brick red precipitate was collected and dried in vacuo. Yield: 0.31 g (38%). Anal. Calcd. for $\text{CuC}_{50}\text{H}_{80}\text{N}_8(\text{Cl})_3\text{PF}_6 \cdot 2\text{CH}_3\text{CCH}_3 \cdot 2\text{H}_2\text{O}$: C, 53.46; H, 7.71; N, 8.91; Cu, 5.05. Found: C, 53.51; H, 7.92; N, 8.71; Cu, 4.97.

Physical Measurements.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The proton NMR spectra of the guest species, in the presence and absence of the paramagnetic Cu(II) host, were acquired at three different frequencies using Bruker WP200, Bruker WM300, Bruker AM500, and Nicolet NT500 MHz NMR spectrometers. Samples were allowed to equilibrate for thirty minutes at 304 K using a variable temperature control unit. Five millimeter o.d. Wilmad Royal Imperial sample tubes, 528-PP, seven inches in length, were used to contain the host-guest sample solutions. Aldrich Gold Label 99.96% hydrogen-2 deuterium oxide, low in paramagnetic impurities, was used as the solvent in all experiments. A 10 μl Hamilton syringe was used to prepare the host-guest solutions. The organic guest molecules used during inclusion complexation experiments were of spectrophotometric grade, Gold Label quality, purchased from Aldrich Chemical Company, and were used without further purification.

Electrochemical data were obtained using a Princeton Applied Research Corporation Potentiostat/Galvanostat Model 173 equipped with a Model 175 linear programmer and a Model 179 digital coulometer. Current vs. potential curves were measured on a Houston Instruments Model 200 XY recorder. the working electrode for voltammetric curves was a platinum disc with potentials measured vs. an Ag^0/Ag^+ (0.1M) reference. Peak potentials were measured from cyclic voltammograms at 100 mv s^{-1} scan rate. Half-wave potentials were taken as the average of the anodic and cathodic peak potentials.

Experimental Precautions. (1) All glassware used in the study of the host-guest phenomena were soaked in 0.5M EDTA for twenty-four hours prior to use. (2) The deuterium oxide was low in paramagnetic impurities and degassed by freeze-pump thaw techniques on a vacuum line at 10^{-5} torr. Guest solutions were also degassed in this manner. (3) All samples for the study of the intramolecular association phenomena were prepared in an inert atmosphere glove box and sealed.

Procedure for Host-Guest Studies. (1) A stock solution of the host compound was prepared by accurately weighing an amount of the chloride salt of the host species and dissolving the complex in a 5 ml volumetric flask containing deuterium oxide (typically 1.5×10^{-2} M). (2) a 10 μl syringe was used to deliver an aliquot of the stock host solution into a 2 ml volumetric flasks and placed into the two 5 mm NMR sample tubes. (4) Measurement of $T_{1\rho}$ was achieved by two sets of standard inversion recovery experiments obtained at each of three different frequencies. At least 12 different values of the variable delay parameter were used to determine accurately the relaxation times. The program used to

calculate T_1 values was from the Bruker library of software programs, (Invrec.Au), and the errors indicated in the table are standard deviations of the fit. The equation to which the points are fit is $Y = A_3 - A_2 \exp(-T/T_1)$, where:

A_3 = the normalized intensity of the largest point.

A_2 = the nucleus flip angle in units of $\pi/2$.

T = tau value.

The convergence limit was set to 1.0×10^{-5} , which provided a very accurate fit to the data.

Collection and Data Reduction of the Structure $[\text{Ni}\{\text{Me}_2(\text{bipiperidine})_2\text{-3,6-dur[16]cyclidene}\}](\text{PF}_6)_4$.¹⁶

$[\text{NiC}_{50}\text{H}_{104}\text{N}_8\text{Ni}](\text{PF}_6)_4 \cdot 2\text{C}_6\text{H}_5\text{CN}$ monoclinic, space group $P2_1/c$; $a = 14.172(4)$, $b = 16.235(5)$, $c = 34.705(10)\text{\AA}$, $\beta = 109.76(2)^\circ$, $V = 7515(4)\text{\AA}^3$, $Z = 4$, Mo - K_α radiation, $\lambda = 0.71069\text{\AA}$, $T = 299\text{K}^\circ$, $\mu(\text{Mo}-K_\alpha) = 4.45 \text{ cm}^{-1}$, $F(000) = 3480$, $R = 0.12$ for 1775 unique observed ($I/\sigma(I) > 2.5$) reflections.

Crystal character: orange-red plates from benzonitrile. Data was collected with a Syntex $P2_1$ four circle diffractometer. Maximum 2θ 40° , with a scan range from $-0.9 + 1.0(2\theta)$ around the $K_{\alpha 1} - K_{\alpha 2}$ angles, scan speed $2 - 29^\circ \text{ min}^{-1}$, depending on the intensity of a 2s pre-scan; backgrounds were measured at each end of the scan for 0.25 of the scan time. hkl ranges: 0-13; 0-15; -33-+33.

Three standard reflections were monitored every 200 reflections, and showed no changes during data collection. Unit cell dimensions and standard deviations were obtained by least-squares fit to 15 reflections

($15 < 2\theta < 20^\circ$). To give 7052 unique reflections ($R_{\text{int}} = 0.05$); 1775 considered observed ($I/\sigma(I) \geq 2.5$) and used in refinement; corrected for Lorentz, and polarization but not absorption effects. Crystal dimensions 0.07 x 0.2 x 0.4 mm. Systematic absences $h0l, l \neq 2n; ok0, k \neq 2n$ indicate space group $P2_1/c$.

Solution and Refinement of the Crystal Structure¹⁶

The Ni atom position was readily located from a Patterson synthesis, but initial Fourier syntheses showed no chemically recognizable structures. Additional atoms were found by the SHELXTL FIND procedure, involving recycling the peaks on sequential E-maps. After 10 cycles, 55 atomic positions had been found, which were virtually all correct. Remaining light atoms were then found on successive Fourier syntheses, including two molecules of benzonitrile (given ideal geometry in final refinement). PF_6 groups were held as rigid octahedra (P-F 1.536), with anisotropic temperature factors. These were used otherwise only for Ni. Hydrogen atoms were given fixed isotropic temperature factors, $U = 0.07 \text{ \AA}^2$. Those defined by the molecular geometry inserted at calculated positions and not refined; H-atoms of methyl groups omitted. One atom (C(6)) disordered, with occupancy 0.65(3) and 0.35(3); H-atoms attached to C(5) to C(7) included only for the higher occupancy position.

Final refinement on F by cascaded least squares methods. Largest positive and negative peaks on a final difference Fourier synthesis of height $\pm 0.5 \text{ e.l. \AA}^3$. The relatively high final R-value is clearly due to the poor diffracting power (responsible also for the low ratio of

observed to total reflections despite the low $2\theta_{\max}$), and to the poorly ordered PF_6^- groups.

A weighting scheme of the form $W = 1/\sigma^2(F) + gF^2$ with $g = 0.0011$ was used and shown to be satisfactory by a weight analysis. Final $R = 0.112$ $R_w = 0.12$. Maximum shift/error in final cycle 0.2. Computing with SHELXTL (Sheldrick, 1983) on a Data General DB30, apart from data reduction on a Burroughs B6800. Scattering factors in the analytical form and anomalous dispersion factors taken from International Tables (1974). Final atomic coordinates are given in Table 12, and bond lengths and angles in Tables 13 and 14.

