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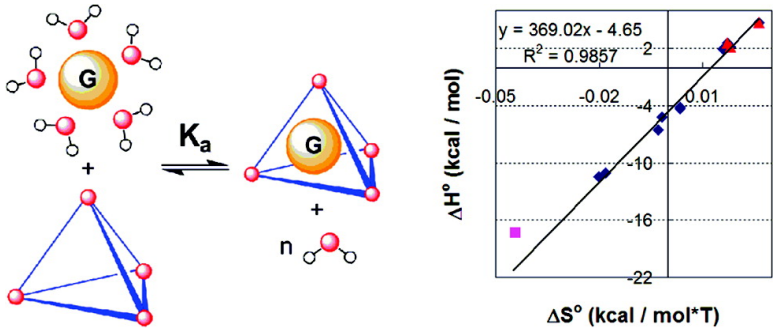

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Enthalpy−Entropy Compensation Reveals Solvent Reorganization as a Driving Force for Supramolecular Encapsulation in Water

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Abstract: A chiral self-assembled M_4L_6 host assembly has been shown to be a suitable host for the supramolecular encapsulation of a series of guests in polar solvents, ranging from simple organic ammonium cations to more complex organometallic species. This molecular recognition process creates highly selective reactivity within the host cavity. In order to understand the factors driving the molecular recognition process, the standard thermodynamic parameters for encapsulation were determined for a series of protiated and fluorinated iridium guests in a variety of polar solvents using van't Hoff analysis. The encapsulation process for these guests exhibited enthalpy−entropy compensation effects. In solvents such as water and methanol, error analysis suggests a chemical origin for this behavior. In contrast, error analysis of this compensation behavior in polar aprotic solvents such as dimethyl sulfoxide reveals that this correlation is due to an artifact inherent in the intrinsic correlation between the enthalpy and entropy terms in the van't Hoff analysis. Guest encapsulation in polar protic solvents such as water appears to be driven by initial desolvation of the guest with concomitant rearrangement of the hydrogen bond networks in solution. This behavior shares common characteristics with other synthetic and natural host−guest and molecular recognition processes in aqueous solution, ranging from simple crown ether to complex enzyme−ligand interactions.

Introduction

Molecular recognition is frequently defined as supramolecular noncovalent interactions between molecules, many of which are essential in naturally occurring systems. For example, enzymes are remarkably selective and reactive catalysts, and much of this efficiency is due to the highly precise molecular recognition of both substrates and transition states. In synthetic chemistry, molecular recognition has played an important role in fields as diverse as chemical sensing, sequestering, crystallization, catalysis, self-assembly, and drug−receptor interactions.[1−3] In particular, synthetic host−guest chemistry, involving the selective recognition and encapsulation of guest molecules, has emerged as an important area of molecular recognition.[4−6]

Although a fundamental understanding of molecular recognition is critical in the design of host−guest systems with high selectivity and binding affinity, it is often difficult to dissect the many different forces that govern the binding process. The most common driving force for receptor−ligand binding is typically a result of specific preorganized interactions between the various functional groups of the host assembly and guest molecules, as exemplified in many enzymatic systems. There can also be nonspecific weak, supramolecular interactions between the host and guest that may make significant contributions to the binding affinity and specificity. Additionally, solvation often plays a critical role in guest encapsulation. In solution, displacement and desolvation of the guest species from the bulk solvent must occur before encapsulation by the host assembly. Depending upon the solvent, desolvation can become the most important determinant in shifting the binding equilibrium, as in the case of the important hydrophobic effect in protein folding.[7] Besides these major forces, there are more subtle factors that may affect guest recognition, including changes in solvation around and within the host assembly during encapsulation. These factors can have different and even opposing enthalpic and entropic contributions, making the analysis of supramolecular recognition highly complicated.

Due to the many elements that can contribute to molecular recognition, one major question we seek to answer is whether there are common factors that govern this process in a general manner for a diverse range of phenomena. In a recent review Houk and co-workers have compiled the binding affinities of a wide variety of synthetic host−guest, enzyme−ligand, and enzyme−transition-state systems in water.[6] A strong correlation was found between the change in the solvent-exposed surface area of the guest molecule and the overall binding affinity. This correlation exists in diverse, structurally distinct systems ranging from simple synthetic cation-crown ether assemblies to multikilodalton enzymes with complex architectures and suggests that

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desolvation plays an important, general role in molecular recognition. Similarly, Gilli and co-workers have suggested that an important driving force for molecular recognition of enzymes in drug−receptor interactions is the rearrangement of the hydrogen bond networks in aqueous solution rather than specific host−guest attractive interactions.[8]

These studies provided the initial clues to our understanding of the factors that are crucial in determining molecular recognition. One major limitation of these studies is that biological systems are often confined to aqueous solution within a narrow temperature range. Particularly, while solvation has often been implicated as a crucial factor in molecular recognition, it is practically challenging to study the direct solvent effects of many enzyme systems due to the denaturation of the enzymes in organic solvents or extreme temperature ranges. Due to this limitation, a synthetic supramolecular system would serve as an excellent complementary tool for the systematic study of solvent effects in host−guest systems. Insights obtained from such studies can be compared to results from molecular recognition processes related to biological systems.

