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Hydrophobic, Regiospecific Guest Binding by Transition-Metal Host Complexes Having Permanent Voids as Revealed by FT-NMR Relaxation Studies

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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 crystal structure is reported for an example of the host molecules used in these studies. 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 counterexamples, 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 the inclusion complex 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 the alcohols 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.

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 1).[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, 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 2). 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 2, parts A and 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 structure of the vaulted cyclidenes for the inclusion of organic guest molecules. The smaller voids characteristic of the lacunar cyclidene complexes (Figure 2C and 2D) are only big enough for coordination of such small molecules as O_2 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

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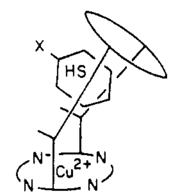

Figure 1. Concept of inclusion complex formation with a copper-containing host suitable for relaxation studies.

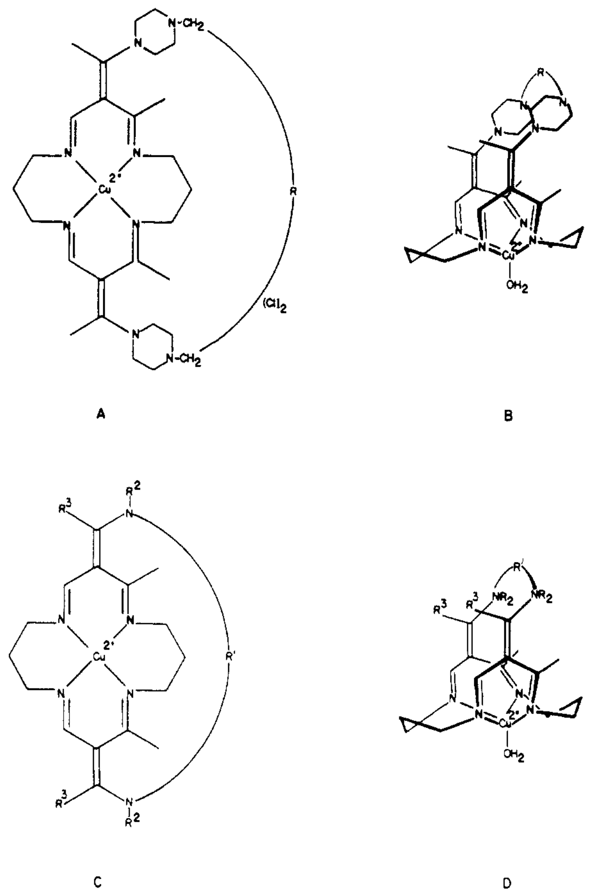

Figure 2. Structures of the vaulted and lacunar macrobicyclic cyclidene complexes: (A) flat and (B) three-dimensional representation of the vaulted complexes; (C) flat and (d) three-dimensional representation of the lacunar complexes.

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]

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 3 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] 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 describes the rate of spin–lattice relaxation of a nucleus in a molecule bound in the proximity of a paramagnetic ion (eq 1).

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

The first term in eq 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 (eq 2). The coefficient C in eq 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 eq 3. The rotational

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$$r\,(\text{Å}) = C\left[T_{1\text{m}}\left\{\frac{3\tau_c}{1 + (3.94 \times 10^{13}\nu_I^2\tau_c^2)} + \frac{7\tau_c}{1 + (1.71 \times 10^{19}\nu_I^2\tau_c^2)}\right\}\right]^{1/6} \quad (2)$$

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

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

greatest contribution to τ_c. It is known that τ_s for Cu(II) is of the order of 10^{-8} s 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, $1/T_{1\text{p}}$, is given by eq 4.

$$\frac{1}{T_{1\text{p}}} = \frac{1}{T_1} - \left(\frac{1}{T_1}\right)_0 = \frac{pq}{\tau_m + T_{1\text{m}}} + \left(\frac{1}{T_1}\right)_{\text{os}} \quad (4)$$

$(1/T_1)_0$ 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. $T_{1\text{m}}$ 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 $T_{1\text{m}} \gg \tau_m$; then $T_{1\text{m}} = pT_{1\text{p}}$ (if $q = 1$ and $(1/T_1)_{\text{os}}$ is negligible) and the paramagnetic contribution to the relaxation rate is magnetically determined. Equation 5 incorporates these relationships and is the form used for distance calculations associated with our experiments.[19,20] The use of the dipolar com-

$$r\,(\text{Å}) = C\left[pT_{1\text{p}}\left(\frac{3\tau_c}{1 + (3.94 \times 10^{13}\nu_I^2\tau_c^2)} + \frac{7\tau_c}{1 + (1.71 \times 10^{19}\nu_I^2\tau_c^2)}\right)\right]^{1/6} \quad (5)$$

ponent 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 the 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 the following: (1) the hyperfine contribution to the relaxation process must be negligible; (2) the outer-sphere contributions, $(1/T_1)_{\text{os}}$, must be small; (3) $(1/T_{1\text{p}})$ 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 expressed[33] about the validity of neglecting the hyperfine term in those cases, little importance can be expected for the hyperfine contribution to interactions in the nonbonded 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 model.[34]