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CHAPTER FOUR

A HIGHLY NOVEL INCLUSION COMPLEX CONTAINING THE DIOXYGEN MOLECULE
AND AN ORGANIC GUEST MOLECULE COHABITING WITHIN A
VAULTED COBALT(II) CYCLIDENE HOST

INTRODUCTION

Given the enormous strides made recently in elaborating its active site chemistry, the static relationships and dynamic consequences of the ternary complex of cytochrome P-450 should provide the basis for understanding the elegant oxidation chemistry orchestrated by that enzyme. We present here the first credible model for this ternary complex. In the natural system, the binding of dioxygen to the heme iron atom is possible only after a substrate molecule is in place, a design feature that prohibits activation of the enzyme in the absence of substrate.¹ The extreme reactivity of the activated site toward organic substances indicates that selectivity is achieved largely through the details of the substrate binding process. The crystal structure of the enzyme has confirmed this.² A hydrophobic region surrounds the coordination site at the heme group where the activation of dioxygen takes place. This enables the complex to bind organic substrates hydrophobically while simultaneously providing a site for the activation of dioxygen.

The elucidation of the interrelationships and possible synergisms that operate within such a ternary complex requires good models and the

family of cyclidene complexes developed in these laboratories have now been applied to this purpose. The cyclidene ligand is especially favorable to the formation of dioxygen complexes by both iron(II)³ and cobalt(II)⁴ while the ease of synthesis and diversity of superstructures that can be appended to the cyclidene facilitates the study of inclusion complex formation with potential organic substrates.^{5,6,7} Simultaneous substrate binding and dioxygen binding in a single synthetic complex are demonstrated for the first time here (Figure 78). Further, the spin density on the dioxygen species,^{8,9} that is bound to cobalt(II), is exploited to disclose the regiospecific binding of the substrate. The ultimate goal of these studies is the development of a new class of selective oxidation catalysts with the full capabilities of the family of cytochromes P-450.

The structure of the vaulted cyclidene complexes are represented in projection and in perspective in structures I and II (Figure 79). Previous work with the copper(II) derivatives of the macrobicyclic cyclidene complexes has shown them to be capable of binding organic substrates regiospecifically.^{6,7} Simultaneously, a coordination site remains vacant on the metal atom and, theoretically, it is available for the coordination of dioxygen. Substrate binding studies have been carried out in aqueous solutions using paramagnetic relaxation techniques and the formation of these inclusion complexes has been attributed to hydrophobic forces. Much attention has focused on experimental justification of the simplified dipolar form^{7,10} of the

Figure 78. Schematic representation of the ternary complex;
vaulted anthracene; aliphatic alcohol; dioxygen.

A

B

Figure 79. (a) and (b): Flat and three-dimensional representation of the vaulted cyclidene complex.

Solomon-Bloembergen equation¹¹ (below) for the reduction of T_1 data to

$$r(\text{\AA}) = C \rho T_{1p}^{-1/6} \frac{3\tau_c}{1+(3.94 \times 10^{13} \nu_1^2 \tau_c^2)} + \frac{7\tau_c}{1+(1.71 \times 10^{19} \nu_1^2 \tau_c^2)} \quad 1/6$$

distance parameters. For the present studies, it was necessary to synthesize the cobalt(II) complex of the vaulted ligand¹² and demonstrate its efficacy in paramagnetic relaxation studies. The stability of the dioxygen adduct of the vaulted cyclidene ligand was then assessed and conditions defined wherein relaxation studies could be made using the paramagnetism of the dioxygen adduct itself. The positioning of a bound substrate was then determined in the presence of bound dioxygen; i.e., the ternary complex was defined in a regiospecific manner.

Our interpretations concerning the ternary complex are justified by the following observations: (1) T_1 data for both cobalt(II) and for the cobalt(III)-- O_2^- adduct give reproducible distances over some variation in conditions of measurement. (2) The cobalt(III)-- O_2^- adduct binds dioxygen reversibly and it remains stable in solution long enough to obtain reliable T_1 data.

ASSESSMENT OF THE TERNARY COMPLEX

[{COBALT(II)CYCLIDENE}-N-BUTANOL-DIOXYGEN]

Results from the determination of relaxation rates for the protons of the guest n-butanol, using the paramagnetism of the dioxygen adduct are given in Table 18. Data were taken at two spectrometer frequencies, 300 and 500 MHz. These data indicate that the distance from the mean

Table 18

Relaxation Data and Calculated Distances for the Host
 Co(III)O_2^- Vaulted Anthracene Cyclidene and the Guest
 n-butanol at 274K

Host = Co(III)O_2^-

R^1 = Anthracene $\text{HO}-\overset{\alpha}{\text{CH}}_2-\overset{\beta}{\text{CH}}_2-\overset{\gamma}{\text{CH}}_2-\overset{\delta}{\text{CH}}_3$

Guest = n-butanol ($p = 1.22 \times 10^{-3}$)

Protons	α	β	γ	δ
$\nu = 300$				
$(T_1)_0, \text{sec}$	1.55 ± 0.02	1.49 ± 0.04	1.72 ± 0.03	1.98 ± 0.07
T_1, sec	1.40 ± 0.08	1.31 ± 0.02	1.33 ± 0.09	1.09 ± 0.04
$r, \text{\AA}$	7.3 ± 0.2	6.8 ± 0.1	6.3 ± 0.2	5.4 ± 0.1

$\nu = 500$

$(T_1)_0, \text{sec}$	1.74 ± 0.06	1.67 ± 0.03	1.86 ± 0.09	2.14 ± 0.1
T_1, sec	1.57 ± 0.05	1.41 ± 0.01	1.49 ± 0.1	1.19 ± 0.05
$r, \text{\AA}$	7.3 ± 0.2	6.7 ± 0.1	6.4 ± 0.2	5.5 ± 0.1

spin density on the dioxygen to the methyl group of the n-butanol is 5.5Å while that to the protons α to the hydroxyl group is 7.3Å. Thus we immediately observe the same class of regioselectivity that was found in the absence of dioxygen for both copper(II) and cobalt(II) (see below) hosts. Clearly, the hydrophobic portion of the n-butanol molecule penetrates into the vault of the host and the hydrophilic functional group extends out into the solvent.

The distance parameters measured with the cobalt(II) host, in the absence of dioxygen (Table 19) are approximately 1Å greater than those measured for the dioxygen adduct. Since the bound dioxygen moiety extends up into the cavity (distant oxygen atom, about 2.9Å),¹³ this difference is in the expected direction. From molecular model studies (ChemGraph)¹⁴ on the structures of the inclusion complexes, using data obtained on the copper(II) vaulted cyclidene hosts, we have concluded that the n-butanol is positioned at the top of the cavity and is about as far from the metal as it can be while remaining within the host. If the guest is assumed to remain in the same location, the center of action of the spin density on the dioxygen adduct is placed uncomfortably close to the cobalt atom. Consequently, the substrate is pushed slightly away from its previous average position when it must share the cavity with a dioxygen molecule.

The measurement of these relationships involves a number of special considerations. Because the dioxygen adduct autoxidizes at room temperature, the measurements were made at 274K. At this temperature the viscosity of water is substantially increased and this affects the relaxation times. This has been studied using the cobalt(II) complex.

Table 19

Relaxation Data^a and Calculated Distances for the
Host [Co{Me₂(piperazine)₂9,10-anthra[16]cyclidene}](Cl)₂
and the Guest n-butanol

Host = Vaulted Complex^b

R¹ = Anthracene

Guest = n-butanol^c

Protons	α	β	γ	δ
T = 304K				
(T ₁) ₀ ,sec	6.18±0.1	5.65±0.13	6.19±0.05	6.40±0.03
T ₁ ,sec	5.30±0.05	4.59±0.10	4.41±0.09	3.50±0.01
r, Å	8.4±0.2	7.8±0.2	7.2±0.1	6.5±0.1

T = 274K

(T ₁) ₀ ,sec	2.11±0.02	1.90±0.05	2.20±0.4	2.37±0.1
T ₁ ,sec	1.99±0.03	1.75±0.03	1.96±0.1	1.71±0.01
r, Å	8.3±0.2	7.7±0.2	7.4±0.1	6.3±0.1

a. ν = 500 MHz.

b. [Host] = 6.69 x 10⁻⁵M.

c. [Guest] = 5.48 x 10⁻²M.

