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Calorimetric Study on Coordination of Tridentate Imidazolyl Calix[6]arene Ligands to Zinc Ion in Organic Solvents

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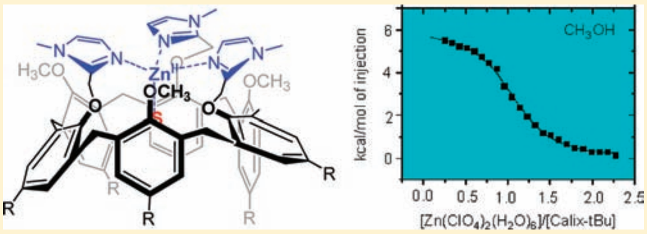
S *Supporting Information*



ABSTRACT: Complexation of three kinds of tris(imidazolyl)-calix[6]arenes containing alternate *p*-substituents (Calix-tBu, $R_1 = R_2 =$ *tert*-butyl; Calix-NH_2, $R_1 =$ *tert*-butyl, $R_2 = NH_2$; Calix-NO_2, $R_1 =$ *tert*-butyl, $R_2 = NO_2$) with $Zn(ClO_4)_2(H_2O)_6$ in acetonitrile, methanol, and THF was investigated via isothermal titration calorimetry (ITC). For the coordination of these calixarene ligands to Zn(II) in acetonitrile, typical one-phase exothermic titration curves were obtained, indicating the formation of 1:1 ligand−Zn(II) complexes accompanied by large conformational changes of the ligands. In contrast, the complexation in methanol was endothermic and dominated by favorable entropy changes. The entropy gains were achieved by extensive desolvation from both Zn(II) and the ligands. ITC measurements suggest a 2:1 ligand−Zn(II) complex formation in THF in the presence of excess ligands (Calix-NH_2 and Calix-NO_2). The 2:1 complexes were converted to 1:1 complexes upon further addition of $Zn(ClO_4)_2(H_2O)_6$. The results indicate the important role of a coordinating solvent (acetonitrile) for direct formation of the 1:1 complexes under the conditions of excess ligand. Complexation of a ditopic ligand (Calix-Tri) with three triazole moieties on the wider rim was also studied via ITC. The first coordination of the imidazole moieties to Zn(II) was an exothermic process. This was followed by the entropically favorable coordination of the triazole moieties to the divalent cation. We have also investigated exchange of the fourth ligand (H_2O) of the Zn(II) complex of Calix-NH_2 with butylamine, heptylamine, acetonitrile, and acetamide in a noncompetitive solvent, THF. The ΔH^0 tended to decrease upon increasing the electron-pair-donating ability of the guest ligand, whereas it was also affected by an entropic term due to restricted rotation of the guest ligand inside the calixarene cavity.

■ INTRODUCTION

The behavior of a metal complex in solution is often discussed on the basis of the results obtained by X-ray crystallography. In such cases, it is important to note whether the structure of the metal complex in solution is identical to that in a single crystal state. UV−vis, NMR, and soft-ionization MS spectrometry are generally employed for estimating the structure of the complex in solution. However, these analytical methods are not always applicable, especially in the analysis of fragile and/or paramagnetic metal complexes. In contrast, isothermal titration calorimetry (ITC) is a very powerful and commonly available tool for studying the thermodynamics of a chemical process. The exothermic or endothermic heat during a reaction can be directly measured via ITC, enabling the determination of a stability constant (K) and an enthalpy change (ΔH^0) for the reaction. Another benefit of ITC is that a stoichiometry of certain complexation can be easily determined. Many ITC studies have reported ion−dipole interactions between various metal ions and crown ethers,[1] cryptands,[2] and calix[*n*]arenes.[3] In most cases, the complexation of these cyclic Lewis bases with metal ions is enthalpically dominated ($\Delta H^0 < 0$, $\Delta S^0 < 0$), and coordinating solvents such as acetonitrile and *N*,*N*-dimethylformamide (DMF) cause an increase in both ΔH^0 and ΔS^0 because of desolvation during complexation. Cyclic polyamine ligands are also placed in the same category.[4] In the field of coordination chemistry, ITC has been mainly utilized to investigate interactions of metal ions with proteins or peptides in aqueous solutions.[5] ITC, which measures only the heat value that is generated or consumed during a chemical event, exercises its benefit in complicated systems. Very few ITC measurements have been carried out about coordination of simple ligands to metal ions in organic solvents, and therefore, little information related to solvent effects on coordination to metal ions is available. Meanwhile, it is very important to determine the stoichiometry of metal ion in a coordination complex in solution. The stoichiometry of a complexation event can be easily determined from the inflection point in the titration curve plotting heat vs molar ratio of metal ion to ligand (or vice versa). Curiously, however, there are a few examples illustrating the application of ITC for determining the stoichiometries of coordination complexes.[6]