Table I. Relaxation Times (T_1, s) 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 = 304 K)

Guest = Tetramethylammonium Ion^b $(CH_3)_4N^+$ ($p = 1.4 \times 10^{-3}$)^a		
$(T_1)_0$, s	10.22 ± 0.20	
(T_1), s	10.16 ± 0.20	
r, Å	>17	
Guest = 1,4-Dioxane^b ($p = 1.10 \times 10^{-3}$)^a		
protons	1,4-dioxane	
$(T_1)_0$, s	8.51 ± 0.50	
(T_1), s	7.95 ± 0.50	
r, Å	>14	
Guest = 1,4-Butanediol^c ($p = 1.15 \times 10^{-3}$)^a		
protons	$\alpha(CH_2)$	$\beta(CH_2)$
$(T_1)_0$, s	3.52 ± 0.16	3.24 ± 0.1
(T_1), s	3.46 ± 0.1	3.20 ± 0.1
r, Å	>11	>11

^{a} p = [host]/[guest]. ^{b} υ = 300 MHz. ^{c} υ = 500 MHz.

The magnitude of the outer-sphere, or bulk susceptibility, contribution $(1/T_1)_{\text{os}}$ 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 I. 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 interactions. The results given in Table I 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 eq 4). Rationally, one expects hydrophobically driven host–guest complexation to be very rapid, and experimental verification can be straightforward 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 $1/T_{1\text{p}}$ 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 1-butanol and 2,6-dimethylphenol. As the data in Table II show, the value of $1/T_{1\text{p}}$ decreases as the temperature increases, indicating that the process is not exchange limited.[22,35,36]

An accurate means of estimating the value of τ_c for the host is also required, and the frequency (ν) dependence of $T_{1\text{p}}$ is an appropriate method for this determination. When $1 \gg \omega_I^2\tau_c^2$ as in the case here, this method is valid.[36] Three field strengths of

Table II. Temperature Dependence of Relaxation Rate ($1/T_{1p}$, s^{-1}) with Host 1 (υ = 300 MHz)

	$1/T_{1p}$ at T = (K)		
protons	(A) 291/(B) 274	304	314
	A. Guest = 2,6-Dimethylphenol (p = 1.54 × 10^{-3})		
CH_3	0.381	0.0724	0.0261
meta	0.439	0.132	0.0676
para	0.817	0.218	0.1413
	B. Guest = 1-Butanol (p = 1.18 × 10^{-3})		
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 III. Saturation^a of the Host–Guest Equilibrium as Determined by T_1 Measurements.^{b} Host = Host 1; Guest = 1-Butanol; T = 304 K

	r (Å) calcd for the indicated protons			
host/guest p	α	β	γ	δ
1.23 × 10^{-1}	13.7	13.3	12.6	11.9
1.23 × 10^{-2}	12.9	11.2	10.5	10.2
1.18 × 10^{-3}	9.0	7.7	7.4	6.6
7.89 × 10^{-4}	8.9	7.6	7.4	6.6
1.24 × 10^{-4}	8.8	7.9	7.6	6.5

^{a} Note that the calculated values for r become constant as saturation is achieved. $^b\upsilon$ = 500 MHz.

200, 300, and 500 MHz were used to determine T_{1p} values of each proton for several guest species. The calculated value of τ_c is the result of the solution of pairs of simultaneous equations based on eq 5 using the relaxation data above. The value calculated is 1.2 ± 0.3 × 10^{-10} s and was used in all distance calculations.

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 III reveal that as p = [host]/[guest] is varied, the distances calculated are independent of the 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 1/10000, the distances are constant, well within experimental error. However, when the ratio of host to guest falls below 1/100, the distances calculated are erroneously high and concentration-dependent. This result reflects the rather low binding constants of the host–guest complexes.

As eq 4 shows, it is necessary to either determine or assume the ratio of the 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 IV summarizes the relaxation data for host I and the guest 1-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 1-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.

Table IV. Relaxation Data^a for the 1-Butanol Guest in the Presence of Host I in Acetonitrile Solvent

	protons			
	α	β	γ	δ
$(T_1)_0$, s	7.63 ± 0.1	6.45 ± 0.08	6.65 ± 0.1	6.26 ± 0.01
T_1, s	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

$^a\upsilon$ = 500 MHz. [host] = 6.85 × 10^{-5}; [guest] = 5.47 × 10^{-2}.

Table V. Relaxation Times^a for Water (HDO) under Several Conditions (T = 304 K)

host	guest	p (or conc)	T_1, s
none	none		61.7 ± 0.9
1	none	6.48 ± 10^{-5}	42.9 ± 0.5
1	MeOH	1.54 × 10^{-3}	43.5 ± 0.5
1	n-BuOH	2.5 × 10^{-3}	48.1 ± 0.5

$^a\upsilon$ = 300 MHz.

