Hydrophobic Chemistry in Aqueous Solution: Stabilization and Stereoselective Encapsulation of Phosphonium Guests in a Supramolecular Host

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Encapsulation of guest molecules inside supramolecular host assemblies provides a way to stabilize reactive species in aqueous solution. The stabilization of reactive phosphonium/ketone adducts of the general formula $[R^1MeC(OH)PR_3]^+$ by encapsulation as guest molecules within a $[Ga_4L_6]^{12-}$ tetrahedral metal–ligand assembly is reported; although these cations decompose in aqueous solution, encapsulation inside the hydrophobic cavity of the assembly lengthens their lifetimes considerably, in some cases up to weeks. By varying the phosphane (PMe_3, PEt_3, $PPhMe_2$, and PPh_2Me) and ketone (acetone, methyl ethyl ketone, 1,1,1-trifluoroacetone, and fluoroacetone) which form these adducts, as well as the pD of the solutions, it was determined that the pH of the solution as well as the size and shape of the guest cations play an important role in the stability of these host–guest complexes. Encapsulation of chiral guests in the chiral $[Ga_4L_6]^{12-}$ assembly results in the formation of diastereomers, as characterized by ^1H, ^{19}F, and ^{31}P NMR spectroscopy. Although the $[Ga_4L_6]^{12-}$ assembly is formed from non-chiral ligands, the assembly itself has ΔΔΔΔ or ΛΛΛΛ chirality around the metal centers. Due to the chirality of this assembly, diastereomeric selectivity is observed upon initial guest encapsulation (typical diastereomeric excesses are 30–50%). This initial diastereomeric selectivity decreases over time to reach an equilibrium but does not become 1:1, indicating both kinetic and thermodynamic processes promote selective guest encapsulation. These experiments demonstrate further the applications of nanoscale reaction vessels, self-assembled by design from non-chiral ligands, in providing a chiral and hydrophobic environment for guest molecules in aqueous solution.

Introduction

Stabilization of reactive species by encapsulation within molecular capsules has been demonstrated using both covalently linked cage molecules,[1−5] and, more recently, using supramolecular assemblies held together by weaker interactions such as hydrogen or metal coordination bonds.[6−9] Encapsulation of an amine has been shown to slow the rate of nitrogen inversion from a rate of 10^7 s^{-1} to 2 s^{-1}, and make this interconversion easily observable on the NMR timescale.[10] A guest-templated synthesis of a coordination supramolecular assembly, which results in the formation of a thermally switchable molecular lock, has also been reported.[11] It is clear from these examples, that encapsulation of molecules inside supramolecular hosts has the ability to alter and control the reactivities of these guest molecules. Thus, the potential exists to control chemical reactions or to examine reactive species or reaction intermediates using the controlled environment of an appropriately chosen supramolecular host.

Utilization of supramolecular assemblies as molecular reaction vessels[12−19] and the possibility of employing a chiral host assembly to control the selective encapsulation and reactivity of incorporated guest molecules is a driving purpose of this research.[10,20−26] Control of the enantioselectivity of a reaction occurring within a chiral host molecule, or taking advantage of the chirality of the host assembly to augment or even control enantioselectivity of catalytic reactions is a major goal. The introduction of chiral guest molecules within supramolecular assemblies has only recently been demonstrated.[27,28]

Rebek and co-workers have reported the synthesis and encapsulation behavior of a chiral bowl-shaped molecular vessel.[23] In aromatic solvents, two of these molecules form a roughly spherical capsule held together by hydrogen bonding, capable of encapsulating small hydrophobic guest molecules. Chiral selectivity is introduced around the edge of the bowl by covalent attachment of chiral groups. Upon addition of a racemic mixture of guest molecules to these chiral supramolecular assemblies, a diastereomeric excesses of up to 60% was reported for *trans*-1,2-cyclohexanediol, depending on the size of the chiral substituent.[23] In previous reports we have described the $[Ga_4L_6]^{12-}$ (L shown in Figure 1) supramolecular assembly which is easily synthesized from its component building blocks. Instead of requiring synthetic modification to achieve a chiral host assembly, this assembly spontaneously forms as a racemic mixture of ΔΔΔΔ and ΛΛΛΛ enantiomers which can easily be resolved.[29] The assembly is soluble in water, the ideal

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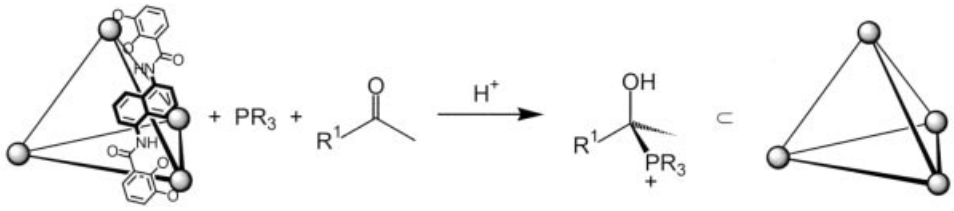


Figure 1. Representative reaction of phosphonium/ketone adduct encapsulation inside the $[Ga_4L_6]^{12-}$ tetrahedral assembly; the ligand (L) is shown on the left; lines represent ligand molecules, and circles represent gallium atoms

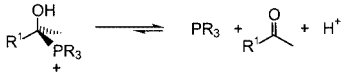
solvent for chemical applications, allowing hydrophobic guest molecules to be stabilized in aqueous solution. We reported earlier the encapsulation and stabilization of the phosphonium/acetone adduct, the $[Me_2C(OH)PEt_3]^+$ cation, as a guest inside the $[Ga_4L_6]^{12-}$ tetrahedral assembly.[7] Here we report the further exporation of that chemistry.

The synthesis of such phosphonium/ketone adducts under oxygen- and water-free conditions has been reported for PMe_3.[30] The general formation and encapsulation of the adduct guest molecules is shown in Figure 1. Formation of the adduct with a prochiral ketone affords a chiral guest molecule. The focus of our research was twofold: to expand the range of phosphonium/ketone guests to investigate the factors affecting host−guest interactions, and to determine the selectivity of chiral guest molecule recognition by the chiral tetrahedral assembly. ^1H, ^{31}P, and ^{19}F NMR spectroscopy were employed to observe the adducts in aqueous solution. Varying the size of the phosphonium/ketone adducts demonstrated that efficient encapsulation and stabilization was greatly dependent upon the nature of the guest molecule. Studies of such host−guest complexes illustrate the possibility of using these supramolecular assemblies as chiral nanoscale reaction vessels encapsulated (denoted by ⊂) in the host cluster.