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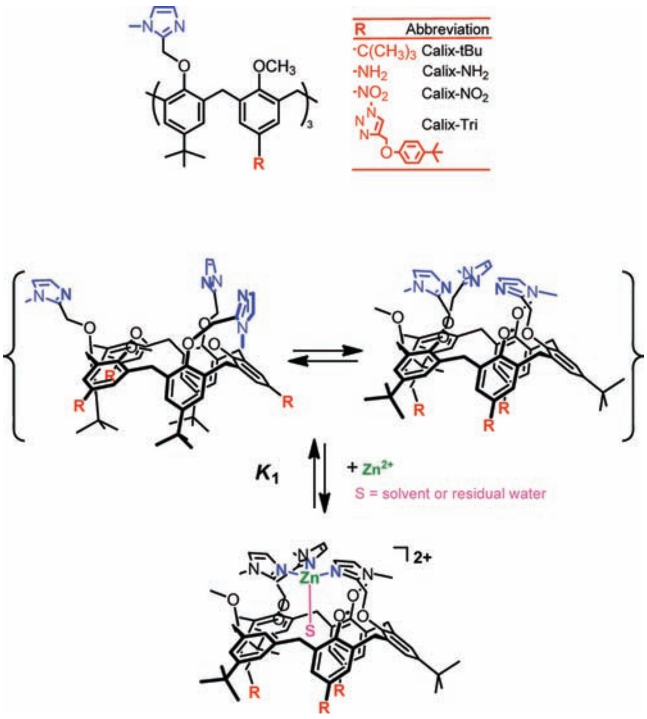
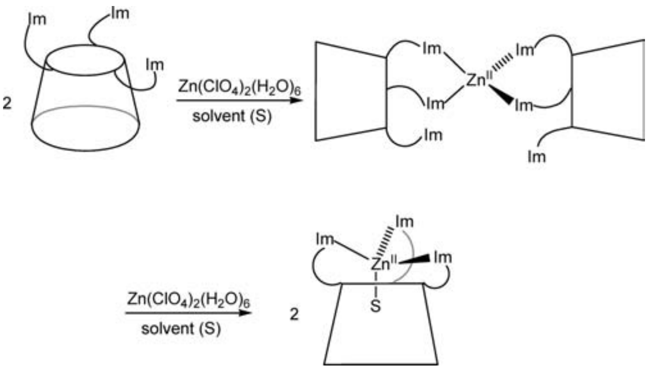


Figure 1. Calixarenes used in this study and formation of their Zn(II) complexes in THF. The structure of the Zn(II) complex was pictured on the basis of X-ray crystallography of the Zn(II)−Calix-tBu complex (see refs 7 and 8).

Scheme 1. Plausible 2:1 and 1:1 Complexes of Tris(imidazolyl)calix[6]arene and Zn(II)



Complexation of metal ions to cavity-based ligands is a very appealing subject for ITC study. These ligands possess several characteristics that are keys in metalloenzymes, such as large reorganization of the ligand induced by coordination to a metal ion, host−guest binding synergistically induced by coordination, and restricted access of solvent to the metal center. Determination of the thermodynamic parameters associated with these phenomena is fundamental for deep understanding of coordination in such a biomimetic system. Because metalation of proteins is generally accompanied by conformational changes of the proteins, heat generation or absorption measured by ITC is the result of various events occurring during metalation. Therefore, ITC study of a simple biomimetic system becomes meaningful. We are currently interested in a flexible calix[6]arene macrocycle as the biomimetic platform. When such a calix[6]arene framework is functionalized by three imidazole groups at the narrow rim, it may provide a coordination core that mimics the polyhistidine site encountered in many metalloenzymes.[7] Reinaud et al. synthesized various calix[6]arenes having such tridentate coordination sites, and they studied the complexation of these ligands with metal ions such as Zn(II), Cu(II), Co(II), and Ni(II) by means of X-ray crystallography and NMR spectroscopy.[7−9] Figure 1 shows some of the tris(imidazolyl)calix[6]arene ligands that give stable complexes of metal ions. In so far as Zn(II), they all form tetrahedral metal complexes coordinated by the three imidazole moieties and a fourth guest ligand included in the calixarene cavity. When metalation is carried out in a noncoordinating solvent such as THF, the fourth ligand is a water molecule from a hydrated metal source (Figure 1).[9] X-ray crystallography has revealed that the cavity of Calix-tBu acts as a host of a second water guest that is bound to the water ligand via hydrogen bonding,[10] while the second water does not bind to the coordinated water in the cavity of Calix-NH$_2$.[11] Solution studies showed that the water guests are readily displaced by various organic ligands, such as primary alkyl amines, alcohols, amides, and nitriles, but not by relatively bulky ligands, such as secondary and tertiary amines or amides.[9,11] Hydrogen bonding and CH−π interactions between the fourth ligand bound to the metal center and the aromatic walls of the calix[6]arene macrocycle also play an important role in maintaining the circular truncated cone structure of the complexes.[12] These results on the complexation of the tris(imidazolyl)calixarenes with Zn(II) have been obtained by X-ray crystallography and NMR spectroscopy.[7] However, the previous studies provide insufficient information regarding the coordination mechanisms involving stabilities of the metal complexes, solvent effects on coordination, and detailed reaction pathway to a final product. To study these subjects by ordinary spectroscopy, we need many experiments under various conditions. In the present study, we utilized ITC as a convenient tool for studying detailed mechanisms for the coordination of the four tris(imidazolyl)calix[6]arenes shown in Figure 1 to Zn(II).

■ RESULTS AND DISCUSSION

The synthetic experiments have shown that equimolar mixtures of the tris(imidazolyl)calix[6]arene ligands and Zn(ClO$_4$)(H$_2$O)$_6$ in a noncoordinating solvent, THF, yield tetrahedral (Td) Zn(II) complexes, as shown in Figure 1, where a water guest from the metal source coordinates to Zn(II) as a fourth ligand.[9−11] In a coordinating solvent such as acetonitrile, a Td complex with an acetonitrile molecule as the fourth ligand is formed.[13] Whereas the 1:1 stoichiometry has been well-established under equimolar ligand/metal ion conditions, it is plausible to form a 2:1 ligand−Zn(II) complex (Scheme 1) when Zn(ClO$_4$)(H$_2$O)$_6$ is added to a solution of excess Calix-tBu. ITC is useful for determining whether the 2:1 complex is formed as a precursor of the 1:1 complex.

