Inclusion Complex Formation by Transition-Metal Complexes Containing a Void in Proximity to a Site That Can Be Made Catalytically Active

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Abstract: Carbon-13 chemical shift studies show that, in aqueous solutions, a variety of alcohols and phenols enter the hydrophobic void of a new family of host molecules. Each carbon atom of the host shows a distinctive chemical shift change as the concentration of inclusion complex is increased by incrementally increasing the guest concentration. This and the fact that all of the chemical shift changes reach saturation simultaneously establish the proposed guest–host association. The signs and magnitudes of the total chemical shift changes at saturation of the equilibrium can be accounted for semiquantitatively with a model in which solvent water is displaced from the cavity by the guest. The significance of inclusion complex formation in these systems to the development of a new class of oxidation catalysts is discussed.

The broad significance of guest–host complexes has been addressed most extensively in the course of studies on the cyclodextrins.[1,2] Those compounds have served as vehicles for the study of inclusion complexes both in the solid state[3–6] and in solutions.[7] The fundamental nature of the process of inclusion complex formation by cyclodextrins involves hydrophobic interactions,[2,13] and analogies have been drawn to the hydrophobic binding of substrates in enzymes.[1,2,13] Appropriately, the catalytic actions of cyclodextrins[14–16] and their derivatives[17–24] have been investigated.

As reported earlier,[25–27] we have designed a new family of molecular species specifically to facilitate the simultaneous binding of substrates and molecular dioxygen in a ternary complex. The structures of these vaulted macrobicyclic nickel(II) complexes are given in Figure 1. While the model for these studies has been the ternary complex of cytochrome P450,[28–30] the ultimate goal is to contribute to the design of a new class of selective oxidations.[26,27] The activation of dioxygen by cytochrome P450 produces an extremely reactive species capable of oxygenating even saturated hydrocarbons.[29,31] The extreme reactivity of such intermediates simultaneously provides the possibility of oxygenating such notably unreactive substrates as alkanes and dictates the necessity for special measures to hinder self-destruction of the catalyst. Competitive protection of the catalyst may be facilitated by the omnipresence of a substrate, maintained in a particularly vulnerable location with regard to the catalytic site. This strongly suggests the virtue of a hosting site that would accommodate inclusion of a substrate as guest in a location very near the active site. Further, since alkanes are prospective substrates, the driving force for inclusion complex formation is limited to the array of phenomena labeled as hydrophobic interactions. In the case of cytochrome P450, it has been concluded that the substrate–enzyme association derives principally from hydrophobic interactions.[28]

An earlier paper[26] details the design, synthesis, and characterization of a new family of vaulted macrobicyclic ligands, designed to facilitate, at the same time, the hydrophobic binding of a substrate and the coordination of a dioxygen molecule to an appropriate transition-metal ion. We have previously reported the reversible O_2 adduct formation by the cobalt(II)[32,33] and iron(II)[33,35] complexes of very closely related ligands.[36] Recent studies in these laboratories have also shown that the O_2 adducts can be converted into interesting new species by one-electron reduction, in analogy to the activation step in cytochrome P450 chemistry.