Also, it must be kept in mind that the delocalization of the spin density over the dioxygen moiety increases the uncertainty in the calculated distances.^{10,15} However, the reproducibility of the experiment is evident from the results obtained at two spectrometer frequencies.

To verify that the cobalt(II) complex of the vaulted cyclidene ligand (deoxygenated form) is capable of effectively relaxing guest protons, data was obtained with this complex and the guest n-butanol. At 304K, the distances calculated are within experimental error for that obtained with the corresponding copper(II) complex.^{6,7}

Figure 80 is the stack plot of the guest n-butanol in the presence of the paramagnetic cobalt(II) vaulted anthracene complex. When the variable delay value is three seconds, the differences in measured T_1 's for the various protons of the guest are clearly evident. Figure 81 is a comparison of the three second delay values for the standard (T_1) (from a stack plot not shown) and for the same delay value lifted from the stack plot in Figure 80. The triplet in the spectrum at 3.54 ppm is assigned to the methylene protons adjacent to the OH group of n-butanol. In the presence of the cobalt(II) host, these protons have not inverted, although, as expected, their intensity has decreased in comparison to the standard (T_1)₀ spectrum. In contrast, the triplet assigned to the methyl group of n-butanol at 0.88 ppm has inverted, indicating a significantly greater reduction in the T_1 value. The methylene protons assigned to β and γ positions are in intermediate states. The relaxation phenomena is distance dependent, showing that the methyl protons are indeed closer to the cobalt(II) center

Figure 80. Stack plot of the guest n-butanol and host
Co(II) vaulted anthracene.

Figure 81. Comparison of three second delay values of the standard
 $(T_1)_0$ and T_1 of the host-guest complex.

than are the methylene protons adjacent to the OH group. This regio-specificity of guest binding is consistent with the copper(II) results for the same guest.^{6,7} In addition, when the temperature of the system is reduced to 274K (Table 18), the distances calculated are the same, within experimental error, as those obtained at 304K. The considerable reduction in T_1 values for both the standard $(T_1)_0$ and host-guest complex (T_1) are due in part to solvent broadening at reduced temperature.

Attention is now drawn to the reversibility and stability of the dioxygen adduct of cobalt-vaulted cyclidene complex. Figure 82 shows the visible spectral changes observed when the $[\text{Co}\{\text{Me}_2(\text{piperazine})_{2,9,10}\text{-anthracene[16]cyclidene}\}(\text{Cl})_2]$ is exposed to dioxygen in water. Trace 1 is the cobalt(II) species removed from the dry box and run at 1°C. Trace 2 corresponds to the complex after bubbling 760 torr of dioxygen through the solution for sixty seconds. Finally, trace 3 is the complex after bubbling nitrogen through the solution for thirty-three minutes. As shown, the removal of dioxygen from the fully oxygenated solution results in an almost complete return of spectrum 1, the non-oxygenated cobalt(II) spectrum. Thus, the visible spectra show qualitatively that the dioxygen binding characteristics of the cobalt(II) vaulted anthracene compound is reversible, and that the complex is stable in water at 1°C for at least thirty-three minutes.

Figure 83 is the EPR spectrum of the cobalt(II) chloride complex with $\text{R}^1 = \text{anthracene}$ in water. Spectrum A represents the deoxygenated form of the cobalt(II) complex. The spectrum was obtained at -40°C with no axial base present. This accounts for the lack of hyperfine splitting normally seen for this complex in acetonitrile.¹² The complex

Figure 82. Visible spectral changes resulting from dioxygen
[Co{Me₂(piperazine)₂9,10-anthracene[16]cyclidene}](Cl)₂ adduct formation.

Figure 83. EPR spectral changes resulting from dioxygen
[Co{Me₂(piperazine)₂9,10-anthracene[16]cyclidene}](Cl)₂
adduct formation at -40°C.

was warmed to 1°C and then exposed to 100 torr of dioxygen for sixty seconds and spectrum B was obtained with a g value of 2.04. Finally, in spectrum C, the sample was allowed to warm to 0°C and held there for thirty minutes and rerun at -40°C. The result shows that the dioxygen adduct of the cobalt vaulted anthracene complex is, from a qualitative standpoint, still present.

CONCLUSIONS

Spin lattice relaxation rates of guest protons in the presence of a cobalt(II)--O₂⁻--cyclidene complex have shown that regiospecific binding of a substrate takes place while the metal center is simultaneously coordinated to a dioxygen molecule. Results obtained for the deoxygenated forms of the Co(II) complex are the same, within experimental error, as those with the analogous copper(II) complexes of these ligands, as previously studied.⁷ EPR and visible spectral measurements indicate that a stable, reversible dioxygen adduct of cobalt(II) is present during the distance determinations using T₁ measurements. Results at two spectrometer frequencies demonstrate the reproducibility of the results. This system represents a credible model of the ternary complexes of cytochrome P-450.

EXPERIMENTAL

Reagents and Materials

All reagents used in the synthesis and subsequent study of cobalt(II) cyclidene complexes were of reagent grade and used without further purification unless otherwise noted.

Synthesis of the Cobalt(II) Vaulted Cyclidene Complexes

[(2,21,23,29-Tetra-3,6,17,20,24,28,31,35-octaazaheptacyclo-[20.7.-7.6⁸,15.23,6.217,20.09,14.037,42]hexatetraconta-1,8(37),9,11,13,15(42),-21,23,28,30,35,38,40-tridecaene- κ^4 N)cobalt(II)]chloride[Co(II){Me₂(CH₂-piperazine)₂,6-dur[16]cyclidene}](CH₂)₂. This complex was prepared by previous methods described by Takeuchi.¹²

Physical Measurements

Electronic spectra were obtained using a Varian 2300 spectrophotometer. EPR spectra were obtained using a Varian E-112 spectrometer in the x band of 9.3 GHz with g values quoted relative to external DPPH (g = 2.00036). Samples in water were run at -40°C in quartz tubes. The proton NMR spectra of the guest species, in the presence and absence of the paramagnetic Co(II) and Co(III)O₂⁻ hosts, were acquired at two different frequencies using Bruker WM300 and Bruker AM500 spectrometers. Samples were allowed to equilibrate at 274 and

304K using a variable temperature control unit. Five millimeter o.d. Wilmad Royal Imperial sample tubes, 528-PP, seven inches in length, were used to contain the guest and host-guest sample solutions. Aldrich Gold Label 99.96% hydrogen-2 deuterium oxide, low in paramagnetic impurities, was used as the solvent in all experiments. A 10 μ l Hamilton syringe was used to prepare the host-guest solutions. The organic guest molecules used during inclusion complexation experiments were of spectrophotometric grade, Gold Label quality, purchased from Aldrich Chemical Company, and used without further purification.

Experimental Precautions. (1) All glassware used in the study of the host-guest phenomena were soaked in 0.5M EDTA for twenty-four hours prior to use. (2) The deuterium oxide was low in paramagnetic impurities and degassed by freeze-pump thaw techniques on a vacuum line at 10^{-5} torr. Guest solutions were also degassed in this manner. (3) All samples for the study of the intramolecular association phenomena were prepared in an inert atmosphere glove box and sealed.

Procedure for Host-Guest Studies. (1) A stock solution of the host compound was prepared by accurately weighing an amount of the chloride salt of the host species and dissolving the complex in a 2 ml volumetric flask containing deuterium oxide (typically 1.5×10^{-2} M). (2) A 10 μ l syringe was used to deliver an aliquot of the stock host solution into a 2 ml volumetric flask containing D₂O and accurately measured amount of the guest solution. The referenced solution was prepared in an identical manner, excluding the paramagnetic host complex. (3) Aliquots were then taken from each of the two 2 ml volumetric flasks and placed into the two 5 mm NMR sample tubes.

(4) Each sample was removed from the drybox and placed in an ice bath at 0°C and allowed to cool for fifteen minutes. One hundred torr of O₂ was then bubbled through the solution for one minute while still at 0°C.