Complexation in Coordinating Solvents: Acetonitrile and Methanol. Figure 2a shows the calorimetric titration curve obtained by adding an acetonitrile solution of Zn(ClO$_4$)$_2$(H$_2$O)$_6$ from a syringe into an acetonitrile solution of Calix-tBu in a cell. At the initial stage of such a titration, the solution in the cell is composed of a small amount of Zn(II) and an excess amount of Calix-tBu. If the 2:1 ligand−Zn(II) complex is formed, the inflection point should be observed at n = [Zn(II)]/[Calix-tBu] = 0.5 on the titration curve. As shown in Figure 2a, however, the inflection point was observed only at n = 0.94, strongly suggesting the direct formation of a 1:1 ligand–Zn(II) complex, where the fourth ligand was an acetonitrile molecule. Analysis of the titration curve shown in Figure 2a afforded the binding constant (K) and the enthalpy change (ΔH^0) for the coordination of Calix-tBu to Zn(II) in acetonitrile. Because the enthalpy change for complexation is directly measured by the calorimeter, the ΔH^0 value is reliable even if the corresponding K value is significantly large. However, the reliability of K depends on its magnitude. The analysis of the titration curve for the Zn(II)/Calix-tBu system provided a K value of $(1.45 \pm 0.17) \times 10^7$ M^{-1}. Because it is significantly large, we checked the reliability of this value by varying initial K values entered into the curve fitting program. Consequently, no better value other than $(1.45 \pm 0.17) \times 10^7$ M^{-1} was obtained. The results for Calix-tBu as well as those for Calix-NH_2 and Calix-NO_2 are listed in Table 1. Entropy changes (ΔS^0) were calculated using the following equation

$$-RT \ln K = \Delta H^0 - T\Delta S^0 \qquad (1)$$

where R and T are the gas constant and the absolute temperature, respectively. In all cases, the coordination in acetonitrile is characterized by K values spanning from 2.4×10^6 to 1.5×10^7 M^{-1} with large negative ΔH^0 and ΔS^0 values and little dependence on the substitution pattern at the wide rim of the calixarene cavity. The free ligands are flexible and take various conformations in acetonitrile. However, they become fixed upon coordination to Zn(II) to take a circular truncated cone structure. Such a process causes the negative ΔS^0 values. On the other hand, the formation of coordination bonds is an exothermic process, resulting in negative ΔH^0. Acetonitrile is a coordinating solvent. Desolvation from Zn(II) upon complexation causes an increase in both ΔH^0 and ΔS^0. The experimental data indicate that the combined effect of these thermodynamic processes results in large negative ΔH^0 and ΔS^0. The reduction in the flexibility of the ligands and the formation of stable coordination links (three imidazole–Zn(II) bonds) are the main factors that determine the thermodynamic parameters.

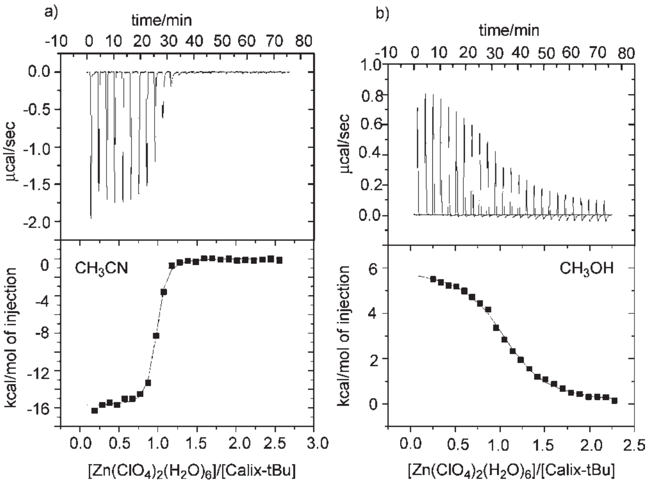


Figure 2. Calorimetric titrations of Calix-tBu with 25 aliquots (10 μL each) of $Zn(ClO_4)_2(H_2O)_6$ in acetonitrile (a) and methanol (b) at 298.15 K. The initial concentrations of Calix-tBu in a cell and $Zn(ClO_4)_2(H_2O)_6$ in a syringe are given in Table 1 (runs 1 and 4).

Methanol is also a coordinating solvent. Complexation in methanol, however, was thermodynamically different from that in acetonitrile, as shown in Figure 2b and Table 1 (runs 4–6). The K values for Calix-tBu and Calix-NO_2 in methanol are much smaller than those in acetonitrile. For each calixarene-based ligand, the coordination to Zn(II) in methanol is an endothermic reaction, and it is dominated by the entropy term. It is known that the complexation of Eu(III), Am(III), and Cm(III) with dicarboxylates such as oxalate, malonate, succinate, and adipate in an aqueous solution of high ionic strength is an endothermic and entropically dominated process because of the extended dehydration from the metal cations.[14] However, very few examples have been reported for endothermic complexation of ligands with metal ions in organic solvents. In the case of the ion–dipole interaction between Li^+ and cryptand [2,2,2] in methanol, the ΔH^0 and ΔS^0 values were reported to be +0.7 kJ mol^{-1} and +52 J mol^{-1} K^{-1}, respectively, though the complexation of other ions such as Na^+, K^+, Rb^+, Cs^+, and Ag^+ was exothermic.[2a] Enthalpy–entropy compensation theory predicts an increase in ΔH^0 when ΔS^0 increases, because of extended desolvation. The ability of a solvent to donate electron pairs to a metal ion can be evaluated on the basis of donor number (D_N), donor strength (D_S), and coordination power (CP):[15] the larger the D_N, D_S, and CP, the higher the ability to donate the electron pair to the metal ion. D_N, D_S, and CP are 14.1, 12, and 0, respectively, for CH_3CN and 19, 18, and 0.11, respectively, for methanol. These solvent parameters of methanol are larger than those of acetonitrile, indicating that solvation by methanol to Zn(II) occurs more extensively than that by acetonitrile. In addition, the calixarene ligands possess hydrogen-bonding sites such as ethereal oxygen and imidazole nitrogen atoms. Upon complexation in methanol, desolvation from both Zn(II) and the ligands should be more extensive than that in acetonitrile, resulting in the large positive entropy changes in the complexation in methanol.