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(1) Bender, M.; Komiyama, M. "Cyclodextrin Chemistry and Structures. Concepts in Organic Chemistry"; Springer-Verlag: Berlin, 1978; Vol. 6.
(2) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(3) Saenger, W.; McMullan, R.; Rayos, R.; Mootz, D. *Acta. Crystallogr., Sect. B* **1974**, *30B*, 2019.
(4) Harata, K.; Uedaira, H.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1975**, *51*, 1627.
(5) Harata, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2409.
(6) Harata, K.; Uedaira, H. *Nature (London)* **1975**, *253*, 190.
(7) Bergeron, R.; Channing, M. *Bioorg. Chem.* **1976**, *5*, 437.
(8) Gelb, R.; Schwartz, L.; Laufer, D. *J. Am. Chem. Soc.* **1978**, *100*, 5875.
(9) Damarco, P.; Thakker, A. *Chem. Commun.* **1970**, 2.
(10) Bergeron, R.; Rowan, R., III *Bioorg. Chem.* **1976**, *5*, 425.
(11) Gelb, R.; Schwartz, L.; Markinac, J.; Laufer, D. *J. Am. Chem. Soc.* **1979**, *101*, 1864.
(12) Gelb, R.; Schwartz, L.; Cardelino, B.; Fuhrman, H.; Johnson, R.; Laufer, D. *J. Am. Chem. Soc.* **1981**, *103*, 1750.
(13) Tabushi, I.; Kuyosuke, Y.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916.
(14) Cramer, F.; Dietschi, J. *Chem. Ind. (London)* **1958**, 892.
(15) Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(16) Cramer, F. *Angew. Chem.* **1961**, *73*, 49.
(17) Cramer, F.; Mackensen, G. *Angew. Chem.* **1966**, *78*, 641.
(18) Iwakura, Y.; Uno, K.; Toda, F.; Onozuka, S.; Hattori, K.; Bender, M. L. *J. Am. Chem. Soc.* **1975**, *97*, 4432.
(19) Gruhn, W. B.; Bender, M. L. *Bioorg. Chem.* **1974**, *3*, 324.
(20) Breslow, R.; Hammond, M.; Lauer, J. *J. Am. Chem. Soc.* **1980**, *102*, 421.
(21) Breslow, R.; Doherty, J.; Guillot, G.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 2115.
(22) Breslow, R.; Bovy, P.; Hersch, C. L. *J. Am. Chem. Soc.* **1980**, *102*, 2115.
(23) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100.
(24) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614.
(25) Takeuchi, K. J.; Busch, D. H.; Alcock, N. *J. Am. Chem. Soc.* **1981**, *103*, 2421.
(26) Takeuchi, K. J.; Busch, D. H.; Alcock, N. *J. Am. Chem. Soc.* **1983**, *105*, 4261.
(27) Kwik, W.-L.; Herron, N.; Takeuchi, K. J.; Busch, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 409.
(28) White, R. E.; Coon, M. J. *Annu. Rev. Biochem.* **1980**, *49*, 315.
(29) Sato, R.; Omura, T. "Cytochrome P450"; Academic Press: New York, 1978.
(30) Gunsalus, I. C.; Meeks, J. R.; Lipscomb, J. V.; Debrunner, P. G.; Munck, E. "Molecular Mechanisms of Oxygen Activation"; Haiyaishi, O., Ed.; Academic Press: New York, 1974; p 559 ff.
(31) Groves, J. T. "Metal Ion Activation of Dioxygen"; Spiro, T., Ed.; Wiley-Interscience: New York, 1974; p 559 ff.
(32) Stevens, J. C.; Busch, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 3286.
(33) Cameron, J. H.; Kojima, M.; Daszkiewicz, B. K.; Jackson, P. J.; Chavan, M.; Busch, D. H., submitted.
(34) Herron, N.; Busch, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 1236.
(35) Herron, N.; Cameron, J. H.; Neer, G. L.; Busch, D. H. *J. Am. Chem. Soc.* **1983**, *105*, 298.
(36) The ligands were originally designed only to facilitate dioxygen binding. Reference 26 describes the alteration of the superstructure in order to accommodate a substrate as well.

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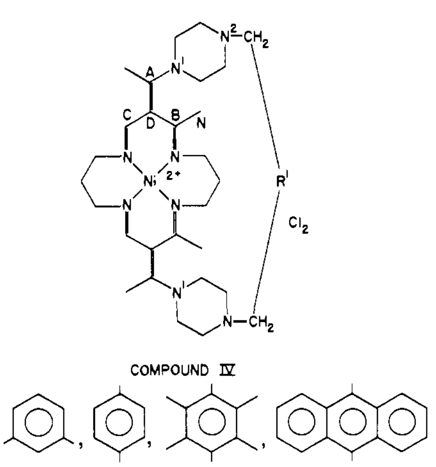


COMPOUND IV

Figure 1. Structures of the vaulted macrobicyclic nickel(II) host compounds with labels to indicate atoms of interest in their carbon-13 NMR spectra.

This report demonstrates the formation of inclusion compounds by the nickel(II) complexes of the new ligands. Nickel(II) is chosen for convenience in NMR spectrometric studies; clearly the metal ion can be changed according to the needs of a particular study. The experimental procedures use NMR techniques developed in studies on cyclodextrins. Laufer[8] has shown that the carbon-13 chemical shift values, $\delta_{\mathrm{obsd}}{}^{i}$, of the six unique cyclodextrin carbon atoms, c^i, vary as a function of guest concentration. For the formation of a 1:1 inclusion complex, the observed chemical shift value, $\delta_{\mathrm{obsd}}{}^{i}$, can be expressed by eq 1, where H =

$$\delta_{\mathrm{obsd}}{}^{i} = \delta_{H}{}^{i}\frac{H}{H_{\mathrm{T}}} + \delta_{\mathrm{GH}}{}^{i}\frac{\mathrm{GH}}{H_{\mathrm{T}}} \tag{1}$$

the concentration of free host; GH = the concentration of guest–host complex; H_{T} = the total concentration of host; $\delta_{H}{}^{i}$ = the chemical shift of carbon atom c^i in the absence of a guest molecule; and $\delta_{\mathrm{GH}}{}^{i}$ = the chemical shift of carbon atom c^i in the guest–host complex. In the carbon-13 NMR experiments, the relationship between $\delta_{\mathrm{obsd}}{}^{i}$ and the guest substrate concentration yields the association constant as defined in eq 2. A Benesi–

$$K = \frac{(\mathrm{GH})}{(G)(H)} \tag{2}$$

Hildebrand analysis[37] yields a value for the equilibrium constant. The equation to be solved is

$$\frac{\Delta\delta}{\Delta\delta_{\mathrm{m}}} = \frac{KG_{\mathrm{T}}}{1 + KG_{\mathrm{T}}} \tag{3}$$

where G_{T} is total guest concentration and $\Delta\delta_{\mathrm{m}}$ is the maximum chemical shift (saturation of equilibrium) for the resonance being examined. The reciprocal of this is readily solved by the usual grapical or linear least-squares methods.