(5) Measurement of T_{1p} was achieved by two sets of standard inversion recovery experiments obtained at each of three different frequencies. At least twelve different values of the variable delay parameter were used to determine accurately the relaxation times. The D₁ relay value = 5T₁ was = 30 sec. The program used to calculate the T₁ values was from the Bruker library of software programs and the error indicated in the table are standard deviations of the fit. The equation to which the points are fit is $Y = A_3 - A_2 \exp(-T/T_1)$, where:

A₃ = the normalized intensity of the largest point.

A₂ = the nucleus flip angle in units of pi/2.

T = tau value.

The convergence limit was set to 1.0×10^{-5} , which provided a very accurate fit to the data.

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CHAPTER FIVE

2D-NMR OF SEVERAL TRANSITION METAL CYCLIDENE COMPLEXES:

ELUCIDATION OF STRUCTURAL RELATIONSHIPS AND THE

ASSIGNMENT OF ^1H NMR SPECTRA

INTRODUCTION

The broad family of transition metal complexes with the cyclidene ligands has provided the means by which a variety of phenomena may be studied simultaneously. These include, among others, template directed synthesis reactions,¹ dioxygen binding and activation,^{2,3} and host-guest chemistry.⁴⁻⁷ An enormous inventory of these complexes presently exists and many have been fully characterized by a variety of techniques including x-ray crystallography, infrared, UV visible, ESR, and ^{13}C and ^1H NMR spectroscopy.^{8,9} Due to the number of protons in these complexes and the concomitant ambiguities in their assignments, ^1H NMR has been of limited use in their characterization. Total assignment of the proton spectra of the cyclidene complexes would make available a highly sensitive probe capable of furnishing a great deal of structural information. NMR spectrometers operating below 300 MHz are incapable of resolving the myriad of overlaps typically seen in the proton NMR of these complexes. Even when the overlap of signals can be resolved, accurate assignments are extremely difficult. Two-dimensional NMR techniques provide the means to eliminate signal overlap and yield

additional information that is critical to solving this challenging problem.^{10,12} In this chapter, the complete assignment of the proton NMR spectra of five cyclidene complexes (Figure 84) is described using the NMR techniques called DEPT (distortionless enhancement by polarization transfer) and 2D-NMR techniques which include ^1H - ^{13}C shift correlation, COSY (correlated shift) and NOESY (nuclear Overhauser enhanced correlated shift) experiments.* These assignments have resulted in conclusions regarding intermolecular spatial relationships of the cyclidene complexes and will be treated in detail.

RESULTS AND DISCUSSION

The absolute assignments of resonances in the proton NMR spectra of the cyclidene complexes whose structures are shown in Figure 84, has awaited the arrival of field strengths that are high enough and techniques that are powerful enough to facilitate adequate resolution and assignment of signals. The complexity of the problem may be apparent if one realizes that the cyclidene complexes reported here have as many as forty-five protons. In addition to the identification of detailed structural considerations, such as lid-on and lid-off isomers,^{1,11} information concerning solution behavior, notably inclusion complex formation, may be accessible from proton spectra. This would be strictly analogous to the previously reported use of chemical shift changes in ^{13}C NMR absorptions as a probe for investigating host-guest association.⁵ However, since ^1H NMR is inherently more sensitive than ^{13}C , these spectra may be more useful in delineating the subtle changes that occur during inclusion complex formation.

Figure 84. Flat projections of five transition metal cyclidene complexes.

The first step in assigning the signals in the proton spectra has been to assign the resonances in the far less complicated ^{13}C spectra. The cyclidene complexes, almost exclusively, possess mirror symmetry, so the number of carbon resonances is relatively low. Coupled ^1H - ^{13}C NMR and ^{13}C enrichment studies have been used in this regard and the assignment of the majority of the ^{13}C resonances has been accomplished previously.^{2,4} An additional technique that helps rapid general identification of ^{13}C signals is distortionless enhancement by polarization transfer (DEPT).¹² The phase properties of the magnetization of quaternary carbon atoms and of CH, CH_2 , and CH_3 groups may be displayed by the proper choice of pulse angles, θ .¹⁰ The results from ^{13}C DEPT experiments on complexes I, II, and V are shown in Figures 85, 86, and 87, respectively. The broad band (BB) spectrum is shown for each of the three complexes and successive plots (from lower to upper) reveal the methine (CH), methylene (CH_2), and methyl (CH_3) carbons, respectively. The quaternary carbon atoms may be identified by the remaining peaks present in the broad band spectra. The methylene carbons adjacent to nitrogen atoms in the complex are commonly found in the region from forty to sixty ppm. The methylenes not adjacent to nitrogen are located from twenty-eight to thirty-five ppm and methyl groups are consistently seen to be in the range of fifteen to twenty-two ppm unless they are adjacent to an electronegative atom, as evident for the methyl group on the nitrogen in complexes I and II which resides at 40 ppm. As expected, quaternary carbon resonances reside at much lower fields. Once assignment of the ^{13}C spectra is completed, 2D- ^1H - ^{13}C correlated

Figure 85. Broadband proton-decoupled and DEPT carbon-13 NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{NME})_2(\text{CH}_2)_6[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 86. Broadband proton-decoupled and DEPT carbon-13 NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{NMe})_2\text{m-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 87. Broadband proton-decoupled and DEPT carbon-13 NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{CH}_2\text{piperazine})_{2,3,6}\text{-dur[16]cyclidene}\}](\text{PF}_6)_2$.

shift experiments can be used, in a single measurement, to assign the proton signals to the carbon atoms to which they are bonded.^{10,13}

When the Larmor frequencies of the two different nuclei can be related through scalar coupling, this hetero scalar correlated 2D-NMR experiment is ideal for making assignments.¹² The results of applying this method to complexes I and V are shown in Figures 88 and 89, respectively. The abscissa in the correlation diagram corresponds to the $\delta(^{13}\text{C})$ values listed in ppm, while the ordinate shows the $\delta(^1\text{H})$ values also in ppm. Due to the correlative nature of the technique, assignments made previously in the ^{13}C spectrum may be translated directly into assignments of proton signals. In Figures 88 and 89 are the expanded regions for the $\delta(^{13}\text{C})$ values from 10 to 65 ppm for complexes I and V. An additional resonance not shown is at 160 ppm (for both complexes I and V) and corresponds to the lone methine carbon, C. The proton on C has been assigned to the signal at 7.45 ppm in the ^1H NMR spectrum of complex I and 7.32 ppm in the ^1H NMR spectrum of complex V using this technique. In Figure 88 the carbon atom signal at 57 ppm, which corresponds to the methylene carbon K (Figure 85), is related to possess proton resonances at approximately 3.3 and 3.7 ppm. Examining the high resolution ^1H NMR spectrum of complex I (Figure 93) reveals signals at these chemical shifts. Each of the remaining signals in the ^{13}C spectrum may also be correlated with their respective proton resonances simply by drawing a perpendicular line to the ordinate and reading the ^1H chemical shift. However, due to the limited data collection in the ^1H - ^{13}C correlated shift experiment (e.g., 2000 data points), an overlap of methylene protons signals, unambiguous assignment

Figure 88. 2D- ^{13}C ^1H correlation diagram of
 $[\text{Ni}\{\text{Me}_2(\text{NMe})_2(\text{CH}_2)_6[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 89. 2D-¹³C ¹H correlation diagram of
 $[\text{Ni}\{\text{Me}_2(\text{CH}_2\text{piperazine})_2\}_{3,6}\text{-dur}[15]\text{cyclidene}\}]\text{IPF}_6)_2$.

cannot be made of every proton in the spectra. At this juncture, the protons on C, K, I, J, N, O, and P of complex I may be assigned with confidence (Table 20). Further, the protons on C, K, N, and O of complex II have been assigned (Table 20). The remaining methylene carbon signals at ~30 ppm and from 48 to 57 ppm are not easily distinguished since their carbon resonances were not previously known and due to the large degree of overlap in these regions. When these situations prevail, 2D-NOESY and COSY experiments may be used to unambiguously assign the remaining protons and indistinguishable carbon atoms in the ^{13}C NMR spectra.