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 studies[13] 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 (HDO) were determined under four separate conditions in D_2O: (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 × 10^{-2} M); and (4) the rate was measured in the presence of host I plus 1-butanol (5.48 × 10^{-2} M). The results have been summarized in Table V. The value of 61.7 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 s, 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 experimental error, unchanged from the value measured when the paramagnetic host alone was present. Finally, when 1-butanol is introduced as the guest, there is a reproducibly measureable increase in the T_1 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 T_1 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 T_1 increases upon addition of 1-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 (1-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 T_1 value for water.

Table VI. Calculated Distances for Various Protons in Several Alcohols for Host I[a,b]

	distance,[c] Å			
alcohols	α	β	γ	δ
CH_3OH	8.6			
CH_3CH_2OH	8.4	7.5		
$CH_3CH_2CH_2OH$	9.0	8.2	7.5	
$CH_3CH_2CH_2CH_2OH$	9.0	7.7	7.4	6.6
av	8.8 ± 3	7.8 ± 3	7.5	6.6
t-$(CH_3)_3COH$		7.4		
i-$(CH_3)_2CHOH$	9.2	8.2		
$CH_2{=}C(CH_3){-}CH_2{-}OH$	9.0		7.6	
		(7.2)		
overall av	8.9 ± 2	7.8 ± 3	7.4 ± 1	(6.6)

[a] Data: υ = 300 MHz and T = 304 K using a Bruker WM300 spectrometer. T_1 and $(T_1)_0$ values are reported in supplementary material. [b] [Host] = 6.48×10^{-5} M; [guest] = 10^{-2} M. [c] From eq 5, using a measured value of $\tau_c = 1.2 \times 10^{-10}$ s.

Quantitative interpretations of the water relaxation data have not been thoroughly justified by the experiments reported here. We have not demonstrated saturation of the equilibrium nor have we proven that the process is not exchange limited. With the limitations that this implies in mind, it remains interesting to experiment with the data. When the relaxation data for host I and water (T_1), and the value for water itself $(T_1)_0$, are inserted into the Solomon–Bloembergen equation, a distance of 3.3 Å is obtained from Cu to a hydrogen on a proposed axially coordinated water molecule. This corresponds to a distance of 2.8 Å for Cu to the oxygen of water. 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 VI. 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, 1-propanol, 2-propanol, 2-methyl-2-propen-1-ol, and 1-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 1-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 3 which was created by using the computer program named CHEMGRAPH. The coordinates of the atoms composing the host molecule were obtained from the previously reported[9] 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. Some mutual accommodation of host and guest occurs during the energy minimization calculation using CHEMGRAPH. Figure 3A, 3B, and 3C consists of side views of the inclusion complex between host I and 1-butanol. Figure 3A provides a space-filling representation of the structure, while Figure 3B and 3C makes it easy to distinguish between the host and guest by successively reducing each of them to a stick representation. Figure 3D–F shows similar illustrations, but the viewer is looking directly into the cavity. Outstanding features implied by these drawings are as follows: (1) The 1-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 1-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 nestlike site is formed. While the details of these features are more suggestive than factual, certain ones 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.

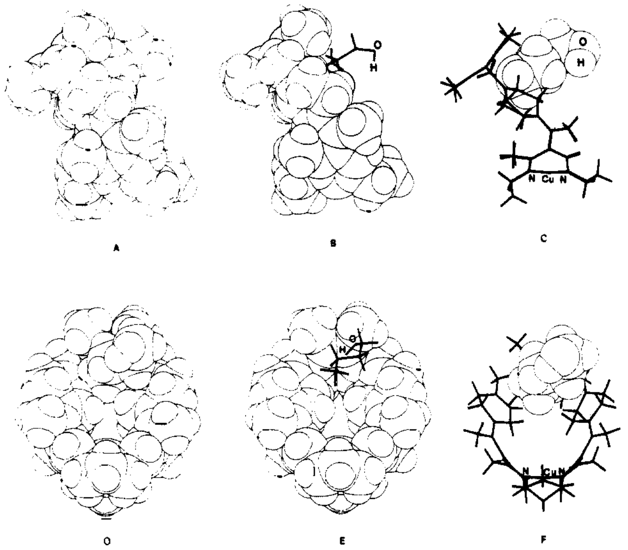

Figure 3. Inclusion complex between host I and 1-butanol guest.

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

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

	protons		
	Me	meta	para
$(T_1)_0$, s	4.08 ± 0.09	9.45 ± 0.20	7.88 ± 0.13
T_1, s	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] ($p = 1.78 \times 10^{-3}$)

	protons		
	Me	ortho	para
$(T_1)_0$, s	2.41 ± 0.08	13.78 ± 0.35	8.80 ± 0.35
T_1, s	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] ($p = 2.50 \times 10^{-3}$)

	protons			
	ortho-methyl	meta	ortho + para	meta-methyl
$(T_1)_0$, s	3.01 ± 0.05	6.39 ± 0.08	9.25 ± 0.07	3.20 ± 0.05
T_1, s	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] υ = 300 MHz. [b] υ = 500 MHz.

Data have also been obtained by using substituted phenols as the guest species in the 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 4,

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(38) "International Tables for X-Ray Crystallography"; MacGillary, C. H., Rieck, G. D., Eds.; Kynock Press: New York, 1974.