The total change in chemical shift value (eq 4) is interpreted to be a function of the distance between carbon atom c^i and the guest molecule, with a large $\Delta\delta_{\mathrm{m}}{}^{i}$ value corresponding to a small intermolecular guest–host distance. The geometry of the

$$\Delta\delta_{\mathrm{m}}{}^{i} = \delta_{\mathrm{GH}}{}^{i} - \delta_{\mathrm{H}}{}^{i} \tag{4}$$

guest–host association can be inferred qualitatively through a spatial analysis of all of the $\Delta\delta_{\mathrm{m}}{}^{i}$ values.[8,9] Similarly, carbon-13 NMR studies on the nickel(II) complexes of the new vaulted host ions provide much insight into the character and geometry of the guest–host association, but, as in other cases, the values of K obtained in this way are only approximate.

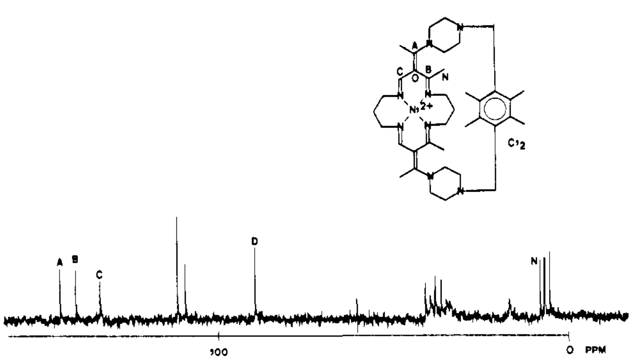
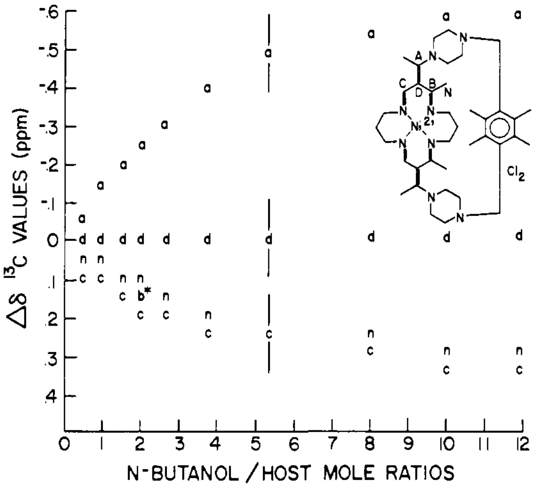


Figure 2. The carbon-13 NMR spectrum of [Ni(3,6-durene(CH$_2$-piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$)](Cl)$_2$.



*The Δδ values for carbon atom B coincide with the values for carbon atoms N or C.

Figure 3. The carbon-13 NMR Δδ values for selected carbon atoms as a function of 1-butanol/host mol ratios for the [Ni(3,6-durene(CH$_2$-piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$)](Cl)$_2$.

Table I. ^{13}C Δδ Values for [Ni{3,6-durene(CH$_2$piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}](Cl)$_2$[b] Using 1-Butanol As a Guest Molecule Δδ (ppm)[d]

[guest] (M)[c]	guest/host	*A*	*B*	*C*	*D*	*N*
0.020 (7)	0.54 (6)	−0.049		+0.097	-	+0.049
0.041 (4)	1.0 (9)	−0.146	+0.049	+0.097	-	+0.049
0.062 (0)	1.6 (4)	−0.194	+0.097	+0.146	-	+0.097
0.082 (4)	2.1 (8)	−0.243	+0.146	+0.194	-	+0.097
0.10 (3)	2.7 (3)	−0.297	+0.146	+0.194	-	+0.146
0.14 (3)	3.8 (2)	−0.389	+0.195	+0.243	-	+0.194
0.20 (4)	5.4 (6)	−0.486	+0.243	+0.243	-	+0.243
0.30 (3)	8.1 (9)	−0.534	+0.292	+0.292	-	+0.243
0.40 (0)	10.9 (9)	−0.582	+0.292	+0.340	-	+0.292
0.43 (8)	12 (0)	−0.583	+0.292	+0.340	-	+0.291

[a] Δδ = (^{13}Cδ(host in presence of guest) − ^{13}Cδ(host)). [b] Moles of host = 9.89×10^{-5}. [c] Calculated based on additivity of D$_2$O (2.6 mL) and volume of 1-butanol (5 μL = 5.40×10^{-5} mol). [d] Uncertainty = ±0.10 ppm: Lettering scheme from Figure 1.