Although the thermodynamic behavior in methanol is different from that in acetonitrile, the stoichiometry of the coordination complexes is the same in both coordinating solvents. ITC measurements were also attempted in ethanol. However, highly complex titration curves showing endothermic complexation were obtained and they could not be analyzed (Supporting Information).

Table 1. Thermodynamic Parameters for Coordination of Calix-tBu, Calix-NH_2, and Calix-NO_2 to Zn(II) in Acetonitrile and Methanol

run	cell[a]	syringe[b]	solvent	n[c]	K (M^{-1})	ΔH^0 (kJ mol^{-1})	ΔS^0 (J mol^{-1} K^{-1})
1	Calix-tBu (1.97×10^{-5} M)	Zn(II) (2.70×10^{-4} M)	CH_3CN	0.94 ± 0.01	$(1.45 \pm 0.17) \times 10^7$	-66.1 ± 0.45	−84.6
2	Calix-NH_2 (6.50×10^{-5} M)	Zn(II) (7.05×10^{-4} M)	CH_3CN	0.97 ± 0.01	$(2.39 \pm 0.27) \times 10^6$	-69.3 ± 0.06	−110
3	Calix-NO_2 (3.99×10^{-5} M)	Zn(II) (4.75×10^{-4} M)	CH_3CN	0.94 ± 0.01	$(5.92 \pm 0.71) \times 10^6$	-66.8 ± 0.51	−94.3
4	Calix-tBu (2.50×10^{-5} M)	Zn(II) (3.05×10^{-4} M)	CH_3OH	1.07 ± 0.01	$(7.19 \pm 0.47) \times 10^5$	$+24.9 \pm 0.29$	+196
5	Calix-NH_2 (3.05×10^{-4} M)	Zn(II) (2.94×10^{-3} M)	CH_3OH	0.91 ± 0.01	$(2.52 \pm 0.71) \times 10^6$	$+20.3 \pm 0.25$	+191
6	Calix-NO_2 (3.01×10^{-4} M)	Zn(II) (3.02×10^{-3} M)	CH_3OH	1.03 ± 0.01	$(6.11 \pm 0.27) \times 10^4$	$+29.7 \pm 0.45$	+191

[a] The numbers in parentheses are the initial concentrations of the ligands in the cell. [b] The numbers in parentheses are the initial concentrations of $Zn(ClO_4)_2(H_2O)_6$ in the syringe. [c] The molar ratio ([Zn(II)]/[ligand]) at which an inflection point was observed on the titration curve.

Coordination in Acetonitrile Containing Small Amounts of Water. ITC measurements were carried out in acetonitrile containing small amounts of water (Figure 3) to assess the effects of polar protic solvents on thermodynamic parameters for the coordination of Calix-tBu to Zn(II). The thermodynamic parameters obtained are listed in Table 2. Whereas the binding constants K were slightly affected as the water content increased, both ΔS^0 and ΔH^0 dramatically increased. Upon the addition of 0.1% (v/v) H_2O (run 7), the measured variations in the enthalpy and entropy changes as compared to pure acetonitrile (run 1) were enormous ($\Delta\Delta H^0 = 16.2$ kJ mol^{-1}, $\Delta\Delta S^0 = 47.8$ J mol^{-1} K^{-1}), whereas the effect of 0.1% (v/v) methanol (run 10) was negligible. Further addition of water led to further increase in ΔS^0 up to +25 J mol^{-1} K^{-1} in the presence of only 0.3% of water from −85 J mol^{-1} K^{-1} in pure acetonitrile. These results evidence the drastic effect of a small amount of water on the complexation process of a metal ion. In the presence of 0.5% water, endothermic peaks appeared after the exothermic process was completed (Figure 3b). The concentrations of 0.1 and 0.5% (v/v) H_2O in acetonitrile are 5.6×10^{-5} and 2.8×10^{-4} M, respectively. Since such a small amount of H_2O does not induce the fourth ligand exchange,[9] we must consider hydration/dehydration processes of the ligand and Zn(II) in a bulk phase. D_N, D_S, and CP of water are 18.0, 17, and 0.79, respectively,[15] which are much larger than those of acetonitrile. Therefore, Zn(II) may be hydrated in acetonitrile even in the presence of a small amount of water. Water has a strong hydrogen-bonding ability, whereas acetonitrile cannot act as the hydrogen donor. Thus, it is possible to envisage that the solvation core around Zn(II) as well as that of the calixarene ligand is composed of both CH_3CN and H_2O molecules in acetonitrile containing a small amount of water. Upon addition of the first drop of $Zn(ClO_4)_2(H_2O)_6$ from the syringe, the complexation in the cell promotes dehydration from both Calix-tBu and Zn(II), resulting in a slight increase of the concentration of free water in the bulk phase. When the second drop of Zn(II) solution is added, the added Zn(II) ion becomes more hydrated than the Zn(II) in the syringe. Such a phenomenon may continuously alter the thermodynamics of the coordination from exothermic to endothermic. Although the D_N and D_S values of methanol are almost the same as those of water, the CP of methanol is significantly smaller than that of water. In addition, the hydrogen-bonding ability of methanol is much weaker than that of water. Consequently, addition of only small amounts of methanol scarcely affects the thermodynamics of the complexation.