Results and Discussion

Effect of pH on Guest Encapsulation

The equilibrium in Scheme 1 implies that the $[Me_2C(OH)PEt_3]^+$ cation would be more stable in acid solution. Therefore the pH dependence on the formation, inclusion, and stability of the encapsulated adduct was investigated. NMR samples of the acetone-precipitated tetrahedral assembly[31] were prepared in 0.1 M KD_2PO_4 buffer adjusted to selected pD values. After addition of PEt_3, NMR spectra of these samples were acquired.



Scheme 1

The ^1H NMR resonances for the encapsulated $[Me_2C(OH)PEt_3]^+$ cation obtained for various pD values

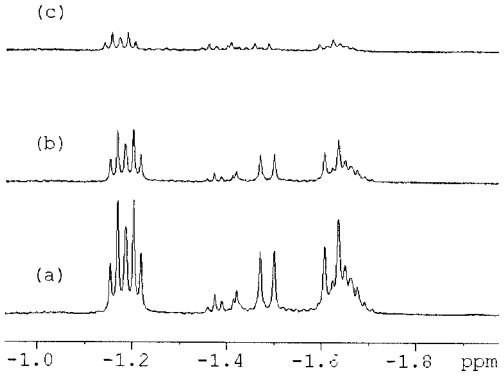


Figure 2. ^1H NMR spectra of encapsulated $[Me_2C(OH)PEt_3]^+$ showing pD dependence: (a) pD = 7.5, (b) pD = 8.3, (c) pD = 10.8; all spectra were acquired with the same parameters and are shown with the same scale

are shown in Figure 2. It is clear that lower pD values promote more encapsulation of the adduct, as seen by the growing intensity of the encapsulated signals with decreasing pD. Ten percent or less of the encapsulated adduct was observed at the highest pD values (> 10), based on integration of the assembly ^1H NMR resonances compared to those of the encapsulated species. It is interesting to note that a small amount of adduct does form above the pK_a of PEt_3 (8.69). As expected, the $^{31}P\{^1H\}$ NMR spectra of these samples follow the same trend: the signal for the adduct at δ = 36.5 ppm becomes less intense at higher pD (data not shown). After 6 h, the encapsulated adduct significantly decomposes even at pD = 8. At pD ≈ 5.2, however, the adduct remains encapsulated for 2 d in D_2O with very little decomposition. Because of the stability of the encapsulated $[Me_2C(OH)PEt_3]^+$ guest at lower pD, subsequent experiments were performed using phosphate buffer at this pD. Below this pD, the $[Ga_4L_6]^{12-}$ host complex is not stable.

Because synthesis of the $[Ga_4L_6]^{12-}$ assembly involves precipitation of the assembly with acetone,[32] the resulting $[Ga_4L_6]^{12-}$ assembly has closely associated acetone (see Supporting Information; for Supporting Information see also the footnote on the first page of this article). To determine the differences in encapsulation behavior of the $[Ga_4L_6]^{12-}$ tetrahedron with and without this closely associated acetone, the $[Ga_4L_6]^{12-}$ tetrahedron was synthesized in the absence of ketones. This required both precipitation of the assembly with diethyl ether instead of acetone

and the use of $Ga(NO_3)_3 \cdot xH_2O$ as the gallium source to avoid 2,4-pentanedione impurities derived from the $Ga(acac)_3$ (acac = acetylacetonate) starting material.When PEt_3 was added to this ketone-free assembly, broad signals were seen between $\delta = -1.3$ and -1.6 ppm. This encapsulated species is $HPEt_3^+$, and its formation occurs primarily at pD < 7. As soon as acetone is added, however, the encapsulated $[Me_2C(OH)PEt_3]^+$ adduct is observed. If more than 1 equiv. of this adduct is formed, resonances for the unencapsulated adduct are observed for a short time before decomposition in D_2O. It is not possible from these experiments, however, to determine whether formation of the phosphonium/acetone adduct occurs inside the cavity of the assembly (Figure 3, A) or outside the assembly with subsequent guest encapsulation (Figure 3, B). In both cases, the encapsulated adduct is then in equilibrium with the unencapsulated adduct. The $[Me_2C(OH)PEt_3]^+$ adduct is stable at pD $\approx$ 7 for < 1 h, while lowering the pD to $\approx$ 5.2 increases this lifetime to approximately 24 h.

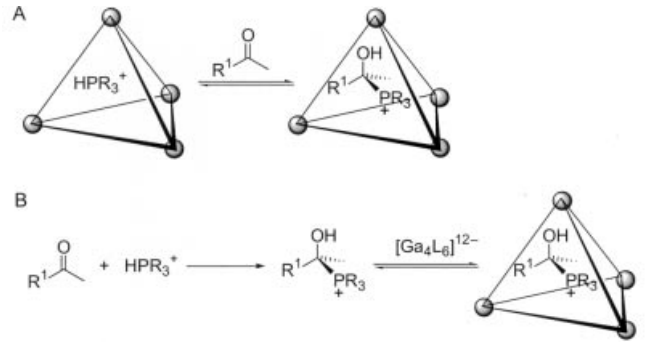


Figure 3. Proposed mechanisms for formation of the encapsulated phosphonium/acetone adduct; in A, the HPR_3^+ cation is encapsulated inside the chiral $[Ga_4L_6]^{12-}$ assembly and reacts with the incoming ketone to form the adduct inside the assembly; in B, the adduct forms outside the assembly, and is then encapsulated

Effects of Phosphane Variation on Guest Encapsulation

With the successful inclusion of the $[Me_2C(OH)PEt_3]^+$ cation as a guest inside the $[Ga_4L_6]^{12-}$ assembly, a systematic exploration was undertaken of the properties of similar guest molecules which could be encapsulated in the host cavity. To test the effect of size on potential guest molecules, phosphanes used in formation of the acetone adduct cations were varied from the small and basic PMe_3 (pK_a = 8.65) to the larger and less basic $PPhMe_2$ (pK_a = 6.50) and PPh_2Me (pK_a = 4.57).[33] When encapsulated, the size of the phosphonium cation is probably not determined as much by the cone angle of the phosphane as it is by the number of carbon atoms present, due to the restricted size of the cavity. Literature syntheses of the phosphonium/ketone adducts indicate that both PEt_3 (pK_a = 8.69) and PMe_3 form adducts with ketones, but the less basic PPh_3 does not.[30] Reactivity of the mixed alkylphosphanes $PPhMe_2$ and PPh_2Me with ketones was not reported.