Results and Discussion

The carbon-13 NMR experiments involved a titration of guest into host solution, in accompanyment to repetitive recording of the spectrum. For example, 2.6 mL of a 0.038 M solution of the host compound [Ni{3,6-durene(CH$_2$piperazineEthi)$_2$Me$_2$[16]tetraeneN$_4$}](Cl)$_2$ was prepared in deuterium oxide. The carbon-13 NMR spectrum of this solution was measured (Figure 2). A 5-μL aliquot (5.4×10^{-5} mol) of the guest compound 1-butanol was added to the carbon-13 NMR tube, and the NMR spectrum of the solution was again recorded. Additional 5-μL aliquots of 1-butanol were added, and the corresponding carbon-13 NMR spectra measured, until the total concentration of 1-butanol reached approximately 0.6 M. The chemical shift changes, Δδ, observed during such a titration are illustrated in Table I (Δδ = δ of host in the presence of guest minus δ of host in the absence of guest). The uncertainty of the Δδ values (±0.1 ppm) arises from the combined uncertainties of the individual resonances.

Because of such complications as solvent-induced broadening, uncertainty in the assignments of some resonances, and overlap with guest molecule resonances, only resonances for carbon atoms A, B, C, D, and N (Figure 2) were considered in the analysis of the guest–host association. Because in the best of cases the total range observed for $\Delta\delta$ is only 5 to 6 times the uncertainty in the quantity, extensive calculations cannot be justified.

The behaviors of the various guest–host systems are nicely illustrated by a specific example. The pattern of $\Delta\delta$ values displayed in Figure 3 and Table I was found for all nickel(II) vaulted guest–host interactions. The $\Delta\delta$ values for host carbon atom A are usually the largest in magnitude and negative in sign; the $\Delta\delta$ values for host carbon atoms B, C, and N are usually similar to each other in magnitude and positive in sign; and the values for host carbon atom D are usually small. The $\Delta\delta$ values for host carbon atoms A, B, C, D, and N display a saturation behavior in which the $\Delta\delta$ values all approach constancy simultaneously at large guest/host ratios. Although the mole ratios were always large as the saturation point was approached (>8:1) the total guest concentrations remained less than 1.0 M. Since the $\Delta\delta$ values for host carbon atoms A, B, C, D, and N display unique signs and magnitudes, yet display saturation behavior at similar guest/host ratios, a specific guest–host process involving all host carbon atoms must be occurring.

It was observed that the carbon-13 chemical shifts for the guest compounds did not change as a function of guest concentration in aqueous solutions at concentrations of 1.0 M or less. Thus the changes in bulk solvent due to changes in guest concentration do not affect the chemical shift values of the guest. Since the $\Delta\delta$ of saturation for the host carbon atom resonances occur at similar moderate guest concentrations (<1.0 M), the $\Delta\delta$ saturation phenomenon is not due to changes in the bulk solvent, but to a specific guest–host association phenomenon.

On the basis of these general observations and specific experiments to be discussed later, a scheme for guest–host association between the nickel(II) vaulted host and various guest compounds has been devised. Central to this model is the concept that in aqueous solution the host ion initially possesses intercalated water molecules which form hydrogen bonds with the N^1 atoms of the superstructure arch of the host (Figure 1). Upon guest-host association, the guest molecule is enclosed within the confines of the hydrophobic vault, resulting in displacement of the intercalated water molecules. Several sets of carbon-13 NMR experiments will be discussed in terms of this scheme. The first set of carbon-13 NMR experiments shows the effect of varying the guest compounds on the guest–host association, using the same host compound that is described in the example above. The second set of experiments was directed in a similar way at the effects of varying the host compounds while the guest compound remained fixed, namely 1-butanol. The third set of experiments involved the effect of variation of solvent on the guest–host association between the typical guest and host compounds.