The NOESY contour correlation plot for complex II is given in Figure 90. The peaks along the diagonal may be viewed as looking down on the proton NMR spectrum (see Figures 96 and 97). This spectrum is also shown in the normal manner along the abscissa for clarity. The off-diagonal elements in the NOESY experiment represent correlations due to the through space coupling between proton atoms and are limited to detectable distances of ~4Å. Due to the 2D nature of the experiment, the off-diagonal elements occur as mirrored pairs on either side of the diagonal proton spectrum. Proton atoms that are through space coupled to each other may be observed by selecting a peak on the diagonal and drawing a line which is parallel to the base line to an off-diagonal element and then proceeding 90° back to the diagonal (dashed lines in Figure 90). Drawing an additional perpendicular line to the ordinate or abscissa of the contour plot allows the corresponding chemical shift in ppm of the through space coupled atoms to be read.

Figure 90. Homoscalar correlated 2D ^1H NMR spectrum of
 $[\text{Ni}\{\text{Me}_2(\text{NMe})_{2m}\text{-xylylene[16]cyclidene}\}](\text{PF}_6)_2$.

Result of a NOSEY experiment.

When considering through space interactions in the cyclidene complexes it is important to be aware of the overall saddle shape of the macrocycle that has been revealed by x-ray crystallographic data and is shown below.

From the $2D-^1H-^{13}C$ correlation experiments discussed previously, the signal at 7.21 ppm in the proton spectra of complex II has been assigned to the methine proton, C (Figure 92, Table 20). It may be seen from the off-diagonal elements in Figure 90, that through space coupling is occurring between this proton and protons located at 2.88 and 2.44 ppm. By constructing a molecular model of the complex, it is clear that the nearest neighbors, through space, to proton C are located on carbons Y and O. The protons on the methyl group O were previously assigned at approximately 2.4 ppm for complex I, and therefore the proton at 2.88 ppm must correspond to the equatorial proton on Y. However, there is no detectable correlation observed for the axial proton of Y with C. This result is reasonable on the basis of x-ray crystallographic results and

and molecular models which show that proton C is closer to Y_a than Y_e (Figure 92). An additional example may be seen by observing that the protons on K (4.65 ppm) show through space correlations with P and N (Figure 90). This is consistent with the assignments discussed previously and dramatically depicts the saddle shape of the cyclidene complex. Other through space interactions, and therefore tentative assignments that may be made, include P and T,T', S and K, P and O, N and X, and, perhaps most importantly in terms of the final assignments, Y with what could be E. This observation, together with the strong Y and O through space coupling, provides the means to distinguish between the two "sides" of the macrocycle (i.e., Y and X).

Results from COSY experiments may be used to resolve the remaining protons and serve as a cross check for assignments already made (Figure 91). COSY contour diagrams are analyzed in a manner strictly analogous to that used with NOESY plots, however they reveal interactions that are the result of coupling through the bonds. As an example, the diagonal peak at 3.89 ppm of complex II (Figure 91) has three off-diagonal elements which indicate that this single proton (via integration) is coupled to protons at 3.20, 2.88, and 2.28 ppm. Exploiting the data obtained on complex I with 2D- ^1H - ^{13}C correlation and DEPT experiments discussed previously (Figures 85 and 88), the proton at 3.89 ppm is on a carbon whose chemical shift is ~ 30 ppm. This carbon has been assigned to either E or F on the macrocycle. Therefore, the three off-diagonal elements described above in Figure 91 may be attributed to coupling with the two protons X or Y and the third correlation accounts for the other proton of the same carbon E and F. Since Y was already assigned using

Figure 91. Homoscalar correlated 2D ^1H NMR spectrum of
 $[\text{Ni}\{\text{Me}_2(\text{NMe})_2\text{m-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Result of a COSY experiment.

Figure 92. The high resolution ^1H NMR spectrum including assignments of $[\text{Ni}\{\text{Me}_2(\text{NMe})_2\text{m-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$.

NOESY, the interactions observed must be due to the two protons on X and the other F proton. Additional correlations confirm this conclusion. The X protons are expected to couple with each other and this is clearly seen in Figure 91. The Y_e and Y_a protons are seen to couple, as do the E_e and E_a protons. The remaining assignments in the aromatic region and any other correlations may be cross checked by use of the NOESY and COSY techniques. The final assignments for complex I and NOESY contour plot are shown in Figures 93 and 94 and listed in Table 20.

The assignments of protons for complexes I and II reveal that the methylene protons on the saturated chelate rings of the parent macrocycle are fixed in axial and equatorial sites, with the equatorial proton residing downfield from those of the axial protons. The protons F_e and F_a in both complexes depict a feature common to the spectra of all five cyclidenes studied here. The large splitting between these equatorial and axial protons of F, (~ 1.6 – 1.7 ppm), indicates the boat conformation present in X-F-X carbons. This conformation draws the equatorial proton on F into close proximity to the dipositive metal atom and apparently, significant deshielding takes place, resulting in a downfield shift of 3.9 ppm for F_e . Presumably the methyl carbon N forces the X-F-X chain to adopt the boat form (see earlier 3D schematic). In contrast, the E protons are at much higher field and the difference in their chemical shifts is small (2.1 and 1.7 ppm). This may be a consequence of a chair conformation. The absence of a methyl group on that side of the macrocycle permits this favorable configuration. These results are confirmed by numerous x-ray crystal structures of cyclidene complexes^{2,11} which reveal that the occurrence of boat and chair conformations is in agreement with the discussion above.

Table 20.

¹H NMR Chemical Shift Data¹ and Assignments for Complexes I-V

Protons ^{3,4}		Complex				
$\delta(\text{ppm})$	<u>I</u>	<u>II</u>	<u>III</u> ²	<u>IV</u>	<u>V</u>	<u>Code</u>
C	7.45	7.21	7.59, 7.32	7.51	7.32	a
Ke(Ka)	3.73(3.38)	4.65	4.83, 4.52	3.72(2.90)	3.89	c, e, f
Fe	3.95	3.89	3.89-->4.01	3.91	3.87	f
Fa	2.28	2.27	~2.4	2.34	2.20	b
X _e	3.20	3.20	3.31, 3.07	3.22	3.09	b
X _a	2.88	2.92	2.89	2.81	2.77	e
Y _e	3.48	3.31	3.47	3.49	3.49	c
Y _a	3.17	2.88	3.17	3.14	3.14	e
E _e	2.18	2.08	~2.1	~2.2	2.07	e
E _a	1.69	1.39	1.95, 1.60	1.61	1.56	d
Q	-	-	8.15, 6.60	6.30	-	h
Z, Z'	-	-	-	-	2.27, 2.26	a
P	3.20	3.62	-	-	-	a
O	2.38	2.44	2.31, 2.29	2.29	2.31	a
N	1.88	2.16	2.21, 2.09	2.15	1.84	a
R	-	7.23	7.49	0.73	-	g
S	-	6.98	7.02	1.82, 1.33	-	h
T, T'	-	7.04, 7.03	7.37, 7.35 7.25, 7.24	1.73, 0.90	-	b
I	1.68	-	-	-	3.68	e, d
J	1.40	-	-	-	3.33, 2.98	e, h
Me	-	-	-	-	1.79	e
Ma	-	-	-	-	1.53	e
L	-	-	-	-	2.87	e, f

a. Singlet.

b. Doublet multiplet.

c. Triplet multiplet

d. Broad multiplet

e. Complex multiplet

f. Chemical shifts listed are the centers of an AB quartet.

g. Triplet

h. Broad singlet.

1. Proton NMR spectra were acquired using a Bruker-AM 500 NMR spectrometer operating a 500.13 MHz, and using 32K data points.