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

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

			protons		
A.	host		(CH_3) av	para-H	meta-H av
T = 304 K	lacunar complex[a]	$(T_1)_0$, s	3.69 ± 0.05	8.11 ± 0.15	9.45 ± 0.2
	$R^1 = (CH_2)_4$	T_1, s	3.54 ± 0.06	7.92 ± 0.08	9.19 ± 0.06
		r, Å	>12	>14	>14
T = 304 K	vaulted complex[a]	$(T_1)_0$, s	4.08 ± 0.09	9.45 ± 0.20	7.88 ± 0.13
	R^1 = duryl = host I	T_1, s	3.15 ± 0.13	4.20 ± 0.06	2.90 ± 0.1
		r, Å	7.6 ± 0.4	6.8 ± 0.1	6.1 ± 0.1

Guest = 1-Butanol ($p = 2.48 \times 10^{-3}$)

			protons			
A.	host		α	β	γ	δ
T = 304 K	lacunar complex[a]	$(T_{)0}$, s	6.62 ± 0.10	5.5 ± 0.10	5.40 ± 0.10	6.33 ± 0.10
	$R^1 = (CH_2)_4$	T_1, s	5.66 ± 0.15	4.70 ± 0.10	4.40 ± 0.10	4.40 ± 0.15
		r, Å	9.7 ± 0.20	9.2 ± 0.20	9.4 ± 0.20	8.3 ± 0.20

Guest = 1-Butanol ($p = 6.90 \times 10^{-4}$)

			protons			
A.	host		α	β	γ	δ
T = 304 K	vaulted complex[a]	$(T_1)_0$, s	5.60 ± 0.15	5.48 ± 0.05	6.22 ± 0.20	6.11 ± 0.10
	R^1 = anthracene = host II	T_1, s	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

Guest = 1-Butanol ($p = 4.62 \times 10^{-3}$)

			protons			
B.	host		α	β	γ	δ
T = 304 K	$R^1 = R^2 = R^3$ = Me	$(T_1)_0$, s	6.16 ± 0.03	5.64 ± 0.02	5.99 ± 0.04	5.73 ± 0.05
Unbridged T = 304 K		T_1, s	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] υ = 300 MHz. [b] υ = 500 MHz.

Table VII). As Figure 4 shows, the phenol does not nearly enter the cavity to the extent that 1-butanol does; however, it is binding with the same preferred orientation. Similarity to the 1-butanol case is apparent in the way the phenol lies across the entry of the cavity.

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 the 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 the 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 reveal results closely similar to those described above, Table VIII. The distances calculated for the internuclear separation between 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 counterexample involves the use of lacunar complexes[14-16] 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 VIII reveal that the effect of the paramagnetic center of the Cu(II) lacunar complex, having only a tetramethylene bridge (Figure 3)[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

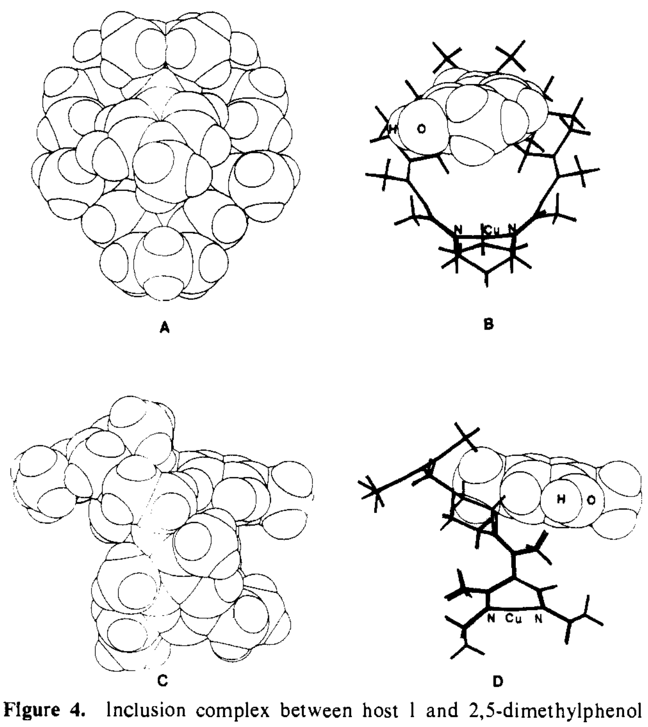
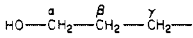


Figure 4. Inclusion complex between host I and 2,5-dimethylphenol guest.