In this study we examined the fundamental forces that govern the selectivity and binding affinity of a synthetic supramolecular host−guest complex. This M_4L_6 host assembly, developed by Raymond and co-workers,[9−12] has been shown to efficiently recognize and encapsulate a variety of monocationic guests. The supramolecular host has been found to encapsulate many different guests, ranging from simple ammonium cations to highly reactive organometallic species, with high binding affinities.[9−27] The equilibrium binding constants K_a for these guests are relatively high ($\sim 10^3-10^4$ M^{-1}) and result in the formation of thermodynamically stable host−guest assemblies. Upon encapsulation, reactive organic and organometallic guests can react with substrates in a highly selective manner dictated by the host cavity.[13,18,22−27]

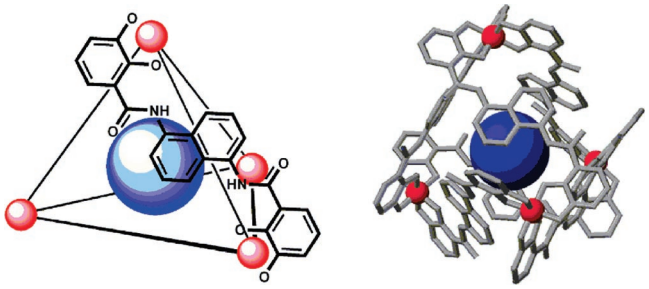

Figure 1. Left: Schematic of $[M_4L_6]^{12-}$ containing a large void cavity. Four metal centers comprise the vertices of the tetrahedron while six bis-bidentate catecholamide ligands span the edges of the tetrahedron (only one of the ligands is drawn for clarity). Right: X-ray structure of $Fe_4L_6^{12-}$ displaying the large void cavity.

This host−guest system provided us with a versatile platform to investigate the factors governing guest recognition and encapsulation. The M_4L_6 host assembly is soluble in a variety of polar solvents ranging from protic solvents, such as water and methanol, to aprotic solvents such as dimethyl sulfoxide (DMSO), allowing for the direct examination of specific solvent effects. In addition, since a wide variety of guests can be encapsulated, the guest species can be varied both structurally and electronically in order to distinguish the important forces contributing to encapsulation. Moreover, the supramolecular host lacks functional groups that may provide specific complementary interactions contributing to guest encapsulation; in this way, the sole effect of solvent on molecular recognition can be isolated and studied. The factors affecting the enthalpic and entropic parameters governing guest recognition can be determined, and any resultant correlations can be investigated, which may provide general insight into the factors governing molecular recognition.

Results and Discussion

Solvent Effects on Guest Encapsulation. For this study, we chose a robust supramolecular tetrahedral assembly of the general form $M_4L_6^{12-}$ (M = Ga(III), Fe(III), Al(III); H_4L = bis-catecholamide naphthalene).[9−11] This $M_4L_6^{12-}$ assembly contains a large, well-defined internal cavity that is capable of complete three-dimensional encapsulation of a variety of guest molecules (Figure 1). This host is only soluble in polar solvents due to its highly anionic nature.

Our initial studies indicated that most of the guests that are encapsulated with high binding affinities are monocationic. Together with the fact that the host is highly anionic, our initial hypothesis suggested that the major driving force for encapsulation was electrostatic interactions between the host and guest. Contrary to this hypothesis, we have very recently shown that neutral guests are also encapsulated, suggesting that there are other factors involved in the molecular recognition process.[28] Furthermore, despite their potentially strong electrostatic attraction for the highly anionic host, none of the many dicationic species screened were encapsulated, suggesting that the high desolvation energy of these species works against binding in these cases. Consistent with this observation, strongly solvated monocationic species such as Li^+ and Na^+ are also not encapsulated, although the more hydrophobic crown ether complexes of these ions have been shown to be good guests.[15]

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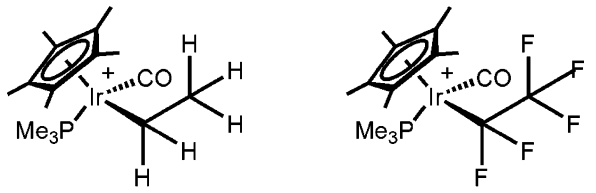


2-Et **3-Et$_F$**

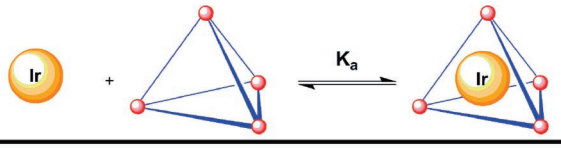
Figure 2. Left: Example of an iridium ethyl carbonyl complex **2-Et**. Right: Example of an iridium perfluoroethyl carbonyl complex **3-Et$_F$**.