2. The chemical shifts listed for this complex are at the centers of complex multiplets. Due to asymmetry, more than one set of peaks may be assigned to the signal.

3. Chemical shifts are versus 1.930 ppm as determined for the solvent CD₃CN.

4. In several of the spectra there appears a triplet at ~1.1 and a multiplet at 3.5 ppm: this is assigned to ethanol used in solvent recrystallization. In addition, water is present at ~2.2 ppm.

Figure 93. The high resolution ^1H NMR spectrum including assignments of $[\text{Ni}\{\text{Me}_2(\text{NMe})_2(\text{CH}_2)_6[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 94. Homoscalar correlated 2D ^1H NMR spectrum of
 $[\text{Ni}\{\text{Me}_2(\text{NMe})_2(\text{CH}_2)_6[16]\text{cyclidene}\}](\text{PF}_6)_2$.
Result of a NOSEY experiment.

The assigned ^1H NMR spectra of complexes III and IV along with COSY and NOESY contour plots are shown in Figures 95 through 99. The structures of these two species have been confirmed by x-ray crystallography and by ^{13}C NMR experiments to involve the isomeric lid-on structure, while complexes I and II adopt a lid-off configuration. The structures for the lid-on, lid-off isomers are schematically shown below.

It is clear from x-ray crystallographic data that there is a profound difference in cavity shape between the two species.¹⁴ The cavity of the lid-on isomer is 7.57Å high and 5.20Å wide, while the cavity in lid-off species is 5.02Å high and 7.37Å wide. It has been previously noted that the ^1H -coupled ^{13}C NMR, and the chemical shifts of methyl groups N and O in ^{13}C spectra can be used to distinguish between lid-on and lid-off isomers in the absence of x-ray structural information.¹¹ This identification of isomer type is also possible using the ^1H NMR signal

Figure 95. The high resolution ^1H NMR spectrum including assignments of $[\text{Ni}\{\text{Me}_2(\text{NH})_2\text{m-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 96. Homoscalar correlated 2D ^1H NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{NH})_2\text{-xylylene[16]cyclidene}\}](\text{PF}_6)_2$. Result of a COSY experiment: upper, flat projection; lower, stacked plot.

Figure 97. Homoscalar correlated 2D ^1H NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{NH})_2\text{m-xylene[16]cyclidene}\}](\text{PF}_6)_2$. Result of a NOSEY experiment: upper, flat projection; lower, stacked plot.

Figure 98. The high resolution ^1H NMR spectrum including assignments of $[\text{Ni}\{\text{Me}_2(\text{NH})_2(\text{cis-1,3-cyclohexa})[16]\text{cyclidene}\}]\text{IPF}_6)_2$.

Figure 99. Homoscalar correlated 2D ¹H NMR spectrum of
[Ni(Me₂(NH)₂(cis-1,3-cyclohexa)[16]cyclidene)](PF₆)₂.

Result of a COSY experiment.

from the same two methyl groups (N and O), as the probe. The separation in PPM of the N and O methyl proton peaks is consistently greater than .35 ppm when the complex is of the lid-off isomer type (complexes I and II; Figures 92 and 93). When the isomer type is lid-on, the separation is less than .15 ppm (complex IV and other lid-on complexes not discussed here; Figure 98). Due to the intensity of the methyl proton signals (N and O), and their consistent chemical shifts in the ^1H NMR spectra, future assignment of lid-on and lid-off isomers may be routinely accomplished on a low field spectrometer, such as an EM-360 CW instrument.

The ^1H NMR spectrum of complex III presents special problems. From the multiple peaks seen in the ^1H NMR spectrum (Figure 95), the molecule either does not have mirror symmetry or the sample is a mixture of species. The relatively small differences in chemical shifts between the doubled peaks support the first possibility and suggests that the loss of symmetry is due to some very small, nonfluxional structural perturbation. The relative chemical shifts of the protons is consistent with previous determinations, including the chair-boat conformational dichotomy of the E and F carbons. Rotation about one of the A-D double bonds would produce asymmetry, but this modification would undoubtedly have a much larger impact on the coupling of the methyl protons than can be accounted for in the ^1H spectrum. The x-ray crystal structure of the complex shows what appears to be a symmetric cavity formed by the complex.¹⁴ The ^{13}C NMR spectra of complex III contains several additional signals that cannot be accounted for on the basis of the number of carbon atoms, however the spectrum suggests a lid-on

isomer.¹¹ NOESY and COSY contour plots of the complex do not reveal any outstanding features that may account for the asymmetry of the complex.

A plausible solution to this apparent enigma may be found in the N and O methyl protons used to assign the lid-on and lid-off isomers. There are four distinct peaks corresponding to the N and O protons. One set is split by 0.1 ppm, indicating that the isomer is lid-on. The other set of N and O methyl protons is split by 0.22 ppm. This splitting falls between the range of the standard of greater than 0.35 ppm determined for lid-off and less than 0.15 ppm for lid-on. It is possible that complex III possesses both lid-on and lid-off planar nitrogen moieties on opposite sides of the complex. This phenomenon would account for the asymmetry of the complex and the observation of slightly different environments as seen for the majority of the protons in the ^1H spectra. The protons that would be most affected by such a conformational change are K and Q (the protons on nitrogen). The two NH protons, Q, on either side of the macrocycle, are clearly in significantly different environments as indicated by their chemical shifts of 6.6 ppm and 8.15 ppm. The proposed structural relationships may be seen with the aid of molecular models of the complex and are consistent with the NMR spectral observations.

Finally, the assigned ^1H NMR spectrum and the COSY contour diagram for complex V are shown in Figures 100 and 101. The DEPT and ^{13}C - ^1H shift correlation for this complex were discussed earlier (Figures 87 and 89). The proton spectrum of Figure 100 is a blow-up of the region from 1.4 to 4.2 ppm and the peak due to the lone methine proton at 7.32 ppm is not shown. There are similar features in the ^1H NMR spectrum of

Figure 100. The high resolution ^1H NMR spectrum including assignments of $[\text{Ni}\{\text{Me}_2(\text{CH}_2\text{piperazine})_{2,3,6}\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_2$.

Figure 101. Homoscalar correlated 2D ^1H NMR spectrum of $[\text{Ni}\{\text{Me}_2(\text{CH}_2\text{piperazine})_2\}_{3,6}\text{-dur}[16]\text{cyclidene}]\text{(PF}_6)_2$.

Result of a COSY experiment.

this vaulted complex when compared to those of the lacunar cyclidene complexes (I - IV). The familiar chair-boat conformations of E and F are indicated since the peaks for the protons on these carbon atoms reside at approximately the same chemical shifts as those of the analogous protons in the lacunar complexes. This is consistent with the crystal structure of the complex (Figure 35), which shows the E resides in a chair conformation and F is a boat conformation.⁴ The protons labeled K show a typical A-B splitting pattern from 3.8 to 4.0 ppm. The protons on X and Y give peaks at similar positions relative to those of the lacunar complexes. Absolute assignment of the peaks for the protons on I, J, L, and M is more complicated due to the symmetry of the piperazine rings. In the COSY contour plot (Figure 101), the signals of the protons on the carbon atoms adjacent to each other on the piperazine rings may be assigned due to the strong coupling between the nearest neighbors. Therefore, the protons on L and I, and J and M should produce strong off-diagonal elements demonstrating the coupling between them. This result is apparent upon inspection of the COSY plot (Figure 101). With all other peaks assigned, the signal at 3.68 ppm (4 protons via integration) possess a very strong off-diagonal element with the protons resonating at 2.87 ppm which also integrate to yield 4 protons. This result indicates that these two peaks are on nearest neighbor carbon atoms of the piperazine ring. Further, two protons whose peaks reside at 3.30 ppm reveal coupling with two protons at 2.98 ppm and also with two protons where peaks occur at 1.79 and 1.53 ppm. These proton resonances correspond to the other "half" of the piperazine ring.