When added to a solution of the acetone-precipitated $[Ga_4L_6]^{12-}$ in D_2O, PMe_3 and $PPhMe_2$ form phosphonium/acetone adducts which are good guest molecules, while addition of the larger PPh_2Me forms no encapsulated guest adduct. Despite the sensitivity of PMe_3 to oxygen, the resulting acetone adduct, $[Me_2C(OH)PMe_3]^+$, is stable inside the assembly for several days. For both the encapsulated $[Me_2C(OH)PMe_3]^+$ and $[Me_2C(OH)PPhMe_2]^+$ cations, ^1H NMR signals are shifted far upfield (Figure 4). For the $[Me_2C(OH)PMe_3]^+$ guest (see a in Figure 4), one doublet is displayed for the phosphonium methyl protons ($\delta = -1.68$ ppm), while the diastereotopic methyl groups from the acetone show separate signals at $\delta = -1.87$ and -1.95 ppm. This same resonance pattern is seen for the ^1H NMR spectrum of the $[Me_2C(OH)PPhMe_2]^+$ guest (see b in Figure 4). The corresponding $^{31}P\{^1H\}$ NMR spectra of these encapsulated adducts show single resonances at δ = 28.4 $\{[Me_2C(OH)PMe_3]^+\}$ and 24.8 ppm $\{[Me_2C(OH)PPhMe_2]^+\}$.

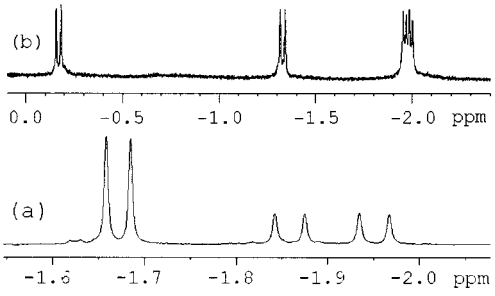


Figure 4. ^1H NMR spectra of encapsulated (a) $[Me_2C(OH)PMe_3]^+$ and (b) $[Me_2C(OH)PPhMe_2]^+$ (aromatic guest resonances not shown)

No decomposition of the $[Me_2C(OH)PPhMe_2]^+$ guest is observed over several days. These phosphonium/ketone adducts are otherwise quite unstable in water, showing that it is possible to encapsulate and stabilize these reactive species in aqueous solution. It is interesting to note that while complete formation of the encapsulated $[Me_2C(OH)PMe_3]^+$ cation occurs within minutes, formation and encapsulation of the larger $[Me_2C(OH)PPhMe_2]^+$ is much slower, taking nearly 30 min.

Encapsulation of Chiral Guest Cations

Phosphonium/acetone adducts are readily encapsulated inside the $[Ga_4L_6]^{12-}$ tetrahedron, and extending this reactivity to asymmetric ketones would afford chiral adducts. Since the assembly is chiral and easily resolved,[29] study of the diastereoselective host–guest interactions provides a critical step in extending such host–guest chemistry to other applications such as asymmetric catalysis. Upon addition of ethyl methyl ketone and phosphane (PMe_3, PEt_3, or $PPhMe_2$) to the ether-precipitated $[Ga_4L_6]^{12-}$ assembly, phosphonium/ethyl methyl ketone adducts form and are observed as encapsulated guests. Because the adducts formed are chiral, encapsulation of these asymmetric adducts can lead to four different stereoisomers: the assembly itself is a racemic mixture of ΛΛΛΛ and ΔΔΔΔ forms and

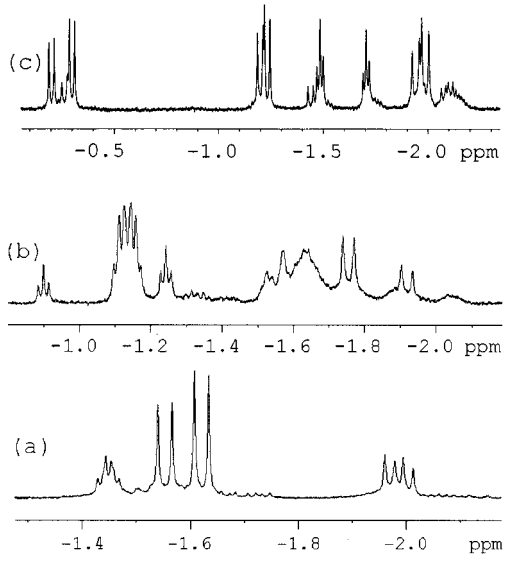


Figure 5. ^{1}H NMR spectra of encapsulated $[MeEtC(OH)PMe_3]^+$ (a), $[MeEtC(OH)PEt_3]^+$ (b), $[MeEtC(OH)PPhMe_2]^+$ (c) (aromatic guest resonances not shown)

each isomer of the assembly encapsulates either the (*R*) or the (*S*) isomer of the adduct. Two sets of these four isomers are diastereomers and therefore distinguishable by NMR spectroscopy. As can be seen in Figure 5 (a), encapsulation of a chiral PMe_3/ethyl methyl ketone adduct results in the expected doubling of the guest signals in the NMR spectra of the $[MeEtC(OH)PMe_3\subset Ga_4L_6]^{11-}$ complex. The two doublets for the phosphonium methyl groups can be seen at $\delta = -1.56$ and -1.63 ppm, as can the doublets for the methyl group of the ethyl methyl ketone ($\delta = -1.98$ and -2.01 ppm). Although resonances for the methylene protons of the adduct appear to be missing, a 2D TOCSY ^{1}H NMR spectrum (Supporting Information) reveals that resonances for one set of diastereotopic methylene protons occur at $\delta = -1.95$ and -1.99 ppm, while the second set is found at $\delta = -2.06$ and -2.20 ppm. Due to their small intensity and extensive coupling, these signals are not easily observable in the ^{1}H NMR spectrum. Diastereomeric pairs are also seen in the ^{1}H NMR spectrum for some of the ligand resonances of the assembly, although the differences in chemical shift are typically small and sometimes not observed at all (see Exp. Sect.).

Under the conditions used for these experiments (pD $\approx$ 5.2 in D_2O), the signals for the ethyl methyl ketone adducts in the encapsulated region remain sharp even after weeks. This is a remarkable increase in stability for adducts which typically decompose under these conditions in $<$ 24 h. Despite this dynamic behavior of the host assembly, which exposes the reactive encapsulated guest molecule to the surrounding aqueous solution, these host–guest complexes retain their integrity for long periods.