Table IX. Frequency Dependence of Calculated Distances (T = 304 K): Host-Vaulted Complex,[a] R^1 = Duryl = Host 1; Guest = 1-Butanol[b]


$$\overset{}{HO}-\overset{\alpha}{CH_2}-\overset{\beta}{CH_2}-\overset{\gamma}{CH_2}-\overset{\delta}{CH_3}$$

	protons			
	α	β	γ	δ
		υ = 200		
$(T_1)_0$, s	5.30 ± 0.08	4.95 ± 0.02	5.95 ± 0.4	6.18 ± 0.1
T_1, s	4.71 ± 0.10	3.90 ± 0.1	4.18 ± 0.05	3.68 ± 0.1
r, Å	8.7 ± 0.2	7.5 ± 0.2	7.2 ± 0.1	6.7 ± 0.2
		υ = 300		
$(T_1)_0$, s	5.70 ± 0.1	5.33 ± 0.18	6.25 ± 0.2	6.20 ± 0.1
$T_{(}$, s	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
		υ = 500		
$(T_1)_0$, s	6.27 ± 0.05	5.5 ± 0.03	6.16 ± 0.1	6.22 ± 0.02
T_1, s	5.45 ± 0.02	4.33 ± 0.01	4.40 ± 0.03	3.61 ± 0.01
r, Å	8.6 ± 0.1	7.6 ± 0.1	7.3 ± 0.1	6.6 ± 0.1

[a] [Host] = 6.48×10^{-5}. [b] [Guest] = 5.49×10^{-2}.

the T_1 vs. T_{1_0} seen for the vaulted host I (included in Table VIII for comparison), which clearly indicate inclusion of the guest within the host species. Similar results are observed when 1-butanol is used as the guest (Table VIII); however, the effect of diminishing the cavity is less extreme. This is in keeping with the smaller size of the guest 1-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 VIII) indicate that some moderate nonregiospecific 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. This confirms 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 IX shows that the distances calculated from data obtained at 200, 300, and 500 MHz are the same, within experimental error, for host I and 1-butanol. All the data obtained in these studies is available as supplementary material.

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 the paramagnetic host. The results obtained for the relaxation rates of the guest protons, in the presence of the diamagnetic host I complex, are within experimental error of those values measured in the absence of the Ni^{2+} diamagnetic host I.

X-ray Crystal Structure Determinations

Figure 2A and 2B shows the flat and three-dimensional representations of the vaulted cyclidene structure. Crystallographic data has been collected with this complex having three different R groups, namely 9,10-anthracene,[9] 3,6-durene, and 1,4-benzene. Comparison of the three complexes reveals a systematic variation in their behavior toward solvent molecules. As shown by earlier work,[9] the anthracene-capped complex has the largest lid of the three and incorporates an acetonitrile molecule within the cavity. The 3,6-durene-capped complex incorporates solvent into the crystal lattice; however, this solvent is lost so readily that crystallographic data could not be obtained (see Experimental Section). Figure 5 is the ORTEP diagram of the nickel(II) vaulted cyclidene structure with 1,4-benzene as the roof. The complex has the smallest and least restrictive cap of the three complexes. The structure clearly shows that there is no solvent molecule associated within the confines of the crystalline lattice. The benzene cap is essentially parallel to the NiN_4 floor and has a wide cavity somewhat restricted in the crystal by the rotation of the piperazine rings (dihedral angle of 132.8°) between the near planes through these rings, where a parallel orientation would correspond to 0°. It is clear, however, that rotation of the piperazine is possible because in the anthracene structure,[9] the rings are more nearly parallel (angle 117.7°). This rotation is attributed to the interaction with a molecule of acetonitrile in the cavity. Structure factors and thermal parameters are provided in supplementary material.

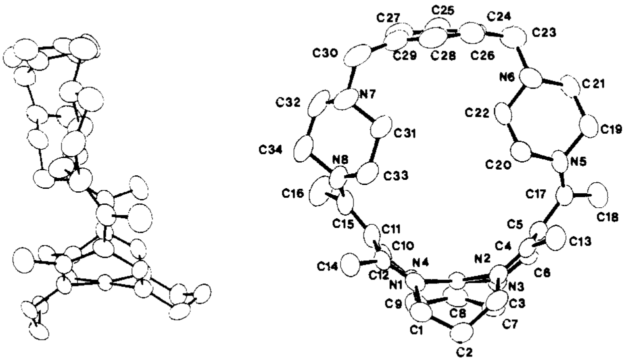


Figure 5. Structure and numbering scheme for $[Ni\{Me_2(CH_2\text{-piperazine})_2 1,4\text{-benzene}[16]\text{cyclidene}\}](PF_6)_2$.

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 the guest and host, relaxation effects should only involve dipolar contributions. The detailed structures of the vaulted cyclidene hosts here have been revealed by X-ray studies.

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 the 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 the 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, or course, gratifying to see that the alcohol and phenol guests are not coordinated to the metal ion. These results suggest the possibility that the sixth coordination site of the metal atom 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.