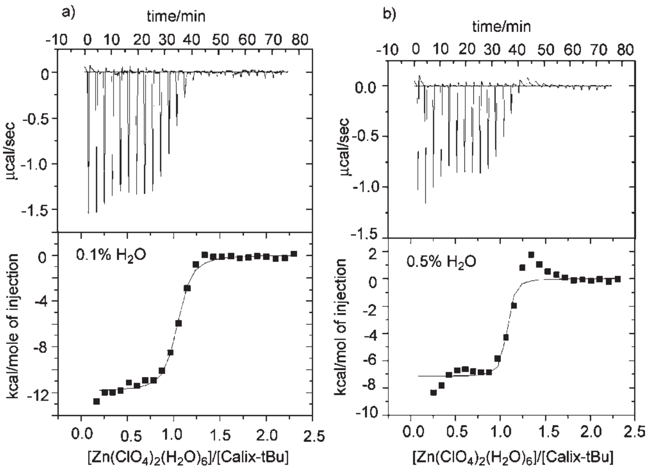


Figure 3. Calorimetric titrations of Calix-tBu with 25 aliquots (10 μL each) of $Zn(ClO_4)_2(H_2O)_6$ in acetonitrile containing 0.1% (a) and 0.5% (v/v) water (b) at 298.15 K. The initial concentrations of Calix-tBu in the cell and $Zn(ClO_4)_2(H_2O)_6$ in the syringe are given in Table 2 (run 7) for the measurement with 0.1% H_2O. The initial concentrations of Calix-tBu in the cell and $Zn(ClO_4)_2(H_2O)_6$ in the syringe are 2.50×10^{-5} and 3.01×10^{-4} M, respectively, for the measurement with 0.5% H_2O.

Coordination in THF. THF is a noncoordinating solvent that is usually used as a solvent for the synthesis of metal complexes of the tris(imidazolyl)calix[6]arenes. The ITC titration curves of Calix-NH_2 and Calix-NO_2 were obtained by injecting $Zn(ClO_4)_2(H_2O)_6$ in THF from a syringe into the THF solution of the calixarene in a cell. Therefore, excess ligand existed in the system at the initial stage of the titration. The ITC titration curves obtained for Calix-NH_2 and Calix-NO_2 are shown in Figure 4. Unlike the case of acetonitrile, two inflection points were observed at around 0.5 and 1.0, indicating that a 2:1 ligand−Zn(II) complex was formed at the initial stage[16] and that such a 2:1 complex was subsequently converted to a 1:1 complex by the further addition of $Zn(ClO_4)_2(H_2O)_6$ in THF (Scheme 1). The titration curves shown in Figure 4 were

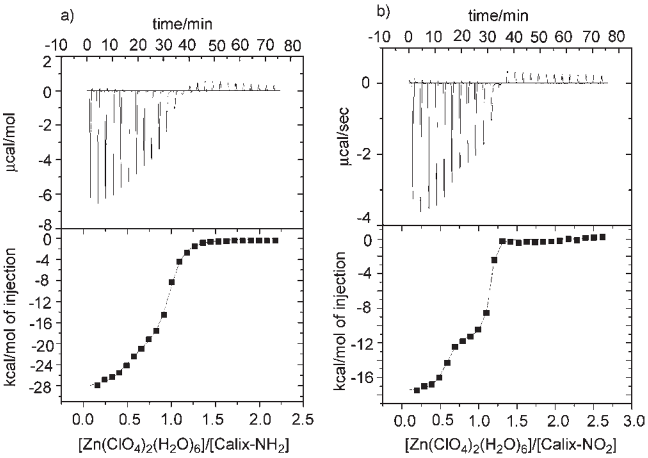


Figure 4. Calorimetric titrations of Calix-NH_2 (a) and Calix-NO_2 (b) with 25 aliquots (10 μL each) of $Zn(ClO_4)_2(H_2O)_6$ in THF at 298.15 K. The initial concentrations of Calix-NH_2 and Calix-NO_2 in a cell and $Zn(ClO_4)_2(H_2O)_6$ in a syringe are given in Table 3 (runs 11 and 12).

Table 2. Effects of Small Amounts of H_2O and CH_3OH on Thermodynamic Parameters for Coordination of Calix-tBu to Zn(II) in Acetonitrile

run	cell[a]	syringe[b]	solvent	n[c]	K (M^{-1})	ΔH^0 (kJ mol^{-1})	ΔS^0 (J mol^{-1} K^{-1})
7	Calix-tBu (2.50×10^{-5} M)	Zn(II) (3.00×10^{-4} M)	CH_3CN + 0.1% H_2O	1.01 ± 0.01	$(7.59 \pm 1.46) \times 10^6$	−49.9 ± 0.96	−36.8
8	Calix-tBu (2.53×10^{-5} M)	Zn(II) (3.05×10^{-4} M)	CH_3CN + 0.2% H_2O	1.00 ± 0.01	$(9.68 \pm 1.52) \times 10^6$	−38.0 ± 0.36	+6.33
9	Calix-tBu (2.50×10^{-5} M)	Zn(II) (3.06×10^{-4} M)	CH_3CN + 0.3% H_2O	0.91 ± 0.01	$(2.31 \pm 0.48) \times 10^7$	−34.5 ± 0.35	+25.4
10	Calix-tBu (4.28×10^{-5} M)	Zn(II) (3.41×10^{-4} M)	CH_3CN + 0.1% CH_3OH	0.91 ± 0.01	$(7.96 \pm 0.95) \times 10^6$	−67.9 ± 0.48	−95.9

[a] The numbers in parentheses are the initial concentrations of Calix-tBu in the cell. [b] The numbers in parentheses are the initial concentrations of $Zn(ClO_4)_2(H_2O)_6$ in the syringe. [c] The molar ratio ([Zn(II)]/[ligand]) at which an inflection point was observed on the titration curve.