Variation of Guest Compound. The carbon-13 chemical shift values of the host $[\mathrm{Ni}\{3,6\text{-durene}(\mathrm{CH_2PiperazineEthi})_2\mathrm{Me}_2\text{-}[16]\mathrm{tetraeneN}4\}](\mathrm{Cl})_2$ were measured as a function of guest/host ratios for the guest compounds methanol, ethanol, 1-butanol, benzyl alcohol, phenol, 2,6-dimethylphenol, and 3,5-dimethylphenol. For purposes of this discussion the chemical shift changes ($\Delta\delta$) of carbon atom A (Figure 2) of the host compound are plotted against the guest/host mole ratios for the various guest compounds (Figure 4). Similar trends can be seen from the $\Delta\delta$ values of the resonances for carbon atoms B, C, and N but the resonance for carbon atom A was chosen because the $\Delta\delta$ values for that atom display the largest shifts upon addition of the guest compound. Initially, the $\Delta\delta$ values for carbon atom A decrease sharply as the guest/host ratio increases; they then approach limiting negative values at large guest/host ratios. These limiting $\Delta\delta$ values, or saturation values, are negative in sign, which is indicative of an upfield shift of the chemical shift of the guest–host complex relative to that for the host alone. For guest substrates 1-propanol, 1-butanol, and benzyl alcohol, the general shapes of the respective graphs of $\Delta\delta$ vs. guest/host ratio are very similar, with similar saturation values, and one might suspect that the guest–host association constant is of similar magnitude for these substrates. Application of eq 3 (Gauss–Jordan least-squares fit) gives values of K (M^{-1}) and $\Delta\delta_m$ (ppm) as follows (resonance A): 1-BuOH, 4.2 ± 0.5, −0.98 ± 0.08; 1-PrOH, 7.8 ± 0.7, −.74 ± 0.04; $C_6H_5CH_2OH$, 5.2 ± 0.2, −0.87 ± 0.02% *t*-BuOH, 0.77 ± 0.30, −2.6 ± 0.96. The correlation coefficients are 0.9966, 0.9983, 0.9999, and 0.9994, respectively. From these values one may be tempted to conclude complexing by the guests 1-BuOH, 1-PrOH, and benzyl alcohol is indistinguishable, while *t*-BuOH may bind slightly more weakly.

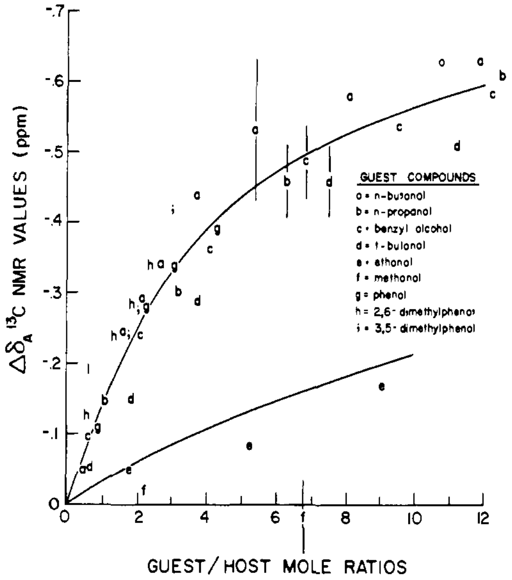


Figure 4. The carbon-13 NMR $\Delta\delta$ values tor carbon atom A of the host compound $[\mathrm{Ni}(3,6\text{-durene}(\mathrm{CH_2piperazineEthi})_2\mathrm{Me}_2[16]\mathrm{tetraeneN}_4)](\mathrm{Cl})_2$ as a function of guest/host mol ratios for a variety of guest compounds.

We believe it is more rational to indicate the approximate magnitude of K by comparing the experimental data to calculated curves corresponding to different K values. Using $\delta H = 0$ ppm and $\delta GH = -0.80$ ppm, several theoretical curves were drawn (Figure 4). From these curves, the data can be qualitatively ordered in terms of their K magnitudes. Within experimental error, K for 2-propanol, 1-butanol, *tert*-butyl alcohol, and benzyl alcohol appear to be in the vicinity of the theoretical curve having $K = 7$. Although the host compound appears to be non-discriminating toward these four guest compounds, the apparent noninteraction of the host with the guest compound methanol (Figure 4) is most impressive. Up to guest/host ratios of 6.7:1, as $\Delta\delta$ value for carbon atom A remains very small, 0.07 ppm. Thus, this particular host compound appears to discriminate sharply between methanol and the guest compounds discussed immediately above. As might be expected, the behavior of ethanol is intermediate between that of methanol and the other alcohols. It appears that a hydrocarbon chain of some minimum length is required in order to favor inclusion complex formation.[38]

Phenol and its 2,6-dimethyl- and 3,5-dimethyl-substituted derivatives were also studied. The observed chemical shift changes were quite similar to those found for most alcohols, both in sign and magnitude. Solubilities of the phenols limited the maximum concentrations of guest that was attainable, so that the guest/host ratios span only the narrow range 0–4.0. However, within the range, the behavior seems to signal association constants of about 10 M^{-1}. In an effort to extend the range of guest/host ratios, mixed solvent containing 10% CD_3OD in D_2O was tested.

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(37) Benesi, A.; Hildebrand, J. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

(38) Admittedly, this tentative conclusion assumes that inclusion of ethanol and methanol within the cavity will lead to the same $\Delta\delta$ effect. This is consistent with the mechanism suggested for implementation of the chemical shift change as described in the section The Nature of the Guest–Host Equilibria.