Initially, a difference in intensities of the diastereomeric resonances is observed, implying one set of isomers is formed preferentially to the other [i.e. the $\Delta\Delta\Delta\Delta$ cluster preferentially encapsulates either the (*R*) or (*S*) isomer of the adduct, while the $\Lambda\Lambda\Lambda\Lambda$ cluster preferentially encapsulates the other]. Over time, the difference in the integrated intensities of the diastereomeric pairs decreases, but is never observed to equalize completely, implying the two sets of diastereomers are slightly different in energy. This is not yet understood.

A range of phosphonium/ketone adducts were investigated to determine the diastereomeric excess (*de*) upon encapsulation as a function of steric interactions between the guest molecule and the host assembly. For the smallest encapsulated adduct, the $[MeEtC(OH)PMe_3]^+$ cation, the *de* decreases from 24% after 5 min to 14% after 1 h and approaches 0% after 3 weeks. As seen for the proton signals of the encapsulated $[MeEtC(OH)PMe_3]^+$ adduct, two signals of unequal intensity are also observed in the $^{31}P\{^1H\}$ NMR spectrum at $\delta = 28.3$ (major diastereomer) and 28.1 ppm (minor diastereomer). As expected, the ratio of the intensities of these resonances also approaches 1:1 over time. This phenomenon of decreasing *de*, also observed with the encapsulation of other chiral guest molecules,[23] indicates an equilibration process takes place *after* the initial encapsulation of the chiral guest molecules.

NMR spectra for both the encapsulated PEt_3 and $PPhMe_2$ adducts with ethyl methyl ketone (Figure 5, b and c) are very similar to those observed for the $[MeEtC(OH)PMe_3]^+$ cation. Again, resonances for the encapsulated species in the $[MeEtC(OH)PEt_3\subset Ga_4L_6]^{11-}$ and $[MeEtC(OH)PPhMe_2\subset Ga_4L_6]^{11-}$ complexes are doubled because of diastereomeric pairs formed upon guest encapsulation. This doubling effect can most easily be seen for both methyl resonances derived from the ethyl methyl ketone and these were therefore the resonances integrated to determine *de* values for this host–guest complex. In the $^{31}P\{^1H\}$ NMR spectrum the two signals for the $[MeEtC(OH)PEt_3]^+$ cation are observed at $\delta = 36.8$ (minor diastereomer) and 36.7 ppm (major diastereomer). Similarly to the $[MeEtC(OH)PMe_3\subset Ga_4L_6]^+$ complex, the diastereomeric excess for the $[MeEtC(OH)PEt_3\subset Ga_4L_6]^{11-}$ complex decreases from 50% after 20 min, to 36% after 2 d, to 28% after 9 d.

The $^{31}P\{^1H\}$ NMR spectrum for the $[MeEtC(OH)PPhMe_2\subset Ga_4L_6]^{11-}$ complex shows two signals for the encapsulated guest diastereomer pairs at $\delta = 22.8$ (minor diastereomer) and 22.1 ppm (major diastereomer). The observed diastereomeric excess is 22% after 3 d, but it is difficult to observe the initial *de* due to the slow encapsulation of this adduct.

To increase the range of encapsulated guests formed from asymmetric ketones, the fluorinated ketones 1,1,1-trifluoroacetone and fluoroacetone were tested for their ability to form encapsulated phosphonium adducts. Using fluorinated ketones gains the advantage of allowing observation of the encapsulated guest molecules by ^{19}F NMR spectroscopy. Because of the generally weak encapsulation behavior of the trifluoroacetone adducts, further experiments focused on formation and encapsulation of the phosphonium/fluoroacetone adducts.

Fluoroacetone adducts of the phosphanes (PMe_3, PEt_3, and $PPhMe_2$) readily form 1:1 host−guest complexes. Signal doubling caused by formation of diastereomeric pairs is observed for the encapsulated $[Me(CFH_2)C(OH)PMe_3]^+$ cation. Although the expected doublets are overlapping in the ^1H NMR spectrum, the $^{31}P\{^1H\}$ NMR shows two resonances at $\delta = 29.1$ (major diastereomer) and 28.8 ppm (minor diastereomer), and the ^{19}F NMR displays two triplets at $\delta = -274.1$ (major diastereomer) and −274.2 ppm (minor diastereomer). The diastereomeric excess for the $[Me(CFH_2)C(OH)PMe_3\subset Ga_4L_6]^{11-}$ complex was 14% after 20 min.

The ^1H NMR spectrum of the encapsulated $[Me(CFH_2)C(OH)PEt_3]^+$ cation also shows an unequal ratio of the doubled signals (*de* = 24% after 20 min) indicating chiral selectivity. An even larger *de* is observed for the encapsulated $[Me(CFH_2)C(OH)PPhMe_2]^+$ cation (Figure 6, c). After 18 h, the diastereomeric excess of 38% is still greater than the initially measured diastereomeric excesses for the analogous $[Me(CFH_2)C(OH)PMe_3]^+$ (*de* = 14%) and $[Me(CFH_2)C(OH)PEt_3]^+$ (*de* = 24%) cations. The greater diastereomeric excess and observed splitting in the NMR spectra for the larger $[Me(CFH_2)C(OH)PPhMe_2]^+$ adduct are again consistent with the expected increase in steric interaction between the chiral host and the chiral guest.

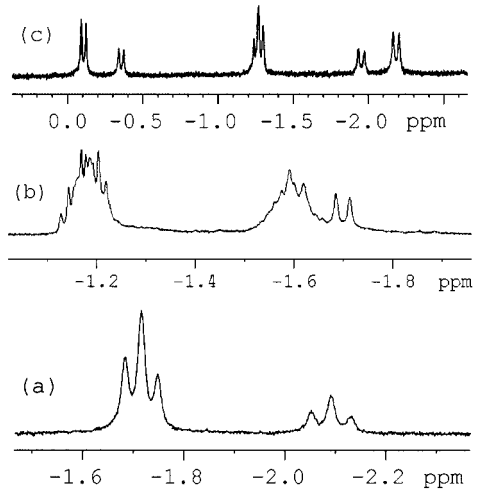


Figure 6. ^1H NMR spectra of encapsulated $[Me(CFH_2)C(OH)PMe_3]^+$ (a), $[Me(CFH_2)C(OH)PEt_3]^+$ (b), $[Me(CFH_2)C(OH)PPhMe_2]^+$ (c) (aromatic guest resonances not shown)