Experimental Section

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-nonaene-κ^4N)copper(II) Hexafluorophosphate, [Cu{3,6-durene(CH_2-piperazino)$_2$-[16]cyclidene}](PF_6)$_2$. One gram (1.0 mmol) of [Ni{3,6-durene(CH_2-piperazine)$_2$[16]cyclideneN_4}](PF_6)$_2$ (see ref 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 mmol) of [H_4{3,6-durene(CH_2-piperazine)$_2$cyclideneN_4}]B_4 dissolved in 50 mL of hot methanol was added 0.12 g (0.40 mmol) of copper acetate monohydrate and 0.080 g (0.48 mmol) of sodium acetate 3-hydrate. The solution was allowed to stir, and a solution of 0.15 g (0.36 mmol) 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 $CuC_{38}H_{60}N_8P_2F_{12}$: 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[20.7.7.6^{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-κ^4N)copper(II) Hexafluorophosphate, [Cu{9,10-anthracene(CH_2-piperazine)$_2$[16]cyclideneN_4}](PF_6)$_2$. This reaction was performed in the same way as the preceding reaction by using 0.6 g (0.6 mmol) of [Ni{9,10-anthracene(CH_2-piperazine)$_2$[16]-cyclideneN_4}](PF_6)$_2$ (see ref 8) and 0.36 g (0.1 mmol) of copper acetate monohydrate, 0.24 g (1.44 mmoles) of sodium acetate 3-hydrate, and 0.45 g (0.08 mmol) of ammonium hexafluorophosphate: yield, 0.09 g (35%). Anal. Calcd for $CuC_{42}H_{54}N_8P_2F_{12}\cdot CH_3CN\cdot H_2O$: 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[16.7.7.2^{8,11}.2^{3,6}.2^{13,16}]hexatetraconta-1,8,10,17,19,24,26,31,33-nonaene-κ^4N)copper(II) Chloride, [Cu{3,6-durene(CH_2-piperazine)[16]-cyclideneN_4}]Cl_2. In an inert atmosphere glovebox, 1 g (1.0 mmol) of [Cu{3,6-durene(CH_2-piperazine)$_2$[16]cyclideneN_4}](PF_6)$_2$ was dissolved in 20 mL of acetone and 1.5 g (5.3 mmol) 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 $CuC_{38}H_{58}N_8Cl_2\cdot 2HCl\cdot 6H_2O$: 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-tridecaeneN_4)copper(II) Chloride, [Cu{9,10-anthracene-(CH_2-piperazine)[16]cyclidene-κ^4N}]Cl_2. The reaction was performed as the preceding reaction by using 0.2 g (0.2 mmol) of [Cu{9,10-anthracene(CH_2-piperazine)$_2$[16]cyclideneN_4}](PF_6)$_2$ in 20 mL of dried acetone and 0.25 g (0.5 mmol) of tetrabutylammonium chloride dissolved in 10 mL of acetone: yield, 0.039 g (22%). Anal. Calcd for $CuC_{42}H_{54}N_8Cl_2\cdot 6H_2O$: 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.

Synthesis of the Bridged Nickel(II) Complex. (2,17,19,25-Tetramethyl-3,6,13,16,20,24,27,31-octaazapentacyclo[16.7.7.2^{8,11}.2^{3,6}.2^{13,16}]octatriconta-1,8,10,17,19,24,26,31,33-nonaene-κ^4N)nickel(II) Hexafluorophosphate [Ni{Me_2(CH_2-piperazine)$_2$1,4-benzene[16]cyclidene}](PF_6)$_2$. This material was synthesized by previous methods.[13]

Measurements. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. 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 NT 500-MHz NMR spectrometers. Samples were allowed to equilibrate for 30 min at 304 K using a variable-temperature control unit. Five-millimeter outside diameter Wilmad Royal Imperial sample tubes, 528-PP, 7 in. 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 Co., and were used without further purification.

Experimental Precautions. (1) All glassware used in the study of the host–guest phenomena were soaked in 0.5 M EDTA for 24 h 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 glovebox and sealed.

Procedure for Host–Guest Studies. (1) A stock solution of the host compound was prepared by accurately weighting 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 flask containing D_2O 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 $\pi/2$, and $T = \tau$ value. The convergence limit was set to 1.0×10^{-5}, which provided a very accurate fit to the data.

Crystal Structure Parameters for [Ni(Me_2(piperazine)$_2$1,4-benzene-[16]cyclidene)](PF_6)$_2$: $C_{34}H_{50}F_{12}N_8P_2Ni$; monoclinic; space group $P2_1$; $a = 15.579$ (3) Å, $b = 11.887$ (2) Å; $c = 12.617$ (2) Å; $\beta = 117.63$ (1)°; $U = 2070.0$ (6) Å^3; $M = 919.5$; $Z = 2$; $D_c = 1.48$ g cm^{-3}; $D_m = 1.48$ g cm^{-3}; Mo Kα radiation; $T = 298$ K; $\lambda = 0.71069$ Å; μ(Mo Kα) = 6.33 cm^{-1}; $F(000) = 952$; $R = 0.052$ for unique observed $I/\sigma(I) > 3.0$ reflections; crystal character, well-formed red–brown blocks; data collected with a Syntex P2_1 four-circle diffractometer; maximum 2θ, 50°, with scan range ± 0.85° (2θ) around the Kα_1 – Kα_2 angles; scan speed 2–29° min^{-1}, depending on the intensity of a 2-s prescan; backgrounds measured at each end of the scan for 0.25 of the scan time; hkl ranges, 0–16, 0–13, −14–12.