The large upfield shift of the protons at 1.79 and 1.53 ppm (M) from the other 3 sets of protons of the piperazine ring J, I, and L, indicate a strong shielding contribution unique to M. With the aid of molecular models it may be seen that a single proton on the piperazine ring is in very close proximity to the durene (tetramethyl benzene) ring. Using crystallographic data of a similar complex in order to approximate the position and distance of this proton to the durene ring, and using a table of predicted values of shielding contributions from ring currents^{15,16} a value of -1.7 ppm is predicted for the shielding contribution. This is relatively close to the observed -1.2 ppm shift of M, upfield from free piperazine. With M assigned, the nearest neighbor proton may be assigned to J. Likewise, I and L are assigned in a similar manner.

With the assignments described above, it is likely that by the judicious choice of a guest species that precludes overlap of proton resonances with J and I of the piperazine ring, that binding constant data for a host-guest complex could be obtained in a similar manner to that described for ^{13}C $\Delta\delta$ measurements.⁵ These protons should be extremely sensitive to small perturbations in their environments such as the loss of hydrogen bonding during inclusion complex formation.

CONCLUSIONS

2-D NMR techniques have been used to unambiguously assign the resonances in the ^1H NMR spectra of five cyclidene complexes. Several 3-dimensional structural relationships are exhibited and the proton

spectra has been assigned. A number of features are common to all five cyclidenes studied. The chair and boat conformations of macrocyclic ring components are apparent from the ^1H spectra and agree with the results of x-ray crystallographic data. The saddle shaped nature of the cyclidene ligand is observed with through space coupling of protons using NOESY experiments. The identification of lid-on and lid-off isomers of the complexes may be routinely performed with NMR measurements even at low magnetic fields.

Finally, the absolute assignment of ^1H NMR spectra of the vaulted cyclidene complex facilitates the study of inclusion complex formation. These assignments may be used as a highly sensitive probe to detect the exclusion of hydrogen bonded water molecules from the interior of the pocket.

EXPERIMENTAL

Synthesis of the Bridged Ni(II) Cyclidenes.

[(2,3,10,11,13,19-Hexamethyl-3,10,14,18,21,25-hexaazabicyclo-[10.7.7]hexacos-1,11,13,18,20,25-hexaene- $\kappa^4\text{N}$)nickel(II)] hexafluorophosphate $[\text{Ni}\{\text{Me}_2(\text{NME})_2(\text{CH}_2)_6[16]\text{cyclidene}\}](\text{PF}_6)_2$. This complex was prepared by published procedure.¹

[(2,3,11,12,14,20-Hexamethyl-3,11,15,19,22,26-hexaazatricyclo-[11.7.7.1^{5,9}]octacos-1,5,7,9(28),12,14,19,21,26-nonaene- $\kappa^4\text{N}$)nickel(II)] Hexafluorophosphate $[\text{Ni}\{\text{Me}_2(\text{NME})_2\text{-}m\text{-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$. This complex was prepared by published procedure.¹⁴

[(2,12,14,20-tetramethyl-3,11,15,19,22,26-hexaazatricyclo-[11,7,7,1^{5,9}]octacos-1,5,7,9(28),12,14,19,21,26-nonaene- $\kappa^4\text{N}$)nickel(II)] Hexafluorophosphate $[\text{Ni}\{\text{ME}_2(\text{NH})_2\text{-}m\text{-xylylene}[16]\text{cyclidene}\}](\text{PF}_6)_2$. This complex was prepared by published procedures¹⁴ and was the generous gift of Dr. C. Cairns.

[(2,12,14,20-Tetramethyl-3,11,15,19,22,26-hexaazatricyclo-[11.7.7.1^{5,9}]octacos-1,12,14,19,21,26-hexaene- $\kappa^4\text{N}$)nickel(II)] Hexafluorophosphate $[\text{Ni}\{\text{Me}_2(\text{NH})_2(\text{cis-1,3-cyclohexa})[16]\text{cyclidene}\}]\text{nickel(II)}](\text{PF}_6)_2$. This complex was prepared by published methods and was the generous gift of Dr. D. Nosco.

[(2,9,10,17,19,25,33,34-Octamethyl-3,6,13,16,20,24,27,31-octaazapentacyclo[16.7.7.2^{8,11}.2^{3,6}.2^{13,16}]hexatetraconta-1,8,10,17,19,24,26,-

31,33-nonaene- κ^4 N)nickel(II)] Hexafluorophosphate $[\text{Ni}\{\text{Me}_2(\text{CH}_2\text{piperazine})_{2,3,6}\text{-dur}[16]\text{cyclidene}\}](\text{PF}_6)_2$. This complex was also prepared by published methods.⁴

Physical Measurements

Proton NMR were acquired using a Bruker WM300, AM500, and Nicolet NT500 spectrophotometers. All NMR spectra were obtained in deutero acetonitrile. ^1H - ^{13}C shift correlation measurements were acquired on Bruker WM300 spectrometer with SI = 4K, and $\text{TD}_1 = 256$, $\text{P}_{90}\text{H} = 44$ usec and $\text{P}_{90}\text{C} = 29$ usec. The 2D-NOESY and COSY experiments were acquired with the Bruker Coco-NOESY Shift-Related 2-D sequence with a a 0.5 mixing time. The SW = 4000 Hz and SI = 16K. This program allows for the COSY data to be acquired during the mixing time and has been adapted from Haansnoot et al.^{17,18} ^{13}C DEPT experiments were carried out on a Bruker NR-80 spectrophotometer with a sweep width of 4500 Hz, PW = 35, and data acquired over 16K data points.

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APPENDIX

MISCELLANEOUS

Binuclear Transition Metal Complexes as Non-Coordinating Hosts.

The dimer complexes of the cyclidene ligand systems^{1,2} provide a large pocket suitable for inclusion complex formation (Figure 42). This class of cyclidene hosts are unique due to their ability to bind guest molecules inside these cavities by coordination and also by non-covalent interactions. The discussion of host-guest association via coordination of a guest between the two metal centers was briefly presented in Chapter One (page 58) and is discussed in detail elsewhere.¹

In order to use the dimer complex as a paramagnetic probe for spin lattice relaxation measurements, it is essential that only one of the two metals in the complex possess an unpaired electron. The synthesis and subsequent purification of the copper(II)-nickel(II) dimer complex was performed by N. Hoshino¹ (Figure 102). The "walls" of the pocket are m-xylylene groups and the complex possesses an overall 4⁺ charge. The relaxation data in Table 21 summarizes the ability of the hetero-binuclear complex to accommodate the guests n-butanol and 2,6-dimethylphenyl in a regiospecific manner reminiscent of the vaulted (Chapter Two) and supervaulted (Chapter Three) mononuclear complexes. The data reveal that the guests are located approximately equidistant from the Ni(II) and Cu(II) metal centers. In previous studies involving host-guest association with raised cyclidenes, q (the coordination number)

Figure 102. Structure of
 $[\text{CuNi}\{(\text{Me}_2(\text{NH})_2\text{m-xylylene})_2([16]\text{cyclidene})_2\}]^{4+}$.

Table 21.