Aside from simple cationic guests, the supramolecular host can also accommodate highly reactive cationic organometallic complexes, such as $[Cp^*(PMe_3)Ir(Me)(cis\text{-butene})]^+$ (**1**), that can undergo selective C−H bond activation.[25−27] The products of these reactions are often thermodynamically stable iridium species. For example, the C−H bond activation of aldehydes by **1** results in the formation of inert iridium alkyl carbonyl complexes $[Cp^*(PMe_3)Ir(CO)(R)]^+$ (**2-R**) that can also be suitable guests for encapsulation. The iridium compounds **2-R** provided us with a tool for assessing the impact of size and shape of the guest on encapsulation, as the size and structure of the iridium guest can be easily tuned by adjusting the steric properties of the R group.

The versatility of our host−guest system also allowed us to look beyond varying only the steric properties of the guest. The use of perfluoroalkyliridium complexes in the form of $[Cp^*(PMe_3)Ir(CO)(R_F)]^+$ (**3-R$_F$**) provided a means for the direct assessment of solvation effects between guests of different solubilities but similar steric properties (Figure 2).[29−31] Fluorinated species are relatively similar in size to their corresponding protiated counterparts although the fluorine atom's van der Waals radius is larger than that of hydrogen (1.47 Å compared to 1.20 Å), and perfluoroalkyl substituents have slightly larger Tolman cone angles (θ) compared with their alkyl counterparts.[31] However, in spite of the similarity in size, perfluorinated species are often more hydrophobic and less soluble in water.[32] Because of the powerful inductive effect of fluorine, its electronic and solubility properties should outweigh changes caused by steric effects.

Using this system, diagnostic information on the effect of size and shape on the affinity of iridium guests was obtained by measuring the binding constants for the set of iridium carbonyl complexes **2-R** and **3-R** (Table 1).[33] The binding constants for these guests were determined directly both by ^{1}H NMR spectroscopy of the host−guest assembly and by stoichiometric competition with tetraalkylammonium guests with known binding constants,[34] which gave consistent results. Aside from the versatility of guest identity, the $Ga_4L_6^{12-}$ host is soluble in not only water but also other highly polar, organic solvents such as methanol and DMSO.

Table 1. Thermodynamic Parameters for the Encapsulation of Various Iridium Guests by $Na_{12}[Ga_4L_6]$ in D_2O Buffered with TRIS/DOTf (100.0 mM) at pD = 8.0, CD_3OD, and DMSO-d_6[a]



Entry	Guest	Solvent	$\Delta H_{tot}°$	$\Delta S_{tot}°$	K_a
1	**1**	D_2O	2.0 (5)	16 (2)	0.12 (1)
2	**2-Me**	D_2O	-4.3 (4)	3 (1)	17 (2)
3	**2-Et**	D_2O	-6.5 (3)	-3 (1)	15 (2)
4	**2-Pr**	D_2O	-11 (1)	-20 (4)	5.9 (6)
5	**2-^{i}Pr**	D_2O	-4.2 (3)	3 (1)	2.3 (2)
6	**3-Me$_F$**	D_2O	-11.1 (8)	-18 (3)	7.0 (7)
7	**3-Et$_F$**	D_2O	-5.2 (7)	-2 (2)	1.7 (2)
8	**3-^{i}Pr$_F$**	D_2O	-17 (2)	-44 (6)	0.16 (2)
9	**2-Me**	CD_3OD	-12 (1)	-23 (4)	5.9 (6)
10	**2-Et**	CD_3OD	-12 (2)	-21 (7)	16 (2)
11	**2-Pr**	CD_3OD	-16 (1)	-38 (3)	2.7 (3)
12	**2-^{i}Pr**	CD_3OD	-11.3 (8)	-22 (3)	3.0 (3)
13	**3-^{i}Pr$_F$**	CD_3OD	-26 (3)	-73 (8)	1.3 (1)
14	**2-Me**	DMSO-d_6	-8 (1)	-6 (4)	36 (4)
15	**2-Et**	DMSO-d_6	-4.8 (7)	4 (2)	25 (3)
16	**2-Pr**	DMSO-d_6	-3.3 (2)	1 (1)	0.44 (4)
17	**2-^{i}Pr**	DMSO-d_6	4.0 (9)	27 (3)	1 (1)

[a] $\Delta H°$ units are in kcal mol^{-1}. $\Delta S°$ units are in eu. K_a units are 10^3 M^{-1} and determined at 298 K for both diastereomers.