Three standard reflections wee monitored every 200 reflections and showed slight decreases during data collection: data were rescaled to correct for this. The density was measured by flotation. Unit cell dimensions and standard deviations were obtained by a least-squares fit to 15 reflections ($18 < 2\theta < 20°$): 3975 unique reflections ($R_{int} = 0.007$, observed only); 3268 considered observed ($I/\sigma(I) > 3.0$) and used in refinement; corrected for Lorentz, polarization, and absorption effects, the last with ABSCOR (Alcock, 1970); maximum and minimum transmission factors, 0.91 and 0.84; crystal dimensions $0.31 \times 0.48 \times 0.43$ mm; systematic absences $0k0$, $k \neq 2n$ indicating either $P2_1$ or $P2_1/m$, the former selected initially on the basis of the z value, and shown to be correct by the successful refinement. Heavy atoms were located by the Patterson interpretation section of SHELXTL and the light atoms then found on succesive Fourier syntheses. Anisotropic temperature factors were used for all non-H atoms. Hydrogen atoms were given fixed isotropic temperature factors, $U = 0.07$ Å^2. Those defined by the molecular geometry were inserted at calculated positions and not refined; methyl groups were treated as rigid CH_3 units, with their initial orientations taken from the strongest H-atom peaks on a difference Fourier synthesis. The hand of the individual chiral crystal chosen was checked by refinement of a $\delta f''$ multiplier. The y coordinate of the Ni atom was fixed to define the origin. The final refinement on F was by cascaded least-squares methods. The largest positive and negative peaks on a final difference Fourier synthesis were of heights +0.8 and −0.3 e Å^{-3}.

The weighting scheme of the form $W = 1/(\sigma^2(F) + gF^2)$ with $g = 0.0027$ was used and shown to be satisfactory by a weight analysis. Final $R = 0.0515$ and $R_w = 0.058$. The maximum shift/error in the final cycle was 1.0. Computing was with SHELXTL (Sheldrick, 1983) on a Data

General DG30, apart from absorption correction on a Burroughs B6700. Scattering factors in the analytical form and anomalous dispersion factors were taken from ref 38. Final atomic coordinates are given in Table X and bond lengths and angles in Tables XI and XII of the supplementary material.

Crystal Structure Parameters for $\mathbf{[Ni\{Me_2(piperazine)_2 3,6\text{-}durene\text{-}[16]cyclidene\}](PF_6)_2}$: $C_{38}H_{58}N_8P_2F_{12}Ni$ (plus solvent); monoclinic; space group $P2_1/c$; at −80 °C, $a = 9.738$ (2) Å, $b = 23.710$ (6) Å, $c = 21.380$ (9) Å, $\beta = 94.72$ (3)°, $U = 4920$ (3); at −100 °C, $a = 9.772$ (2) Å, $b = 23.733$ (6) Å, $c = 21.278$ (6) Å, $\beta = 94.97$ (2)°, $U = 4916$ (3) Å, $M = 975.5$; $Z = 4$; $D_c = 1.32$ g cm^{-3}; Mo Kα radiation; $T = -80$ °C; $\lambda = 0.71069$ Å; crystal character, well-formed laths; crystals from acetonitrile. Data collection attempted with a Syntex $P2_1$ four-circle diffractometer. Despite holding crystals at −80 and −100 °C with the Syntex LT-1 attachment, the crystals decomposed rapidly (>50% after 30 h). The best attempt gave 800 reflections and less than a complete 0–35° (2θ) shell. Attempts to solve the structure from these data were not successful, and the problem was abandoned.

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Supplementary Material Available: Relaxation data, atomic coordinated, isotropic thermal parameters, bond lengths and bond angles (8 pages). Ordering information is given on any current masthead page.

Novel Pathways for Ligand Substitution Reactions of Dinuclear Platinum(I) Complexes

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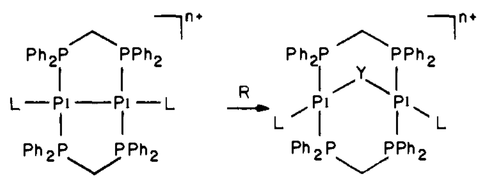
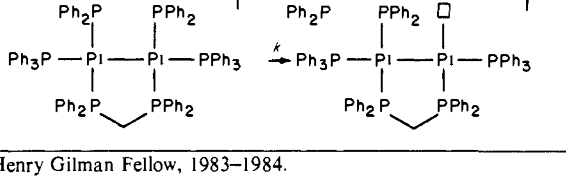
Abstract: The terminal halide and/or triphenylphosphine ligands L in dinuclear platinum(I) complexes $[Pt_2L_2(\mu\text{-dppm})_2]^{n+}$ (where dppm = $Ph_2PCH_2PPh_2$) undergo ready substitutions. The reaction of $[Pt_2Cl_2(\mu\text{-dppm})_2]$, abbreviated (Cl--Cl), with PPh_3 follows a second-order rate law, with $k = 15.2 \pm 0.7$ M^{-1} s^{-1} at 25 °C in CH_2Cl_2. The product is exclusively $(Cl\text{--}PPh_3)^+$; $(Ph_3P\text{--}PPh_3)^{2+}$ forms only in a more polar solvent like methanol. The complex $(Ph_3P\text{--}PPh_3)^{2+}$ reacts in CH_2Cl_2 with halide ions ($X^- = Cl^-$, Br^-, and I^-) also to yield $(X\text{--}PPh_3)^+$. In the presence of inert salts such as perchlorates, the reaction proceeds by rate-limiting dissociation of PPh_3, unusual for square-planar, 16-electron platinum, but further evidence for the large trans influence of the metal–metal bond. In the absence of such salts, however, the reaction occurs in three distinct kinetic stages, although eventually leading to $(Cl\text{--}PPh_3)^+$. One of the intermediates can be stabilized at low temperature; its ^{31}P NMR spectrum identifies it (for $X^- = I^-$ and Cl^-) as a species containing both bridging and chelating dppm, $[Pt_2(X)(PPh_3)(\mu\text{-dppm})(\eta^2\text{-dppm})]^+$. Substitution of PPh_3 in $(Ph_3\text{--}PPh_3)^{2+}$, like the "A"-frame forming reactions of the same complex, starts with dissociation of one arm of a bridging dppm ligand.