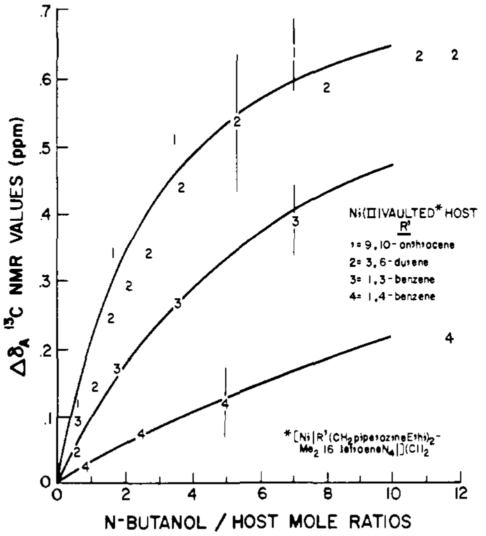

Figure 5. The carbon-13 NMR $\Delta\delta$ values for carbon atom A of various nickel(II) vaulted host compounds as a function of 1-butanol/host mol ratios.

However, the $\Delta\delta$ values were somewhat smaller than in pure D_2O, as might be expected if the association is indeed hydrophobic in nature.

Variation of Host Compound. The carbon-13 chemical shift values (δ) of the host carbon atoms were measured as a function of the guest/host ratios for the guest compound 1-butanol and the various nickel(II) vaulted host compounds (Figure 5) as distinguished by different bridging groups: R^1 = 1,3-benzene, 1,4-benzene, 3,6-durene, and 9,10-anthracene. As an example, the carbon-13 chemical shift changes $\Delta\delta$ of host carbon atoms A are plotted vs. guest/host mol ratios in Figure 5. Smooth curves are drawn to unify the data for each case. Similar trends can be seen from the $\Delta\delta$ values of the carbon-13 resonance for carbon atoms B, C, and N, but, as before, the carbon-13 resonance for carbon atom A was chosen for analyses.

The rough estimation of the values of K when eq 3 is used reveal no convincing trends. The values found for the various bridges are the following: durene, 4.2 ± 0.47; anthracene, 3.1 ± 0.52; 1,4-benzene, 3.7 ± 1.1; 1,3-benzene, 7.9 ± 1.3, with correlation coefficients of 0.9966, 0.9985, 0.9922, and 0.9950. It must be emphasized that these K values are highly imprecise. They do, however, direct attention to the probability that the diverse behavior in Figure 5 derives from a different cause rather than K.

The variation of the R^1 linkage is expected to affect the magnitude of the guest–host association constant, but it is assumed that the general nature of the guest–host association remains unchanged. This is the behavior observed for cyclodextrins when the hydrophobic voids in those molecules are enhanced by the addition of caps. The four methyl substituents on the R^1 group in the durene-bridged vaulted complex increase the hydrophobic volume of the host vault relative to the unsubstituted benzene derivative, and this is expected to favor the hydrophobic interaction between guest and host compounds.[2] Unfortunately, the present data do not provide useful information on this matter.

Variation of Solvent Media. The solvent dependence of the guest–host phenomenon is a critical matter since the association is expected to be of hydrophobic origin.[13] The guest–host association behavior of the nickel(II) vaulted host compounds in D_2O has been the subject of the preceding discussion. In contrast, when acetonitrile-d_3, acetone-d_6, or nitromethane-d_3 was the solvent, no variation of $\Delta\delta$ values was observed for the carbon atom resonances of the host ion, R^1 = 3,6-durene, with varying concentrations of guest compound 1-butanol. Thus, the solvent dependence of the guest–host association is consistent with the assumption of hydrophobic interaction.

The Nature of the Guest–Host Equilibria. Two important facts concerning the guest–host association properties of the host compound having a durene bridge derive from the data obtained in studies involving the variation of the guest compounds. First, with the guests 1-propanol, 1-butanol, 2,2-dimethyl-2-ethanol, and benzyl alcohol, and with three phenols, chemical shifts change in closely similar ways in response to changes in guest/host ratios. The general shapes of the curves and the associated saturation phenomenon are both consistent with the assumption that the guest compound is included within the vault of the host compound. Second, the host compound having R^1 = 3,6-durene displays remarkable discrimination between the early members of the series of alchols, methanol, and ethanol and the remaining guest molecules that were studied. This suggests that an important aspect of this particular guest–host association is the number of $-CH_2-$ linkages or CH_3 groups present in the guest molecule, or equivalent hydrophobic matter in the case of aromatic derivatives. The relationship between the number of $-CH_2-$ linkages and hydrophobicity, first observed by Traube[39] through surface activity experiments, suggests that hydrophobic forces related to those involved in micelle formation[40] may play an important role in this guest–host association. Thus, the hydrophobic guest molecule may be driven into the hydrophobic vault, in part, by hydrophobic repulsion due to the bulk aqueous medium. This would simultaneously drive out any water contained in the vault.