Relaxation Times and Calculated Distances for

Guest = n-butanol $(\text{P} = 4.33 \times 10^{-4})^{\text{b}}$

Protons	α	β	γ	δ
$(\text{T}_1)_0, \text{sec}$	5.48 ± 0.10	4.52 ± 0.05	5.26 ± 0.06	6.06 ± 0.2
T_1, sec	5.24 ± 0.05	4.55 ± 0.1	4.76 ± 0.07	5.27 ± 0.01
$r, \text{\AA}$	8.4 ± 0.2	7.9 ± 0.2	7.3 ± 0.1	7.0 ± 0.2

Guest = 2,6-dimethylphenol $(\text{P} = 5.62 \times 10^{-4})$

Protons	Me	Meta	Para
$(\text{T}_1)_0, \text{sec}$	3.70 ± 0.08	8.22 ± 0.01	6.93 ± 0.01
T_1, sec	3.05 ± 0.02	5.23 ± 0.07	4.66 ± 0.05
$r, \text{\AA}$	6.6 ± 0.1	6.1 ± 0.1	6.2 ± 0.1

a. Proven to be a mixture of CuNi and Ni₂ binuclear species. The concentration of CuNi host was calculated based on analyzed copper content.

b. $[\text{Host}]/[\text{Guest}]$.

was assumed to be 1 (e.g., Host:Guest = 1:1). This result was based on molecular model and x-ray crystal structure data indicating that while the host is able to accommodate a single guest, a second guest would be precluded from simultaneously entering the void. This assumption is suspect when considering the Cu-Ni dimer complex and the guest n-butanol. It is possible that the observed distances are an average of two molecules of n-butanol in the pocket. However, it is unlikely that the host dimer can accommodate two 2,6-dimethylphenol molecules in the pocket and the observed distances in Table 21 are for the 1:1 host-guest complex. The data for 2,6-dimethylphenol may reflect an additional binding force present in the dimer host-guest complex. The aromatic ring of 2,6-dimethylphenol appears to be positioned between the unsaturated m-xylylene rings. Pi-pi interactions between these rings would be expected to increase the overall binding constant of a guest.

¹³C Δδ Measurements for [Ni{(CH₂)₈(piperazine)₂[16]cyclidene)](Cl)₂ with n-butanol.

The vaulted doubly bridged cyclidene complex first synthesized by Coltrain³ is potentially the most interesting host complex yet designed. The x-ray crystal structure of the complex reveals that the dimensions of the cavity are defined by the piperazine risers and the durene roof, while the second (CH₂)₈ bridge effectively closes one side of the void and is shown below.⁴ The ¹³C NMR spectrum of [Ni{(CH₂)₈(piperazine)₂[16]cyclidene)]Cl₂ is shown in Figure 103. The IR spectrum of the complex revealed the absence of a PF₆ stretch.

Efforts to prepare the ligand salt using HBr proved unsuccessful. The Cu(II) Jager complex was synthesized, however all attempts to methylate the complex failed. The Ni(II) chloride complex was prepared in order to study inclusion complex formation using $\Delta\delta$ measurements.⁴ The data in Table 22 reveal very small differences between the chemical shifts of the carbon atoms most sensitive to loss of internally hydrogen-bound water molecules. In addition, the sign of the shifts are all positive and this result is in marked contrast to that observed for the singly bridged vaulted systems.⁴ These results, although disappointing, provide insight into the nature of vaulted doubly bridged pockets. It is probable that due to the presence of the second bridge, the cavity has become sufficiently hydrophobic as to exclude the hydrogen bonded water molecules.

Figure 103. Broad band proton-decoupled ^{13}C NMR spectrum of
 $[\text{Ni}\{(\text{CH}_2)_8(\text{piperazine})_2[16]\text{cyclidene}\}]\text{Cl}_2$.

Table 22.

^{13}C $\Delta\delta^a$ Values for $[\text{Ni}\{(\text{CH}_2)_8(\text{piperazine})_2[16]\text{cyclidene}\}](\text{Cl})_2^b$
Using n-butanol as a Guest Molecule.

[Guest](M) ^c	Guest/Host	$\Delta\delta$ (ppm) ^d				
		A	B	C	D	N
.025	.65	+.090	+.092	+.099	+.042	+.024
.050	1.3	+.075	+.095	+.097	+.037	+.024
.11	2.6	+.080	+.091	+.083	+.039	+.025
.14	3.9	+.075	+.090	+.094	+.044	+.041
.23	6.0	+.132	+.158	+.087	+.082	+.114
.29	7.8	+.150	+.246	+.122	+.177	+.161
.35	9.0	+.153	+.266	+.144	+.221	+.191
.43	12.9	+.216	+.272	+.152	+.207	+.209
.51	14.0	+.216	+.271	+.155	+.200	+.202

a. $\Delta\delta = (^{13}\text{C } \delta \text{ (host in presence of guest)} - ^{13}\text{C } \delta \text{ (host)})$.

b. Moles of host = 7.17×10^{-5} M.

c. Calculated based on additivity of D_2O (2.0 ml) and volume of n-butanol ($5 \mu\text{l} = 5.40 \times 10^{-5}$ moles).

d. Uncertainty = ± 0.02 ppm.

Crystal Structure of $[\text{Cu}\{\text{Ph}_2(\text{piperazine})_{2,3,6}\text{-dur[16]cyclidene}\}](\text{PF}_6)_2$.

The crystal structure data of the title complex was collected and solved by Dr. W. Davis and is shown in Figure 104. Several features are consistent with previous structures of vaulted complexes. The piperazine rings appear to be pivoted so they are directed into the interior of the cavity. No solvent molecule was detected in the vicinity of the cavity for this complex. The phenyl rings are directed away from the pocket and appear to do little in the way of closing off one side. The conformations of the saturated portion of the parent macrocycle are in a boat-boat configuration. There R^3 substituted complexes should provide the necessary hydrophobic surface area for increasing the binding constants of organic guests and provide protection from autoxidation.

Figure 104. Pluto diagram of
 $[\text{Cu}\{(\text{Ph})_2(\text{piperazine})_2[16]\text{cyclidene}\}](\text{PF}_6)_2$.

EXPERIMENTAL

Synthesis of $[\text{CuNi}\{(\text{Me})_2(\text{NH})_2\text{m-xyl}\}_2[16]\text{cyclidene}\}_2]^{4+}$.

This complex was the generous gift of Dr. Naomi Hoshino.

Synthesis of $[\text{Ni}\{(\text{CH}_2)_8(\text{piperazine})_2[16]\text{cyclidene}\}]\text{Cl}_2$.

The hexafluorophosphate salt of the above complex was synthesized by published procedure.^{3,5} 1.0 Gram of the $[\text{Ni}\{(\text{CH}_2)_8(\text{piperazine})_2[16]\text{-cyclidene}\}](\text{PF}_6)_2$ was dissolved in 20 ml of dried acetone in an inert atmosphere glove box. 1.3 Grams of tributylammonium chloride was dissolved in 25 ml of dried acetone and allowed to slowly drip into the stirred solution of metal complex. The resulting yellow micro-crystalline product was recovered and dried in vacuo.

Synthesis of $[\text{Cu}\{(\text{PH})_2(\text{piperazine})_2[16]\text{cyclidene}\}](\text{PF}_6)_2$.

The nickel(II) complex of the title complex was synthesized by previous methods.³ 1.2 Grams of $[\text{Ni}\{(\text{Ph})_2(\text{piperazine})_2[16]\text{cyclidene}\}](\text{PF}_6)_2$ was slurried in 100 ml of methanol. Dry hydrogen bromide gas was bubbled vigorously through the solution until a green-blue color appeared (ca. 15 minutes). The solution was rotary evaporated to an oil and dissolved in 100 ml of doubly distilled water. 0.96 Grams of ammonium hexafluorophosphate dissolved in 15 ml of ethanol was slowly dripped into the solution and a yellowish-white precipitate immediately appeared. The solid was recovered and dried in vacuo. 0.36 Grams of copper acetate

monohydrate and 0.44 g of sodium acetate were dissolved in 10 ml of methanol. The ligand salt of the macrocycle was slurried in 15 ml of hot metal and the copper(II) solution added to it with stirring. The immediate formation of a brick red solid was observed and collected and dried in vacuo. The solid was recrystallized from acetonitrile/ethanol. **Anal.** Calcd. for $\text{CuC}_{48}\text{H}_{62}\text{N}_8(\text{PF}_6)_2$: C, 52.19; H, 5.67; N, 10.13; Cu, 5.75. Found: C, 52.17; H, 5.99; N, 9.83; Cu, 5.82.

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