Despite these structural and electronic differences, the overall binding affinities for the series of iridium guests are remarkably similar regardless of solvent and are on the order of $\sim 10^3$. The small differences in binding affinity may be due to subtle host−guest interactions, particularly as the size of the guest becomes larger and approaches the limitations of the host cavity. Such similar binding constants suggest a common driving force for guest encapsulation by the M_4L_6 host assembly that is independent of guest structure and identity. In agreement with this, Houk and co-workers have reviewed the binding affinities of a wide variety of synthetic host−guest systems in water.[6] The synthetic hosts examined included crown ethers, cyclodextrins, calixarenes, resorcinarenes, cyclophanes, and porphyrins among others. Compiling data for nearly 1000 synthetic host−guest systems, they found that the average binding K_a values are $10^{3.4\pm1.6}$ M^{-1}. The results reported here for the encapsulation of cationic iridium guests within the tetrahedral $M_4L_6^{12-}$ host fall within this range. These binding affinities are unusually similar for a wide variety of host−guest assemblies and suggest that there is some common factor that governs binding for all of these systems.

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(33) Since both the iridium species **2-R** and the Ga_4L_6 host are chiral, two diastereomeric host−guest assemblies are formed upon encapsulation, with varying degrees of diastereoselectivity depending upon the size and shape of the guest. For the current study, since we were primarily interested in determining the driving force for encapsulation, the total binding constants for encapsulation were measured, taking into account the contributions from both host−guest diastereomers.
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Encapsulation of iridium *cis*-butene complex **1** in water was found to be enthalpically unfavorable but entropically favorable (Table 1, entry 1). Similar entropy-driven encapsulation of ammonium cations by the M_4L_6 host was also previously reported.[34] This effect is consistent with hydrophobic effects found in many entropy-driven processes in biological interactions[35] and in other model host−guest systems.[36−38]

However, in polar protic solvents such as water and methanol, as the iridium guests become larger and more hydrophobic, encapsulation is no longer entropically driven but becomes enthalpically favorable. For example, homologously increasing the alkyl substituent from **2-Me** to **2-Pr** in water (Table 1, entries 2−4) results in increasingly favorable enthalpy values, ranging from −4 to −11 kcal/mol. In general, the encapsulation of the more hydrophobic perfluoroalkyl iridium analogues also continues this trend (Table 1, entries 6−8). Nevertheless, this enthalpic trend is matched by an opposite trend for the entropic contributions for guest recognition. For example, for the same set of iridium complexes **2-Me** to **2-Pr**, there is a corresponding decrease in the entropy from 3 to −20 eu.

Notably, the observed trend in the standard thermodynamic parameters for encapsulation in our system in water and methanol is the opposite of that expected for systems governed by the classical hydrophobic effect. In typical entropy-driven systems, as guest molecules become larger and more hydrophobic, desolvation is more *enthalpically* unfavorable but more *entropically* favorable as more solvent molecules are released into the bulk solution. The opposite trend observed here implies that the encapsulation process is quite different. Similar enthalpy-driven molecular recognition systems have been reported previously and are examples of nonclassical hydrophobic effects.[39−43]

The encapsulation of these iridium guests was then investigated in the polar aprotic solvent DMSO-d_6 (Table 1, entries 14−17). In DMSO, however, the fluorinated iridium complexes **3-R$_F$** were not encapsulated. Furthermore, despite having similar binding affinities to the studies performed in polar protic solvents, the reverse trend in $\Delta H°$ and $\Delta S°$ was observed in the encapsulation of the iridium guests **2-R** in DMSO. In DMSO, as the iridium guest becomes larger and more hydrophobic, the encapsulation process becomes more enthalpically disfavored and entropy driven, similar to the trend expected by the classical hydrophobic effect.

Enthalpy−Entropy Compensation Effects. The results presented thus far provide a qualitative picture of the enthalpy−entropy compensation effects found in water and methanol versus DMSO, wherein as the encapsulation process becomes more enthalpically favorable, there is a greater loss of entropy. We therefore adopted a quantitative approach to establishing this relationship for our system. As shown in Figure 3, a remarkably linear relationship between $\Delta H°$ and $\Delta S°$ for encapsulation in water was observed for the series of iridium guests as well as several ammonium guests studied previously.[34]

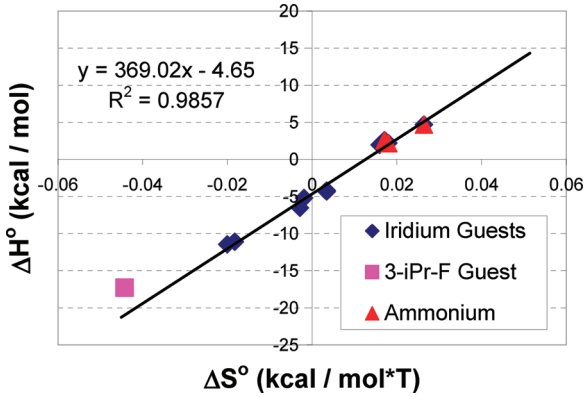

Figure 3. Plot of the enthalpy versus entropy values for the encapsulation of a variety of guests by $Na_{12}[Ga_4L_6]$ in D_2O buffered with TRIS/DOTf (100.0 mM) at pD = 8.0. The bold line indicates the enthalpy−entropy correlation for iridium species **2-R**, **3-R$_F$**, and ammonium guests. The thermodynamic values for the weakly binding **3-^{i}Pr$_F$** (pink square) fall outside this trend.