Factors Affecting Observed Diastereomeric Excesses

While the diastereomeric excesses found for chiral guest encapsulation are not large, it is informative to consider the observable trends. Larger guest molecules (as determined from the number of non-hydrogen atoms) have generally higher equilibrium *de* percentages, i.e. the *de* values generally increase with the size of the phosphane used to form the adduct with any given ketone ($PMe_3 < PEt_3 < PPhMe_2$). Thus, the $[MeEtC(OH)PMe_3\subset Ga_4L_6]^{11-}$ complex shows almost no isomer preference at equilibrium, while the $[MeEtC(OH)PEt_3\subset Ga_4L_6]^{11-}$ and $[MeEtC(OH)PPhMe_2\subset Ga_4L_6]^{11-}$ complexes have roughly the same equilibrium *de* (28% and 22%, respectively). The same trend can be seen with adducts formed from fluoroacetone. Although the *de* upon encapsulation of the $[Me(CFH_2)(OH)PPhMe_2]^+$ cation was measured only after 3 d due to its slower encapsulation rate, the initial *de* would be expected to be significantly higher than 38%, reinforcing this trend. This size dependence we attribute to increased steric contact between the chiral cavity of the assembly and the chiral guest molecule. Also significant is the stabilization of reactive cationic species while encapsulated in the host assembly in aqueous solution.

Factors Affecting Guest Stability

Several different factors must be taken into account when considering the stability of the guest molecules within the host cavity. While all of these phosphonium/ketone adducts are not stable in aqueous solution for long periods, as encapsulated guests, these molecules are stable for several days and > 3 weeks {the $[MeEtC(OH)PMe_3\subset Ga_4L_6]^{11-}$ complex at pD ≈ 5.2}. This is a very large increase in stability due to encapsulation in the hydrophobic cavity of the assembly. As is evident from Figure 2 and the decomposition equilibrium shown in Scheme 1, the stability of these reactive guests is also greatly dependent upon pD of the solution. This strong effect of pD on guest stability is reflected in the need for a proton in addition to the phosphane and ketone molecules in order to form the adduct cation. Additionally, the guest molecules are probably in equilibrium between the greatly favored encapsulated state and the unencapsulated state. A lower pD would prevent decomposition of the unencapsulated adduct as seen in Scheme 1.

Size is one property of the encapsulated guest molecules which significantly contributes to the stability of the host−guest complex. Adducts formed from acetone (stable in encapsulated form for several days at pD ≈ 5.2) are less stable than the corresponding adducts formed from ethyl methyl ketone (stable for several weeks). Aromatic groups on the adducts formed from $PPhMe_2$ also have the potential to π-stack or form edge-to-face interactions with the naphthyl rings of the host assembly when encapsulated, perhaps contributing added stability to these host−guest complexes.

The presence of fluorine atoms in the adducts also decreases the stability of the host−guest complex. The phosphonium/ethyl methyl ketone adducts are the most stable when encapsulated, while the phosphonium/fluoroacetone adducts are less stable as guests, and phosphonium/trifluoroacetone adducts are generally weak guest molecules if they encapsulate at all. It is not clear whether the observed reduction of encapsulation is due to instability of phosphonium/ketone adduct formation with increasing fluorination or unfavorable host−guest interactions. This trend of decreasing stability of the encapsulated guests with increasing fluorine substitution is reflected in the stability of the adducts formed from PMe_3. The $[MeEtC(OH)PMe_3]^+$ cation is stable and remains encapsulated for > 3 weeks, while the $[Me(CFH_2)C(OH)PMe_3]^+$ guest is stable for up to 1

week, and the $[Me(CF_3)C(OH)PMe_3]^+$ guest is only stable for only a few days. Similar trends are also observed for the adducts derived from PEt_3 and $PPhMe_2$. It is not surprising that the size and substituents of the guest molecules is of great importance in determining the stability of the host−guest complex, since the size and properties of the host cavity are essential to formation of these complexes.

The formation of phosphonium/ketone adducts and their incorporation as guest molecules within the tetrahedral $[Ga_4L_6]^{12-}$ assembly is a fairly general phenomenon which can be extended to a range of phosphane and ketone molecules. From these results we have shown that stability of these encapsulated phosphonium/ketone guest cations increases with decreasing pH, and fit of the guest molecule into the host cavity is an important consideration for these host−guest complexes. Dramatic increases in stability of these reactive adducts are observed upon encapsulation. The ability of supramolecular encapsulation to stabilize these reactive, hydrophobic guest molecules is an important step toward examining hydrophobic chemistry in aqueous solution. This stabilization, combined with the diastereomeric selectivity of chiral guest incorporation, opens up the possibility of designing supramolecular assemblies specifically to carry out aqueous enantioselective reactions using hydrophobic catalysts.

Experimental Section

General: ^1H and $^{31}P\{^1H\}$ NMR spectra were obtained with DRX-500 or AMX-400 spectrometers at 500 or 400 MHz and 202 or 161.6 MHz, respectively. ^{19}F NMR spectra were obtained with an AMX-400 spectrometer at 376 MHz. Chemical shifts for ^1H NMR and $^{31}P\{^1H\}$ spectra are reported in ppm (δ) relative to $SiMe_4$ and 40% H_3PO_4, respectively. Chemical shifts for ^{19}F NMR spectra are reported in ppm (δ) relative to CCl_3F. PEt_3, $PPhMe_2$, PPh_2Me, ethyl methyl ketone, 1,1,1-trifluoroacetone, fluoroacetone, and $Ga(NO_3)_3{\cdot}xH_2O$ were purchased from Aldrich and used as received. PMe_3 was obtained as a gift from Professor John Arnold; manipulations of PMe_3 were carried out under argon. Unless otherwise noted, the $K_{12}Ga_4L_6$ assembly was synthesized using $Ga(NO_3)_3{\cdot}xH_2O$ as the gallium source.