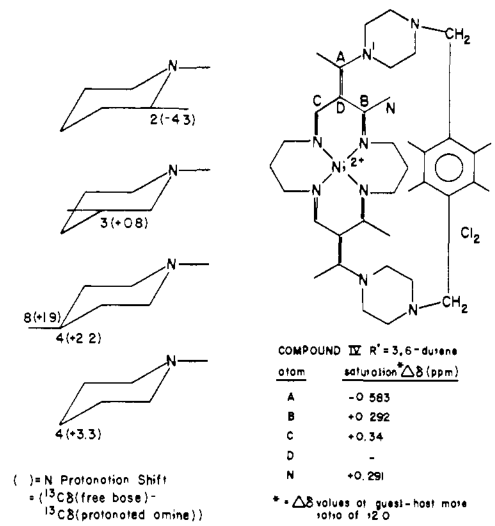

Figure 6. Comparison between the N-protonation shift values of substituted *N*-methylpiperazines and the saturation $\Delta\delta$ values for a nickel(II) vaulted host compound.

From the above observations, the general characteristics of guest–host association between nickel(II) vaulted host ions and small organic guest compounds are as follows: the guest–host association requires a minimum number of CH_3-, $-CH_2-$, or $>CH-$ linkages, or, more generally, a minimum hydrophobic bulk in the guest compounds; the guest–host association requires water (D_2O) as the solvent. From these properties and from the magnitudes and signs of the saturation $\Delta\delta$ values of the host compound, a more intimate model for this guest–host association can be proposed.

As indicated earlier, the model that has been developed to account for the behavior of these systems is based on the assumption that water molecules originally occupy the void but can be displaced by a guest molecule. We assume that the vaulted host compound has a number of molecules of deuterium oxide included within the host vault. These intercalated D_2O molecules form hydrogen bonds with nitrogen atoms N^1 of the ligand superstructure (Figure 6). Upon saturation of the guest–host equilibrium, the guest molecule, e.g., 1-butanol, resides within the confines of the vault, crowding out the D_2O molecules and thus breaking the hydrogen bonds between N_1 and the included D_2O. The concept that host-intercalated water must be displaced upon

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(39) Traube, J. *Ann.* **1981**, *265*, 27.

(40) Tanford, C. "The Hydrophobic Effect: Formation of Micelles and Biological Membranes"; Wiley-Interscience: New York, 1980; Chapter 6.

inclusion of the guest in the cavity was recognized by Bender to be a major aspect of guest–host association involving cyclodextrins.[1] On the basis of thermodynamic and X-ray crystal structure observations, Bender concluded that two molecules of water are present within the cyclodextrin host in aqueous solution, and that these water molecules are removed from the cyclodextrin void when a guest enters the host.

This model (displacement of water by guest) is consistent with the signs and relative magnitudes of the changes in chemical shifts of the host carbon atoms as shown in Figure 6. Initially, the N^1 nitrogen atom has a slight positive charge due to hydrogen bond formation. Upon guest inclusion, the D_2O molecules are replaced by the guest compound, causing disruption of the N^1–D_2O hydrogen bonds. The N^1 nitrogen atom then loses its slight positive charge. The effect of charge variance on the nitrogen atom of aliphatic amines on the carbon-13 NMR spectra of the amines has been studied by Morishima[41] and Reilly.[42] The carbon-13 chemical shift changes due to complete protonation of the amines by the acid have been called the N-protonation shift values, specifically, N-protonation shift = δ(amine) - δ (protonated amine). Using the N-protonation shift values for substituted *N*-methyl piperidines, the chemical shift changes for vaulted host ions can be interpreted as resulting from the disruption of hydrogen bonds between D_2O and nitrogen atom N^1. Since both $\Delta\delta$ and the N-protonation shift are defined in the same direction [δ(free base = amine or GH) - δ(protonated or hydrogen bonded base)], the two effects can be compared directly. Hydrogen bond formation with the N^1 nitrogen atom should produce similar effects to protonation, but to a lesser degree. For all vaulted host compounds, carbon atom A (Figure 6) has the largest and most negative saturation $\Delta\delta$ value. Similarly, for *N*-methyl-2-methylpiperidine, carbon atom 2 displays the largest and most negative N-protonation shift. Thus, the negative saturation value $\Delta\delta$ of carbon atom A is consistent with disruption of the hydrogen bond between the nitrogen atom and D_2O upon inclusion of the guest and simultaneous elimination of D_2O. Carbon atom D displays little or no chemical shift effect and therefore is similar to carbon atom 3 of *N*-methyl-3-methylpiperidine. Carbon atoms B and C (Figure 6) display positive $\Delta\delta$ values, in analogy to carbon atom 4 of *N*-methyl-4-methylpiperidine and *N*-methylpiperidine, respectively. The carbon atom N also displays a positive $\Delta\delta$ value, like carbon atom 8 of *N*-methylpiperidine. Both the signs and relative magnitudes of the saturation $\Delta\delta$ values corresponding to carbon atoms A, B, C, D, and N are consistent with their respective counterparts from among the N-protonation shift values for substituted piperidines.