Table 3. Binding Constants for Complexation of Zn(II) with Calix-NH_2 and Calix-NO_2 in THF

run	cell[a]	syringe[b]	solvent	K (M^{-1})[c]
11	Calix-NH_2 (6.37×10^{-5} M)	Zn(II) (7.26×10^{-4} M)	THF	$(1.94 \pm 0.71) \times 10^7$ $(8.42 \pm 3.80) \times 10^4$
12	Calix-NO_2 (4.65×10^{-5} M)	Zn(II) (6.36×10^{-4} M)	THF	$(8.03 \pm 3.43) \times 10^8$ $(5.37 \pm 2.12) \times 10^5$

[a] The numbers in parentheses are the initial concentrations of the ligands in the cell. [b] The numbers in parentheses are the initial concentrations of $Zn(ClO_4)_2(H_2O)_6$ in the syringe. [c] The calorimetric titration curves were composed of two phases, indicating the formation of the 2:1 and 1:1 complexes (see the text). The inflection points were observed around n = 0.5 and 1.0. The larger and smaller K values are the binding constants for the 1:1 and 2:1 ligand−Zn(II) complexes, respectively.

analyzed to afford the K_1 and K_2 values defined as follows:

$$\text{ligand} + \text{Zn(II)} \xrightleftharpoons{K_1} \text{ligand}-\text{Zn(II)} \quad (2)$$

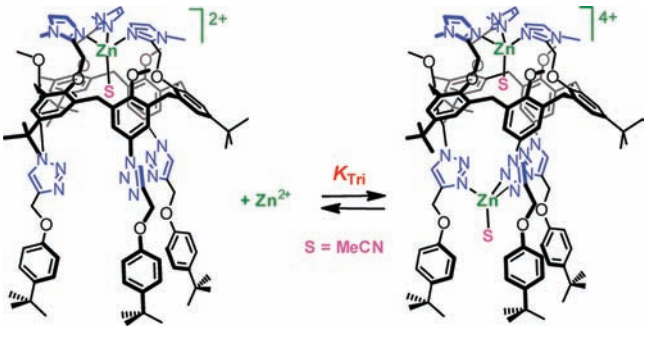
$$\text{ligand}-\text{Zn(II)} + \text{ligand} \xrightleftharpoons{K_2} (\text{ligand})_2-\text{Zn(II)} \quad (3)$$

The results are listed in Table 3. For both ligands, the 1:1 complex formation is more favorable than the 2:1 complex formation. The K_1 values are about 1 order of magnitude larger than those measured in acetonitrile, in agreement with the fact that THF is a poor coordinating solvent in which the Zn(II) does not need to be desolvated upon coordination. Table 3 does not give the ΔH^0 and ΔS^0 values because of poor reproducibility in evaluation of these parameters. Especially, no reproducibility was achieved in the complexation of Calix-tBu with Zn(II) in THF. The results obtained from several ITC measurements suggest that a 2:1 Calix-tBu−Zn(II) complex is unlikely to be formed and the K value for the 1:1 complex formation is about 3×10^6 M^{-1} (Supporting Information).

The difference between complexation in acetonitrile and THF may be ascribed to the difference in their ability to coordinate to the Zn(II) ion between these solvents. In the case of acetonitrile, the four-coordinate 1:1 complex involving an acetonitrile molecule as a fourth ligand is stabilized by the solvent (Figure 1). Meanwhile, the fourth ligand, H_2O, that stabilizes the 1:1 complex is provided by the metal source, $Zn(ClO_4)_2(H_2O)_6$, in the complexation in THF. The amount of the water molecules is not enough to form the 1:1 complex at the initial stage of titration, resulting in the formation of the four-coordinate 2:1 ligand−Zn(II) complex, as illustrated in Scheme 1. The poor reproducibility in the ITC measurements seems to be due to an uncertain contribution of very small amounts of the water molecules to the complexation at the initial stage of the titration. Namely, the 1:1 complexation competes against the 2:1 one to uncertain extent under conditions of excess ligand.

Coordination of Ditopic Ligand to Zn(II) in Acetonitrile. Calix-Tri is a ditopic ligand having three imidazole moieties at the narrow rim and three triazole moieties at the wide rim of the calix[6]arene cavity (Scheme 2).[17] It has been reported that the addition of 1 equiv of Zn(II) to a solution of Calix-Tri in acetonitrile selectively affords the Zn(II) complex coordinated by three imidazole moieties and a solvent molecule. Further addition of Zn(II) yields a 1:2 ligand−Zn(II) complex whose triazole moieties coordinate to the second Zn(II) ion.[17a] In the present study, the results of the previous study were thermodynamically reexamined by ITC. The calorimetric titration curve for the Calix-Tri/Zn(II) system in acetonitrile is shown in Figure 5. A biphasic titration curve showing clear inflection points at the molar ratios ([Zn(II)]/[Calix-Tri]) of 1 and 2 was obtained, indicating that the coordination independently occurs at two sites. The thermodynamic parameters are listed in Table 4. The first complexation that occurred at the imidazole site showed a very large K value [$(1.6 \pm 0.2) \times 10^9$ M^{-1}], as

Scheme 2. Binding of Second Zn(II) at the Tris(triazolyl) Core Taking Advantage of the Preorganization of the Calixarene Core Induced by the First Zn(II) Binding at the Tris(imidazolyl) Site



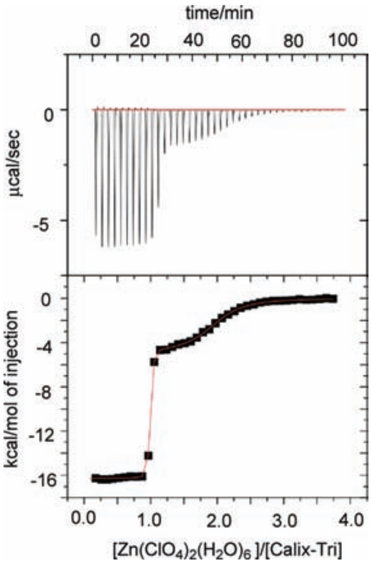


Figure 5. Calorimetric titration of Calix-Tri with 40 aliquots (10 μL each) of $Zn(ClO_4)_2(H_2O)_6$ in CH_3CN at 298.15 K. The initial concentrations of Calix-Tri in the cell and $Zn(ClO_4)_2(H_2O)_6$ in the syringe are given in Table 4 (run 13).