NMR Spectra of Acetone Associated with the $K_{12}Ga_4L_6$ Assembly: The acetone-precipitated $K_{12}Ga_4L_6$ assembly [synthesized from $Ga(acac)_3$ [32]] was dried in a vacuum oven at 60 °C overnight, and an NMR sample (0.5 mL, 12 mM) was prepared in 0.1 M KCl in D_2O. ^1H NMR spectra were obtained at room temperature, at 50 °C, upon cooling to room temperature, and after the addition of 1 equiv. of Et_4NCl (Supporting Information).

pH Dependence of $[Me_2C(OH)PEt_3]^+$ Encapsulation: NMR samples (0.75 mL) were prepared by adding $K_{12}Ga_4L_6$ to solutions of KD_2PO_4 (0.1 M) in D_2O and adding the appropriate amount of NaOD to achieve the desired pD (as calculated using the Henderson-Hasselbach equation). The pD values were experimentally determined by determination of the pH with a pH meter after the NMR experiments were completed. Conversion of pH into pD was performed using the formula $p[D^+] = 0.4 + p[H^+]$. The pD values for the samples were 7.5, 8.3, 10.8, and 12.9. A sample was also prepared without the addition of NaOD (pD = 5.2). To each of these samples was added PEt_3 (1 equiv., 0.9 μL), and ^1H and $^{31}P\{^1H\}$ NMR spectra were taken within 5 min of addition. For samples which showed the best encapsulation of the $[Me_2C(OH)PEt_3]^+$ adduct, additional spectra were taken after 1 h, 6 h, and 2 d.

Synthesis of $K_{12}Ga_4L_6$ from $Ga(NO_3)_3{\cdot}xH_2O$: The tetrahedral assembly $K_{12}Ga_4L_6$ was synthesized as described previously,[32] using 1.5 equiv. of $Ga(NO_3)_3{\cdot}xH_2O$ as the gallium source. The reaction mixture was stirred for 4 h in methanol and the volume of the pale yellow solution was reduced to < 1 mL under N_2. Diethyl ether (ca. 30 mL) was added to precipitate the assembly, and the yellow-green precipitate was collected by centrifugation and dried under vacuum overnight. The assembly formed using this method is more sensitive to oxidation in solution than the assembly formed from $Ga(acac)_3$. Yield: 84 mg (94%; MW ≈ 3650).

Formation of Encapsulated Phosphonium/Acetone Adducts: NMR experiments were performed on solutions of acetone-precipitated $K_{12}Ga_4L_6$ (8 mM, 0.75 mL) in buffered D_2O (0.1 M KD_2PO_4, pD ≈ 5.2). To these samples was added the neat phosphane (1.5 equiv.). NMR signals in the aromatic region are assigned as Ar_NH for hydrogen atoms on the naphthyl rings and Ar_CH for hydrogen atoms on the catecholate rings of the $[Ga_4L_6]^{12-}$ assembly.

$[Me_2C(OH)PMe_3{\subset}Ga_4L_6]^{11-}$ (1): ^1H NMR: δ = 7.94 (d, J = 7.5 Hz, Ar_NH), 7.69 (d, J = 8.0 Hz, Ar_NH), 7.20 (d, J = 8.0 Hz, Ar_CH), 6.97 (t, J = 8.0 Hz, Ar_NH), 6.63 (d, J = 7.5 Hz, Ar_CH), 6.51 (t, J = 7.5 Hz, Ar_CH), −1.68 (d, J = 10 Hz, PMe_3), −1.87 (d, 17.5 Hz, Me), −1.95 (d, J = 17.5 Hz, Me) ppm. $^{31}P\{^1H\}$ NMR: δ = 28.4 ppm.

$[Me_2C(OH)PPhMe_2{\subset}Ga_4L_6]^{11-}$ (2): ^1H NMR: δ = 7.86 (d, J = 8.0 Hz, Ar_NH), 7.73 (d, J = 7.5 Hz, Ar_NH), 7.21 (dd, J = 8.0, 0.5 Hz, Ar_CH), 6.84 (t, J = 8.0 Hz, Ar_NH), 6.66 (d, J = 7.5 Hz, Ar_CH), 6.50 (t, J = 8.0 Hz, Ar_CH), 6.24 (dt, J = 1, 7 Hz, guest aromatic H), 5.83 (t, J = 7 Hz, guest aromatic H), 4.26 (t, J = 7 Hz, guest aromatic H), −0.19 (d, J = 13 Hz, Me), −1.34 (d, J = 13 Hz, Me), −1.98 (d, J = 17 Hz, PMe_2), −2.00 (d, J = 17 Hz, PMe_2). $^{31}P\{^1H\}$ NMR: δ = 24.8 ppm.

Formation of Encapsulated Phosphonium/Ethyl Methyl Ketone Adducts: NMR experiments were performed on solutions of ether-precipitated $K_{12}Ga_4L_6$ (8 mM, 0.75 mL) in buffered D_2O (0.1 M KD_2PO_4, pD ≈ 5). To these samples were added 2 equiv. of the neat phosphane and 2 equiv. of ethyl methyl ketone. NMR signals in the aromatic region are assigned as Ar_NH for hydrogen atoms on the naphthyl rings and Ar_CH for hydrogen atoms on the catecholate rings of the $[Ga_4L_6]^{12-}$ assembly. Where observed, diastereomeric pairs of resonances are denoted as major and minor isomers.

$[MeEtC(OH)PMe_3{\subset}Ga_4L_6]^{11-}$ (3): ^1H NMR: δ = 8.07 (d, J = 7.8 Hz, Ar_NH), 7.78 (d, J = 8.6 Hz, Ar_NH), 7.33 (dd, J = 8.3, 1.6 Hz, Ar_CH), 7.08 (t, J = 8.2 Hz, major diastereomer Ar_NH), 7.07 (t, J = 8.2 Hz, minor diastereomer Ar_NH), 6.76 (dd, J = 7.4, 1.7 Hz, Ar_CH), 6.61 (t, J = 8.0 Hz, Ar_CH), −1.45 (overlapping "q", $J \approx 7$ Hz, CH_2CH_3), −1.56 (d, J = 17 Hz, minor diastereomer PMe_3), −1.63 (d, J = 17 Hz, major diastereomer PMe_3), −1.98 (d, J = 14 Hz, major diastereomer Me), −2.01 ppm (d, J = 14 Hz, minor diastereomer Me). 2D TOCSY (Supporting Information; parameters: ns = 1, td = 1024, swh = 1600, O1 = −980 Hz, phc0 = −119.443, phc1 = −18.0, $D1$ = 2 s, $T1$ = 504 ms) showed cross peaks for all expected coupling and identified the four signals for the two sets of diastereotopic methylene protons of the encapsulated $[MeEtC(OH)PMe_3]^+$ at δ = −1.95 and −1.99 ppm for the first set, and −2.06 and −2.20 ppm for the second one. $^{31}P\{^1H\}$

NMR: δ = 28.3 (major diastereomer), 28.1 ppm (minor diastereomer).