The graph of enthalpy versus entropy values for the encapsulation of the iridium guests in water produces a highly linear trend and can be expressed mathematically by eq 1:

$$\Delta H° = \beta \Delta S° - 4.65 \text{ kcal/mol} \qquad (1)$$

The slope of the correlation, or β, has units of temperature and is called the compensation temperature (T_c).[44] At this temperature, any variation in the standard enthalpy for a series of compounds is balanced by a compensating variation in the standard entropy, such that the total free energy ($\Delta G°$) of the encapsulation remains constant at −4.65 kcal/mol, the *y*-intercept of the plot. Therefore, guests with any combination of $\Delta H°$ and $\Delta S°$ values that lie on this slope (i.e., that occur at this T_c) are isoenergetic and have the same total binding affinity.

In water the iridium guests **2-R** and **3-R$_F$** have highly correlated standard enthalpies and entropies of encapsulation, with $T_c = 369 \pm 15$ K. The sole exception is **3-^{i}Pr$_F$**, which is a much weaker guest ($K_a = (0.16 \pm 0.02) \times 10^3$ M^{-1}) and as a result falls well beyond the compensation trend. The sterically demanding **3-^{i}Pr$_F$** may be large enough that unfavorable host−guest interactions may override the inherent binding affinity of the guest. Remarkably, this enthalpy−entropy compensation effect appears to be general; the standard enthalpies and entropies for the encapsulation of a series of structurally distinct ammonium guests previously reported by the Raymond group (NPr_4^+, $NMe_2Pr_2^+$, and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine) also fall on this line.[34]

Similarly, the standard enthalpies and entropies of encapsulation in methanol and DMSO also display linear compensation effects. When methanol was used as a solvent, a linear compensation was observed with a T_c of 271 ± 8 K (Figure 4). A roughly linear correlation was also observed when DMSO was used as the solvent, with a T_c of 337 ± 58 K (Figure 5),

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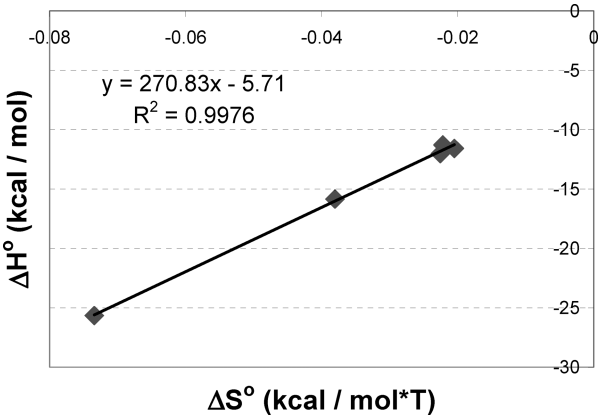

Figure 4. Plot of the enthalpy versus entropy values for the encapsulation of iridium guests **2-R** and **3-R** by $Na_{12}[Ga_4L_6]$ in CD_3OD.

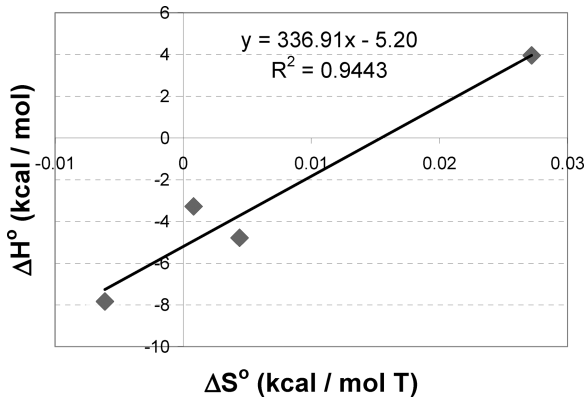

Figure 5. Plot of the enthalpy versus entropy values for the encapsulation of iridium guests **2-R** by $Na_{12}[Ga_4L_6]$ in DMSO-d_6.

although there is a much larger error in the correlation than in the case for water and methanol.

A body of literature has emerged that suggests that the enthalpic and entropic parameters for molecular recognition are highly correlated for a wide variety of phenomena.[44−49] Such high correlations, with R values often exceeding 0.95, would seem to suggest some common chemical phenomena behind the forces governing molecular recognition for a wide range of systems. However, in spite of the prevalence of these enthalpy−entropy compensation effects in the literature, they remain controversial and many authors have noted that their appearance may be artifactual.[50−56] This is because indirect methods, such as van't Hoff analysis, do not independently measure the $\Delta H°$ and $\Delta S°$ of an equilibrium. For measurements spanning only a small temperature range, any true determination of the $\Delta H°$ and $\Delta S°$ may be obscured by a dominant statistical correlation that arises from the linear least-squares regression.[53,54] Additionally, the assumption in van't Hoff analysis that $\Delta H°$ is constant (i.e., the heat capacity change is negligible) may be invalid.