Table 4. Thermodynamic Parameters for Coordination of Calix-Tri to Zn(II)

run	cell[a]	syringe[b]	solvent	n[c]	K (M^{-1})	ΔH^0 (kJ mol^{-1})	ΔS^0 (J mol^{-1} K^{-1})
13	Calix-Tri (6.16×10^{-5} M)	Zn(II) (1.09×10^{-3} M)	CH_3CN	0.96 ± 0.01	$(1.6 \pm 0.2) \times 10^9$	-68 ± 0.1	-52
				1.96 ± 0.01	$(2.96 \pm 0.17) \times 10^5$	-20.5 ± 0.22	$+36.0$

[a] The number in parentheses is the initial concentration of the ligand in the cell. [b] The number in parentheses is the initial concentration of $Zn(ClO_4)_2(H_2O)_6$ in the syringe. [c] The molar ratios ([Zn(II)]/[ligand]) at which the inflection points were observed on the titration curve.

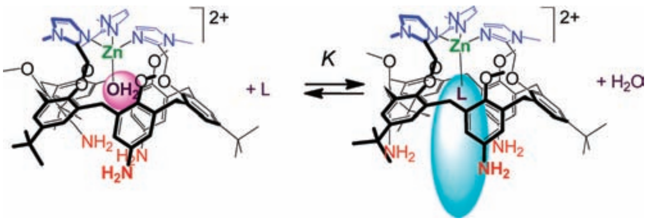
Table 5. Thermodynamic Parameters for Fourth Ligand Exchange Reactions of Zn^{II}−Calix-NH_2 in THF[a]

run	cell[b]	syringe[c]	solvent	n[d]	K (M^{-1})	ΔH^0 (kJ mol^{-1})	ΔS^0 (J mol^{-1} K^{-1})
14	Zn−Calix-NH_2 (6.40×10^{-5} M)	$C_4H_9NH_2$ (6.90×10^{-4} M)	THF	0.98 ± 0.01	$(8.83 \pm 0.59) \times 10^5$	-33.1 ± 0.24	$+2.89$
15	Zn−Calix-NH_2 (6.20×10^{-5} M)	$C_7H_{15}NH_2$ (6.99×10^{-4} M)	THF	0.90 ± 0.01	$(2.73 \pm 0.10) \times 10^5$	-45.0 ± 0.34	-46.9
16	Zn−Calix-NH_2 (6.30×10^{-4} M)	CH_3CN (7.22×10^{-2} M)	THF	1.05 ± 0.32	$(2.43 \pm 0.10) \times 10^2$	-3.51 ± 1.12	$+33.9$
17	Zn−Calix-NH_2 (6.16×10^{-4} M)	CH_3CONH_2 (6.98×10^{-2} M)	THF	1.00	68.1 ± 3.1	-6.43 ± 0.19	$+13.6$

[a] Zn−Calix-NH_2 means the equimolar mixture of Calix-NH_2 and $Zn(ClO_4)_2(H_2O)_6$ in THF. The fourth ligand of Zn−Calix-NH_2 is H_2O. [b] The numbers in parentheses are the initial concentrations of Zn−Calix-NH_2 in the cell. [c] The numbers in parentheses are the initial concentrations of the ligands in the syringe. [d] The molar ratio ([Zn(II)]/[ligand]) at which a inflection point was observed on the titration curve.

compared with that for the complexation of Calix-tBu with Zn(II) [$K = (1.45 \pm 0.17) \times 10^7$ M^{-1}, run 1]. It should be noted that the accuracy of the K value for the first coordination must be somewhat poor because of the too large K value for ITC measurement. The difference in the K values between Calix-tBu and Calix-Tri is mainly ascribed to the difference in the ΔS^0 values. Since this difference cannot be ascribed to the difference in desolvation, we have to consider the difference in the extent of the conformational changes upon coordination to Zn(II). It is assumed that the more preferable ΔS^0 value for the Calix-Tri/Zn(II) system is ascribed to preferable preorganization, as compared with the Calix-tBu/Zn(II) system. Indeed, ^{1}H NMR studies have shown large difference in the free ligand conformations between Calix-tBu and Calix-Tri.[13,17] The two major flattened cone conformations are depicted in Figure 1. At room temperature, the spectrum of Calix-tBu (500 MHz in $CDCl_3$) is sharp and corresponds to the conformation for which the three methoxy groups are projected in an in position and the imidazole arms in an out position. Such a conformation is the inverse one adopted by the complex (Figure 1). Meanwhile, the ^{1}H NMR spectrum of the Calix-Tri ligand is extremely broad. At higher temperature, the spectrum becomes sharper, suggesting a preorganized conformation whose conformational change is somewhat restricted. Accordingly, the ΔS^0 value is less negative for Calix-Tri than for Calix-tBu. The ability of the Calix-Tri ligand to bind a second Zn(II) at the triazole core was evidenced by NMR and UV−vis spectroscopy that indicated the K_{Tri} value of 3×10^5 M^{-1}.[17a] The K_{Tri} value from ITC is in remarkable agreement with that from NMR spectroscopy, which fully validates the interpretation of the ITC results. The thermodynamic parameters obtained for coordination of the triazole ligands are $\Delta H^0 = -20$ kJ mol^{-1} and $\Delta S^0 = +36$ J mol^{-1} K^{-1}. Compared to the thermodynamic parameters for the first binding event shown in Table 4, it becomes clear that (i) the smaller enthalpy change is ascribed to the weaker σ-donor ability of a triazole ligand when compared with an imidazole ligand and (ii) the preorganization of the triazole core due to the first coordination is reflected in the positive entropy change in the second coordination event. Because the first complexation shapes the circular truncated cone structure, the second coordination of the triazole moieties to Zn(II) does not require the extensive conformational change of the ligand (Scheme 2). Therefore, the positive entropy change for the second complexation is mainly ascribed to the desolvation from Zn(II). The enthalpy−entropy compensation effect may account for the relatively large ΔH^0 value.