$[Ga_4L_6{\subset}MeEtC(OH)PEt_3]^{11-}$ (4): ^{1}H NMR: δ = 8.00 (d, J = 8.0 Hz, minor diastereomer Ar_NH), 7.99 (d, J = 8.0 Hz, major diastereomer Ar_NH), 7.64 (d, J = 8.5 Hz, major diastereomer Ar_NH), 7.63 (d, J = 8.5 Hz, minor diastereomer Ar_NH), 7.24 (dd, J = 8.0, 1.5 Hz, Ar_CH), 7.23 (dd, J = 8.0, 1.5 Hz, Ar_CH), 6.91 (t, J = 8.0 Hz, Ar_NH), 6.65 (dd, J = 7.0, 1.5 Hz, major diastereomer Ar_CH), 6.64 (dd, J = 7.0, 1.5 Hz, minor diastereomer Ar_CH), 6.50 (t, J = 7.5 Hz, Ar_CH), −0.90 (t, J = 7 Hz, minor diastereomer CH_2CH_3), −1.15 (m, 5-line pattern, J = 7 Hz, PCH_2CH_3), −1.24 (t, J = 7 Hz, major diastereomer CH_2CH_3), −1.63 (br. m, PCH_2CH_3), −1.78 (d, J = 16 Hz, major diastereomer Me), −1.92 (d, J = 16 Hz, minor diastereomer Me). 2D TOCSY (Supporting Information; parameters: ns = 1, td = 1024, swh = 1795, O1 = −300.08 Hz, phc0 = −13.792, phc1 = 3, $T1$ = 504 ms) showed cross peaks for all expected coupling and identified the four signals for the two sets of diastereotopic methylene protons of the encapsulated $[MeEtC(OH)PEt_3]^+$ at δ = −1.85 and −2.20 ppm for the first set and δ = −1.93 ppm (overlapping) for the second one. $^{31}P\{^1H\}$ NMR: δ = 36.8 (minor diastereomer), 36.7 ppm (major diastereomer).

$[MeEtC(OH)PPhMe_2{\subset}Ga_4L_6]^{11-}$ (5): ^{1}H NMR: δ = 7.88 (d, J = 7.9 Hz, Ar_NH), 7.57 (d, J = 8.6 Hz, Ar_NH), 7.21 (d, J = 8.3 Hz, minor diastereomer Ar_CH), 7.20 (d, J = 8.3 Hz, major diastereomer Ar_CH), 6.83 (t, J = 8.3 Hz, major diastereomer Ar_NH), 6.82 (t, J = 8.3 Hz, minor diastereomer Ar_NH), 6.64 (dd, J = 7.5, 1.5 Hz, Ar_CH), 6.49 (t, J = 7.9 Hz, Ar_CH), 6.29 (dt, J = 1.0, 7.0 Hz, major diastereomer guest aromatic H), 6.20 (dt, J = 1.0, 7.0 Hz, minor diastereomer guest aromatic H), 6.08 (t, J = 7.0 Hz, major diastereomer guest aromatic H), 5.98 (t, J = 7.0 Hz, minor diastereomer guest aromatic H), 4.37 (dd, J = 7.0, 3.0 Hz, major diastereomer guest aromatic H), 4.32 (dd, J = 7.0, 3.0 Hz, minor diastereomer guest aromatic H), −0.20 (d, J = 13 Hz, minor diastereomer Me), −0.30 (d, J = 13 Hz, major diastereomer Me), −1.20 (d, J = 13 Hz, minor diastereomer PMe_2), −1.23 (d, J = 13 Hz, major diastereomer PMe_2), −1.44 (t, J = 73 Hz, major diastereomer CH_2CH_3), −1.71 (t, J = 7.0 Hz, minor diastereomer CH_2CH_3), −1.94 (d, J = 17 Hz, minor diastereomer PMe_2), −1.99 ppm (d, J = 17 Hz, major diastereomer PMe_2); signals of diastereotopic methylene protons were not identified. $^{31}P\{^1H\}$ NMR: δ = 22.8 (minor diastereomer), 22.1 ppm (major diastereomer).

Formation of Encapsulated Phosphonium/1,1,1-Trifluoroacetone Adducts: NMR experiments were performed on solutions of ether-precipitated $K_{12}Ga_4L_6$ (8 mM, 0.75 mL) in buffered D_2O (0.1 M KD_2PO_4, pD ≈ 5). To these samples were added 2 equiv. of the neat phosphane and 2 equiv. 1,1,1-trifluoroacetone. NMR signals in the aromatic region are assigned as Ar_NH for hydrogen atoms on the naphthyl rings and Ar_CH for hydrogen atoms on the catecholate rings of the $[Ga_4L_6]^{12-}$ assembly. Where observed, diastereomeric pairs of resonances are denoted as major and minor isomers.

$[Me(CF_3)C(OH)PMe_3{\subset}Ga_4L_6]^{11-}$ (6): ^{1}H NMR: δ = 7.93 (d, J = 7.5 Hz, Ar_NH), 7.63 (d, J = 8.5 Hz, major diastereomer Ar_NH), 7.62 (d, J = 8.5 Hz, minor diastereomer Ar_NH), 7.20 (d, J = 8.0 Hz, Ar_CH), 6.92 (t, J = 8.5 Hz, major isomer Ar_NH), 6.91 (t, J = 8.5 Hz, minor diastereomer Ar_NH), 6.62 (d, J = 7.5 Hz, Ar_CH), 6.48 (t, J = 8.0 Hz, Ar_CH), −1.57 (d, J = 18 Hz, PMe_3), −1.74 (d, J = 16 Hz, major diastereomer Me), −1.86 ppm (d, J = 16 Hz, minor diastereomer Me). $^{31}P\{^1H\}$ NMR: δ = 32.7 (d, J = 10 Hz, minor diastereomer), 32.6 ppm (d, J = 10 Hz, major diastereomer). ^{19}F NMR: δ = −13.1 (minor diastereomer), −13.3 ppm (major diastereomer).