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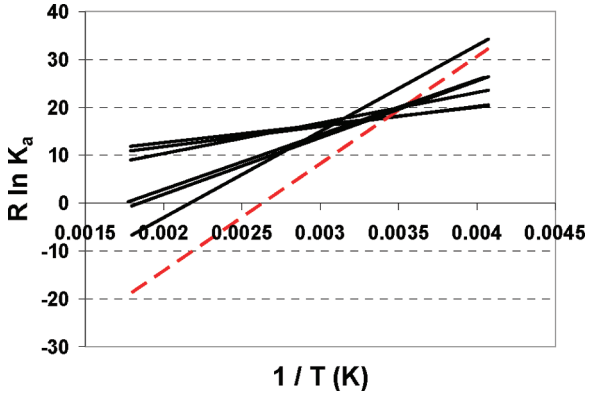

Figure 6. Plot of van't Hoff slopes for the encapsulation of iridium species **2-R** and **3-R_F** by $Na_{12}[Ga_4L_6]$ in D_2O buffered with TRIS/DOTf (100.0 mM) at pD = 8.0. Most of the iridium species meet at a common intersection point at $1/T_c$. The red dashed line indicates the slope for the encapsulation of **3-^{i}Pr$_F$** and does not meet at the common intersection point.

To address these concerns, some researchers have proposed several forms of error analyses on the observed enthalpy−entropy compensation data in order to distinguish between statistical artifacts and genuine chemical phenomena. Krug and co-workers have proposed several tests that can be applied to evaluate whether there is possible chemical significance to an apparent enthalpy−entropy correlation.[53−55] First, the observed compensation temperature T_c must be significantly different from the average experimental temperature T_{exp}. In addition, when plotted together, the van't Hoff slopes for the set of related reactions should intersect at a common temperature. When these criteria are satisfied, the compensation behavior between $\Delta H°$ and $\Delta S°$ may be indicative of chemical phenomena rather than simply an artifact of statistical correlation.

When water or methanol (both of which are capable of forming hydrogen bonds) was used as the solvent, the T_{exp}'s for the encapsulation of these iridium guests were significantly different from the observed T_c's (337 vs 369 ± 15 K for water and 328 vs 271 ± 8 K for methanol). Furthermore, the van't Hoff slopes for the encapsulation of each iridium species intercept at a common point at $1/T_c$ in water (Figure 6) and methanol (see Supporting Information). A notable exception is that the van't Hoff plot for the encapsulation of **3-^{i}Pr$_F$** in water does not cross this intersection; as observed previously in the enthalpy−entropy plot, **3-^{i}Pr$_F$** has a much weaker binding affinity and lies significantly beyond the standard correlation of the other iridium and ammonium guests. These results suggest that the observed correlation between the thermodynamic values for the encapsulation process in water and methanol has true chemical significance, suggesting that they share similar thermodynamic characteristics.

While water and methanol gave similar results, when the data were examined for DMSO, it became evident that the compensation behavior observed in DMSO does not have real chemical significance. In this case, the observed T_c (337 ± 58 K) was very similar to the average experimental temperature T_{exp} (341 K). In addition, when the van't Hoff trends for the encapsulation of each iridium guest are plotted together, they do not meet at a common intersection (Figure 7). This strongly suggests that

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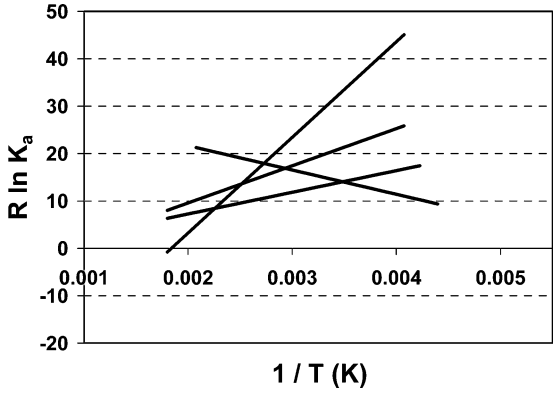

Figure 7. Plot of van't Hoff slopes for the encapsulation of iridium species **2-R** by $Na_{12}[Ga_4L_6]$ in DMSO-d_6. In this case, the iridium species do not meet at a common intersection point.

the apparent enthalpy−entropy correlation in DMSO was an artifact from the initial van't Hoff study. While the overall $\Delta G°$ and K_{eq} values can be measured for encapsulation in DMSO, the actual $\Delta H°$ and $\Delta S°$ values derived from the van't Hoff analyses are masked by an inherent statistical correlation error and as a result cannot be determined accurately.[53,54] Since the individual enthalpic and entropic contributions toward the encapsulation process could not be revealed, deeper insight into the encapsulation process in DMSO remains obscured.