Compounds containing two or more metal atoms have attracted much recent interest,[1] in part because of the analogies drawn between homogeneous and heterogeneous catalysis. The insertion of atoms and small molecules into metal–metal bonds leads to "A"-frame structures. Thus platinum(I) complexes containing bridging bis(diphenylphosphino)methane ligands, $[Pt_2Cl_2(\mu\text{-dppm})_2]$ and $[Pt_2(PPh_3)_2(\mu\text{-dppm})_2]^{2+}(PF_6^-)_2$ abbreviated[2] as (Cl--Cl) and $(Ph_3P\text{--}PPh_3)^{2+}$, react in dichloromethane with diazomethane, carbon monoxide, sulfur, sulfur dioxide, and hydrogen chloride.[3] They yield so-called molecular "A"-frame complexes $Pt_2Cl_2(\mu\text{-}Y)(\mu\text{-dppm})_2$ and $[Pt_2(PPh_3)_2(\mu\text{-}Y)(\mu\text{-dppm})_2]^{2+}$, respectively, with Y = CH_2, CO, S, SO_2, and H^+; e.g., eq 1, L = Cl^-, PPh_3; and R = CH_2N_2, CO, S_8, SO_2, HCl.



(1)

Although kinetics and other data suggest a direct bimolecular reaction for (Cl--Cl), data for the complex $(Ph_3P\text{--}PPh_3)^{2+}$ suggest[5] an intermediate derived by dissociation of one arm of the bridging diphosphine ligand.



(2)

We sought to substantiate the involvement of the "chelate-opened" intermediate by other evidence. If the $(Ph_3P\text{--}PPh_3)^{2+}$ is, indeed, too hindered to allow direct attack (by virtue of the seven phenyl groups around each platinum atom), then its other reactions, including ligand substitution, would be subject to the same effect.[6-8]

Thus we considered reactions leading to the mixed halide–phosphine complexes, $[Pt_2(X)(PPh_3)(\mu\text{-dppm})_2{}^+]$ or $(X\text{--}PPh_3)^+$. They can be formed not only by halide addition to $(Ph_3P\text{--}PPh_3)^{2+}$ but also by PPh_3 addition to (Cl--Cl). Each route to $(X\text{--}PPh_3)^+$ may adopt a different mechanism. This work concerns these issues as they relate to the formation of $(X\text{--}PPh_3)^+$ for X = Cl^-, Br^-, and I^-.

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(1) Puddephatt, R. J. *Chem. Soc. Rev.* **1983**, *12*, 99.

(2) It is convenient for certain equations to abbreviate the structure of the parent complexes, which we have chosen to do by showing only the pair of terminal ligands bound to the $Pt_2(\mu\text{-dppm})_2$ core, as in the examples (Cl--Cl), $(Cl\text{--}PPh_3)^+$, and $(Ph_3P\text{--}PPh_3)^{2+}$.

(3) Brown, M. P.; Fisher, J. R.; Puddephatt, R. J.; Seddon, K. R. *Inorg. Chem.* **1979**, *18*, 2808.

(4) Muralidharan, S.; Espenson, J. H. *Inorg. Chem.* **1983**, *22*, 2786.

(5) Muralidharan, S.; Espenson, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 8104.

(6) That is not to say that terminal ligand substitution, usually a facile process[7-9] for this family of Pt_2 complexes, constitutes a general or preferred route for insertion. In fact, we rather doubt that and consider that terminal substitution may more likely be a "dead-end" for A-frame formation. Quite irrespective of that, however, if insertion into the parent complex is indeed hindered, then other reactions, including substitution, may be as well.

(7) (a) Brown, M. P.; Franklin, S. J.; Puddephatt, R. J.; Thomson, M. A.; Seddon, K. R. *J. Organomet. Chem.* **1979**, *178*, 281. (b) Brown, M. P.; Puddephatt, R. J.; Rashidi, M.; Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1978**, 1540.

(8) Shimura, M.; Espenson, J. H. *Inorg. Chem.* **1984**, *23*, 4069.

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