$[Me(CF_3)C(OH)PPhMe_2{\subset}Ga_4L_6]^{11-}$ (7): ^{1}H NMR: δ = 7.91 (d, J = 7.7 Hz, minor diastereomer Ar_NH), 7.90 (d, J = 7.7 Hz, major diastereomer Ar_NH), 7.63 (d, J = 8.4 Hz, Ar_NH), 7.26 (d, J = 8.2 Hz, Ar_CH), 6.90 (t, J = 8.1 Hz, minor diastereomer Ar_NH), 6.89 (t, J = 8.1 Hz, major diastereomer Ar_NH), 6.70 (d, J = 8.1 Hz, Ar_CH), 6.55 (t, J = 9.6 Hz, Ar_CH), 6.28 (br; guest aromatic H), 5.90 (br; guest aromatic H), 4.39 (dd, J = 7.0, 3.0 Hz, major diastereomer guest aromatic H), 4.27 (dd, J = 7.0, 3.0 Hz, minor diastereomer guest aromatic H), −0.10 (d, J = 13 Hz, major diastereomer PMe_2), −0.35 (d, J = 13 Hz, minor diastereomer PMe_2), −1.24 (d, J = 13 Hz, minor diastereomer Me), −1.29 (d, J = 13 Hz, major diastereomer Me), −1.94 (d, J = 16 Hz, minor diastereomer PMe_2), −2.19 ppm (d, J = 16 Hz, major diastereomer PMe_2). $^{31}P\{^1H\}$ NMR: δ = 25.0 (d, J = 10 Hz, major diastereomer), 25.1 ppm (d, J = 10 Hz, minor diastereomer). ^{19}F NMR: δ = −12.3 (major diastereomer), −13.4 ppm (minor diastereomer).

Formation of Encapsulated Phosphonium/Fluoroacetone Adducts: NMR experiments were performed on solutions of ether-precipitated $K_{12}Ga_4L_6$ (8 mM, 0.75 mL) in buffered D_2O (0.1 M KD_2PO_4, pD ≈ 5). To these samples were added 1.5 equiv. of the neat phosphane and 1.5 equiv. of fluoroacetone. NMR signals in the aromatic region are assigned as Ar_NH for hydrogen atoms on the naphthyl rings and Ar_CH for hydrogen atoms on the catecholate rings of the $[Ga_4L_6]^{12-}$ assembly. Where observed, diastereomeric pairs of resonances are denoted as major and minor isomers.

$[Me(CH_2F)C(OH)PMe_3{\subset}Ga_4L_6]^{11-}$ (8): ^{1}H NMR: δ = 8.00 (d, J = 7.3 Hz, Ar_NH), 7.71 (d, J = 8.1 Hz, Ar_NH), 7.26 (d, J = 7.8 Hz, Ar_CH), 7.02 (t, J = 7.2 Hz, Ar_NH), 6.70 (d, J = 7.0 Hz, Ar_CH), 6.54 (t, J = 7.3 Hz, Ar_CH), −1.70 (d, J = 15 Hz, major diastereomer PMe_3), −1.74 (d, J = 15 Hz, minor diastereomer PMe_3), −2.13 (d, J = 20 Hz, major diastereomer Me), −2.16 ppm (d, J = 20 Hz, minor diastereomer Me), diastereotopic protons on FH_2C group not observed. $^{31}P\{^1H\}$ NMR: δ = 29.1 (major diastereomer), 28.8 ppm (minor diastereomer). ^{19}F NMR: δ = −274.1 (t, J = 38 Hz, major diastereomer), −274.2 ppm (t, J = 38 Hz, minor diastereomer).

$[Me(CH_2F)C(OH)PEt_3{\subset}Ga_4L_6]^{11-}$ (9): ^{1}H NMR: δ = 8.04 (d, J = 7.6 Hz, Ar_NH), 7.68 (d, J = 8.4 Hz, Ar_NH), 7.29 (d, J = 8.2 Hz, Ar_CH), 6.98 (t, J = 8.1 Hz, Ar_NH), 6.70 (d, J = 8.0 Hz, Ar_CH), 6.55 (t, J = 7.8 Hz, Ar_CH), −1.23 (m, PCH_2CH_3), −1.65 (m, PCH_2CH_3), −1.68 (d, J = 13 Hz, minor diastereomer Me), −1.77 ppm (d, J = 13 Hz, major diastereomer Me), diastereotopic protons on FH_2C group not observed. $^{31}P\{^1H\}$ NMR: δ = 38.3 (major diastereomer), 38.5 ppm (minor diastereomer). ^{19}F NMR: δ = −272.1 (m) ppm.

$[Me(CH_2F)C(OH)PPhMe_2{\subset}Ga_4L_6]^{11-}$ (10): ^{1}H NMR: δ = 7.93 (d, J = 9.3 Hz, minor diastereomer Ar_NH), 7.91 (d, J = 9.3 Hz, major diastereomer Ar_NH), 7.62 (d, J = 7.6 Hz, Ar_NH), 7.25 (d, J = 8.2 Hz, Ar_CH), 6.90 (t, J = 8.2 Hz, minor diastereomer Ar_NH), 6.89 (t, J = 8.2 Hz, major diastereomer Ar_NH), 6.70 (d, J = 7.2 Hz, Ar_CH), 6.54 (t, J = 8.0 Hz, Ar_CH), 6.30 (br.; guest aromatic H), 5.93 (t, J = 7.0 Hz, major diastereomer guest aromatic H), 5.90 (t, J = 7.0 Hz, minor diastereomer guest aromatic H), 4.39 (dd, J = 7, 3 Hz, major diastereomer guest aromatic H), 4.32 (dd, J = 7, 3 Hz, minor diastereomer guest aromatic H), −0.10 (d, J = 13 Hz, major diastereomer PMe_2), −0.36 (d, J = 13 Hz, minor diastereomer PMe_2), −1.26 (d, J = 12 Hz, minor diastereomer Me), −1.28 (d, J = 12 Hz, major diastereomer Me), −1.96 (d, J =

16 Hz, minor diastereomer PMe_2), −2.18 ppm (d, J = 16 Hz, major diastereomer PMe_2), diastereotopic protons on FH_2C group not observed. $^{31}P\{^1H\}$ NMR: δ = 25.1 (m) ppm. ^{19}F NMR: δ = −271.6 (t, J = 38 Hz, major diastereomer), −273.3 ppm (t, J = 38 Hz, minor diastereomer).

Supporting Information Available: NMR spectra of the $[Ga_4L_6]^{12-}$ assembly showing association of acetone molecules, and 2D ^1H TOCSY NMR spectra of the encapsulated $[MeEtC(OH)PMe_3]^+$ and $[MeEtC(OH)PEt_3]^+$ cations showing the assignments for the diastereotopic methylene protons. See also the footnote on the first page of this article.

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