Solvent Reorganization as a Driving Force. The results presented thus far indicate that there is a compensating effect between the enthalpic and entropic component of the encapsulation process. The next question we seek to answer is what is the chemical driving force behind such enthalpy−entropy compensation effects? At first glance, one possible explanation may be attractive interactions between the host cavity and the guest. Though in our system there are no specific functional group-driven interactions, there may be weak, nonspecific supramolecular interactions that guide the binding of the guest to host. The approach of the guest toward the host would lead to an increase in favorable enthalpic interactions, while leading to a decrease in entropic contributions as the motions of the host and guest become more restricted. This would predict that, as the iridium guests become larger and more hydrophobic, they may have more favorable interactions with the host cavity while becoming more tightly locked into the confined environment and this effect may be exhibited in a linear fashion. Williams and co-workers have shown how such supramolecular interactions may lead to enthalpy−entropy compensation.[57,58]

However, the dramatically different trends observed for the iridium guests in different solvents suggest that solvation plays a key factor in the encapsulation process, not host−guest interactions alone. Gilli and co-workers have argued that observed enthalpy−entropy compensation effects in drug−receptor binding in water are due to solvent reorganization, not specific drug−receptor interactions.[8] Specifically, they propose that the hydrogen bond networks in aqueous solution control the intermolecular association between guest and host. The observed $\Delta H°$ values are primarily assigned to the energetic balance of the hydrogen bonds released and formed during the reaction, while the observed $\Delta S°$ values are due to the rearrangement of solvent. The enthalpic and entropic factors in solvent hydrogen bond rearrangements are inversely related, which may result in the observed compensation behavior. In this view, enthalpically favorable hydrogen bond formation leads to a loss of entropy as the water molecules lose degrees of freedom.[59]

This solvent reorganization rationale explains the observed trend in the standard enthalpies and entropies of encapsulation in polar protic solvents for our system. The encapsulation process is a continuum involving guest desolvation and solvent rearrangement. Encapsulation involves complete desolvation of the guest and host cavity. Upon desolvation, the released water molecules can subsequently form more hydrogen bonds with each other and the bulk solution, resulting in favorable $\Delta H°$ values. The formation of this hydrogen-bonding network results in a decrease in $\Delta S°$ as the solvent becomes more ordered. When encapsulation of larger guests occurs, a larger void cavity is produced that the surrounding water molecules can reoccupy, resulting in the formation of more hydrogen bonds that lead to more favorable $\Delta H°$ values and more unfavorable $\Delta S°$ values. In contrast, smaller guests such as the ammonium cations leave a smaller void cavity that forms fewer hydrogen bonds. In addition, these smaller guests are more strongly solvated, and subsequent desolvation entails a substantial enthalpic loss that is compensated by an increase in entropy due to the release of solvent molecules. This relationship between the enthalpy and entropy values results in the observed compensation effect. Our results obtained from polar protic solvents are in strong support of this theory. In solvents without hydrogen-bonding networks such as DMSO, no such correlation would be expected and none is observed.

To further establish that such effects are due to solvent reorganization and not host−guest interactions, we used an alternative method of analyzing the data introduced by Inoue and co-workers.[60] A linear correlation is obtained by plotting $T\Delta S°$ versus $\Delta H°$ (T = 298 K) for the encapsulation of the iridium guests in water and methanol (see Supporting Information). At a $\Delta H°$ value of 0, positive $T\Delta S°$ values of 3.9 ± 0.4 and 6.2 ± 0.4 kcal/mol are observed in water and methanol, respectively. The significance of this is that, at $\Delta H° = 0$, while there is no net enthalpic driving force resulting from host−guest interactions or hydrogen bond formation, there is still a favorable $\Delta S°$ of 13−20 eu, which we assign to the release of solvent molecules from the host cavity and the guest solvation sphere. This supports the hypothesis that desolvation of the guest species and rearrangement of the hydrogen bonds in solution are the driving forces for the encapsulation process.

These entropic gains are similar to the values determined in studies of other host−guest interactions. The encapsulation of cations by crown ethers in water has an intrinsic $\Delta S°$ of 8.1 kcal/mol.[60] In contrast, the encapsulation of cations by cryptands in water is more extensive, resulting in greater desolvation and an increased $\Delta S°$ of approximately 13.4 kcal/mol. This value is similar to the result obtained in the encapsulation of the iridium guests in water and methanol and is consistent with complete, three-dimensional encapsulation by the Ga_4L_6 host assembly.

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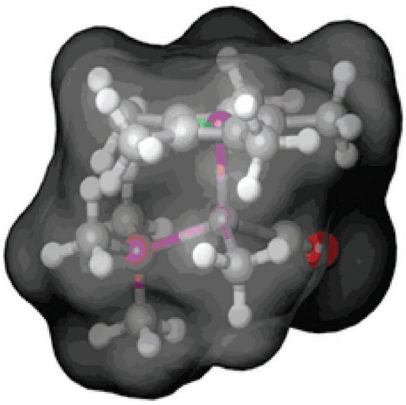

Figure 8. The solvent accessible surface area of **2-Me** determined using a 1.4 Å^3 probe is approximately 275 Å^2. This total surface area is buried upon encapsulation by $Na_{12}[Ga_4L_6]$.