Scheme 3. Ligand Exchange of a 1:1 Tris(imidazolyl)calix[6]arene−Zn(II) Complex Involving a Fourth H_2O Ligand with Butylamine in THF



Thermodynamics for Ligand Exchange of Zn(II)−Calix-NH_2. Calix-NH_2 was used for studying ligand exchange in the noncoordinating solvent, THF. With this ligand, we have previously shown that a single water molecule occupies the cavity space of the Zn(II) complex in a noncoordinating solvent,[11] while the second water molecule is bound to the fourth H_2O ligand coordinating to Zn(II)−Calix-tBu.[10] Such a difference can be interpreted in terms of that the smaller NH_2 substituents allow one aromatic unit of the calixarene to undergo partial self-inclusion in the cavity, resulting in a better fit with a single water guest.[11] In the case of Zn(II)−Calix-NH_2, the guest exchange process always involves a single molecule out and in (Scheme 3). H_2O−Zn(II)−Calix-NH_2 was placed in a cell of the calorimeter and a ligand such as butylamine, heptylamine, acetonitrile, or acetamide in THF was added in a stepwise fashion from a syringe to obtain a calorimetric titration curve. The results are listed in Table 5. The K values listed in Table 5 clearly point out the primary amines as the best guests, in agreement with a previous study based on ^{1}H NMR spectroscopy.[9−11] The ΔH^0 values clearly reflect the electron-pair-donor ability of the guest ligand: amines > amides > nitriles. The ΔS^0 value for ligand exchange greatly depends on the ligand: for example, -44 J mol^{-1} K^{-1} for heptylamine and $+34$ J mol^{-1} K^{-1} for acetonitrile. The ΔS^0 for the ligand exchange depends on the size of a guest ligand: the smaller the guest, the more positive the ΔS^0. This likely reflects the supramolecular aspect of the system: the restriction of the guest freedom once included into the calixarene cavity. Cavity effects were also reflected in the enthalpy changes. Indeed, the more negative enthalpy change for heptylamine compared to butylamine cannot be ascribed to a difference in the electron-pair donor ability of the guest but is rather interpreted in terms of bigger van der Waals and/or multiple C−H/π interactions between heptylamine and the calixarene.[7,18]

■ CONCLUSIONS

Results previously reported by Reinaud et al. for the coordination of the tris(imidazolyl)calix[6]arenes to Zn(II) were reexamined by ITC. The present study provides thermodynamic parameters for the complexation, which are crucial to the elucidation of detailed mechanisms of coordination complex formation. In particular, the contribution of the solvent to the metal complex formation was highlighted by ITC. In the present cavity-based system, coordinating solvents such as acetonitrile and methanol shows an important role in the stabilization of the 1:1 calixarene ligand−metal complex formation. In contrast, in a noncoordinating solvent such as THF, the competing formation of the 1:1 and 2:l ligand−metal ion complexes has been evidenced. The determination of the enthalpy and entropy changes for the formation of 1:1 host−guest complexes has highlighted the large reorganization of the calixarene structure that undergoes upon complexation, which results in an important entropic gain in the second coordination event of the ditopic ligand. Guest exchange studies have also evidenced impressive entropic loss due to restricted conformational freedom of large guests at the inside of the cavity. The present study also clearly illustrated that the stability of a metal complex in solution is highly dependent on solvation−desolvation process. It is noteworthy that protic solvents such as water and methanol can potentially promote endothermic complexation because of the extended dehydration or desolvation from a metal ion as well as a ligand. ΔS^0 is indeed a crucial parameter during complexation in a protic solvent. ITC is a powerful tool that is complementary to other spectroscopic methods such as UV−vis, NMR, and soft-ionization MS spectroscopy for detailed study of coordination chemistry in solution.

■ EXPERIMENTAL SECTION

The calix[6]arene ligands used in this study (Figure 1) were synthesized according to previously reported procedures.[9,17a,19,20] The metal source $Zn(ClO_4)_2(H_2O)_6$ (Strem Chemicals) was purchased and used as received. All solvents were of analytical grade and used without further purification. Other materials (reagent grade) were commercially obtained.

Microcalorimetric titrations were carried out using a MicroCal VP-ITC isothermal titration calorimeter at 298.15 K. The concentrations of the ligands in the cell and of the metal source in the syringe are given in each table. The 25−40 aliquots (10 μL each) of $Zn(ClO_4)_2 6H_2O$ in a solvent were added into the ligand solution to measure the heat of complexation. The raw data was corrected by subtracting the heat of dilution, and the titration curve thus obtained was analyzed using ORIGIN software. Each ITC data was collected by two independent measurers and the reproducible data was employed.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ITC traces for complexation of Calix-tBu with $Zn(ClO_4)_2(H_2O)_6$ in ethanol and THF and ^1H NMR spectra of Calix-NH_2 in $CDCl_3$ in the absence and the presence of substoichiometric quantities of Zn(II). This material is available free of charge via the Internet at http://pubs.acs.org.

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