It should be noted that the alcohols and phenols chosen as guests are also capable of forming hydrogen bonds. Thus, it is possible on the basis of the data presented here that the guest molecules might also form hydrogen bonds with the nitrogen atom N^1 (Figure 6). This matter is addressed directly in studies focused on determining the orientation of guests within the host cavities.[27] Those investigations have shown that the guests do not hydrogen bond with the host.

In conclusion, it has been shown that the new vaulted macrobicyclic ligand complexes act as hosts to a variety of guest molecules, specifically alcohols and phenols. The carbon-13 shift changes that are observed are consistent with a model in which the inclusion of the guest within the void displaces water molecules that would otherwise reside within the void. The structure dependence and the solvent dependence of the phenomenon imply that the driving force for the process is hydrophobic in its nature. The detailed manner in which the NMR spectra change in the presence of guest molecules provides very strong evidence that the guest molecules actually do occupy the commodious void provided for them. This opens the way for further studies directed toward the development of a new class of oxidation catalysts in which both a substrate and a dioxygen molecule are bound in a ternary complex prior to the catalytic event. Studies are under way on the orientation and location of guest molecules within the inclusion complex, on the effects of guests on the dioxygen binding capability of the cobalt and iron complexes, and on the possible catalytic abilities of the ternary species.

Experimental Section

Apparatus and Materials. The instrument used to acquire the carbon-13 data was a Bruker WP80 NMR spectrometer operating at 20.0 MHz. Generally, the carbon-13 spectra were obtained at ambient temperatures using ($\sim$30 °C) broad-band proton decoupling, with a sweep width of 4000 Hz acquired over 8K/16K data points. Ten-milliliter o.d. Wilmad Large Volume Sample Tubes, 513-PP, 7 in. in length, were used to contain the host sample solutions. A 50-μL Hamilton Microliter Syringe, fitted with a Chaney adapter and a flat-end needle, was used to introduce guest substrates into the host solutions. Aldrich Gold Label 99.8% hydrogen-2 deuterium oxide was used as the solvent in all experiments. A Wilmad Precision Coaxial Cell, 516-CC, 10-mm o.d., was used to measure carbon-13 NMR spectra in the presence of an external reference.

The host compounds were synthesized by methods that have been reported earlier.[26] The organic guest molecules used in the intermolecular association experiments were spectrophotometric grade, Gold Label chemicals, purchased from Aldrich Chemical Co., and were used without further purification.

Procedure for Studying Intermolecular Association. (1) Approximately 70 mg of a host compound was weighed accurately (+0.1 mg) in a 10-mm o.d. sample tube with use of an analytical balance.

(2) With a volumetric pipet, 2 mL of deuterium oxide was added to the sample tube containing the host compound. The mixture was agitated to achieve thorough solution, then capped tightly.

(3) The sample tube was placed in the NMR spectrometer and allowed to reach thermal equilibrium at probe temperature ($\sim$5 min).

(4) The Bruker WP80 NMR spectrometer was then adjusted to the following settings: (a) sweep width = 4000 Hz; (b) pulse length = 4 μs; (c) memory size = 8K/16K; (d) data collection mode = autorecur.

(5) After a sufficient number of scans was acquired, the assignment of chemical shift values of the host carbon-13 spectrum was effected by setting arbitrary values to the initial host chemical shift values and then retaining these settings throughout the experiment. In this manner, the 8K data points of each spectrum correspond consistently to the same hertz values.

(6) Once the initial host carbon-13 NMR spectrum was obtained, a small aliquot of guest compound was added directly to the host sample tube with use of a syringe fitted with a Chaney adapter. The Chaney adapter facilitates reproducible addition of guest compound.

(7) Steps 3, 4, and 5 were then repeated.

(8) Another identical aliquot of guest compound was added directly to the host sample tube with the same syringe as in step 6. When possible, steps 3, 4, 5, and 8 were repeated until the chemical shift values of the host carbon-13 NMR spectrum cease to change with increasing guest concentration.

Procedure for Measuring Guest–Solvent Interaction. (1) With a volumetric pipet, 2 mL of deuterium oxide was added to the inner cell of a Wilmad Precision Coaxial cell. To the D_2O was added a small aliquot of guest compound, using a syringe fitted with a Chaney adapter.

(2) To the outer cell of the Coaxial cell was added several drops of the external reference compound, cyclooctane.

(3) The two cells were assembled and the carbon-13 NMR spectrum of the guest compound was acquired with the Bruker WP80 NMR spectrometer.

(4) Once the initial guest carbon-13 NMR spectrum was obtained, another small aliquot of guest compound was added directly to the inner cell.

(5) Steps 3 and 4 were repeated until saturation of the D_2O with the guest compound was accomplished.

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[41] Morishima, I.; Yoshikawa, K.; Okada, K.; Yonezawa, T.; Goto, K. *J. Am. Chem. Soc.* **1973**, *95*, 165.

[42] Sarneski, J.; Supereviant, H.; Molen, F.; Reilley, C. *Anal. Chem.* **1975**, *47*, 2116.