Combining all the data presented thus far, we propose that it is solvent reorganization that is the dominant factor in the encapsulation process. This exhibits chemically significant enthalpy−entropy compensation behavior due to the rearrangement of the hydrogen bond network in solution. This desolvation and hydrogen bond rearrangement behavior results in the remarkably similar binding affinity for the wide variety of guests observed. Due to the unusually similar binding affinities of the series of iridium guests in water and methanol as well as DMSO, we believe that desolvation also plays a key role in encapsulation in DMSO. However, since DMSO lacks an extensive hydrogen-bonding network in solution, evidence of this desolvation behavior via enthalpy−entropy compensation is masked by a statistical correlation between the enthalpic and entropic factors involved in encapsulation.

Only when significantly large structural changes are introduced, such as in **3-^{i}Pr$_F$**, do other factors (such as unfavorable host−guest interactions) begin to affect the encapsulation, leading to weaker overall free energy of binding. Energetically favorable solvent rearrangement during guest desolvation also explains the ability of the supramolecular host to encapsulate neutral guests, in spite of the lack of possible electrostatic attraction, π-cation, or even $\pi-\pi$ interactions with the charged host.[28]

Houk has shown that there is a strong correlation between the binding affinity of the substrate and the average buried surface area of the guest upon encapsulation for a wide variety of molecular recognition phenomena.[6] As more of the surface area of the guest is removed from contact with solvent, there is a correspondingly higher binding affinity. Presumably, upon desolvation larger guests release more water molecules, raising the binding affinity through increasingly favorable solvent rearrangement.

In order to quantify this effect, the water accessible surface area of **2-Me** was calculated using a 1.4 Å^3 probe and was found to be approximately 275 Å^2 (Figure 8).[61] Since encapsulation within the M_4L_6 assembly is three-dimensional and completely desolvates the guest molecule, the total surface area of **2-Me** is buried upon binding. With a buried surface area of ca. 275 Å^2, an approximate binding affinity of 10^3-10^4 M^{-1} is predicted from the Houk correlation, which is remarkably close to the observed experimental value.

The hydrogen bond rearrangement of polar protic solvents such as water upon desolvation appears to explain much of the fundamental molecular recognition processes that occur in these solutions, ranging from host−guest interactions of simple synthetic crown ether-cation systems to highly complex naturally occurring enzyme−substrate interactions. Current efforts to use calorimetry to independently measure the enthalpic changes involved in the encapsulation pathway, including initial host−guest ion pairing and the final encapsulation step, are underway.[62]

Summary and Conclusions

We have described here detailed analyses of the factors governing guest encapsulation by an M_4L_6 host. To our knowledge, this represents the first systematic analysis of the major driving force for supramolecular interactions in a synthetic host−guest system. By utilizing a synthetic host without specific functional group driven interactions, the direct effect of various solvents on the recognition effect could be assessed. It was found that a common factor in guest encapsulation by the $Na_{12}[Ga_4L_6]$ host is the rearrangement of solvent molecules and, specifically, the reorganization of hydrogen-bond networks upon desolvation of the guest. We suggest that hydrogen-bond rearrangement upon desolvation of the guest satisfies the observed enthalpy−entropy compensation trends. Due to this effect, the binding affinities for a wide range of structurally distinct guests are remarkably similar. Nevertheless, while the binding affinities for encapsulated guests are the same at T_c, varying the reaction temperature may be crucial in obtaining much higher selectivities for the molecular recognition of particular guests. Optimization of encapsulation selectivities may also involve tuning the specific interactions between the guest molecule and solvent.

This mechanism for guest binding may be general for a remarkable number of synthetic and naturally occurring host−guest assemblies in aqueous solution and points toward a common explanation for molecular recognition in water. Our results provide further experimental support for previous studies that suggest the desolvation of ligands from surrounding water molecules and the resulting rearrangement of the hydrogen-bonding network may actually be the primary driving force for determining ligand binding affinities in the absence of specific functional group interactions. The use of a synthetic, tunable supramolecular host−guest system provides us with a complementary tool in investigating the specific solvent effects of these processes in organic solvents over a broad range of temperatures, which is otherwise incompatible with biological enzymes. The unique insights obtained from our studies provide additional information on supramolecular interactions, which can have broad implications for guiding the design and optimization of host−guest systems with high affinity and specificity.

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Supporting Information Available: General experimental procedures for the preparation of the iridium compounds; general procedures for van't Hoff thermodynamic measurements; plot of van't Hoff trends for the encapsulation of iridium guests in methanol; plots of $T\Delta S°$ versus $\Delta H°$ ($T = 298$ K) for the encapsulation of iridium guests in water and methanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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